Harvard Department of
Chemistry & Chemical Biology

Chemistry 206 & 215: Advanced Organic Chemistry:

Lecture Notes,
Problem Sets and Exams

Lecture Notes by Profs. David A. Evans and Andrew G. Myers

http://www.courses.fas.harvard.edu/~chem206/

http://evans.harvard.edu/problems/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 1

Introduction to FMO Theory

- General Bonding Considerations
- The H_2 Molecule Revisited (Again!)
- Donor & Acceptor Properties of Bonding & Antibonding States
- Hyperconjugation and "Negative" Hyperconjugation
- Anomeric and Related Effects

Reading Assignment for week:

Kirby, Stereoelectronic Effects

Carey & Sundberg: **Part A**; Chapter 1

Fleming, Chapter 1 & 2

Fukui,*Acc. Chem. Res.* **1971**, *4*, 57. (pdf)

Curnow, *J. Chem. Ed.* **1998**, *75*, 910 (pdf)

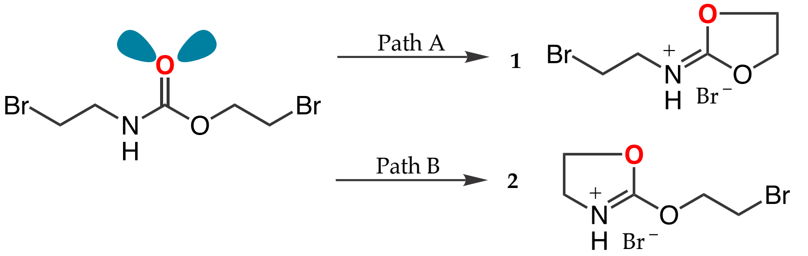
Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)

D. A. Evans

Monday,
September 15, 2003

Problems of the Day

The molecule illustrated below can react through either Path A or Path B to form salt **1** or salt **2**. In both instances the carbonyl oxygen functions as the nucleophile in an intramolecular alkylation. What is the preferred reaction path for the transformation in question?

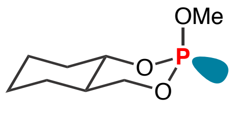


This is a "thought" question posed to me by Prof. Duilo Arigoni at the ETH in Zuerich some years ago

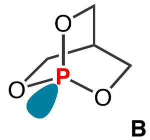
(First hr exam, 1999)

The three phosphites illustrated below exhibit a 750–fold span in reactivity with a test electrophile (eq 1) (Gorenstein, *JACS* **1984**, *106*, 7831).

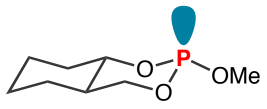
$$(RO)_3P \quad + \quad El(+) \longrightarrow (RO)_3\overset{+}{P}\text{–}El \qquad (1)$$



A



B



C

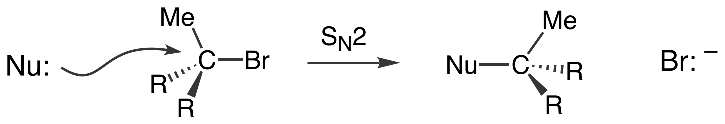
Rank the phosphites from the least to the most nucleophilic and provide a concise explanation for your predicted reactivity order.

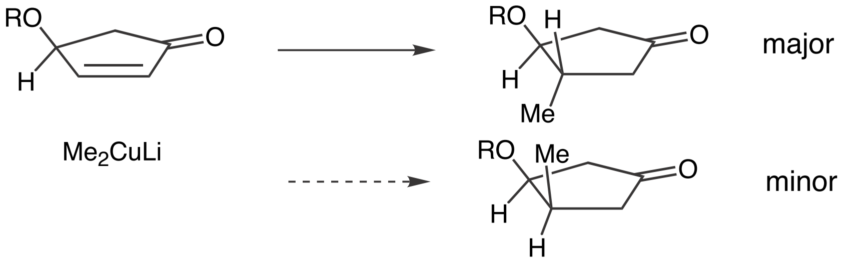
An Introduction to Frontier Molecular Orbital Theory-1

Universal Effects Governing Chemical Reactions
There are three:

■ Steric Effects

Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules

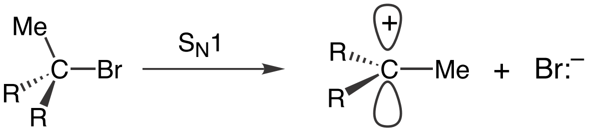




■ Electronic Effects (Inductive Effects):

The effect of bond and through-space polarization by heteroatom substituents on reaction rates and selectivities

Inductive Effects: Through-bond polarization
Field Effects: Through-space polarization



rate decreases as R becomes more electronegative

■ Stereoelectronic Effects

Geometrical constraints placed upon ground and transition states by orbital overlap considerations.

Fukui Postulate for reactions:

"During the course of chemical reactions, the interaction of the highest filled (HOMO) and lowest unfilled (antibonding) molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition structure."

■ General Reaction Types

Radical Reactions (~10%): $A\bullet + B\bullet \longrightarrow A\text{—}B$

Polar Reactions (~90%): $A(:) + B(+) \longrightarrow A\text{—}B$

Lewis Base Lewis Acid

FMO concepts extend the donor-acceptor paradigm to non-obvious families of reactions

■ Examples to consider

$H_2 + 2\ Li(0) \longrightarrow 2\ LiH$

$CH_3\text{–}I + Mg(0) \longrightarrow CH_3\text{–}MgBr$

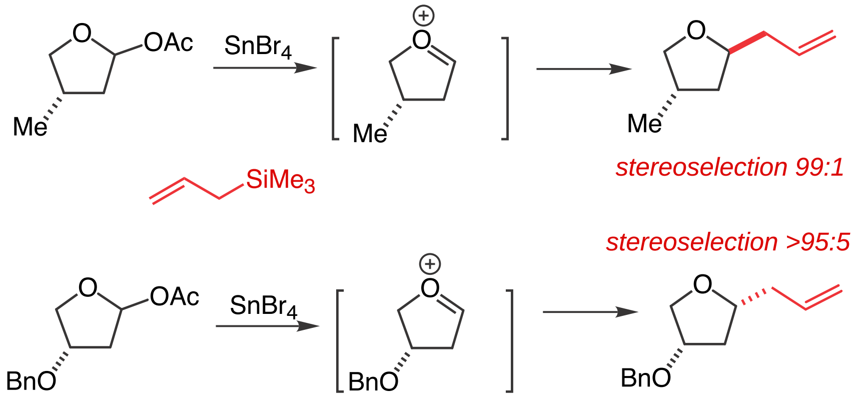
"Organic chemists are generally unaware of the impact of electronic effects on the stereochemical outcome of reactions."

"The distinction between electronic and stereoelectronic effects is not clear-cut."

■ Steric Versus electronic Effects: Some Case Studies

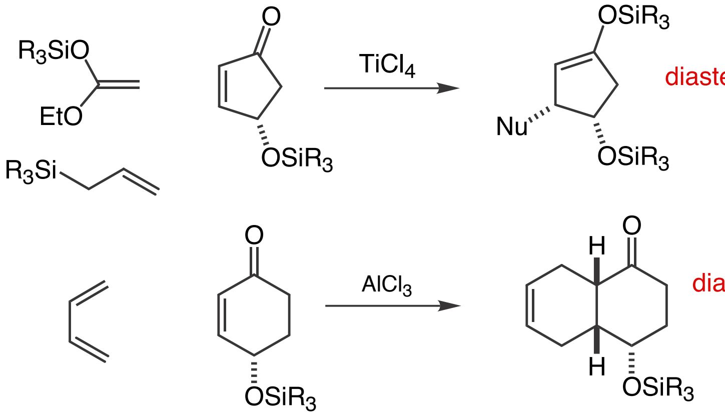
When steric and electronic (stereoelectronic) effects lead to differing stereochemical consequences

Woerpel etal. *JACS* **1999**, 121, 12208.



stereoselection 99:1

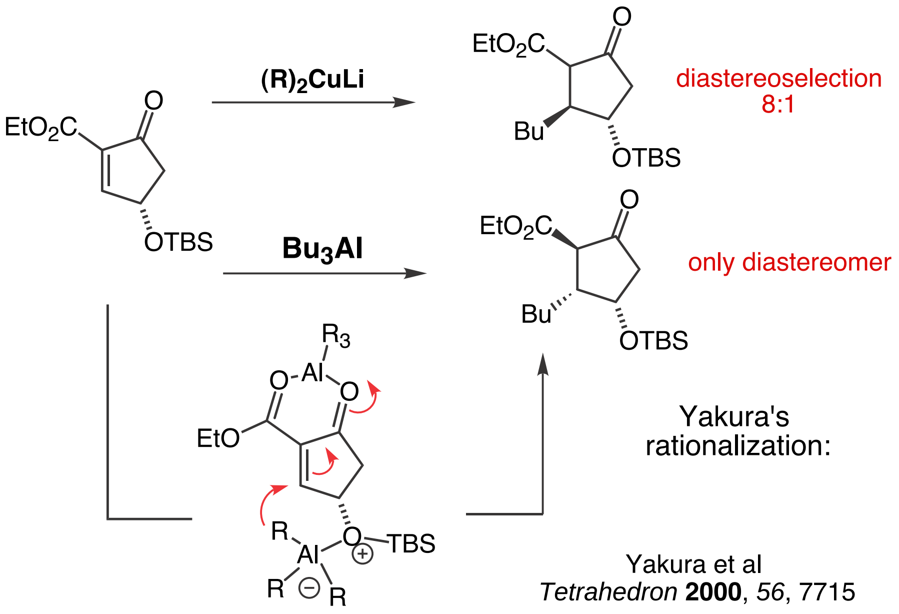
stereoselection >95:5



diastereoselection >94:6

diastereoselection 93:7

Danishefsky et al *JOC* **1991**, *56*, 387

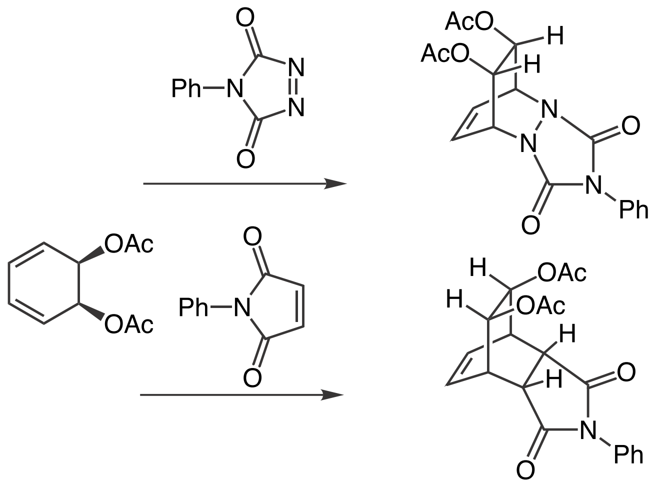


diastereoselection 8:1

only diastereomer

Yakura's rationalization:

Yakura et al *Tetrahedron* **2000**, *56*, 7715



only diastereomer

60-94%

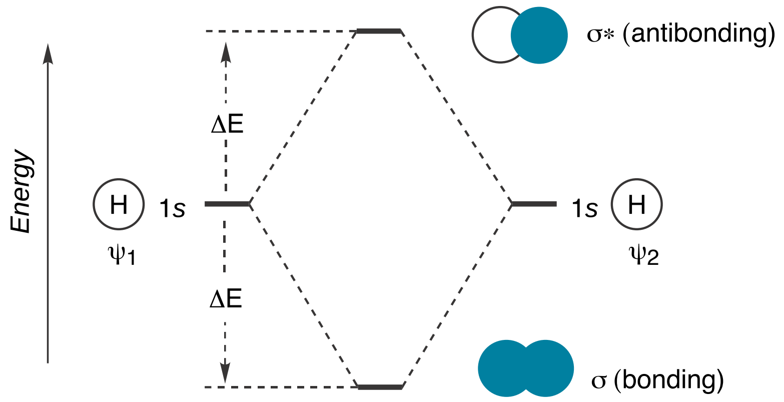
Mehta et al, *Acc Chem. Res*. **2000**, *33*, 278-286

The H_2 Molecular Orbitals & Antibonds

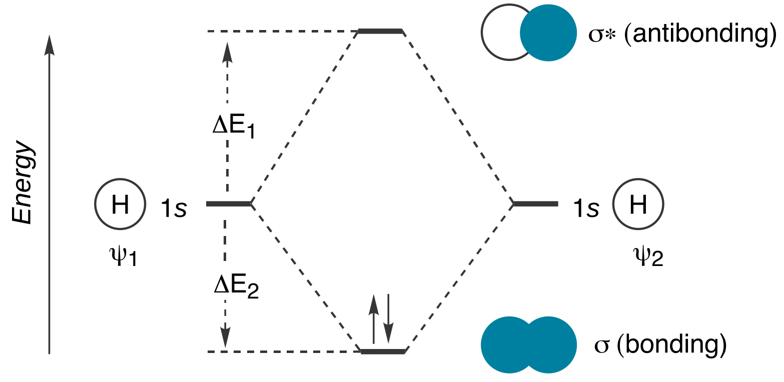
The H_2 Molecule (again!!)

Let's combine two hydrogen atoms to form the hydrogen molecule. Mathematically, linear combinations of the 2 atomic 1s states create two new orbitals, one is bonding, and one antibonding:

- **Rule one**: A linear combination of n atomic states will create n MOs.



Let's now add the two electrons to the new MO, one from each H atom:



Note that ΔE_1 is greater than ΔE_2. Why?

Linear Combination of Atomic Orbitals (LCAO): Orbital Coefficients

- **Rule Two**:

Each MO is constructed by taking a linear combination of the individual atomic orbitals (AO):

Bonding MO $\sigma = C_1\psi_1 + C_2\psi_2$

Antibonding MO $\sigma^* = C^*_1\psi_1 - C^*_2\psi_2$

The coefficients, C_1 and C_2, represent the contribution of each AO.

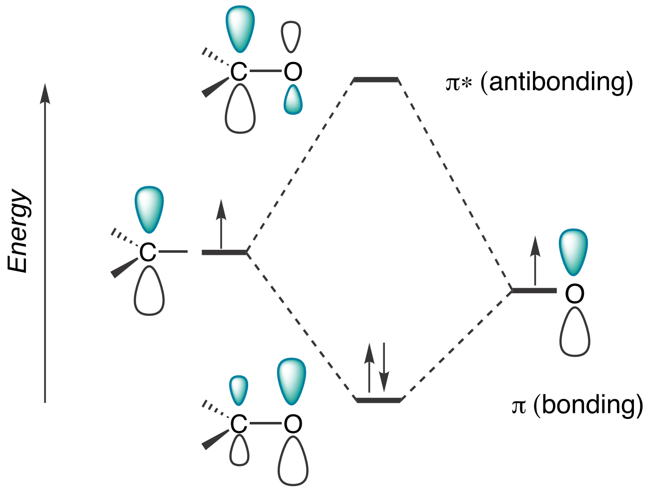
- **Rule Three**: $(C_1)^2 + (C_2)^2 = 1$

The squares of the C-values are a measure of the electron population in neighborhood of atoms in question

- **Rule Four**: bonding$(C_1)^2$+ antibonding$(C^*_1)^2$= 1

In LCAO method, both wave functions must each contribute one net orbital

Consider the pi–bond of a C=O function: In the ground state pi-C–O is polarized toward Oxygen. Note (Rule 4) that the antibonding MO is polarized in the opposite direction.



■ *Bond strengths (Bond dissociation energies) are composed of a covalent contribution (δE_{cov}) and an ionic contribution (δE_{ionic}).*

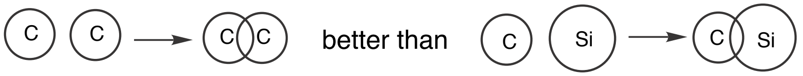
Bond Energy (BDE) = $\delta E_{covalent} + \delta E_{ionic}$ (Fleming, page 27)

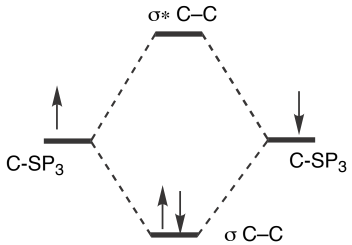
When one compares bond strengths between C–C and C–X, where X is some other element such as O, N, F, Si, or S, keep in mind that covalent and ionic contributions vary independently. Hence, the mapping of trends is not a trivial exercise.

Useful generalizations on covalent bonding

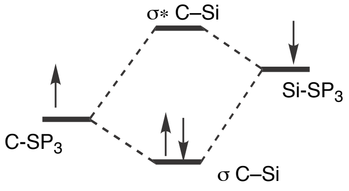
■ *Overlap between orbitals of comparable energy is more effective than overlap between orbitals of differing energy.*

For example, consider elements in Group IV, Carbon and Silicon. We know that C-C bonds are considerably stronger by Ca. 20 kcal mol^{-1} than C-Si bonds.





$H_3C–CH_3$ BDE = 88 kcal/mol
Bond length = 1.534 Å



$H_3C–SiH_3$ BDE ~ 70 kcal/mol
Bond length = 1.87 Å

This trend is even more dramatic with pi-bonds:

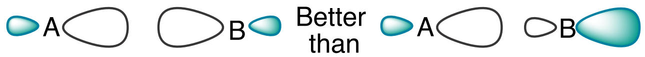
π C–C = 65 kcal/mol π C–Si = 36 kcal/mol π Si–Si = 23 kcal/mol

■ *Weak bonds will have corresponding low-lying antibonds.*

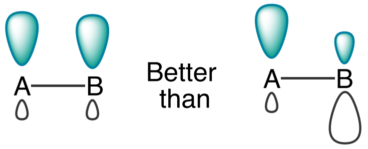
Formation of a weak bond will lead to a corresponding low-lying antibonding orbital. Such structures are reactive as both nucleophiles & electrophiles

■ *Orbital orientation strongly affects the strength of the resulting bond.*

For σ Bonds:



For π Bonds:

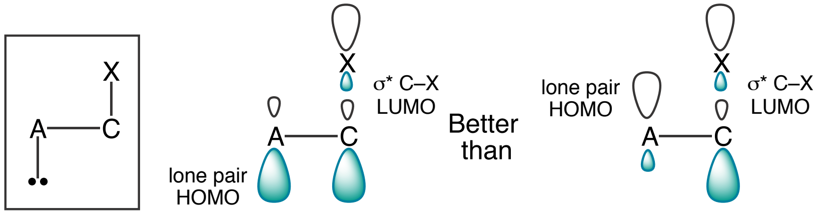


This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

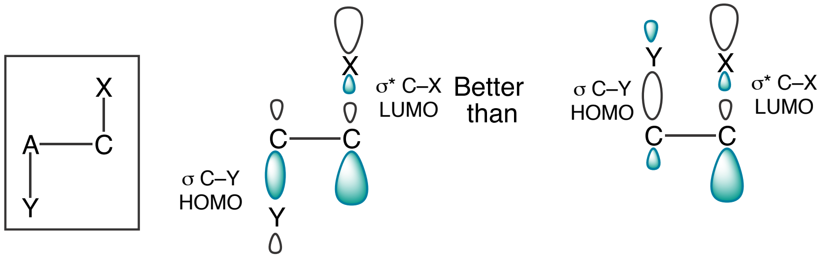
■ *An anti orientation of filled and unfilled orbitals leads to better overlap.*

This is a corrollary to the preceding generalization.
There are two common situations.

Case-1: Anti Nonbonding electron pair & C–X bond



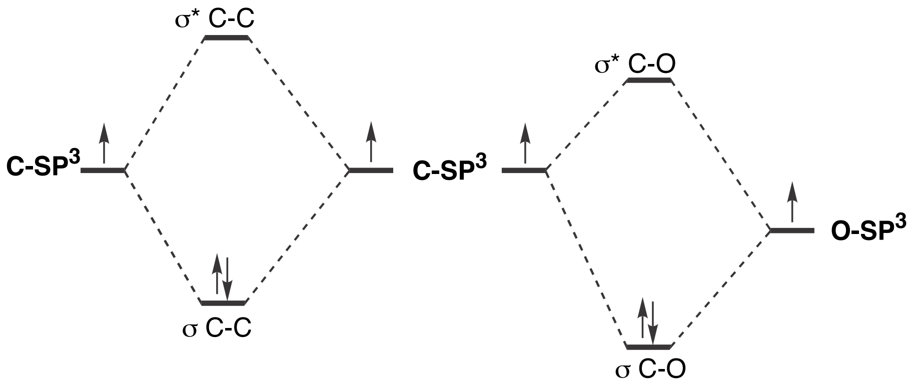
Case-2: Two anti sigma bonds



Donor-Acceptor Properties of Bonding and Antibonding States

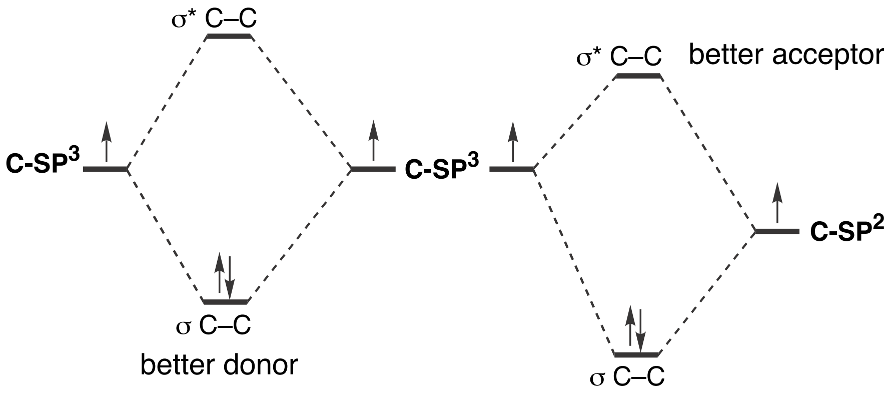
Donor Acceptor Properties of C-C & C-O Bonds

Consider the energy level diagrams for both bonding & antibonding orbitals for C–C and C–O bonds.



- The greater electronegativity of oxygen lowers both the bonding & antibonding C-O states. Hence:
  - σ C–C is a better donor orbital than σ C–O
  - σ^*C–O is a better acceptor orbital than σ^*C–C

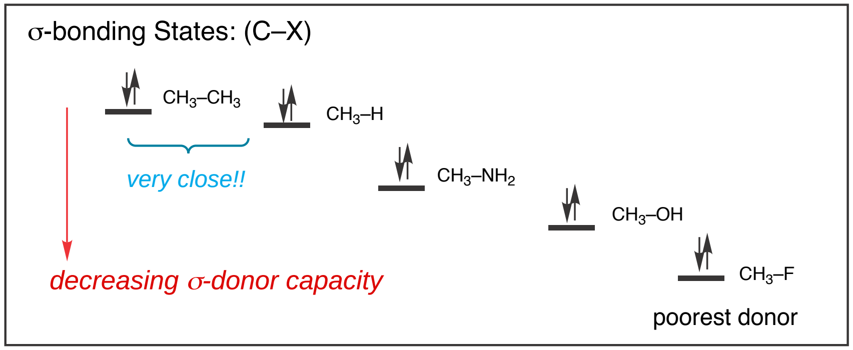
Donor Acceptor Properties of C_{SP3}-C_{SP3} & C_{SP3}-C_{SP2} Bonds

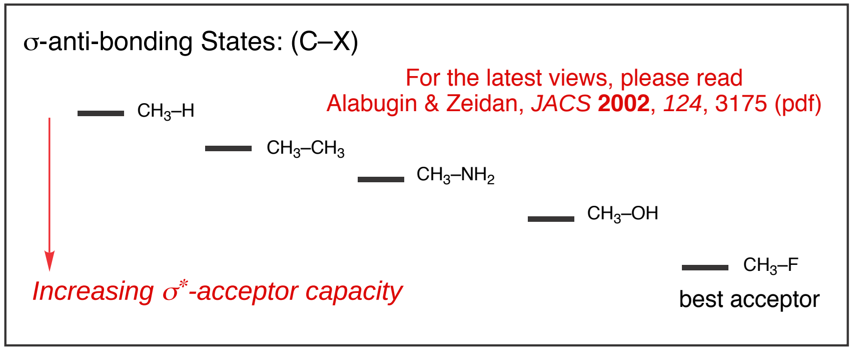


- The greater electronegativity of C_{SP2} lowers both the bonding & antibonding C–C states. Hence:
  - σ C_{SP3}-C_{SP3} is a better donor orbital than σ C_{SP3}-C_{SP2}
  - σ^*C_{SP3}-C_{SP2} is a better acceptor orbital than σ^*C_{SP3}-C_{SP3}

Hierarchy of Donor & Acceptor States

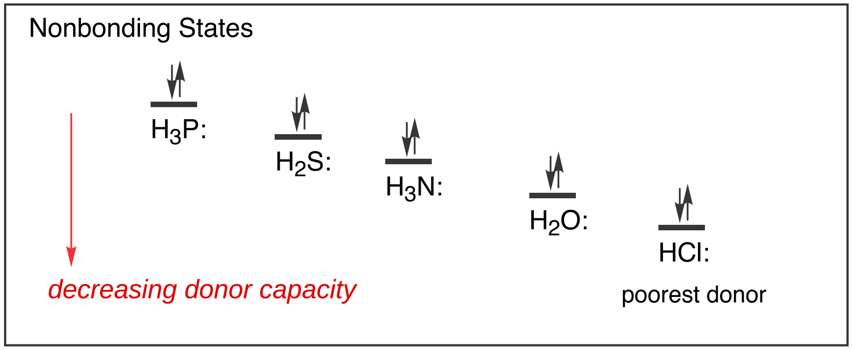
Following trends are made on the basis of comparing the bonding and antibonding states for the molecule CH_3–X where X = C, N, O, F, & H.





For the latest views, please read Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)

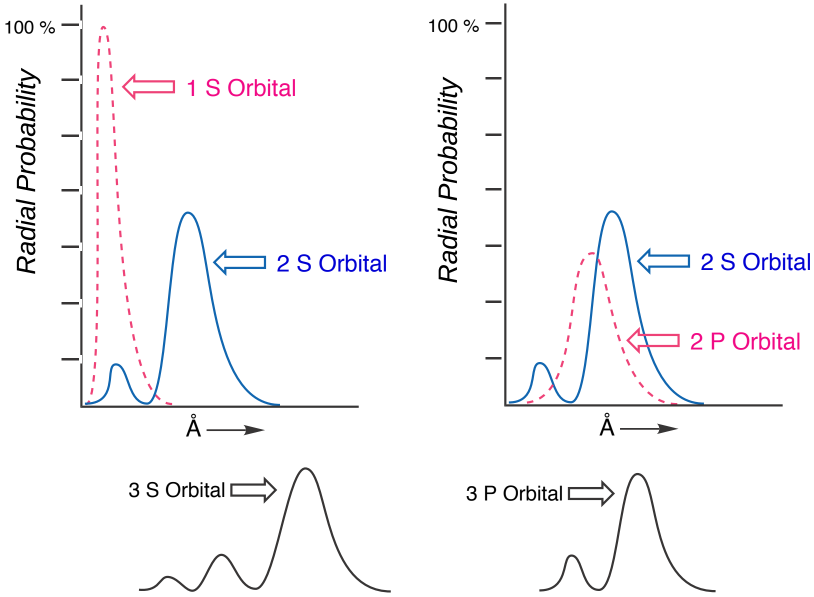
The following are trends for the energy levels of *nonbonding states* of several common molecules. Trend was established by photoelectron spectroscopy.



Hybridization vs Electronegativity

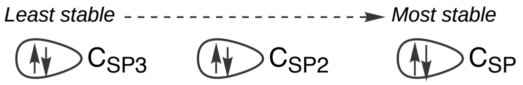
Electrons in 2S states "see" a greater effective nuclear charge than electrons in 2P states.

This becomes apparent when the radial probability functions for S and P-states are examined: The radial probability functions for the hydrogen atom S & P states are shown below.



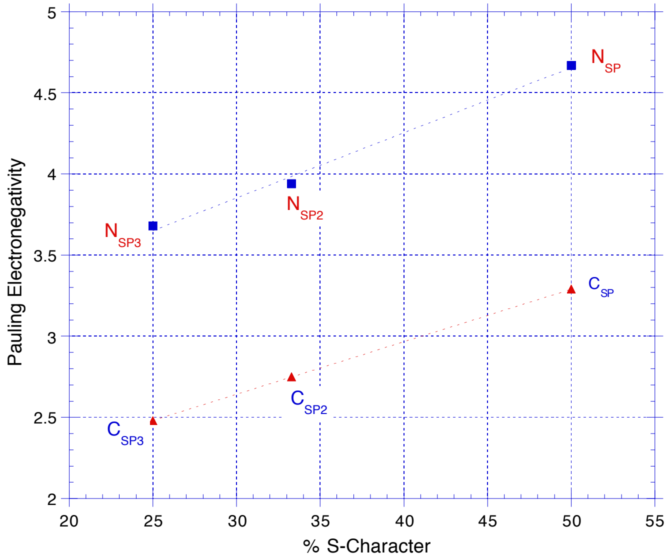
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in S-states "see" a higher nuclear charge.

Above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital

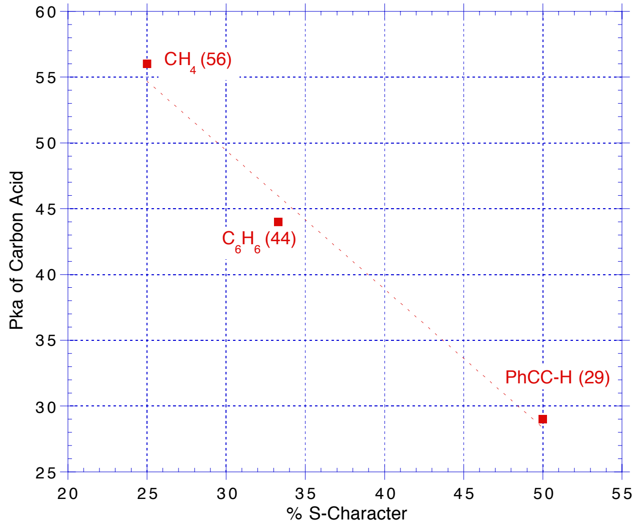


The above trend indicates that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

There is a linear relationship between %S character & Pauling electronegativity



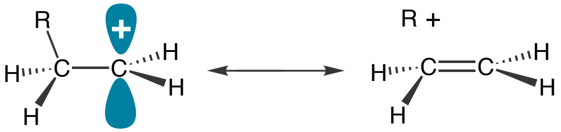
There is a direct relationship between %S character & hydrocarbon acidity



Hyperconjugation: Carbocation Stabilization

■ The interaction of a vicinal bonding orbital with a p-orbital is referred to as hyperconjugation.

This is a traditional vehicle for using valence bond to denote charge delocalization.



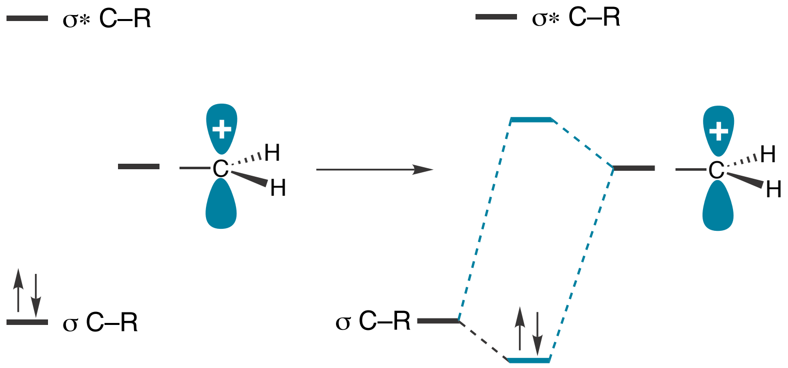
The graphic illustrates the fact that the C-R bonding electrons can "delocalize" to stabilize the electron deficient carbocationic center.

Note that the general rules of drawing resonance structures still hold: the positions of all atoms must not be changed.

Stereoelectronic Requirement for Hyperconjugation:

Syn-planar orientation between interacting orbitals

The Molecular Orbital Description



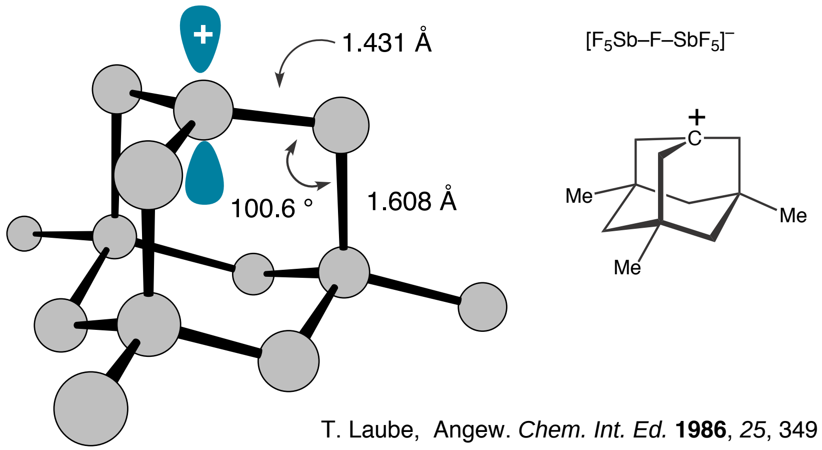
■ Take a linear combination of σ C–R and CSP_2 p-orbital:

"The new occupied bonding orbital is lower in energy. When you stabilize the electrons is a system you stabilize the system itself."

Physical Evidence for Hyperconjugation

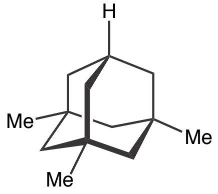
■ Bonds participating in the hyperconjugative interaction, e.g. C–R, will be lengthened while the C(+)–C bond will be shortened.

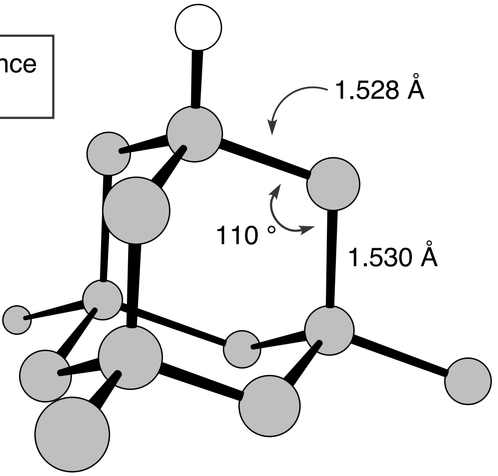
First X-ray Structure of an Aliphatic Carbocation



T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

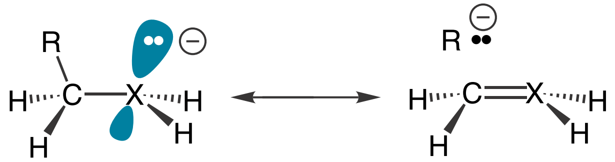
The Adamantane Reference (MM-2)





"Negative" Hyperconjugation

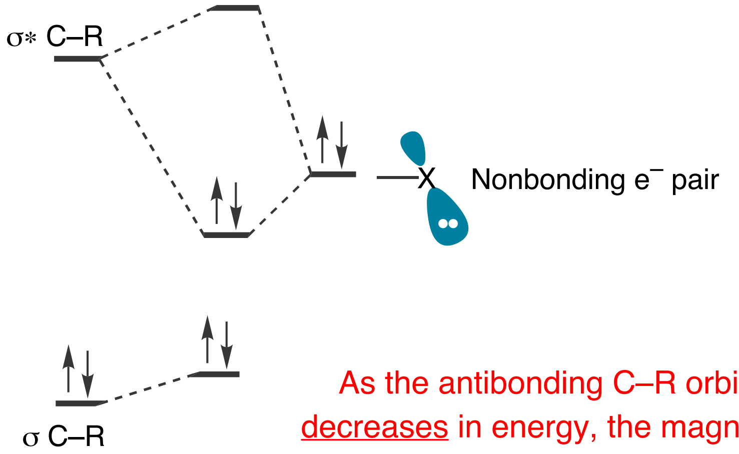
- Delocalization of nonbonding electron pairs into vicinal antibonding orbitals is also possible



This decloalization is referred to as "Negative" hyperconjugation

Since nonbonding electrons prefer hybrid orbitals rather that P orbitals, this orbital can adopt either a syn or anti relationship to the vicinal C–R bond.

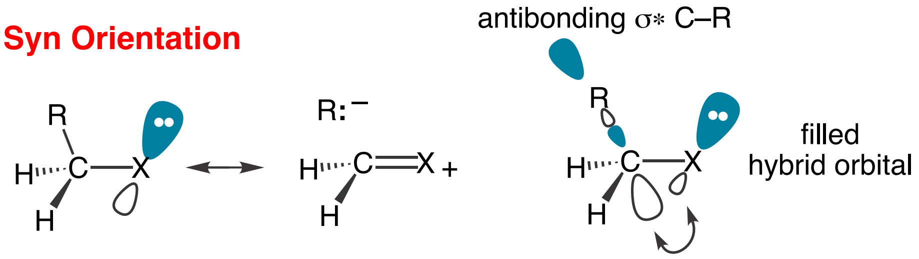
The Molecular Orbital Description



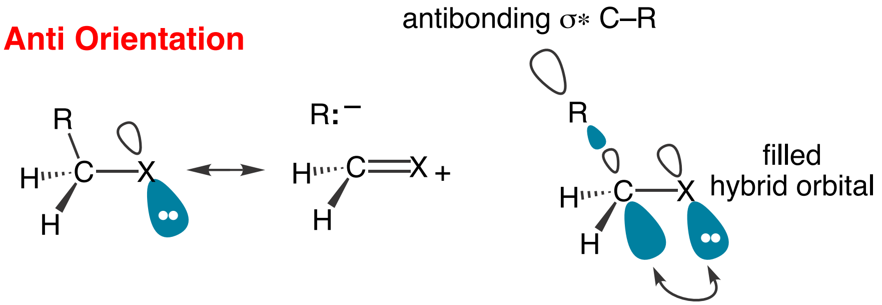
As the antibonding C–R orbital decreases in energy, the magnitude of this interaction will increase

Note that σ C–R is slightly destabilized

Syn Orientation



Anti Orientation



- Overlap between two orbitals is better in the anti orientation as stated in "Bonding Generalizations" handout.

The Expected Structural Perturbations

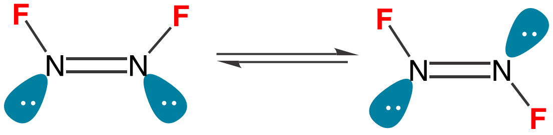
Change in Structure	Spectroscopic Probe
■ Shorter C–X bond	X-ray crystallography
■ Longer C–R bond	X-ray crystallography
■ Stronger C–X bond	Infrared Spectroscopy
■ Weaker C–R bond	Infrared Spectroscopy
■ Greater e-density at R	NMR Spectroscopy
■ Less e-density at X	NMR Spectroscopy

Lone Pair Delocalization: N_2F_2

The interaction of filled orbitals with adjacent antibonding orbitals can have an ordering effect on the structure which will stabilize a particular geometry. Here are several examples:

Case 1: N_2F_2

This molecule can exist as either cis or trans isomers



There are two logical reasons why the trans isomer should be more stable than the cis isomer.

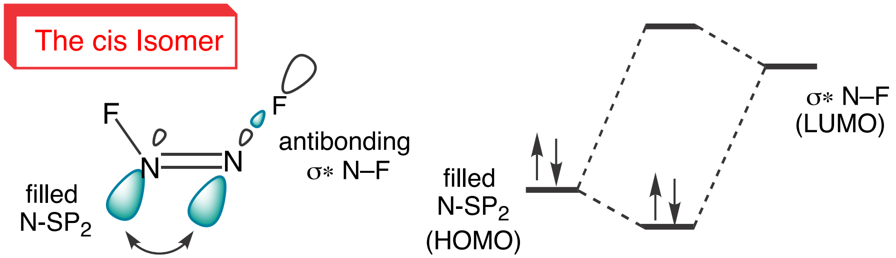
■ The nonbonding lone pair orbitals in the cis isomer will be destabilizing due to electron-electron repulsion.

■ The individual C–F dipoles are mutually repulsive (pointing in same direction) in the cis isomer.

In fact the cis isomer is favored by 3 kcal/ mol at 25 °C.

Let's look at the interaction with the lone pairs with the adjacent C–F antibonding orbitals.

The cis Isomer

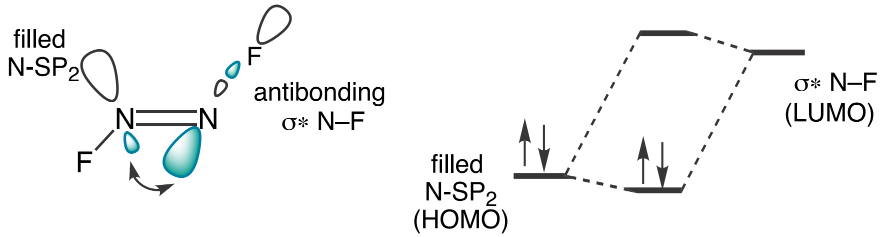


■ Note that by taking a linear combination of the nonbonding and antibonding orbitals you generate a more stable bonding situation.

■ Note that two such interactions occur in the molecule even though only one has been illustrated.

The trans Isomer

Now carry out the same analysis with the same 2 orbitals present in the trans isomer.



■ In this geometry the "small lobe" of the filled N-SP_2 is required to overlap with the large lobe of the antibonding C–F orbital. Hence, when the new MO's are generated the new bonding orbital is not as stabilizing as for the cis isomer.

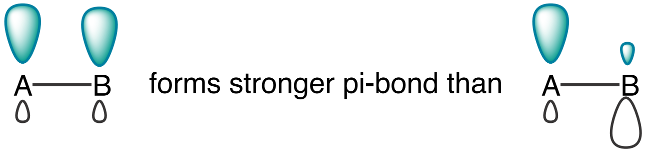
Conclusions

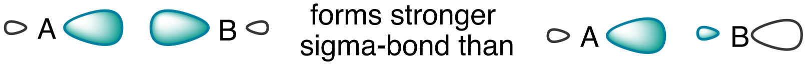
■ Lone pair delocalization appears to override electron-electron and dipole-dipole repulsion in the stabilization of the cis isomer.

■ This HOMO-LUMO delocalization is stronger in the cis isomer due to better orbital overlap.

Important Take-home Lesson

Orbital orientation is important for optimal orbital overlap.





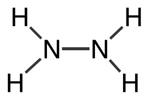
This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

Lone Pair Delocalization: The Gauche Effect

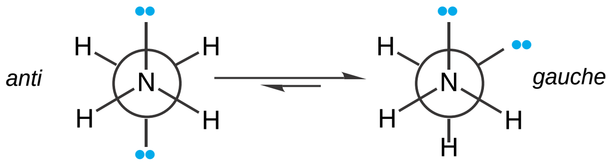
The interaction of filled orbitals with adjacent antibonding orbitals can have an ordering effect on the structure which will stabilize a particular conformation.
Here are several examples of such a phenomon called the gauche effect:

Hydrazine

Hydrazine can exist in either gauche or anti conformations (relative to lone pairs).



observed HNNH
dihedral angle Ca 90°

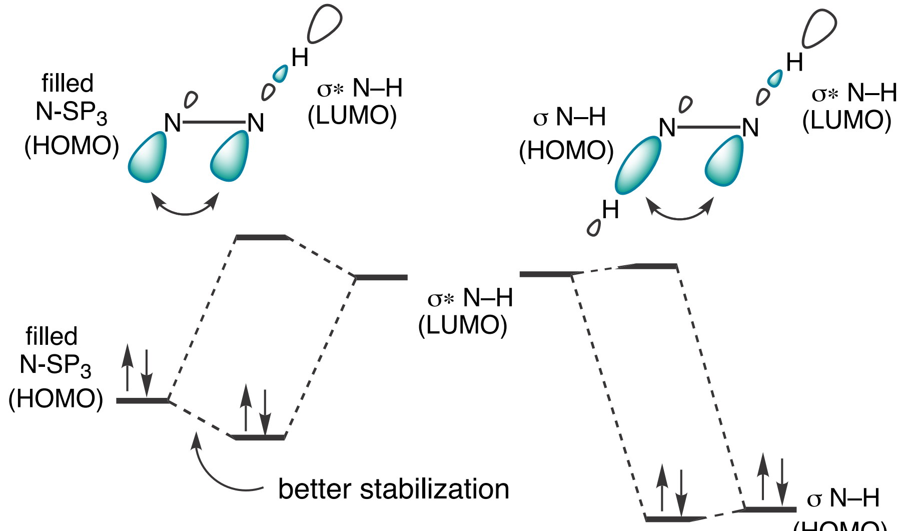


There is a logical reason why the anti isomer should be more stable than the gauche isomer. The nonbonding lone pair orbitals in the gauche isomer should be destabilizing due to electron-electron repulsion.

In fact, the gauche conformation is favored. Hence we have neglected an important stabilization feature in the structure.

HOMO-LUMO Interactions

Orbital overlap between filled (bonding) and antibonding states is best in the anti orientation. HOMO-LUMO delocalization is possible between: (a) N-lone pair ↔ σ* N–H; (b) σ N–H ↔ σ* N–H



The closer in energy the HOMO and LUMO the better the resulting stabilization through delocalization.

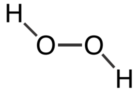
■ Hence, N-lone pair ↔ σ* N–H delocalization better than σ N–H ↔ σ* N–H delocalization.

■ Hence, hydrazine will adopt the gauche conformation where both N-lone pairs will be anti to an antibonding acceptor orbital.

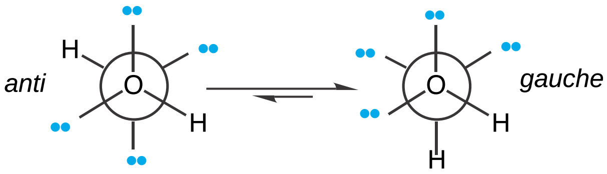
The trend observed for hydrazine holds for oxygen derivatives as well

Hydrogen peroxide

H_2O_2 can exist in either gauche or anti conformations (relative to hydrogens). The gauche conformer is prefered.



observed HOOH
dihedral angle Ca 90°



■ Major stabilizing interaction is the delocalization of O-lone pairs into the C–H antibonding orbitals (Figure A). Note that there are no such stabilizing interactions in the anti conformation while there are 2 in the gauche conformation.

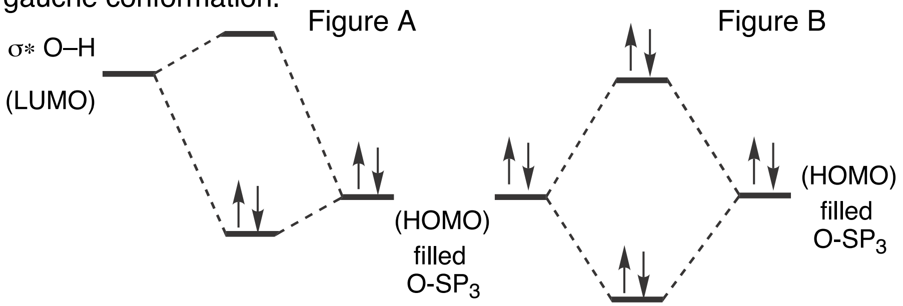


Figure A

Figure B

■ Note that you achieve no net stabilization of the system by generating molecular orbitals from two filled states (Figure B).

Problem: Consider the structures $XCH_2–OH$ where $X = OCH_3$ and F. What is the most favorable conformation of each molecule? Illustrate the dihedral angle relationship along the C–O bond.

The Anomeric Effect: Negative Hyperconjugation

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 2

Stereoelectronic Effects-2

- Anomeric and Related Effects
- Electrophilic & Nucleophilic Substitution Reactions
- The S_N2 Reaction: Stereoelectronic Effects
- Olefin Epoxidation: Stereoelectronic Effects
- Baeyer-Villiger Reaction: Stereoelectronic Effects
- **H**ard & **S**oft **A**cid and **B**ases (Not to be covered in class)

Reading Assignment: Kirby, Chapters 1-3

D. A. Evans

Wednesday,
September 17, 2003

Useful LIterature Reviews

Kirby, A. J. (**1982**). The Anomeric Effect and Related Stereoelectronic Effects at Oxygen. New York, Springer Verlag.

Box, V. G. S. (**1990**). “The role of lone pair interactions in the chemistry of the monosaccharides. The anomeric effect.” *Heterocycles* **31**: 1157.

Box, V. G. S. (**1998**). “The anomeric effect of monosaccharides and their derivatives. Insights from the new QVBMM molecular mechanics force field.” *Heterocycles* **48**(11): 2389-2417.

Graczyk, P. P. and M. Mikolajczyk (**1994**). “Anomeric effect: origin and consequences.” *Top. Stereochem*. **21**: 159-349.

Juaristi, E. and G. Cuevas (**1992**). “Recent studies on the anomeric effect.” *Tetrahedron* **48**: 5019.

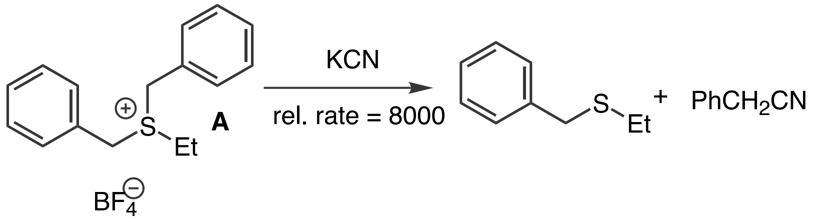
Plavec, J., C. Thibaudeau, et al. (**1996**). “How do the Energetics of the Stereoelectronic Gauche and Anomeric Effects Modulate the Conformation of Nucleos(t)ides?” *Pure Appl. Chem*. **68**: 2137-44.

Thatcher, G. R. J., Ed. (**1993**). The Anomeric Effect and Associated Stereoelectronic Effects. Washington DC, American Chemical Society.

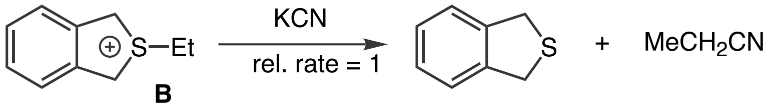
Problem 121

http://evans.harvard.edu/problems/

Sulfonium ions **A** and **B** exhibit remarkable differences in both reactivity and product distribution when treated with nucleophiles such as cyanide ion (eq 1, 2). Please answer the questions posed in the spaces provided below.



(1)

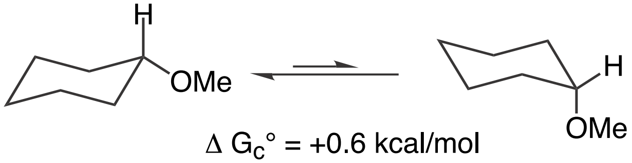


(2)

The Anomeric Effect: Negative Hyperconjugation

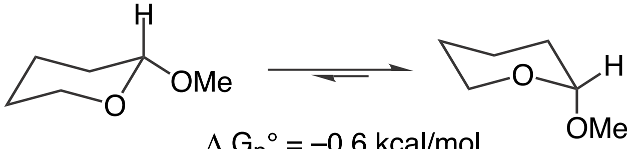
The Anomeric Effect

It is not unexpected that the methoxyl substituent on a cyclohexane ring prefers to adopt the equatorial conformation.



$\Delta G_c^\circ = +0.6$ kcal/mol

What is unexpected is that the closely related 2-methoxytetrahydropyran prefers the axial conformation:



$\Delta G_p^\circ = -0.6$ kcal/mol

That effect which provides the stabilization of the axial OR conformer which overrides the inherent steric bias of the substituent is referred to as the anomeric effect.

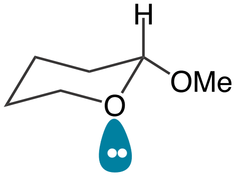
Let anomeric effect = A

$$\Delta G_p^\circ = \Delta G_c^\circ + A$$

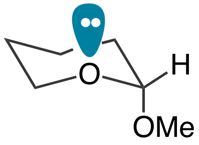
$$A = \Delta G_p^\circ - \Delta G_c^\circ$$

$$A = -0.6 \text{ kcal/mol} - 0.6 \text{ kcal/mol} = -1.2 \text{ kcal/mol}$$

Principal HOMO-LUMO interaction from each conformation is illustrated below:



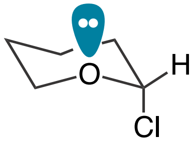
axial O lone pair↔σ* C–H



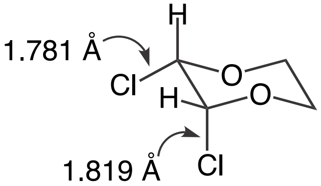
axial O lone pair↔σ* C–O

- Since the antibonding C–O orbital is a better acceptor orbital than the antibonding C–H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

Other electronegative substituents such as Cl, SR etc also participate in anomeric stabilization.

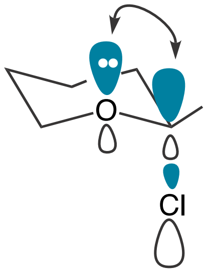


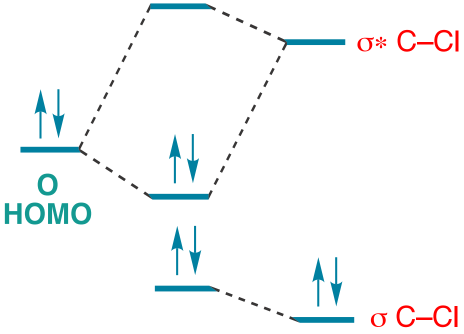
This conformer preferred by 1.8 kcal/mol



Why is axial C–Cl bond longer ?

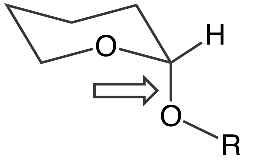
axial O lone pair↔σ* C–Cl

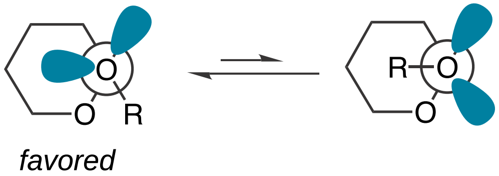




The Exo-Anomeric Effect

- There is also a rotational bias that is imposed on the exocyclic C–OR bond where one of the oxygen lone pairs prevers to be anti to the ring sigma C–O bond

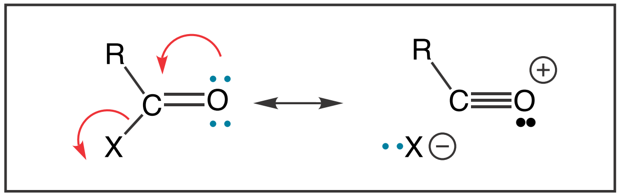




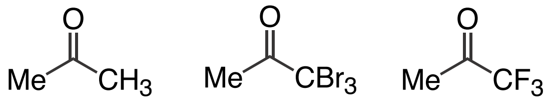
A. J. Kirby, *The Anomeric and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, 1983
E. Jurasti, G. Cuevas, *The Anomeric Effect, CRC Press*, 1995

The Anomeric Effect: Carbonyl Groups

Do the following valence bond resonance structures have meaning?

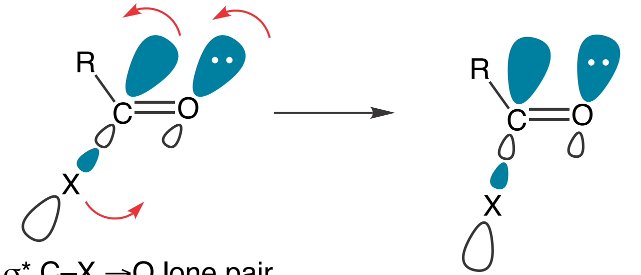


Prediction: As X becomes more electronegative, the IR frequency should increase



$\upsilon_{C=O}$ (cm^{-1})	1720	1750	1780

Prediction: As the indicated pi-bonding increases, the X–C–O bond angle should decrease. This distortion improves overlap.



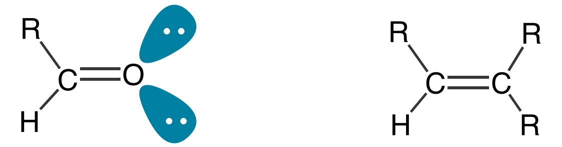
σ* C–X →O lone pair

Evidence for this distortion has been obtained by X-ray crystallography

Corey, *Tetrahedron Lett*. **1992**, *33*, 7103-7106

Aldehyde C–H Infrared Stretching Frequencies

Prediction: The IR C–H stretching frequency for aldehydes is lower than the closely related olefin C–H stretching frequency. For years this observation has gone unexplained.



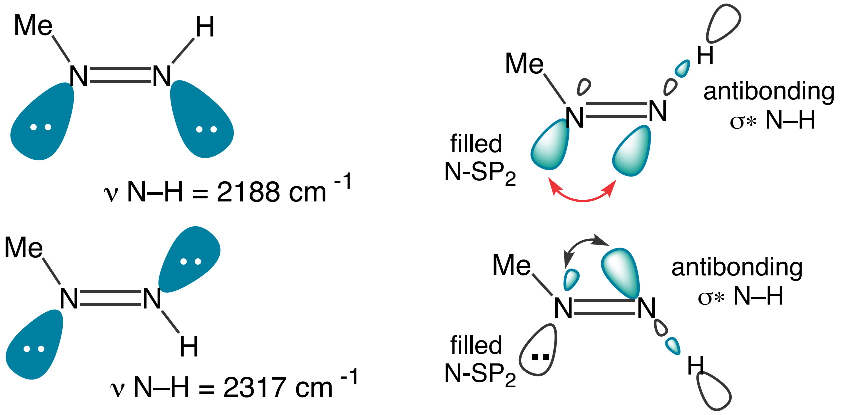
ν C–H = 2730 cm^{-1}

ν C–H = 3050 cm^{-1}

Sigma conjugation of the lone pair anti to the H will weaken the bond. This will result in a low frequency shift.

Infrared evidence for lone pair delocalization into vicinal antibonding orbitals.

The N–H stretching frequency of cis-methyl diazene is 200 cm^{-1} lower than the trans isomer.



ν N–H = 2188 cm^{-1}

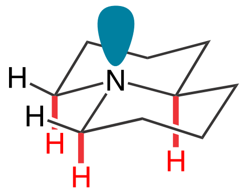
ν N–H = 2317 cm^{-1}

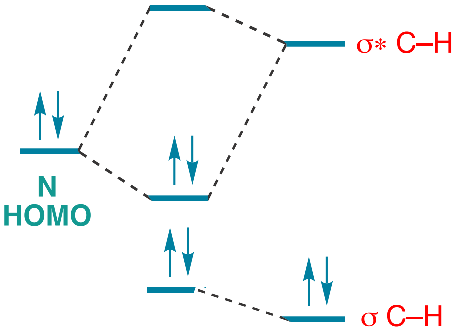
■ The low-frequency shift of the cis isomer is a result of N–H bond weakening due to the anti lone pair on the adjacent (vicinal) nitrogen which is interacting with the N–H antibonding orbital. Note that the orbital overlap is not nearly as good from the trans isomer.

N. C. Craig & co-workers *JACS* **1979**, *101*, 2480.

The Anomeric Effect: Nitrogen-Based Systems

Observation: C–H bonds anti-periplanar to nitrogen lone pairs are spectroscopically distinct from their equatorial C–H bond counterparts





Spectroscopic Evidence for Conjugation

Infrared Bohlmann Bands

Characteristic bands in the IR between 2700 and 2800 cm^{-1} for C-H$_4$, C-H$_6$, & C-H$_{10}$ stretch

Bohlmann, *Ber.* **1958** *91* 2157

Reviews: McKean, *Chem Soc. Rev.* **1978** *7* 399
L. J. Bellamy, D. W. Mayo, *J. Phys. Chem.* **1976** *80* 1271

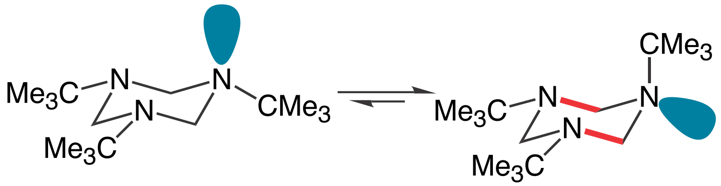
NMR : Shielding of H antiperiplanar to N lone pair

H$_{10}$ (axial): shifted furthest upfield

H$_6$, H$_4$: $\Delta\delta = \delta\ H_{axial} - \delta\ H_{equatorial}$ = -0.93 ppm

Protonation on nitrogen reduces Δδ to -0.5ppm

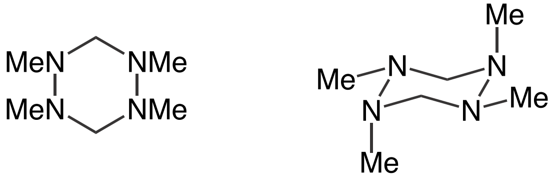
H. P. Hamlow et. al., *Tet. Lett.* **1964** 2553
J. B. Lambert et. al., *JACS* **1967** *89* 3761



$\Delta G°$ = – 0.35kcal/mol

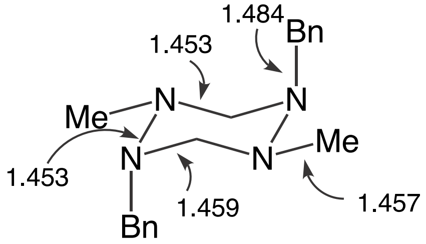
A. R. Katritzky et. al., *J. Chemm. Soc. B* **1970** 135

Favored Solution Structure (NMR)



J. E. Anderson, J. D. Roberts, *JACS* **1967** *96* 4186

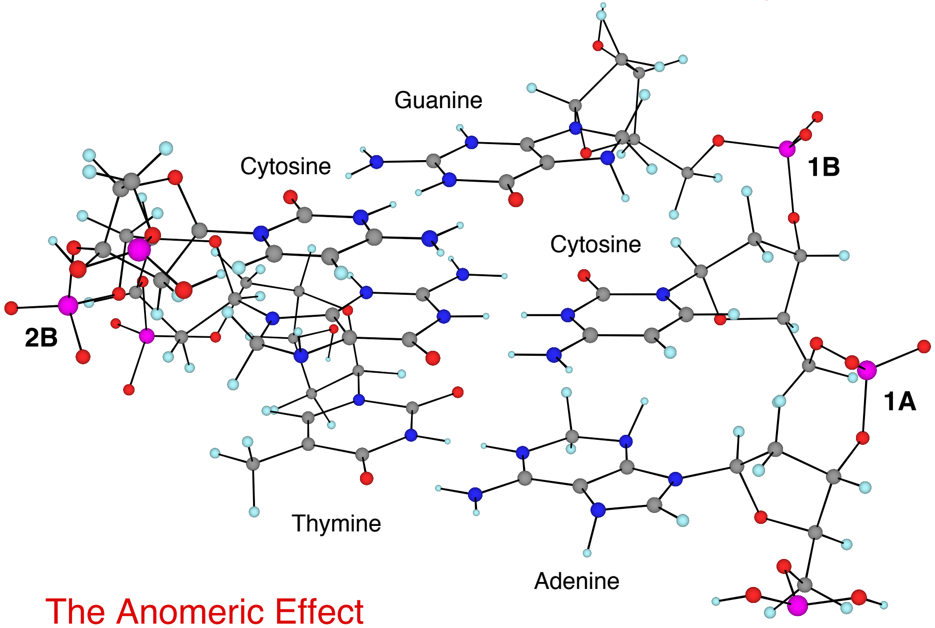
Favored Solid State Structure (X-ray crystallography)



A. R. Katrizky et. al., *J. C. S. Perkin II* **1980** 1733

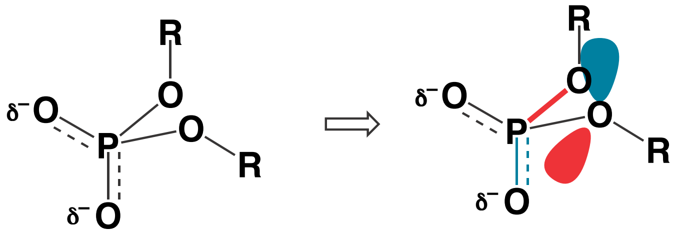
Anomeric Effects in DNA Phosphodiesters

Calculated Structure of ACG–TGC Duplex

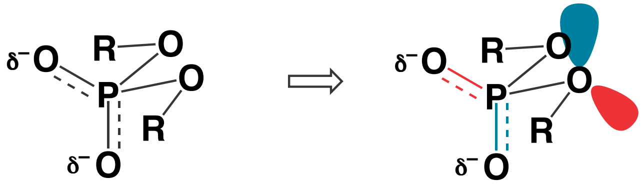


The Anomeric Effect

Acceptor orbital hierarchy: δ^* P–OR * > δ^* P–O$^-$



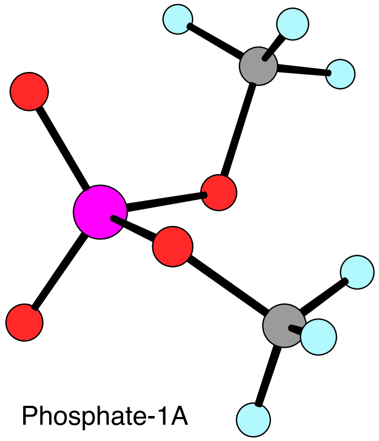
Gauche-Gauche conformation



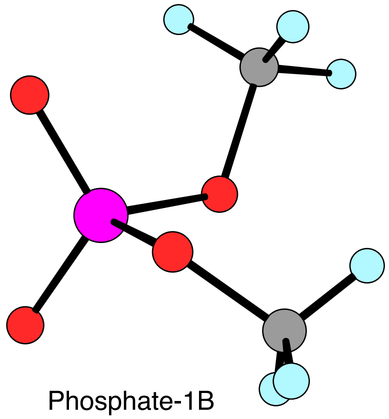
Anti-Anti conformation

Gauche-Gauche conformation affords a better donor-acceptor relationship

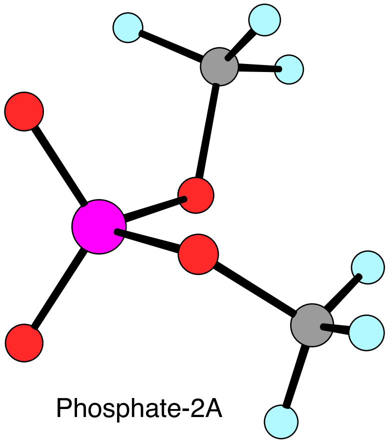
The Phospho-Diesters Excised from Crystal Structure



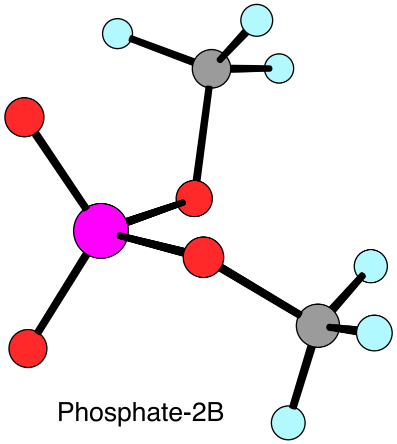
Phosphate-1A



Phosphate-1B



Phosphate-2A



Phosphate-2B

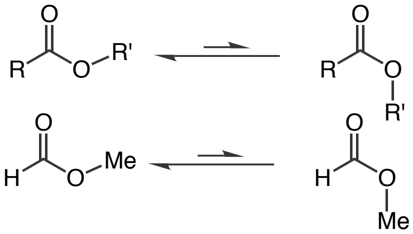
Oxygen lone pairs may establish a simultaneous hyperconjugative relationship with both acceptor orbitals only in the illustrated conformation.

Plavec, et al. (**1996**). "How do the Energetics of the Stereoelectronic Gauche & Anomeric Effects Modulate the Conformation of Nucleos(t)ides? " Pure Appl. Chem. **68**: 2137-44.

■ Conformations: There are 2 planar conformations.

(Z) Conformer **(E) Conformer**

Specific Case:
Methyl Formate

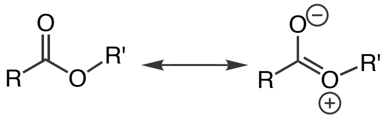


ΔG° = +4.8 kcal/mol

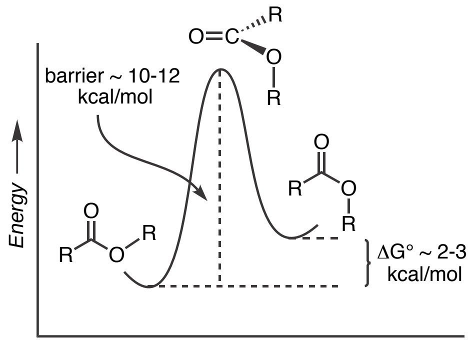
The (E) conformation of both acids and esters is less stable by 3-5 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must also be considered. These effects will be introduced shortly.

■ Rotational Barriers: There is hindered rotation about the =C–OR bond.

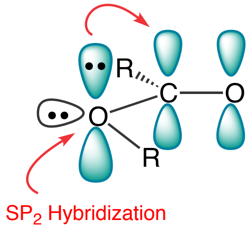
These resonance structures suggest hindered rotation about =C–OR bond. This is indeed observed:



Rotational barriers are ~ 10-12 kcal/mol. This is a measure of the strength of the pi bond.



■ Lone Pair Conjugation: The oxygen lone pairs conjugate with the C=O.

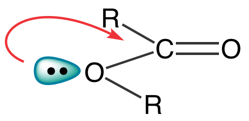


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

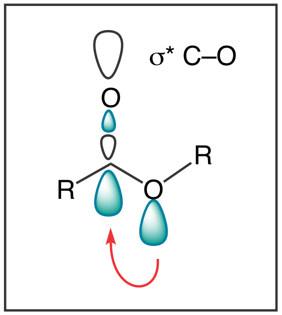
■ Oxygen Hybridization: Note that the alkyl oxygen is Sp2. Rehybridization is driven by system to optimize pi-bonding.

■ Hyperconjugation: Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

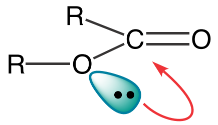
(Z) Conformer



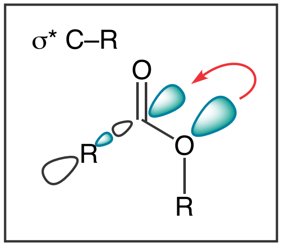
In the (Z) conformation this lone pair is aligned to overlap with σ* C–O.



(E) Conformer

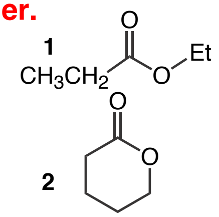


In the (E) conformation this lone pair is aligned to overlap with σ* C–R.



Since σ* C–O is a better acceptor than σ* C–R (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

Esters versus Lactones: Questions to Ponder.



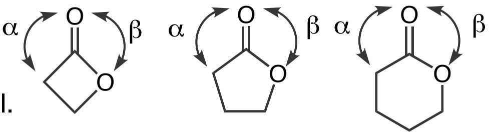
versus

Esters strongly prefer to adopt the (Z) conformation while small-ring lactones such as **2** are constrained to exist in the (Z) conformation. From the preceding discussion explain the following:

1) Lactone **2** is significantly more susceptible to nucleophilic attack at the carbonyl carbon than **1**? Explain.

2) Lactone **2** is significantly more prone to enolization than **1**? In fact the pKa of **2** is ~25 while ester **1** is ~30 (DMSO). Explain.

3) In 1985 Burgi, on carefully studying the X-ray structures of a number of lactones, that the O-C-C (α) & O-C-O (β) bond angles were not equal. Explain the indicated trend in bond angle changes.

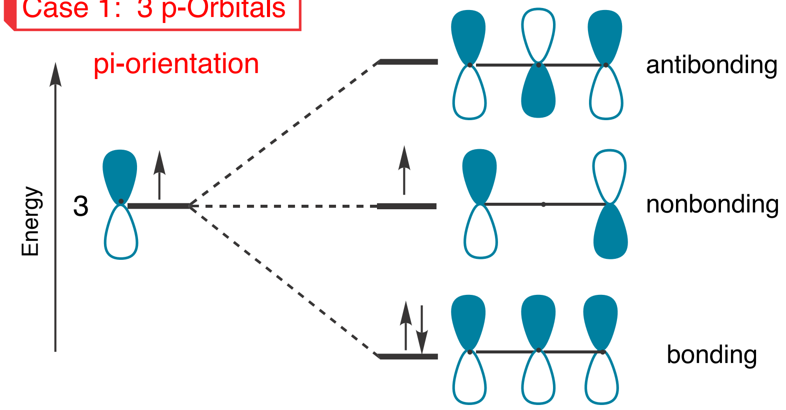


α–β = 12.3 ° α–β = 6.9 ° α–β = 4.5 °

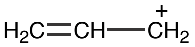
Consider the linear combination of three atomic orbitals. The resulting molecular orbitals (MOs) usually consist of one bonding, one nonbonding and one antibonding MO.

Case 1: 3 p-Orbitals

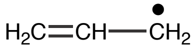
pi-orientation



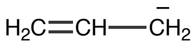
Note that the more nodes there are in the wave function, the higher its energy.



$H_2C{=}CH{-}\overset{+}{C}H_2$ **Allyl carbonium ion:** both pi-electrons in bonding state



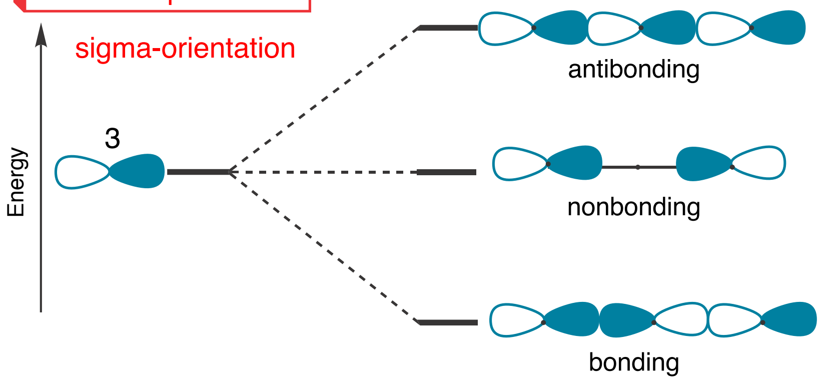
$H_2C{=}CH{-}\overset{\bullet}{C}H_2$ **Allyl Radical:** 2 electrons in bonding obital plus one in nonbonding MO.



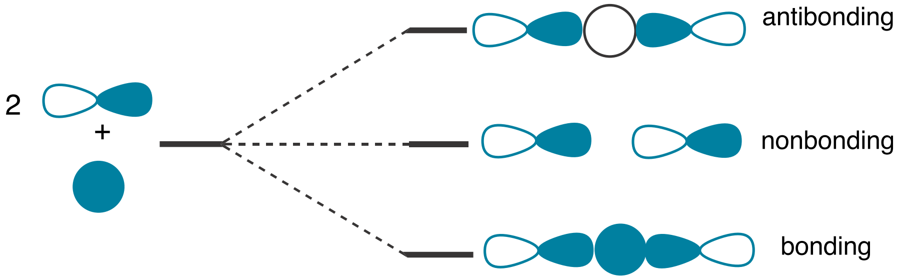
$H_2C{=}CH{-}\overset{-}{C}H_2$ **Allyl Carbanion:** 2 electrons in bonding obital plus 2 in nonbonding MO.

Case 2: 3 p-Orbitals

sigma-orientation



Case 3: 2 p-Orbitals; 1 s-orbital

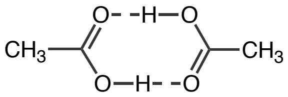


Case 4: 2 s-Orbitals; 1 p-orbital

Do this as an exercise

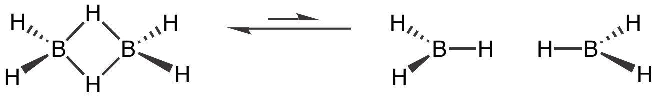
Examples of three-center bonds in organic chemistry

A. H-bonds: (3–center, 4–electron)



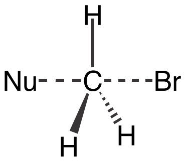
The acetic acid dimer is stabilized by ca 15 kcal/mol

B. H-B-H bonds: (3-center, 2 electron)



diborane stabilized by 35 kcal/mol

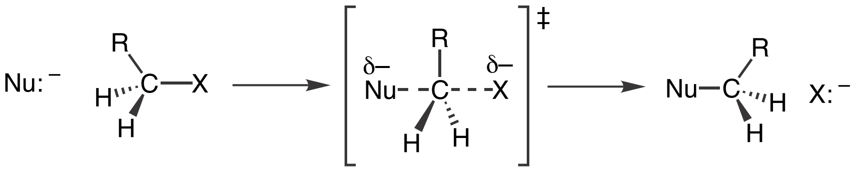
C. The S_N2 Transition state: (3–center, 4–electron)



The S_N2 transition state approximates a case 2 situation with a central carbon p-orbital

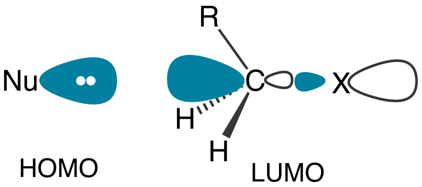
The three orbitals in reactant molecules used are:
1 nonbonding MO from Nucleophile (2 electrons)
1 bonding MO σ C–Br (2 electrons)
1 antibonding MO σ* C–Br

Why do S_N2 Reactions proceed with backside displacement?



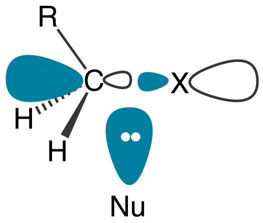
Given the fact that the LUMO on the electrophile is the C–X antibonding orblital, Nucleophilic attack could occur with either inversion or retention.

Inversion



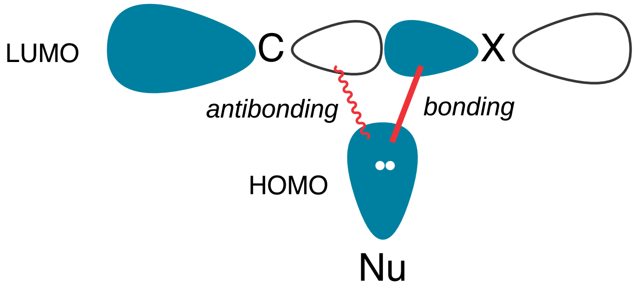
Constructive overlap between Nu & σ*C–X

Retention



Overlap from this geometry results in no net bonding interaction

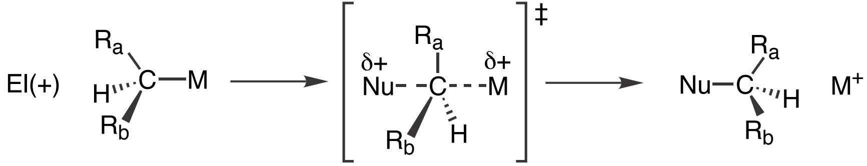
Expanded view of σ*C–X



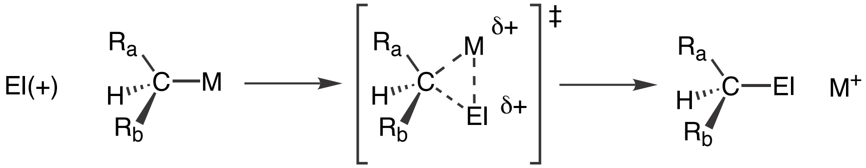
Fleming, page 75-76

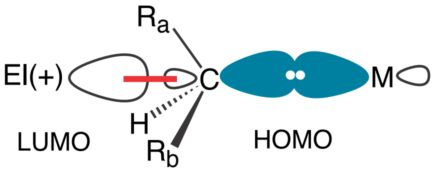
Electrophilic substitution at saturated carbon may occur with either inversion of retention

Inversion

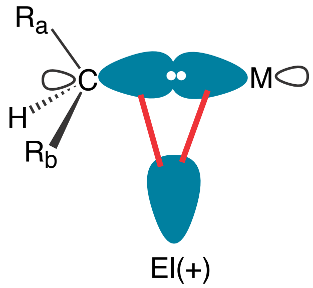


Retention



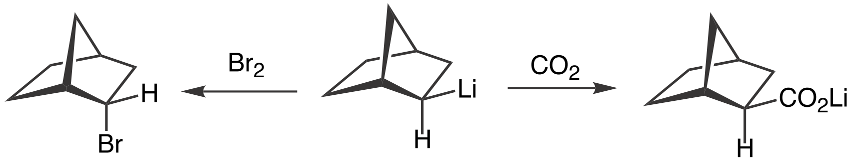


Inversion



Retention

Examples

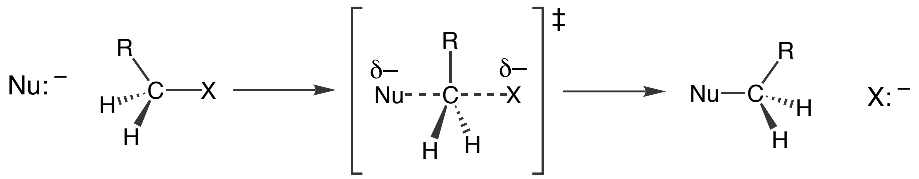


predominant inversion *predominant retention*

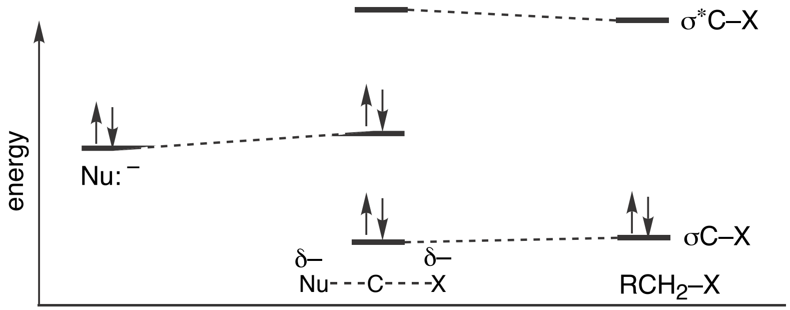
Stereochemistry frequently determined by electrophile structure

See A. Basu, *Angew. Chem. Int. Ed.* **2002**, *41*, 717-738

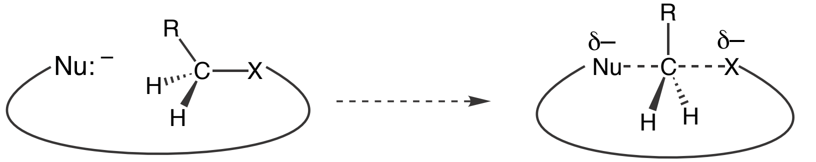
The reaction under discussion:



■ The Nu–C–X bonding interaction is that of a 3-center, 4-electron bond. The frontier orbitals which are involved are the nonbonding orbital from Nu as well as σC–X and σ∗C–X:



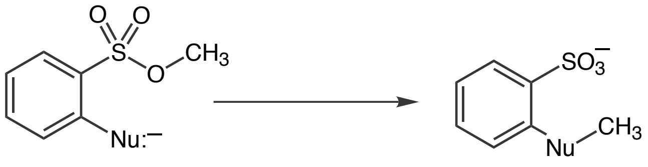
■ Experiments have been designed to probe inherent requirement for achieving a 180 ° Nu–C–X bond angle: Here both Nu and leaving group are constrained to be part of the same ring.



"tethered reactants" "constrained transition state"

The Eschenmoser Experiment (1970): *Helv. Chim Acta* **1970**, *53*, 2059

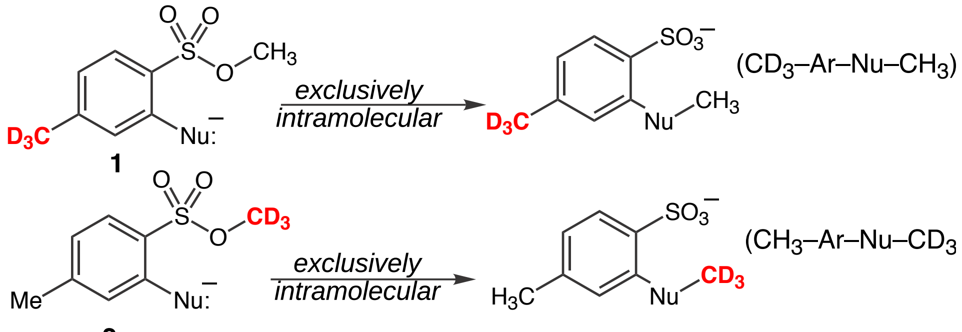
■ The reaction illustrated below proceeds exclusively through bimolecular pathway in contrast to the apparent availability of the intramolecular path.



The use of isotope labels to probe mechanism.

1 and **2** containing deuterium labels either on the aromatic ring or on the methyl group were prepared. A 1:1-mixture of **1** and **2** were allowed to react.

■ If the rxn was **exclusively intramolecular**, the products would only contain only three deuterium atoms:



1

2

(CD_3–Ar–Nu–CH_3)

(CH_3–Ar–Nu–CD_3)

■ If the reaction was **exclusively intermolecular**, products would only contain differing amounts of D-label depending on which two partners underwent reaction. The deuterium content might be analyzed by mass spectrometry. Here are the possibilities:

1 + **1** $\longrightarrow$ D_3-product 2 CD_3–Ar–Nu–CH_3

2 + **2** $\longrightarrow$ D'_3-product 2 CH_3–Ar–Nu–CD_3

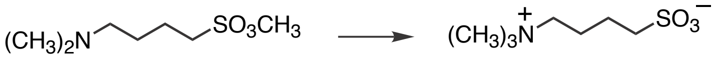
1 + **2** $\longrightarrow$ $\begin{cases} D_6\text{-product} & 1\ CD_3\text{–Ar–Nu–}CD_3 \\ D_0\text{-product} & 1\ CH_3\text{–Ar–Nu–}CH_3 \end{cases}$

Hence, for the strictly intermolecular situation one should see the following ratios $D_0 : D_3 : D'_3 : D_6 = 1 : 2 : 2 : 1$.

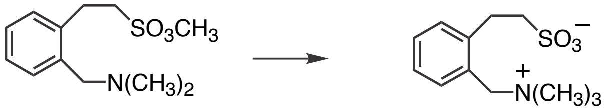
The product isotope distribution in the Eschenmoser expt was found to be exclusively that derived from the intermolecular pathway!

Other Cases:

exclusively intermolecular

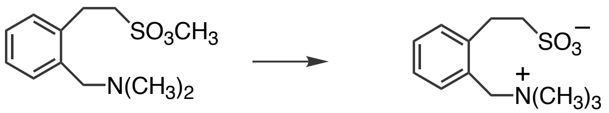


16% intramolecular
84% intermolecular

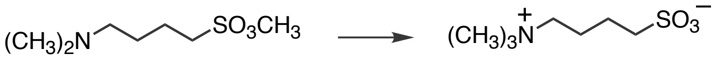


Hence, the Nu–C–X 180 ° transition state bond angle must be rigidly maintained for the reaction to take place.

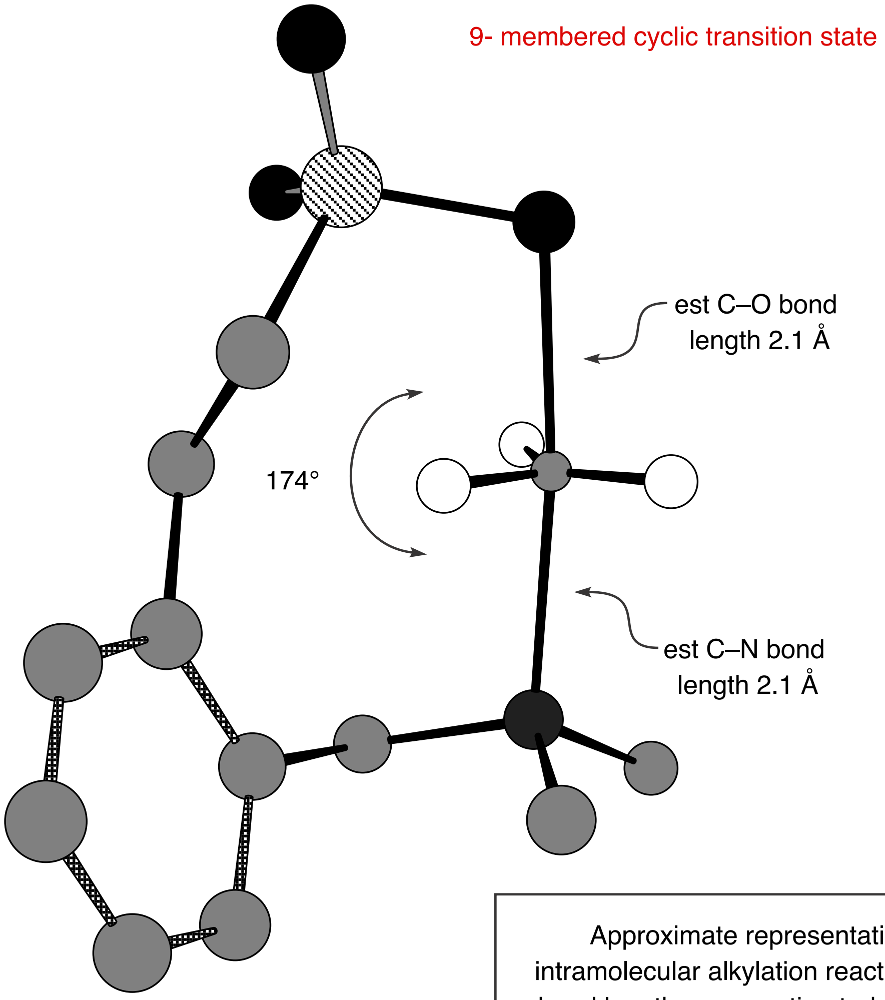
Intramolecular methyl transfer: Speculation on the transition structures

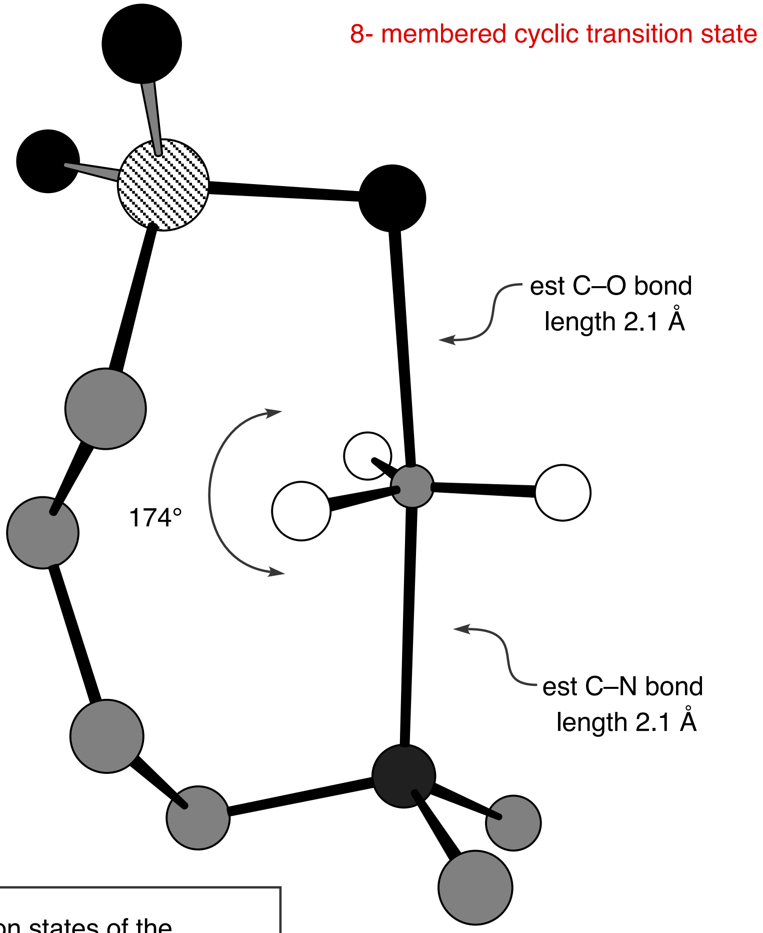


16% intramolecular; 84% intermolecular



exclusively intermolecular

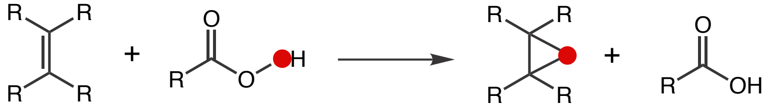

9- membered cyclic transition state
est C–O bond length 2.1 Å
174°
est C–N bond length 2.1 Å


8- membered cyclic transition state
est C–O bond length 2.1 Å
174°
est C–N bond length 2.1 Å

Approximate representation of the transition states of the intramolecular alkylation reactions. Transition state C–O and C–N bond lengths were estimated to be 1.5x(C–X) bond length of 1.4 Å

Olefin Epoxidation via Peracids: An Introduction

■ The General Reaction:

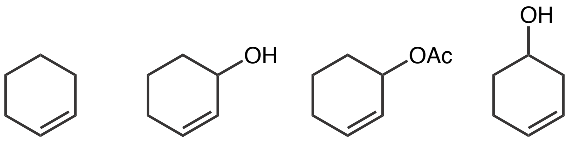


HOMO
πC–C

LUMO
σ*O–O

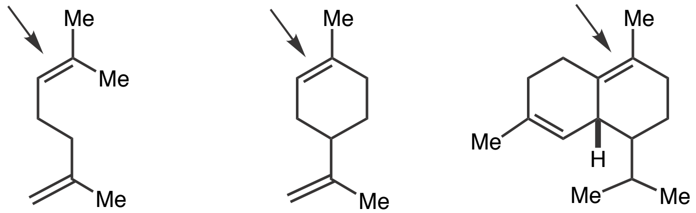
note labeled oxygen is transferfed
O-O bond energy: ~35 kcal/mol

■ Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:

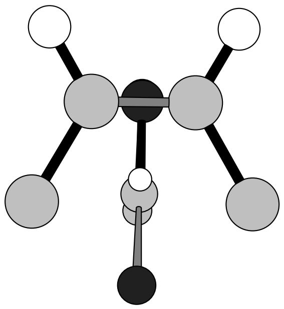


1.0 0.6 0.05 0.4

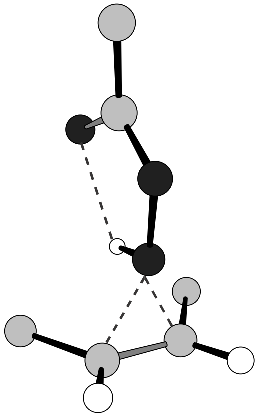
■ The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



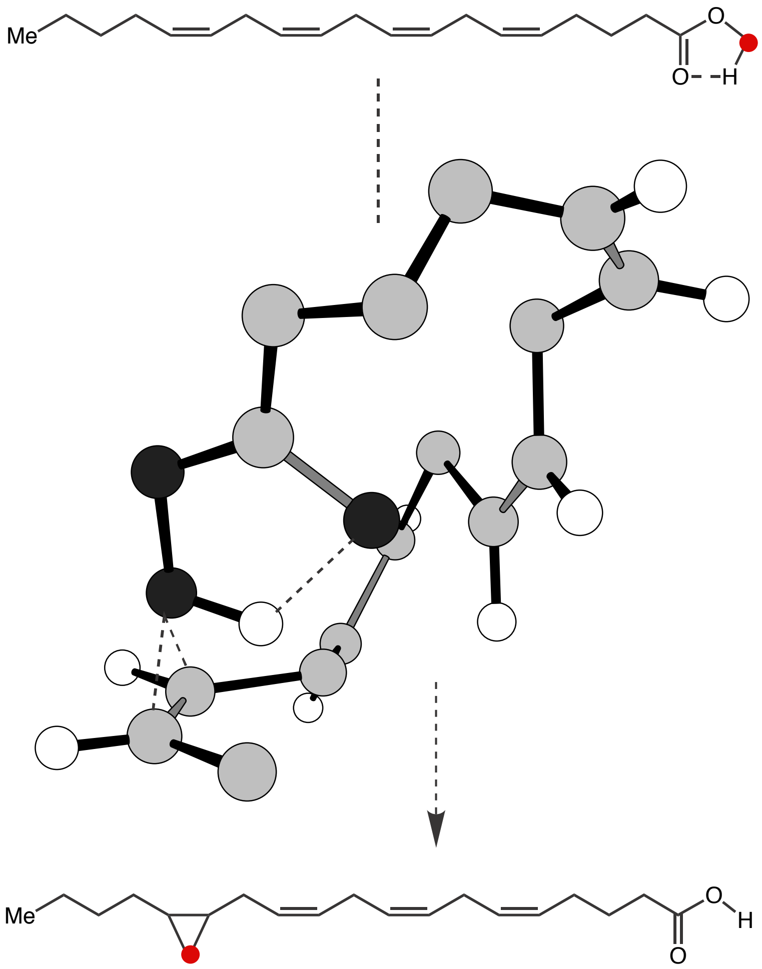
■ The transition state:



View from below olefin



Per-arachidonic acid Epoxidation



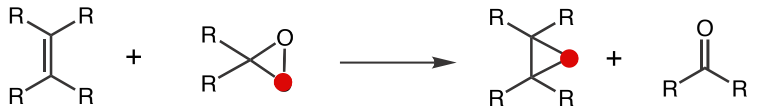
E. J. Corey, *JACS* **101**, 1586 (1979)

For a more detailed study see P. Beak, *JACS* **113**, 6281 (1991)

For theoretical studies of TS see R. D. Bach, *JACS* **1991**, *113*, 2338
R. D. Bach, *J. Org. Chem* **2000**, *65*, 6715

Olefin Epoxidation with Dioxiranes

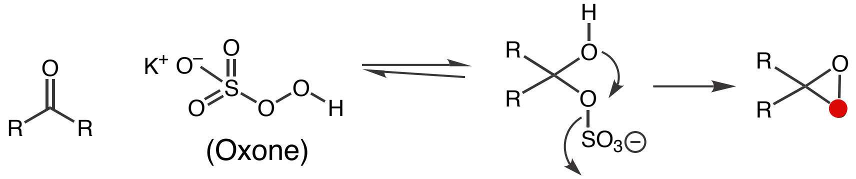
■ The General Reaction:



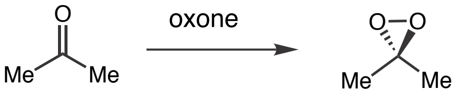
note labeled oxygen is transferfed

O-O bond energy: ~35 kcal/mol

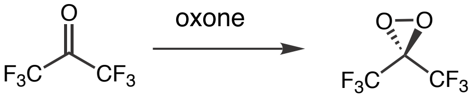
■ Synthesis of the Dioxirane Oxidant



Synthetically Useful Dioxirane Synthesis



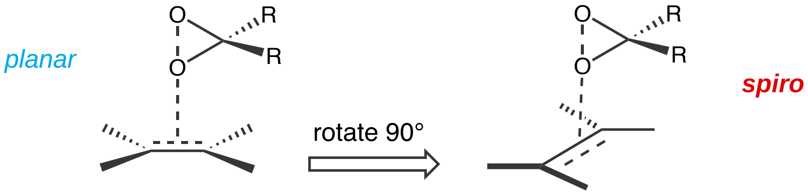
co-distill to give
~0.1 M soln of
dioxirane in acetone



co-distill to give
~0.6 M soln of dioxirane
in hexafluoroacetone

Curci, *JOC*, **1980**, 4758 & **1988**, 3890;
JACS **1991**, 7654.

Transition State for the Dioxirane Mediated Olefin Epoxidation

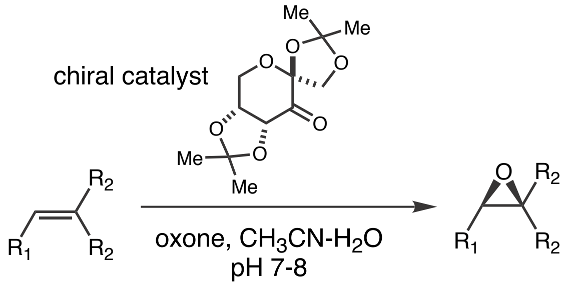


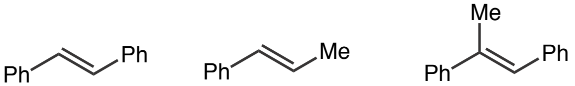
stabilizing $O_{lp} \rightarrow \pi^*$ C=C
cis olefins react ~10 times faster than *trans*

Houk, *JACS*, **1997**, 12982.

Asymmetric Epoxidation with Chiral Ketones

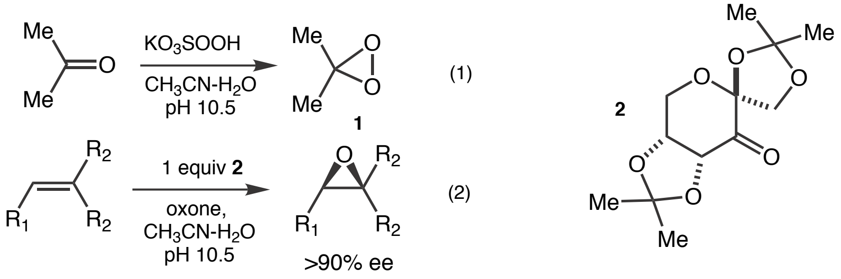
Review: Frohn & Shi, *Syn Lett* **2000**, 1979-2000





Question: First hour Exam 2000 (Database Problem 34)

Question 4. (15 points). The useful epoxidation reagent dimethyldioxirane (**1**) may be prepared from "oxone" (KO_3SOOH) and acetone (eq 1). In an extension of this epoxidation concept, Shi has described a family of chiral fructose-derived ketones such as **2** that, in the presence of "oxone", mediate the asymmetric epoxidation of di- and tri-substituted olefins with excellent enantioselectivities (>90% ee) (*JACS* **1997**, *119*, 11224).

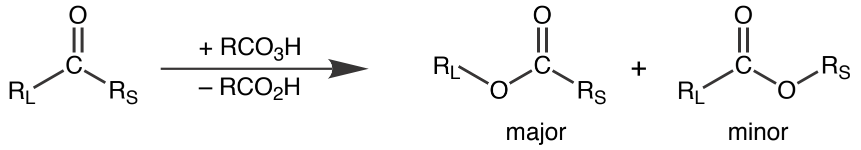


Part A (8 points). Provide a mechanism for the epoxidation of ethylene with dimethyldioxirane (**1**). Use three-dimensional representations, where relevant, to illustrate the ***relative*** stereochemical aspects of the oxygen transfer step. Clearly identify the frontier orbitals involved in the epoxidation.

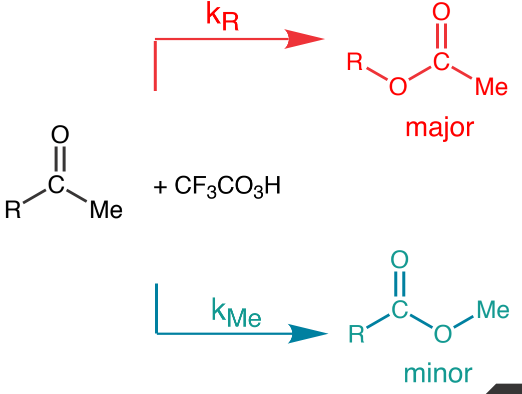
Part B (7 points). Now superimpose chiral ketone **2** on to your mechanism proposed above and rationalize the sense of asymmetric induction of the epoxidation of trisubstituted olefins (eq 2). Use three-dimensional representations, where relevant, to illustrate the ***absolute*** stereochemical aspects of the oxygen transfer step.

The Baeyer-Villiger Reaction: Stereoelectronic Effects

Let R_L and R_S be Sterically large and small substituents.

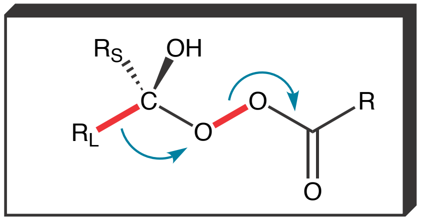


The major product is that wherein oxygen has been inserted into theR_L–Carbonyl bond.



R	k_R / K_{Me}
CH_3CH_2	72
$CH_3(CH_2)_2$	150
$(CH_3)_3C$	830
$PhCH_2$	>2000

The Intermediate

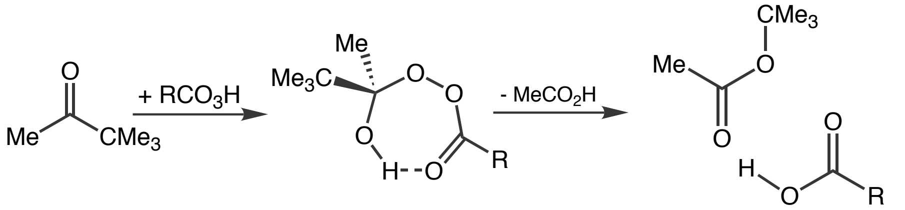


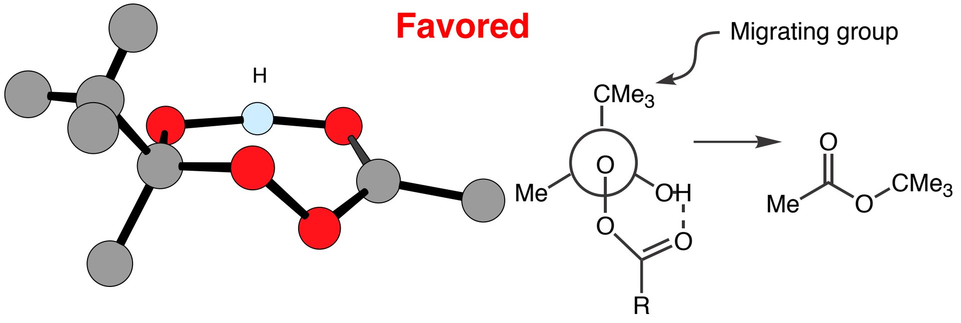
The important stereoelectronic components to this rearrangement:

1. The R_L–C–O–O dihedral angle must be180° due to the HOMO LUMO interaction σ-R_L–C↔σ*–O–O.

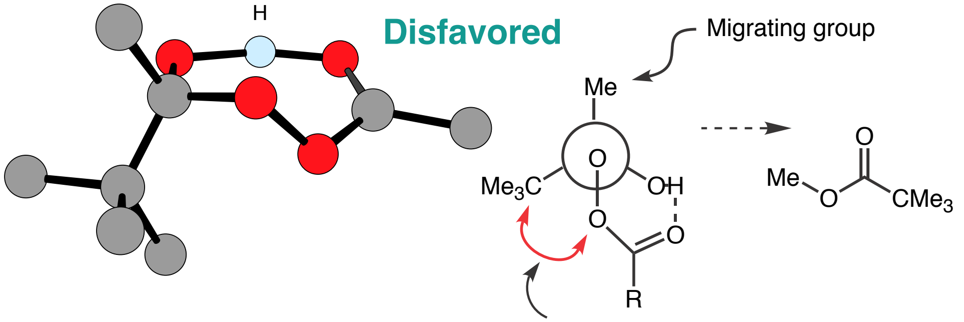
2. The C–O–O–C' dihedral angle will be ca. 60° due to the gauche effect (O-lone pairs↔σ*–C–O).

This gauche geometry is probably reinforced by intramolecular hydrogen bonding as illustrated on the opposite page:





Conformer A



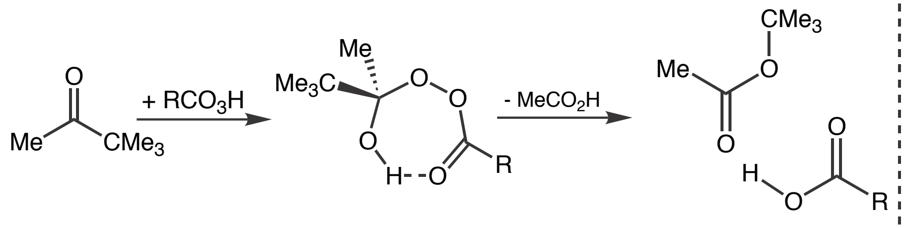
Conformer B

The destabilizing gauche interaction

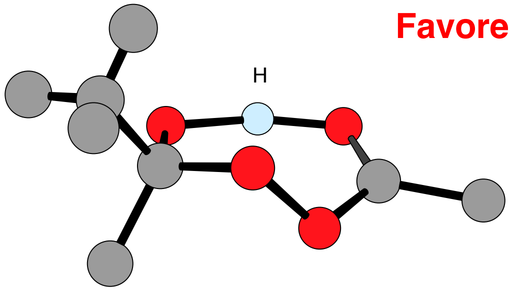
Steric effects destabilize Conformer B relative to Conformer A; hence, the reaction is thought to proceed via a transition state similar to A.

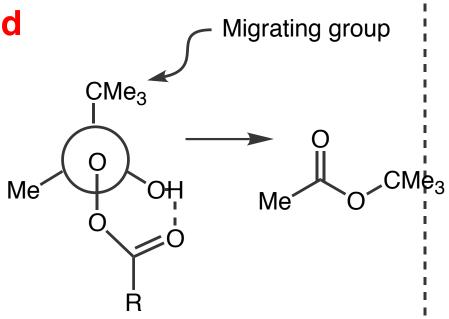
For relevant papers see:
Crudden, *Angew. Chem. Int. Ed* **2000**, *39*, 2852-2855 **(pdf)**
Kishi, *JACS* **1998**, *120*, 9392 **(pdf)**

The Baeyer-Villiger Reaction: Stereoelectronic Effects



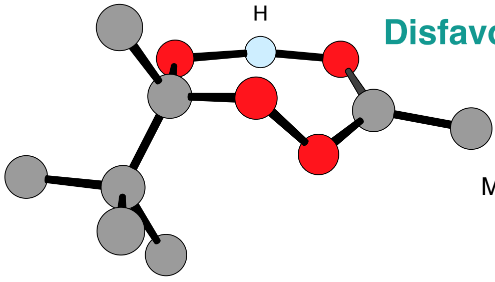
Favored

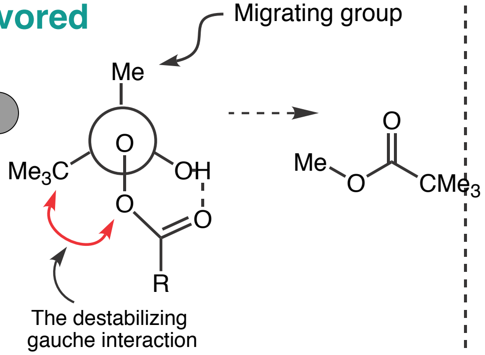




Conformer A

Disfavored





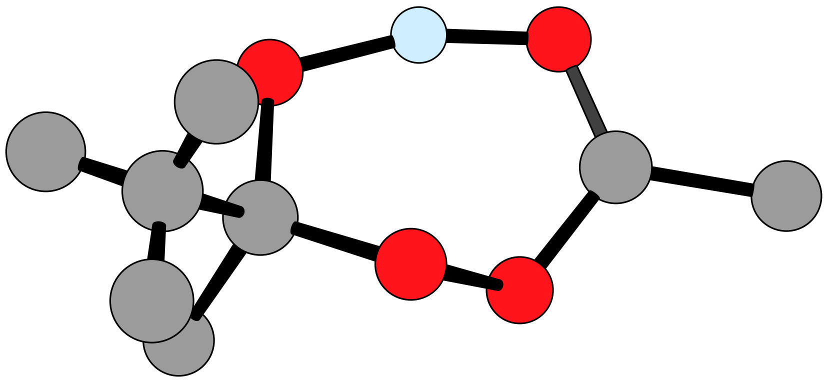
The destabilizing gauche interaction

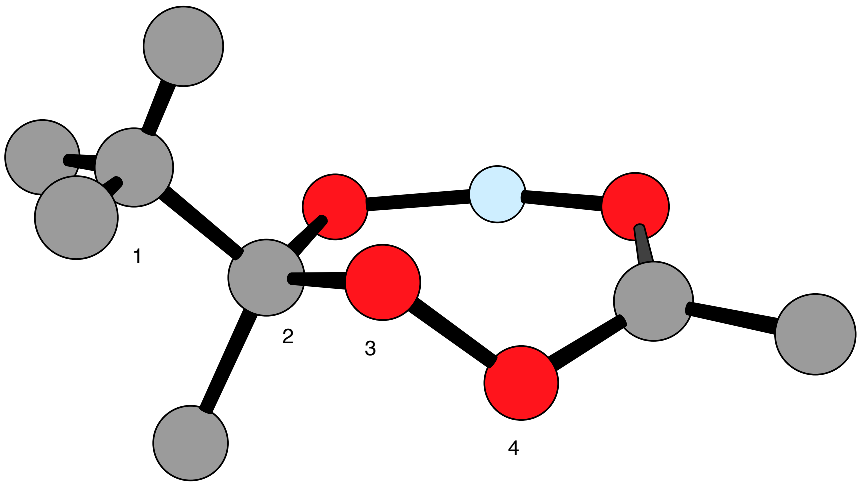
Conformer B

Steric effects destabilize Conformer B relative to Conformer A; hence, the reaction is thought to proceed via a transition state similar to A.

For relevant papers see:
Crudden, *Angew. Chem. Int. Ed* **2000**, *39*, 2852-2855 **(pdf)**
Kishi, *JACS* **1998**, *120*, 9392 **(pdf)**

Conformer A in three dimensions





2–3 dihedral angle ~ 178° from Chem 3D

FMO-Theory/HSAB Principle 1

Hard and Soft Acids and Bases (HSAB-Principle)

Reading Assignment: Fleming, Chapter 3, p33-46

Pearson, *JACS* **1963**, *85*, 3533.

Hard Acids prefer to interact with **hard** bases
Soft acids prefer to interact with **soft** bases.

Softness: Polarizability; soft nucleophiles have electron clouds, which can be polarized (deformed) easily.

Hardness: Charged species with small ion radii, high charge density.

→ Qualitative scaling possible:

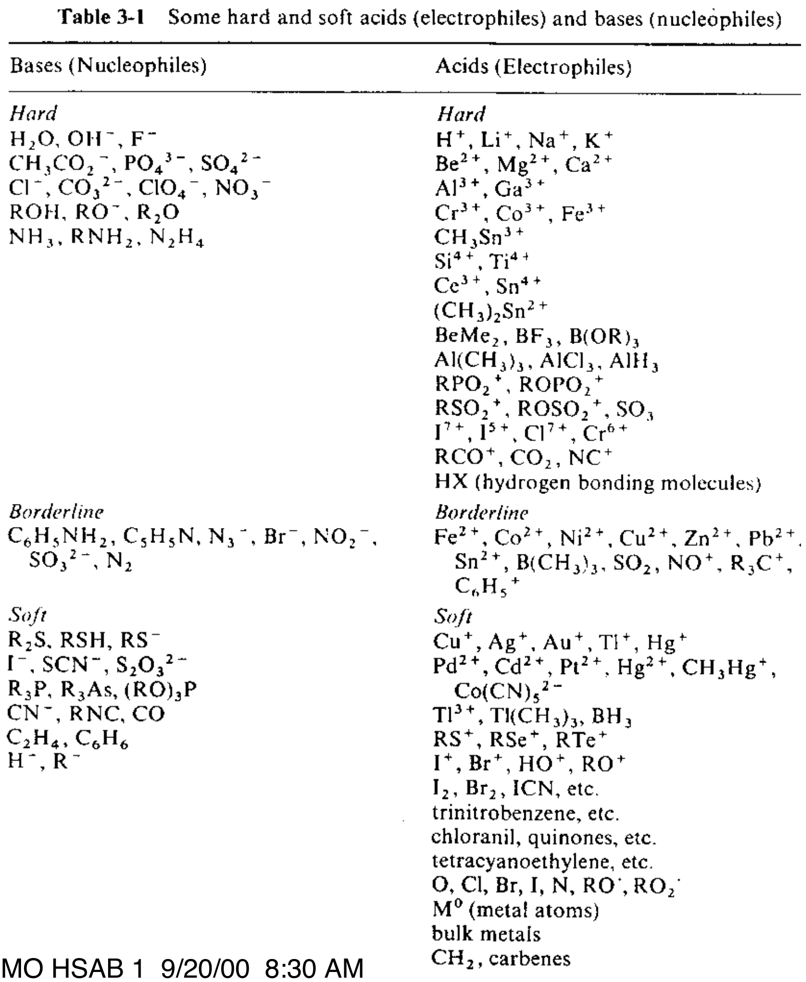


Table 3-1 Some hard and soft acids (electrophiles) and bases (nucleophiles)

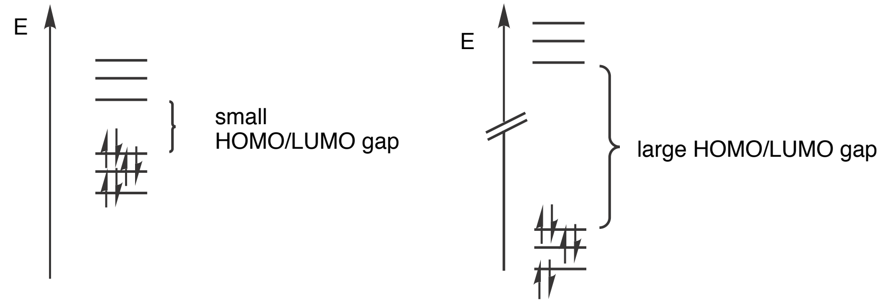
Bases (Nucleophiles)	Acids (Electrophiles)
Hard	*Hard*
H_2O, OH^-, F^- $CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-} Cl^-, CO_3^{2-}, ClO_4^-, NO_3^- ROH, RO^-, R_2O NH_3, RNH_2, N_2H_4	H^+, Li^+, Na^+, K^+ Be^{2+}, Mg^{2+}, Ca^{2+} Al^{3+}, Ga^{3+} Cr^{3+}, Co^{3+}, Fe^{3+} CH_3Sn^{3+} Si^{4+}, Ti^{4+} Ce^{3+}, Sn^{4+} $(CH_3)_2Sn^{2+}$ $BeMe_2$, BF_3, $B(OR)_3$ $Al(CH_3)_3$, $AlCl_3$, AlH_3 RPO_2^+, $ROPO_2^+$ RSO_2^+, $ROSO_2^+$, SO_3 I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+} RCO^+, CO_2, NC^+ HX (hydrogen bonding molecules)
Borderline	*Borderline*
$C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, $B(CH_3)_3$, SO_2, NO^+, R_3C^+, $C_6H_5^+$
Soft	*Soft*
R_2S, RSH, RS^- I^-, SCN^-, $S_2O_3^{2-}$ R_3P, R_3As, $(RO)_3P$ CN^-, RNC, CO C_2H_4, C_6H_6 H^-, R^-	Cu^+, Ag^+, Au^+, Tl^+, Hg^+ Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+, $Co(CN)_5^{2-}$ Tl^{3+}, $Tl(CH_3)_3$, BH_3 RS^+, RSe^+, RTe^+ I^+, Br^+, HO^+, RO^+ I_2, Br_2, ICN, etc. trinitrobenzene, etc. chloranil, quinones, etc. tetracyanoethylene, etc. O, Cl, Br, I, N, $RO^\cdot$, $RO_2^\cdot$ M^0 (metal atoms) bulk metals CH_2, carbenes

FMO-Theory and Klopman-Salem equation provide an understanding of this empirical principle:

Hard Acids have usually a positive charge, small ion radii (high charge density), energy rich (high lying) LUMO.
Soft Acids are usually uncharged and large (low charge density), they have an energy poor (low lying) LUMO (usually with large MO coefficient).
Hard Bases usually have a negative charge, small ion radii (high charge density), energy poor (low lying) HOMO.
Soft Bases are usually uncharged and large (low charge density), energy rich (high lying) HOMO (usually with large MO coefficient).

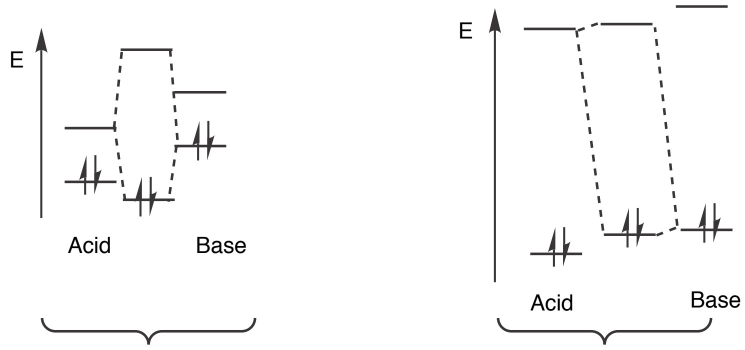
Molecular Orbital Energies of an

idealized Soft Species **idealized Hard Species**



FMO-Theory for interaction:

Soft-Soft **Hard-Hard**



Significant Energy gain through HOMO/LUMO interaction

Only neglectable energy gain through orbital interaction.

Klopman-Salem Equation for the interaction of a Nucleophile N (Lewis-Base) and an Electrophile E (Lewis-Acid).

$$\boxed{\Delta E = -\underbrace{\frac{Q_N Q_E}{\varepsilon R_{NE}}}_{\textbf{Coulomb Term}} + \underbrace{\frac{2(c_N c_E \beta)^2}{E_{HOMO}(N) - E_{LUMO}(E)}}_{\textbf{Frontier Orbital Term}}}$$

Q: Charge density
ε: Dielectricity constant
R: distance (N-E)
c: coefficient of MO
β: Resonance Integral
E: Energy of MO

Soft-Soft Interactions: Coulomb term small (low charge density). Dominant interaction is the frontier orbital interaction because of a small $\Delta E(HOMO_N/LUMO_E)$.
⇒ formation of covalent bonds

Hard-Hard Interactions: Frontier orbital term small because of large $\Delta E(HOMO_N/LUMO_E)$. Dominant interaction is described by the Coulomb term (Q is large for hard species), i.e. electrostatic interaction.
⇒ formation of ionic bonds

Hard-Soft Interactions: Neither energy term provides significant energy gain through interaction. Hence, Hard-Soft interactions are unfavorable.

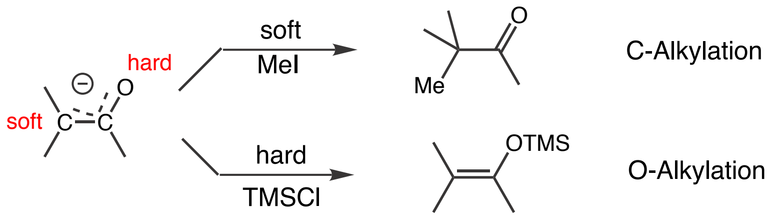
Table 3-2 Calculated softness character for inorganic nucleophiles and electrophiles

Nucleophile	HOMO $E^{\neq}$ (eV)		Electrophile	LUMO $E^{\neq}$ (eV)	
H^-	−7·37	↑ Soft	Al^{3+}	6·01	↑ Hard
I^-	−8·31		La^{3+}	4·51	
HS^-	−8·59		Ti^{4+}	4·35	
CN^-	−8·78		Be^{2+}	3·75	
Br^-	−9·22		Mg^{2+}	2·42	
Cl^-	−9·94		Ca^{2+}	2·33	
HO^-	−10·45		Fe^{3+}	2·22	
H_2O	−(10·73)		Sr^{2+}	2·21	
F^-	−12·18	Hard ↓	Cr^{3+}	2·06	
			Ba^{2+}	1·89	
			Ga^{3+}	1·45	
			Cr^{2+}	0·91	
			Fe^{2+}	0·69	
			Li^+	0·49	
			H^+	0·42	
			Ni^{2+}	0·29	
			Na^+	0	
			Cu^{2+}	−0·55	
			Tl^+	−1·88	
			Cd^{2+}	−2·04	
			Cu^+	−2·30	
			Ag^+	−2·82	
			Tl^{3+}	−3·37	
			Au^+	−4·35	
			Hg^{2+}	−4·64	Soft ↓

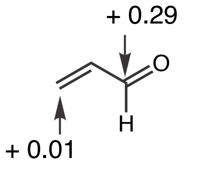
FMO-Theory/HSAB Principle 3

HSAB principle - Application to Chemoselectivity Issues

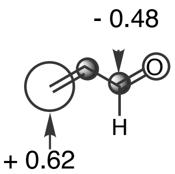
(a) Enolate Alkylation



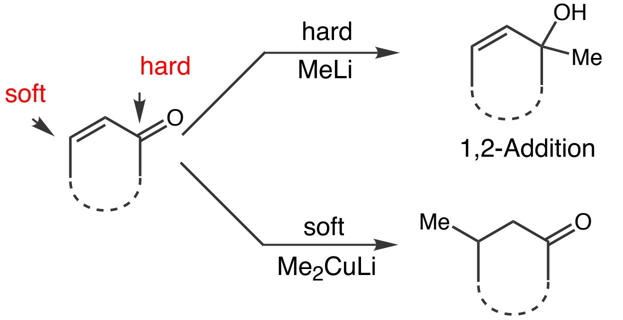
(b) 1,2- vs. 1,4-addition to α,β-unsaturated carbonyl compounds



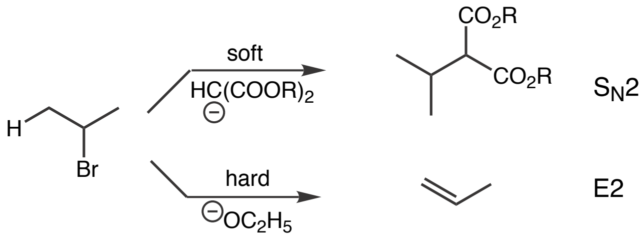
Charge density



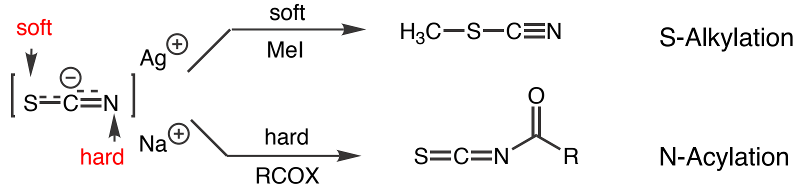
LUMO-coefficients

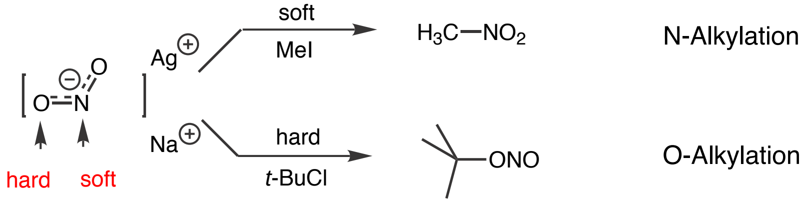


(c) S_N2 vs E2



(d) Ambident Nucleophiles





http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 3

Stereoelectronic Effects-3

"Rules for Ring Closure: Baldwin's Rules"

Kirby, "Stereoelectronic Effects" Chapters 4, 5

Useful LIterature Reviews

Johnson, C. D. (**1993**). “Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules.” *Acc. Chem. Res.* **26**: 476-82. **(Handout)**

Beak, P. (**1992**). “Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms.” *Acc. Chem. Res*. **25**: 215. **(Handout)**

D. A. Evans

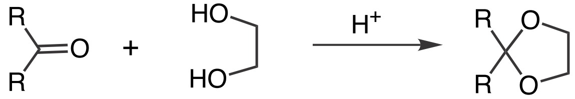
Friday,
September 19, 2003

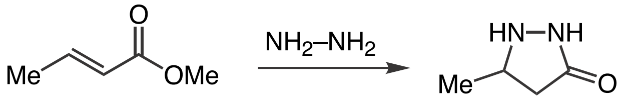
The Primary Literature

Baldwin, *J. Chem. Soc., Chem. Comm.* **1976**, 734, 736.
Baldwin, *J. Chem. Soc., Chem. Comm.* **1977** 233.
Baldwin, J. Org. Chem. **1977**, *42*, 3846.
Baldwin, Tetrahedron **1982**, *38*, 2939.

- Problems of the Day

Propose mechanisms for the following reactions





Rules for Ring Closure: Introduction

Ring Closure and Stereoelectronic Connsiderations
An Examination of Baldwin's Rules

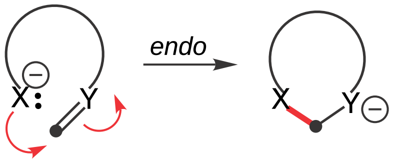
"Baldwin's Rules" provides a qualitative set of generalizations on the probability of a given ring closure.

There are circumstances where the "rules" don't apply.

- They do not apply to non-first-row elements participating in the cyclization event. The longer bond lengths and larger atomic radii of 2nd row elements result in relaxed geometrical constraints.

For example, a change in a heteroatom from O to S could result in relaxation of a given geometric constraint.

X = O vs S

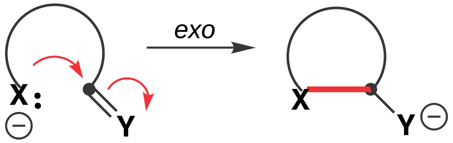


- The "rules" do not apply to electrocyclic processes.

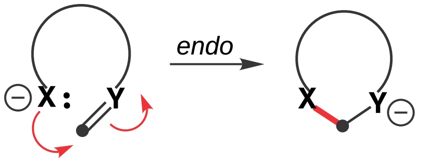
Nomenclature

Classes of Ring Closing Processes

A. Exo-cyclization modes identified by the breaking bond being positioned exocyclic to the forming cycle.



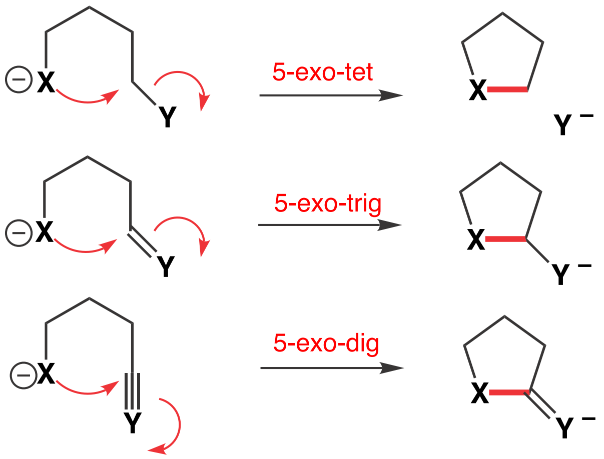
B. Endo-cyclization modes identified by the breaking bond being positioned endocyclic to the forming cycle.



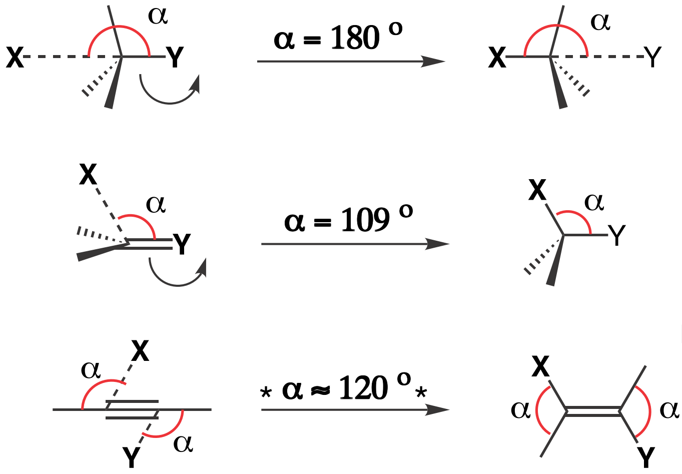
X = first-row element
N, O

C. Nucleophilic ring closures sub-classified according to hybridization state of **electrophilic** component:
(tetrahedral = tet; trigonal = trig; digonal = dig)

D. Nucleophilic ring closures further subclassified according to size of the fomed ring. For example:



Required trajectories (Baldwin):



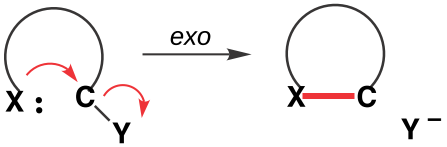
Will come back to this case later

Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

Rules for Ring Closure: SP3 Carbon & Related Systems

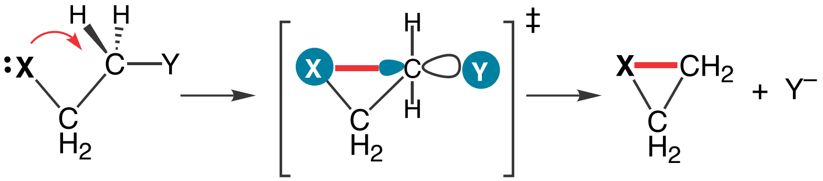
Tetrahedral Carbon

All exo cyclization modes are allowed: (n-exo-tet, n = 3→)



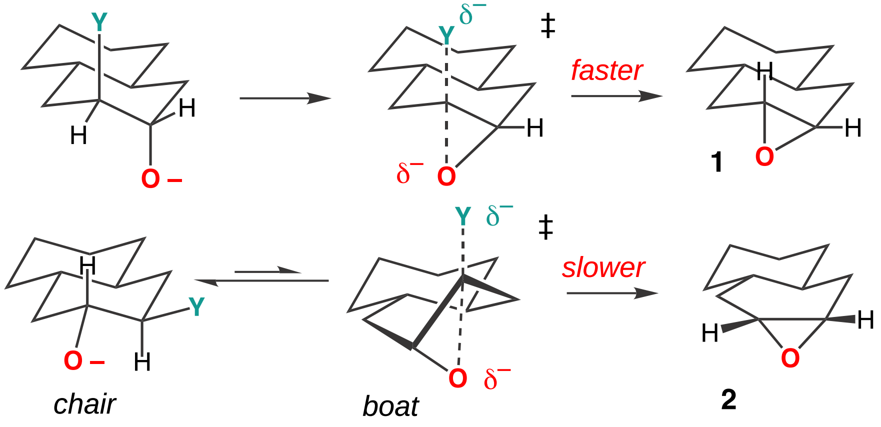
There are stereoelectronic issues to consider for **n-exo-tet** cyclizations

Formation of 3-Membered Rings (3-exo-tet)



Conformational Effects in Epoxide Ring Formation/cleavage

Those stereoelectronic effects that operate in ring cleavage also influence ring formation. Consider a rigid cyclohexene oxide system:



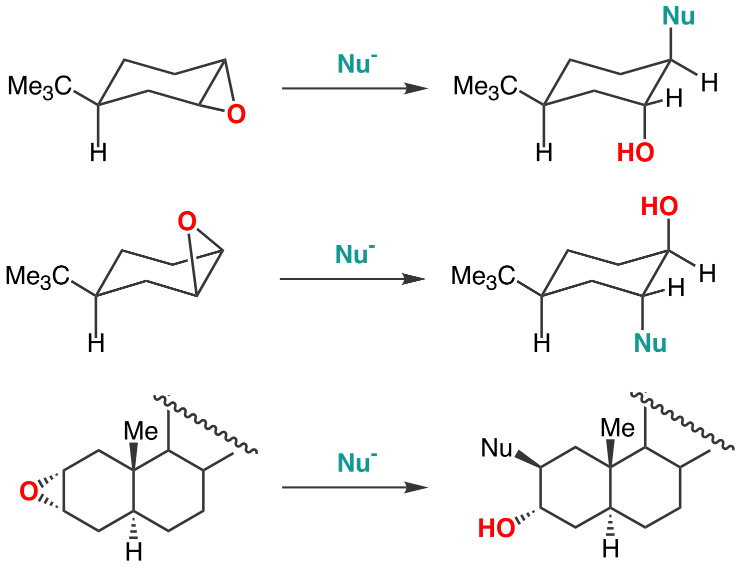
FÜRST-PLATTNER RULE

In this simple model, the transition-state leading to **1** involves the diaxial orientation of nucleophile and leaving group. This orientation affords the best overlap of the anti-bonding C–Y orbital and the nonbonding electron pairs on the nucleophile O^-.

In the formation of the diastereomeric epoxide **2**, the proper alignment of orbitals may only be achieved by cyclization through the less-favored boat conformer. Accordingly, while both cyclizations are "allowed", there are large rate differences the the rates of ring closure.

While the FURST-PLATTNER RULE deals wilth the microscopic reverse, in the opening of epoxides by nucleophiles, the stereoelectronic arguments are the same.

Stereoelectronic Effects in Epoxide Ring Cleavage

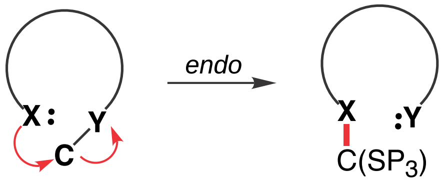


"The diaxial nucleophilic ring cleavage of epoxides"
For more information on epoxide cleavage see **Handout 03A.**

Rules for Ring Closure: SP3 Carbon & Related Systems

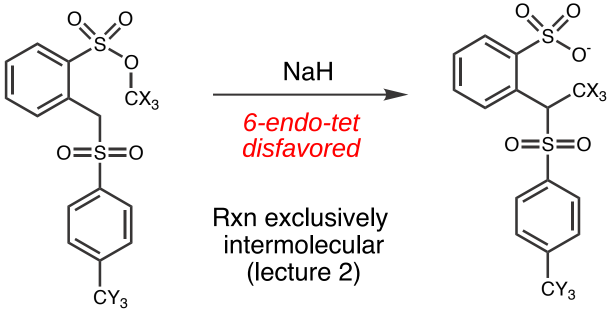
Tetrahedral Carbon

Endo cyclization modes that are disallowed (n-endo-tet, n = 3→~9)



The stereoelectronic requirement for a 180° X–C–Y bond angle is only met when the endo cyclization ring size reaches 9 or 10 members.

Case 1: Eschenmoser, *Helvetica Chim. Acta* **1970**, *53*, 2059.

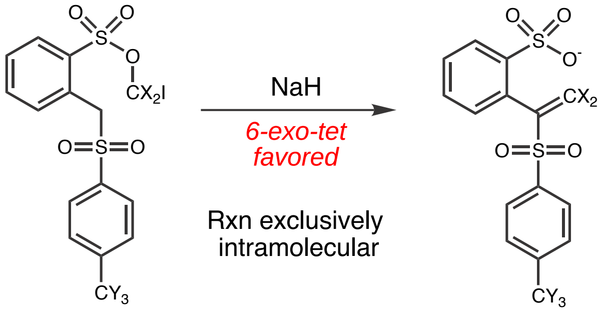


NaH

6-endo-tet disfavored

Rxn exclusively intermolecular (lecture 2)

Cyclization exclusively intermolecular. However the exocyclic analog is exclusively intramolecular

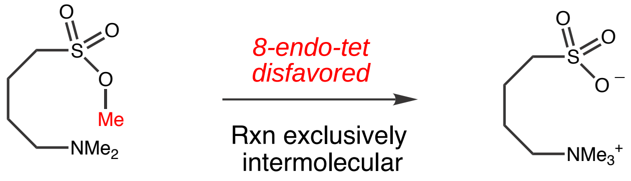


NaH

6-exo-tet favored

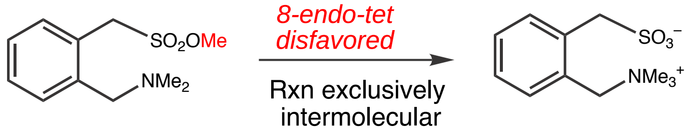
Rxn exclusively intramolecular

Case 2: King, *J.C.S. Chem. Comm.*, **1979**, 1140.



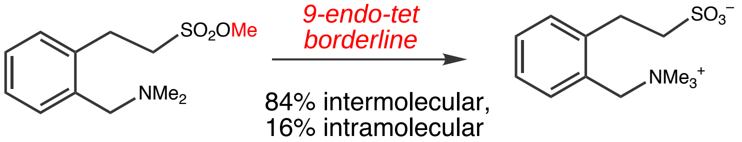
8-endo-tet disfavored

Rxn exclusively intermolecular



8-endo-tet disfavored

Rxn exclusively intermolecular



9-endo-tet borderline

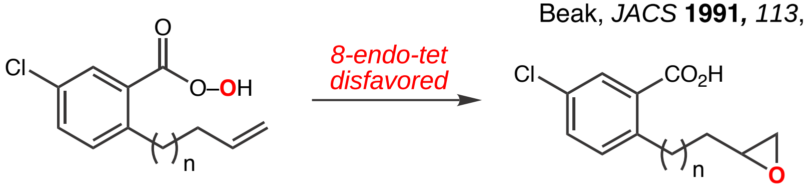
84% intermolecular, 16% intramolecular

Conclusions

Allowed endo cyclization modes will require transition state ring sizes of at least nine members.

Intramolecular epoxidation has also been evaluated

Beak, *JACS* **1991,** *113*, 6281.



8-endo-tet disfavored

n = 1: rxn exclusively intermolecular
n = 9: rxn is intramolecular

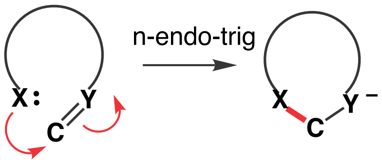
Beak states that the conclusions made with carbon substitution also hold for oxygen atom transfer.

Beak, P. (**1992**). “Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms.” *Acc. Chem. Res.* **25**: 215.

Rules for Ring Closure: SP2 Carbon & Related Systems

Trigonal Carbon

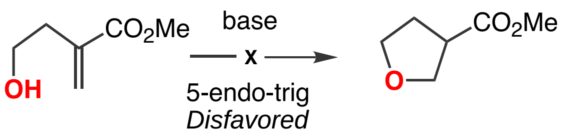
Endo cyclization modes that are disallowed
(3 to 5-endo-trig)



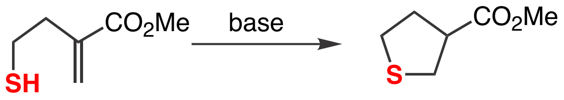
X = first-row element

The 5-endo-trig cyclization is a watershed case

Case 1: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

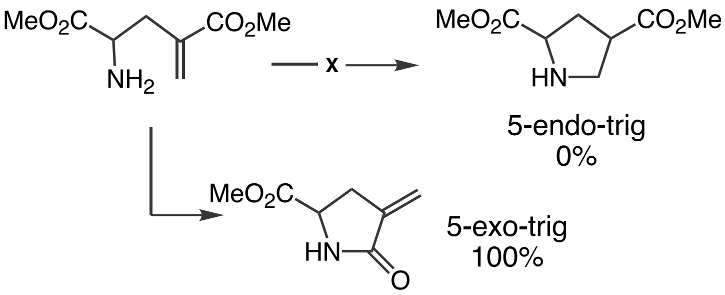


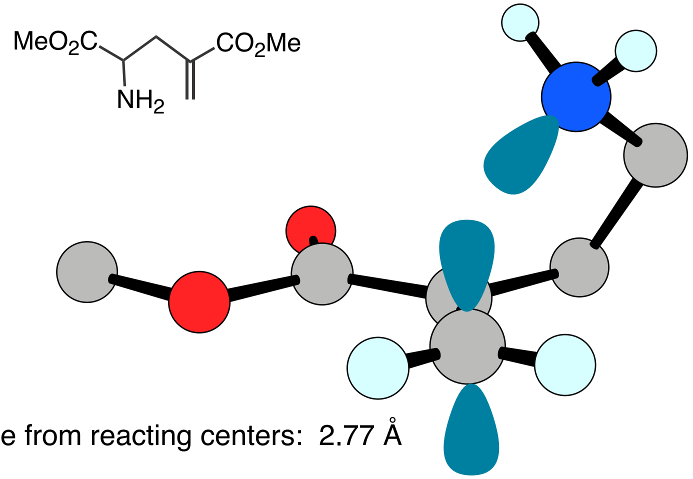
however



Second row atom relaxes the cyclization geometrical requirement

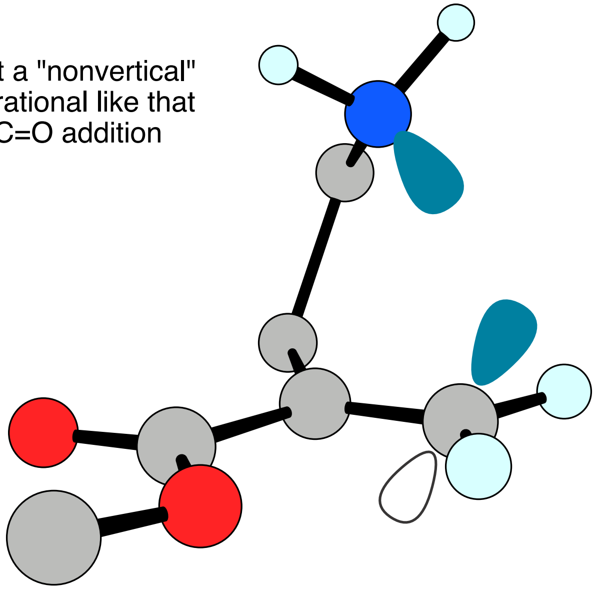
Case 2: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.





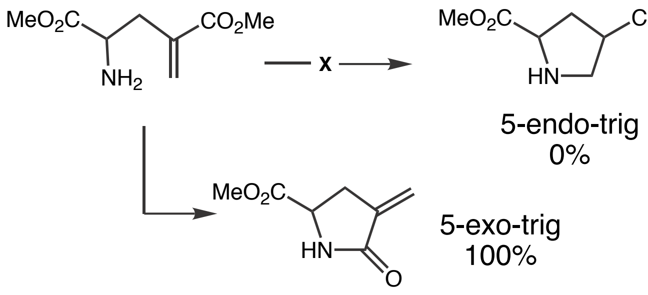
distance from reacting centers: 2.77 Å

It is possible that a "nonvertical" trajectory is operational like that suspected in C=O addition

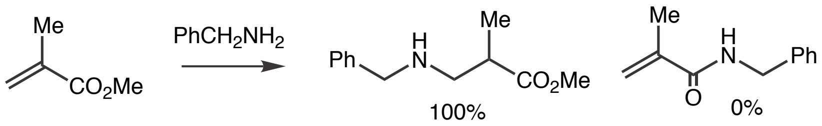


Rules for Ring Closure: SP2 Carbon & Related Systems

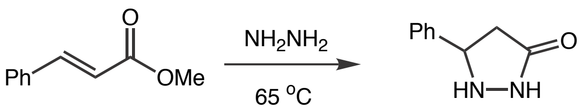
Case 2: continued...

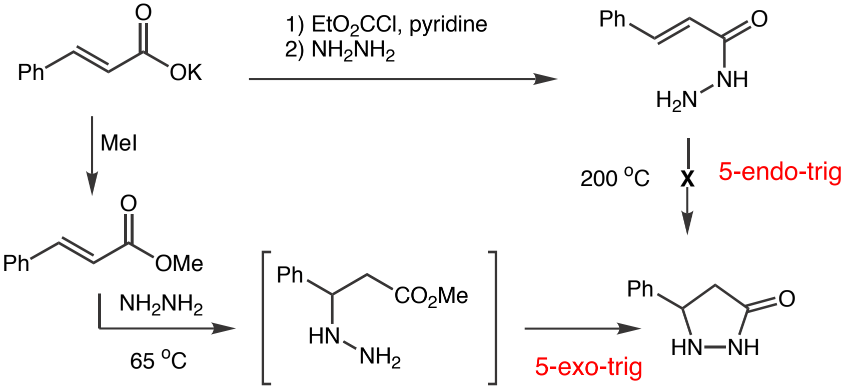


Control experiment: Intermolecular reaction favors conjugate addtion.

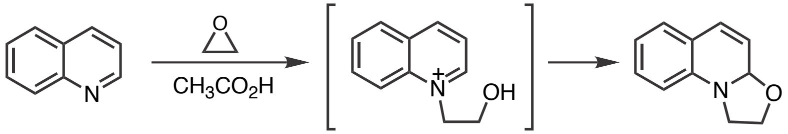


Case 3:

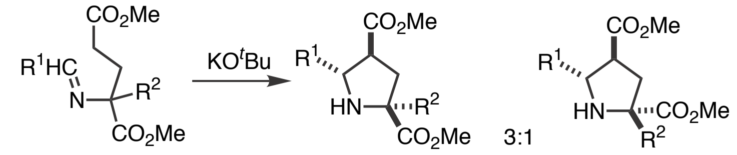




Apparent exceptions to disallowed 5-endo-trig cyclization process



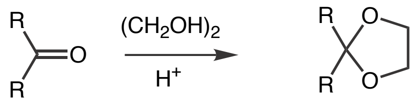
Filer, *J. Am. Chem. Soc.* **1979**, *44*, 285.

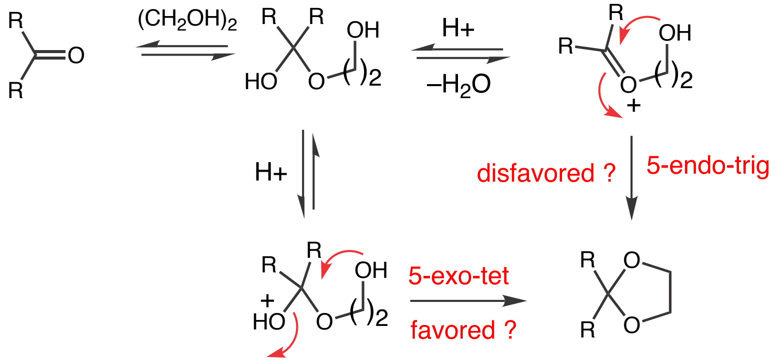


R^1 = aryl, R^2 = aryl, alkyl

Grigg, *J. Chem. Soc., Chem. Commun.* **1980**, 648.

Does the illustrated ketalization process necessarily violate "the rules"?



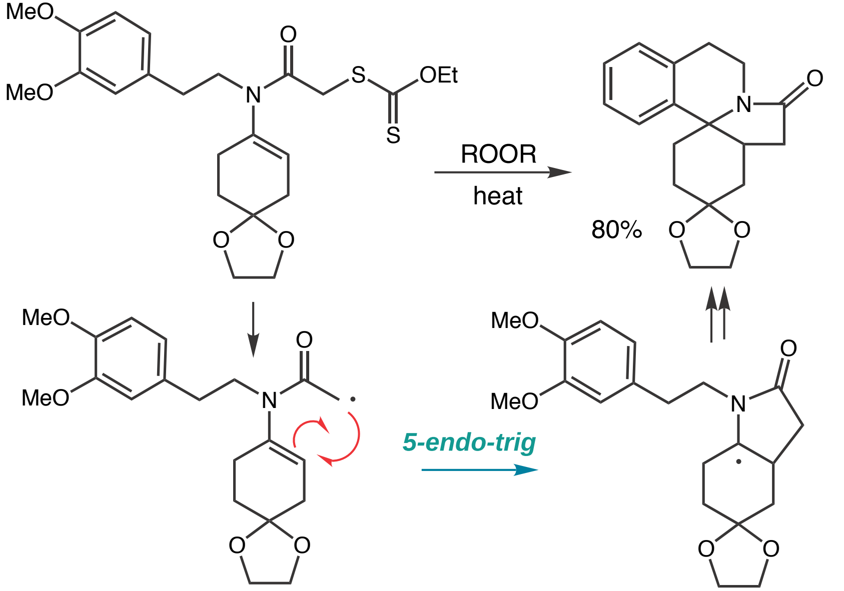


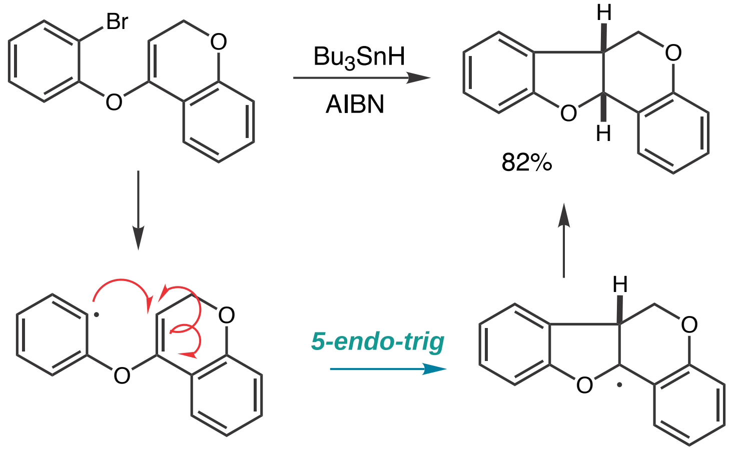
Johnson, C. D. (**1993**). “Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules.” *Acc. Chem. Res.* **26**: 476-82.

Rules for Ring Closure: SP2 Carbon & Related Systems

More Exceptions

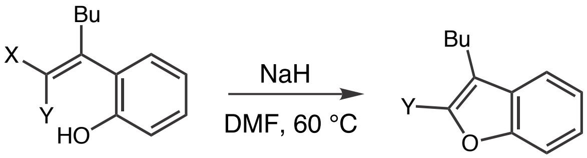
Zard, *Org. Lett.* **2002**, *4*, 1135





Chem. Comm **2088**, 28

Review: "5-Endo-Trig Radical Cyclizatons" Ishibashi, et al *Synthesis* **2002**, 695-713, **PDF on Course Website**

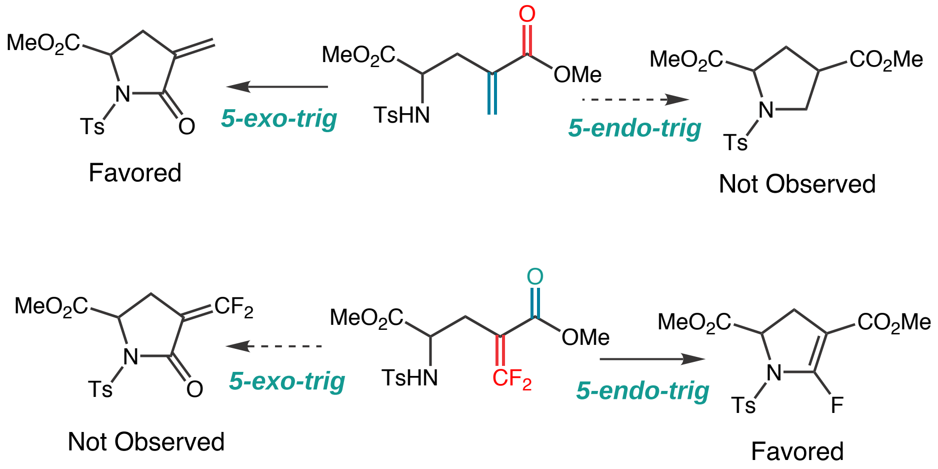


X	Y	Cond	Yield
F	F	DMF, 60 °C, 2 h	80
F	H	DMF, 80 °C, 43 h	17
Cl	Cl	DMF, 60 °C, 8 h	—
Br	Br	DMF, 60 °C, 5 h	15

Ichikawa, et al *Synthesis* **2002**, 1917-1936, **PDF on Course Website**

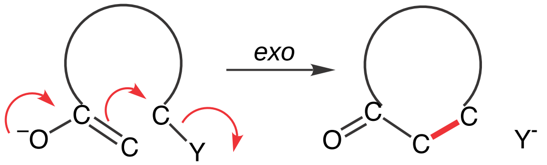
Numerous other cases are provided in this review.

Revisiting Case 2 with Fluorines

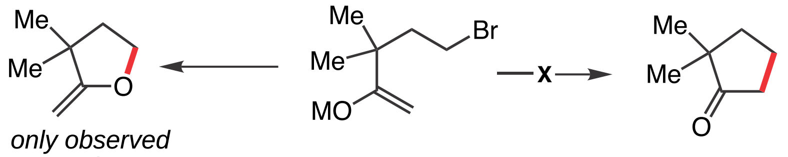


Rules for Ring Closure: SP2 Carbon & Related Systems

Trigonal Carbon: Exocyclic Enolate Alkylation



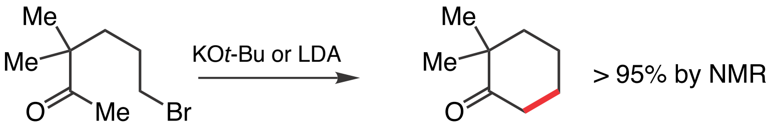
■ By definition, an exo-tet cyclization, but stereoelectronically behaves as an endo trig.



(1)

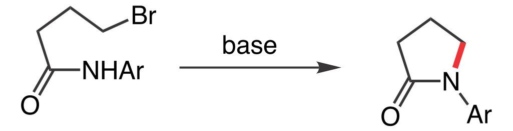
only observed product

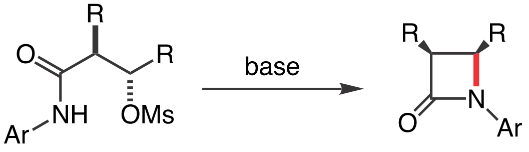
However:

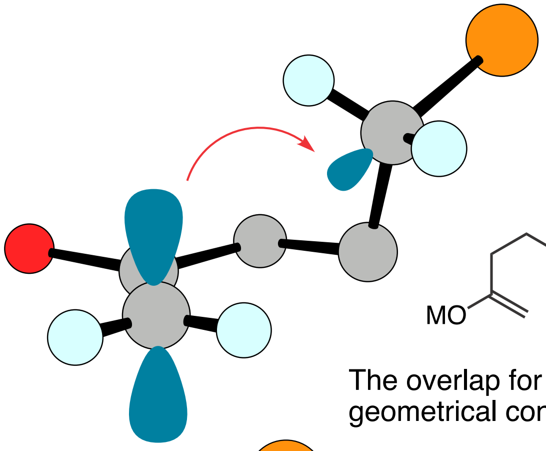


Baldwin, *J. Chem. Soc., Chem. Commun.* **1977**, 233.

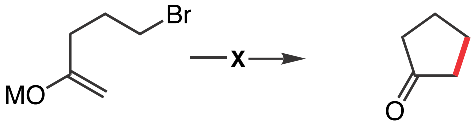
■ Given the failure of the enolate alkylation shown above (eq 1), explain why these two cyclizations are successful.



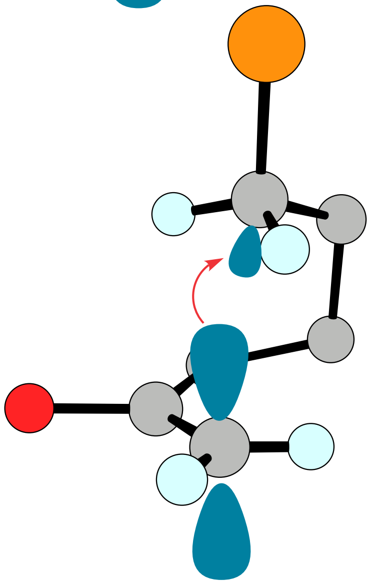




distance between reacting centers: 3.37Å

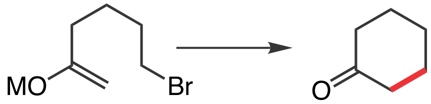


The overlap for C-alkylation is poor due to geometrical constraints of 5-membered ring

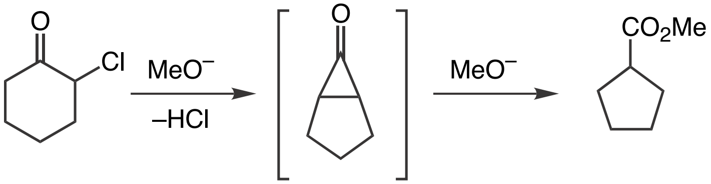


distance between reacting centers: 3.04Å

The relaxed geometrical constraint provided by the added CH_2 group now renders the 6-membered cyclization possible



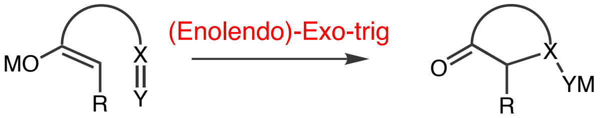
Favorskii Rearrangement (Carey, Pt B, pp 609-610)
Your thoughts on the mechanism



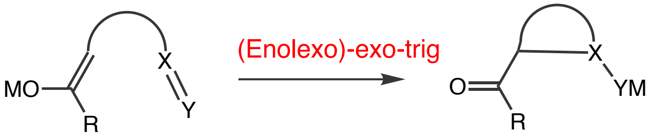
Rules for Ring Closure: SP2 & SP Carbon & Related Systems

Trigonal Carbon: *Intramolecular Aldol Condensations*

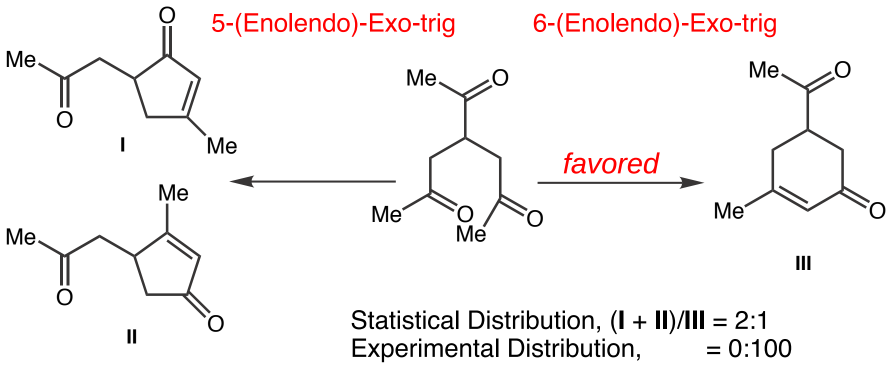
Baldwin, *Tetrahedron* **1982**, *38*, 2939



Favored: 6-7-(enolendo)-exo-trig
Disfavored: 3-5-(enolendo)-exo-trig



Favored: 3-7-(enolexo)-exo-trig



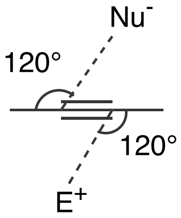
Statistical Distribution, (**I** + **II**)/**III** = 2:1
Experimental Distribution, = 0:100

(KOH, MeOH, r.t., 5 min, 77% y.)

Caution: Baldwin's conclusions assume that the **RDS** is ring closure; however, it is well known (by some!) that the rate determining step is dehydration in a base-catalyzed aldol condensation.

Digonal Carbon: Cyclizations on to Acetylenes

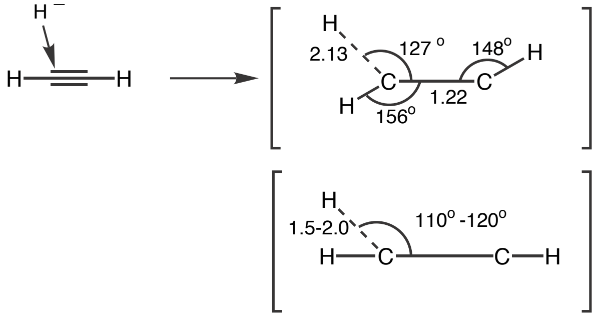
DIGONAL: Angle of approach for attack on triple bonds



Baldwin:

- 3 and 4-Exo-dig are disfavored
- 5 to 7-Exo-dig are favored
- 3 to 7-Endo-dig are favored

Ab initio SCF 4-31G calculations for the interaction of hydride with acetylene:



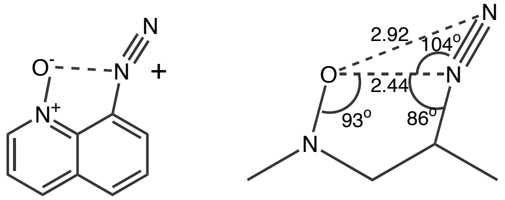
4-31G basis set

Houk, *J.ACS.***1979**, *101*, 1340.

STO-3G minimal basis set

Dunitz, *Helv Chim. Acta* **1978**, *61*, 2538.

Crystal Structures do not support Baldwin

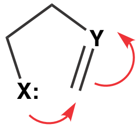


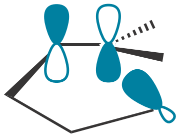
J. Dunitz and J. Wallis *J. C. S. Chem. Comm.* **1984**, 671.

Rules for Ring Closure: SP Carbon & Related Systems

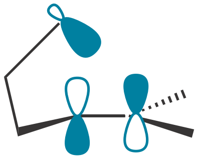
Endo Digonal versus Endo Trigonal Cyclizations

5-endo-trig



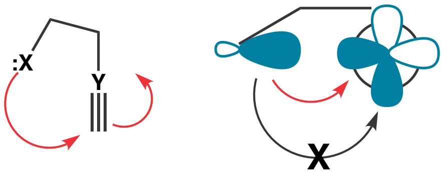


In-plane approach; nucleophile lone pair is orthogonal to π*



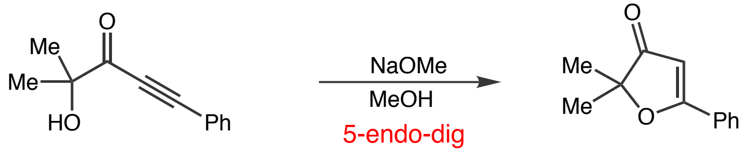
Out-of-plane approach; nucleophile lone pair can't achieve Bürgi-Dunitz angle

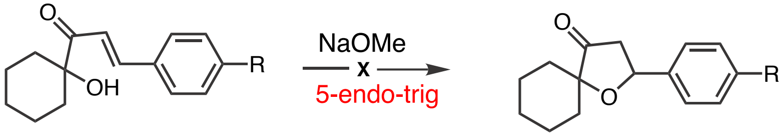
5-endo-dig



Allowed due to in-plane pi orbitals

For an opposing viewpoint to Baldwin's view of nucleophile trajectories, see Menger's article on directionality in solution organic chemistry: *Tetrahedron* **1983**, *39*, 1013.





R = H, OMe

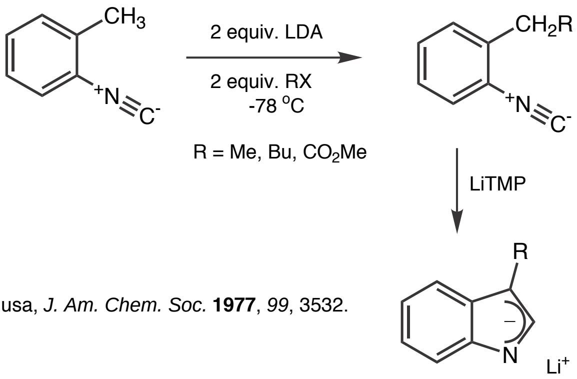
however, the acid catalyzed version does cyclize

Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.

Johnson, *Can. J. Chem.* **1990**, *68*, 1780

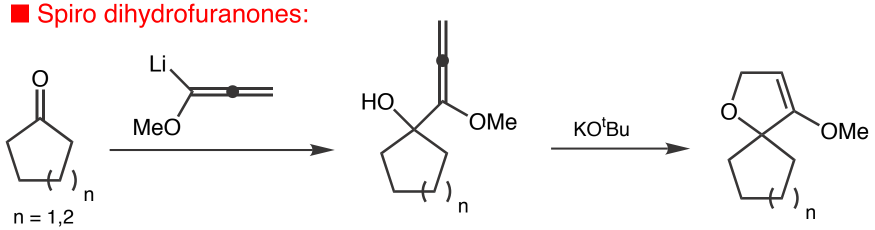
J. Am. Chem. Soc. **1983**, *105*, 5090
J. Chem. Soc., Chem. Commun. **1982**, 36.

■ Indole synthesis:



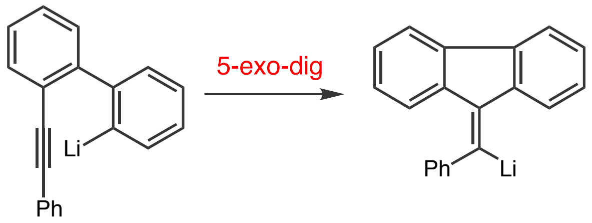
Saegusa, *J. Am. Chem. Soc.* **1977**, *99*, 3532.

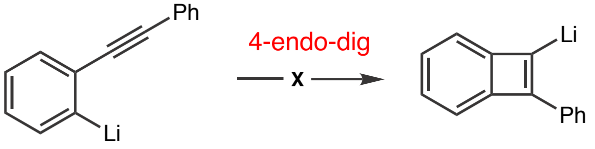
■ Spiro dihydrofuranones:



Developing negative charge on the central allenic carbon is in the same plane as the OMe group

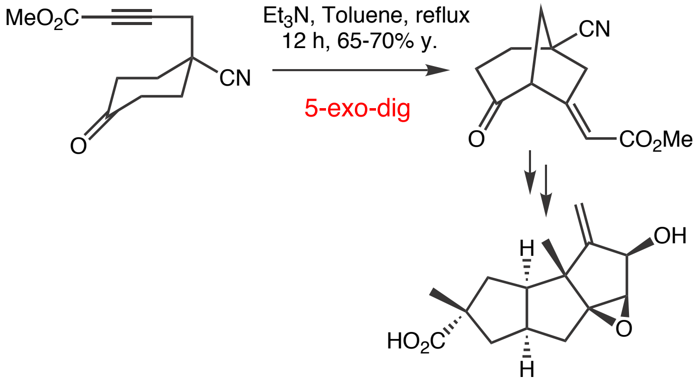
Magnus, *J. Am. Chem. Soc.* **1978**, *100*, 7746.





Rules for Ring Closure: SP Carbon & Related Systems

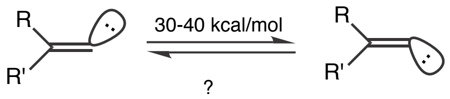
Digonal Cyclizations: Interesting Examples

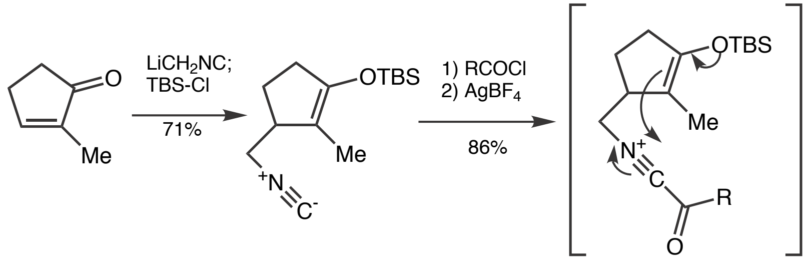


Hirsutic Acid C

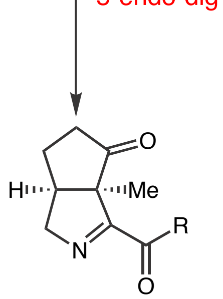
- Trost, *J. Am. Chem. Soc.*, **1979**, *101*, 1284.

Proposes E-olefin geometry, E/Z > 95:5





Works for varying ring sizes and R groups; acylnitrilium ion can also work as an electophile in a Friedel-Crafts type of reaction



- Livinghouse, *Tetrahedron* **1992**, *48*, 2209.

Conclusions and Caveats

- Baldwin's Rules are an effective first line of analysis in evaluating the stereoelectronics of a given ring closure
- Baldwin's Rules have provided an important foundation for the study of reaction mechanism
- Competition studies between different modes of cyclization only give information about relative rates, and are not an absolute indicator of whether a process is "favored" or "disfavored"
- Structural modifications can dramatically affect the cyclization mode; beware of imines and epoxides

	EXO			**ENDO**		
	Tet	**Trig**	**Dig**	**Tet**	**Trig**	**Dig**
3	√	√	x		x	√
4	√	√	x		x	√
5	√	√	√	x	x	√
6	√	√	√	x	√	√
7	√	√	√	x	√	√

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 4

Acyclic Conformational Analysis-1

- Ethane, Propane, Butane & Pentane Conformations
- Simple Alkene Conformations

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapters 2 & 3

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds **(handout)**

The Ethane Barrtier Problem

F. Weinhold, *Nature* ***2001***, *411*, 539-541
"A New Twist on Molecular Shape" **(handout)**

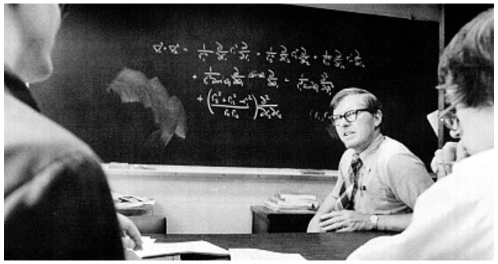
F. M. Bickemhaupt & E. J. Baerends, *Angew. Chem. Int. Ed.* ***2003***, *42*, 4183-4188,*"The Case for Steric Repulsion Causing the Staggered Conformation in Ethane"* **(handout)**

F. Weinhold,, *Angew. Chem. Int. Ed.* ***2003***, *42*, 4188-4194,*"Rebuttal of the Bikelhaupt–Baerends Case for Steric Repulsion Causing the staggered Connformation of Ethane"* **(handout)**

D. A. Evans

Monday,
September 22, 2003

Professor Frank Weinhold
Univ. of Wisconsin, Dept of Chemistry
B.A. 1962, University of Colorado, Boulder
A.M. 1964, Harvard University
Ph.D. 1967, Harvard University
Physical and Theoretical Chemistry.



Useful LIterature Reviews

Eliel, E. L., S. H. Wilen, et al. (1994). Stereochemistry of Organic Compounds. New York, Wiley.

Juaristi, E. (1991). Introduction to Stereochemistry and Conformational Analysis. New York, Wiley.

Juaristi, E., Ed. (1995). Conformational Behavior of Six-Membered Rings: Analysis, Dynamics and Stereochemical Effects. (Series: Methods in Stereochemical Analysis). Weinheim, Germany, VCH.

Schweizer, W. B. (1994). Conformational Analysis. Structure Correlation, Vol 1 and 2. H. B. Burgi and J. D. Dunitz. Weinheim, Germany, V C H Verlagsgesellschaft**:** 369-404.

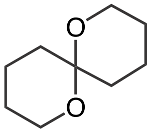
Kleinpeter, E. (1997). “Conformational Analysis of Saturated Six-Membered Oxygen-Containing Heterocyclic Rings.” Adv. Heterocycl. Chem. **69**: 217-69.

Glass, R. R., Ed. (1988). Conformational Analysis of Medium-Sized Ring Heterocycles. Weinheim, VCH.

Bucourt, R. (1973). “The Torsion Angle Concept in Conformational Analysis.” Top. Stereochem. **8**: 159.

Problems of the Day

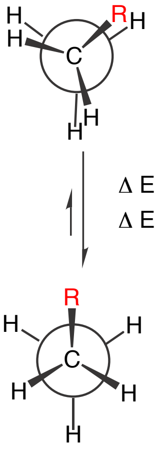
Predict the most stable conformation of the indicated dioxospiran?



The following discussion is intended to provide a general overview of acyclic conformational analysis

Ethane & Propane

The conformational isomerism in these 2 structures reveals a gratifying level of internal consistency.

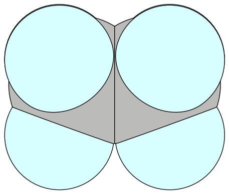


eclipsed conformation

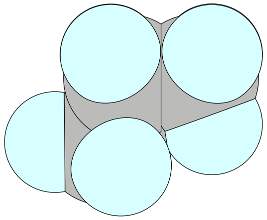
Δ E = +3.0 kcal mol^{-1} (R = H)

Δ E = +3.4 kcal mol^{-1} (R = Me)

staggered conformation



Van derWaals radii of vicinal hydrogens do not overlap in ethane



In propane there is a discernable interaction

For purposes of analysis, each eclipsed conformer may be broken up into its component destabilizing interactions.

Incremental Contributions to the Barrier.

Structure	Eclipsed atoms	δ E (kcal mol $^{-1}$)
ethane	3 (H↔H)	+1.0 kcal mol $^{-1}$
propane	2 (H↔H)	+1.0 kcal mol $^{-1}$
	1 (H↔Me)	+1.4 kcal mol $^{-1}$

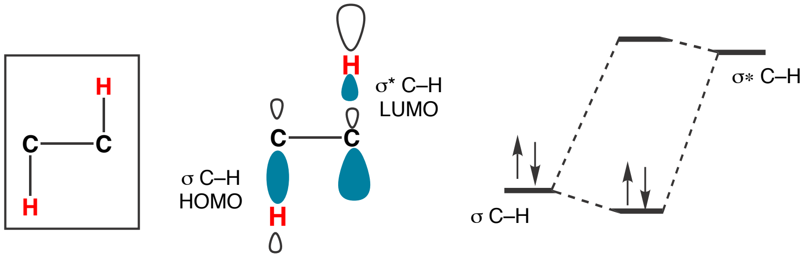
Ethane Rotational Barrier: The FMO View

F. Weinhold, *Angew. nature* **2001**, *411*, 539-541*"A New Twist on Molecular Shape"*

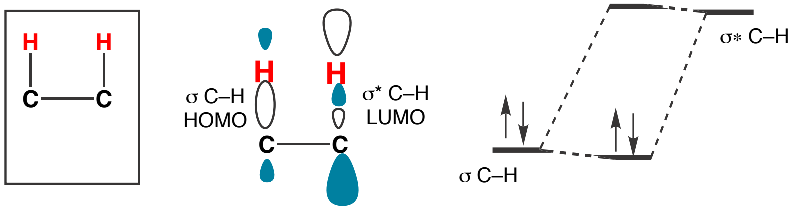
One can see from the space-filling models that the Van der Waals radii of the hydrogens do not overlap in the eclipsed ethane conformation. This makes the steric argument for the barrier untenable.

One explanation for the rotational barrier in ethane is that better overlap is possible in the staggered conformation than in the eclipsed conformation as shown below.

In the staggered conformation there are 3 anti-periplanar C–H Bonds



In the eclipsed conformation there are 3 syn-periplanar C–H Bonds

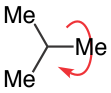


Following this argument one might conclude that:

- The staggered conformer has a better orbital match between bonding and antibonding states.
- The staggered conformer can form more delocalized molecular orbitals.

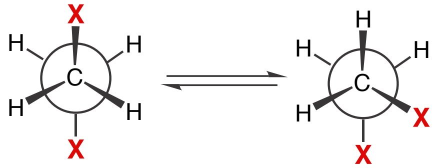
J. P. Lowe was the first to propose this explanation

"A Simple Molecuar Orbital Explanation for the Barrier to Internal Rotation in Ethane and Other Molecules"
J. P. Lowe, *JACS* **1970**, *92*, 3799



Calculate the the rotational barrier about the C1-C2 bond in isobutane

The 1,2-Dihaloethanes



X = Cl; ΔH° = + 0.9–1.3 kcal/mol
X = Br; ΔH° = + 1.4–1.8 kcal/mol
X = F; ΔH° = – 0.6-0.9 kcal/mol

Observation: While the anti conformers are favored for X = Cl, Br, the gauche conformation is prefered for 1,2-difluroethane. Explain.

Discuss with class the origin of the gauche stabiliation of the difluoro anaolg.

Recent Article: *Chem. Commun* **2002**, 1226-1227 **(handout)**

Relationship between ΔG and Keq and pKa

Recall that:

$$\Delta G^\circ = -RT \ln K$$

or

$$\Delta G^\circ = -2.3RT \log_{10} K$$

At 298 K: 2.3RT = 1.4 (ΔG in kcal Mol^{-1})

$$\Delta G^\circ_{298} = -1.4 \log_{10} Keq$$

Since

$$pKeq = -\log_{10} Keq$$

$$\boxed{\Delta G^\circ_{298} = 1.4\ \ pKeq}$$

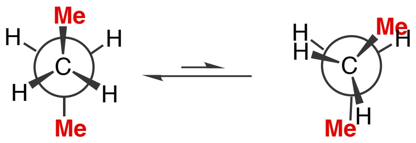
Hence, pK is proportional to the free energy change

Keq	pKeq	ΔG°
1.0	0	0
10	–1	–1.4
100	–2	–2.8 kcal /mol

Butane

Using the eclipsing interactions extracted from propane & ethane we should be able to estimate all but one of the eclipsed butane conformations

staggered conformation



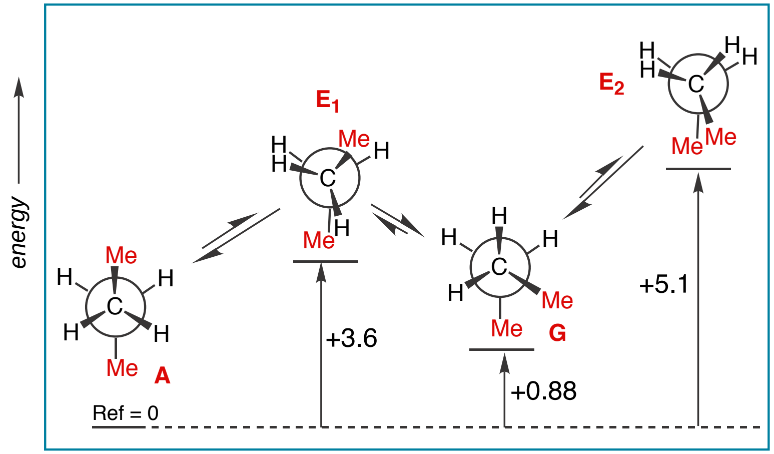
eclipsed conformation

ΔE = ?

Eclipsed atoms	δ E (kcal mol^{-1})
1 (H↔H)	+1.0 kcal mol^{-1}
2 (H↔Me)	+2.8 kcal mol^{-1}
Δ E est =	3.8 kcal mol^{-1}

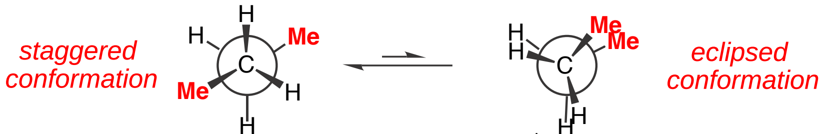
The estimated value of +3.8 agrees quite well with the value of +3.6 reported by Allinger (*J. Comp. Chem.* **1980**, *1*, 181-184)

n-Butane Torsional Energy Profile



Butane continued

From the torsional energy profile established by Allinger, we should be able to extract the contribution of the Me↔Me eclipsing interaction to the barrier:



Δ E = +5.1 kcal mol^{-1}

Let's extract out the magnitide of the Me–Me interaction

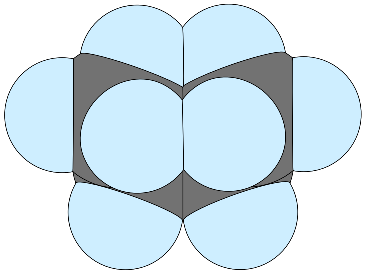
2 (H↔H) + 1 (Me↔Me) = +5.1

1 (Me↔Me) = +5.1 – 2 (H↔H)

1 (Me↔Me) = +3.1

Incremental Contributions to the Barrier.

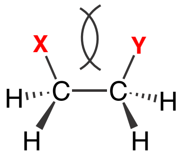
Eclipsed atoms	δ E (kcal mol^{-1})
2 (H↔H)	+2.0
1 (Me↔Me)	+3.1



Eclipsed Butane conformation

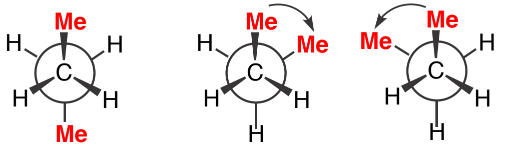
From the energy profiles of ethane, propane, and n-butane, one may extract the useful eclipsing interactions summarized below:

Hierarchy of Eclipsing Interactions



X—Y	δ E kcal mol^{-1}
H—H	+1.0
H—Me	+1.4
Me—Me	**+3.1**

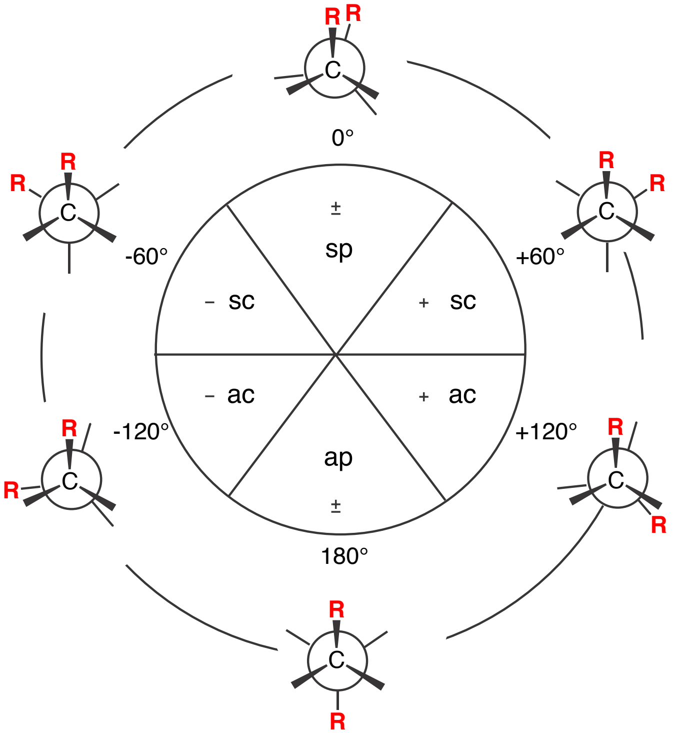
Nomenclature for staggered conformers:



	trans or t or (anti)	gauche(+) or g$^+$	gauche(-) or g$^-$
Conformer population at 298 K:	70%	15%	15%

General nomenclature for diastereomers resulting from rotation about a single bond

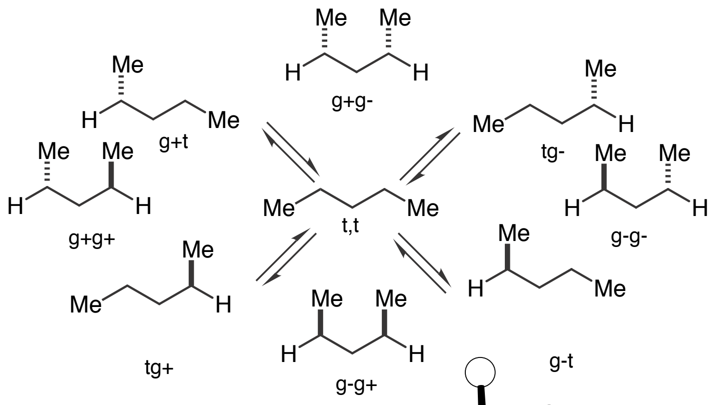
(Klyne, Prelog, *Experientia* **1960**, *16*, 521.)

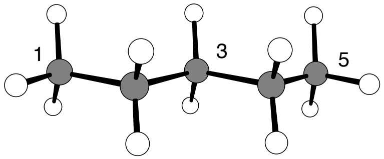


	Torsion angle	Designation	Symbol	*n*-Butane Conformer
Energy Maxima →	0 ± 30°	± syn periplanar	± sp	E$_2$
Energy Minima →	+60 ± 30°	+ syn-clinal	+ sc (g+)	G
→	+120 ± 30°	+ anti-clinal	+ ac	E$_1$
→	180 ± 30°	antiperiplanar	ap (anti or t)	A
→	-120 ± 30°	- anti-clinal	- ac	E$_1$
→	-60 ± 30°	- syn-clinal	- sc (g-)	G

n-Pentane

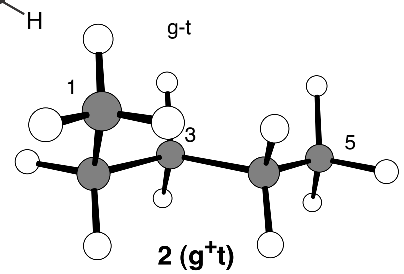
Rotation about both the C_2-C_3 and C_3-C_4 bonds in either direction (+ or -):





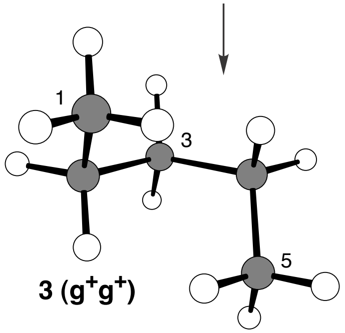
1 (t,t)

Anti(2,3)-Anti(3,4) →



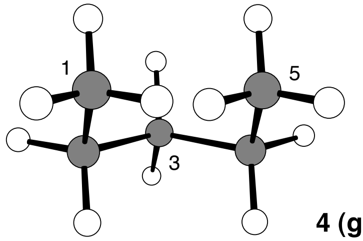
2 (g^+t)

Gauche(2,3)-Anti(3,4) ↓



3 (g^+g^+)

Gauche(2,3)-Gauche(3,4) ←

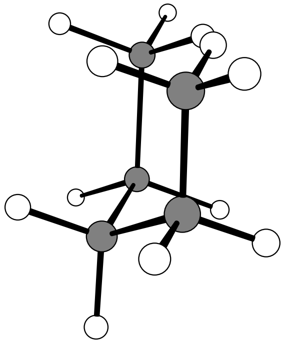


4 (g^+g^-)

Gauche(2,3)-Gauche'(3,4)
double gauche pentane

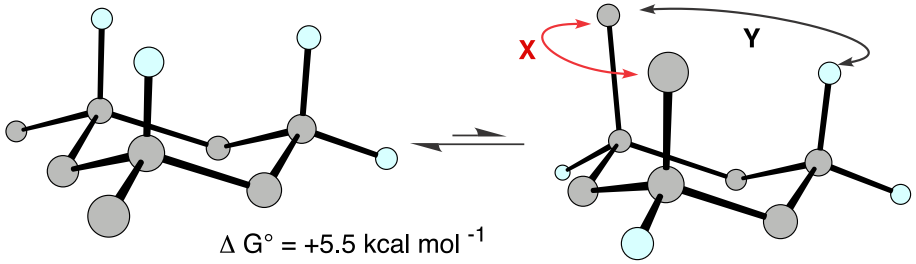
From prior discussion, you should be able to estimate energies of **2** & **3** (relative to **1**). On the other hand, the least stable conformer **4** requires additional data before is relative energy can be evaluated.

The double-gauche pentane conformation



The new high-energy conformation: **(g^+g^-)**

Estimate of 1,3-Dimethyl Eclipsing Interaction



$$\Delta G° = +5.5 \text{ kcal mol}^{-1}$$

$$\Delta G° = X + 2Y \text{ where:}$$

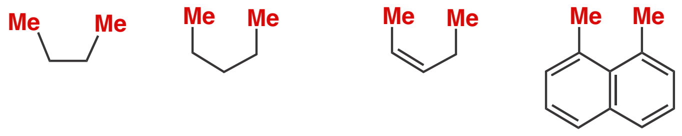
X = 1,3(Me↔Me) & Y = 1,3(Me↔H)

1,3(Me↔H) = Skew-butane = 0.88 kcal mol^{-1}

1,3(Me↔Me) = $\Delta G° - 2Y = 5.5 \; -1.76 = +3.7$ kcal mol^{-1}

$$\boxed{1,3(\text{Me}\leftrightarrow\text{Me}) = +3.7 \text{ kcal mol}^{-1}}$$

Estimates of In-Plane 1,2 &1,3-Dimethyl Eclipsing Interactions

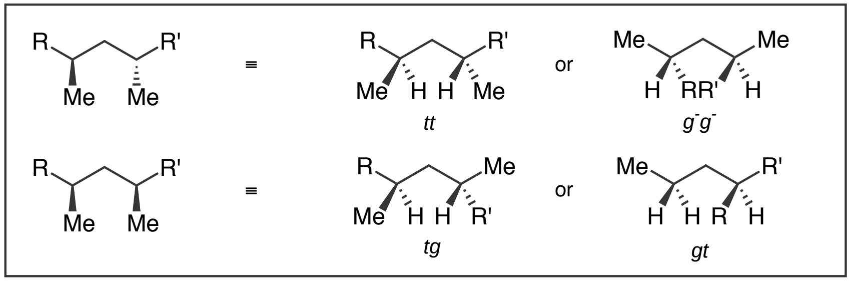


3.1 ~ 3.7 ~3.9 ~ 7.6

It may be concluded that in-plane 1,3(Me↔Me) interactions are Ca +4 kcal/mol while 1,2(Me↔Me) interactions are destabliizing by Ca 2.2 kcal/mol.

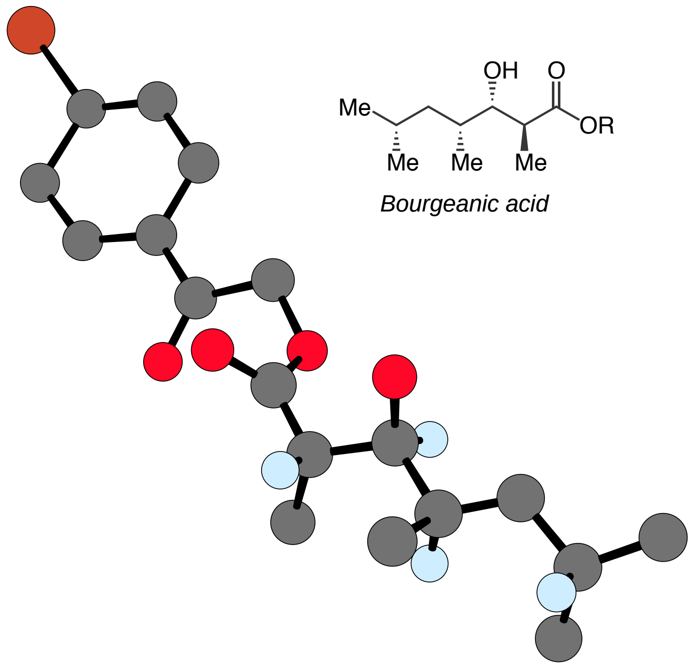
The syn-Pentane Interaction - Consequences

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds **(handout)**



Consequences for the preferred conformation of polyketide natural products

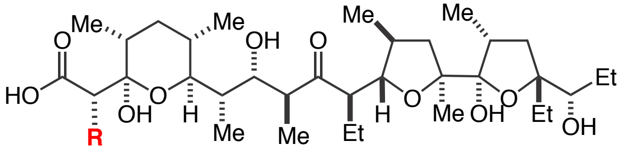
Analyze the conformation found in the crystal state of a bourgeanic acid derivative!



Bourgeanic acid

Lactol & Ketol Polyether Antibioitics

The conformation of these structures are strongly influenced by the acyclic stereocenters

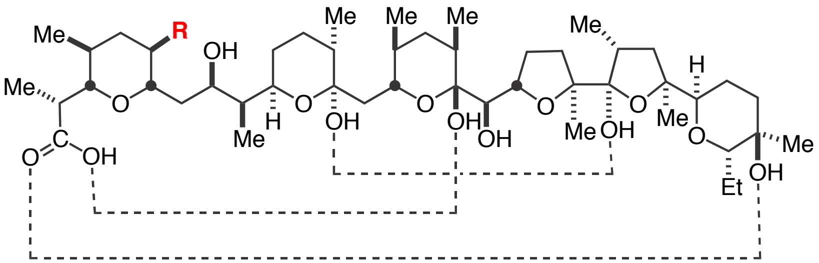


Ferensimycin B, R = Me
Lysocellin, R = H

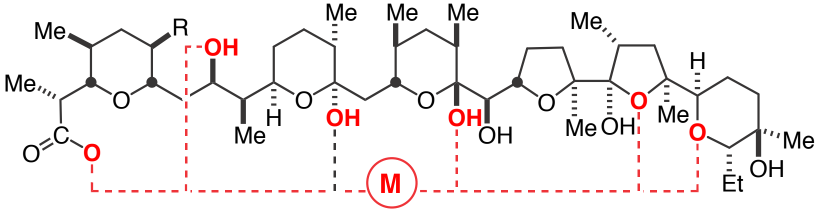
The conformation of these structures are strongly influenced by the acyclic stereocenters and internal H-bonding

Alborixin R = Me; X-206 R = H

Internal H-Bonding



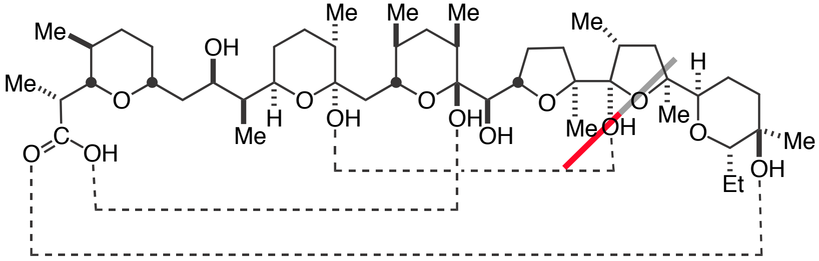
Metal ion ligation sites (M = Ag, K)

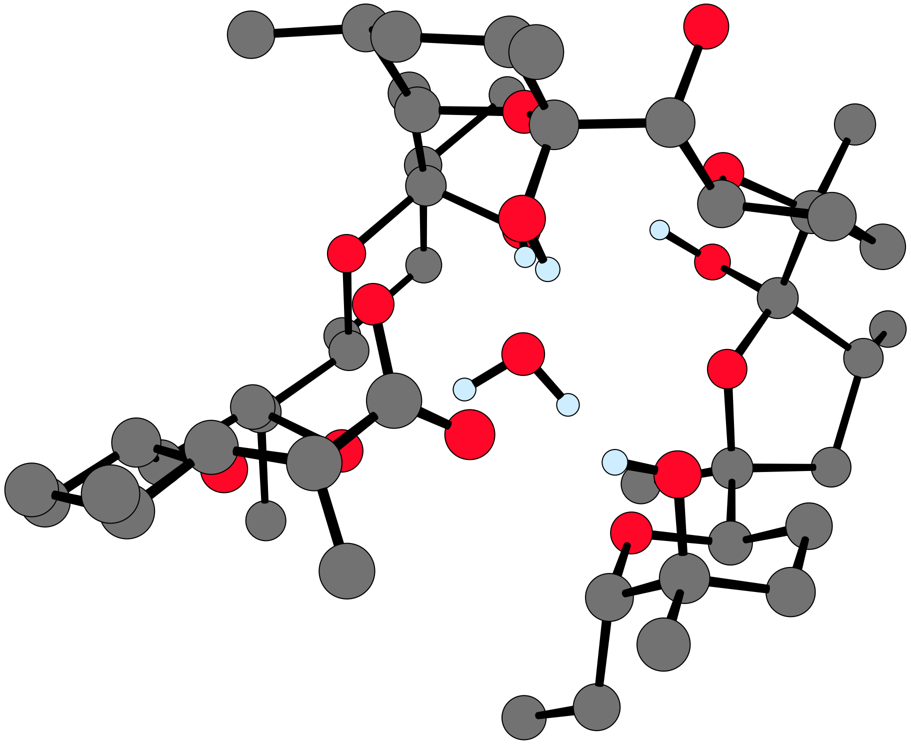


Conformational Analysis: Ionophore X-206/X-rays

X-ray of Ionophore X-206 · H_2O

Internal H-Bonding

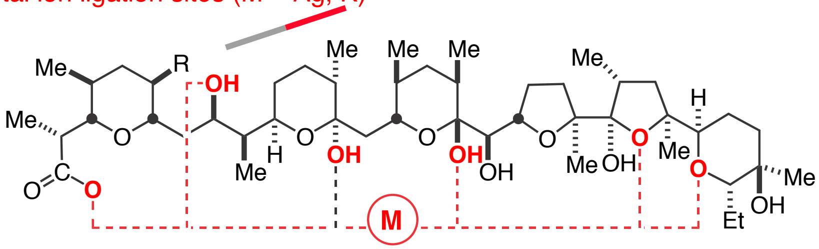


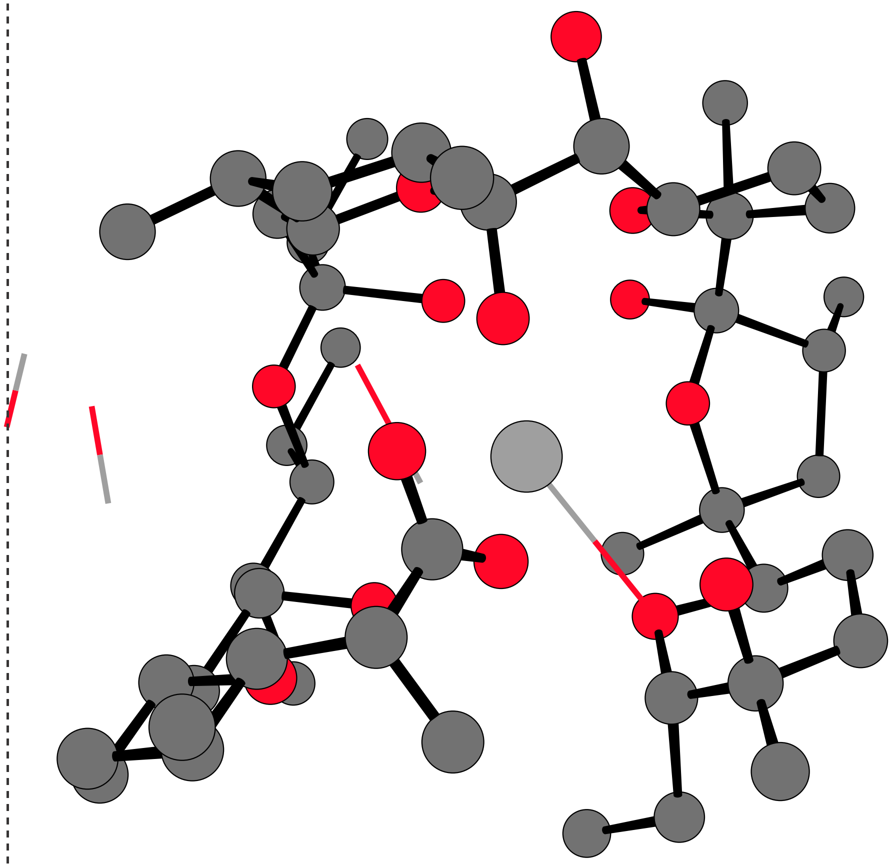


"The Total Synthesis of the Polyether Antibiotic X-206". Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

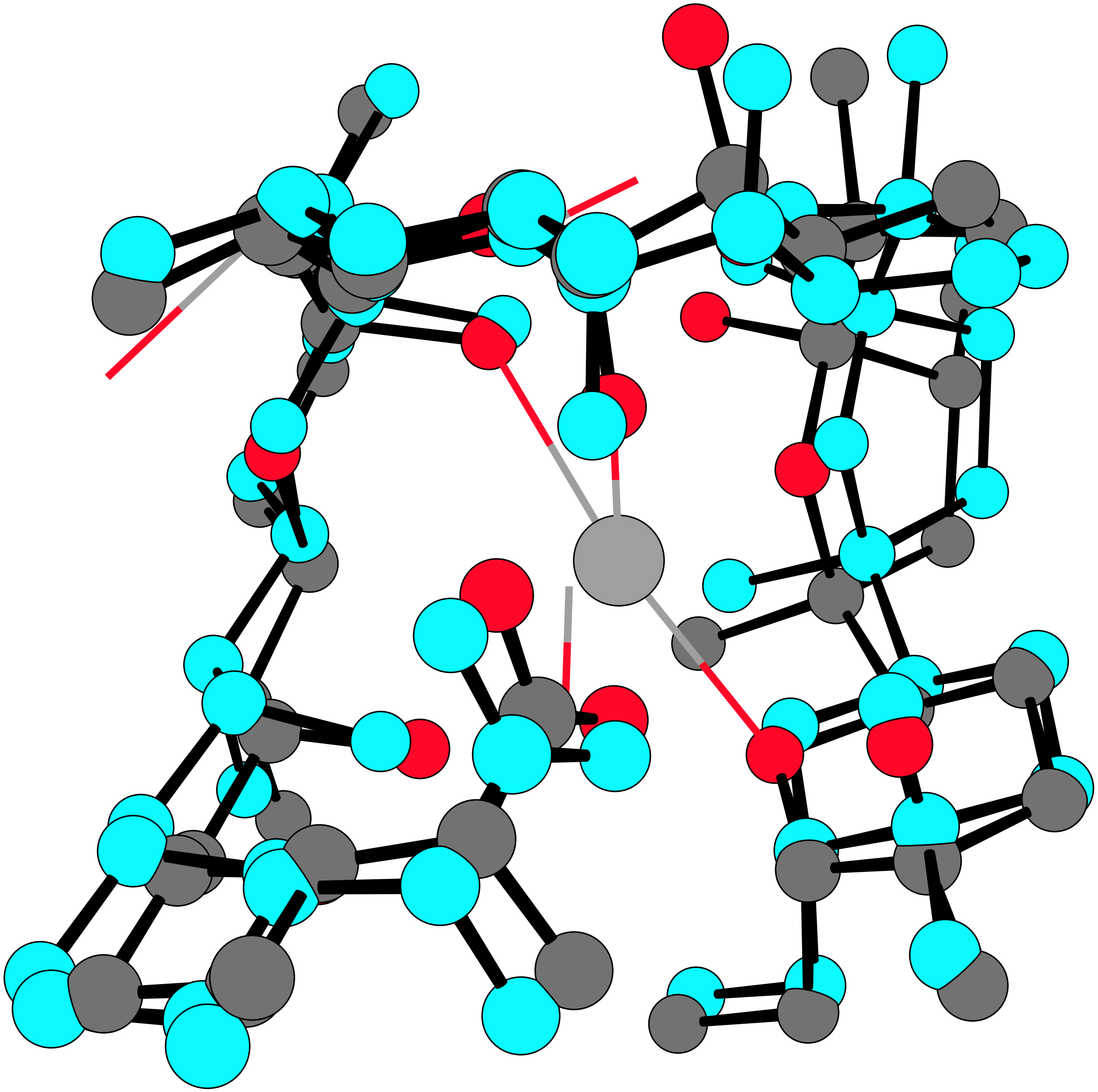
X-ray of Ionophore X-206 - Ag^+ - Complex

Metal ion ligation sites (M = Ag, K)





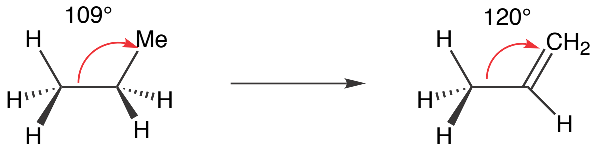
Conformational Analysis: Ionophore X-206/X-ray overlay



Stabilized Eclipsed Conformations in Simple Olefins

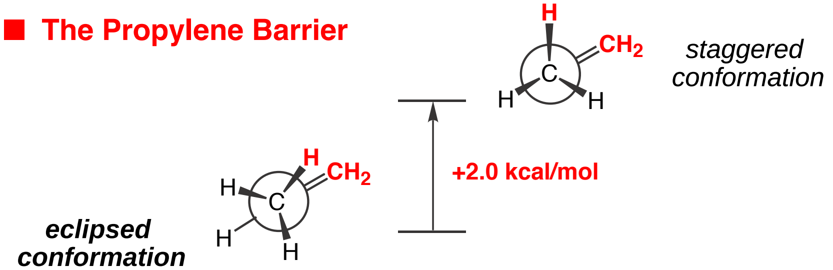
Simple olefins exhibit unusal conformational properties relative to their saturated counterparts

Propane versus Propene



Hybridilzation change opens up the C–C–C bond angle

■ The Propylene Barrier

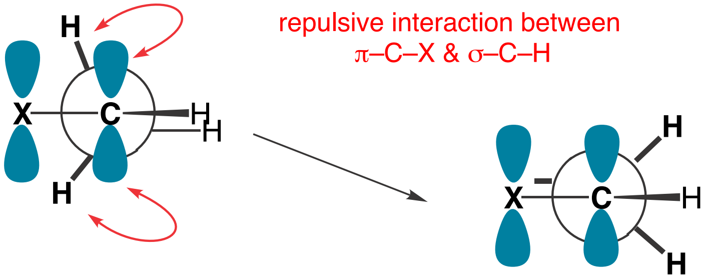


staggered conformation

+2.0 kcal/mol

eclipsed conformation

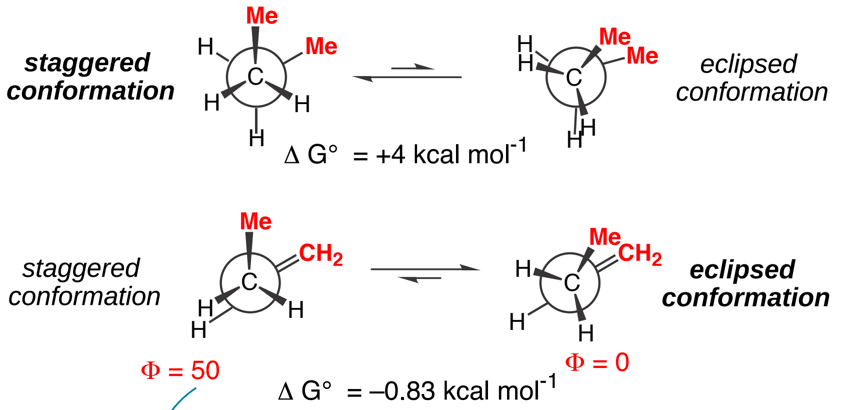
New destabilizing effect



repulsive interaction between π–C–X & σ–C–H

K. Wiberg, *JACS* **1985**, *107*, 5035-5041
K. Houk, *JACS* **1987**, *109*, 6591-6600

Butane versus 1-Butene



staggered conformation

eclipsed conformation

$\Delta G^\circ = +4$ kcal mol^{-1}

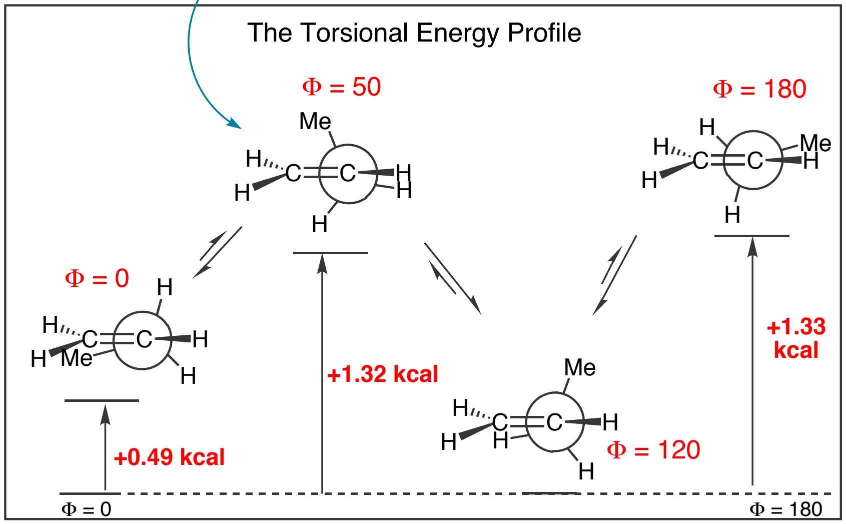
staggered conformation

eclipsed conformation

Φ = 50

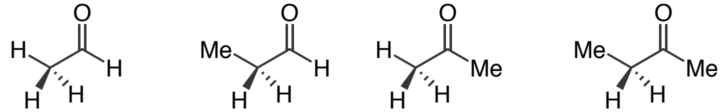
Φ = 0

$\Delta G^\circ = -0.83$ kcal mol^{-1}



Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.

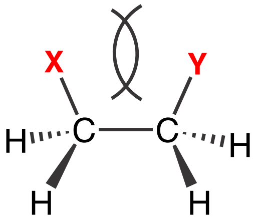
■ Acetaldehyde exhibits a similar conformational bias



The low-energy conformation in each of above cases is eclisped

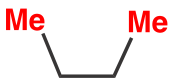
Useful Destabilizing Interactions to Remember

Hierarchy of Vicinal Eclipsing Interactions

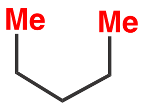


X—Y	δ E kcal mol $^{-1}$
H—H	+1.0
H—Me	+1.4
Me—Me	**+3.1**

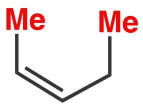
Estimates of In-Plane 1,2 &1,3-Dimethyl Eclipsing Interactions



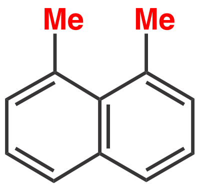
~ 3.1



~ 3.7

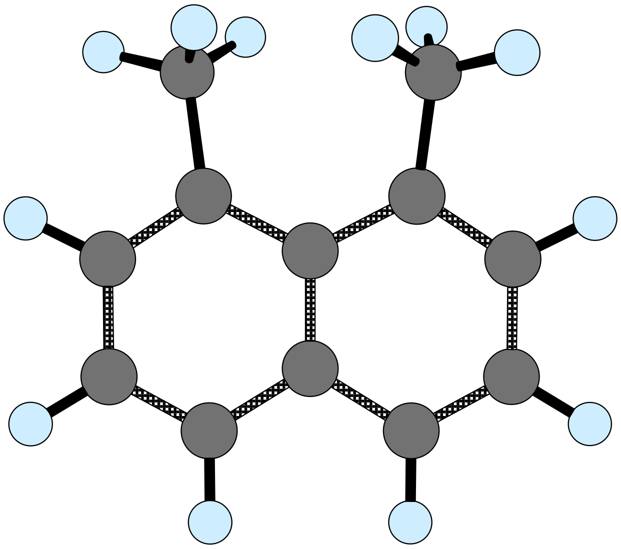


~3.9



~ 7.6

It may be concluded that in-plane 1,3(Me↔Me) interactions are Ca +4 kcal/mol while 1,2(Me↔Me) interactions are destabliizing by Ca +3 kcal/mol.



minimized structure

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 5

Acyclic Conformational Analysis-2

- Conformations of Simple Olefinic Substrates
- Introduction to Allylic Strain
- Introduction to Allylic Strain-2: Amides and Enolates

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapters 2 & 3

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds **(handout)**

R. W. Hoffmann, *Chem. Rev*. **1989**, *89*, 1841-1860
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations **(handout)**

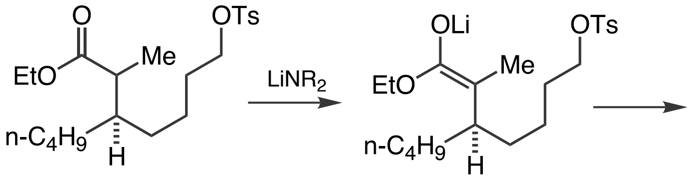
F. Weinhold, *Nature* ***2001***, *411*, 539-541
"A New Twist on Molecular Shape" **(handout)**

D. A. Evans

Wednesday,
September 24, 2001

Problems of the Day:

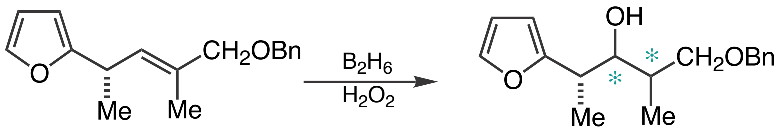
Can you predict the stereochemical outcome of this reaction?



1 + **2**

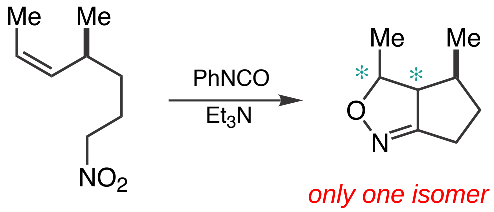
98:2

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.



diastereoselection 8:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc*. **1979**, *101*, 259.



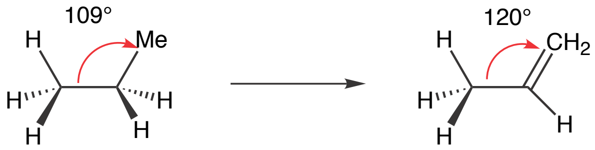
only one isomer

A. Kozikowski & Co-workers, *Tetrahedron Lett*. **1982**, *23*, 2081.

Stabilized Eclipsed Conformations in Simple Olefins

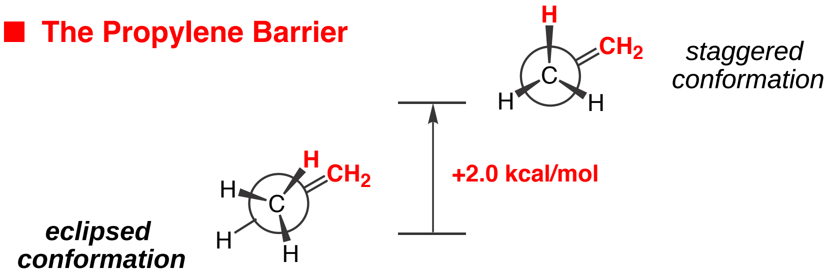
Simple olefins exhibit unusal conformational properties relative to their saturated counterparts

Propane versus Propene



Hybridilzation change opens up the C–C–C bond angle

■ The Propylene Barrier

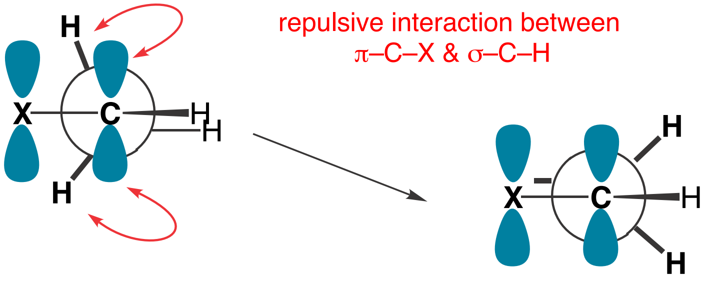


staggered conformation

+2.0 kcal/mol

eclipsed conformation

New destabilizing effect



repulsive interaction between π–C–X & σ–C–H

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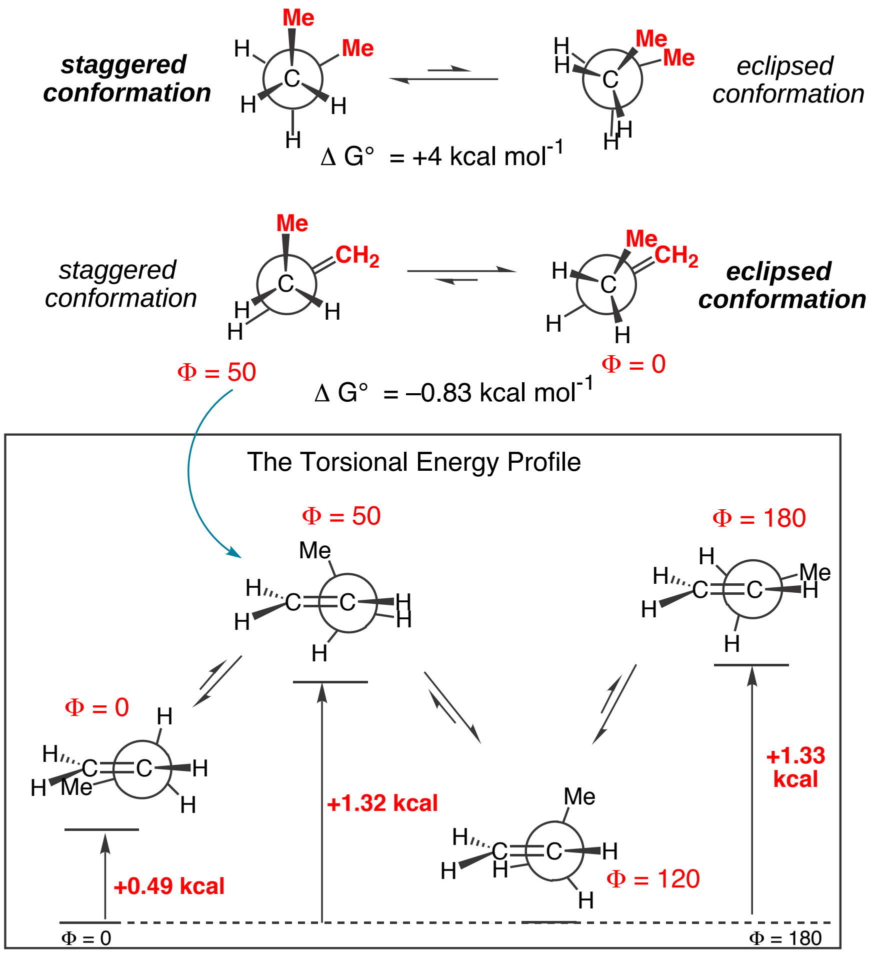
K. Houk, *JACS* **1987**, *109*, 6591-6600

Butane versus 1-Butene



staggered conformation ⇌ *eclipsed conformation*

Δ G° = +4 kcal mol^{-1}

staggered conformation ⇌ *eclipsed conformation*

Δ G° = –0.83 kcal mol^{-1}

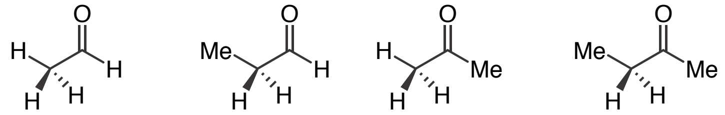
+0.49 kcal

+1.32 kcal

+1.33 kcal

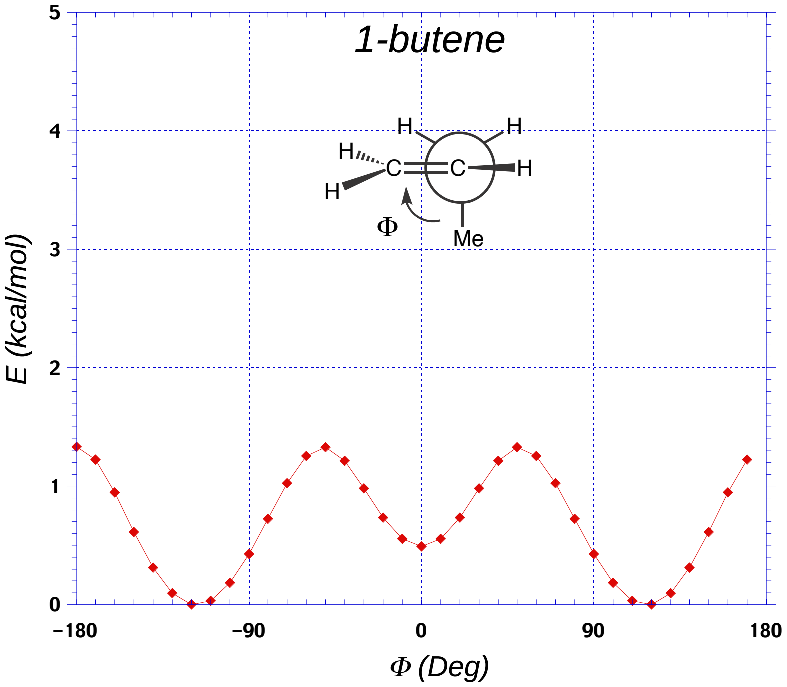
Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.

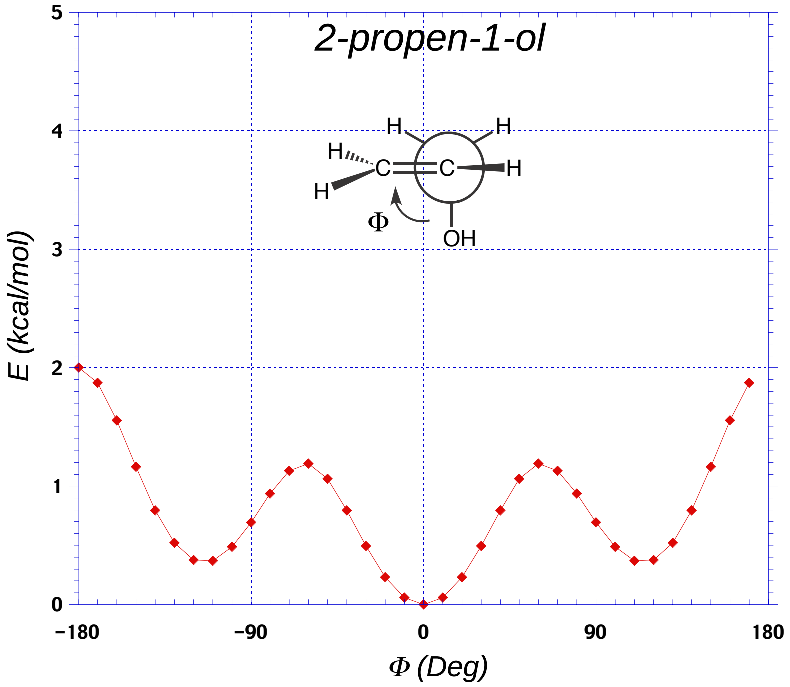
■ Acetaldehyde exhibits a similar conformational bias

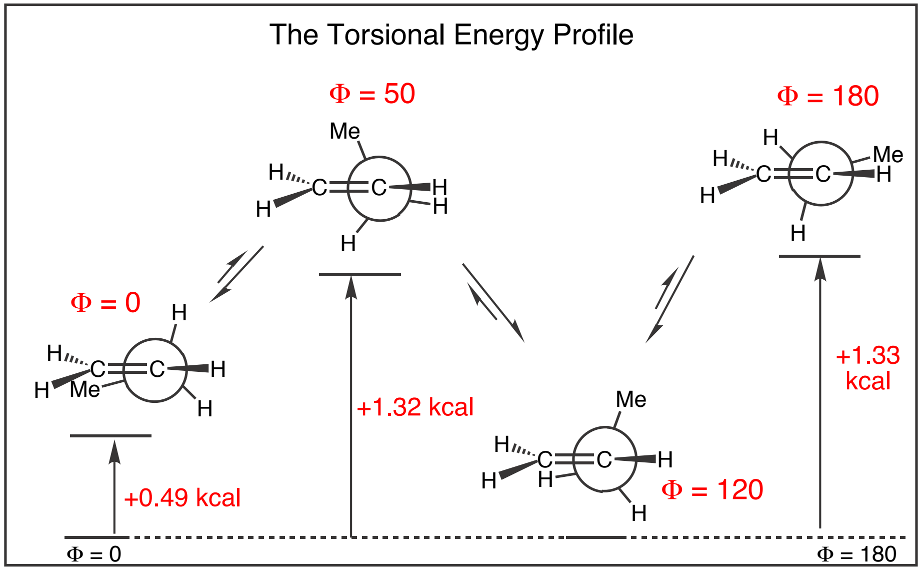


The low-energy conformation in each of above cases is eclisped

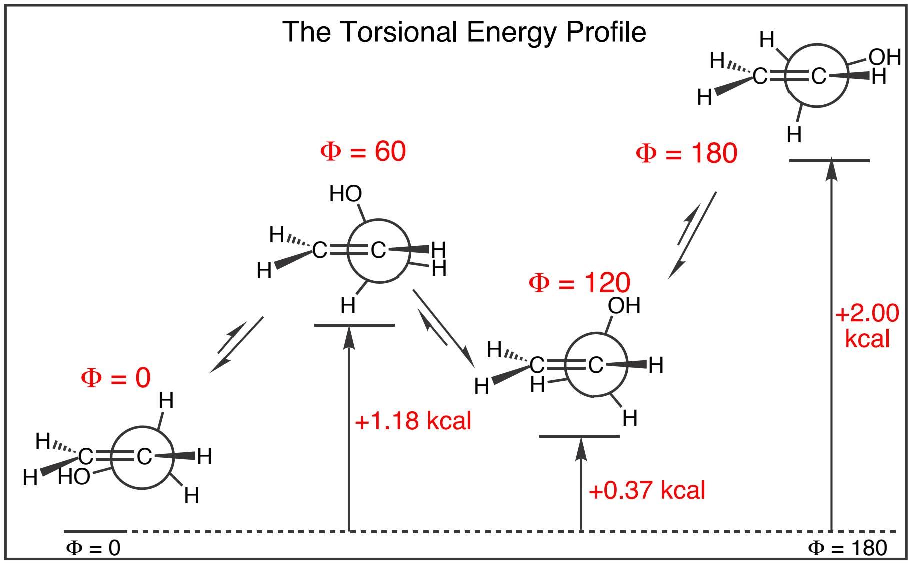
Conformational Barriers to Rotation: Olefin A-1,2 Interactions



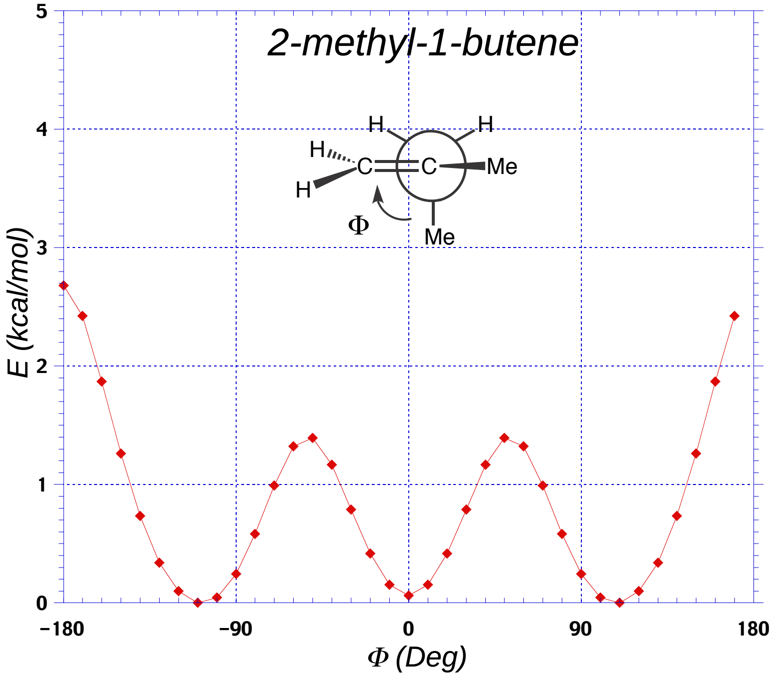




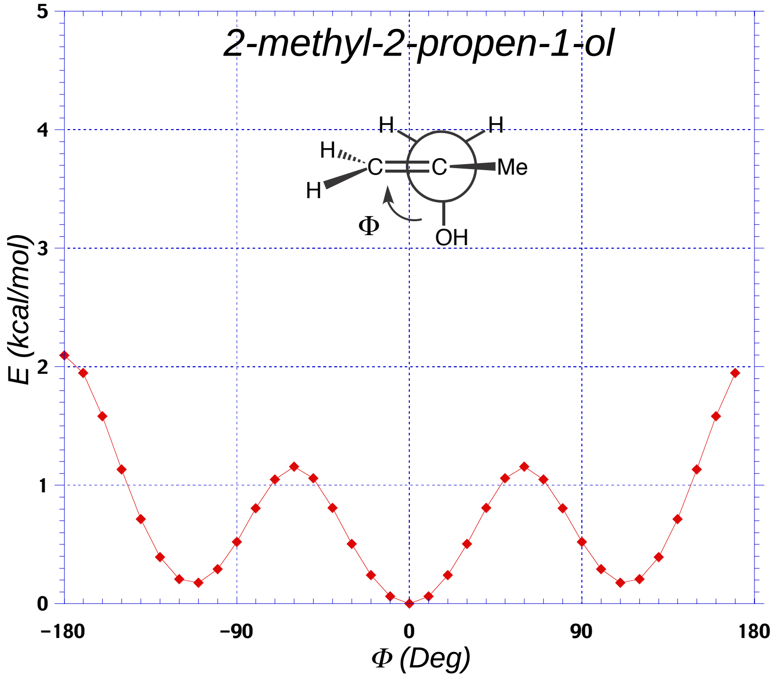
Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.



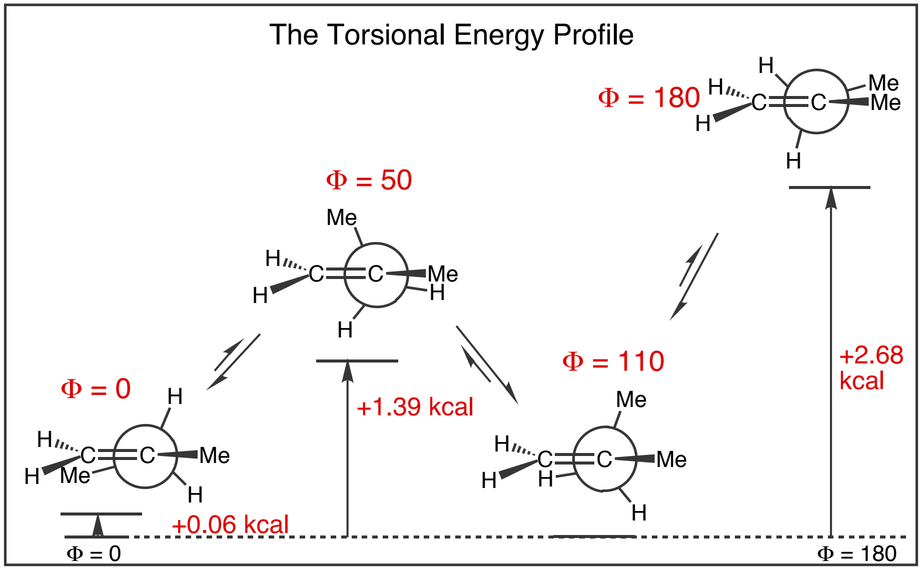
Conformational Barriers to Rotation: Olefin A-1,2 Interactions-2



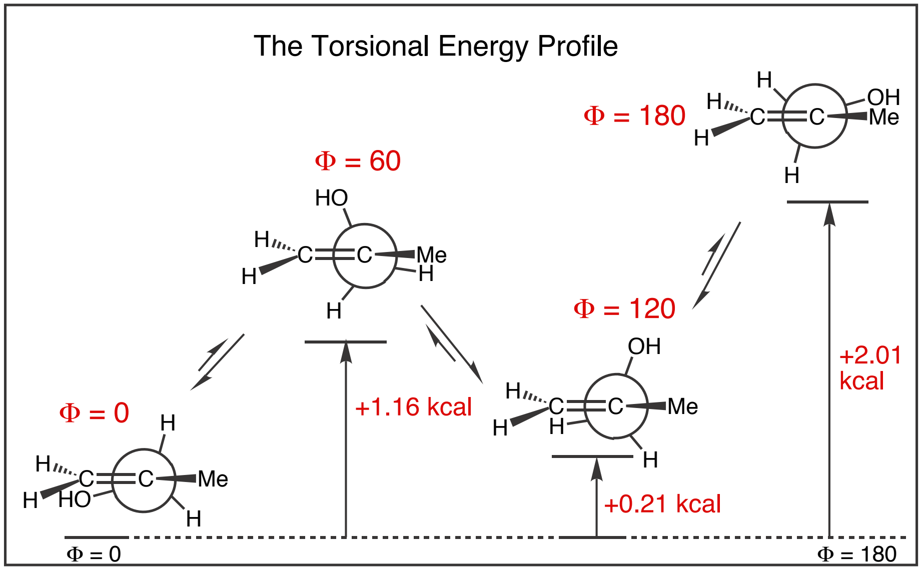
2-methyl-1-butene



2-methyl-2-propen-1-ol

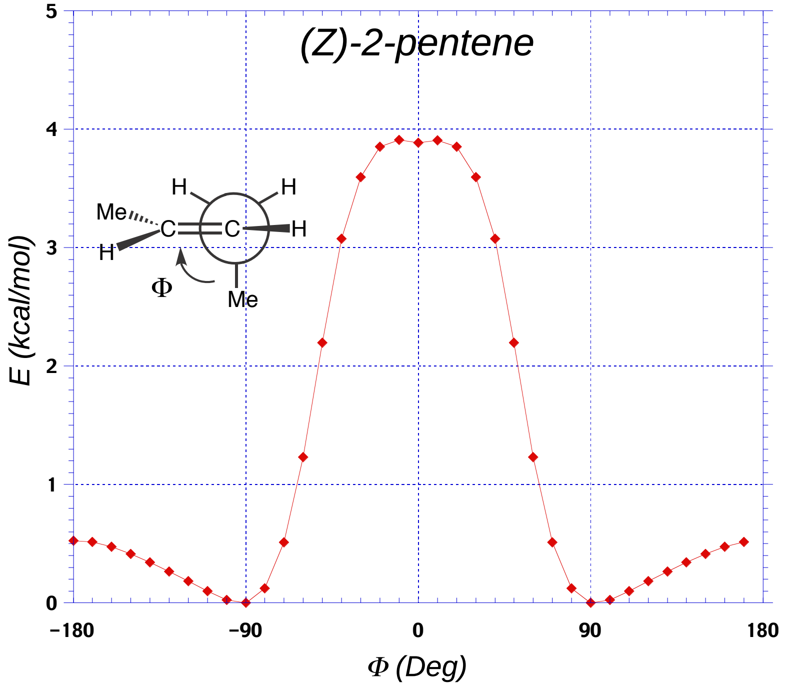


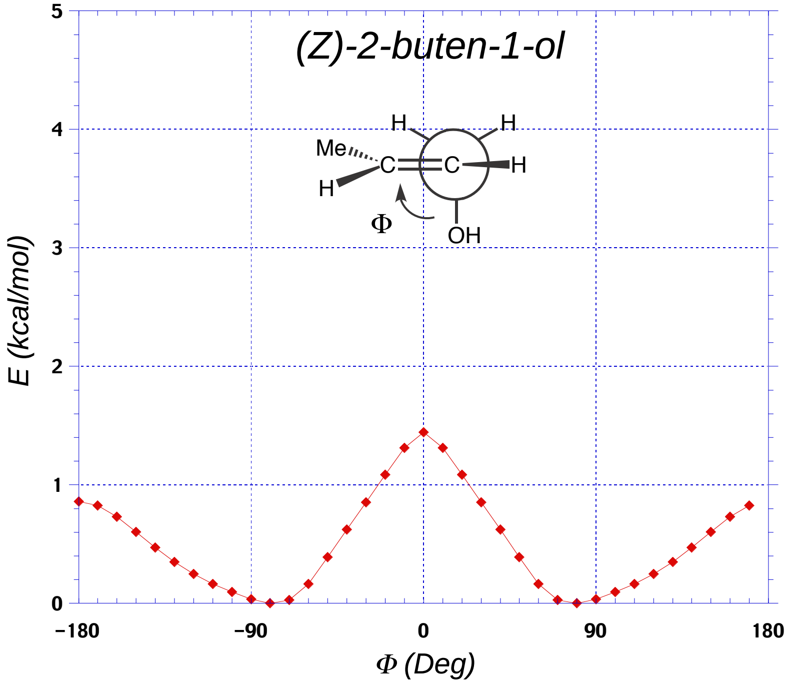
The Torsional Energy Profile

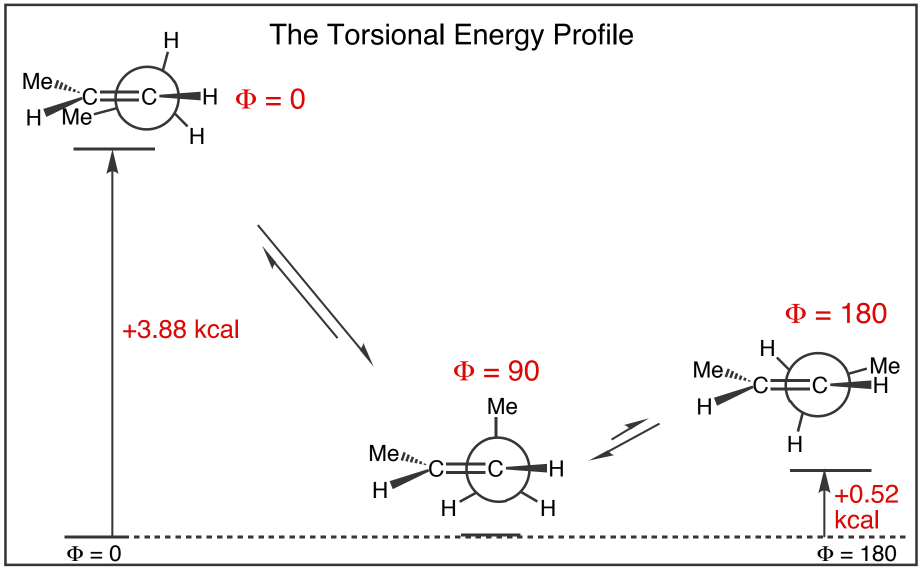


The Torsional Energy Profile

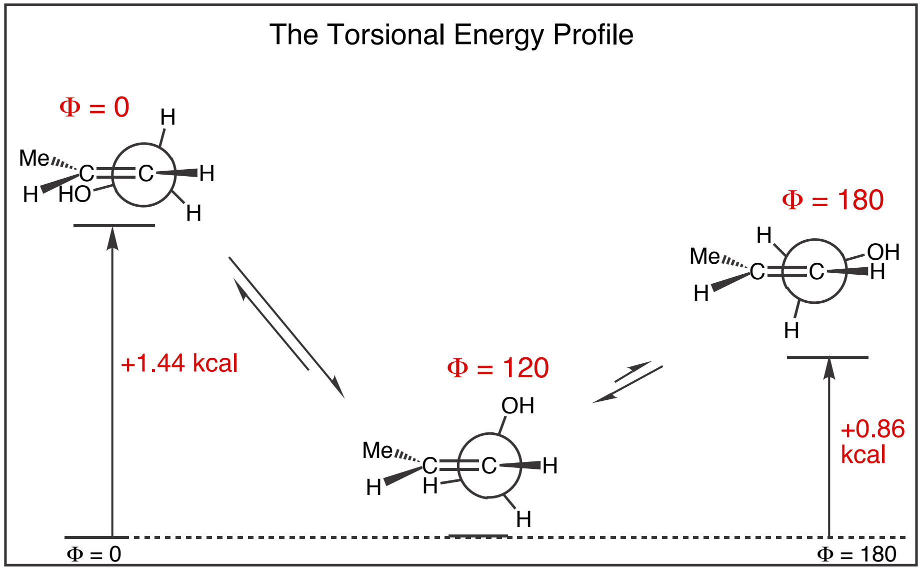
Conformational Barriers to Rotation: Olefin A-1,3 Interactions





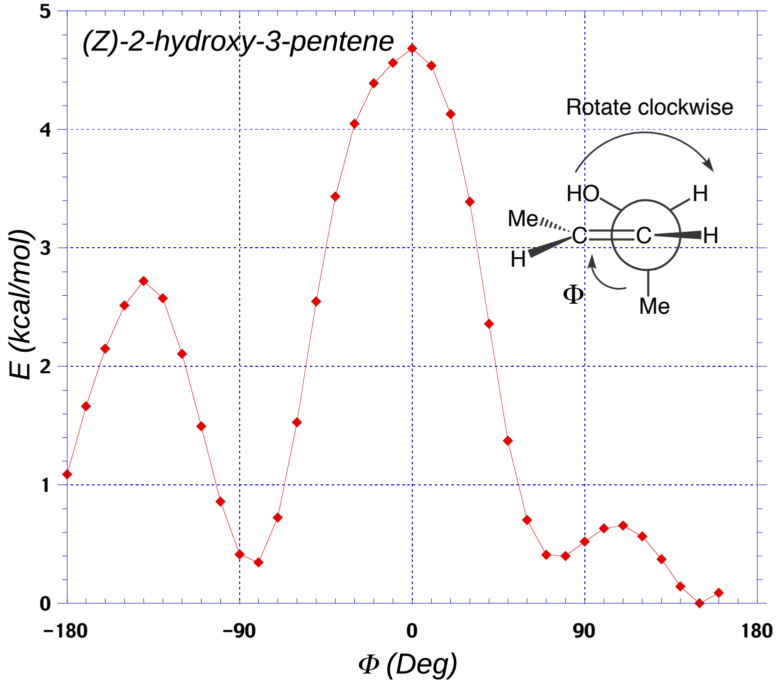


Values calculated using MM2 (molecular mechanics) force fields via the Macromodel multiconformation search.

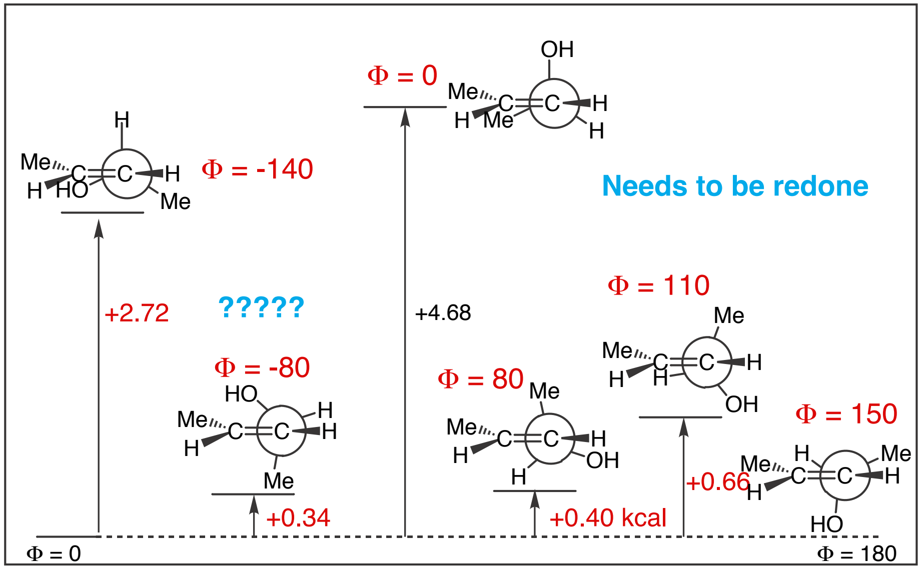


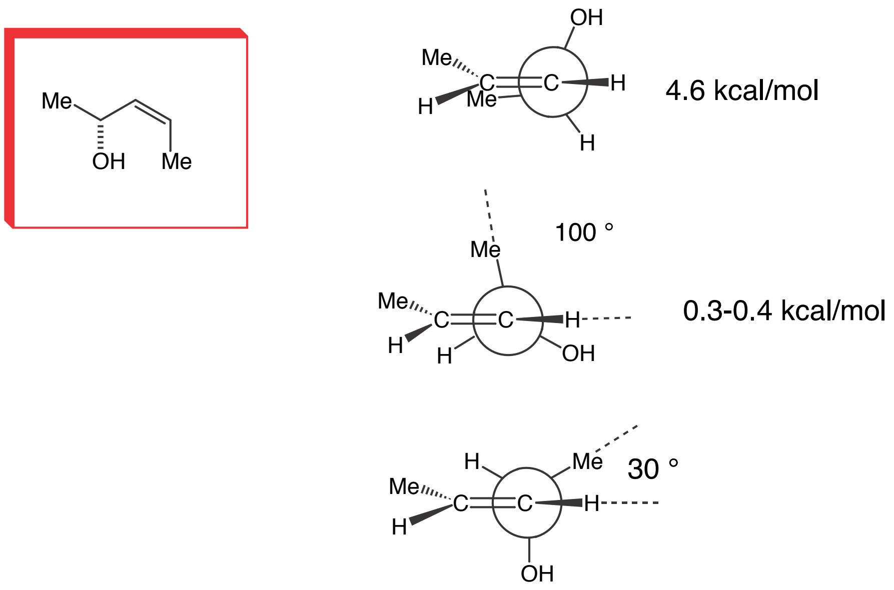
Review: Hoffman, R. W. *Chem. Rev.* **1989,** *89,* 1841.

Conformational Barriers to Rotation: Olefin A-1,3 Interactions-2

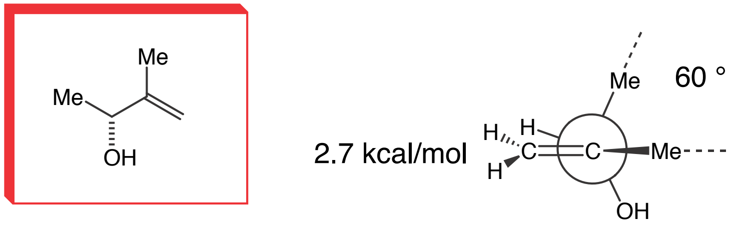


The Torsional Energy Profile

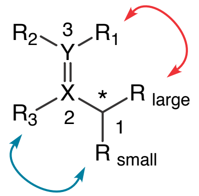




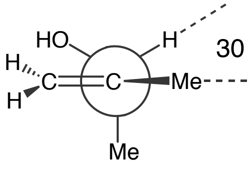
Lowest energy conformer



***A(1,3) interaction* 4.0 kcal/mol**



***A(1,2) interaction* 2.7 kcal/mol (MM2)**



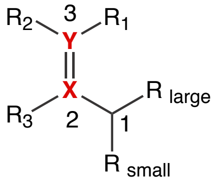
Lowest energy conformer

The Definition of Allylic Strain

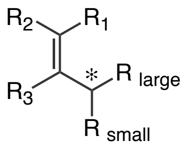
F. Johnson, *Chem. Rev.* **1968**, *68*, 375; *Allylic Strain in Six-Membered Rings*
R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841-1860 **(handout)**
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations

Houk, Hoffmann *JACS* **1991**, *113*, 5006

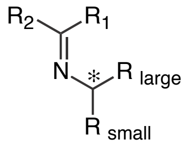
Consider the illustrated general structure where X & Y are permutations of C, N, and O:



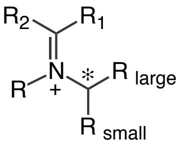
Typical examples:



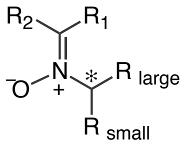
Olefin



Imine



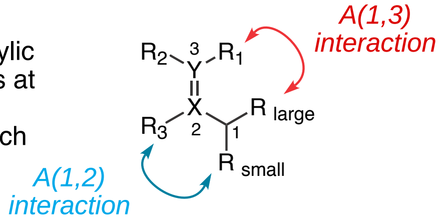
Imonium ion



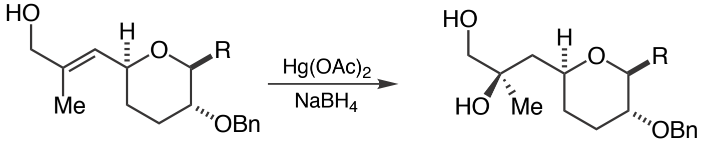
Nitrone

In the above examples, the resident allylic stereocenter (⁎) and its associated substituents frequently impart a pronounced bias towards reactions occuring at the pi-bond.

Nonbonding interactions between the allylic substituents (R_{large}, R_{small}) & substituents at the 2- & 3-positions play a critical role in defining the stereochemical course of such reactions



Representative Reactions controlled by Allylic Strain Interactions

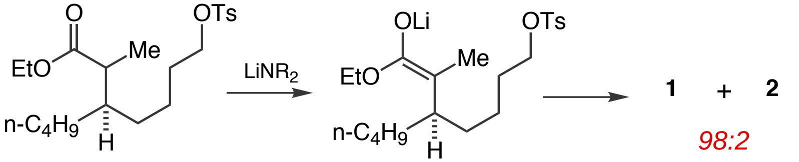


diastereoselection 10:1

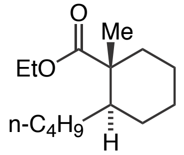
M. Isobe & Co-workers, *Tetrahedron Lett.* **1985**, *26*, 5199.

Can you predict the stereochemical outcome of this reaction?

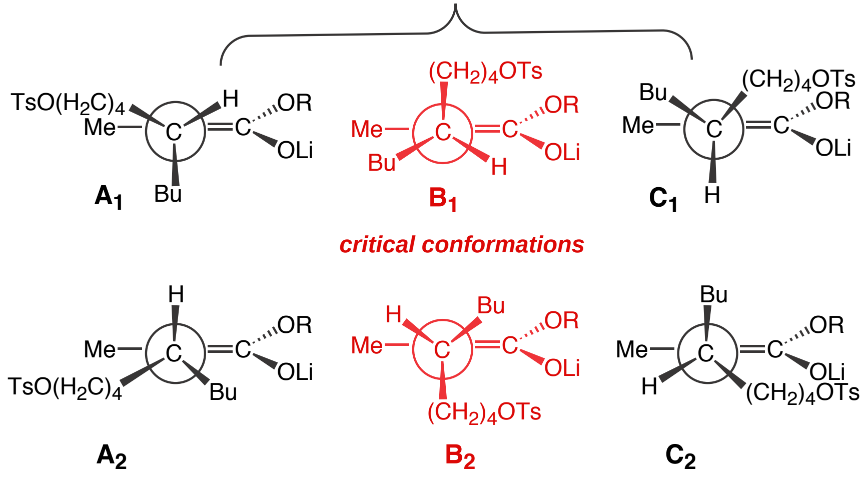
D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, *27*, 943.

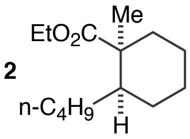


- Relevant enolate conformations



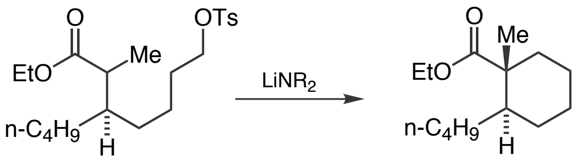
1 ***major***



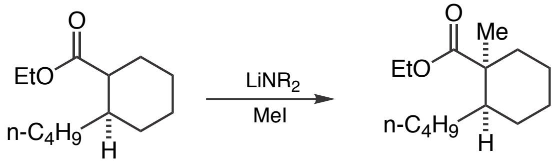


2 ***minor***

Allylic Strain & Enolate Diastereoface Selection

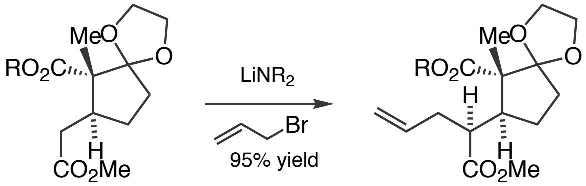


diastereoselection 98:2



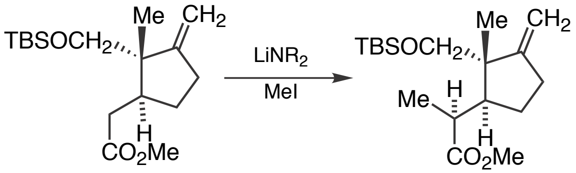
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.



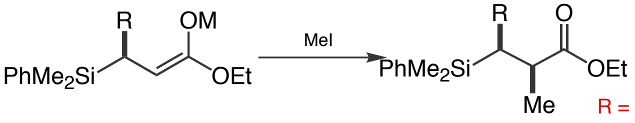
"one isomer"

G. Stork & Co-workers, *Tetrahedron Lett*. **1987**, *28*, 2088.



"one isomer"

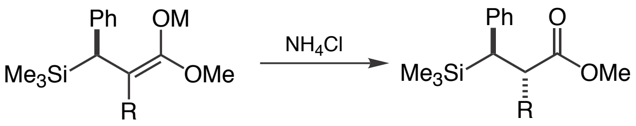
T. Money & Co-workers, *Chem. Commun*. **1986**, 288.



R = Me: *diastereoselection 99:1*

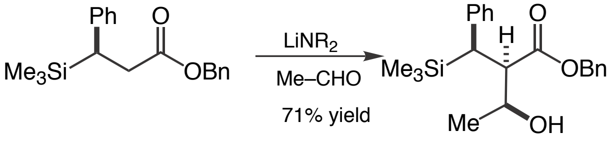
R = Ph: *diastereoselection 97:3*

I. Fleming & Co-workers, *Chem. Commun*. **1984**, 28.



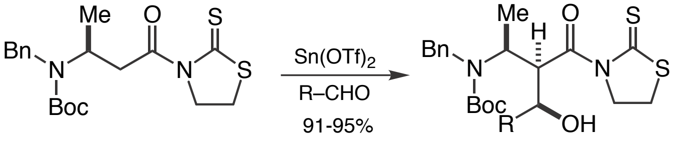
R-substituent	*diastereoselection*
R = Me	87:13
R = Et	80:20
R = $CHMe_2$	40:60 major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun*. **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun*. **1984**, 904.



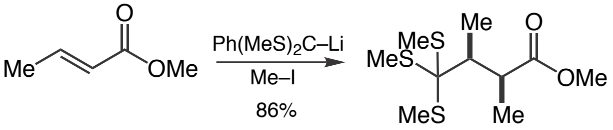
diastereoselection 90:10 at C_3
one isomer at C_2

I. Fleming & Co-workers, *Chem. Commun*. **1986**, 1198.



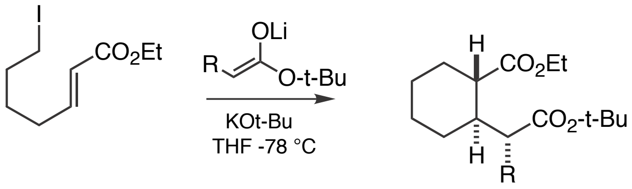
diastereoselection >95%

T. Mukaiyama & Co-workers, *Chem. Letters* **1986**, 637



diastereoselection 99:1

K. Koga & Co-workers, *Tetrahedron Letters* **1985**, *26*, 3031.

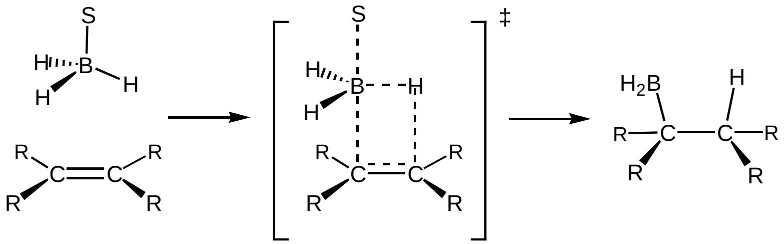


R = H: one isomer
R = Me: > 15 :1

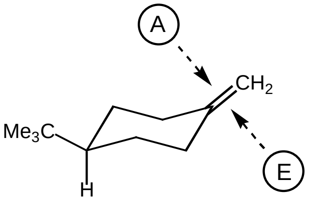
Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, *26*,1723.

Allylic Strain & Olefin Hydroboration

The basic process

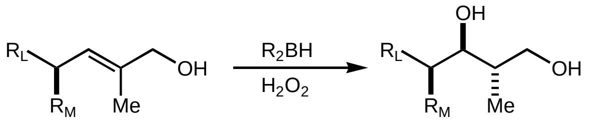


Response to steric effects: Here is a good calibration system:



Oxidant	Ratio, A:E	Reference
MCPBA	69:31	*JOC*, **1967**, *32*, 1363
BH_3, H_2O_2	34:66	*JOC*, **1970**, *35*, 2654

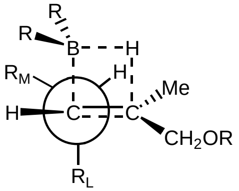
Acyclic hydroboration can be controlled by A(1,3) interactions:

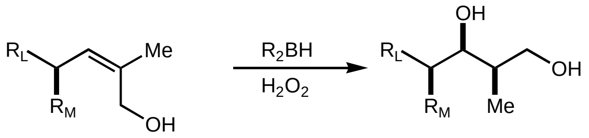


major diastereomer

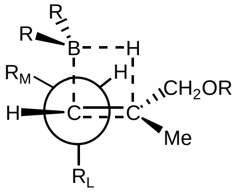
control elements

A(1,3) allylic strain
Steric effects; R_L vs R_M
Staggered transition states



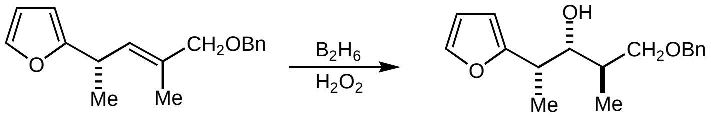


major diastereomer

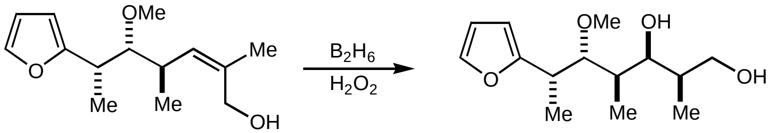


See Houk, *Tetrahedron* **1984**, *40*, 2257

Hydroborations dominated by A(1,3) Strain

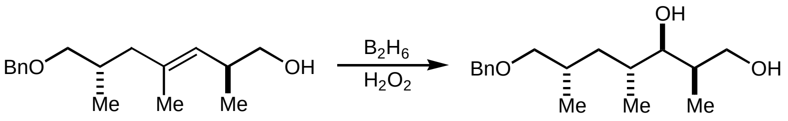


diastereoselection 8:1



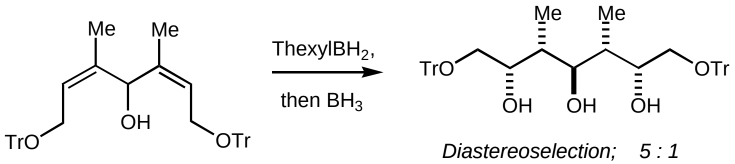
diastereoselection 12:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1979**, *101*, 259.

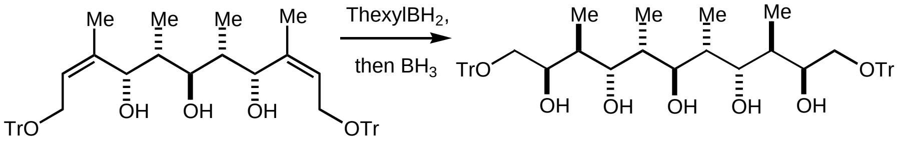


Diastereoselection = 3:1

C. H. Heathcock et. al. *Tetrahedron Lett* **1984** *25* 243.



Diastereoselection;   5 : 1

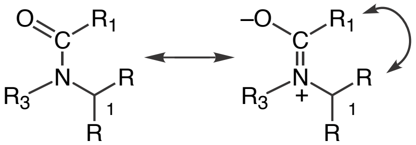


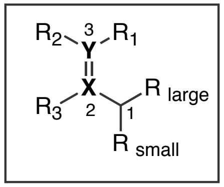
Diastereoselection;   4: 1

Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

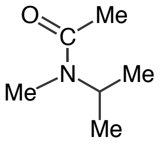
Allylic Strain & Amide Conformation

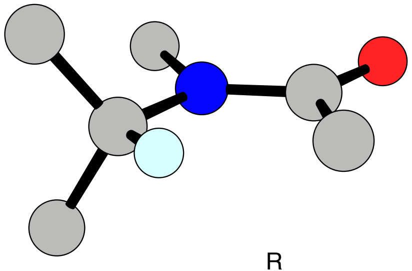
Consider the resonance structures of an amide:



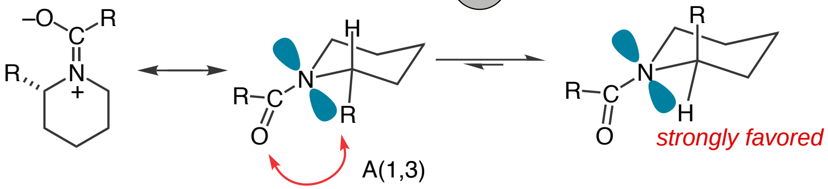


A(1,3) interactions between the "allylic substituent" and the R1 moiety will strongly influence the torsion angle between N & C1.

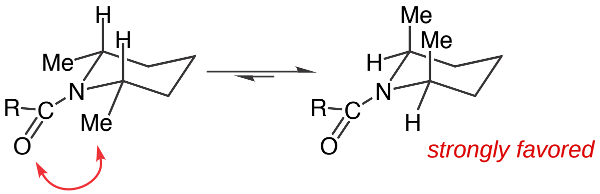


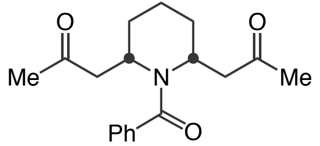


■ conformations of cyclic amides



Chow
Can. J. Chem. **1968**, *46*, 2821



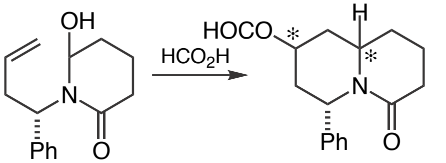


published X-ray structure of this amide shows chair diaxial conformation

Quick, *J. Org. Chem.* **1978**, *43*, 2705

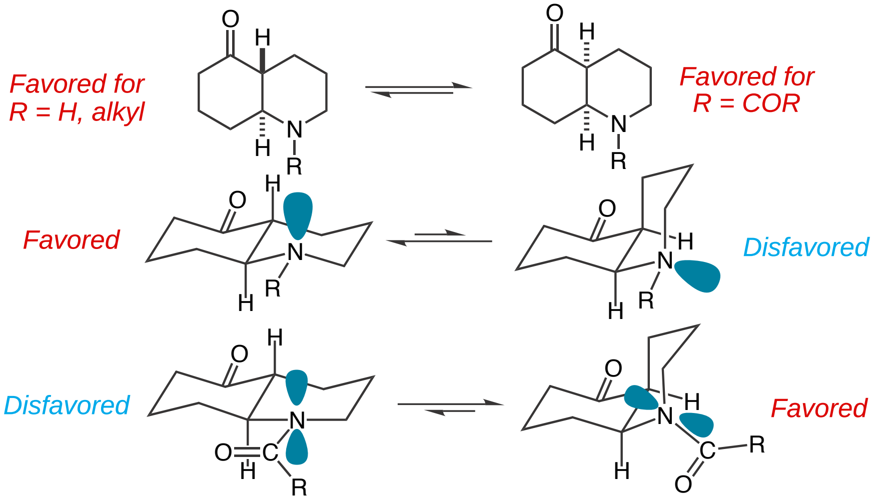
■ Problem: Predict the stereochemical outcome of this cyclization.

D. Hart, *JACS* **1980**, *102*, 397

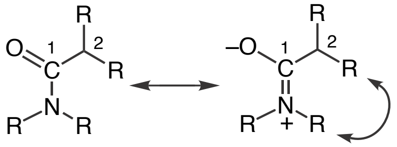


diastereoselection >95%

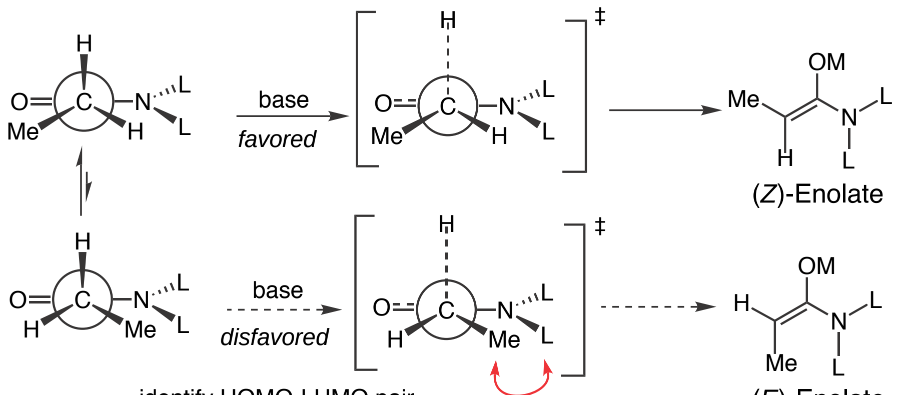
The selection of amide protecting group may be done with the knowledge that altered conformational preferences may result:



A(1,3) interaction between the C2 & amide substituents will strongly influence the torsion angle between C1 & C2.

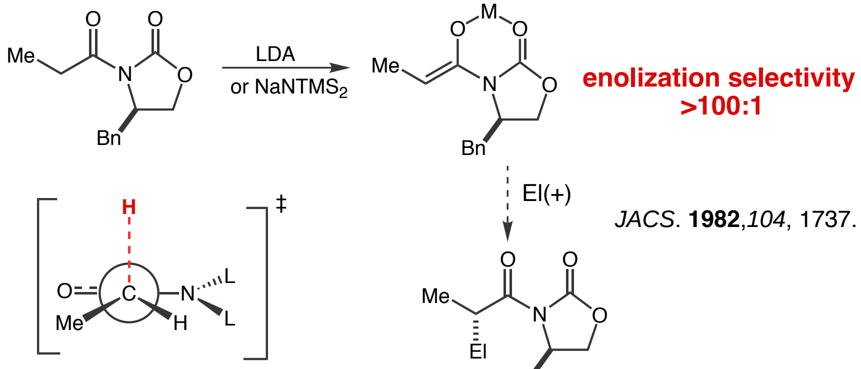


As a result, amides afford (Z) enolates under all conditions



identify HOMO-LUMO pair

A(1,3) Strain and Chiral Enolate Design

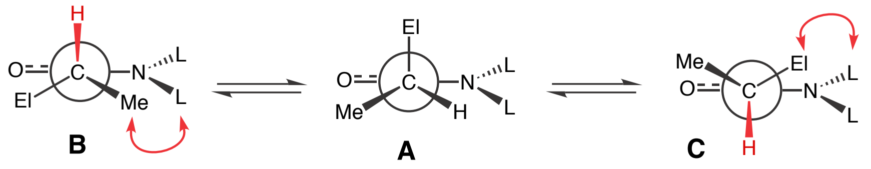


enolization selectivity >100:1

JACS. **1982**,*104*, 1737.

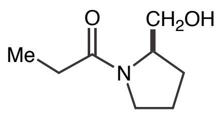
favored
enolization geometry

- In the enolate alkylation process product epimerization is a serious problem. Allylic strain suppresses product enolization through the intervention of allylic strain

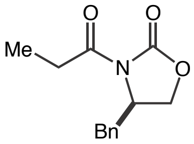


While conformers **B** and **C** meet the stereoelectronic requirement for enolization, they are much higher in energy than conformer **A**. Further, as deprotonation is initiated, A(1,3) destabilization contributes significantly to reducing the kinetic acidity of the system

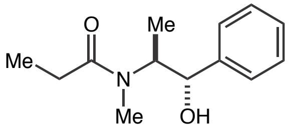
These allylic strain attributes are an integral part of the design criteria of chiral amide and imide-based enolate systems



Evans
Tetr Lett. **1977**, *29*, 2495

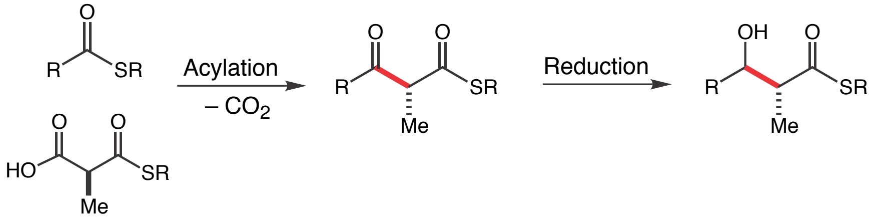


Evans
JACS **1982**,*104*, 1737.

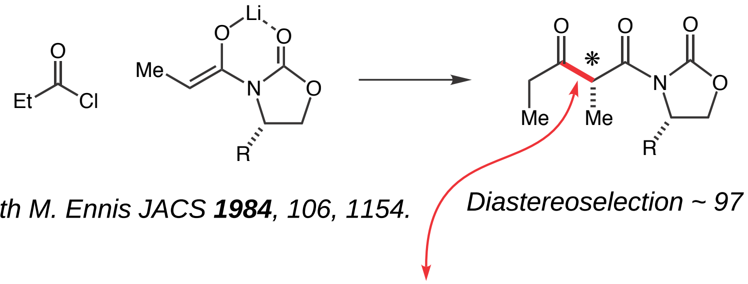


Myers
JACS **1997**, *119*, 6496

Polypropionate Biosynthesis: The Acylation Event



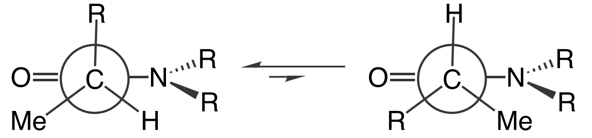
First laboratory analogue of the acylation event



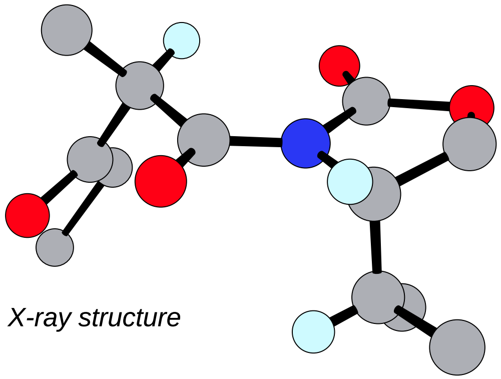
*with M. Ennis JACS **1984**, 106, 1154.*

Diastereoselection ~ 97 : 3

Why does'nt the acylation product rapidy epimerize at the exocyclic stereocenter??

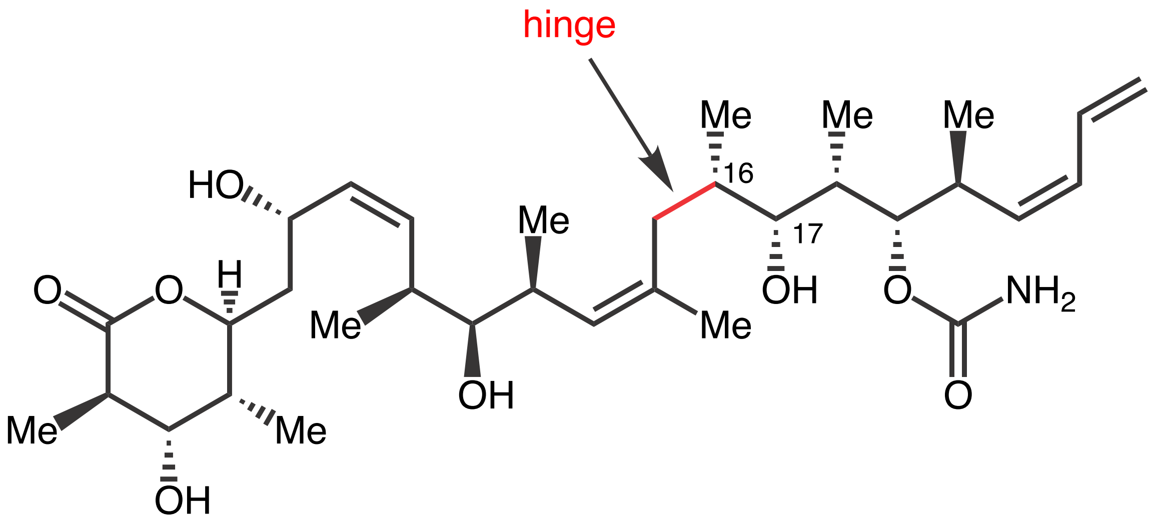


favored



X-ray structure

Discodermolide



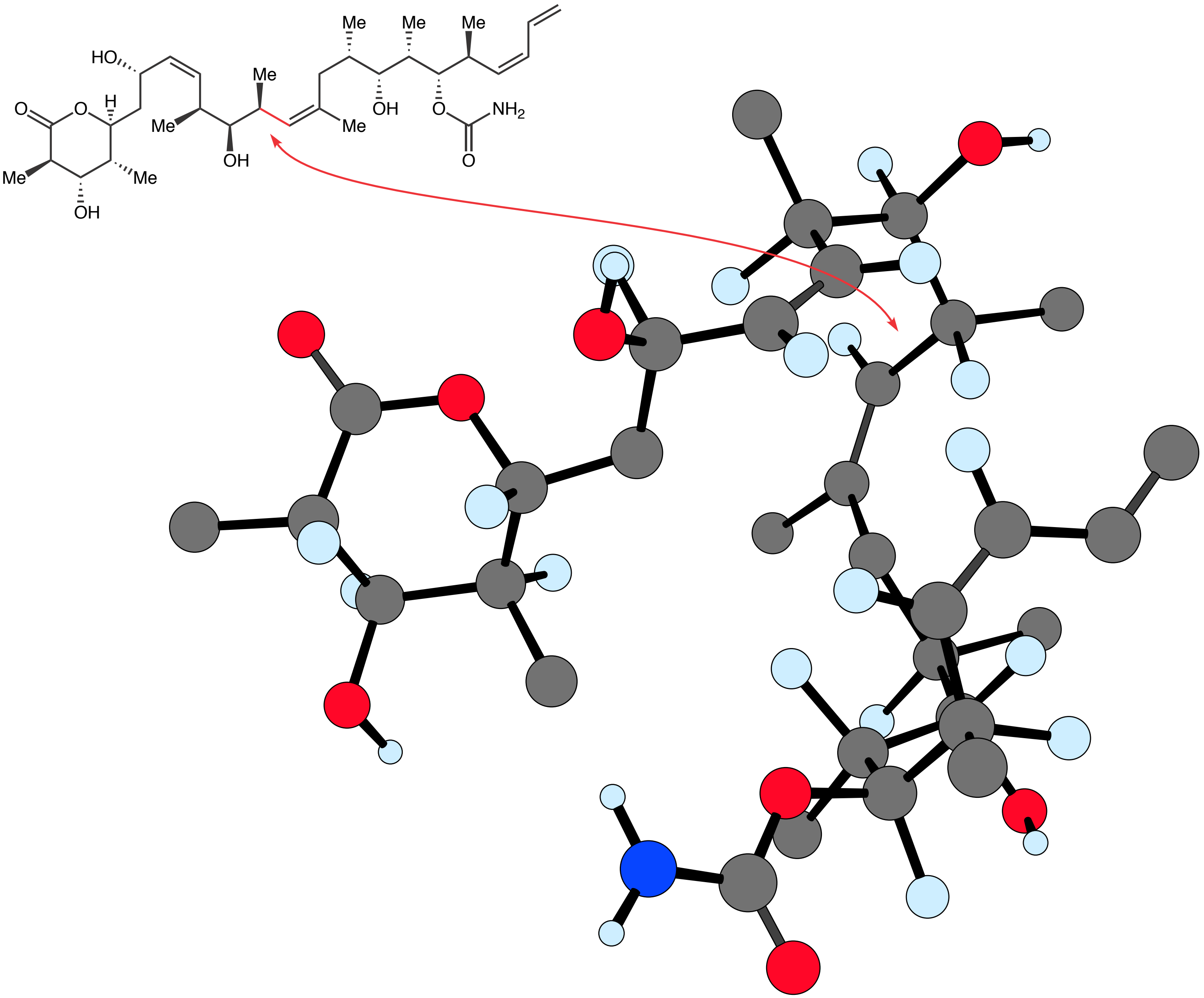
- immunosuppressive activity
- potent microtubule-stabilizing agent
(antitumor activity similar to that of taxol)

The epimers at C16 and C17 have no or almost no biological activity.

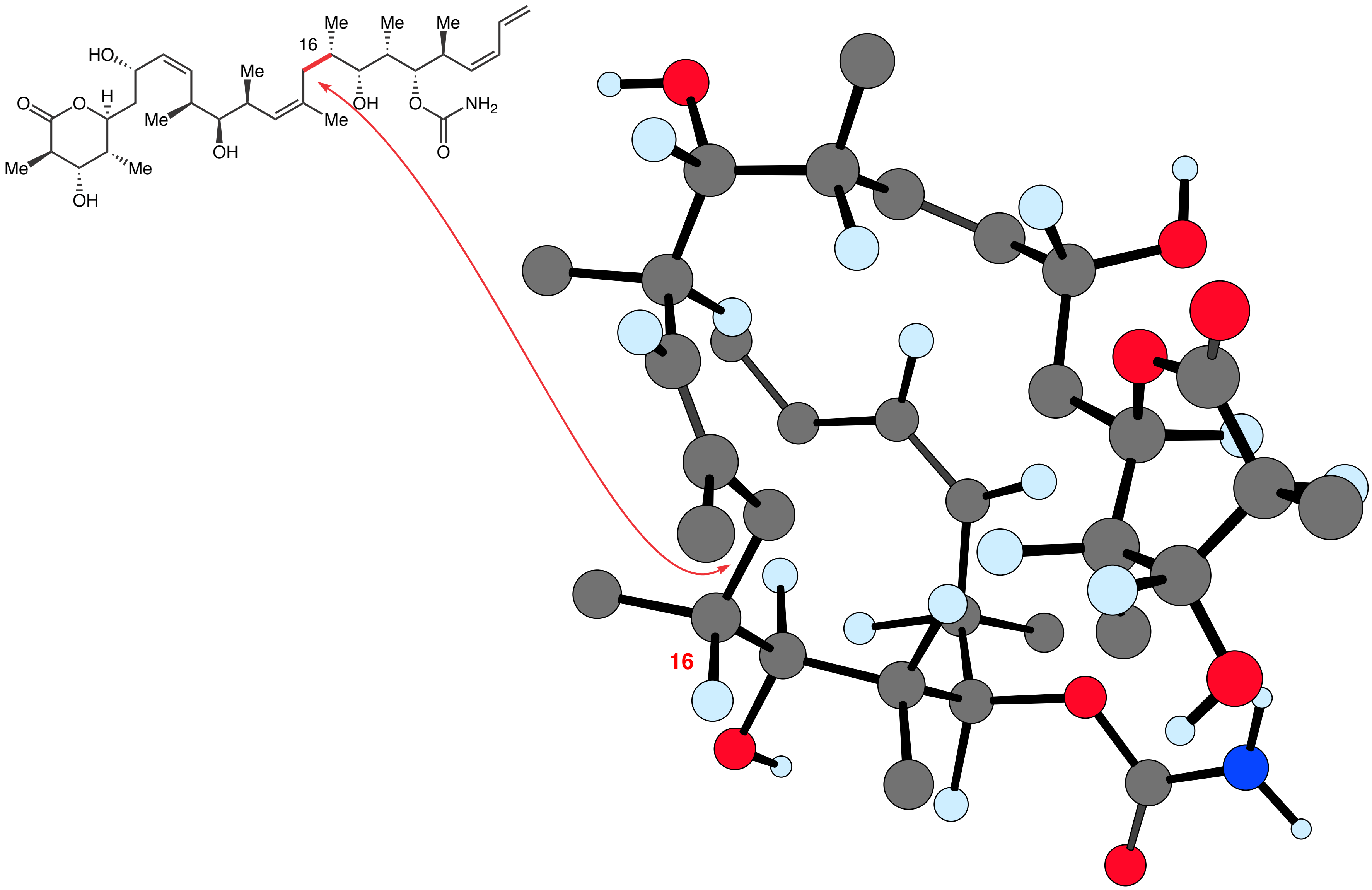
The conformation about C16 and C17 is critical to discodermolide's biological activity.

S. L. Schreiber et al. *JACS* **1996**, *118*, 11061.

Conformational Analysis - Discodermolide X-ray 1



Conformational Analysis - Discodermolide X-ray 2



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 6

Conformational Analysis-3

- Conformational Analysis of $C_4 \rightarrow C_6$ Rings

- Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapter 3

Eliel & Wilen, "Stereochemistry of Organic Compounds, "Chapter 11, Configuration and Conformation of Cyclic Molecules, Wiley, 1994

Ribeiro & Rittner, "The Role of Hyperconjugation in the Conformational Analysis of Methylcyclohexane and Methylheterocyclohexanes" *J. Org. Chem.*, **2003**, *68*, 6780-6787 **(handout)**

de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics" *Angew Chem. Int. Ed.* **1979**, *18*, 809-826

D. A. Evans

Friday,
September 26, 2003

Conformational Analysis of Cyclic Systems

Three Types of Strain:

Prelog Strain: van der Waals interactions

Baeyer Strain: bond angle distortion away from the ideal

Pitzer Strain: torsional rotation about a sigma bond

Baeyer Strain for selected ring sizes

size of ring	Ht of Combustion (kcal/mol)	Total Strain (kcal/mol)	Strain per CH_2 (kcal.mol)	"angle strain" deviation from 109°28'
3	**499.8**	**27.5**	9.17	24°44'
4	656.1	26.3	6.58	9°44'
5	793.5	6.2	1.24	0°44'
6	**944.8**	**0.1**	0.02	-5°16'
7	1108.3	6.2	0.89	
8	1269.2	9.7	1.21	
9	**1429.6**	**12.6**	1.40	
10	**1586.8**	**12.4**	1.24	
11	**1743.1**	**11.3**	1.02	
12	1893.4	4.1	0.34	
13	2051.9	5.2	0.40	
14	2206.1	1.9	0.14	
15	2363.5	1.9	0.13	

Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds* Chapter 11, John Wiley & Sons, 1994.

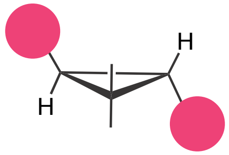
- Baeyer "angle strain" is calculated from the deviation of the *planar* bond angles from the ideal tetrahedral bond angle.

- Discrepancies between calculated strain/CH_2 and the "angle strain" results from puckering to minimize van der Waals or eclipsing torsional strain between vicinal hydrogens.

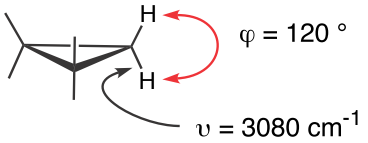
- Why is there an increase in strain for medium sized rings even though they also can access puckered conformations free of angle strain? The answer is *transannular strain*- van der Waals interactions between hydrogens across the ring.

Cyclopropane: Bonding, Conformation, Carbonium Ion Stabilization

Cyclopropane



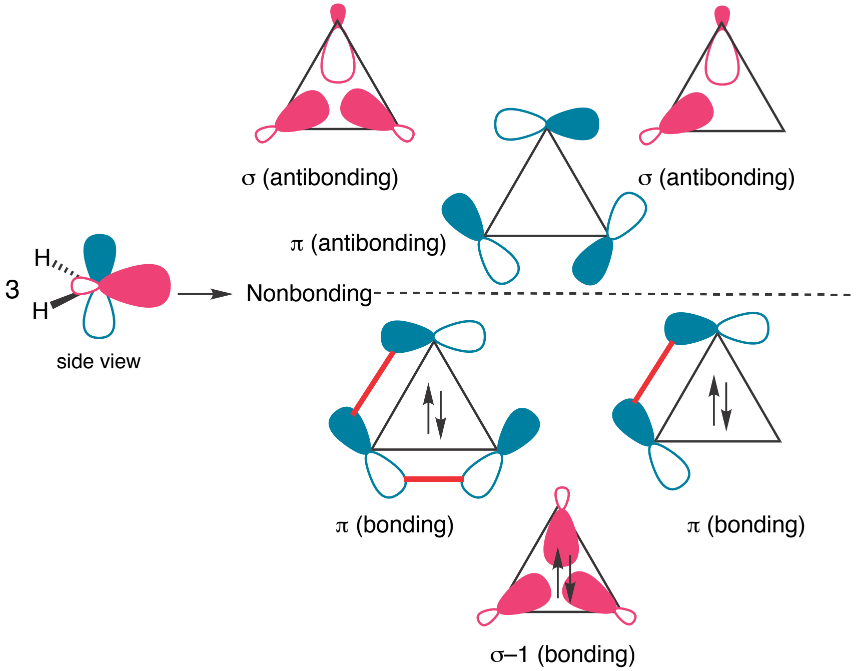
- Necessarily *planar*.
- Subtituents are therefore eclipsed.
- Disubstitution prefers to be *trans.*



- Almost sp^2, not sp^3

Walsh Model for Strained Rings:

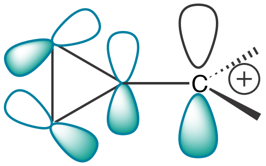
- Rather than σ and σ* c-c bonds, cyclopropane has sp^2 and p-type orbitals instead.



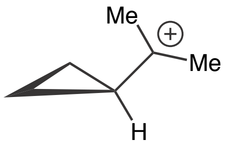
de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics" *Angew Chem. Int. Ed.* **1979**, *18*, 809-826 (handout)

de Meijere, A.; Wessjohann, L. "Tailoring the Reactivity of Small Ring Building Blocks for Organic Synthesis." *Synlett* **1990**, 20.

Carbocation Stabilization via Cyclopropylgroups

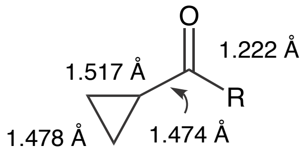


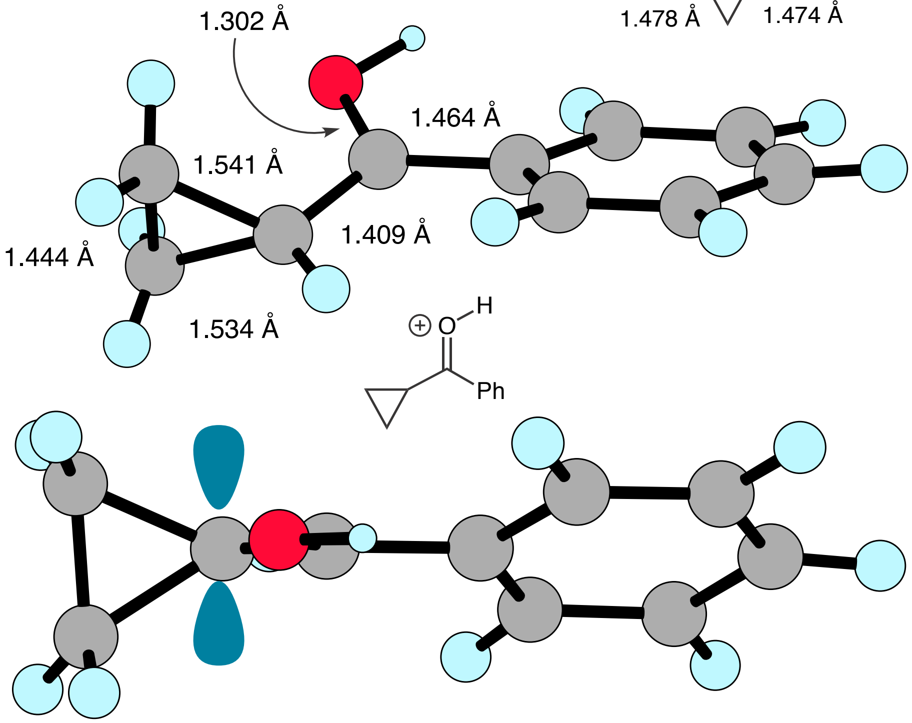
A rotational barrier of about 13.7 kcal/mol is observed in following example:



NMR in super acids δ(CH_3) = 2.6 and 3.2 ppm

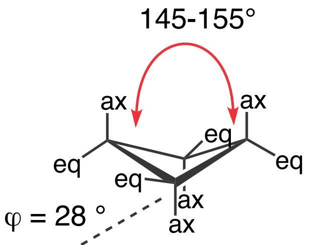
X-ray Structures support this orientation





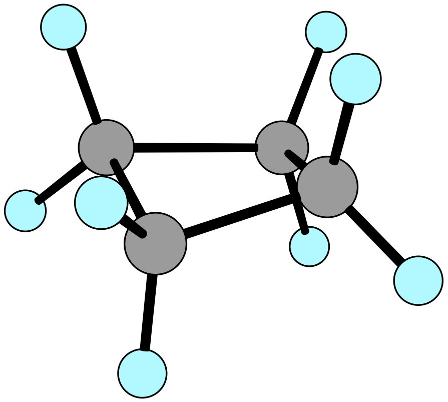
R. F. Childs, *JACS* **1986**, *108*, 1692

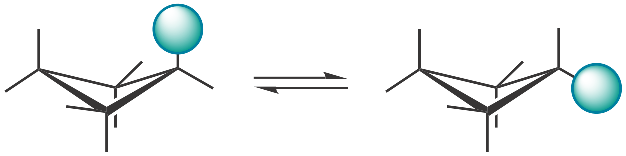
Cyclobutane



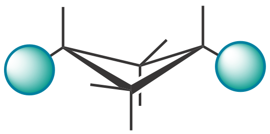
■ Eclipsing torsional strain overrides increased bond angle strain by puckering.

■ Ring barrier to inversion is 1.45 kcal/mol.

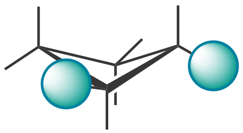

(MM2)



■ ΔG = 1 kcal/mol favoring R = Me equatorial

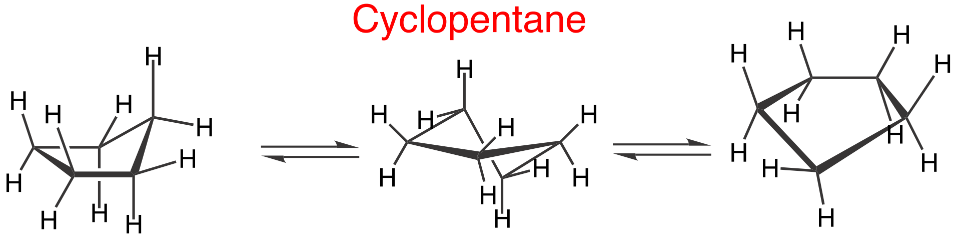


■ 1,3 Disubstitution prefers *cis* diequatorial to *trans* by 0.58 kcal/mol for di-bromo cmpd.



■ 1,2 Disubstitution prefers *trans* diequatorial to *cis* by 1.3 kcal/mol for diacid (roughly equivalent to the cyclohexyl analogue.)

Cyclopentane

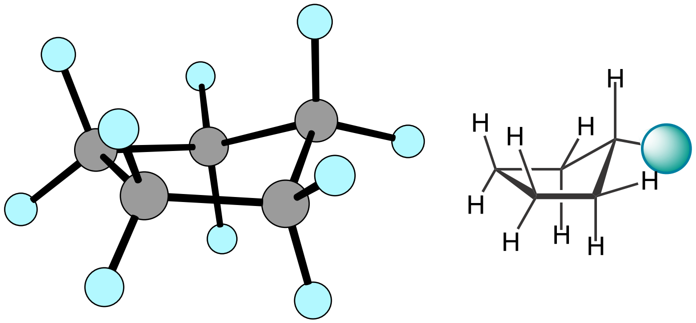

C$_s$ Envelope C$_2$ Half-Chair C$_s$ Envelope

■ Two lowest energy conformations (10 envelope and 10 half chair conformations C$_s$ favored by only 0.5 kcal/mol) in rapid conformational flux (pseudorotation) which causes the molecule to appear to have a single out-of-plane atom "bulge" which rotates about the ring.

■ Since there is no "natural" conformation of cyclopentane, the ring conforms to minimize interactions of any substituents present.

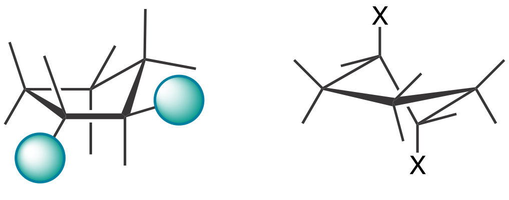
C$_s$ Envelope

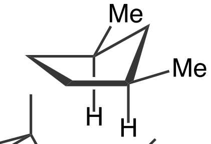
(MM2)



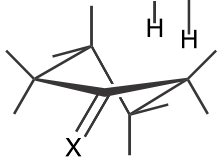
■ A single substituent prefers the equatorial position of the flap of the envelope (barrier ca. 3.4 kcal/mol, R = CH$_3$).

■ 1,2 Disubstitution prefers *trans* for steric/torsional reasons (alkyl groups) and dipole reasons (polar groups).





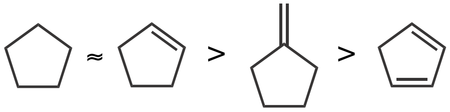
■ 1,3 Disubstitution: **Cis**-1,3-dimethyl cyclopentane 0.5 kcal/mol **more stable** than trans.



■ A carbonyl or methylene prefers the planar position of the half-chair (barrier 1.15 kcal/mol for cyclopentanone).

Methylenecyclopentane and Cyclopentene

Strain trends:

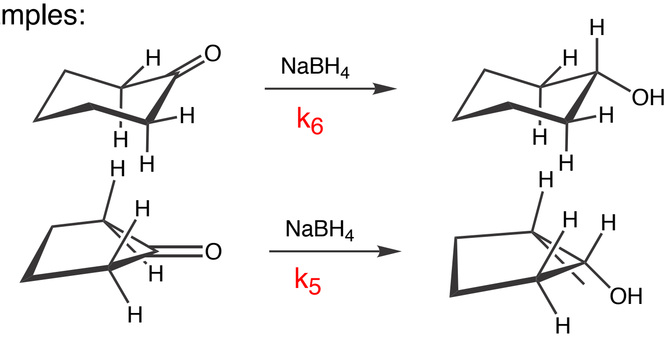


■ Decrease in eclipsing strain more than compensates for the increase in angle strain.

Relative to cyclohexane derivatives, those of cyclopentane prefer an sp^2 center in the ring to minimize eclipsing interactions.

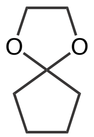
"Reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in the 5-ring and to avoid the formation or retention of the exo double bond in the 6-ring systems." Brown, H. C., Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.

Examples:

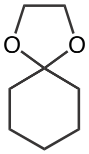


$\frac{k_6}{k_5}$ = 23

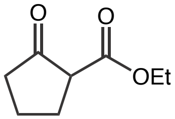
Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.



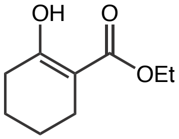
hydrolyzes
13 times faster than



Conan, J-Y.; Natat, A.; Priolet, D. *Bull. Soc. Chim., Fr.* **1976**, 1935.



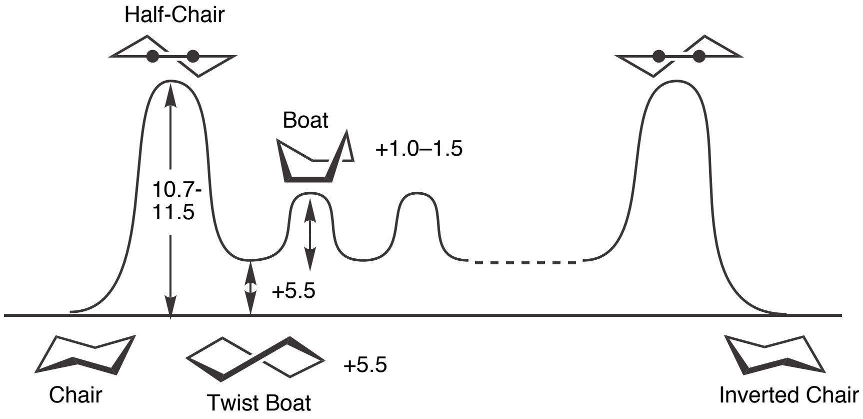
95.5:4.5 keto:enol

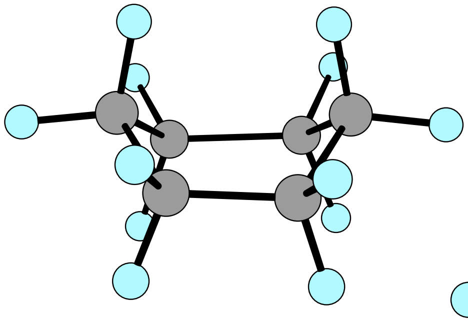


76:24 enol:keto

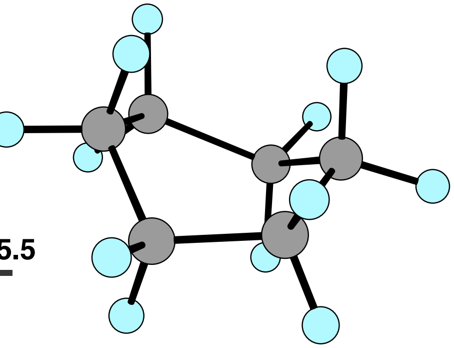
Brown, H. C., Brewster, J. H.; Shechter, H. *JACS* **1954**, *76*, 467.

Cyclohexane Energy Profile (kcal/mol)



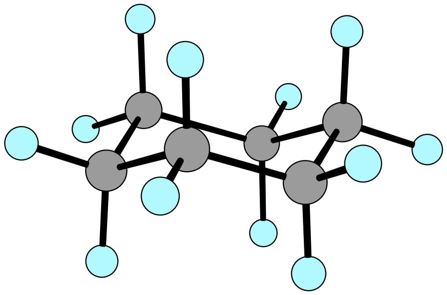


ΔE = +6.5-7.0



ΔE = +5.5

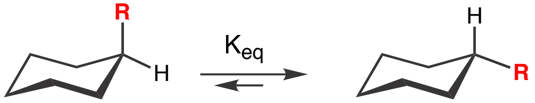
The barrier: +10.7-11.5



E = 0

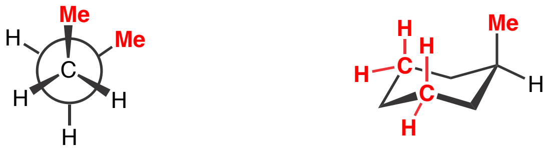
Conformational Analysis: Cyclic Systems-4

Monosubstituted Cyclohexanes: *A* Values



$\Delta G° = -RT\ln K_{eq}$

- Me–axial has **2 gauche butane interactions** more than Me–equatorial.
  Expected destabilization: ≈ 2(0.88) kcal/mol = ~1.8 kcal/mol;
  Observed: 1.74 kcal/mol



- The *A*– Value, or -ΔG°, is the preference of the substituent for the equatorial position.

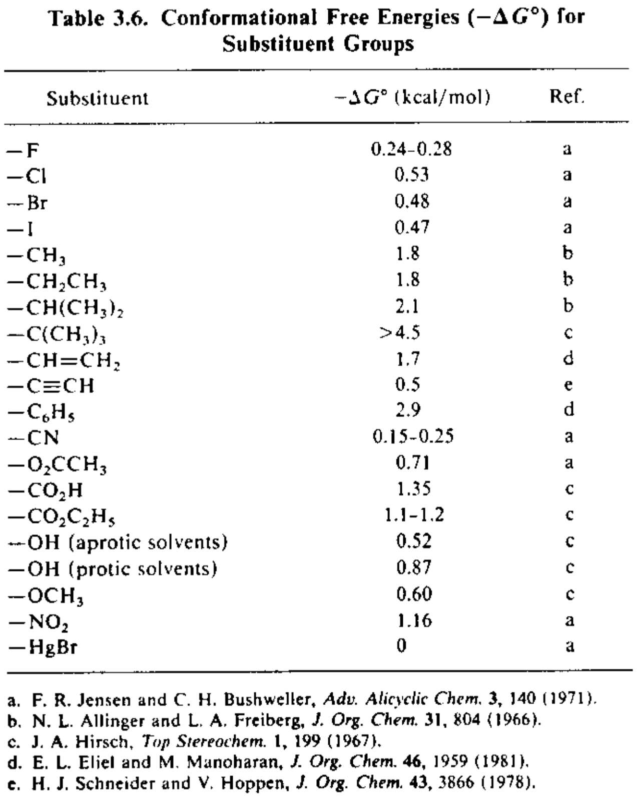
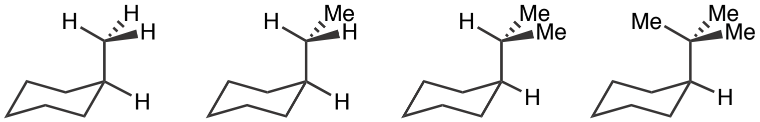


Table 3.6. Conformational Free Energies ($-\Delta G°$) for Substituent Groups

Substituent	$-\Delta G°$ (kcal/mol)	Ref.
$-F$	0.24–0.28	a
$-Cl$	0.53	a
$-Br$	0.48	a
$-I$	0.47	a
$-CH_3$	1.8	b
$-CH_2CH_3$	1.8	b
$-CH(CH_3)_2$	2.1	b
$-C(CH_3)_3$	>4.5	c
$-CH{=}CH_2$	1.7	d
$-C{\equiv}CH$	0.5	e
$-C_6H_5$	2.9	d
$-CN$	0.15–0.25	a
$-O_2CCH_3$	0.71	a
$-CO_2H$	1.35	c
$-CO_2C_2H_5$	1.1–1.2	c
$-OH$ (aprotic solvents)	0.52	c
$-OH$ (protic solvents)	0.87	c
$-OCH_3$	0.60	c
$-NO_2$	1.16	a
$-HgBr$	0	a

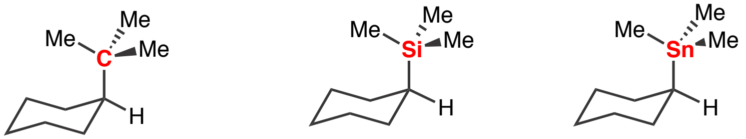
a. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.* **3**, 140 (1971).
b. N. L. Allinger and L. A. Freiberg, *J. Org. Chem.* **31**, 804 (1966).
c. J. A. Hirsch, *Top Stereochem.* **1**, 199 (1967).
d. E. L. Eliel and M. Manoharan, *J. Org. Chem.* **46**, 1959 (1981).
e. H. J. Schneider and V. Hoppen, *J. Org. Chem.* **43**, 3866 (1978).

A Values depend on the *relative size* of the particular substituent.



A–Value 1.74 1.80 2.15 5.0

The "relative size" of a substituent and the associated A-value may not correlate. For example, consider the $-CMe_3$ and $-SiMe_3$ substituents. While the $-SiMe_3$ substituent has a larger covalent radius, it has a smaller A-value:

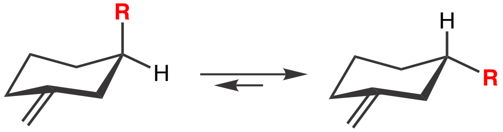


A–Value 4.5-5.0 2.5 1.1

Can you explain these observations?

- The impact of double bonds on A-values:

Lambert, *Accts. Chem. Res.* **1987**, *20*, 454



substituent	$-\Delta G°$	A-value (cyclohexane)
R = Me	0.8	1.74
R = OMe	0.8	0.6
R = OAc	0.6	0.71

The Me substituent appears to respond strictly to the decrease in nonbonding interactions in axial conformer. With the more polar substituents, electrostatic effects due to the trigonal ring carbon offset the decreased steric environment.

Rigberio & Rittner, “The Role of Hyperconjugation in the Conformational Analysis of Methylcyclohexane and Methylheterocyclohexanes”
JOC **2003**, *68*, 6780

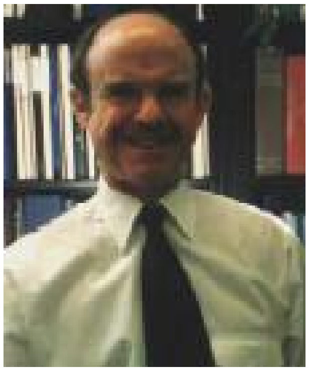
Commentary by Ken Houk University of California, Los Angeles

Department of Chemistry

Dear David,

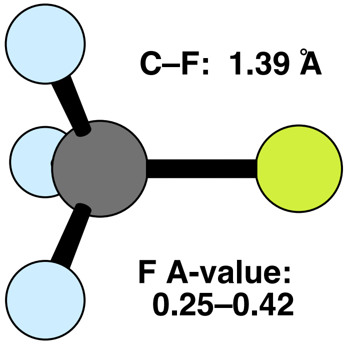
“The calculations in the Ribeiro article look fine, but I am not convinced by the interpretation. It does seem to work pretty well for many systems, but not obviously for the isomeric 1,3-dioxane cases they note early on. There seems no explanation of why C–H hyperconjugates better than C–C. Further, the results with alkyls larger than methyl still require traditional steric arguments. I would say that the equatorial methyl preference has been attributed in part to hyperconjugative effects that occur when the CH bonds are anti-periplanar. But I would not yet go much beyond that!

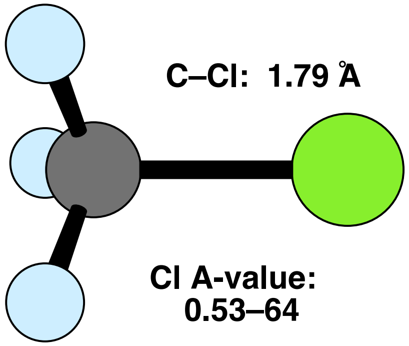
Best regards,

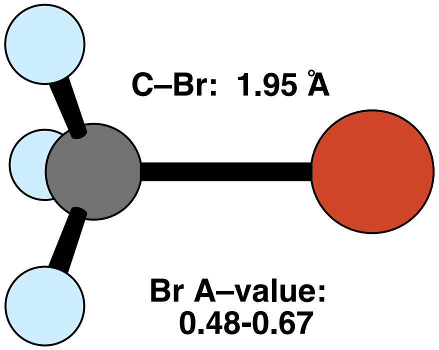


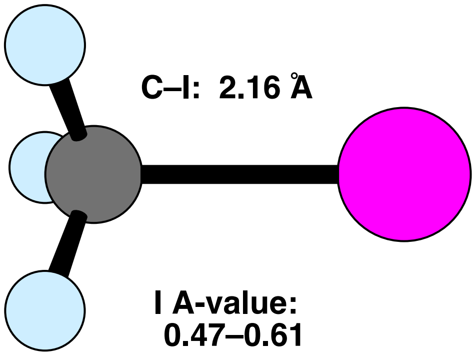
(b. 1943) **A.B. 1964, Ph.D. 1968, Harvard University**; Assistant-Full Professor, Louisiana State University, 1968-1980; Alfred P. Sloan Fellow, 1975-1977; Camille and Henry Dreyfus Teacher-Scholar, 1972-1977; LSU Distinguished Research Master, 1978; Professor, University of Pittsburgh, 1980-1985; Alexander von Humboldt Senior U.S. Scientist Award, 1982; Akron Section, American Chemical Society Award, 1983; Arthur C. Cope Scholar Award, 1988; Director, Chemistry Division, National Science Foundation, 1988-1990; James Flack Norris Award in Physical Organic Chemistry, 1991; Schrödinger Medal, World Association of Theoretically Oriented Chemists, 1998; Tolman Medal, Southern California Section, American Chemical Society, 1999; Fellow of the American Academy of Arts and Sciences, 2002; American Chemical Society Award for Computers in Chemical and Pharmaceutical Research, 2003; International Academy of Quantum Molecular Science, 2003.

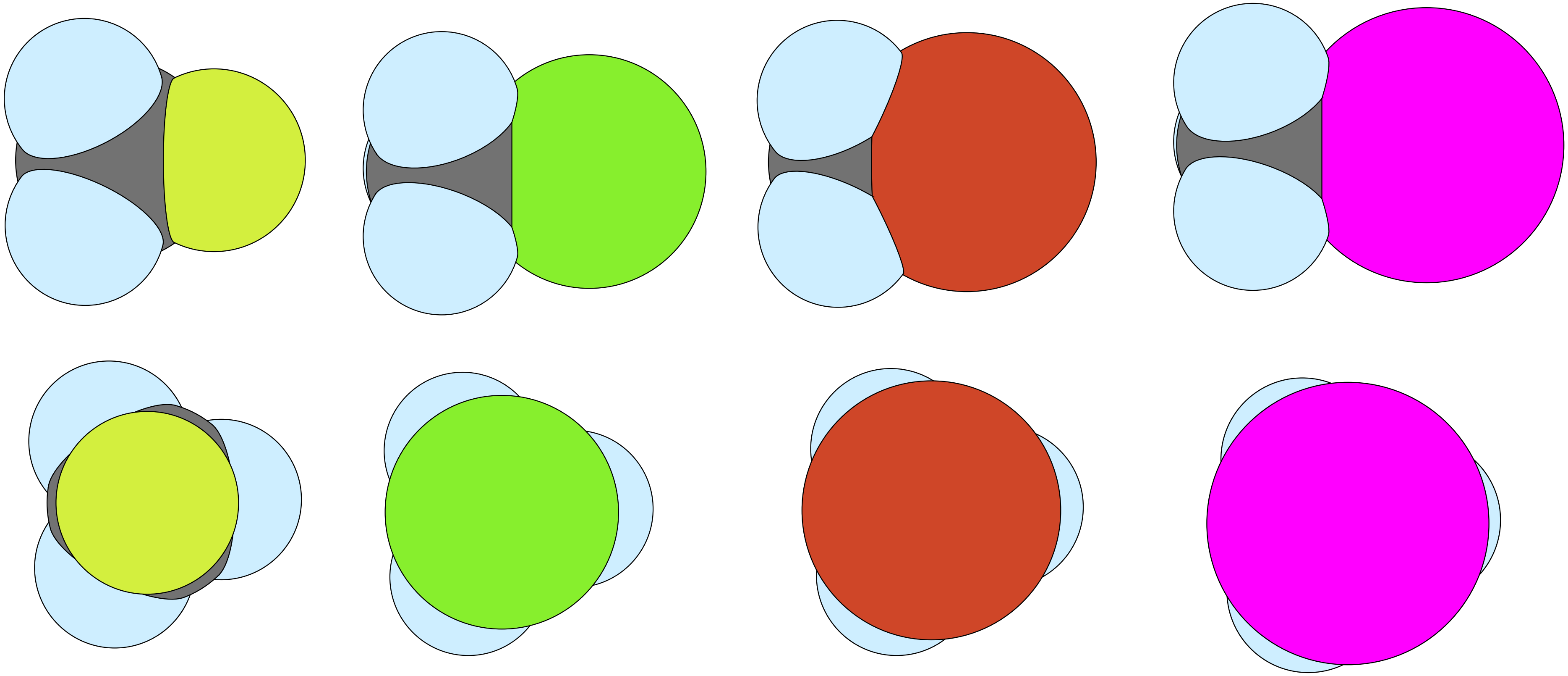
Bond Lengths and A-Values of Methyl Halides







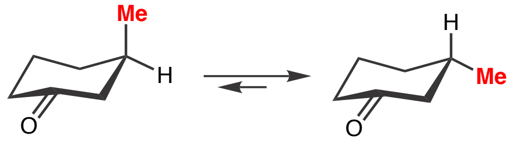




Chem 3D Pro (Verson 5.0)

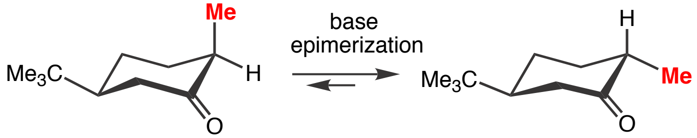
The impact of trigonal Carbon

- Let's now compare look at the carbonyl analog in the 3-position



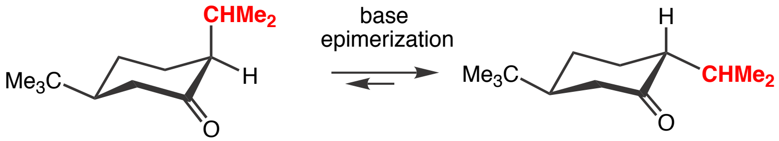
ΔG° = –1.36 kcal/mol
versus –1.74 for cyclohexane

- Let's now compare look at the carbonyl analog in the 2-position

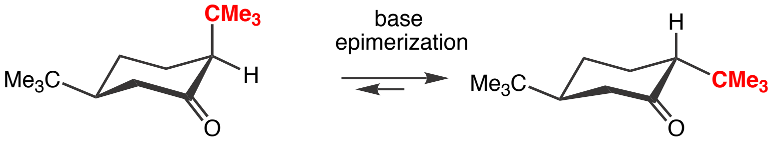


ΔG° = –1.56 kcal/mol
versus –1.74 for cyclohexane

However, the larger alkyl groups do not follow the expected trend. Can you explain? (see Eliel, page 732)



ΔG° = –0.59 kcal/mol
versus –2.15 for cyclohexane

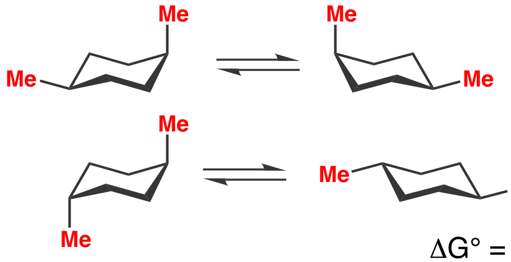


ΔG° = –1.62 kcal/mol
versus –5.0 for cyclohexane

Polysubstituted Cyclohexane *A* Values

- As long as the substituents on the ring do not interact in either conformation, their A-values are roughly additive

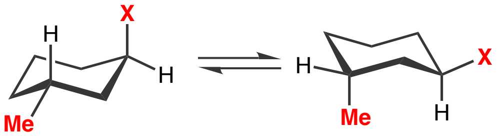
1,4 Disubstitution: *A* Values are roughly additive.



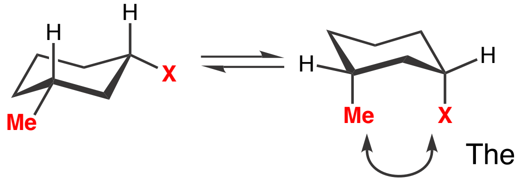
ΔG° = 0 kcal/mol

ΔG° = –2(1.74) = –3.48 kcal/mol

1,3 Disubstitution: *A* Values are only additive in the trans diastereomer

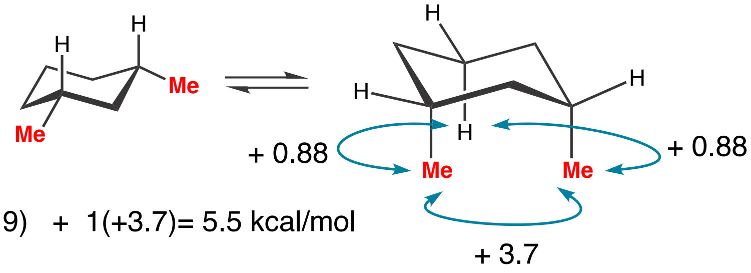


ΔG° = A(Me) – A(X)



The new interaction!

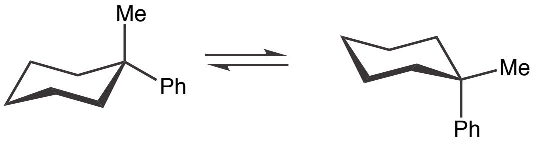
For X = Me



ΔG° = 2(.9) + 1(+3.7)= 5.5 kcal/mol

Conformational Analysis: Cyclic Systems-6

Let's now consider geminal substitution



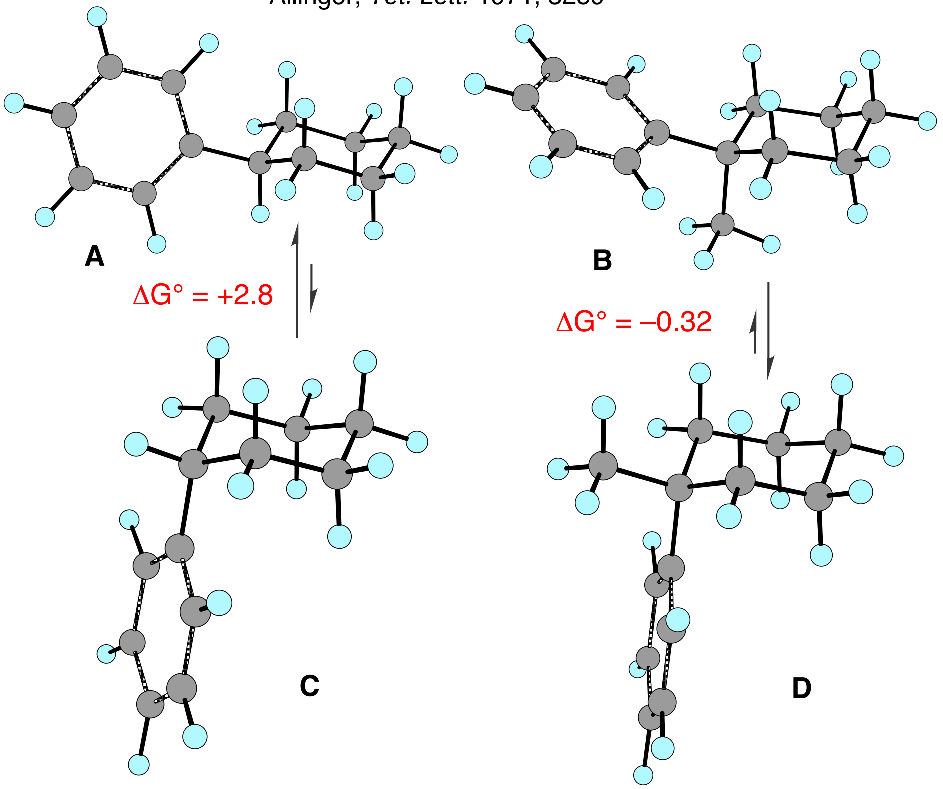
The prediction: ΔG° = A(Ph) – A(Me)

ΔG° = +2.8 – 1.7 = +1.1 kcal/mol

Observed: ΔG° = –0.32 kcal/mol

Hence, when the two substituents are mutually interacting you can predict neither the magnitude or the direction of the equilibrium. Let's analyze this case.

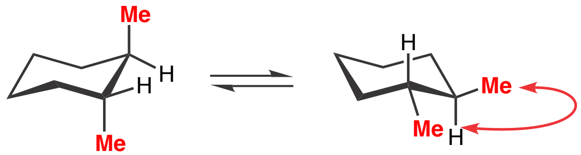
Allinger, *Tet. Lett.* 1971, 3259



Note the difference in the Ph substituent in **A** & **B**.

Let's now consider vicinal substitution

Case 1:



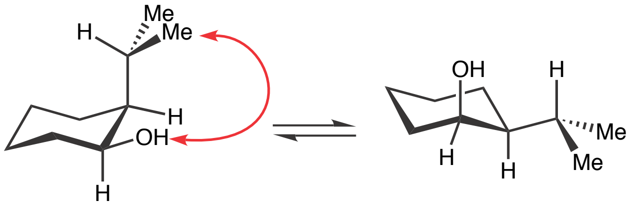
The prediction: ΔG° = 1 gauche butane – 2A(Me)

ΔG° = +0.88 – 2(1.74) = +2.6 kcal/mol

Observed: ΔG° = +2.74 kcal/mol

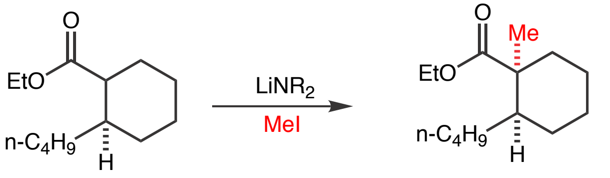
If the added gauche butane destabilization in the di-equatorial conformer had not been added, the estimate would have been off.

Case 2:



The conformer which places the isopropyl group equatorial is much more strongly preferred than would be suggested by *A*- Values. This is due to a syn pentane OH/Me interaction.

Problem:
Can you rationalize the stereochemical outcome of this reaction?



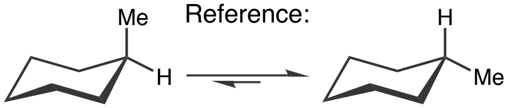
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.

Heteroatom-Substituted 6-Membered Rings

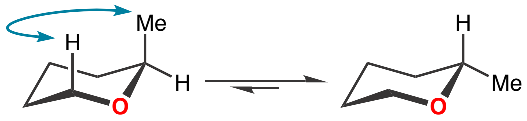
- ■ A-values at the 2-position in both the O & N heterocycles are larger than expected. This is due to the shorter C–O (1.43 Å), and C–N (1.47 Å) bond lengths relative to carbon (C–C; 1.53 Å). The combination of bond length and bond angle change increases the indicated 1,3-diaxial interaction (see eq 1, 4).

Reference:



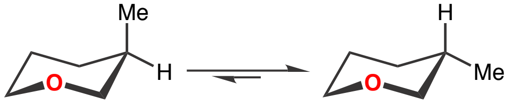
−ΔG° = 1.74 kcal/mol

(1)



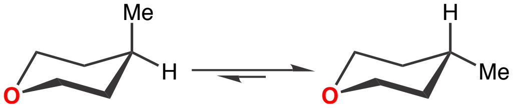
–ΔG° = 2.86 kcal/mol

(2)



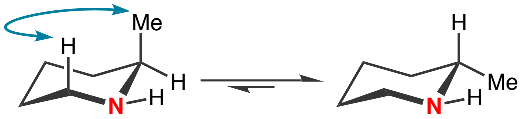
−ΔG° = 1.43 kcal/mol

(3)



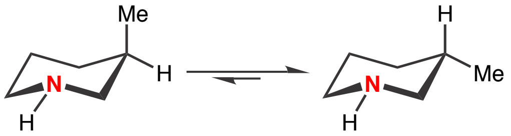
−ΔG° = 1.95 kcal/mol

(4)



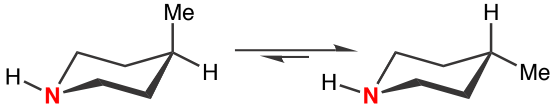
–ΔG° = 2.5 kcal/mol

(5)



−ΔG° = 1.6 kcal/mol

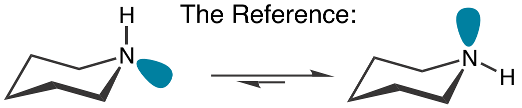
(6)



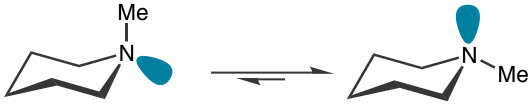
−ΔG° = 1.9 kcal/mol

A-Values for *N*-Substituents in Piperidine

The Reference:

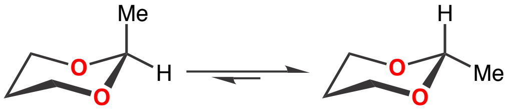


ΔG° = –0.36 kcal/mol

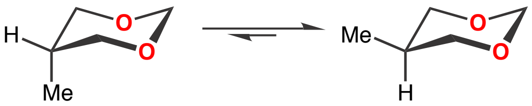


ΔG° = –3.0 kcal/mol

- ■ Hydrogen is "bigger" than the N–lone Pair.
- ■ The A-value of N–substituents is slightly larger than the corresponding cyclohexane value. Rationalize

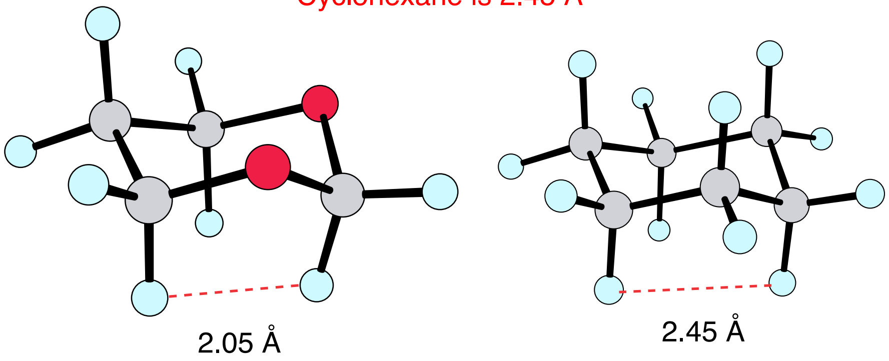


–ΔG° = 4.0 kcal/mol

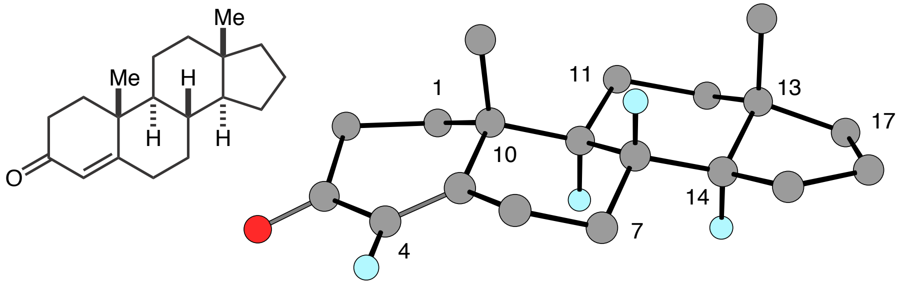


–ΔG° = 0.8 kcal/mol

- ■ The indicated distance is 2.05 Å. The analogous H–H distance in Cyclohexane is 2.45 Å

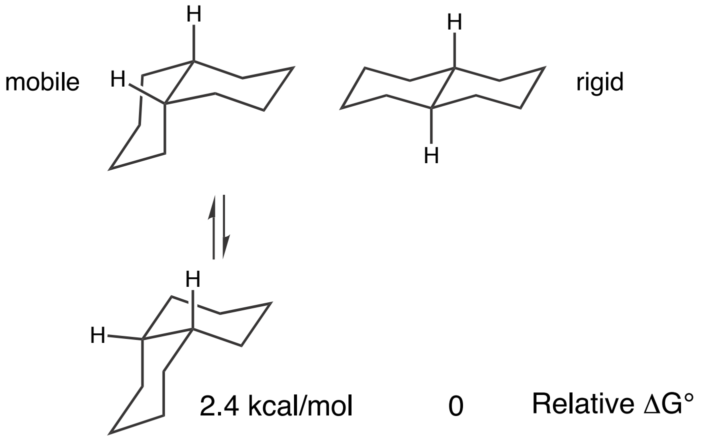


Conformations of Bicyclic Ring Systems

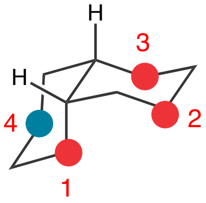


The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

Decalin Ring System (6/6)



Let's identify the destabilizing gauche butane interactions in the cis isomer

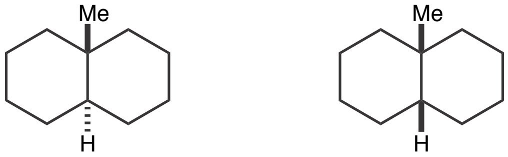


Gauche-butane interactions

C1 → C2
C1 → C3
C4 → C3

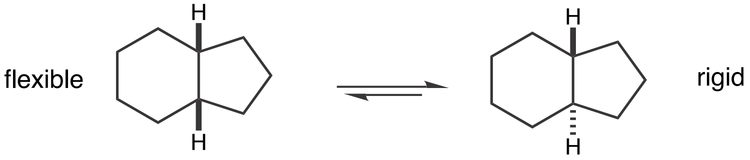
$\Delta G^\circ(\text{est}) = 3(0.88) = 2.64$ kcal/mol

Estimate the energy difference between the two methyl-decalins shown below.



see Elier, p 780

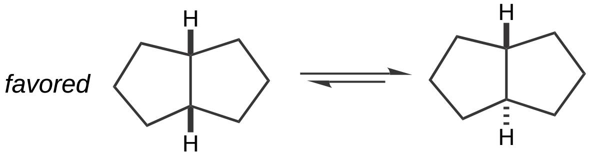
Hydrindane Ring System (6/5)



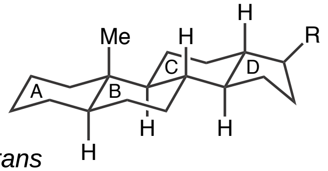
$\Delta G^\circ = -0.5$ kcal/mol

■ The turnover to favor the *cis* fusion results from the entropic preference for the less ordered *cis* isomer.

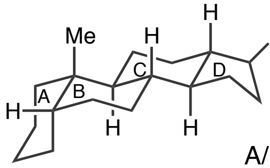
The 5-5 Ring System



$\Delta G^\circ = +6.4$ kcal/mol



A/B *Trans*



A/B *Cis*

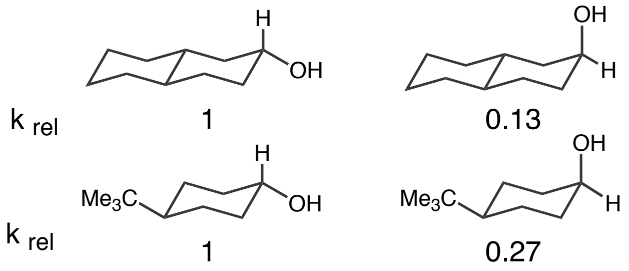
Rationalize the conformational flexibility of a *A/B Trans* vs. *A/B Cis* Steroid!

Conformational Analysis: Axial vs Equatorial Reactivity

Different reactivity for axial and equatorial substituents

Axial substituents are more hindered, thus less reactive in many transformations

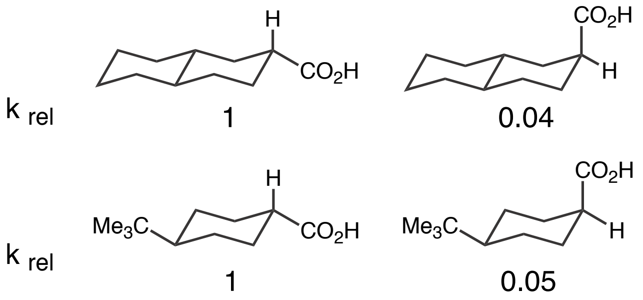
- Acetylation with Ac_2O/Py



k_{rel} 1 0.13

k_{rel} 1 0.27

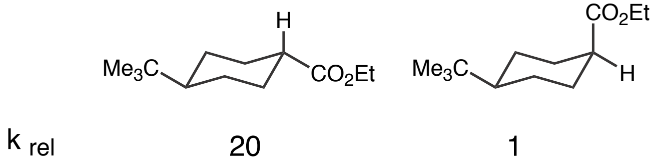
- Acid-catalyzed esterification



k_{rel} 1 0.04

k_{rel} 1 0.05

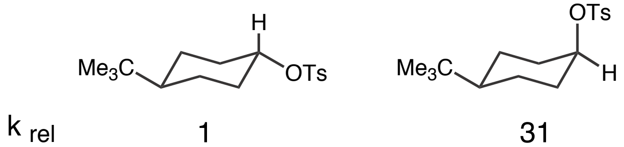
- Ester Saponification



k_{rel} 20 1

For a more detailed discussion of this topic see:
Eliel, E. L., S. H. Wilen, et al. (1994). *Stereochemistry of Organic Compounds pp 720-726*

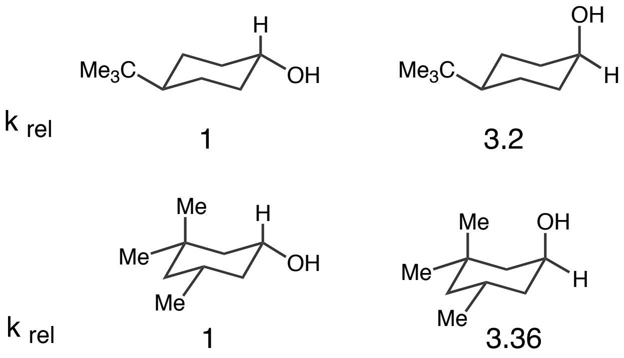
- S_N2 Reactions (Displacement with Ph–S^-)



k_{rel} 1 31

The axial diastereomer is not always slower reacting:

- Alcohol Oxidation with Cr(6+)

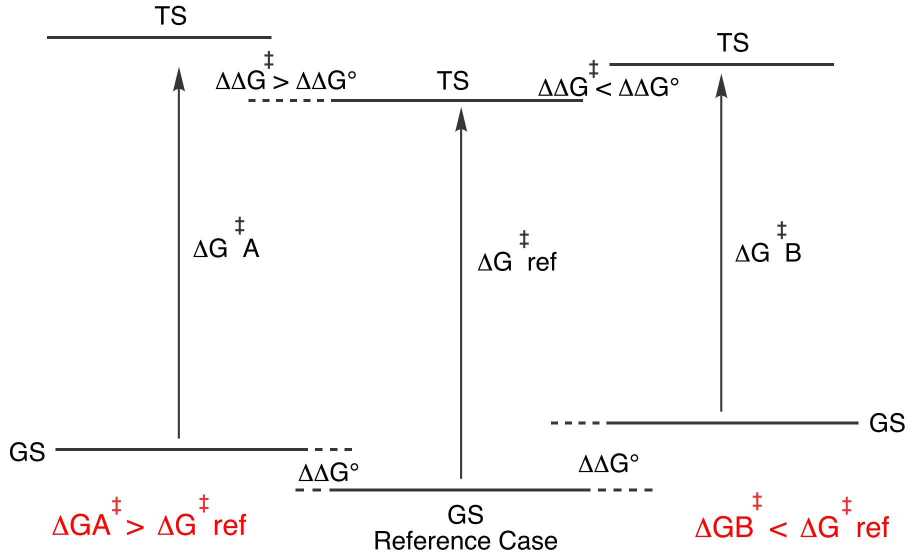


k_{rel} 1 3.2

k_{rel} 1 3.36

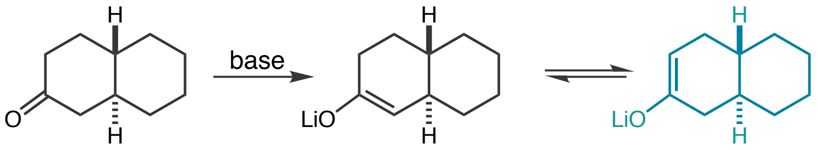
The rate-determining step is breakdown of the chromate ester. This is an apparent case of strain acceleration

Steric Hindrance and Steric Assistance

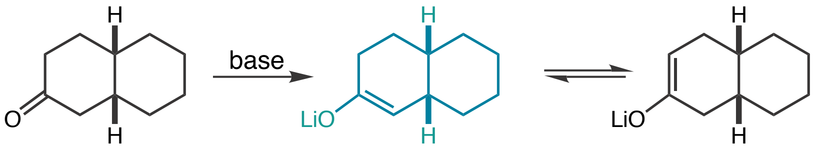


Conformational Transmission

Observation:
Relative enolate stability correlates to ring junction stereochemistry



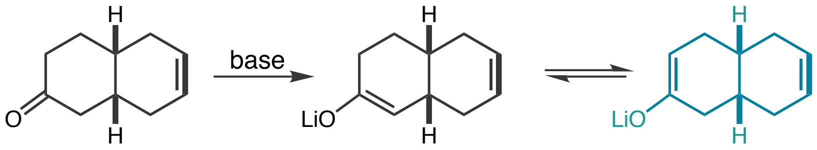
ratio: 13 : 87



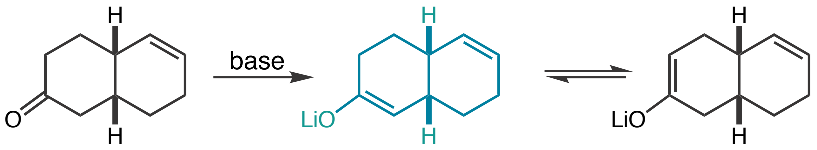
ratio: 70 : 30

House, *JOC* **1965**, *30*, 1341

Observation:
Relative enolate stability seems to be correlated to position of C=C



ratio: 10 : 90

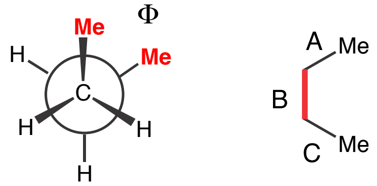


ratio: 92 : 8

How do we explain the experimental observations shown above?

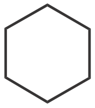
Readings: Velluz etal, *Angew. Chemie, Int Ed*. **1965**, *4*, 181-270

Let Φ be defined as the torsion or dihedral angle for butane



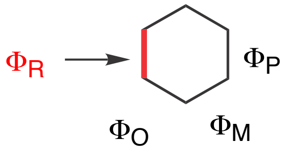
Φ illustrated may be designated as Φ B.

Let's now consider cyclohexane



Perfect chair	real chair
Φ = 60°	Φ = 56°
CCC∠ 109° 28'	CCC∠ 111°

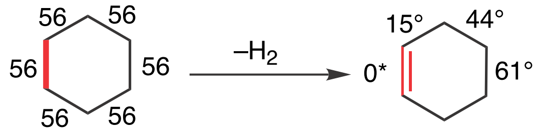
Given cyclohexane with an identified torsion angle ΦR, if ΦR either increases or decreases wht effects in angle change are transmitted to ΦO, ΦM, and ΦP?



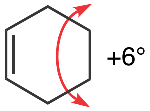
	$\Phi_R = 56°$	$\Phi_R = 0°$	[Δ]
Φ_O	56	15	–41°
Φ_M	56	44	–11°
Φ_P	56	61	+6°

$$[\Delta] = \Phi_R(0°) - \Phi_R(56°)$$

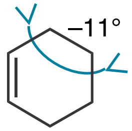
Operation:



Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:



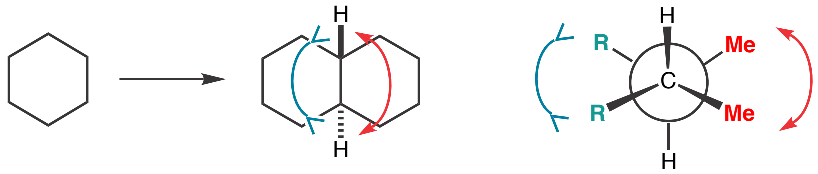
For Φ_P



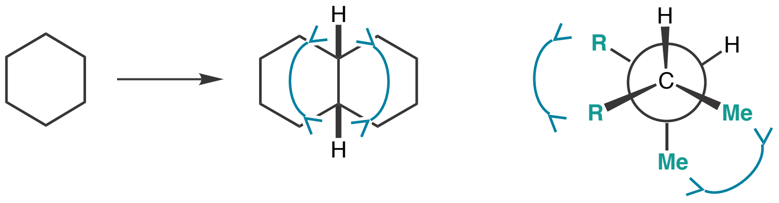
For Φ_M

Conformational Transmission-2

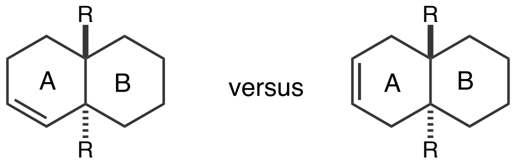
Operation:



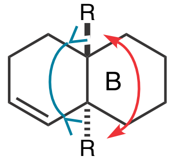
Operation:



Simple Application: Reinforcing Torsional Effects



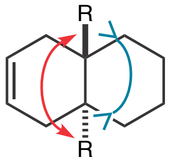
Which C=C bond isomer is more stable?



1) C=C will open up ring=B torsion angle

2) Ring B will resist increase in its ring fusion torsion angle

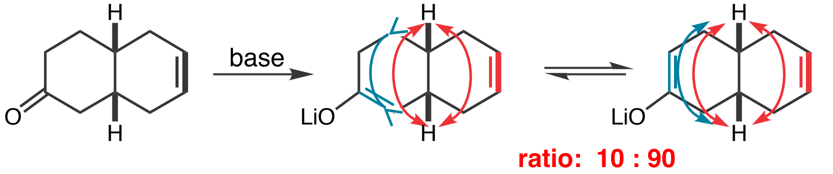
3) Therefore torsion effects are opposed



1) C=C will close down ring=B torsion angle

2) Ring B will accomodate decrease in its ring fusion torsion angle

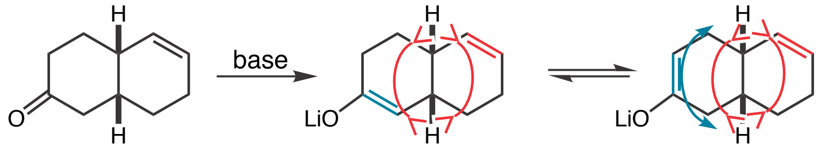
3) Therefore torsion effects are reinforcing



ratio: 10 : 90

effects opposing

effects reinforcing

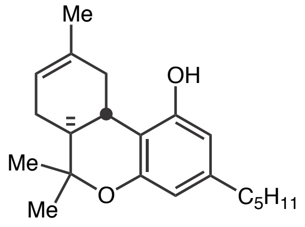


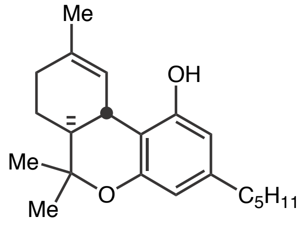
ratio: 92 : 8

effects reinforcing

effects opposing

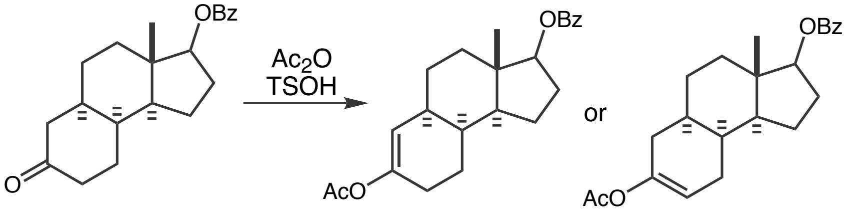
Question: Which is the more stable C=C isomer in the two THC structures?





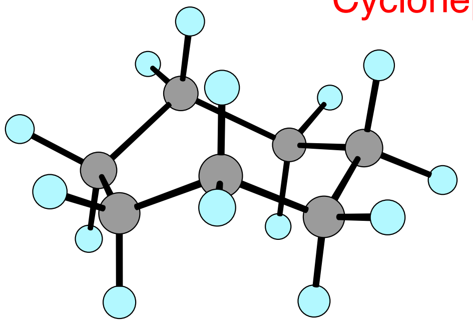
R. W. Kierstead, *JACS* **1967**, *89*, 5934

Question: Which enol acetate is more stable?

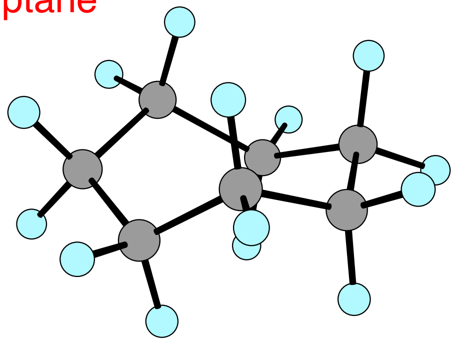


Conformational Analysis: Cylcoheptane

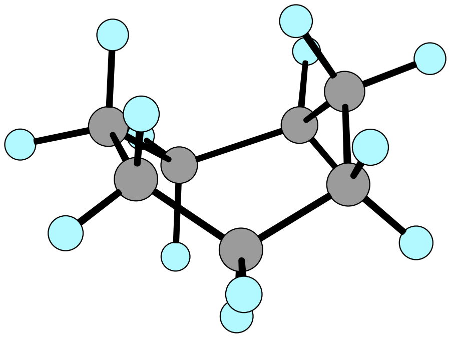
Cycloheptane



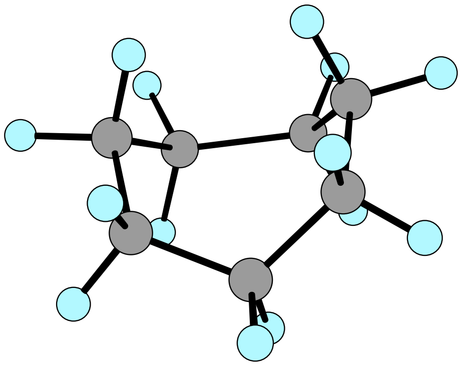
Chair (2.16 kcal/mol)



Twist-Chair (0 kcal/mol)



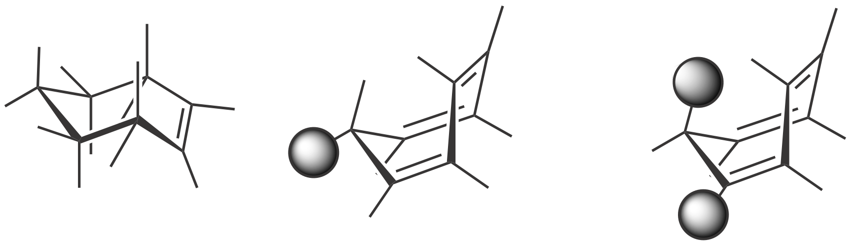
Boat (3.02 kcal/mol)



Twist-Boat (2.49 kcal/mol)

Hendrickson, J. B. *JACS* **1961**, *83*, 4537.
See Eliel, page 762+

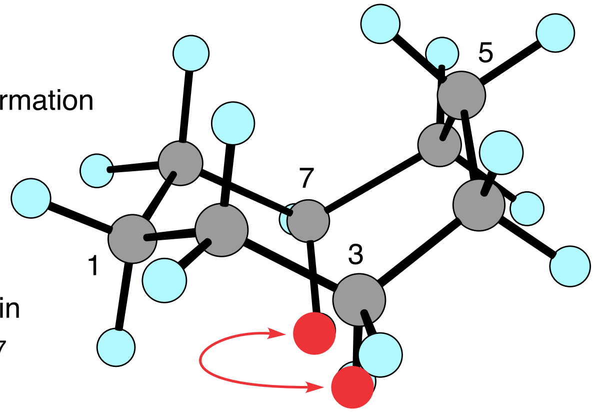
Olefins are preferentially orientated to eliminate eclipsing interactions.



Cyclooctane

Chair-Boat
Lowest-energy conformation

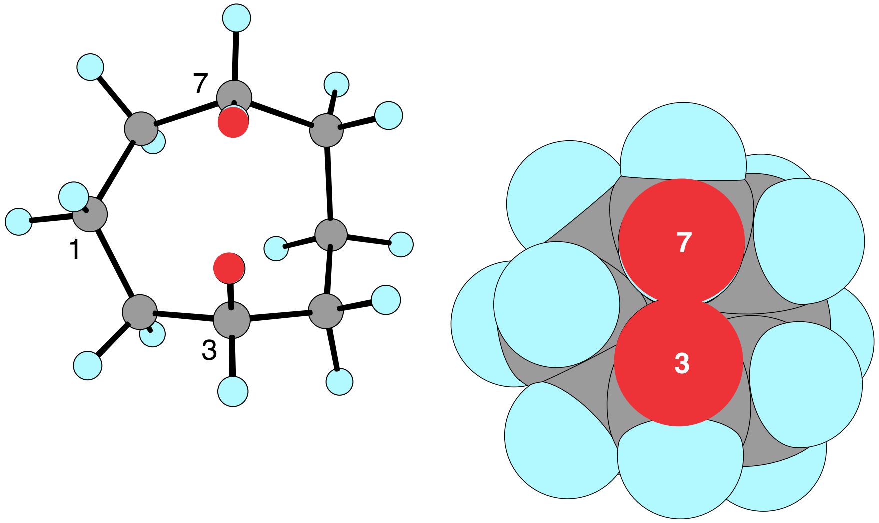
Transannular strain
between C$_3$ & C$_7$



Ring strain originates in eclipsing interactions and transannular van der Waals interactions

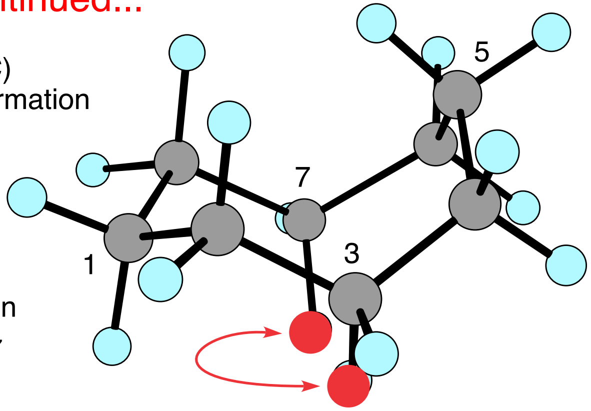
Methyl position	1	2	**3**	4	5
$\Delta G \ \frac{\text{(pseudoeqatorial)}}{\text{(pseudoaxial) (kcal/mol)}}$	1.8	2.8	**>4.5**	-0.3	6.1

Underside view of boat-chair C3 & C7 eclipsing interactions



Cyclooctane continued...

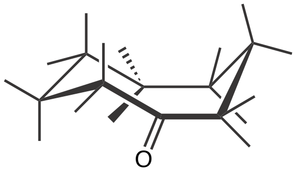
Chair-Boat (**BC**)
Lowest-energy conformation



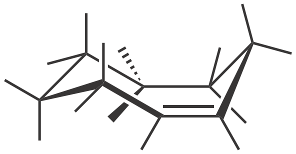
Transannular strain between C_3 & C_7

Methyl position	1	2	3	4	5
$\Delta G \frac{\text{(pseudoeqatorial)}}{\text{(pseudoaxial) (kcal/mol)}}$	1.8	2.8	>4.5	-0.3	6.1

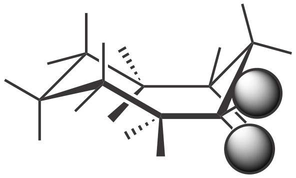
Cyclooctane derivatives



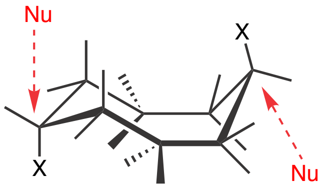
Carbonyl is positioned at C_3 or C_7



Olefin is positioned at C_3-C_4 or C_6-C_7

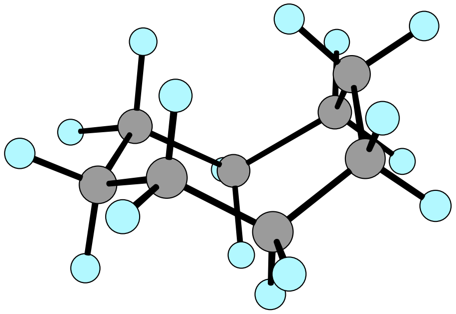


Disubstitution occurs at C_4 or C_6

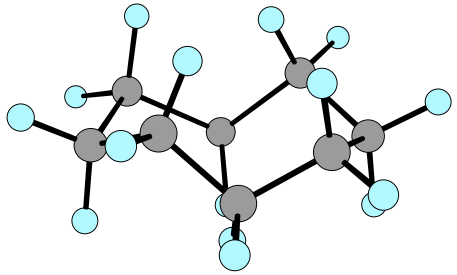


S_N2 occurs at C_1 and C_5

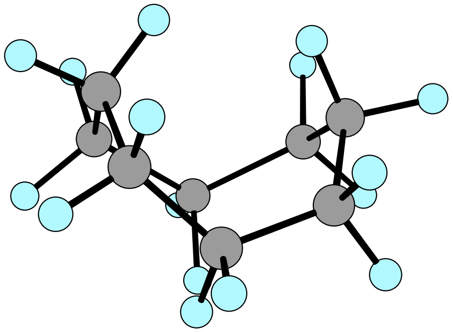
Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 1981.



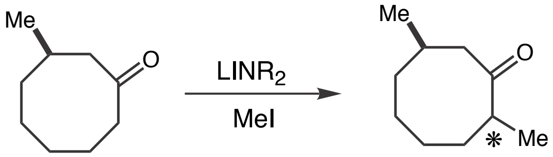
Chair-Boat (**CB**) conformation
reference structure



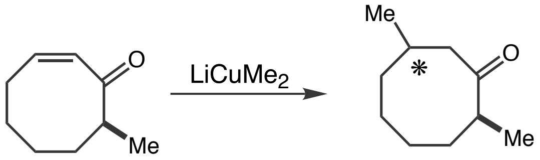
Chair-Chair (**CC**) conformation
(+1-1.6 kcal/mol)



Boat-Boat (**BB**) conformation
(>+ 8 kcal/mol)



Predict stereochemistry



Predict stereochemistry

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 7

Conformational Analysis-4

- Ground State Torsional Effects (Conformational Transmission)
- Conformational Analysis of $C_6 \rightarrow C_8$ Rings continued
- Transition State Torsional Effects
- Curtin–Hammett Principle **(Will not cover in lecture)**

Reading Assignment for week

Eliel & Wilen, Stereochemistry of Carbon Compounds"
Chapter 11
Configuration and Conformation of Cyclic Molecules ***(handout)***

A. Carey & Sundberg: **Part A**; Chapter 4
"Study & Descrption of Reaction Mechanisms"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions ***(Handout)***

D. A. Evans

Monday,
September 29, 2003

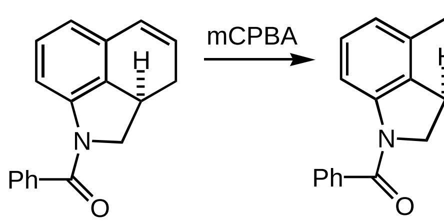
Other Reading Material

The Curtin-Hammett Principle

Leading References:
- **J. I. Seeman, *J. Chem. Ed.* 1986, *63,* 42-48.**
- J. I. Seeman, *Chem Rev.* **1983,** *83,* 83-134.
- Eliel, pp. 647-655
- Carey & Sundberg,Part A, CH 4, pp 187-250

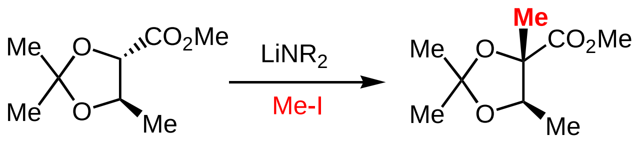
Problems of the Day: (To be discussed)

Predict the stereochemical outcome of this reaction. The diastereoselection is 99:1



Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

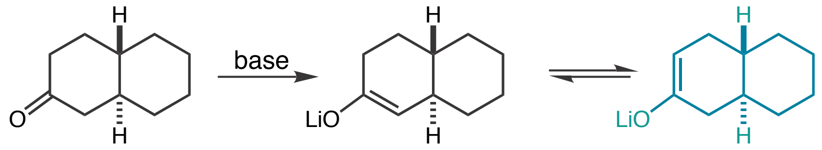
Rationalize the stereochemical outcome of this reaction.



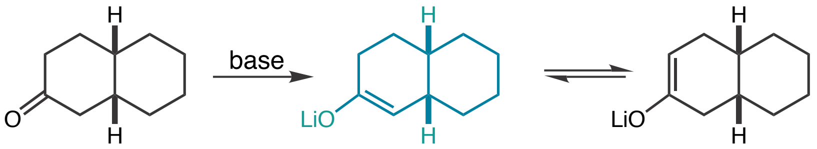
diastereoselection is 8:1.

Ladner, et.al. *Angew. Chemie, Int. Ed* **1982**, *21*, 449-450

Observation:
Relative enolate stability correlates to ring junction stereochemistry



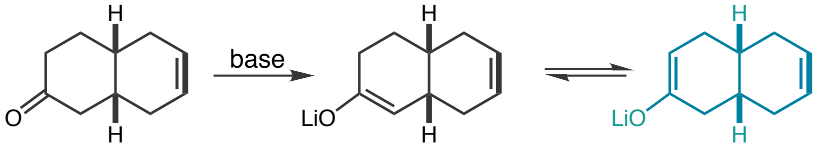
ratio: 13 : 87



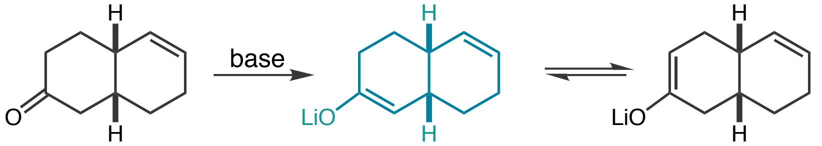
ratio: 70 : 30

House, *JOC* **1965**, *30*, 1341

Observation:
Relative enolate stability seems to be correlated to position of C=C



ratio: 10 : 90

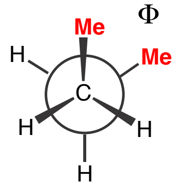


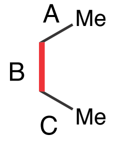
ratio: 92 : 8

How do we explain the experimental observations shown above?

Readings: Velluz etal, *Angew. Chemie, Int Ed*. **1965**, *4*, 181-270

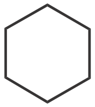
Let Φ be defined as the torsion or dihedral angle for butane





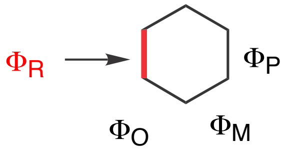
Φ illustrated may be designated as Φ B.

Let's now consider cyclohexane



Perfect chair	real chair
$\Phi = 60°$	$\Phi = 56°$
CCC∠ 109° 28'	CCC∠ 111°

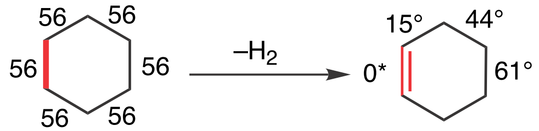
Given cyclohexane with an identified torsion angle ΦR, if ΦR either increases or decreases wht effects in angle change are transmitted to ΦO, ΦM, and ΦP?



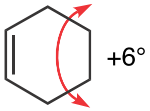
	$\Phi_R = 56°$	$\Phi_R = 0°$	[Δ]
Φ_O	56	15	–41°
Φ_M	56	44	–11°
Φ_P	56	61	+6°

$[\Delta] = \Phi_R(0°) - \Phi_R(56°)$

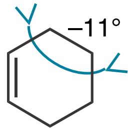
Operation:



Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:



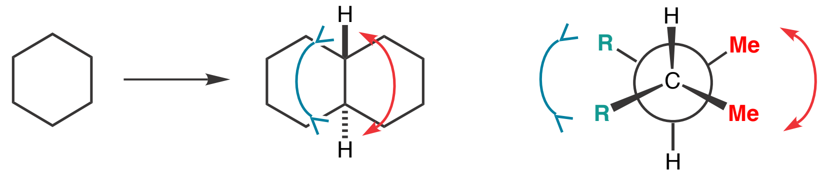
For Φ_P



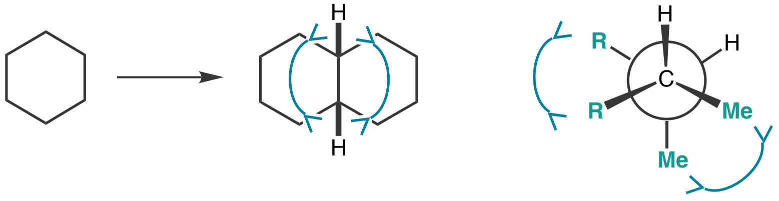
For Φ_M

Conformational Transmission-2

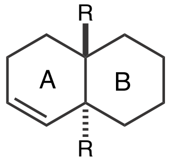
Operation:



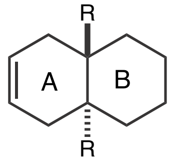
Operation:



Simple Application: Reinforcing Torsional Effects



versus



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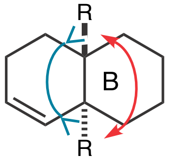

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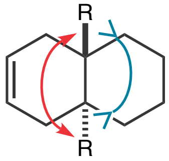

1) C=C will close down ring=B torsion angle
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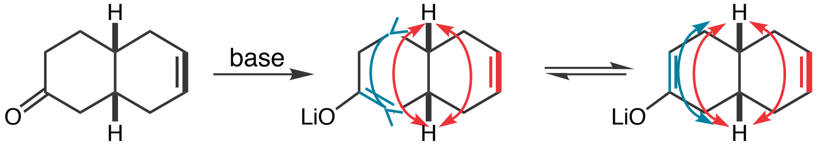
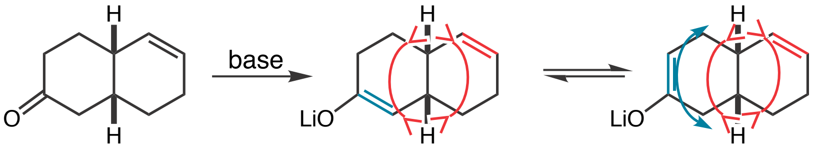
3) Therefore torsion effects are reinforcing



ratio: 10 : 90

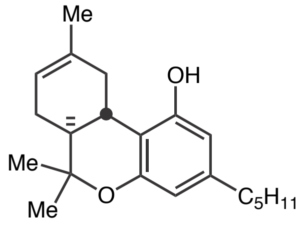
effects opposing　　effects reinforcing

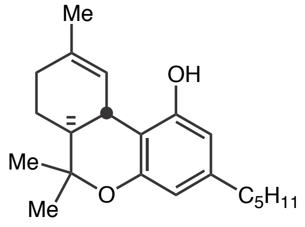


ratio: 92 : 8

effects reinforcing　　effects opposing

Question: Which is the more stable C=C isomer in the two THC structures?





R. W. Kierstead, *JACS* **1967**, *89*, 5934

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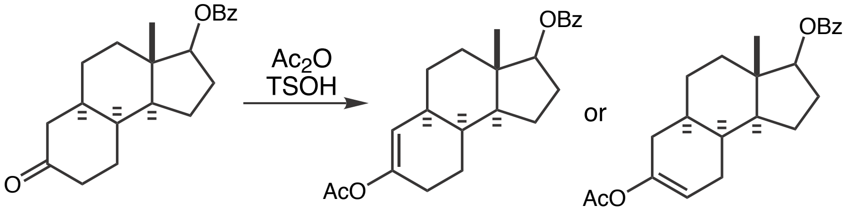

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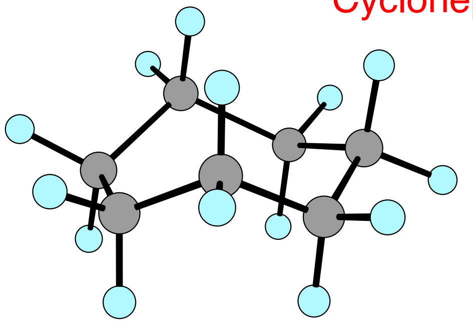
Cycloheptane



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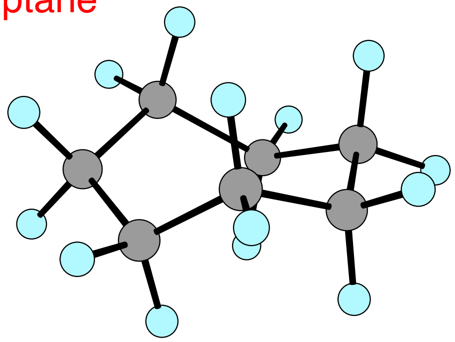
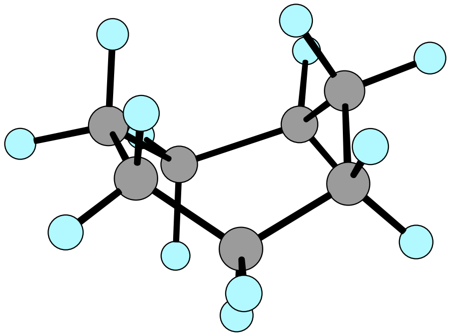


Twist-Chair (0 kcal/mol)



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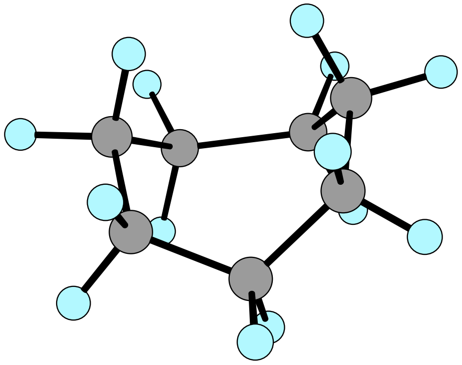

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Hendrickson, J. B. *JACS* **1961**, *83*, 4537.
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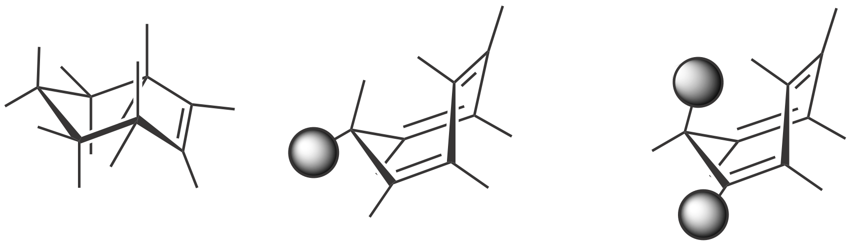
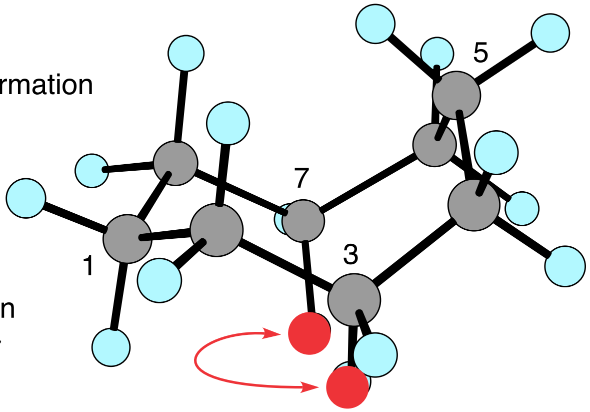


Cyclooctane

Chair-Boat
Lowest-energy conformation

Transannular strain
between C_3 & C_7



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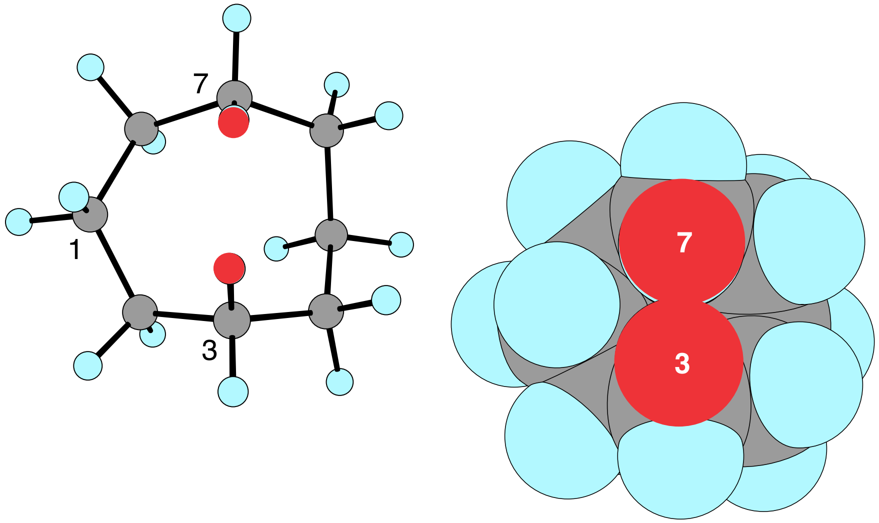
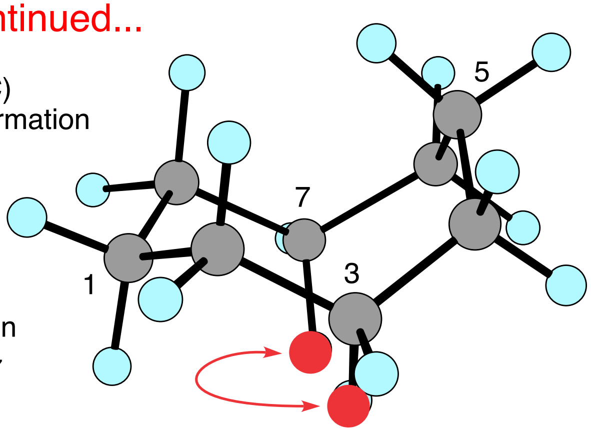
Underside view of boat-chair C3 & C7 eclipsing interactions



Cyclooctane continued...

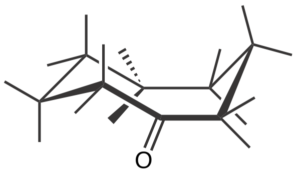
Chair-Boat (**BC**)
Lowest-energy conformation



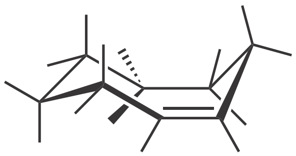
Transannular strain between C_3 & C_7

Methyl position	1	2	3	4	5
$\Delta G \dfrac{\text{(pseudoeqatorial)}}{\text{(pseudoaxial) (kcal/mol)}}$	1.8	2.8	>4.5	-0.3	6.1

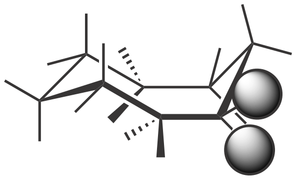
Cyclooctane derivatives



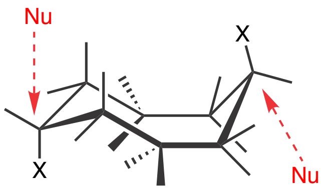
Carbonyl is positioned at C_3 or C_7



Olefin is positioned at C_3-C_4 or C_6-C_7

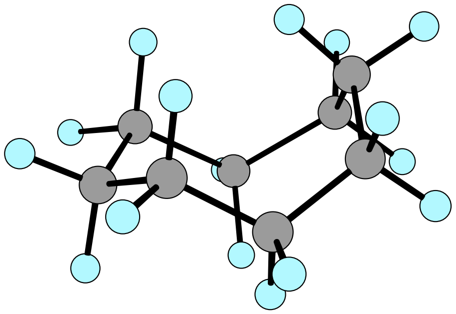


Disubstitution occurs at C_4 or C_6

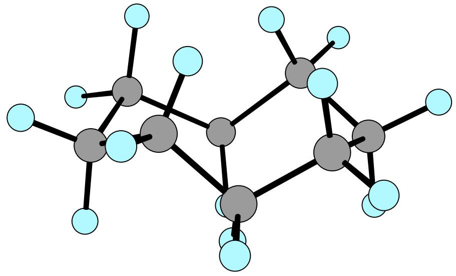


S_N2 occurs at C_1 and C_5

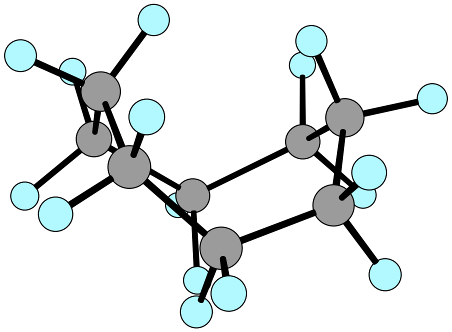
Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.



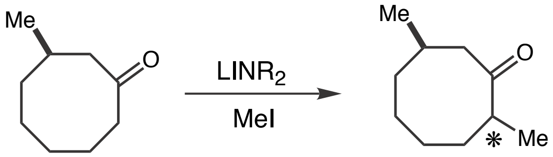
Chair-Boat (**CB**) conformation
reference structure



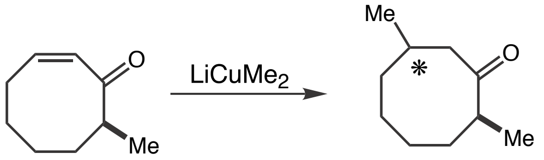
Chair-Chair (**CC**) conformation
(+1-1.6 kcal/mol)



Boat-Boat (**BB**) conformation
(>+ 8 kcal/mol)



Predict
stereochemistry



Predict
stereochemistry

Ground State Torsional Effects

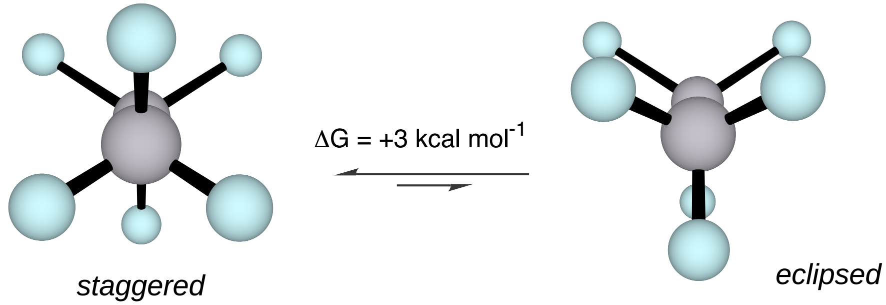
Torsional Effects

Torsional Strain: the resistance to rotation about a bond

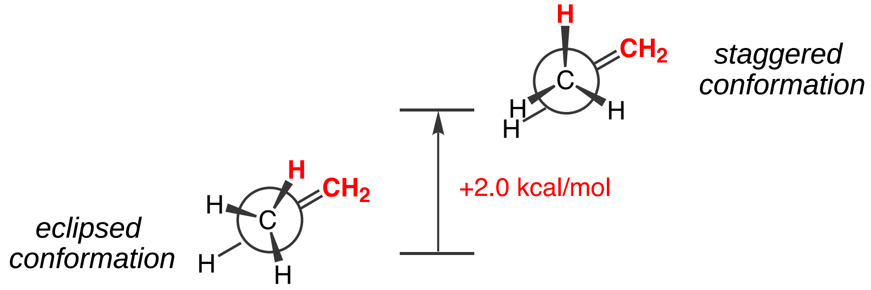
Torsional energy: the energy required to obtain rotation about a bond

Torsional Angle: also known as dihedral angle

Torsional steering: Stereoselectivity originating from transition state torsional energy considerations



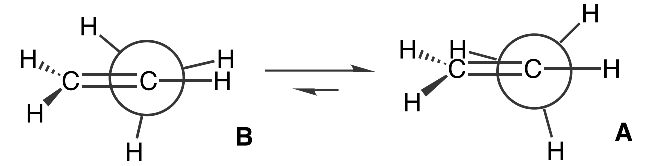
Torsional Strain (Pitzer Strain): Ethane

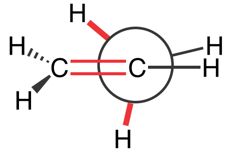


Wiberg K. B.; Martin, E. *J. Amer. Chem. Soc.* **1985**, *107*, 5035-5041.

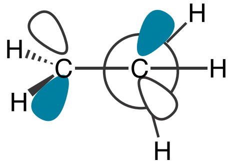
See Lecture 4 for previous discussion

Relevant Orbital Interactions:





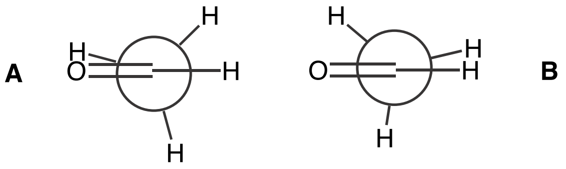
σ C–H & π electrons are destabilizing



σ C–H's properly aligned for π* overlap hence better delocalization

Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *JACS* **1987**, *109*, 6591-6600.

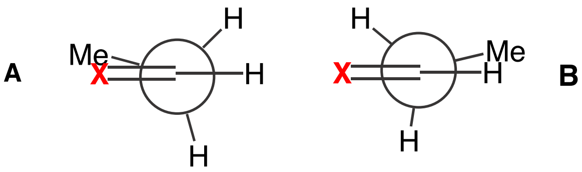
Conformational Preferences: Acetaldehyde



The eclipsed conformation (conformation **A**) is preferred.
Polarization of the carbonyl decreases the 4 electron destabilizing
Rotational barrier: 1.14 kcal/mol

Houk, *JACS* **1983**, *105*, 5980-5988.

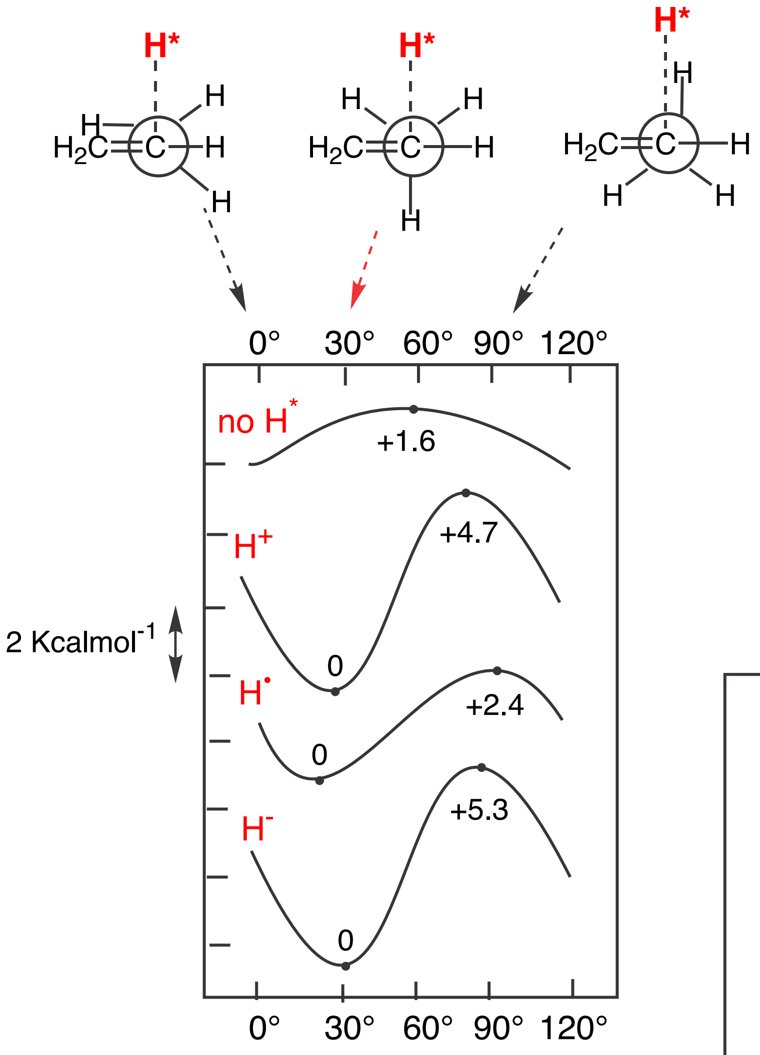
Conformational Preferences 1-Butene (X = CH_2); Propanal (X = O)



Conformation A is preferred. There is little steric repulsion between the methyl and the X-group in conformation A.

Transition State Torsional Effects According to Houk

Houk: "Torsional effects in transition states are more important than in ground states"

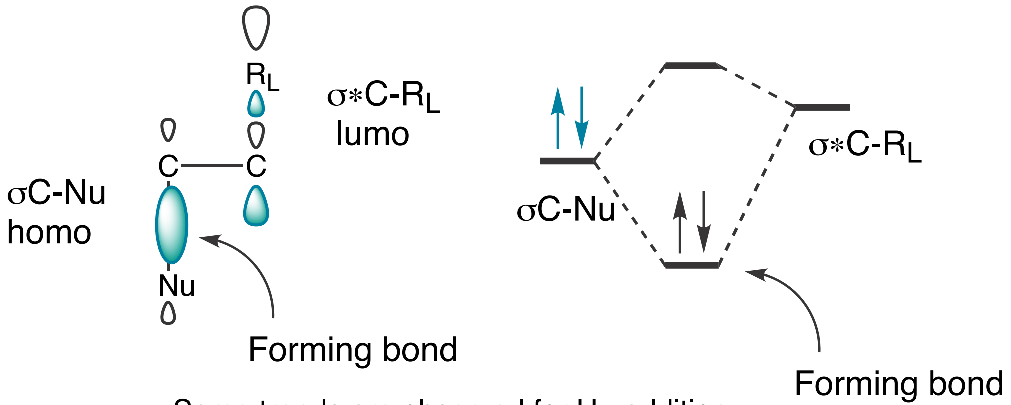


Houk, *JACS* **1981**, *103*, 2438

Houk, *JACS* **1982**, *104*, 7162

Transition states

H-radical and H-anion: antiperiplanar $\sigma*$C–R orbital stabilized the TS
illustrated for Nu addition

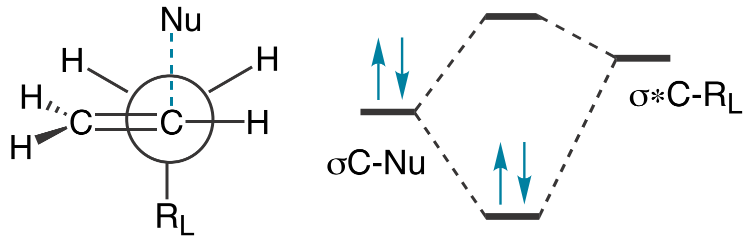


Same trends are observed for H+ addition

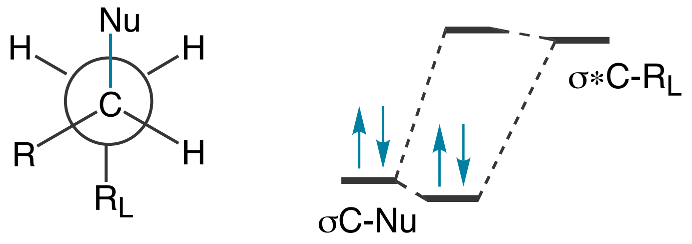
Houk, *Science* **1981**, *231*, 1108-1117

"The Theory and Modeling of Stereoselective Organic Reactions"

Transition state



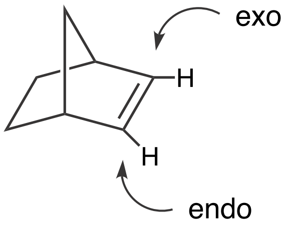
Ground state



Transition State Torsional Effects: Olefin Additions

■ Olefin Addition Reactions: Case one

How do we account for the high exo selectivities in addition reactions to norbornene?



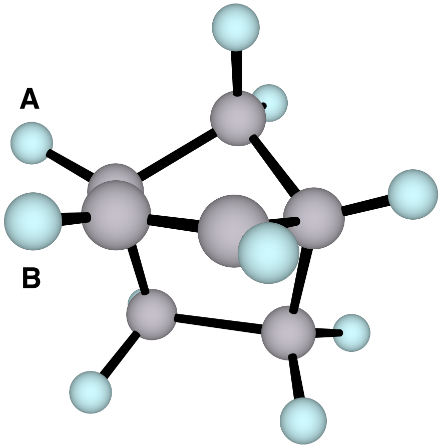
Highly exo selective for electrophilic, nucleophilic and cycloaddition reactions

Rate enhancement due to strain

The Controversy over origin of high exoselectivities

- Steric effects
- Least nuclear motion
- Orbital distortion

Schleyer: torsional steering



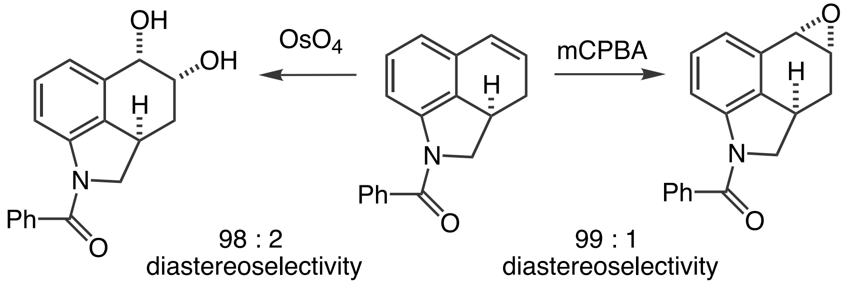
Schleyer, P. R. *J. Amer. Chem. Soc.* **1967**, *89*, 701.

Addition from exo face avoids eclipsing A & B hydrogens

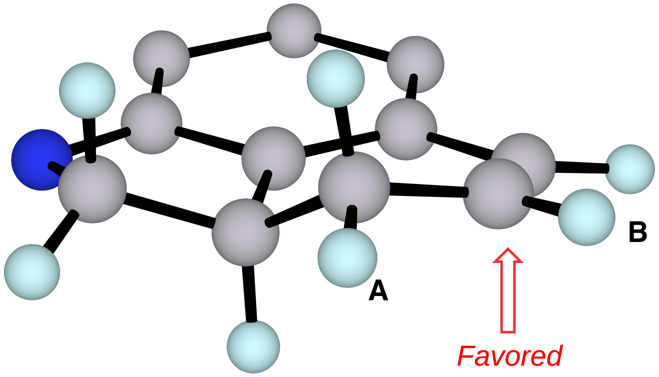
(better hyperconjugative stabilization of transition state)

■ Olefin Addition Reactions: Case two

How do we account for the high selectilvities in the oxidation of the indicated olefin?



Nitrogen protecting group does not affect selectivities



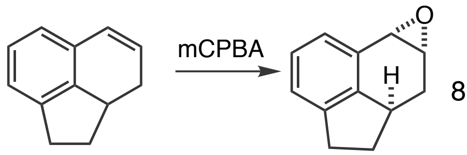
Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

Addition from indicated olefin face avoids eclipsing A & B H's

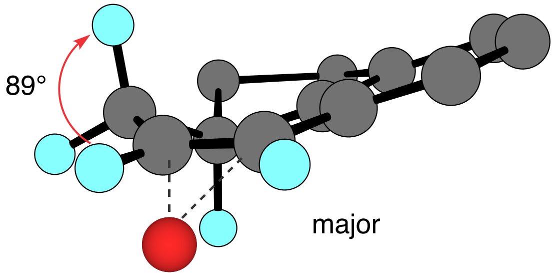
(better hyperconjugative stabilization of transition state)

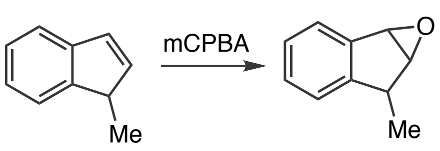
Martinelli has carried out further studies on related structures...........

Martinelli: Torsional steering important in selectivity

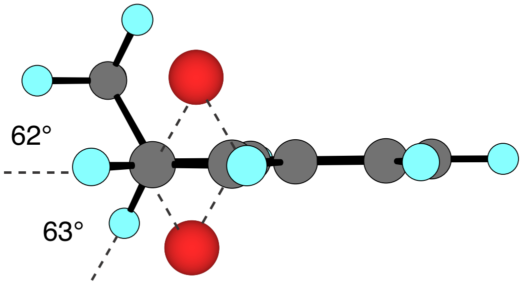


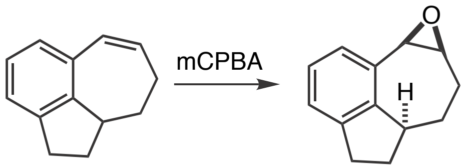
99 : 1 diastereoselectivity



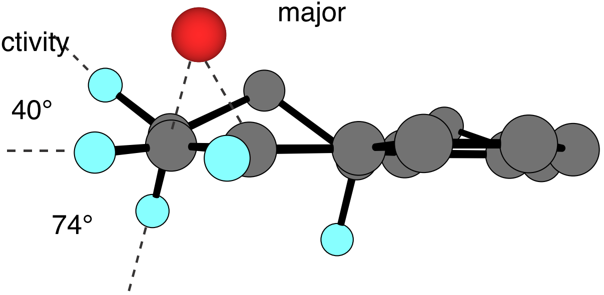


50 : 50 diastereoselectivity





99 : 1 diastereoselectivity

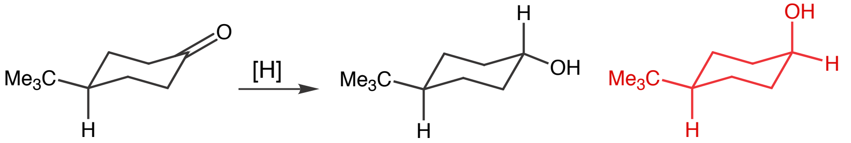


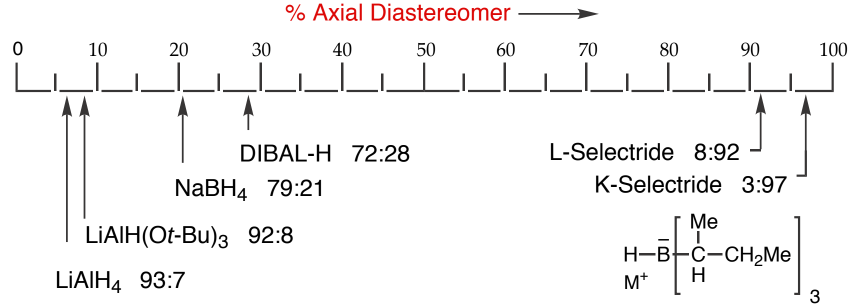
Authors propose that diastereoselection controlled by TS torsional effects

Martinelli & Houk, *J. Org. Chem.* **1994**, *59*, 2204.

Cyclohexanone Addition Reactions: Hydride Reduction

Stereoselective Reductions: Cyclic Systems





LiAlH$_4$ 93:7

LiAlH(O*t*-Bu)$_3$ 92:8

NaBH$_4$ 79:21

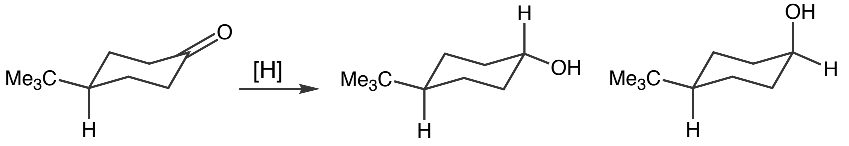
DIBAL-H 72:28

L-Selectride 8:92

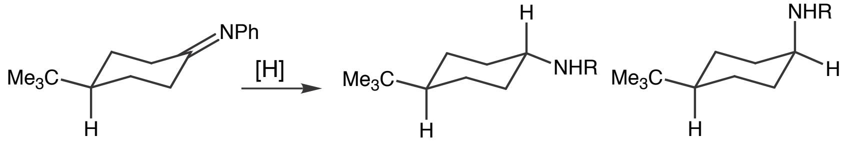
K-Selectride 3:97

Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

The most stereoselective Reductions



Reagent	Ratio
KBH(s-Bu)$_3$	03 :97
Li in NH$_3$	99 :01



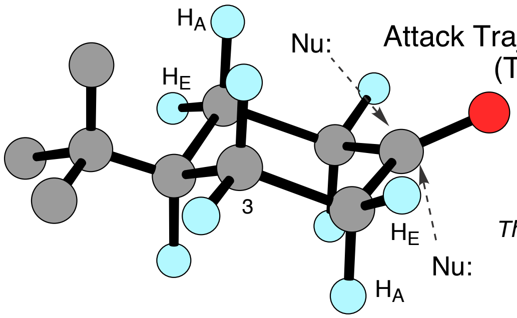
(R)	Reagent	Ratio
R = Bn	LiBH(s-Bu)$_3$	03 :97
R = Ph	LiBH(s-Bu)$_3$	01 :99
	Al/Hg/MeOH	~90 :10

Ganem, *Tet. Let* **1981**, *22*, 3447

Hutchins, *JOC* **1983**, *48*, 3412

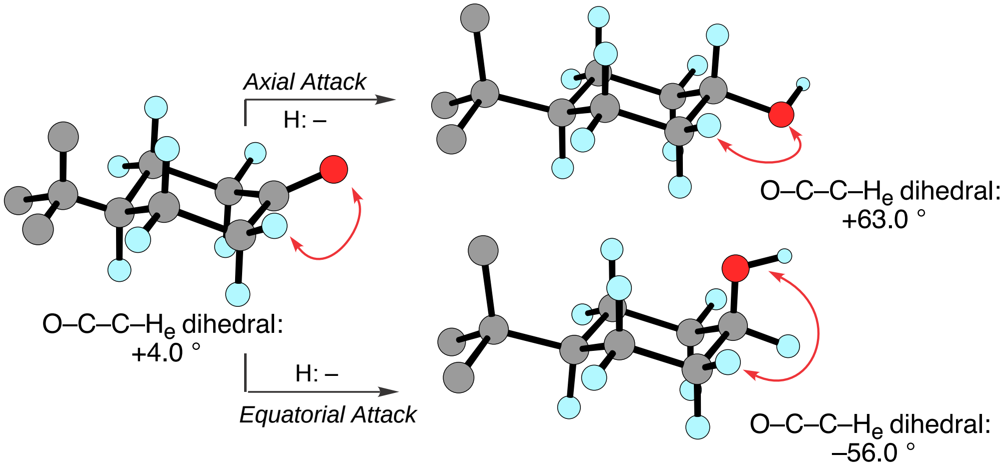
private communication

Attack Trajectories for Cyclohexanone (Torsional Argument)



This approach favored sterically

The steric hindrance encountered by Nu-attack from the axial C=O face by the axial ring substituents (hydrogens in this case) at the 3-positions is more severe than the steric hinderance encountered from Nu-attack from the equatorial C=O face.



O–C–C–H$_e$ dihedral: +4.0 °

O–C–C–H$_e$ dihedral: +63.0 °

O–C–C–H$_e$ dihedral: –56.0 °

The Issues Associated with the Reduction Process

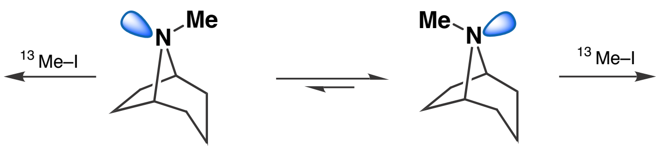
Steric Effects:	Attack across equatorial C=O face sterically more favorable.
Torsional Effects:	However, attack across the axial face of the C=O group avoids development of eclipsing interactions in the transition state. (Note the dihedral angle sign changes between reactants & products shown above). These "torsional effects" favor axial attack.
Prediction	For "small" hydride reagents such as LiAlH$_4$, torsional effects are felt to be dominant and this explains the predisposition for axial attack.
Prediction	For "large" hydride reagents such as H–BR$_4$, steric effects now are dominant and this explains the predisposition for equatorial attack.

K. A. Beaver, D. A. Evans   Conformational Analysis and Reactivity: Curtin-Hammett Principle

Leading References: J. I. Seeman, *J. Chem. Ed*. **1986,** *63,* 42-48.
J. I. Seeman, *Chem Rev*. **1983,** *83,* 83-134.
See also Eliel, pp. 647-655

How does the conformation of a molecule effect its reactivity?

Consider the following example:



Do the two different conformers react at the same rate, or different rates?
What factors determine the product distribution?

The situation:

Consider two interconverting conformers, A and B, each of which can undergo a reaction resulting in two different products, P_A and P_B.

$$\underset{major}{P_A} \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} \underset{minor}{P_B} \qquad (1)$$

We'll consider two limiting cases:

(1) The rate of reaction is *faster* than the rate of conformational interconversion

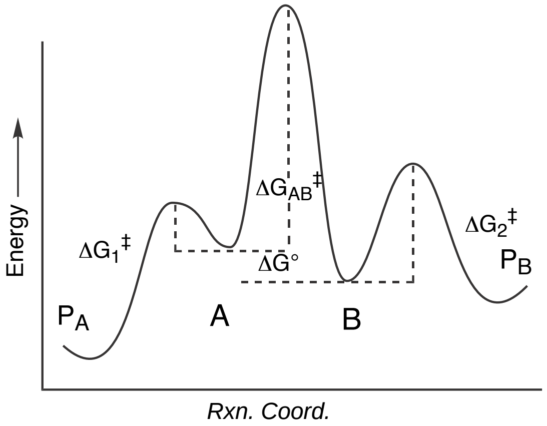
(2) The rate of reaction is *slower* than the rate of conformational interconversion

If the rates of conformationall interconversion and reaction are comparable, the reactants are not in equilibrium during the course of the reaction and complex mathmatical solutions are necessary. See Seeman, *Chem. Rev.* **1983**, 83 - 144 for analytical solutions.

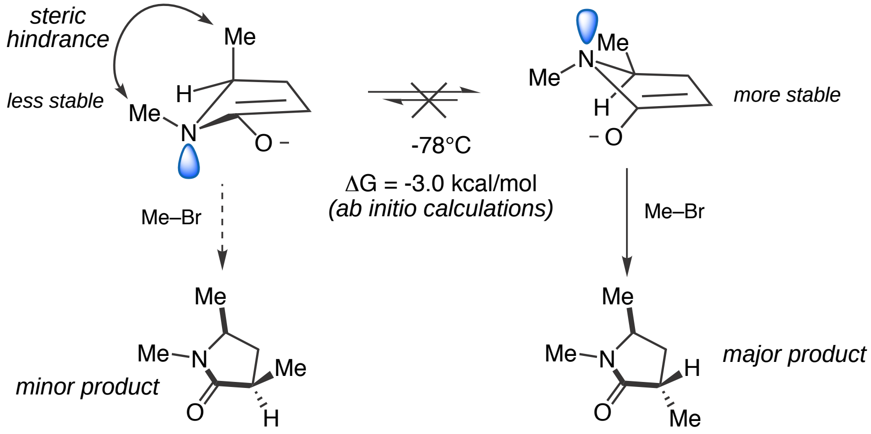
Case 1: "Kinetic Quench"

k_1, k_2 >> k_A, k_B: If the rates of reaction are **faster** than the rate of interconversion, A and B cannot equilibrate during the course of the reaction, and the product distribution (P_B/P_A) will reflect the initial composition.

$$\frac{[P_B]}{[P_A]} = \frac{[B]_o}{[A]_o}$$



In this case, the product distribution depends solely on the initial ratio of the two conformers.



While enolate conformers can be equilibrated at higher temperatures, the products of alkylation at -78° C always reflect the initial ratio of enloate isomers.

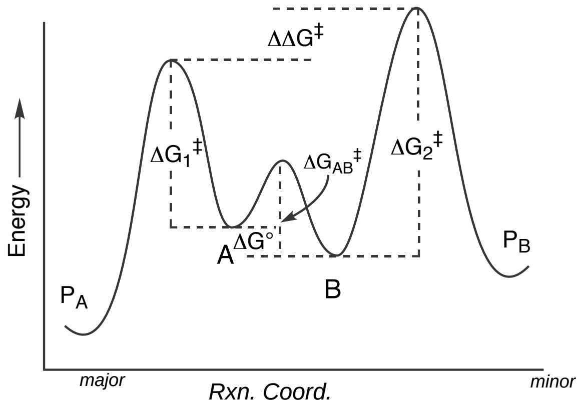
Padwa, *JACS* **1997** 4565

Curtin - Hammett: Limiting Cases

Case 2: Curtin-Hammett Conditons

k_1, k_2 << k_A, k_B: If the rates of reaction are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the ratio of A to B is constant throughout the course of the reaction.

$$P_A \xleftarrow[\text{slow}]{k_1} A \underset{\underset{\text{fast}}{k_B}}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow[\text{slow}]{k_2} P_B \qquad (1)$$



The Derivation:

Using the rate equations $\frac{d[P_A]}{dt} = k_1[A]$ and $\frac{d[P_B]}{dt} = k_2[B]$ we can write:

$$\frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]} \quad \text{or} \quad d[P_B] = \frac{k_2[B]}{k_1[A]} d[P_A] \qquad (2)$$

Since A and B are in equilibrium, we can substitute $K_{eq} = \frac{[B]}{[A]}$

$$\int d[P_B] = \frac{k_2}{k_1} K_{eq} \int d[P_A] \quad \text{Integrating, we get} \quad \frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} \qquad (3)$$

When A and B are in rapid equilibrium, we must consider the rates of reaction of the conformers as well as the equilibrium constant when analyzing the product ratio.

To relate this quantity to ΔG values, recall that $\Delta G^{o} = -RT \ln K_{eq}$ or $K_{eq} = e^{-\Delta G°/RT}$, $k_1 = e^{-\Delta G_1^{\ddagger}/RT}$, and $k_2 = e^{-\Delta G_2^{\ddagger}/RT}$. Substituting this into the above equation:

$$\frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} = \frac{e^{-\Delta G_2^{\ddagger}/RT}}{e^{-\Delta G_1^{\ddagger}/RT}} (e^{-\Delta G°/RT}) = e^{-\Delta G_2^{\ddagger}/RT} e^{-\Delta G°/RT} e^{\Delta G_1^{\ddagger}/RT} \qquad (4)$$

Combining terms:

$$\boxed{\frac{[P_B]}{[P_A]} = e^{-(\Delta G_2^{\ddagger} + \Delta G° - \Delta G_1^{\ddagger})/RT} \quad \text{or} \quad \frac{[P_B]}{[P_A]} = e^{-\Delta\Delta G^{\ddagger}/RT}}$$

Where $\Delta\Delta G^{\ddagger} = \Delta G_2^{\ddagger} + \Delta G° - \Delta G_1^{\ddagger}$

Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

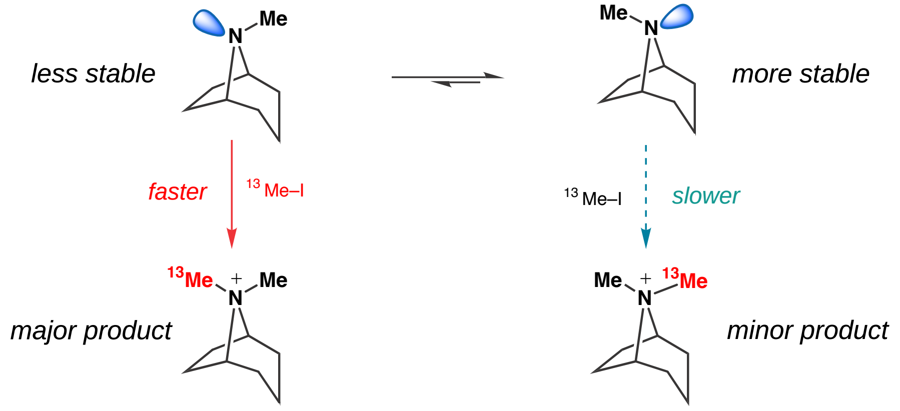
Within these limits, we can envision three scenarios:

- If both conformers react at the **same rate**, the product distribution will be the same as the ratio of conformers at equilibrium.
- If the **major conformer** is also the faster reacting conformer, the product from the major conformer should prevail, and will not reflect the equilibrium distribution.
- If the **minor conformer** is the faster reacting conformer, the product ratio will depend on all three variables in eq (2), and the observed product distribution will not reflect the equilibrium distribution.

This derivation implies that you could potentially isolate a product which is derived from a conformer that you can't even observe in the ground state!

Some Curtin-Hammett Examples

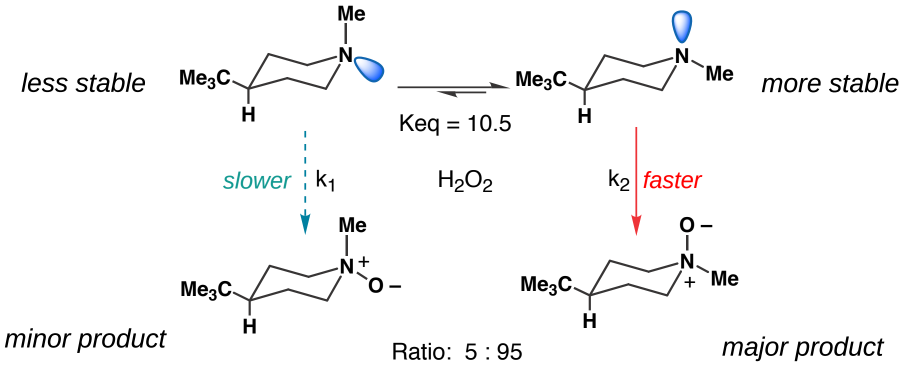
Tropane alkylation is a well-known example.



The less stable conformer reacts much faster than the more stable conformer, resulting in an unexpected major product!

JOC **1974** 319

Oxidation of piperidines:

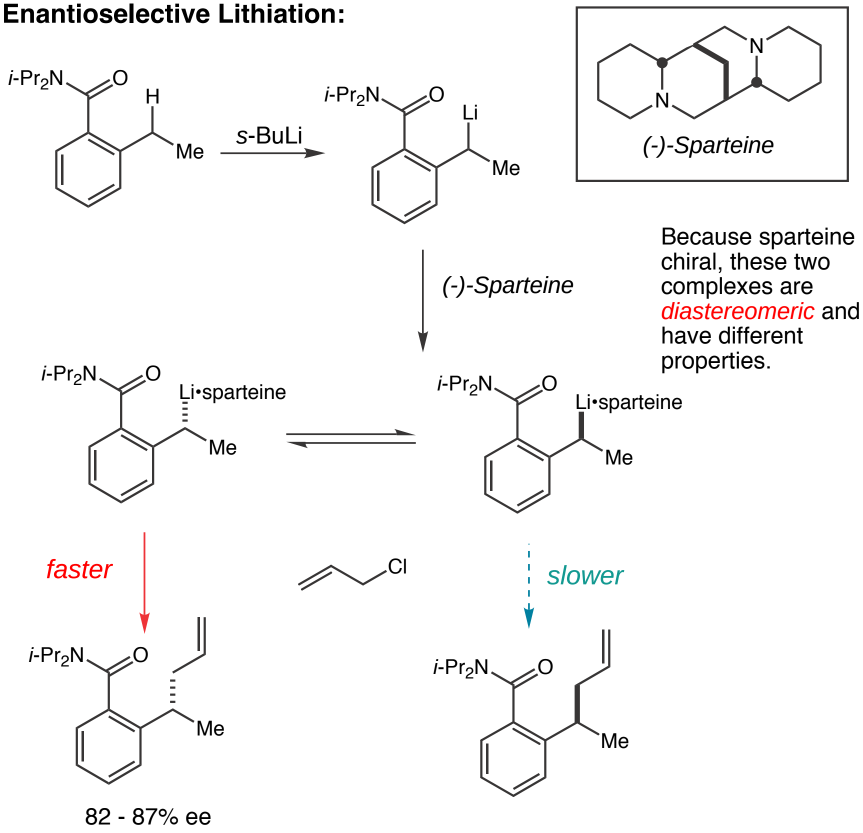


When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

Note that in this case, the more stable conformer is also the faster reacting conformer!

Tet. **1972** 573
Tet. **1977** 915

Enantioselective Lithiation:



Because sparteine is chiral, these two complexes are *diastereomeric* and have different properties.

Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of (-)-sparteine results in racemic product.

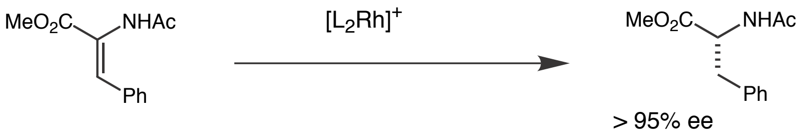
Note that the two alkyllithium complexes MUST be in equilibrium, as the enantioselectivity is the same over the course of the reaction. If they were not equilibrating, the enantioselectivity should be higher at lower conversions.

This is a case of ***Dynamic Kinetic Resolution***: Two enantiomeric alkyl lithium complexes are equilibrating during the course of a reaction with an electrophile.

Beak, *Acc. Chem. Res*, **1996**, 552

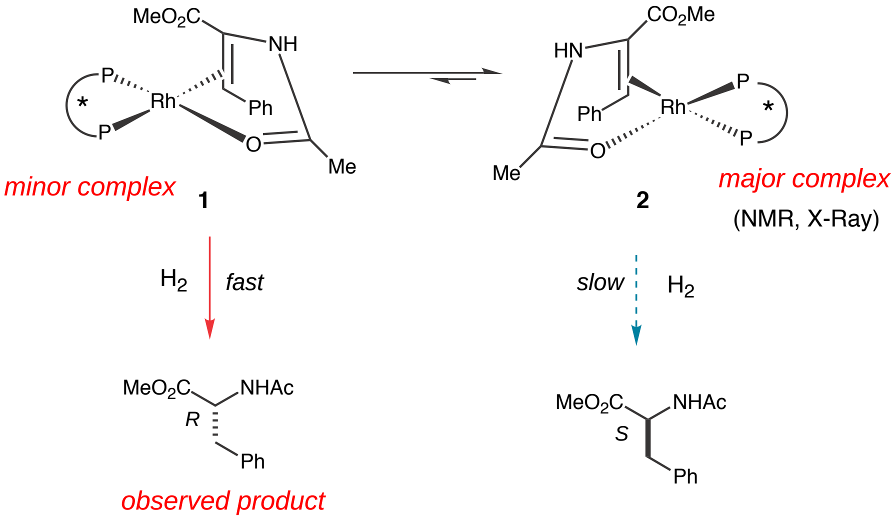
Mechanism of Asymmetric Hydrogenation

The asymmetric hydrogenation of prochiral olefins catalyzed by Rhodium is an important catalytic process.



Enantioselectivities are generally very high when the ligand is a chelating diphosphine. (ee's are given for S,S-CHIRAPHOS)

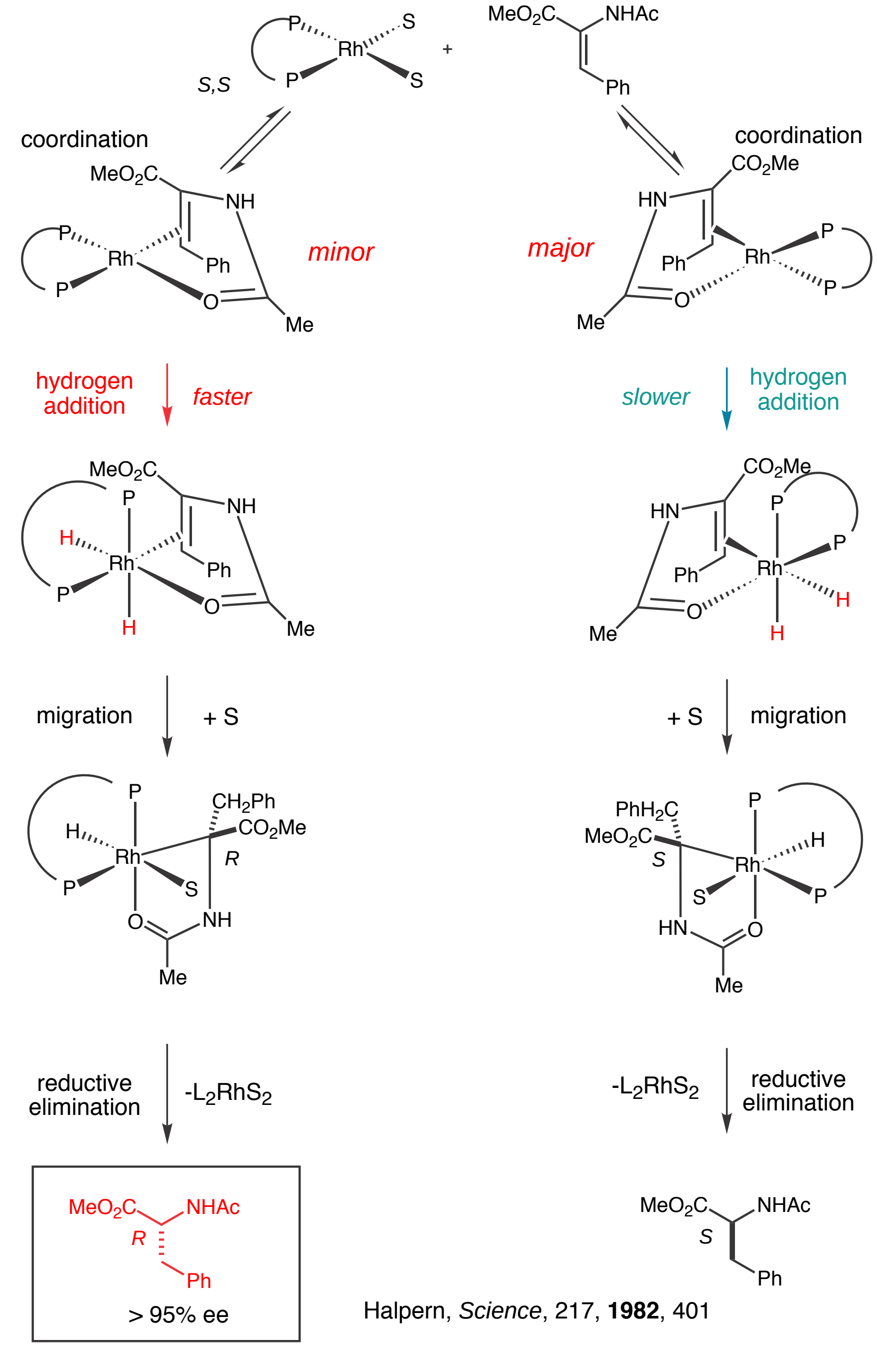
When a chiral ligand is used, there are two diastereomeric complexes which may be formed:



Observations:

- Complex 2 is the only diasteromer observed for the catalyst-substrate complex (1HNMR, X-Ray crystallography) in the absence of hydrogen
- The enantioselectivity is strongly dependant on the pressure of H_2, and degrades rapidly at higher hydrogen pressures
- The observed enantiomer is exclusively derived from the minor complex 2

*These observations may be explained using the **Curtin - Hammett Principle***

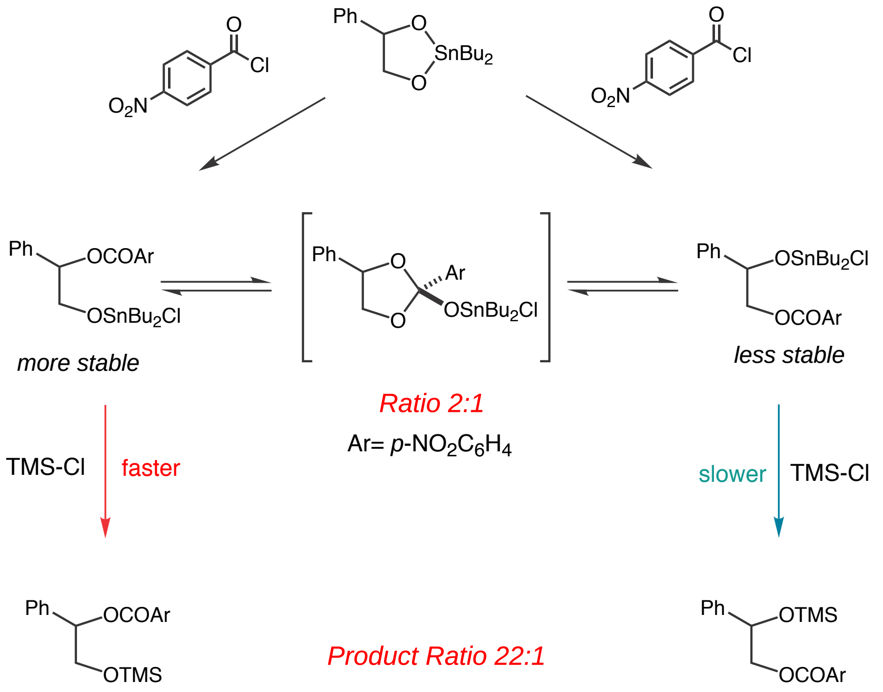


Halpern, *Science*, 217, **1982**, 401

The Curtin-Hammett treatment can be extended to ANY case where different products are formed from two rapidly intereconverting starting materials, whether they are conformers, tautomers or isomers.

$$\underset{\textit{major}}{P_A} \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} \underset{\textit{minor}}{P_B}$$

Stannylene ketals provide an efficient way to acylate the more hindered site of 1,2-diols:



The two stannyl esters are in equilibrium at room temperature, and the more stable isomer is initially formed more slowly. The stannyl esters are allowed to equilibrate before quenching with TMS-Cl, which reacts more rapidly with the less hindered primary alkoxystannane.

JOC **1996**, 5257

"It was pointed out by Professor L. P. Hammett in 1950 (private communication) that ..."

David Y. Curtin, 1954

" Because Curtin is very generous in attributing credit, this is sometimes referrred to as the Curtin-Hammett principle rather than the Curtin principle."

Louis Plack Hammett, 1970

Curtin - Hammett Principle: *The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.*

THE TAKE-HOME LESSON:

Never assume that the most stable conformation of a compound is the most reactive. It may be, but then again, it may not.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 8

Olefin Addition Reactions–1

- Hydroboration
- Epoxidation & Directed Epoxidation

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions ***(Handout)***

K. Houk, *Tetrahedron.* **1984**, *40*, 2257-2274
Theoretical Studies of Stereoselective Hydroboration Reactions ***(Handout)***

Hoveyda, Evans, Fu, *Chem Rev.* **1993**, *93*, 1307-1370
Substrate-Directable Chemical Reactions
(Electronic Handout)

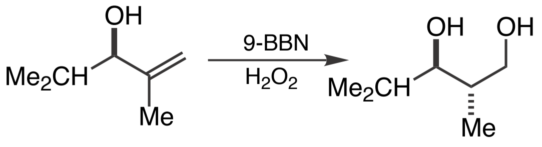
E. Vedejs, *JACS* **2003**, *125*, 10502-3
A Mechanistic Alternative for the Intramolecular Hydroboration of Homoallylic Amine and Phosphine Borane Complexes
(Electronic Handout)

D. A. Evans

Wednesday,
October 1, 2003

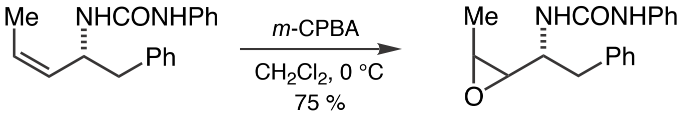
Problems of the Day: (To be discussed)

Rationalize the stereochemical outcome of these reactions.



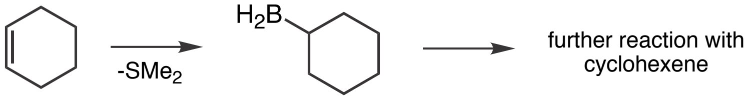
diastereoselection 24:1

W. C. Still & J. C. Barrish, *J. Am. Chem. Soc*. **1983**, *105*, 2487.

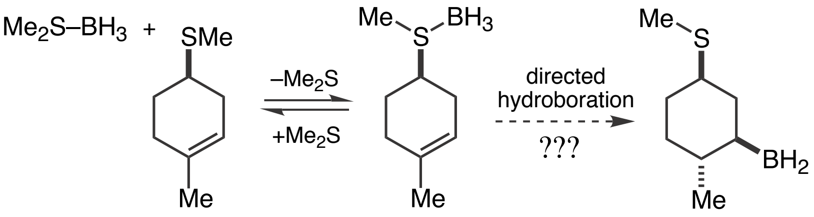


Roush, *J. Org. Chem.* **1987**, *52*, 5127. *Diastereoselection = 95 : 5*

Web Problem 163: The following is an idea that has been proposed to you by a fellow student. The proposal is based on the fact that borane–methyl sulfide complex is an effective hydroboration reagent (eq 1). It is proposed that homoallylic sulfides such as that illustrated below should be capable of "directing" the hydroboration process from this substituent through the borane-substrate complex.



(1)



(2)

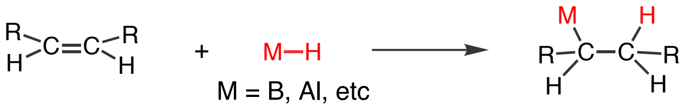
Part A. In order to begin your critique, you must possess a good working knowledge of the details of the hydroboration of olefins with borane–methyl sulfide. Provide a clear depiction of the transition state for the hydroboration process using ethylene as the olefinic substrate and borane–methyl sulfide as the hydroborating agent.

Part B. Now, based on your knowledge of the hydroboration reaction and the principles learned thus far in Chem 206, critique the idea proposed in Eq 2. You must concisely state the logic upon which you base your assessment. *Pictures speak a thousand words.*

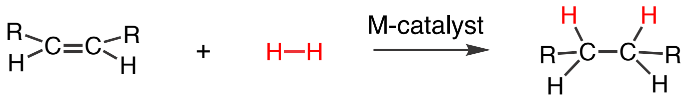
Olefin Addition Reactions: Introduction

Representative Cis-Addition Processes

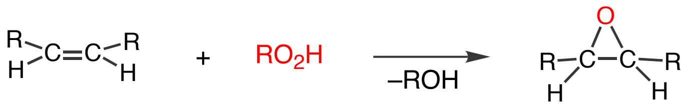
- Hydrometallation



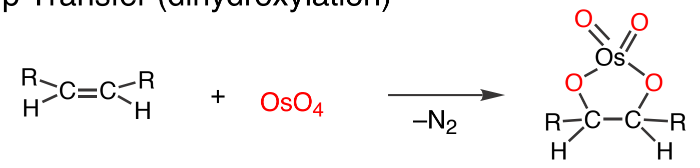
- Hydrogenation



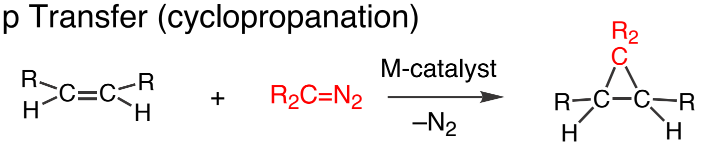
- Group Transfer (epoxidation)



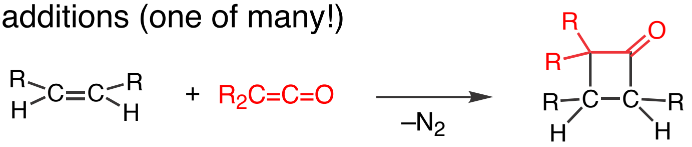
- Group Transfer (dihydroxylation)



- Group Transfer (cyclopropanation)



- Cycloadditions (one of many!)



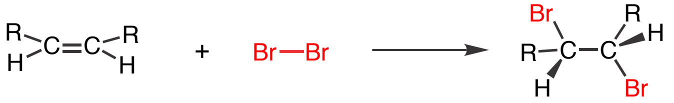
Attributes:

Each process adds to the C=C via a stereospecific process

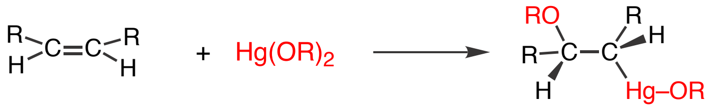
Intermediates *may* be involved in some of the indicated reactions

Representative Trans-Addition Processes

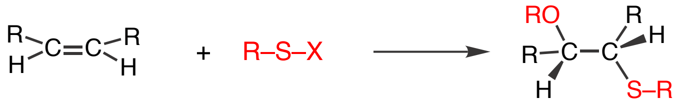
- Halogenation



- Oxy–metallation (M = Hg(II), Tl(III))



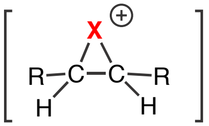
- Oxy–sulfenation (M = S(II), Se(II))



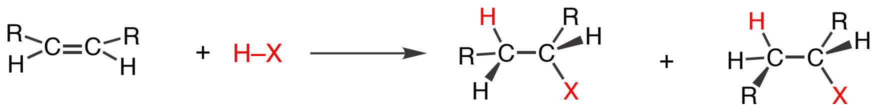
Attributes:

Each process may proceed via an bridged intermediate where X is the initiating electrophile

Olefin substitution may disrupt bridging



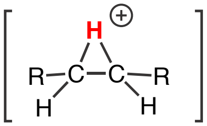
- Addition of hydrogen halides



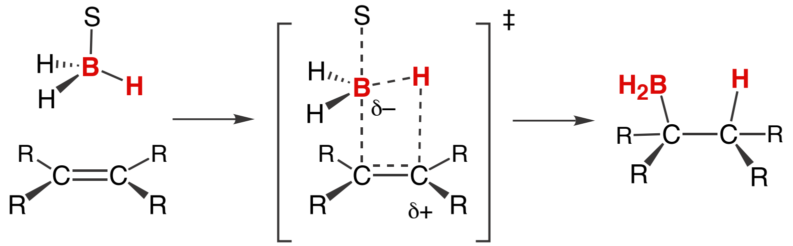
Attributes:

Process may proceed via an bridged intermediate where H+ is the initiating electrophile

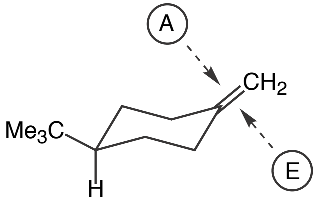
Olefin substitution, reaction conditions as well as halide type may disrupt bridging



The basic process

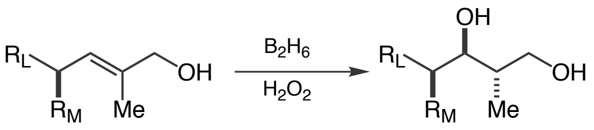


Response to steric effects: Here is a good calibration system:



Oxidant	Ratio, A:E	Reference
MCPBA	69:31	*JOC*, **1967**, *32*, 1363
BH_3, H_2O_2	34:66	*JOC*, **1970**, *35*, 2654

Acyclic hydroboration can be controlled by A(1,3) interactions:

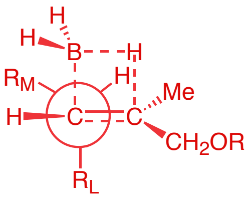


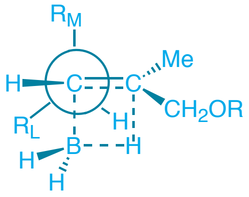
major diastereomer

control elements

A(1,3) allylic strain
Steric effects; R_L vs R_M
Staggered transition states

major

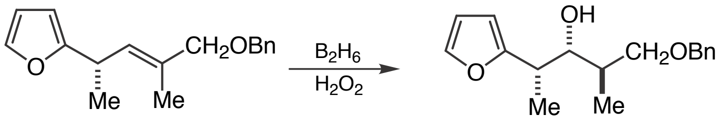




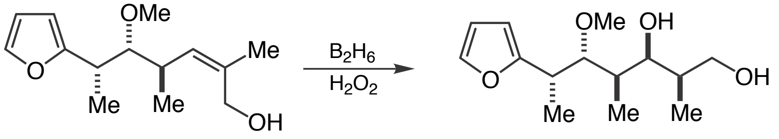
minor

Houk, "*Theoretical Studies of Stereoselective Hydroboration Reactions"*
Tetrahedron **1984**, *40*, 2257 **(Handout)**

Hydroborations dominated by A(1,3) Strain

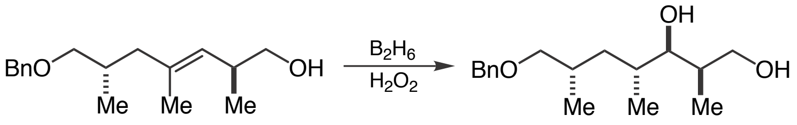


diastereoselection 8:1



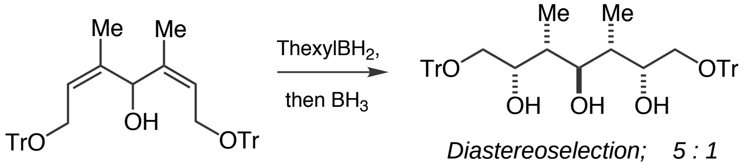
diastereoselection 12:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc*. **1979**, *101*, 259.

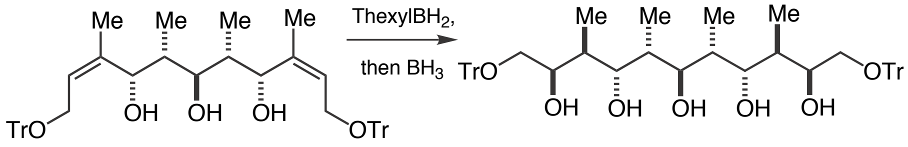


Diastereoselection = 3:1

C. H. Heathcock et. al. *Tetrahedron Lett* **1984** *25* 243.



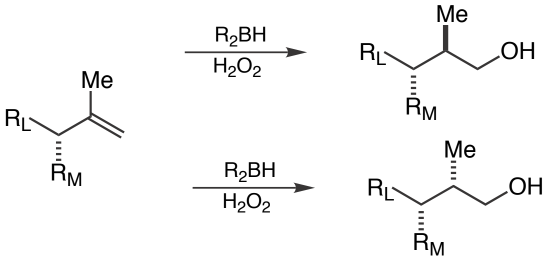
Diastereoselection; 5 : 1



Diastereoselection; 4: 1

Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 2487.

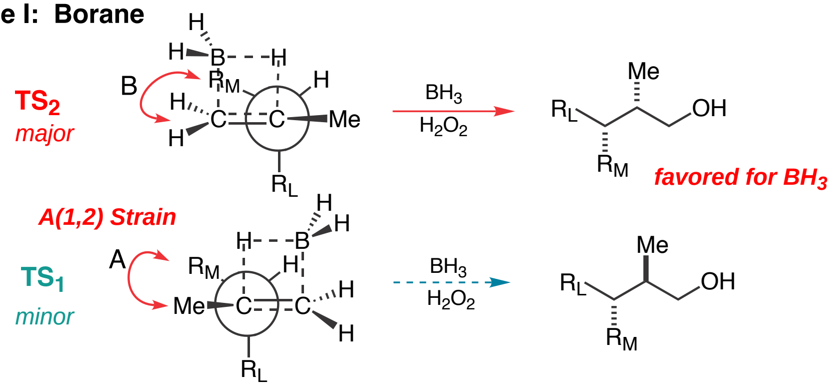
Hydroborations dominated by A(1,2) Strain

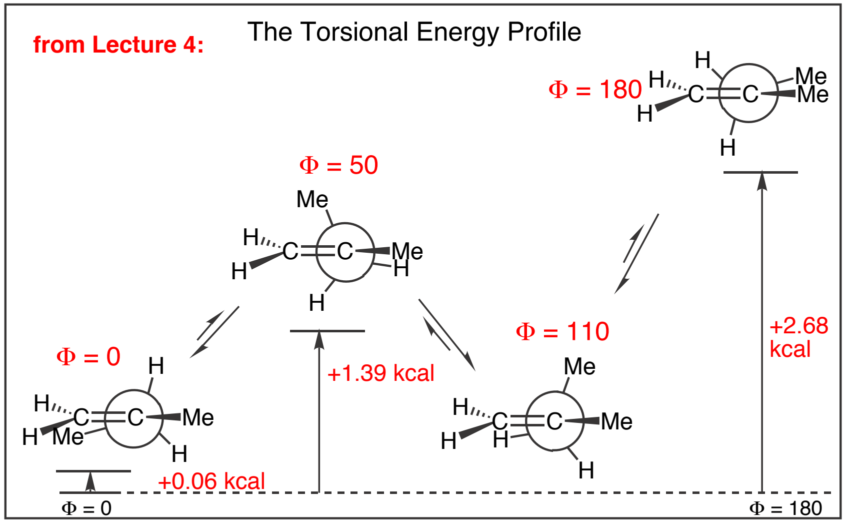


R_2BH structure is a potential variable

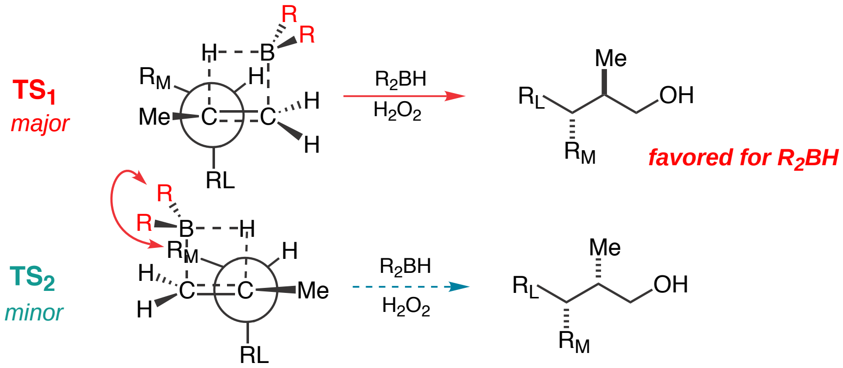
Houk's rules: Orient R_L anti-periplanar to incoming reagents to avoid TS eclipsing:

■ Case I: Borane





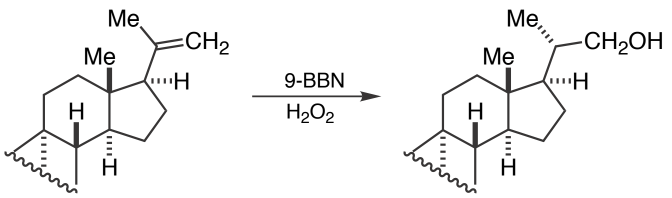
■ Case II: Dialkylboranes



Midland finds that TS_1 favored for R_2BH reagents, but TS_1 ~ TS_2 for BH_3

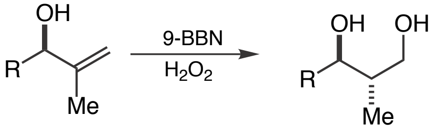
Others have found that TS_1 favored over TS_2 for BH_3

Representative Examples



M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725..

R_2BH	*diastereoselection*
borane methylsulfide	1 : 1
thexylborane	4 : 1
9-BBN	14 : 1
dicyclohexylborane	26 : 1

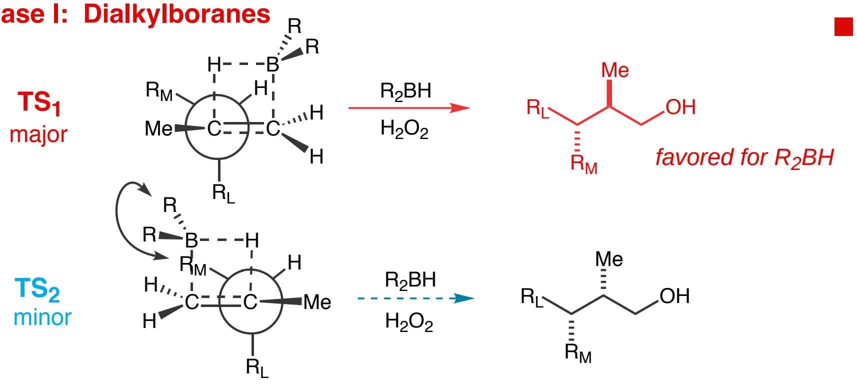


R = n-Bu: *diastereoselection 11:1*
R = $CHMe_2$: *diastereoselection 24:1*

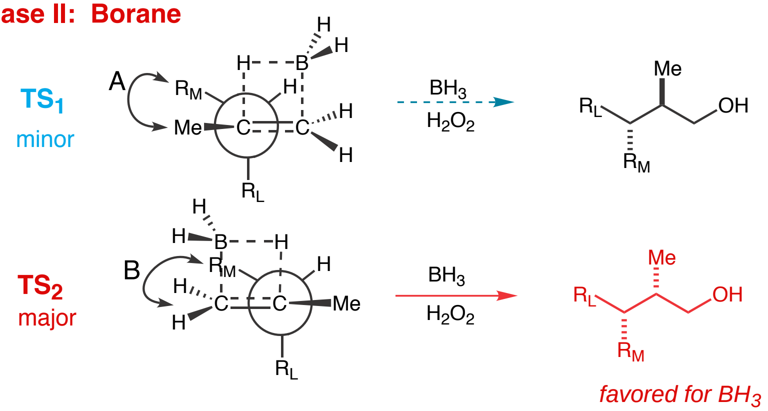
Model is consistent if you presume HO = R_M: R = R_L

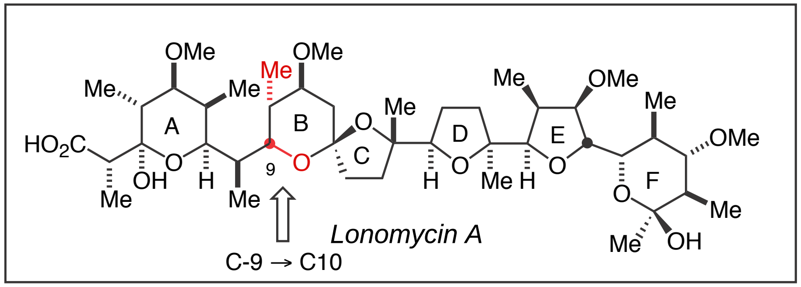
W. C. Still & J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487.

■ Case I: Dialkylboranes

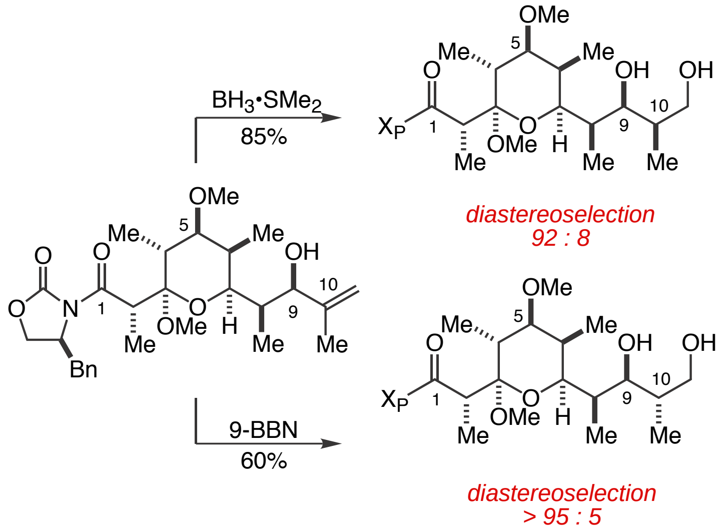


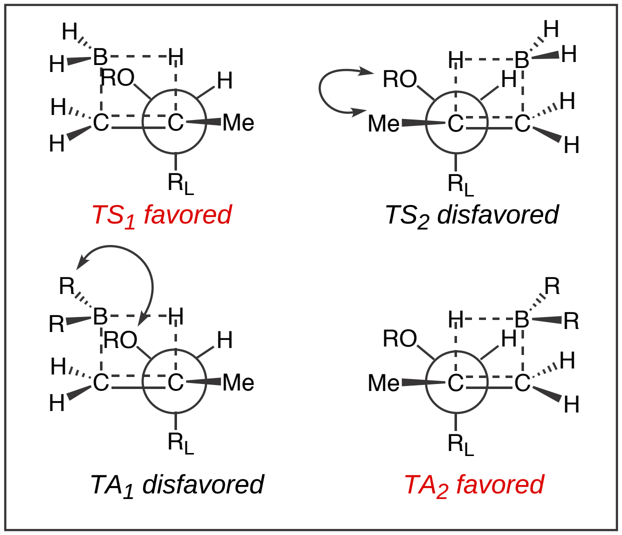
■ Case II: Borane





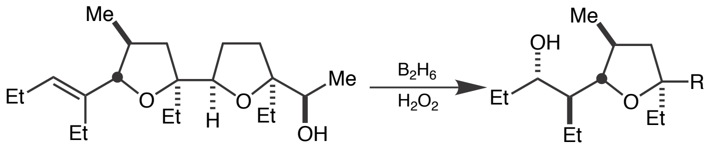
Evans, Ratz, Huff, Sheppard, *JACS* **1995**, *117*, 3448-3467.





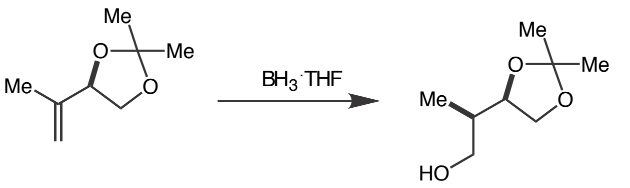
Represetative Hydroboration Examples: Acyclic Control

For each of the examples shown below, attempt to rationalize the stereochemical outcome of the reaction in terms of one of the models presented in the discussion.



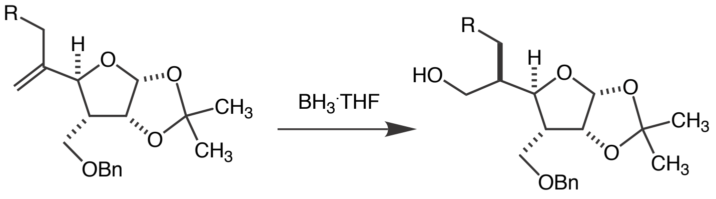
"one isomer"

Y. Kishi & Co-workers, *J. Am. Chem. Soc*. **1978**, *100*, 2933.



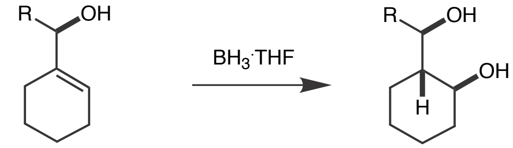
Mori, K.
Tetrahedron **1976**, *32*, 1979

diastereoselection 12:1



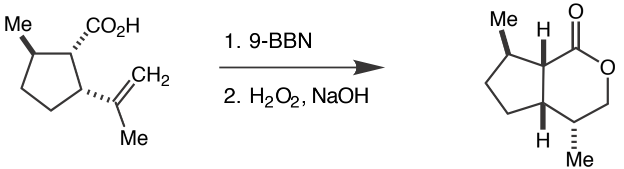
Oikawa et. al.
Tetrahedron Lett. **1983**, *19*, 1987.

R=H; Diastereoselection = 6.8:1
R=OBn Diastereoselection = 6.6:1



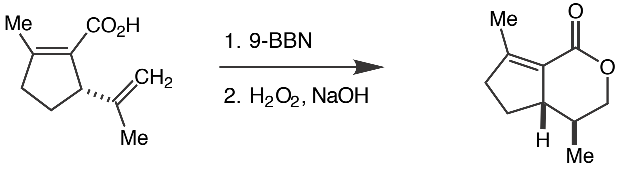
Birtwistle et. al.
Tetrahedron Lett. **1986**, *25*, 243.

R = CH$_3$; Diastereoselction = 6.7:1
R = isopropyl "One Compound"



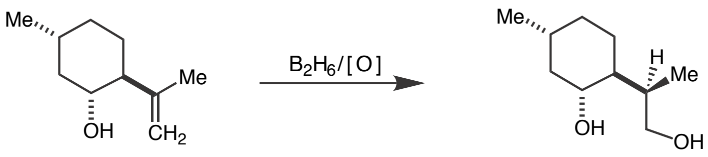
Wolinsky, J.; Eustace, E. J.
J. Org. Chem. **1972**, *37*, 3376.

Diastereoselection = 7:1

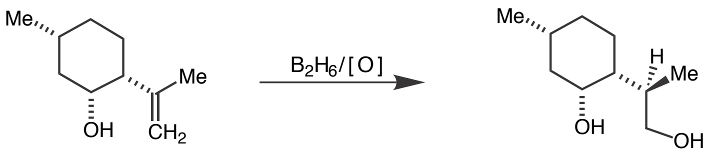


Wolinsky, J.; Nelson, D.
Tetrahedron. **1968**, *25*, 3767.

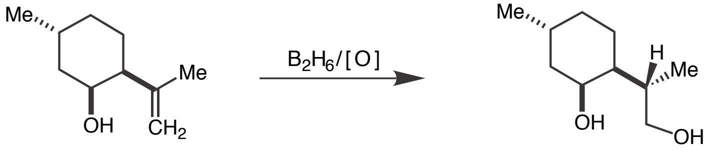
Diastereoselection = 10:1



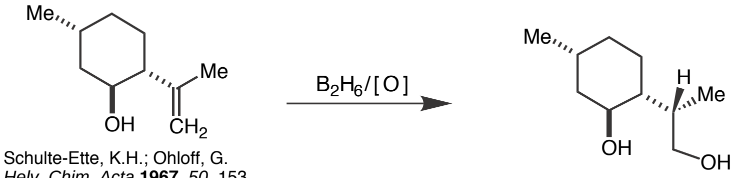
Diastereoselection = 19:1



Diastereoselection = 32:1



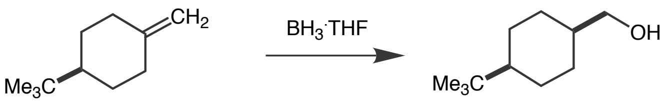
Diastereoselection = 10:1



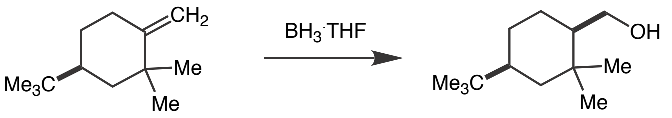
Schulte-Ette, K.H.; Ohloff, G.
Helv. Chim. Acta **1967**, *50*, 153.

Diastereoselection = 4.6:1

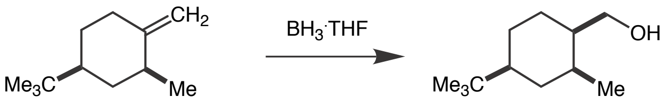
Representative Hydroboration Examples: Cyclic Systems



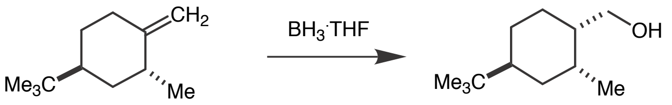
Diastereoselection = 2.1:1



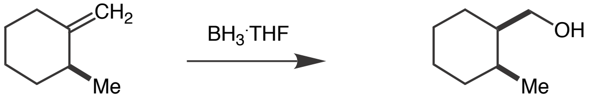
Diastereoselection = 1.2:1



Diastereoselection = 3.3:1

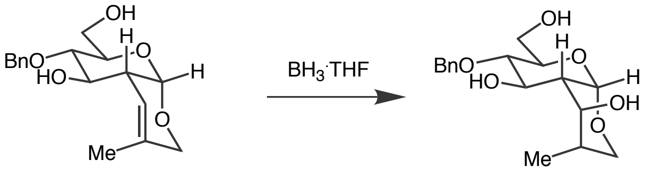


Diastereoselection = 2.4:1



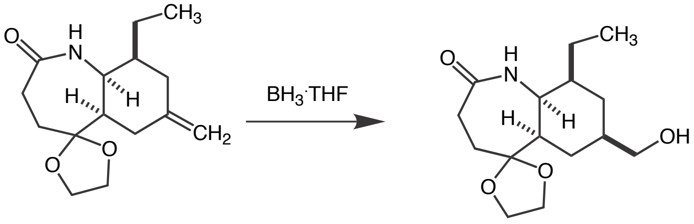
Y. Senda et. al.
Tetrahedron **1977**, *33*, 2933.

Diastereoselection = 4.9:1
(Compare with H.C. Brown's case, with 9-BBN; 1.5:1)



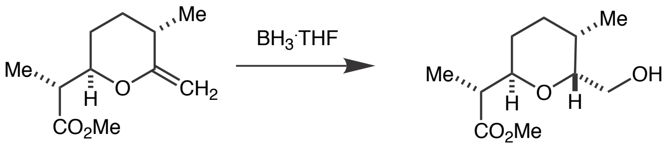
B. Fraser-Reid et. al.
J. Am. Chem. Soc. **1984**, *106*, 731.

Major isomer; no ratio given.



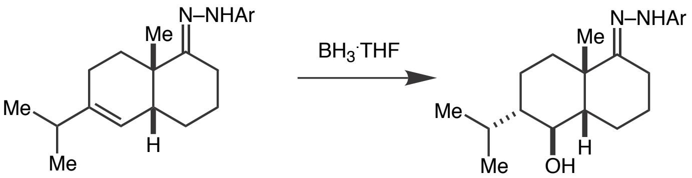
Sallay, S. I.
J. Am. Chem. Soc. **1967**, *89*, 6762.

90% yield, *no diastereoselection given*



Ley, S. et.al.
J. Chem. Soc. Chem. Commun. **1983** 630.

55% yield with the diastereomeric alcohol produced in an unspecified amount. Recycling of the minor isomer further provided 15% of the desired material



McMurry, J. E.
J. Am. Chem. Soc. **1968**, *90*, 6321.

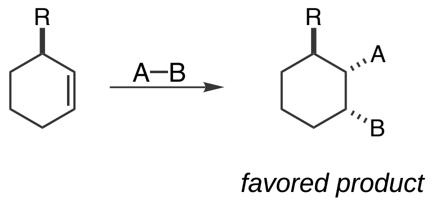
Minor diastereomer not detected

Directed Reactions: An Introduction

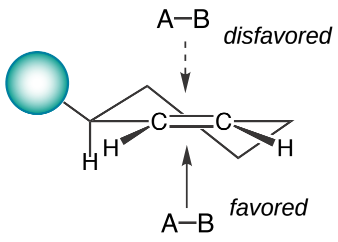
Stereochemical Control Elements for all reactions

- Steric & Electronic Factors
- Stereoelectronic Considerations
- Associative Substrate-Reagent Interactions

■ Steric control:



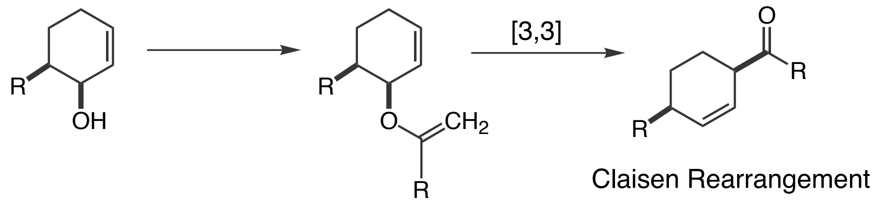
favored product



Nonbonding Interactions disfavor the syn diastereoface

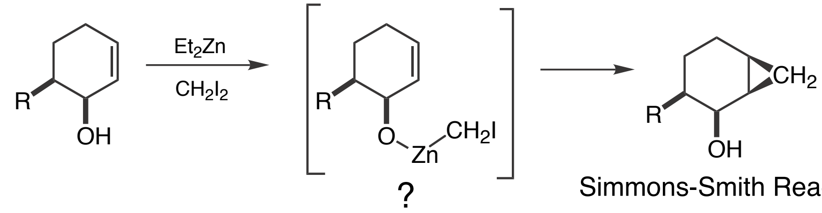
Heteroatom-directed Reactions

Mechanism-based: (HO & C=C must be allylic)



Claisen Rearrangement

via Reagent Ligation

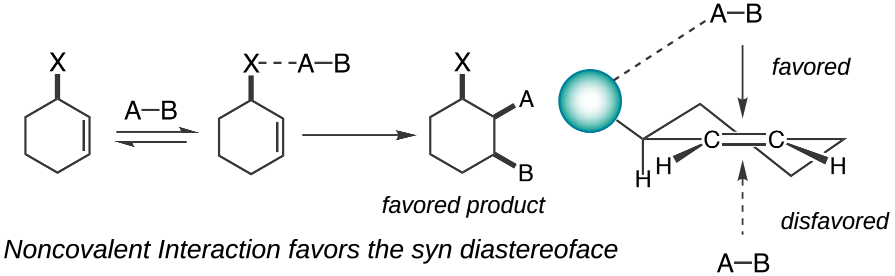


Simmons-Smith Reaction

Directed Reactions

Review: Hoveyda, Evans, Fu *Chem. Reviews* **1993**, *93*, 1307

■ Associative Substrate-Reagent Interactions



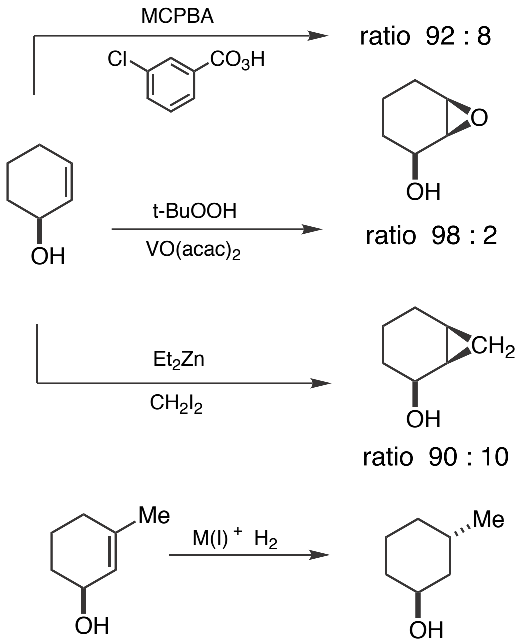
favored product

Noncovalent Interaction favors the syn diastereoface

Agenda

- **Directed Oxidations**
  - Epoxidation
  - Hydroboration
- **Directed Reductions**
  - Hydrogenation
  - Hydride reduction
- **Directed C–C Bond Constructions**

Hydroxyl-directed Reactions



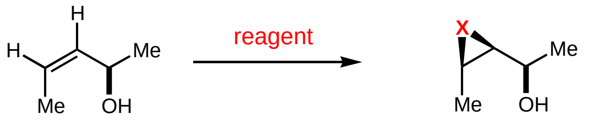
Henbest
J. Chem. Soc. 1958, (1957)

Sharpless
JACS **95**, 6136, (1973)

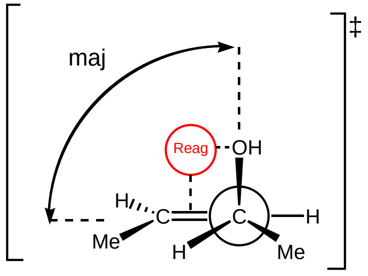
Winstein
JACS **91**, 6892, (1969)

(Ir^+) Stork
JACS **105**, 1072 (1983)
(Rh^+) Evans
JACS **106**, 3866 (1984)

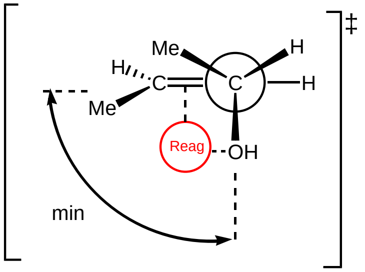
Orientation of the Directing Group



X = O, CH_2



TS_{major}



TS_{minor}

Orientation of directing group is not the same for all reactions

Reagent	Selectivity	Φ Estimate
t-BuO_2H, V^{+5}	71 : 29	~ 50 °
RCO_3H	95 : 5	~ 120 °
CH_2I_2, Zn–Cu	> 99 : 1	?

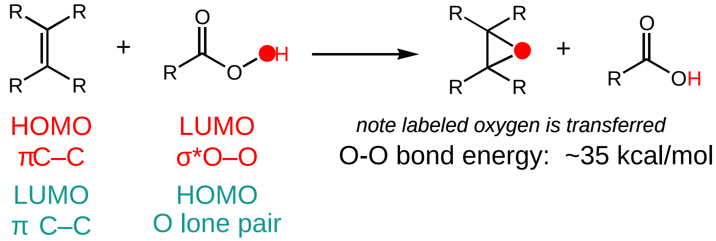
The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

Peracid Epoxidation

A. Rao in *Comprehensive Organic Synthesis,* Trost, Ed., **1992**, Vol 7, Chapter 3.1

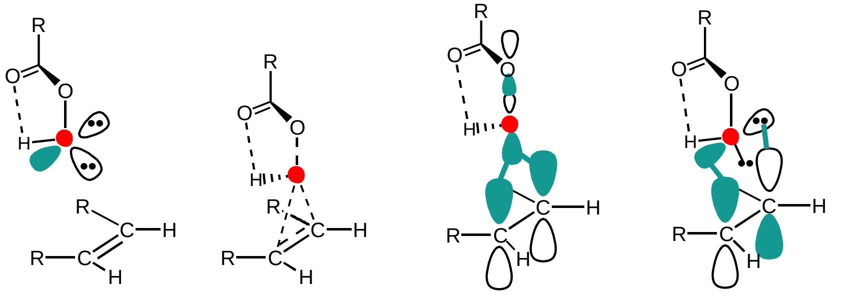
- General Reaction:



note labeled oxygen is transferred

O-O bond energy: ~35 kcal/mol

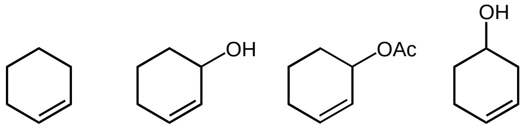
- Transition state: What about lone pairs. [Consider ● to be Sp^2 hybridized].



HOMO πC–C
LUMO: σ O–O

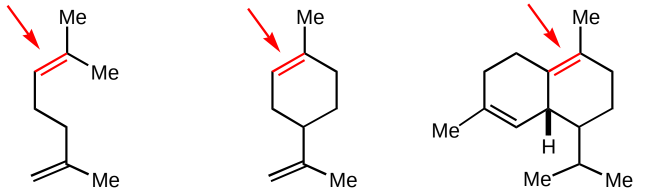
HOMO: O lone pair
LUMO:π C–C

- Reaction rates governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:



1.0 0.6 0.05 0.4

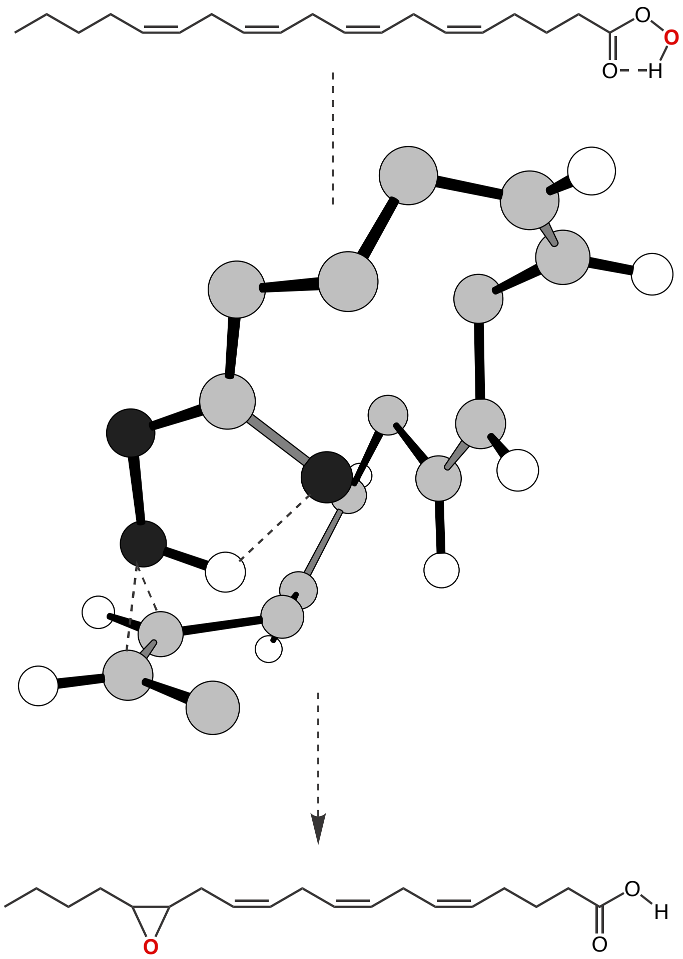
- The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



Diastereoselective Peracid Epoxidation

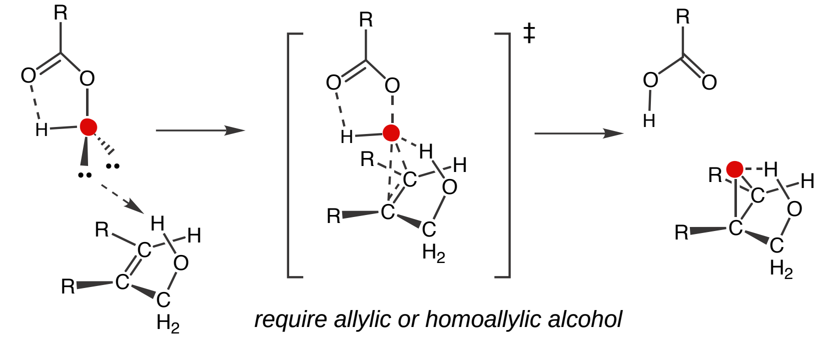
Stereoelectronic Implications of intramolecular Peracid Epoxidation

- Per-arachidonic acid Epoxidation: Corey, *JACS* **101**, 1586 (1979)



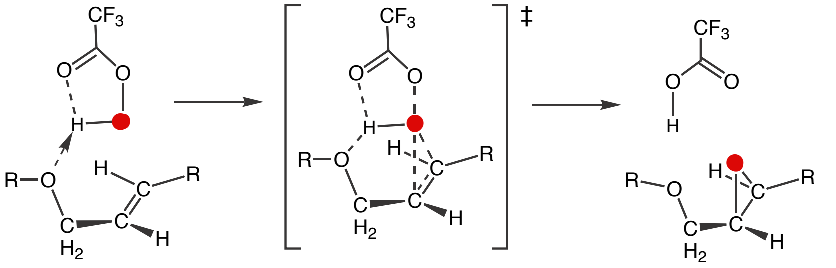
The Directed Peracid Epoxidation

- **Transition State Hydrogen Bonding: Substrate as H-bond donor (Henbest)**

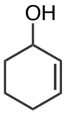
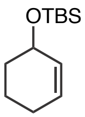
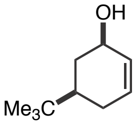
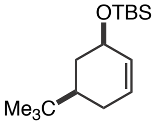
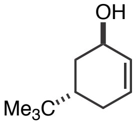
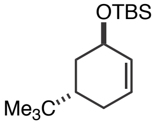


require allylic or homoallylic alcohol

- **Transition State Hydrogen Bonding: Peracid as H-bond donor (Ganem)**



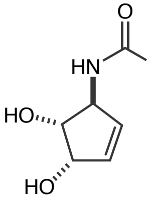
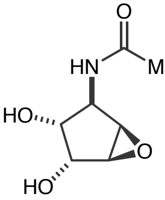
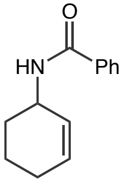
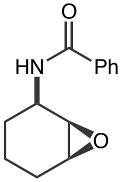
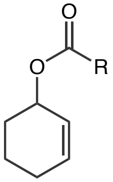
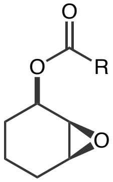
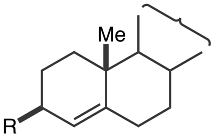
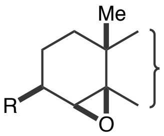
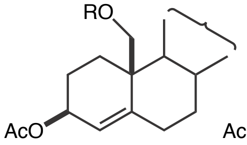
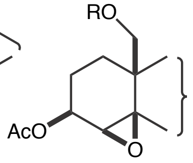
require more acidic peracid both allylic alcohols and ethers OK

	Syn : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)		*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
	24 : 1	50 : 1		1 : 7	5 : 1
	24 : 1	100 : 1		1 : 8	12 : 1
	5 : 1	100 : 1		1 : 4	1 : 6

Ganem *Tet. Let.* **1985**, *26*, 4895

Diastereoselective Peracid Epoxidation

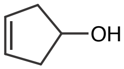
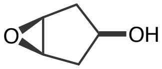
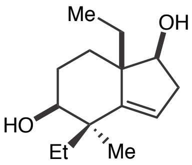
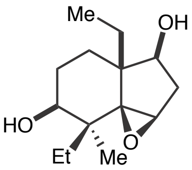
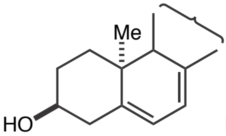
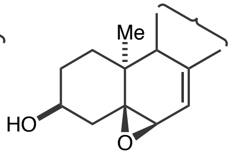
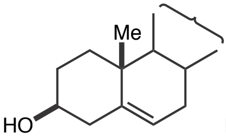
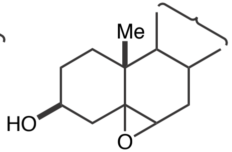
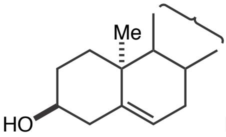
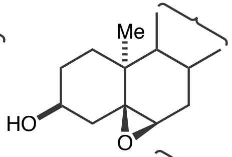
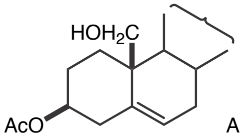
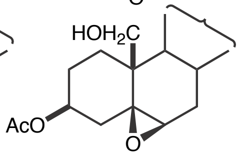
Epoxidation of Cyclic Olefins with Amide &Urethane Directing Groups

Substrate	Major Product		Selectivity
			"highly selective"
			"highly selective"
		a. R = NH_2 b. R = NHBn c. R = NMe_2	3 : 1 5 : 1 10 : 1
		a. R = OCONHBn b. R = $OCONMe_2$	>20 : 1 >20 : 1
		a. R = $CONH_2$ b. R = CONHBn c. R = $CONMe_2$	6 : 1 >10 : 1 2 : 1

Conditions: Perbenzoic acid, or meta-chlorobenzoic acid in benzene.

(Table 11, p1316, from the Evans, Hoveyda, Fu review article)

Epoxidation of Cyclic Homoallylic Alcohols

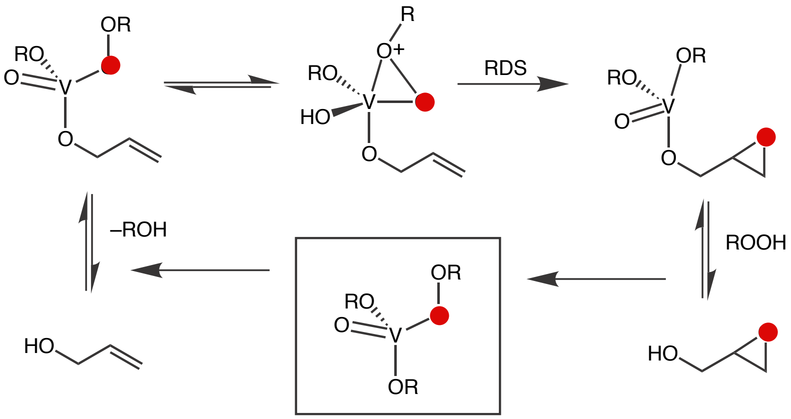
Substrate	Major Product	Selectivity
		9 : 1
		"highly selective"
		16 : 1
		1 : 1
		21 : 1
		5 : 1

Conditions: Perbenzoic acid, or meta-chloroperbenzoic acid in benzene or cyclopentane.

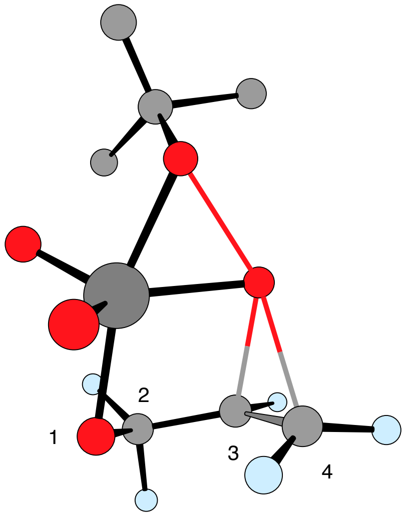
(Table 14, p1318, from the Evans, Hoveyda, Fu review article)

Sharpless Epoxidation (V+5)

The Sharpless Epoxidation

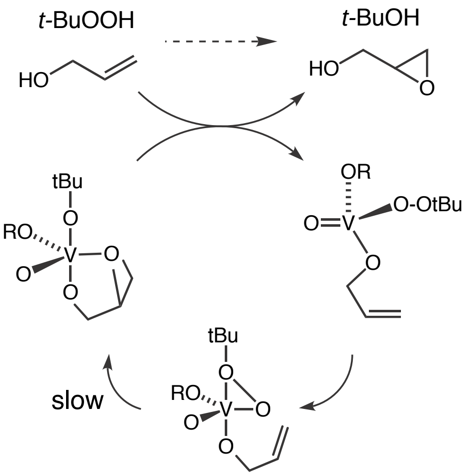


Aldrichimica Acta, **12**, 63 (1979)

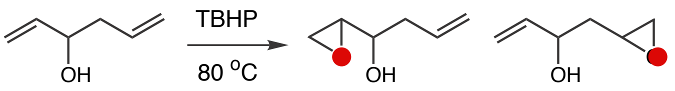


Chem 3D Transition State

O–C_2–C_3–C_4 = 41°
The Sharpless estimate: ~50°

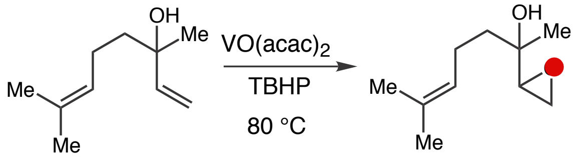


■ The literature precedent: Sheng, Zajecek, *J. Org. Chem.* **1970**, *35*, 1839

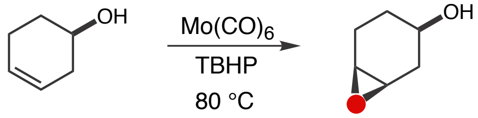


Catalyst		
	VO(acac)$_2$	4 : 1
	Mo(CO)$_6$	1 : 1

■ Next step: Sharpless, Michaelson *JACS* **1973**, *95*, 6136

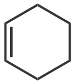
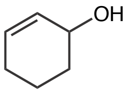
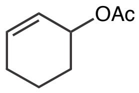
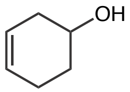


Regioselection 20:1



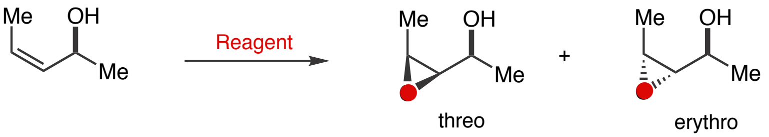
Stereoselection 98:2
(90 % yield)

Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives *JACS* **1973**, *95*, 6136

Substrate	$k_{rel}^{a,b}$ (diastereoselectivity^{c})		
	peracid	Mo(CO)$_6$	VO(acac)$_2$
	1.00	1.00	1.00
	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
	0.046 (37 : 63)	0.07 (40 : 60)	--
	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

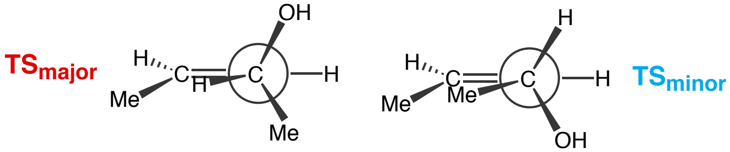
[a,b] The relative rate data apply only to a given column.
Values in parenthesis refer to the ratio of syn:anti epoxide.

■ Allylic Alcohols:

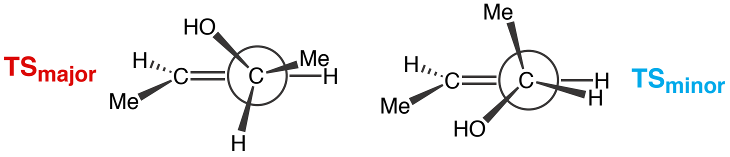


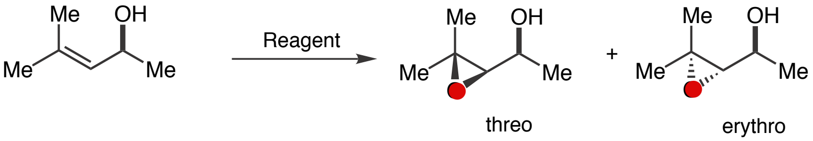
Φ Estimate	Reagent	Ratio
~ 120 °	*m*-CPBA	95 : 5
40-50 °	*t*-BuOOH / VO(acac)$_2$	71 : 29
	t-BuOOH / Mo(CO)$_6$	84 : 16

■ RCO$_3$H Transition States: Φ ~ 120 °



■ V(+) Transition States: Φ ~ 45 °

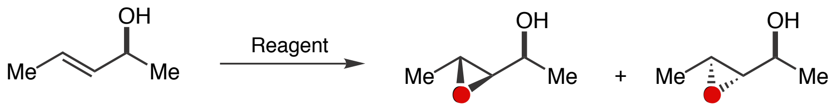




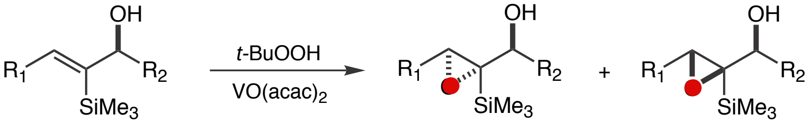
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, *21*, 1657, 4843.

K. B. Sharpless & Coworkers
Tetrahedron Lett. **1979**, *20*, 4733.

Reagent	Ratio
m-CPBA	95 : 5
t-BuOOH / VO(acac)$_2$	86 : 14
t-BuOOH / Mo(CO)$_6$	95 : 5
t-BuOOH / (*t*-BuO)$_3$Al	100 : 0

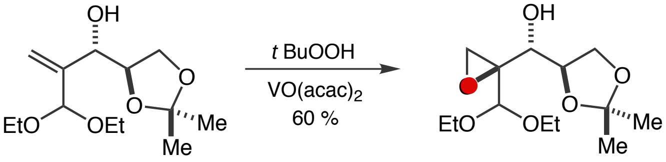


Reagent	Ratio
m-CPBA	64 : 36
t-BuOOH / VO(acac)$_2$	29 : 71
t-BuOOH / Mo(CO)$_6$	62 : 38
t-BuOOH / (*t*-BuO)$_3$Al	64 : 36

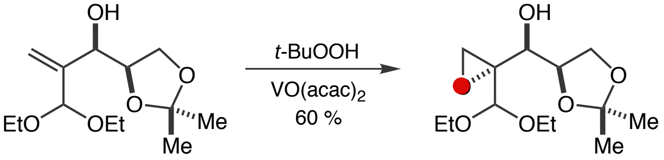


Oshima, *Tetrahedron Lett.* **1982**, *23*, 3387.

R$_1$	R$_2$	Yield	Ratio
H	Bu	84 %	99 : 1
C$_5$H$_{11}$	Me	70 %	99 : 1

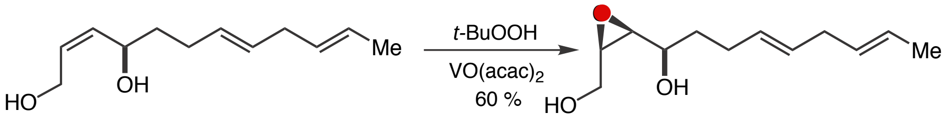


only isomer



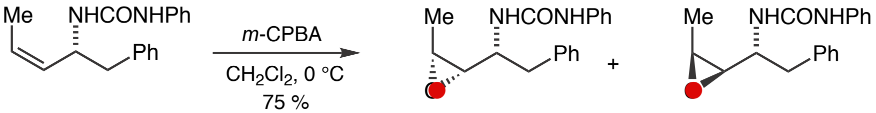
only isomer

Depezay, *Tetrahedron Lett.* **1978**, *19*, 2869.



Boeckman, *JACS* **1977**, *99*, 2805.

Diastereoselection = 7 : 1

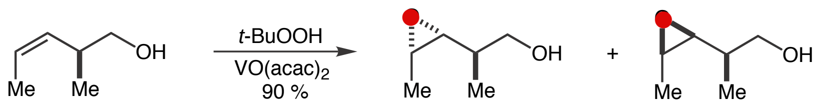


Roush, *J. Org. Chem.* **1987**, *52*, 5127.

Diastereoselection = 95 : 5

Epoxidation of Acyclic Homoallylic Alcohols

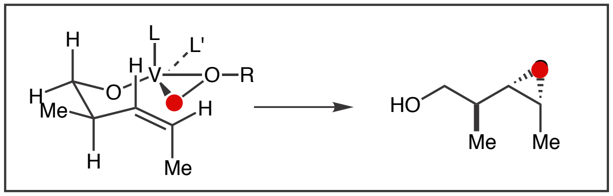
Homoallylic Alcohols (Mihelich, *JACS* **1981**, *103*, 7690)

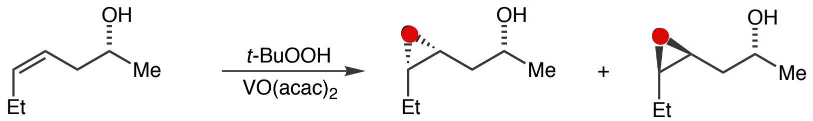


Diastereoselection > 400 : 1

Control Elements

A(1,3) Strain
Directed Rxn

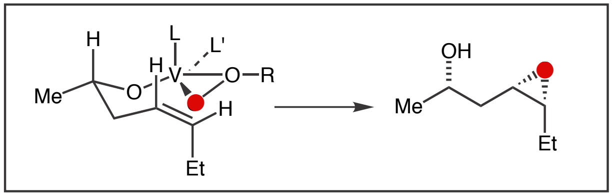




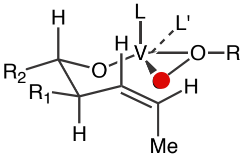
Diastereoselection 12 : 1

Control Elements

Directed Rxn

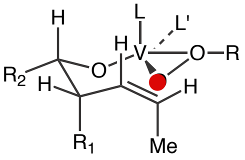


Prediction



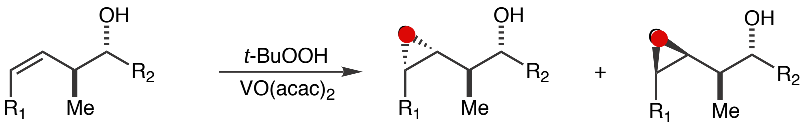
Anti diastereomer

Anti should be more diastereoselective than syn



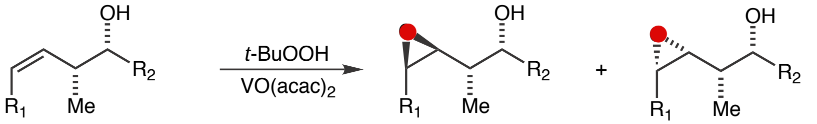
Syn diastereomer

Anti diastereomer

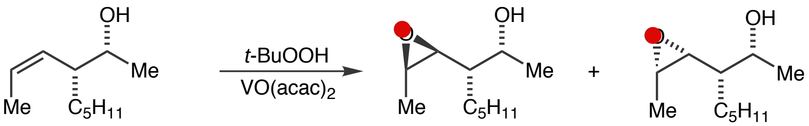


R_1	R_2	Yield	Ratio
C_6H_{13}	Me	92 %	104 : 1
Me	*i*-Pr	97 %	> 400 : 1

Syn diastereomer



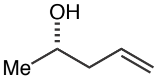
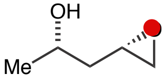
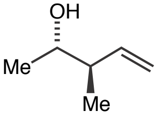
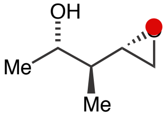
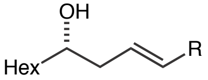
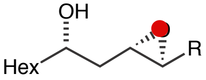
R_1	R_2	Yield	Ratio
C_6H_{13}	Me	73 %	70 : 1
Me	Me	70 %	85 : 1
Me	C_5H_{11}	81 %	16 :1



E. D. Mihelich & Coworkers
J. Am. Chem. Soc. **1981**, *103*, 7690.

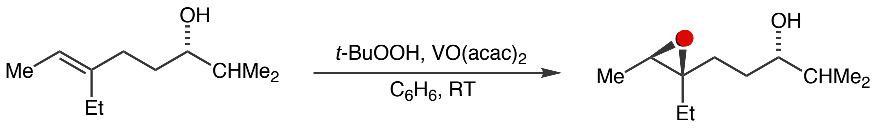
Diastereoselection = 211 : 1

Epoxidation of Homoallylic Alcohols with TBHP, VO(acac)$_2$

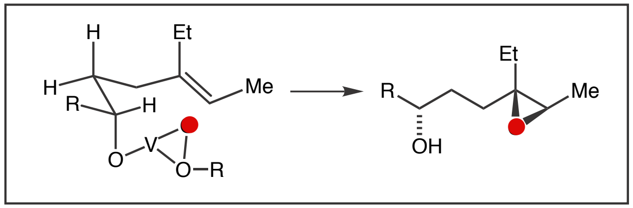
Substrate	Product	Selectivity
		2 : 1
		4.6 : 1
 R = $(CH_2)_7CO_2Me$		1.4 : 1

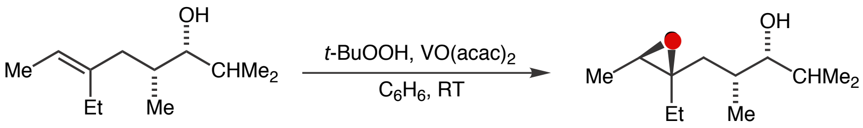
Epoxidation of Acyclic Homoallylic Alcohols

Bishomoallylic Alcohols (Kishi, *Tet. Lett.* **1978**, *19*, 2741)



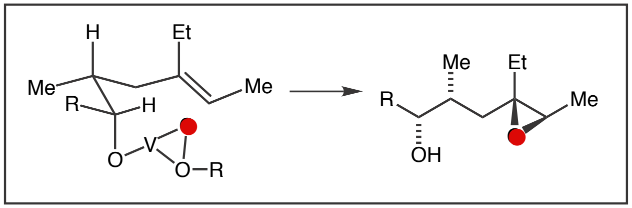
diastereoselection ~ 9 : 1

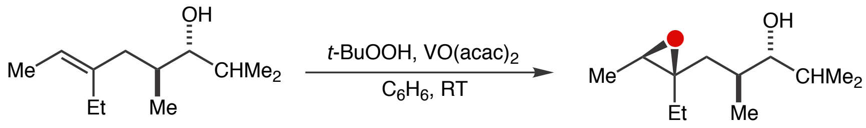




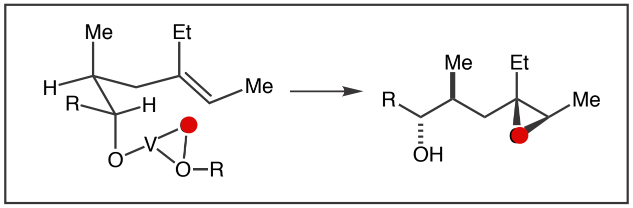
diastereoselection ~ 20 : 1

2nd stereocenter is reinforcing

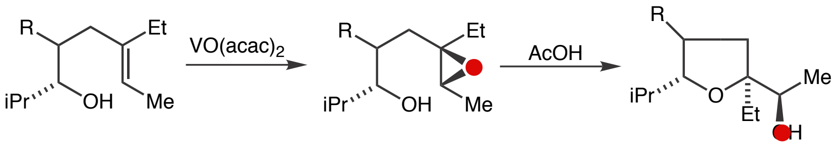




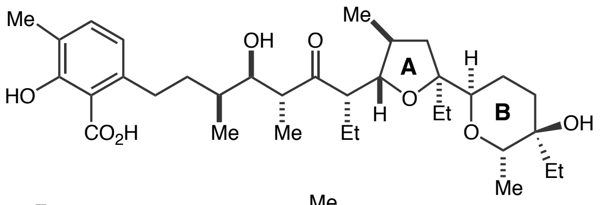
diastereoselection ~ 6 : 1

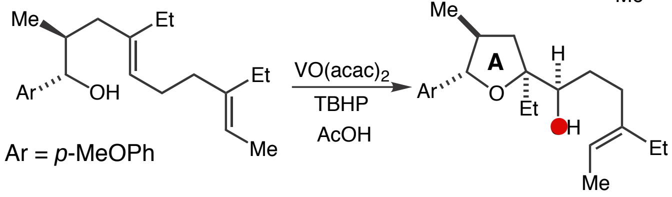


Epoxidation & Cyclization of Bishomoallylic Alcohols



The Kishi Lasalocid Synthesis (*JACS* **1978**, *100*, 2933)

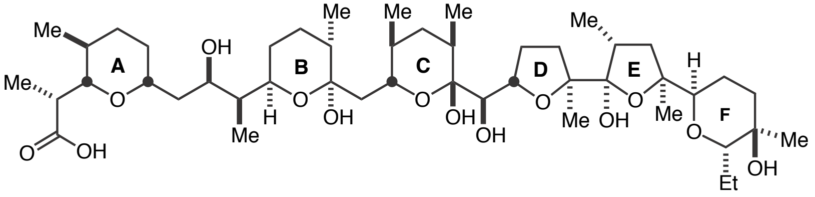


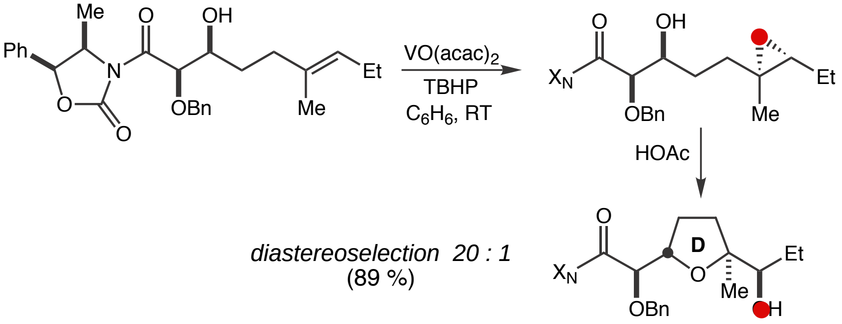


Ar = *p*-MeOPh

Diastereoselection 8:1

Evans X-206 Synthesis JACS **1988**, *110*, 2506.





diastereoselection 20 : 1
(89 %)

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 9

Olefin Addition Reactions–2

- Epoxidation & Directed Epoxidation
- Hydrogenation
- Olefin Bromination

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

Hoveyda, Evans, & Fu (**1993**). *Substrate-directable chemical reactions*. Chem. Rev. 93: 1307-70 ***(Handout)***

J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987) ***(Handout)***

Investigation of the early Steps in Electrophilic Bromination through the Study of the Reaction of Sterically Encumbered Olefins
R. S. Brown, *Accts. Chem. Res.* **1997**, *30*, 131 **(handout)**

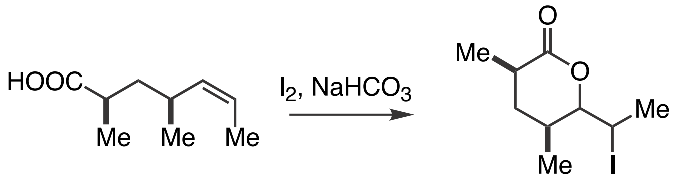
Bromoniun Ions or β-Bromocarbocations in Olefin Bromination. A Kinetic Approach to Product Selectivities
M-F. Ruasse, *Accts. Chem. Res.* **1990**, *23*, 87 **(handout)**

D. A. Evans

Friday,
October 3, 2003

Problems of the Day: (To be discussed)

Predict the stereochemical outcome of the indicated reaction.

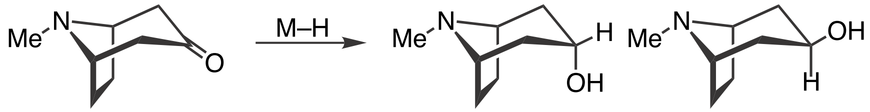


Kinetic Control: 3 eq. I_2, MeCN, $NaHCO_3$, 0°C

diastereoselection: 20:1

Bartlett, P. A.; Richardson, D.; Myerson, J. *Tetrahedron* **1984**, *12*, 2317

Rationalize the stereochemical outcome of the indicated reaction.



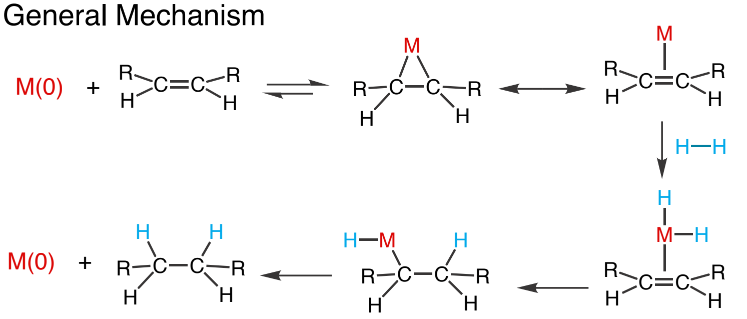
R. Noyori *Bull. Chem. Soc. Japan* **47**, 2617, (1974)	R_2AlH	97 : 3
	$LiAlH_4$	28 : 72

Diastereoselective Hydrogenation: Introduction

The Hydrogenation Reaction

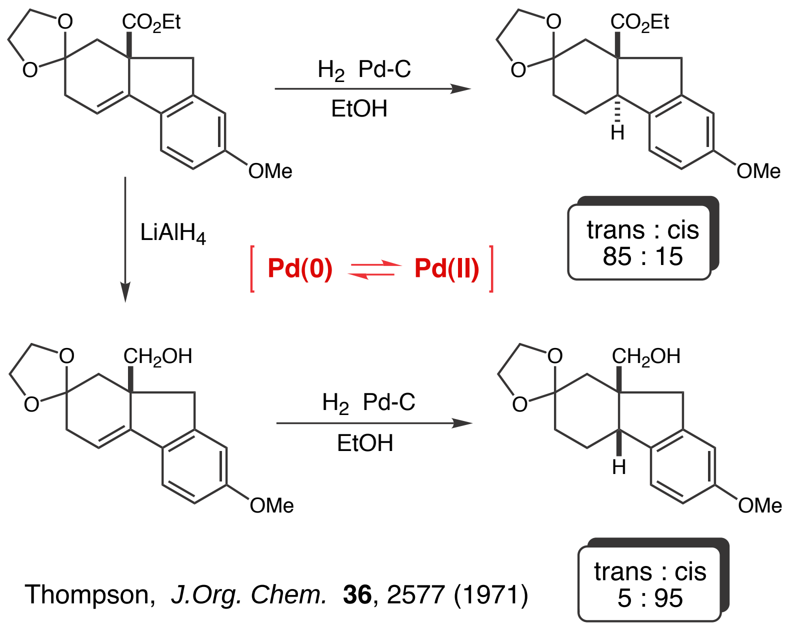
Relevant Review articles: J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987).

■ General Mechanism



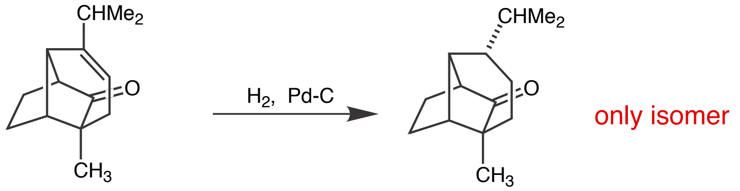
Historically, primary stereochemical control designed around analysis of steric environment in vicinity of C=C.

However, the influence of polar effects was documented

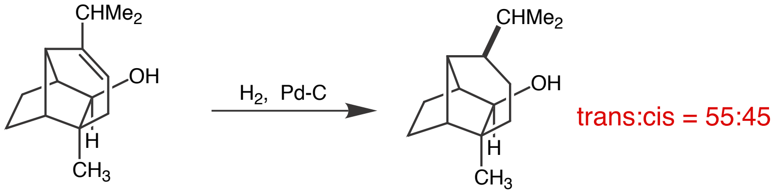


Thompson, *J.Org. Chem.* **36**, 2577 (1971)

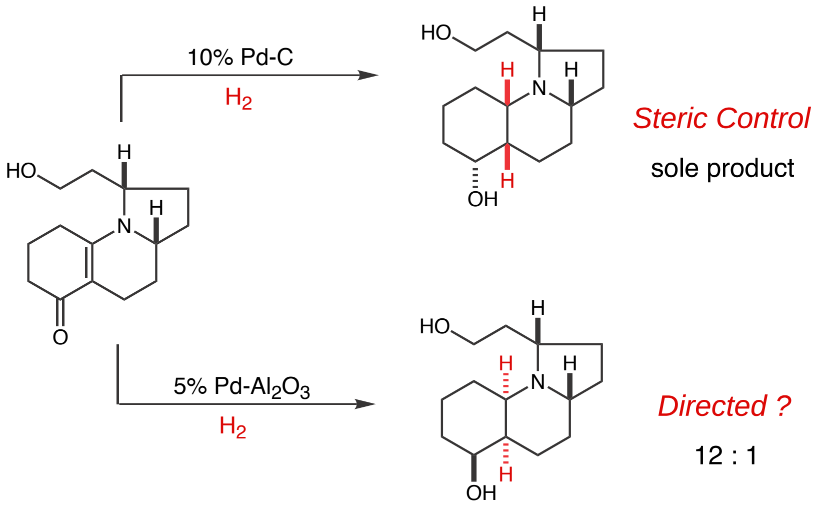
Polar functional groups may play a role in controlling the diastereoselectivity of the hydrogenation process; however, the control elements were not well-defined.



however



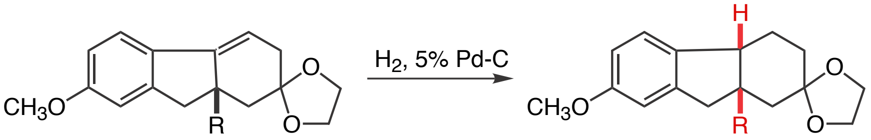
J. E. McMurry & Co-workers, *Tetrahedron Lett.*. 3731 (1970)



Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **102**, 7156 (1980)

Diastereoselective Hydrogenation: Introduction-2

The first rational attempt to identify those FGs which will direct the reaction

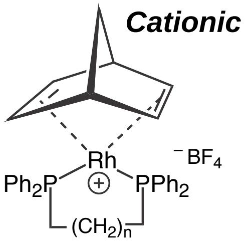


10

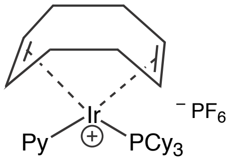
R	cis : trans
CH_2OH	95 : 5
CHO	93 : 7
CN	75 : 25
COONa	55 : 45
COOH	18 : 82
COOMe	15 : 85
COMe	14 : 86
$CONH_2$	10 : 90

H. Thompson & Co-workers, *J. Am. Chem. Soc.* **95**, 838 (1973)

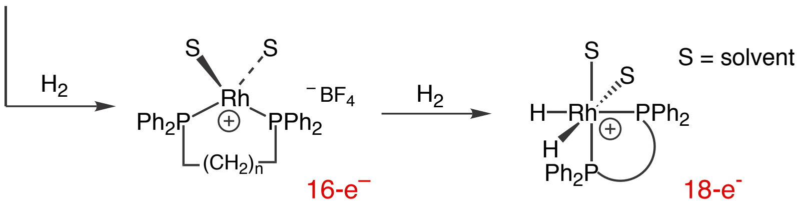
Cationic Hydrogenation Catalysts



Schrock & Osborne,
J. Am. Chem. Soc. **91**, 2816 (1969)

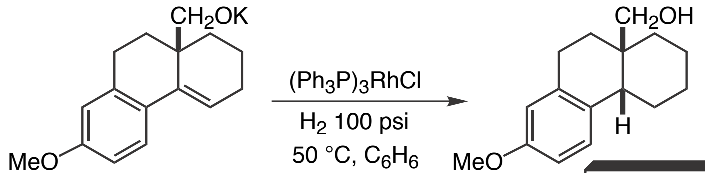


R. Crabtree
J. Organomet. Chem. **168**, 183 (1979)

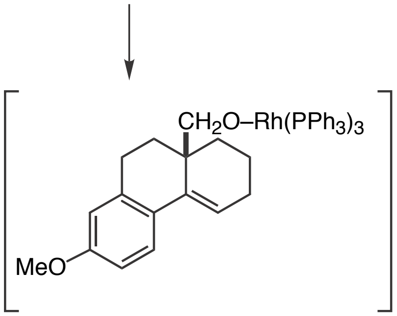


Rh(+I): d8

The first rational attempt to associate catalyst with substrate:



cis : trans
>98 : 2

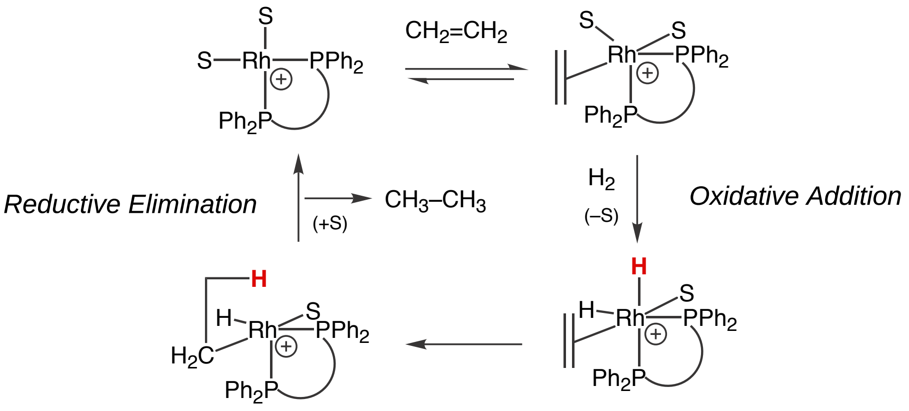


Rxn Catalytic in Rh (4 mol%)

Thompson & Coworkers, *J. Am. Chem. Soc.* **97,** 6232 (1974)

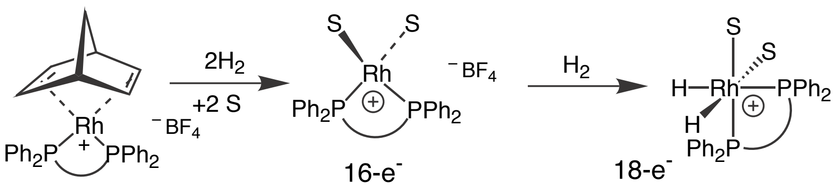
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.

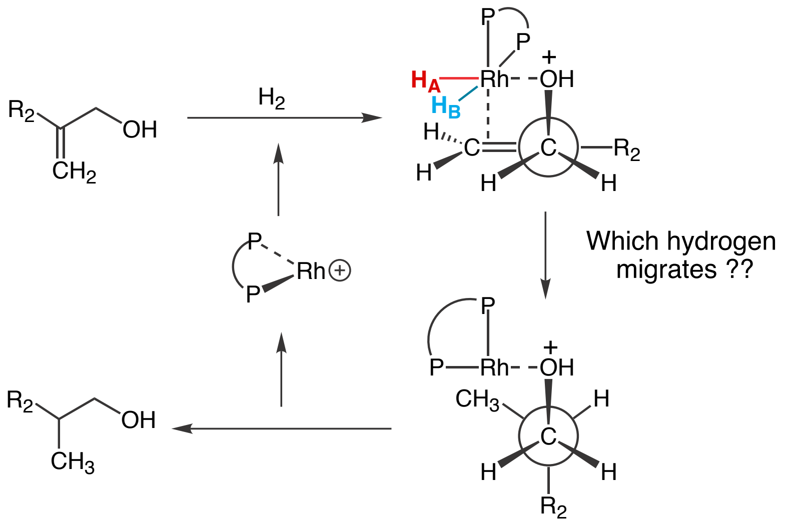
S = solvent



Diastereoaselective Hydrogenation: Cationic Catalysts

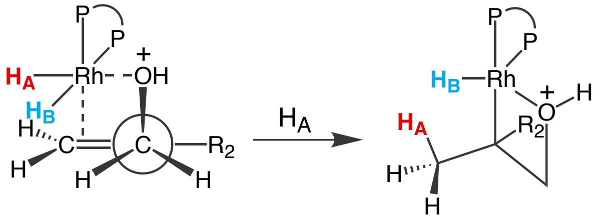
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.





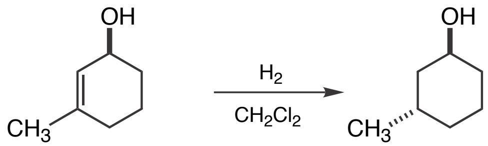
Which hydrogen migrates ??

A potential stereoelectronic effect

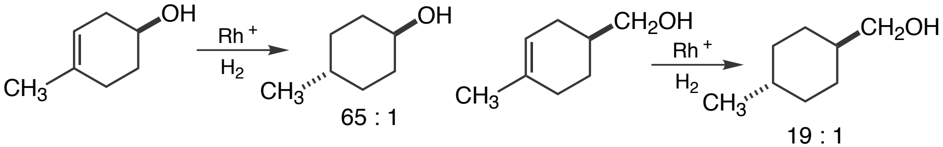


That H atom lying parallel to the pi-system (H_A) should migrate preferentially if the dihydride is an intermediate.

D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)

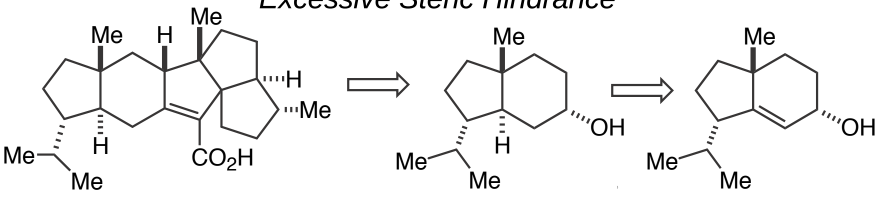


Catalyst	Mol% Catalyst	H_2 Pressure	trans:cis (Yield)
$Rh(DIPHOS\text{-}4)^+$	17.5	15 psi H_2	200 : 1 (89%)
	3.5	375 psi H_2	300 : 1 (95%)
$Ir(pyr)PCy_3$	20.0	15 psi H_2	50 : 1 (82%)
	2.5	15 psi H_2	150 : 1 (85%)

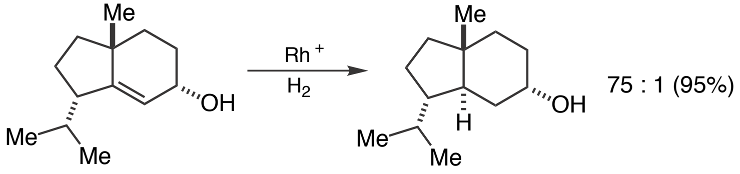


$Rh(DIPHOS\text{-}4)^+$ H_2 1000 psi CH_2Cl_2

Excessive Steric Hindrance



Retigeranic Acid



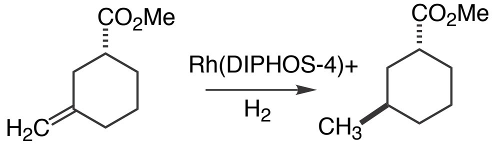
75 : 1 (95%)

$Rh(DIPHOS\text{-}4)^+$ H_2 800 psi THF

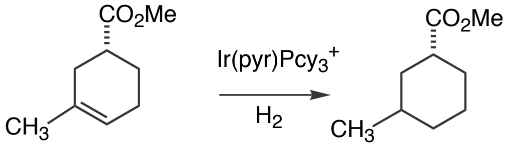
THF is important to success of rxn to buffer the Lewis acidity of the catalyst which causes elimination of ROH under normal conditions

Diastereoaselective Hydrogenation: Cyclic Substrates

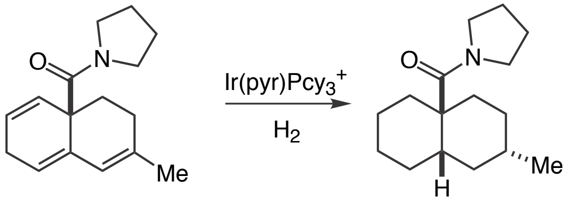
Polar functional groups other than OH may also direct the process



diastereoselection
91 : 9

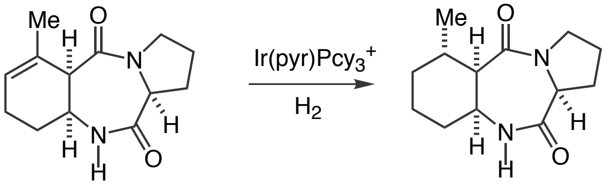


diastereoselection
89:11

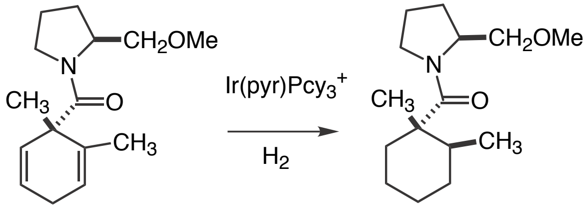


diastereoselection
>99:1

J.M. Brown and S.A. Hall, *J. Organomet. Chem.*, **1985**, *285*, 333.

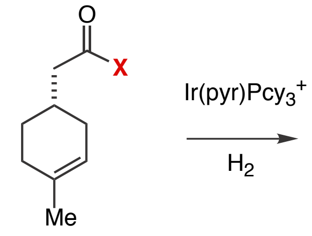


diastereoselection
>99:1

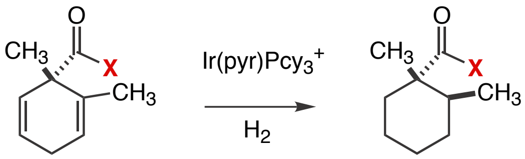


diastereoselection
>99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.

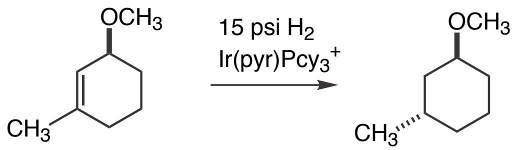


X	Diastereoselection
OMe	55:45
NC$_4$H$_8$	99:1



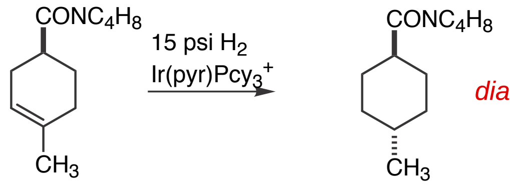
X	Diastereoselection
OMe	99:1
NC$_4$H$_8$	>99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.



diastereoselection
>99:1

R.H. Crabtree and M.W. Davis, *J. Org. Chem.*, **1986**, *51*, 2655.

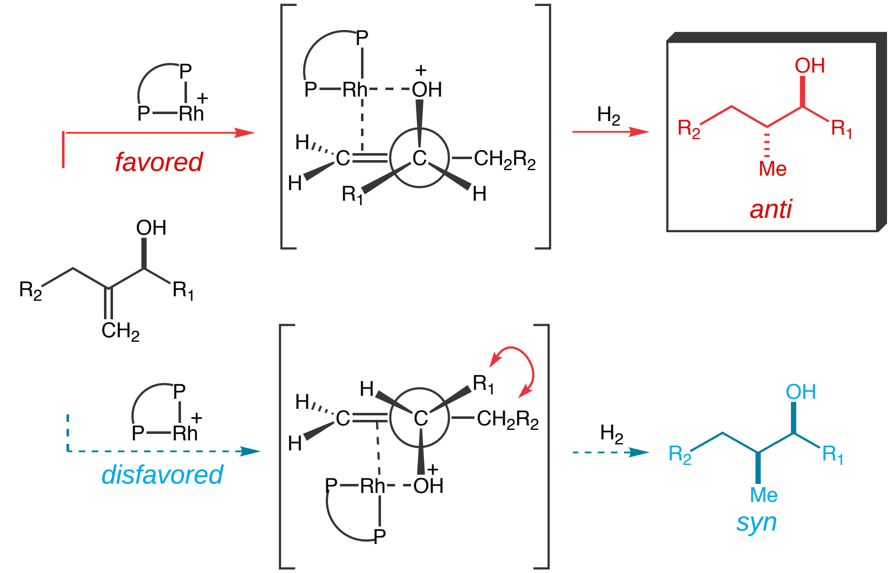


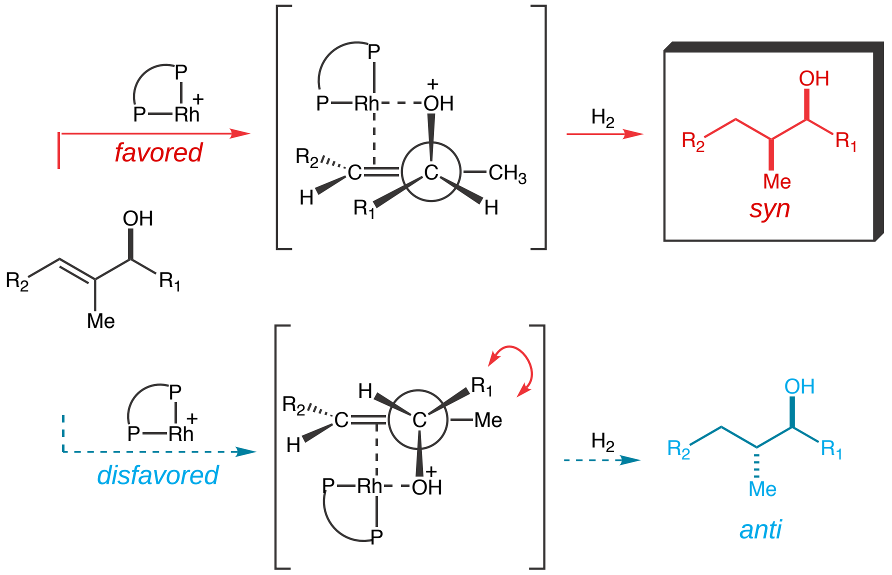
diastereoselection
>99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.

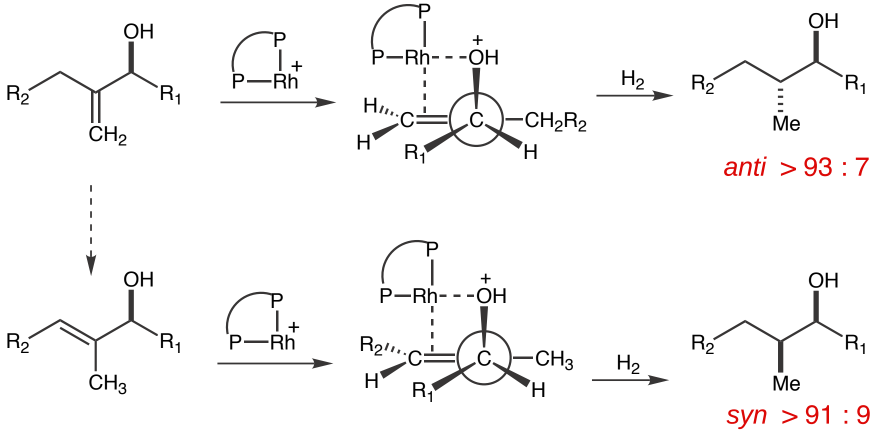
Diastereoaselective Hydrogenation: Acyclic Substrates

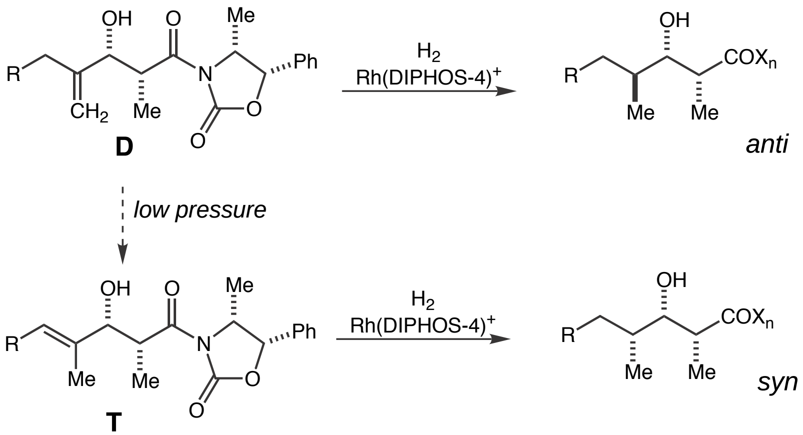
Acyclic Allylic Alcohols





D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)

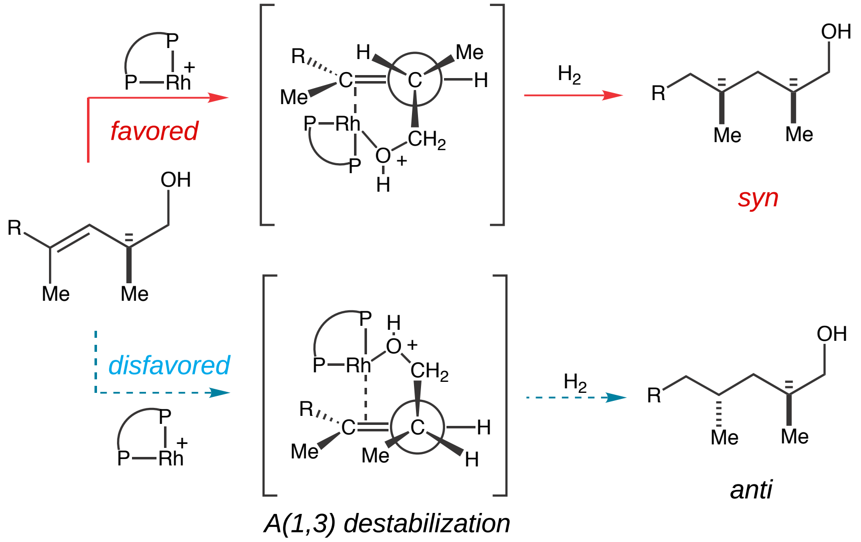




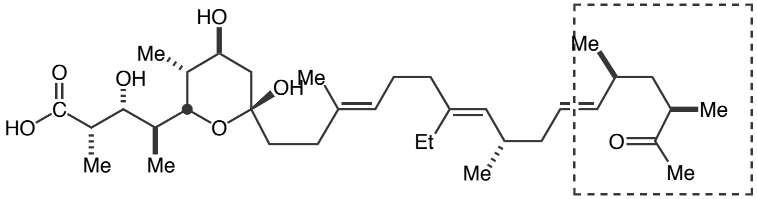
	Hydroxy-Olefin	Anti : Syn Ratio 15 psi H_2	 640 psi H_2
D	R = CH_3	25 : 75 (23%)	93 : 7
	R = $(CH_3)_2CH$	52 : 48 (35%)	94 : 6
	R = Ph	71 : 29 (-)	93 : 7
T	R = CH_3	13 : 87 (6%)	9 : 91
	R = $(CH_3)_2CH$	12 : 88 (8%)	8 : 92
	R = Ph	21 : 79 (-)	6 : 94

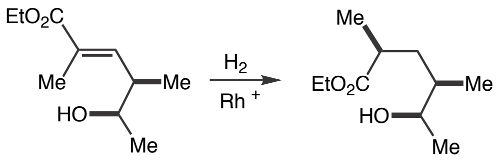
Diastereoaselective Hydrogenation: Acyclic Substrates

Homoallylic Alcohols Evans, Morrissey *Tetrahedron Lett.* **26** 6005 (1985)



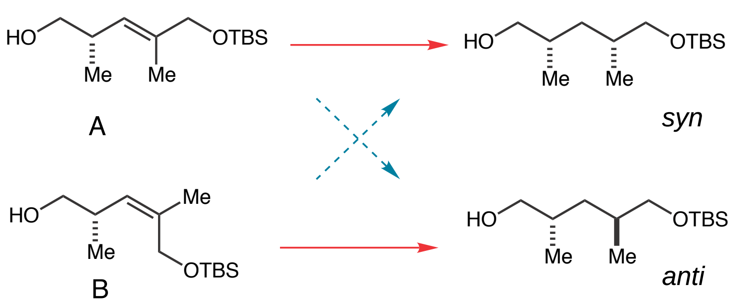
The Premonensin Synthesis





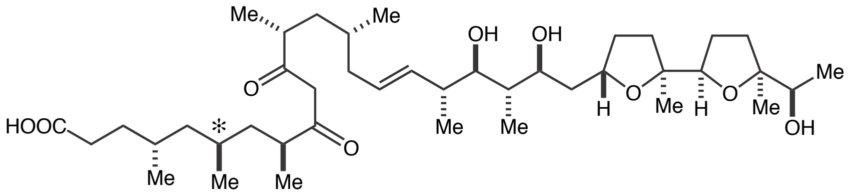
Catalyst	Ratio
Rh(DIPHOS-4) +	85 : 15
Rh(–)(BINAP) +	65 : 35
Rh(+)(BINAP) +	98 : 2 (90%)

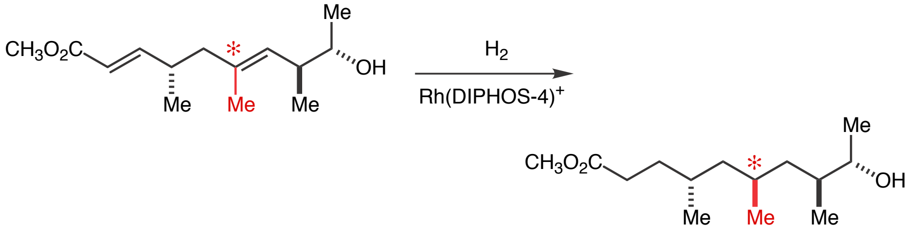
Evans, DiMare, *JACS*, **1986**, *108*, 2476)



Olefin	Catalyst (H_2 Pressure)	syn : anti
A	Rh(DIPHOS-4)$^+$ (1000 psi)	95 : 5
A	Ir(pyr)PCy$_3^+$ (15 psi, 2.5 mol%)	73 : 27
B	Rh(DIPHOS-4)$^+$ (1000 psi)	9 : 91

The Ionomycin Synthesis



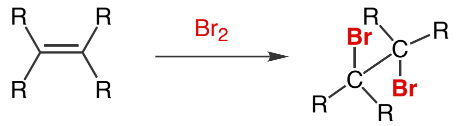


Diastereoselection: 94 : 6 (93%)

with Dow, Shih, Zahler, Takacs, *JACS* **1990**, *112*, 5290

Olefin Bromination-1

Introduction



- Reaction is first order in alkene

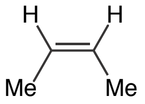
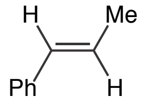
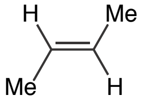
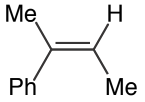
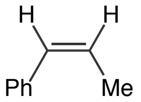
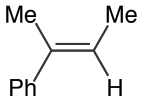
At low concentrations of Br_2, rxn is also **first order in Br_2**

At higher concentrations of Br_2 in nonpolar solvents rxn is **second order in Br_2**.

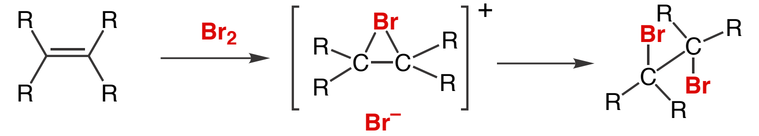
- Substituent Effects on Bromination Rates

Alkene	k_{rel}
$CH_2=CH_2$	1
$CH_3CH=CH_2$	61
n-Pr$CH=CH_2$	70
i-Pr$CH=CH_2$	57
t-Bu$CH=CH_2$	27
$(CH_3)_2C=CH_2$	5470
cis-$CH_3CH=CHCH_3$	2620
trans-$CH_3CH=CHCH_3$	1700
$(CH_3)_2C=CHCH_3$	130,000
$(CH_3)_2C=C(CH_3)_2$	1,800,000

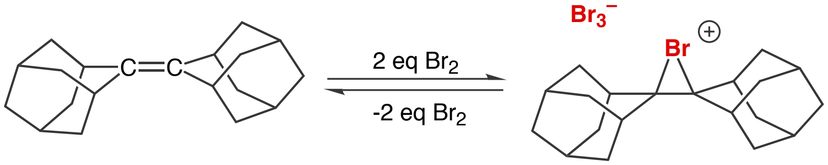
- Stereochemical outcome versus structure (Br_2 in HOAc @ 25°)

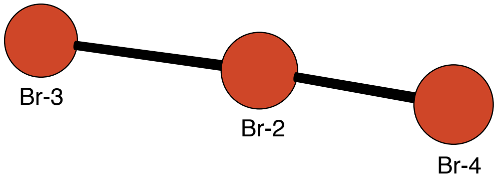
Alkene	% anti addition	Alkene	% anti addition
	100%		83%
	100%		63%
	73%		68%

- Bromonium ion origin of the anti (trans) selectivity first suggested by Roberts, *JACS* **1937**, *59*, 947

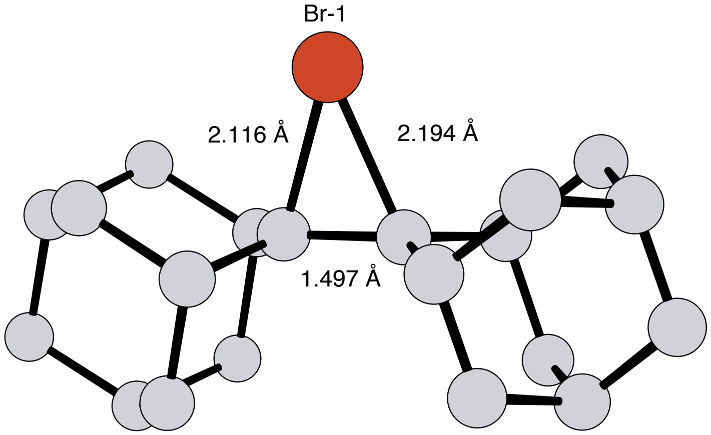


- First X-ray Structure of a bromonuium ion: Brown, *JACS* **1985**, *107*, 4504



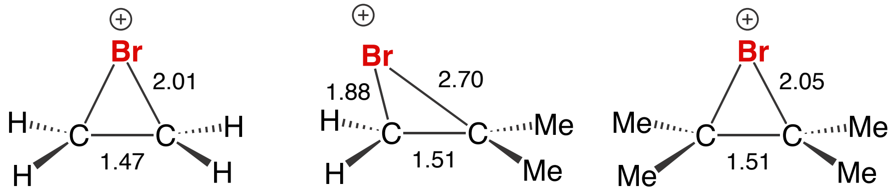


X-ray structure



Calculated Geometries of Substituted Bromonium Ions

Ruasse, *Chem Commun.* **1990**, 898
More recent calculations: Sigalas, *Tetrahedron* **2003**, *59*, 4749

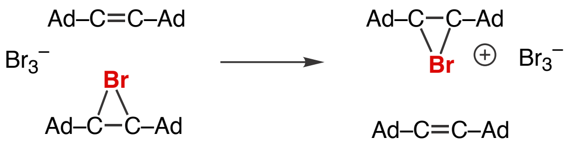


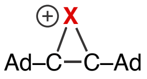
Note; the C–Br bond lengths in previous X-ray structure are 2.116 Å.

Bromonium Ions undergo fast exchange with olefins

Brown, *Accts. Chem. Res.* **1997**, *30*, 131

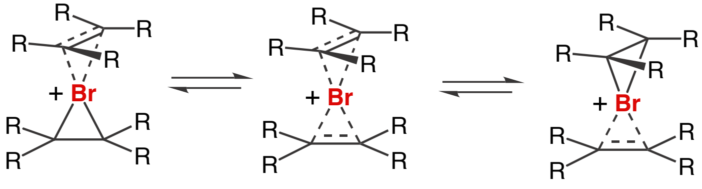
Unprecedented until 1991 (Bennet, JACS **1991**, *113*, 8532)





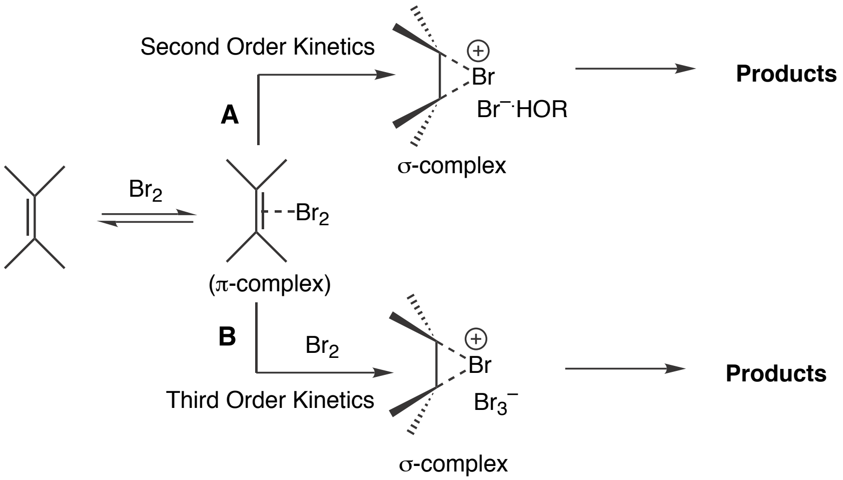
X = Br: exchange rate: 2 x 10^6 M^{-1} s^{-1}
X = I : exchange rate: 8 x 10^6 M^{-1} s^{-1}

There is an intermediate in the halogen transfer (ab initio calcs):

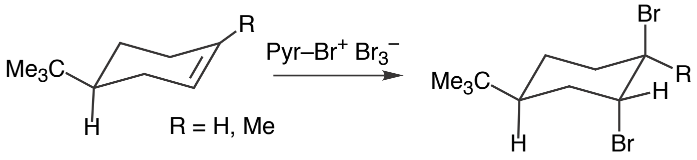


complex **TS** **complex**

Overall Reaction Mechanism

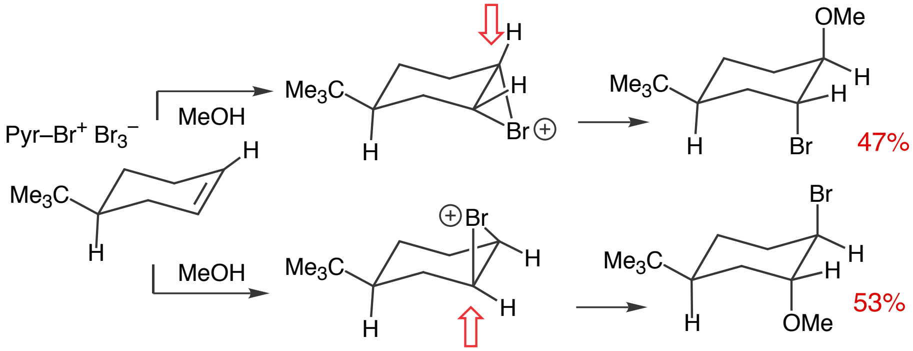


Bromination of Cyclohexene Derivatives Pasto, *JACS* 1970, *92*, 7480



exclusive product

Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening (**Lecture-3**).

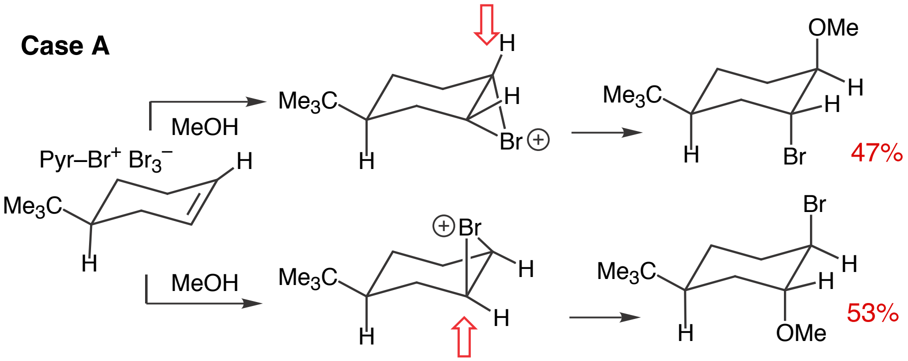


It appears that bromine attack from both olefin faces occurs wilth near equal probability.

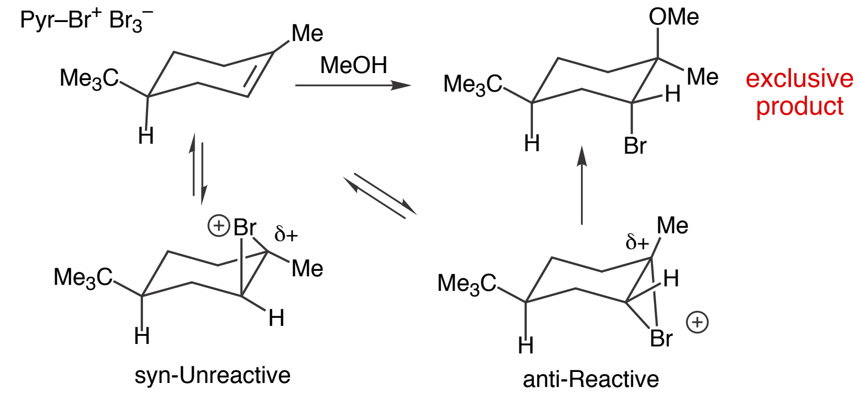
Bromination of Cyclohexene Derivatives **Pasto, *JACS* 1970, *92*, 7480**

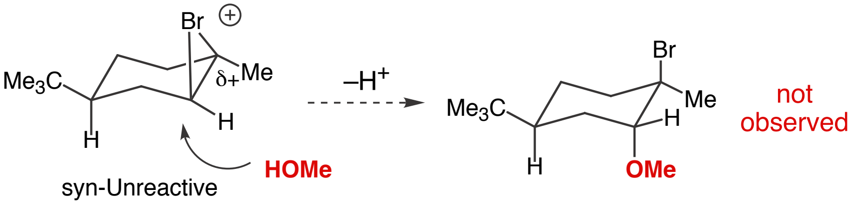
Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

Case A



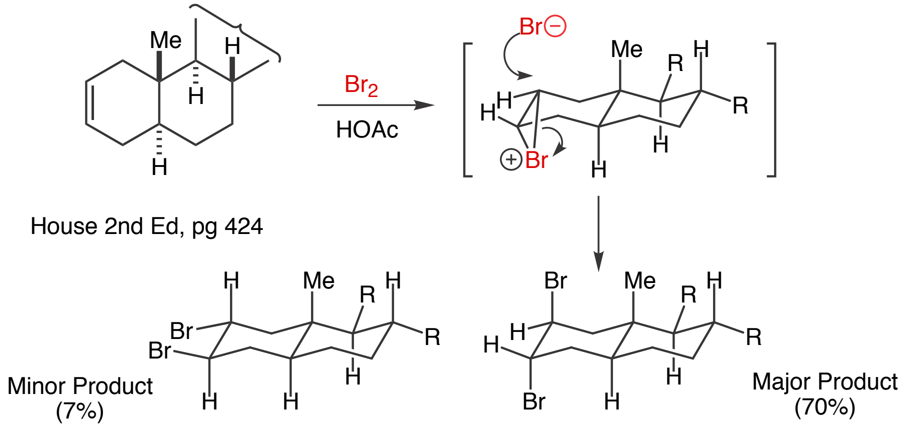
Case B





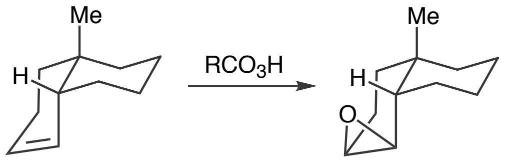
From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opeing must proceed against the polarization due to Methyl substituent.

Representative Examples of Diastereoselective Bromination



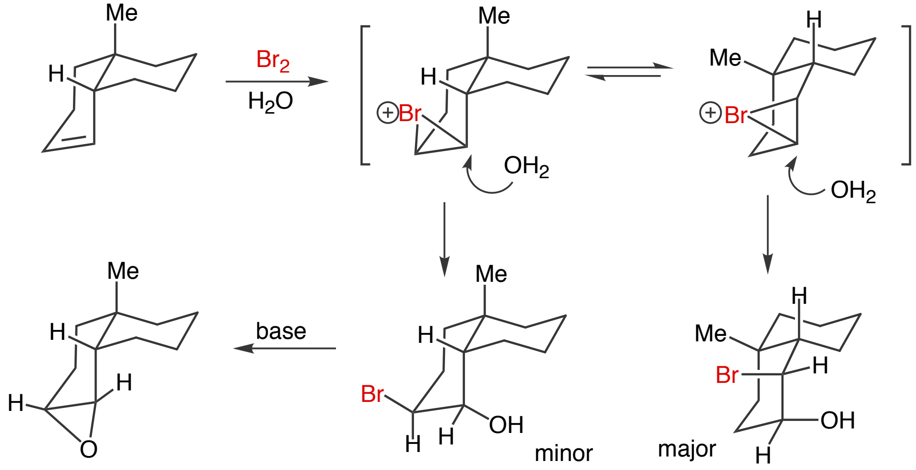
House 2nd Ed, pg 424

How to generate either epoxide from a conformationaly biased olefin



Epoxidation controlled by steric effects imposed by cis-fused ring

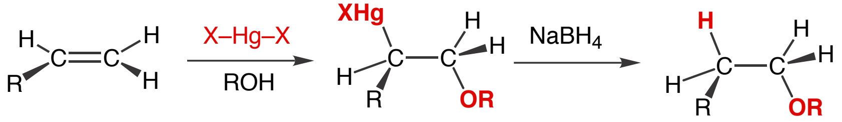
How do we construct the other epoxide diastereomer??



both bromohydrins afford same product

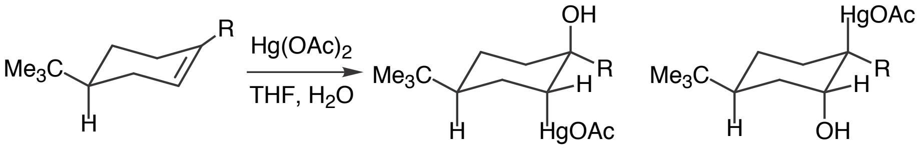
Oxymercuration Pasto, *JACS* 1970, *92*, 7480

The basic process:



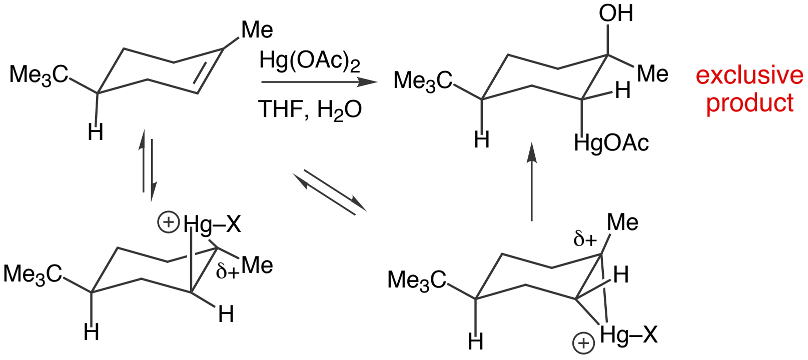
Kinetics: Halpern, *JACS* **1967**, *89*, 6427 Reduction: Pasto, *JACS* **199**, *91*, 719
Overview: B rown, *JOC* **1981**, *46*, 3810.

Oxy-Mercuration & bromination follow identical pathways (Pasto)



R = H 41% 48%

R = Me 100%

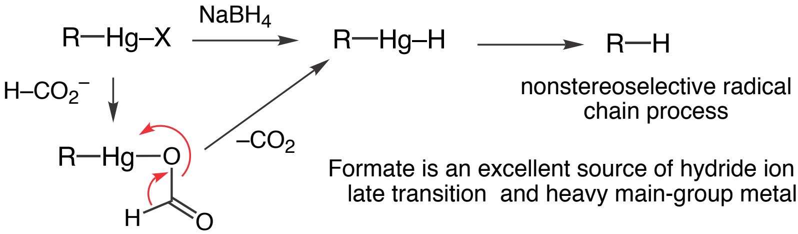


exclusive product

syn-Unreactive

anti-Reactive

Reduction of the Hg–C bond



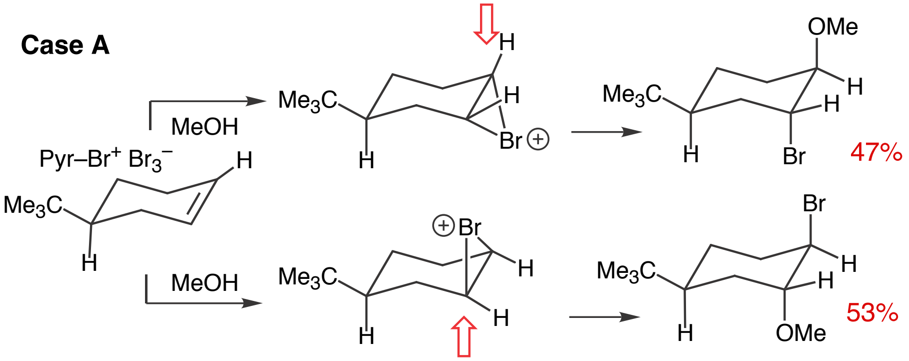
nonstereoselective radical chain process

Formate is an excellent source of hydride ion for late transition and heavy main-group metals

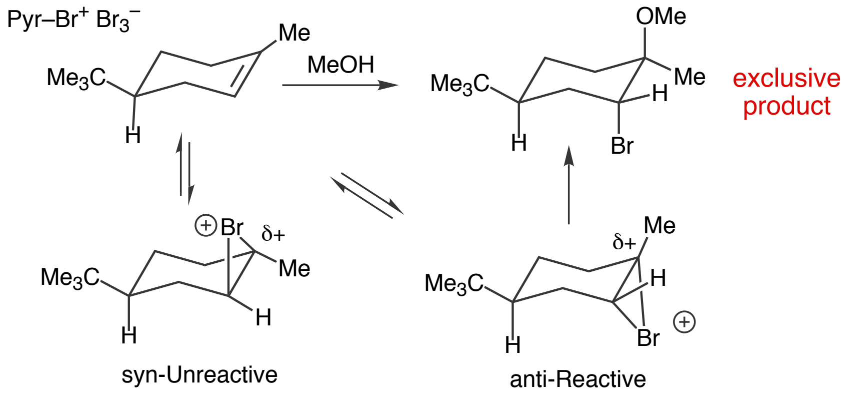
Bromination of Cyclohexene Derivatives Pasto, *JACS* 1970, *92*, 7480

Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

Case A



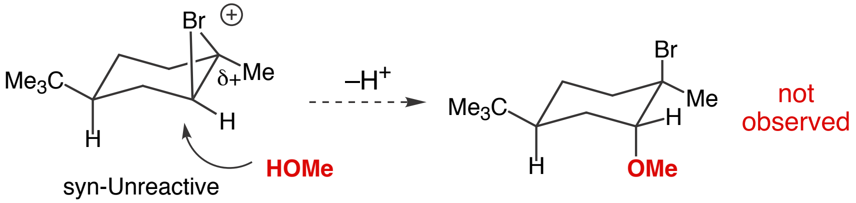
Case B



exclusive product

syn-Unreactive

anti-Reactive



syn-Unreactive

not observed

From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opeing must proceed against the polarization due to Methyl substituent.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 10

Olefin Addition Reactions–3

- Olefin Oxymercuration
- Halolactonization
- Simmons-Smith Reaction

■ Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

Hoveyda, Evans, & Fu (**1993**). *Substrate-Directable Chemical Reactions*. *Chem. Rev*. **93**: 1307-70 ***(Handout)***

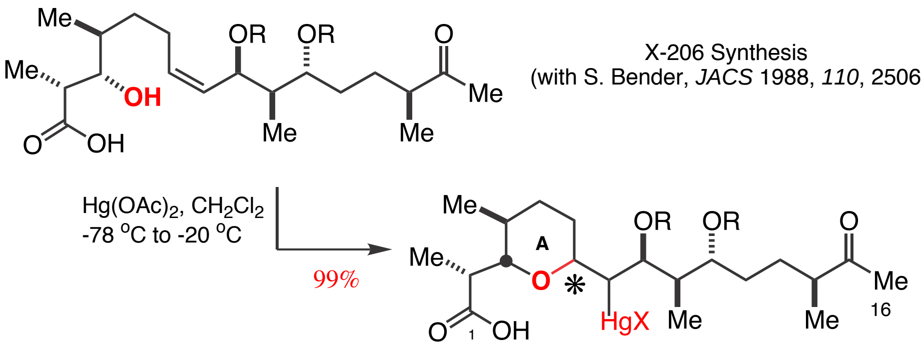
D. A. Evans

Monday,
October 3, 2003

Bromoniun Ions or β-Bromocarbocations in Olefin Bromination. A Kinetic Approach to Product Selectivities
M-F. Ruasse, *Accts. Chem. Res.* **1990**, *23*, 87 **(handout)**

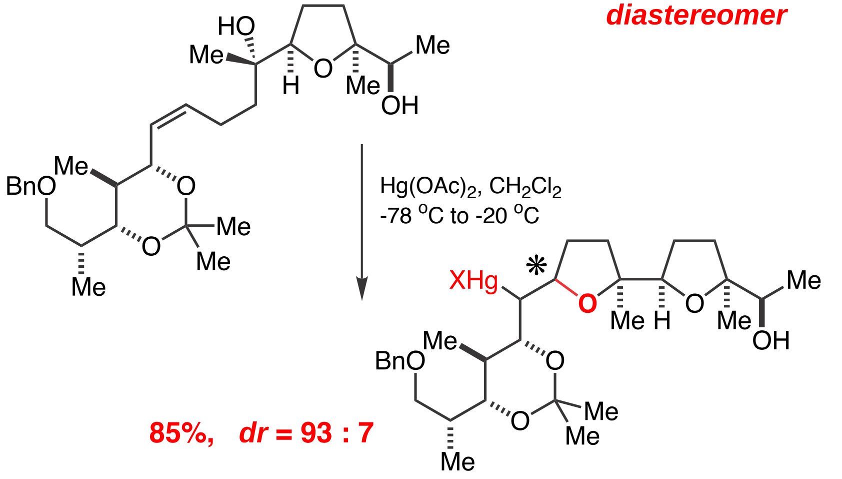
Investigation of the early Steps in Electrophilic Bromination through the Study of the Reaction of Sterically Encumbered Olefins
R. S. Brown, *Accts. Chem. Res.* **1997**, *30*, 131 **(handout)**

■ Predict stereochemical outcome



X-206 Synthesis
(with S. Bender, *JACS* 1988, *110*, 2506)

99%, *single diastereomer*

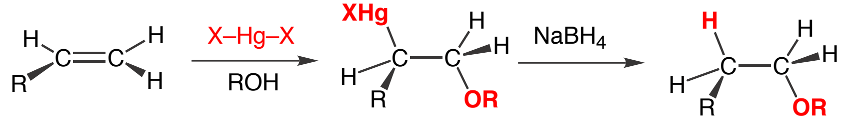


85%, *dr* = 93 : 7

Ionomycin Synthesis
(with Dow & Shih, *JACS* 1990, *112*, 5290)

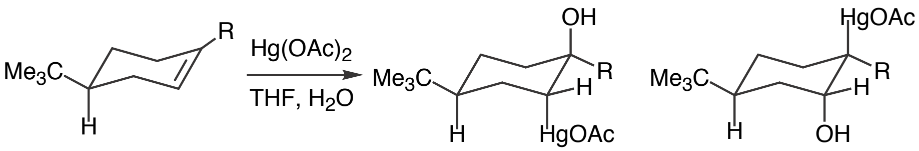
Oxymercuration Pasto, *JACS* 1970, *92*, 7480

The basic process:

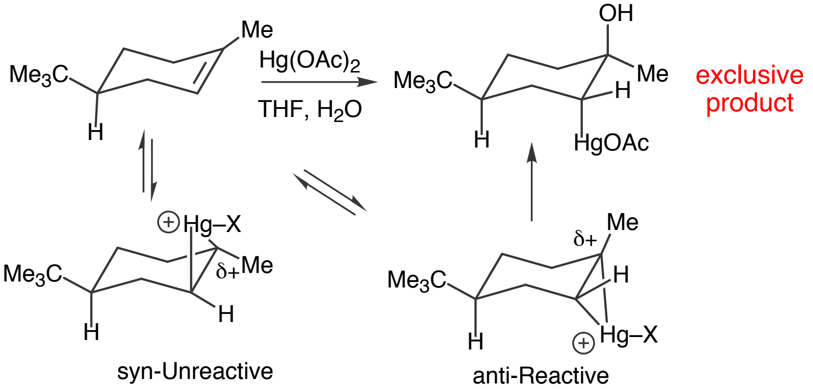


Kinetics: Halpern, *JACS* **1967**, *89*, 6427 Reduction: Pasto, *JACS* **199**, *91*, 719
Overview: B rown, *JOC* **1981**, *46*, 3810.

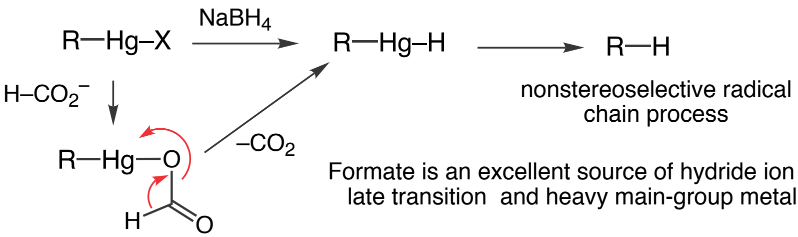
Oxy-Mercuration & bromination follow identical pathways (Pasto)



R = H	41%	48%
R = Me	100%	



Reduction of the Hg–C bond

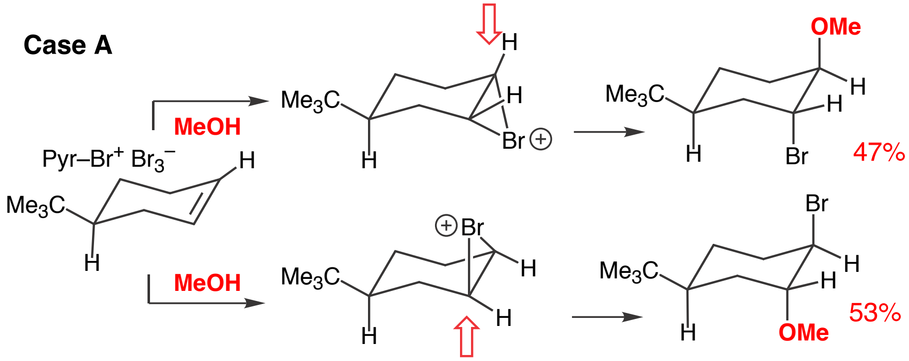


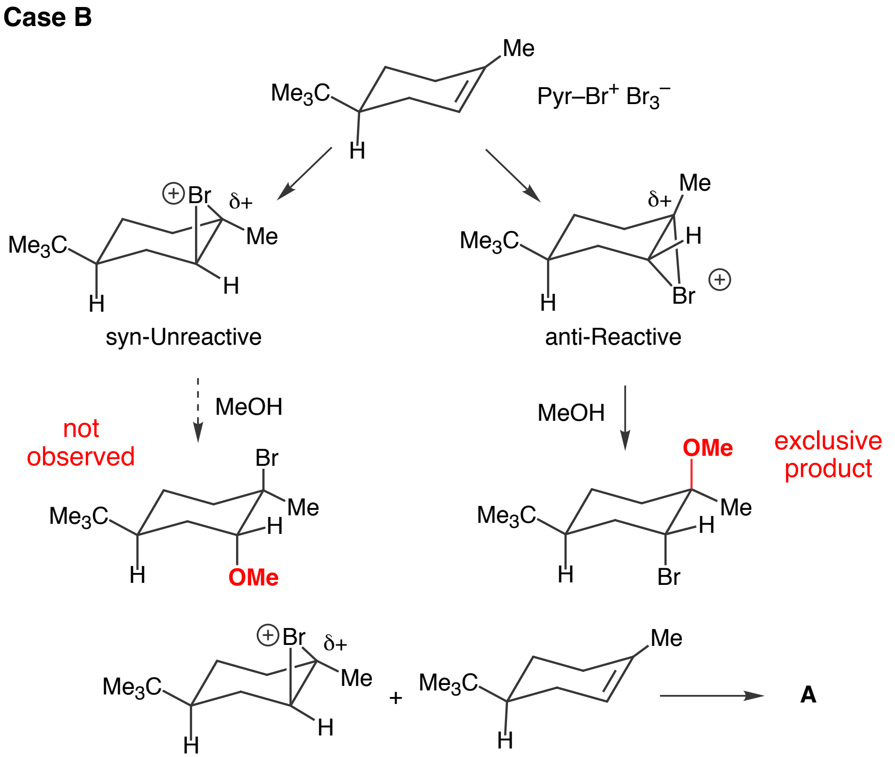
nonstereoselective radical chain process

Formate is an excellent source of hydride ion for late transition and heavy main-group metals

Bromination of Cyclohexene Derivatives Pasto, *JACS* 1970, *92*, 7480

Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

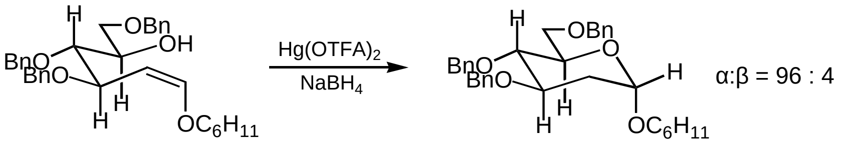




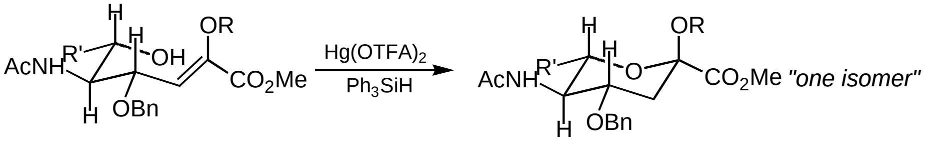
From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opeing must proceed against the polarization due to Methyl substituent.

Oxymercuration Examples

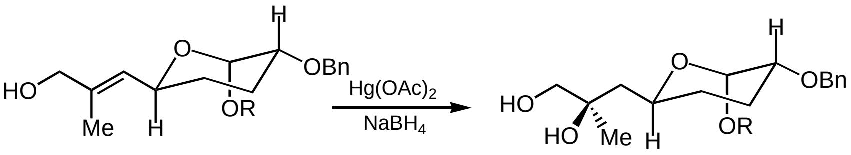
Diastereoselective ring closures via oxymercuration



Mukaiyama, *Chem. Lett.* **1981**, 683

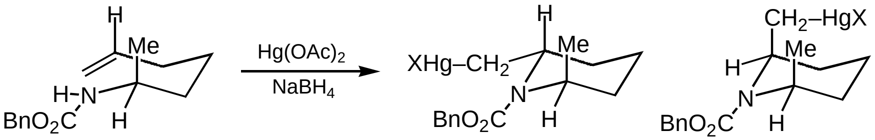


Sinay, *Tet. Lett.* **1984**, *25*, 3071



Isobe, *Tet. Lett.* **1985**, *26*, 5199

■ Kinetic vs Thermodynamic control:



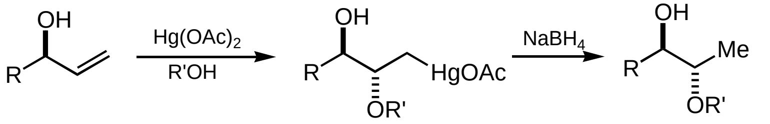
Harding, *JOC* **1984**, 49, 2838

Hg(OAc)$_2$: short rxn times : 40 : 60

Hg(OTFA)$_2$: longer rxn times : 2 : 98

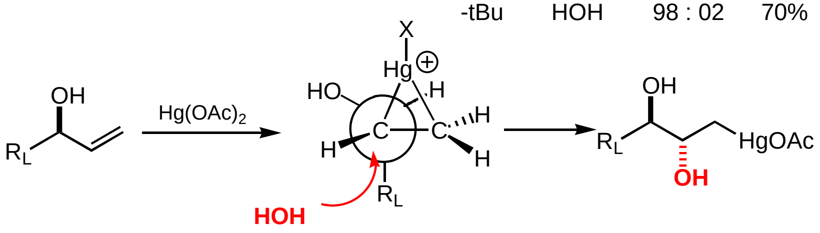
With more electrophilic Hg(II) salt, more polar solvents, and longer rxn times, the rxn may be rendered reversible.

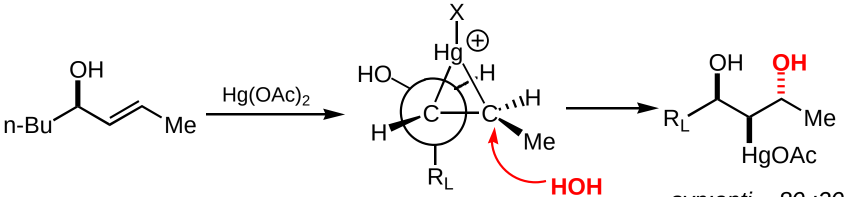
■ Acyclic allylic alcohols:



R	R'OH	Ratio	yield
-Et	HOH	76 : 24	65%
-Et	MeOH	93 : 07	72%
-Ph	HOH	88 : 12	66%
-tBu	HOH	98 : 02	70%

Giese, *Tet. Lett.* **1985**, *26*, 1197

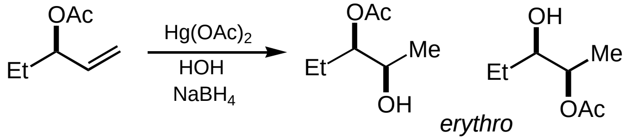




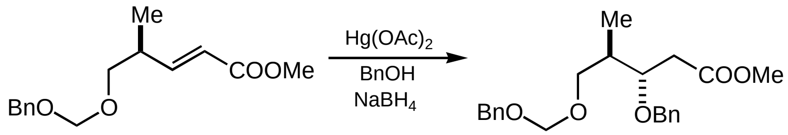
syn:anti = 80 :20

Chamberlin, *Tetrahedron* **1984**, *40*, 2297

O-acetate participation will turn over the stereochemical course of the rxn



erythro:threo = 77 : 23



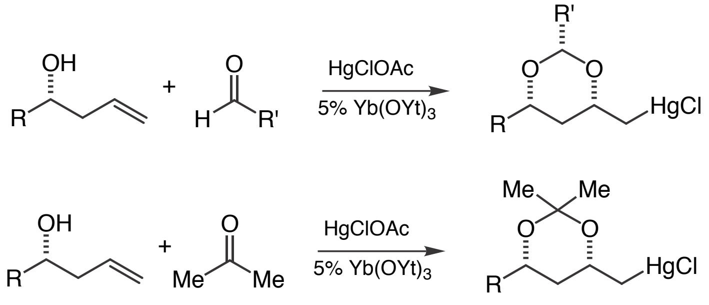
Seebach, *JACS* **1983**, *105*, 7407

diastereoselection = 83 : 17 (79%)

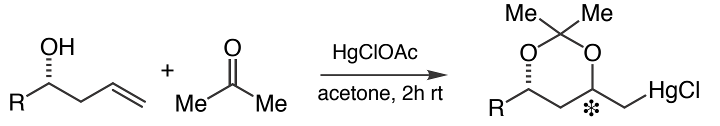
Oxymercuration via Hemiketals & Hemiacetals

J. L. Leighton et. al, *Org. Lett.* **2000**, *2*, 3197-3199

■ General Reaction: diastereoselection >10:1



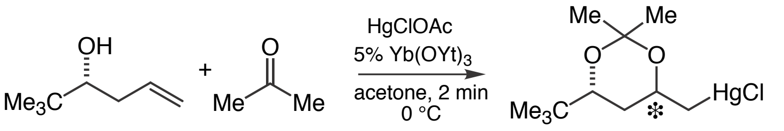
■ Mechanistic Observations:



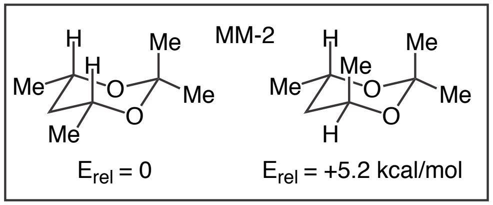
~1:1-mixture of diastereomers
Product formed in low yield.
much recovered starting material

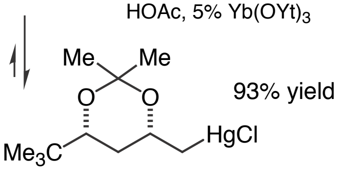
Lewis acid addends were surveyed. the logic for this step was two-fold:

(A) Lewis acid would promote the formation of the putative hemiketal imtermediate.
(B) Lewis acid would promote reversability of the oxymercuration process



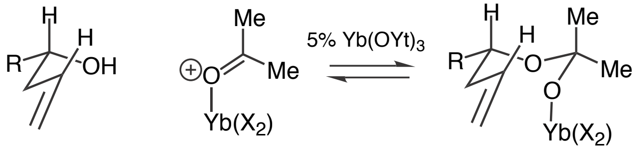
~1:1-mixture of diastereomers



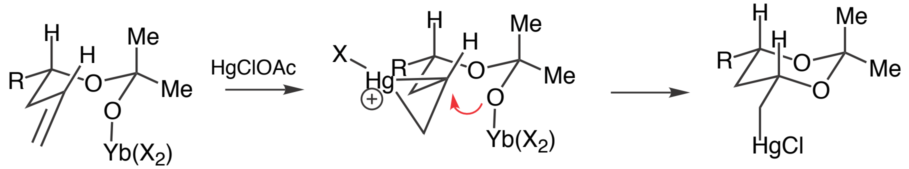


Proposed Mechanism

■ Lewis acid catalyzes formation of hemiketal

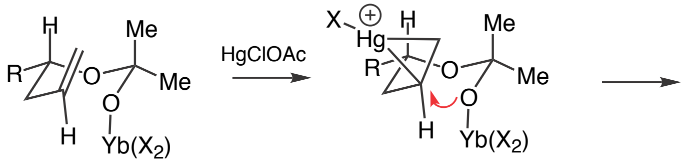


■ The Oxymercuration Step (Kinetic Phase)

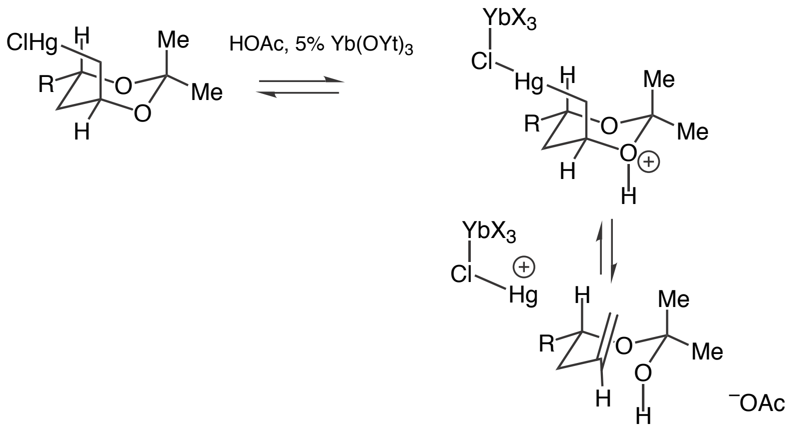


rate-determining step

low diastereoselectivity

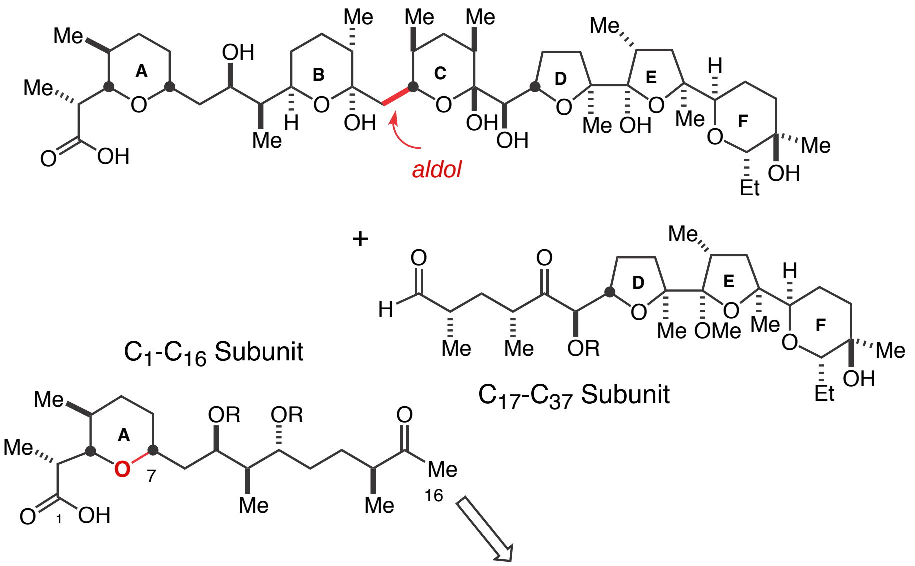


Leighton presumes that mercurium ion formation is rate-determining under kinetic conditions.
At higher temperatures and longer reaction times the products are shown to interconvert.



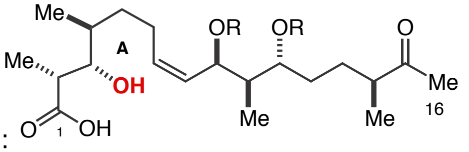
Oxymercuration Examples: X-206 & Lonomycin Syntheses

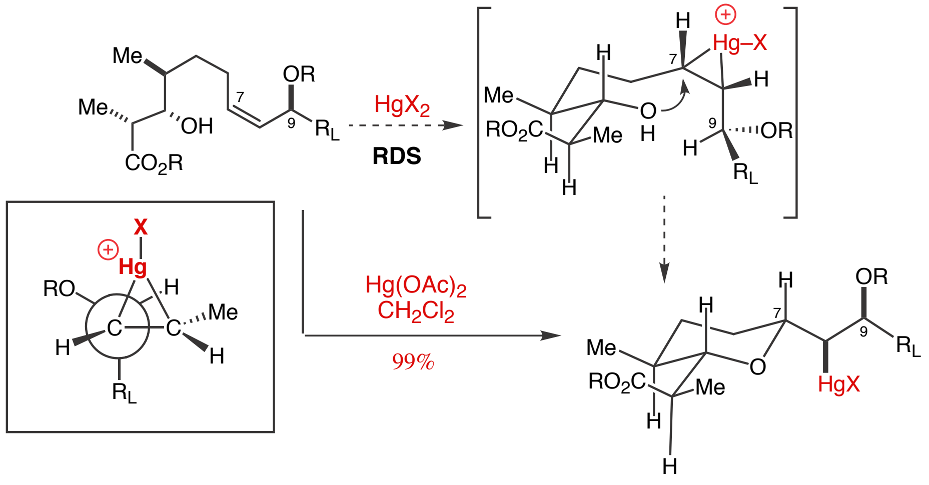
X-206 Synthesis (with S. Bender, *JACS* 1988, *110*, 2506)



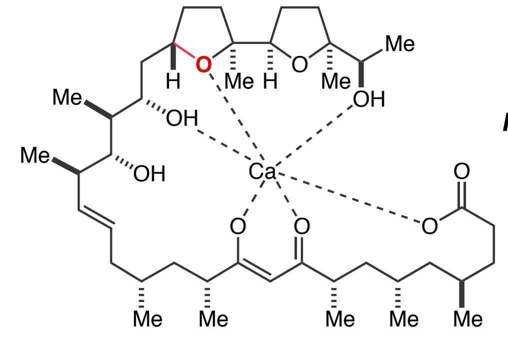
Assemblage strategy for Ring A:

Predicted stereochemical outcome:

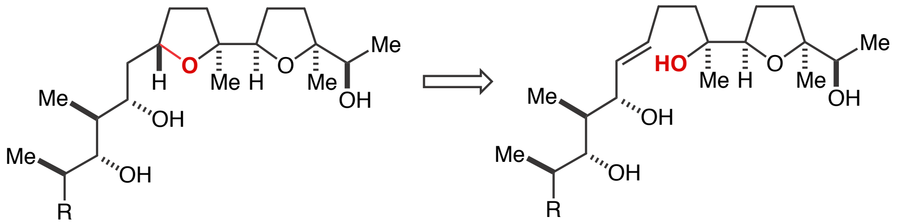


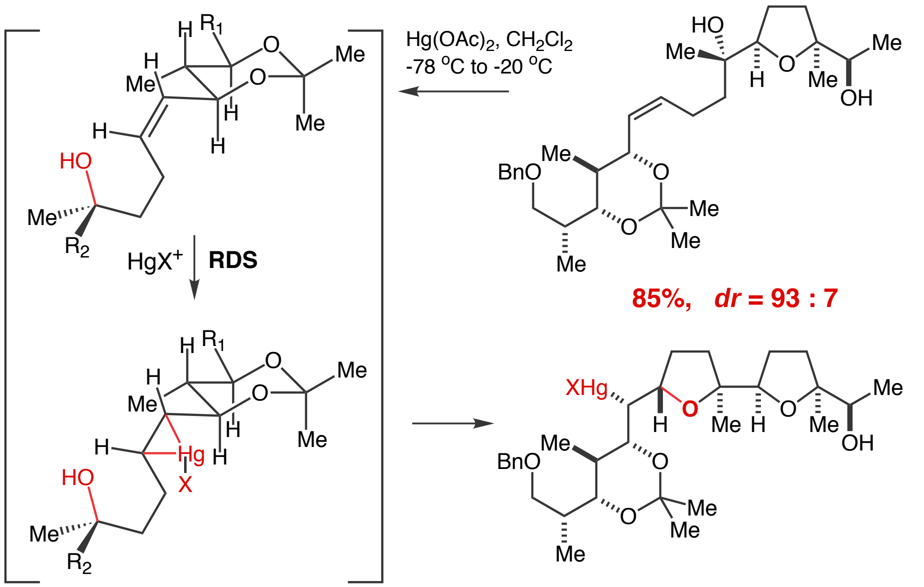


Ionomycin Synthesis (with Dow & Shih, *JACS* 1990, *112*, 5290)



Ionomycin Calcium Complex

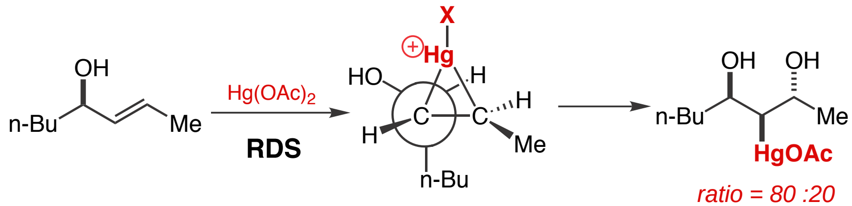




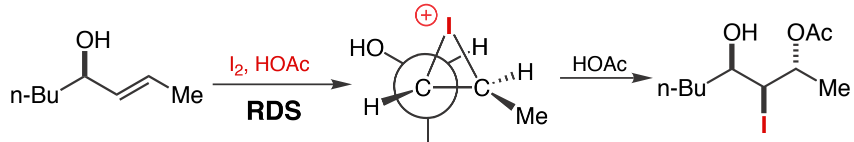
85%, *dr* = 93 : 7

Related Olefin Addition Rxns: Halogen Electrophiles

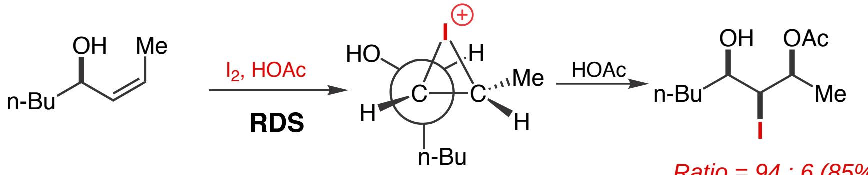
Other electrophilic olefin addition reactions afford the same stereochemical outcome



ratio = 80 :20



Ratio = 98 : 2 (78%)

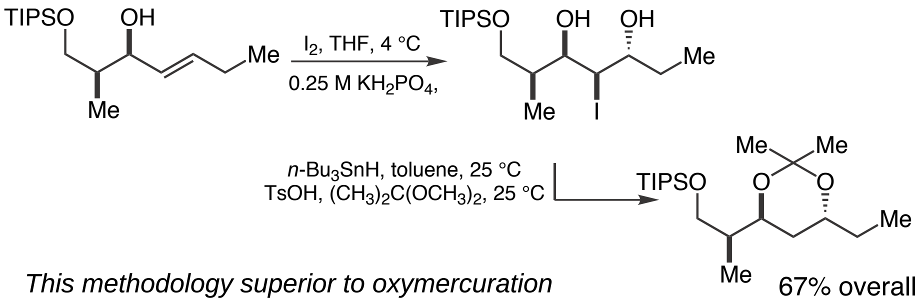


Ratio = 94 : 6 (85%)

Chamberlin, *Tetrahedron* **1984**, *40*, 2297

This is an exceptional approach to the creation of either syn or anti 1,3-dioxygen relationships

Evans, Kaldor, Jones, *J. Am. Chem. Soc.* **1990**, *112*, 7001.



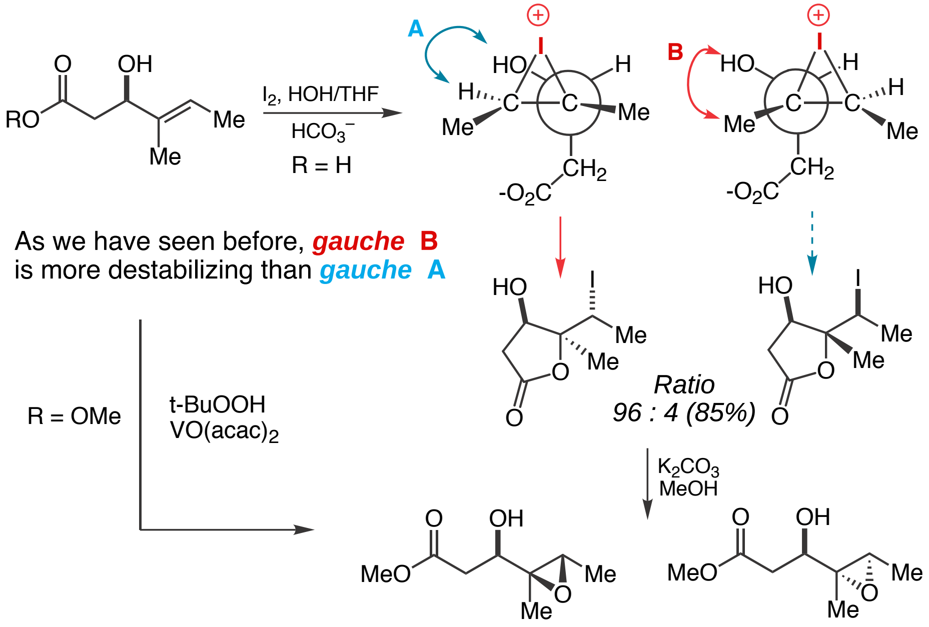
67% overall

This methodology superior to oxymercuration alternative which was evaluated first

diastereoselection 96 : 4

Iodine-induced lactonization is also highly stereoselective

■ Chamberlin (*JACS* **1983**, *105*, 5819)

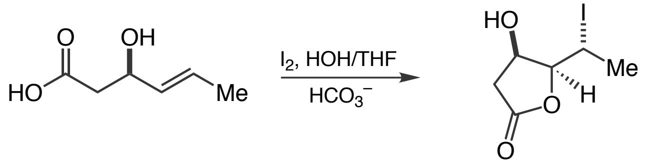


As we have seen before, ***gauche* B** is more destabilizing than ***gauche* A**

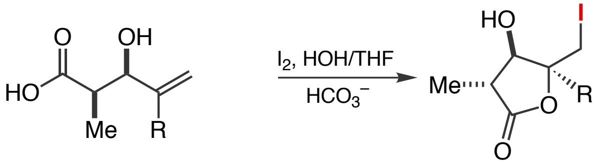
Ratio
96 : 4 (85%)

Lactonization Ratio = 96 : 4
Epoxidation Ratio = 3 : 97

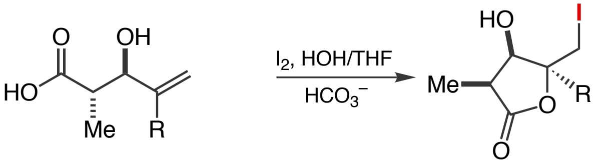
■ Other cases:



Ratio
>95 : 5 (49%)



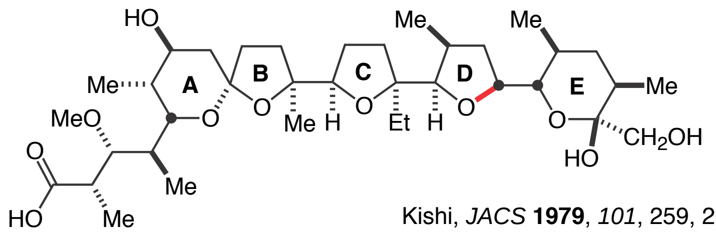
R = H: *77 : 23 (74%)*
R = Me: *42 : 58 (81%)*



R = H: *87 : 13 (41%)*
R = Me: *90 : 10 (94%)*

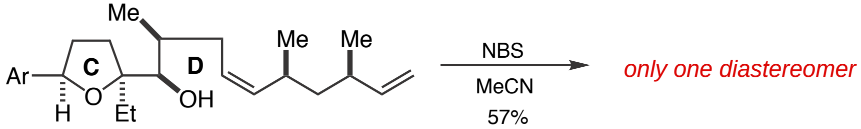
Related Olefin Addition Rxns

Halogen-induced heterocyclization in the synthesis of monensin

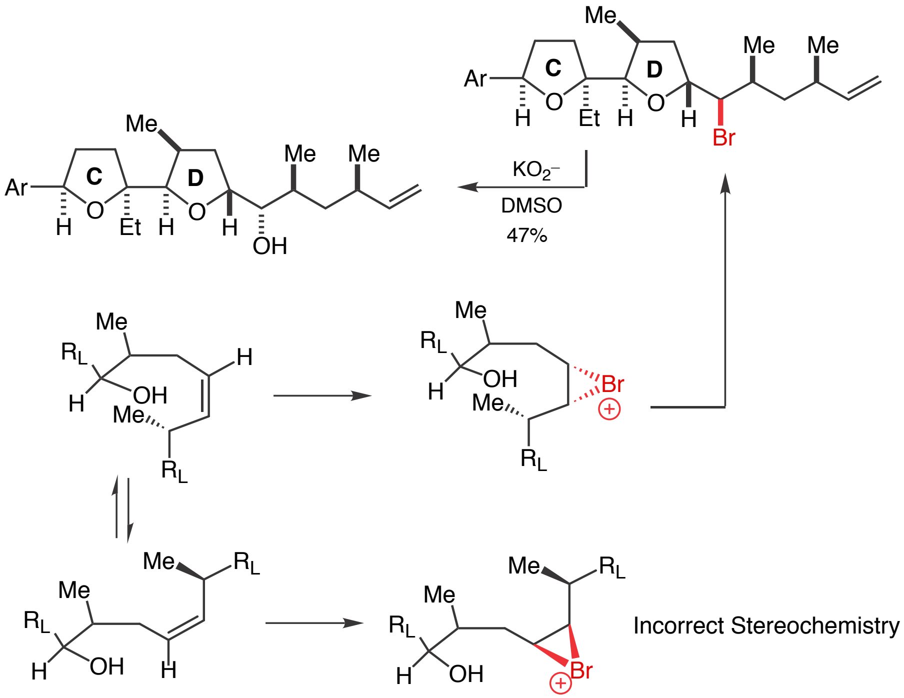


Kishi, *JACS* **1979**, *101*, 259, 260, 262
Still, *JACS* **1980**, *103*, 2117-2121

■ The Kishi Ring D Construction:

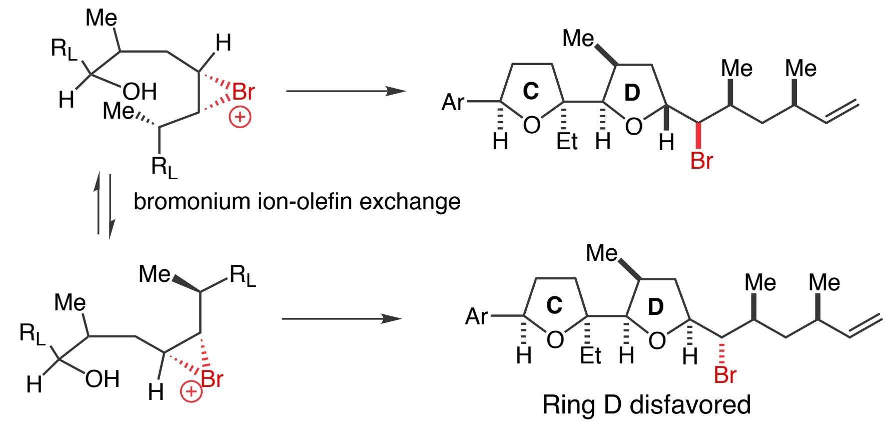


Hypothesis-A: Stereocontrol through A(1,3) Strain??



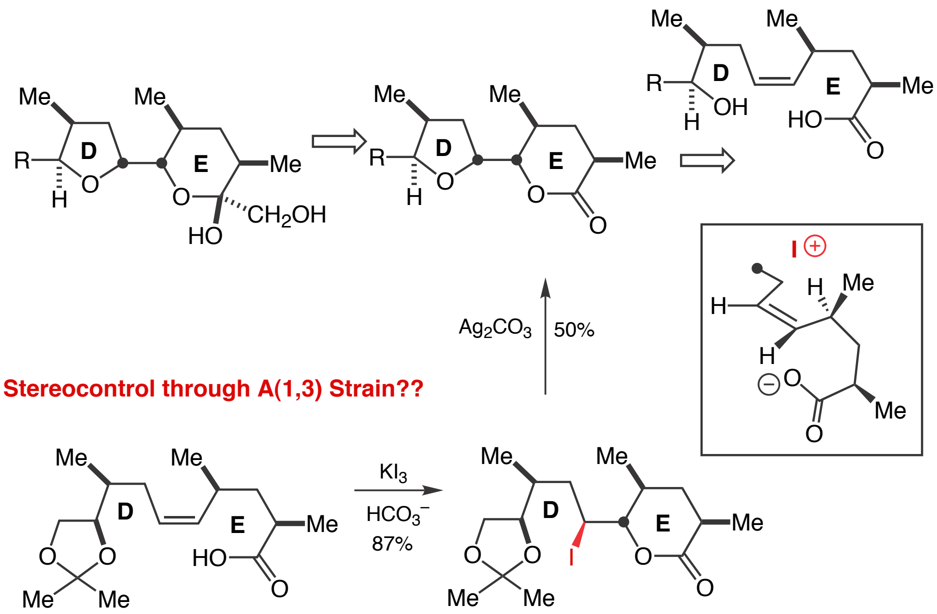
Incorrect Stereochemistry

Hypothesis-B: Stereocontrol through Reversal of Bromonium Ion Intermediate



Ring D disfavored

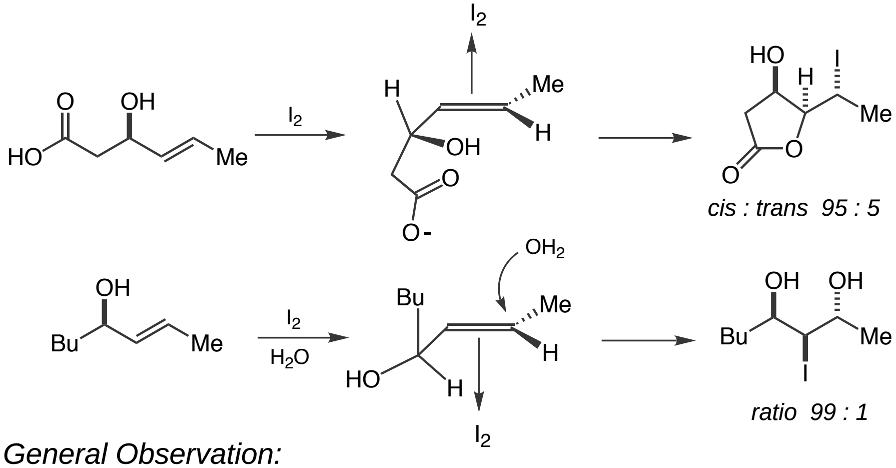
■ The Still Ring E Construction:



Stereocontrol through A(1,3) Strain??

El(+)-induced heterocyclization ⟹ Cardillo, *Tetrahedron* **1990**, *46*, 3321-3408
Bartlett, *Asymmetric Synthesis* **1984**, *3*, Chap 6, 411-454

- A complete turnover in olefin diastereofacial selectivity is observed when adding *internal* and *external* nucleophiles



cis : trans 95 : 5

ratio 99 : 1

General Observation:

For electrophiles that react via onium intermediates (I_2, Br_2, $Hg(OAc)_2$, PhSeCl), the major diastereomer from electrophile-induced cyclization is opposite to that observed in the analogous intermolecular electrophilic addition.

For a review of elctrophilic induced olefin cyclization reactions see:
G. Cardillo & M. Orena, *Tetrahedron* **1990**, *46*, 3321.

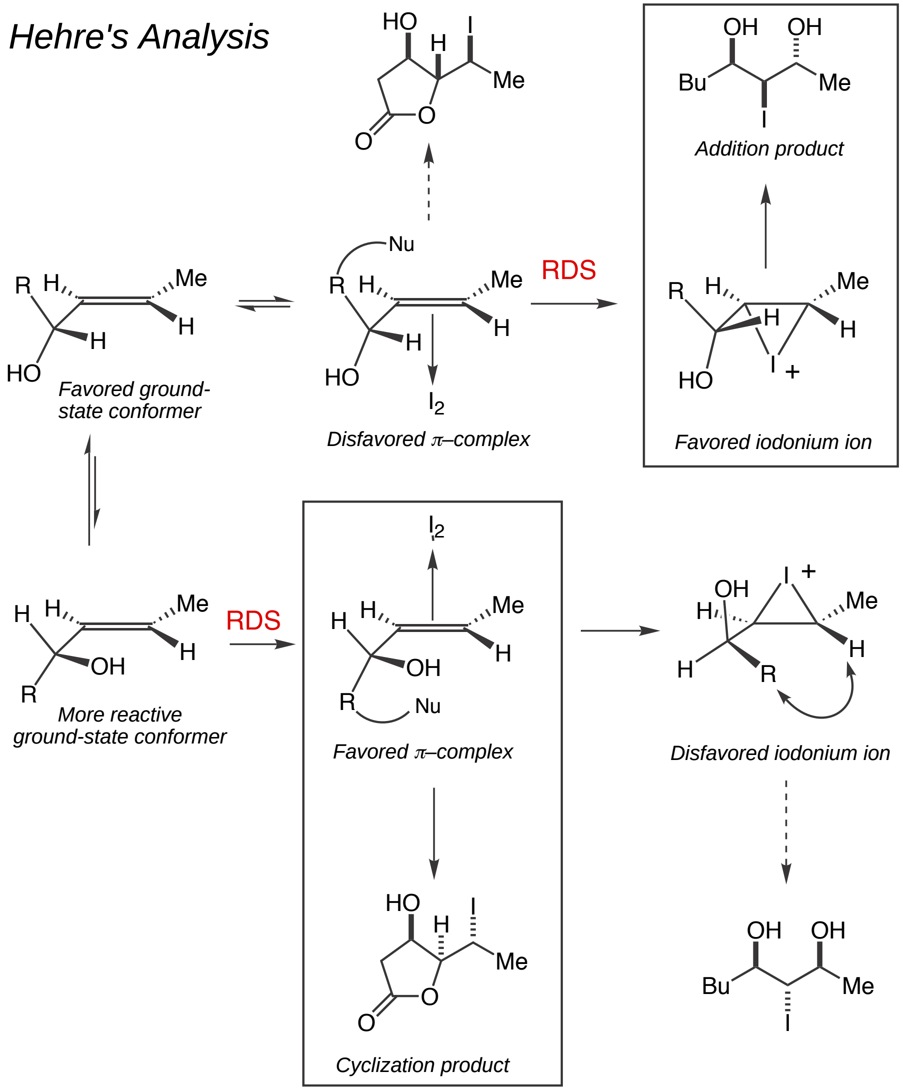
Chamberlin & Hehre's Rationalization

- "Facial preferences in electrophilic addition reactions are *not* invariant with respect to the location of the transition state along the reaction coordinate."
- *Change in diastereoselectivity is a consequence of a change in the* ***rate-limiting step***
  - Addition reactions: Formation of an **onium ion intermediate**
    (subsequently trapped by a Nu from the medium)
  - Cyclization reactions: Intramolecular attack on a **π–complex** (not an onium ion)
- Analysis of the stereoselectivity of electrophilic addition to chiral olefins:

1. Relative abundances of conformational minima
2. *Relative reactivities of the available forms*
3. Stereoselectivies of the individual conformers

Chamberlin & Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 672-677.

Hehre's Analysis

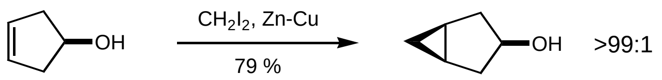


Houk: Argument for the "inside alkoxy effect" in π–complex formation

- π–complex cyclizes if R contains a Nu and its formation is rate determining
- Onium ion formation is rate determing in the addition reactions
- "The presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of transition state.

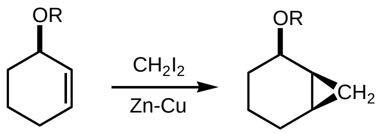
The Simmons-Smith Reaction

For a recent general review of the Simmons-Smith reaction see:
Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



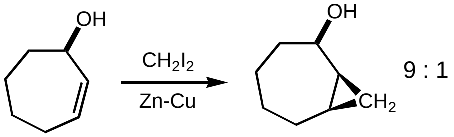
S. Winstein, *JACS* **1959**, *81*, 6523; **1961**, *83*, 3235; **1969**, *91*, 6892

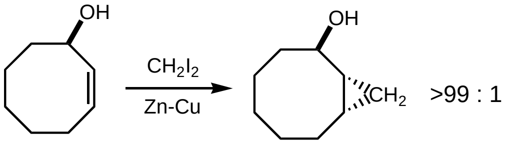
A large rate acceleration relative to simple olefins was observed.



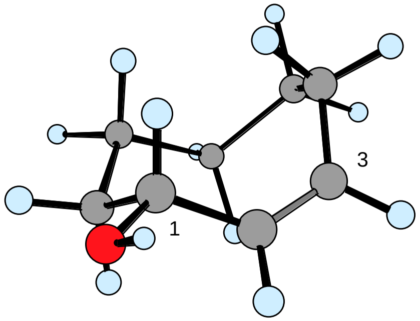
R = OMe: >99:1 Dauben, *JACS* **1963**, *85*, 468

R = OAc: 4:1 Sawada, *JOC* **1968**, *33*, 1767





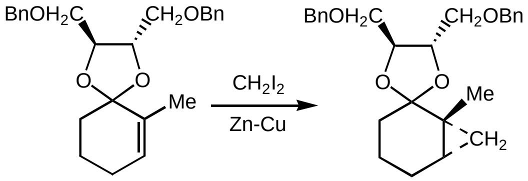
epoxidation also gives anti adduct



O–C_1–C_2–C_3 dihedral = 165 °

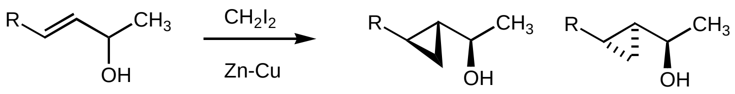
S. Winstein, *JACS*, **1969**, *91*, 6892

Absolute control of stereochemistry is possible through chiral ketal auxiliaries



diastereoselection 20:1

Yamamoto, *JACS*, **1985**, *107*, 8254
Mash, *JACS*, **1985**, *107*, 8256
Yamamoto, *Tetrahedron*, **1986**, *42*, 6458

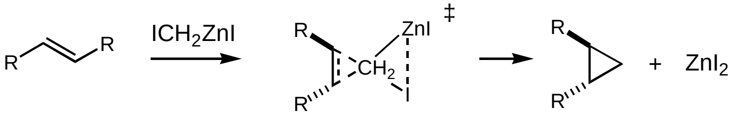


M. Pereyre and Co-workers
J. Chem. Res. (S) **1979**, 179

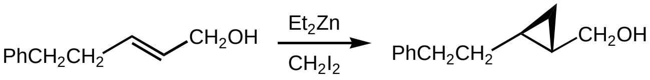
R	Ratio		
CH_3	57	:	43
Et	64	:	36
tBu	67	:	33

■ The classical mechanism

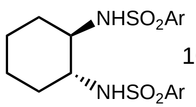
CH_2I_2 + Zn $\longrightarrow$ ICH_2ZnI



■ Enantioselective Simmons-Smith Variants: Kobayashi, *Tet. Let.* **1992**, *33*, 2575



80% ee (82% yield)

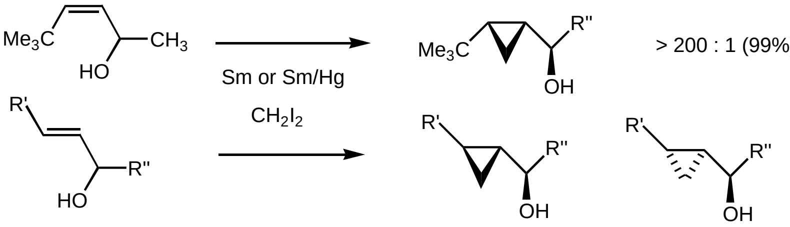


10 mol%

These results suggest that the transition state might be binuclear.

Construct a reasonable transition structure which accomdates the data

■ Low-valent Samarium Variants: Molander,*JOC* **1987**, *52*, 3942



> 200 : 1 (99%)

Isolated alkenes and homoallylic alcohols are inert to these reaction conditions.

G. A. Molander and J. B. Etter
J. Org. Chem. **1987**, *52*, 3942

R'	R"	Ratio		
Ph	nBu	1	:	1.4
Ph	iPr	> 200	:	1
Ph	tBu	> 200	:	1
tBu	CH_3	1	:	5.1
tBu	iPr	> 200	:	1

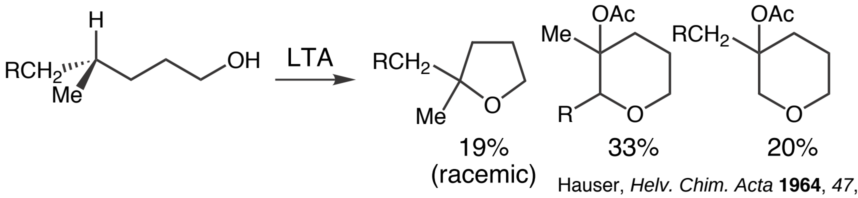
Radical Lead Tetraacetate Mechanism

$$ROH + Pb(OAc)_4 \longrightarrow ROPb(OAc)_3 + {}^{-}OAc$$

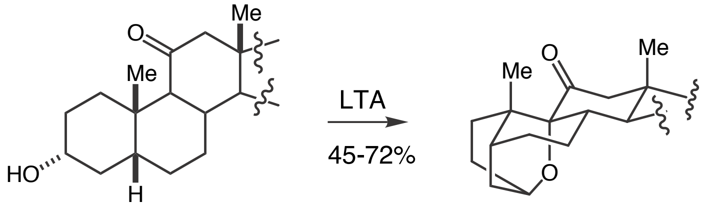
$$ROPb(OAc)_3 \longrightarrow RO\bullet + \bullet Pb(OAc)_3$$

$$RO\bullet + R'H \longrightarrow ROH + R'\bullet$$

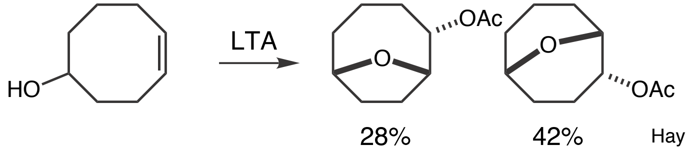
$$R'\bullet + Pb(OAc)_4 \longrightarrow R'OAc + \bullet Pb(OAc)_3$$



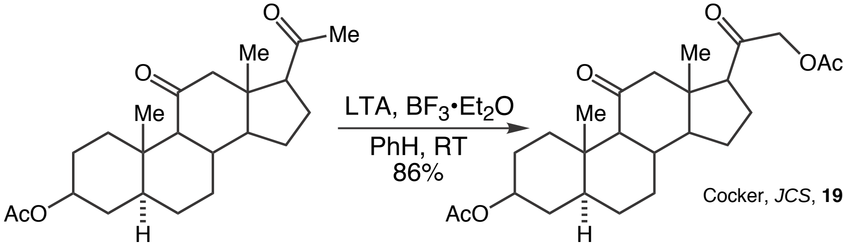
Hauser, *Helv. Chim. Acta* **1964**, *47*, 1883.



Immer, *Helv. Chim. Acta* **1962**, *45*, 753.



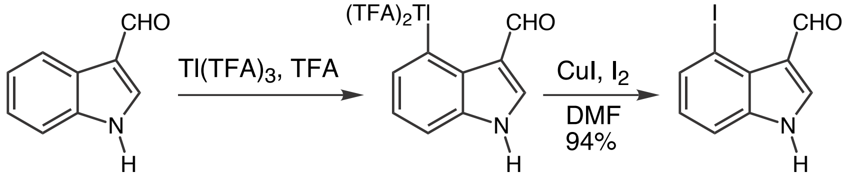
Haynes, *JOC*, **1866**,*31*, 3067.



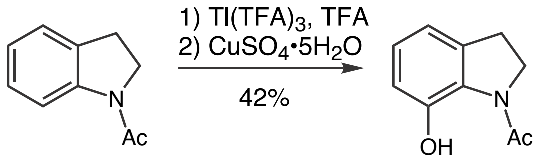
Cocker, *JCS*, **1965**, 6.

Vinyl and Aryl C-H Oxidations

Thallium



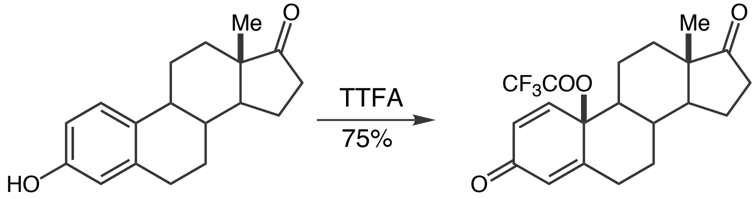
Somei, *Heterocycles* **1984**, *22*, 797.



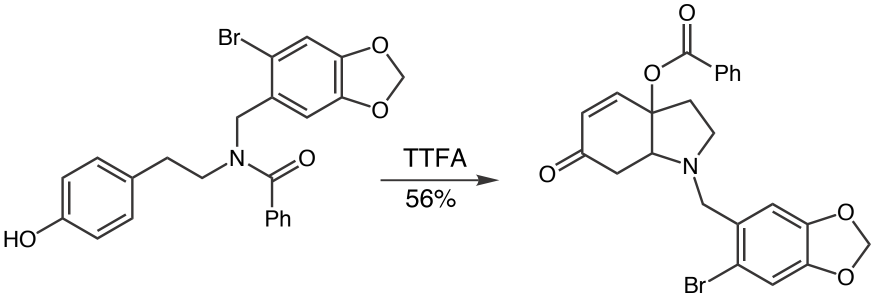
Somei, *Heterocycles*, **1988**, *27*, 2363.

Phenolic Oxidations:

For a review of oxidative aryl couplings, see: Dinsmore, C. Evening Seminar, February 1993.



Coombs, *Chem. Ind.*, **1972**, 169.

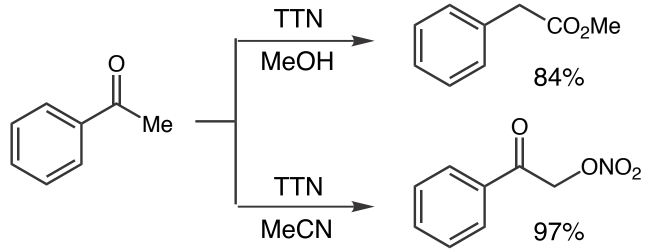


Taylor, *JACS*, **1981**, *103*, 6856.

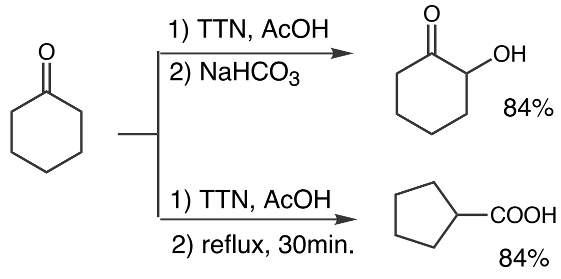
Redox- Thallium.2

Oxythallation of Ketones (Enols) with Ring Contraction

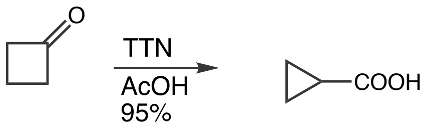
TTN = $Tl(NO_3)_3$



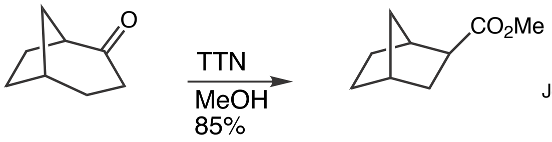
McKillop and Taylor, *JACS*, **1973**, *95*, 3340.
McKillop and Taylor, *JOC*, **1978**, *43*, 3773.



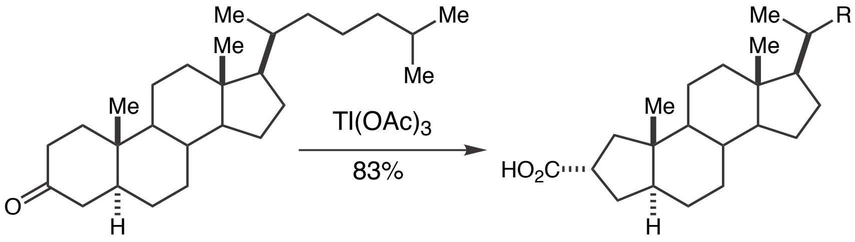
McKillop and Taylor, *JOC*, **1972**, *37*, 3381.



Salaun, *Tet.*, **1974**, *30*, 1423.

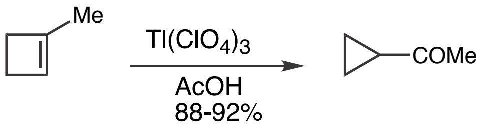


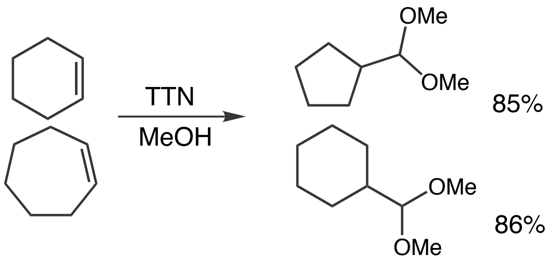
Jones, *JOC*, **1977**, *42*, 2176.



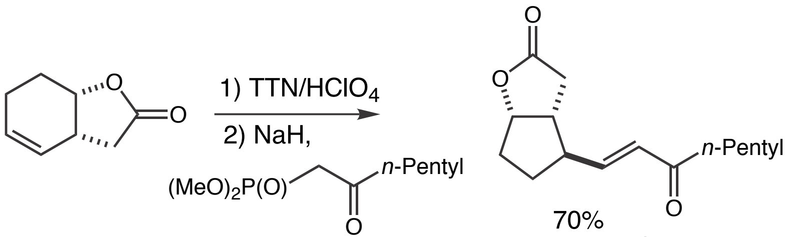
Romeo, *Tet.*, **1972**, *28*, 5337.

Oxythallation of Double and Triple Bonds

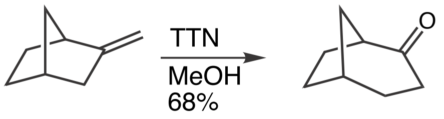




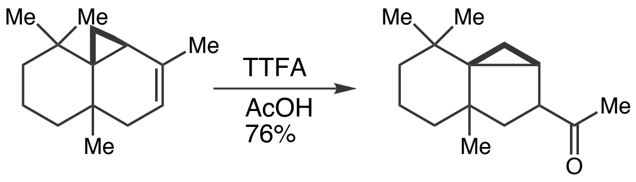
McKillop and Taylor, *JACS*, **1973**, *95*, 3635.



Corey, *TL*, **1971**, 4753.



Jones, *JACS*, **1976**, *98*, 8476.

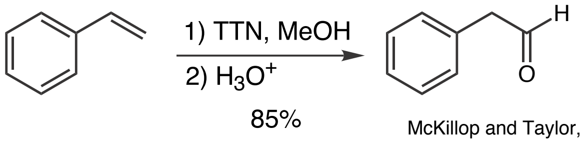


Inoue, *Bull. Chem. Soc. Jpn.* **197**, *51*, 2439.

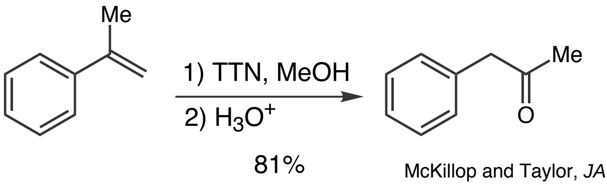
Redox- Thallium.3

Oxidative Rearrangements of Styrenes

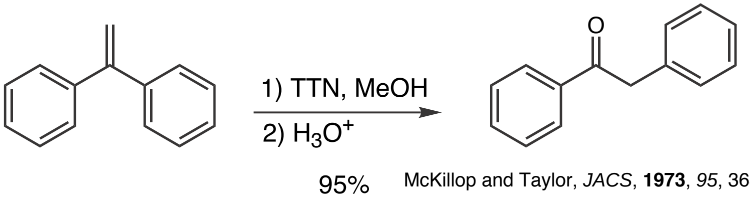
TTN = $Tl(NO_3)_3$



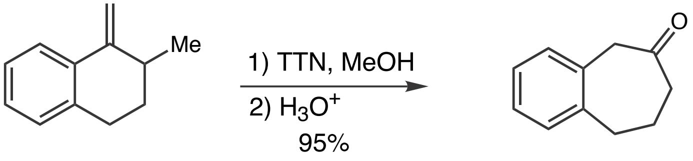
McKillop and Taylor, *JACS*, **1973**, *95*, 3635.



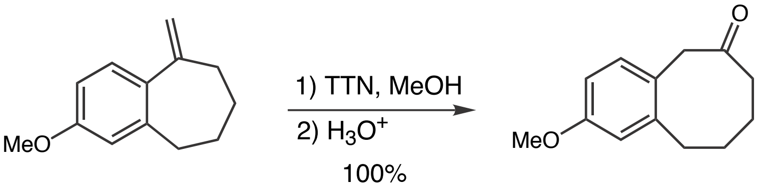
McKillop and Taylor, *JACS*, **1973**, *95*, 3635.



McKillop and Taylor, *JACS*, **1973**, *95*, 3635.

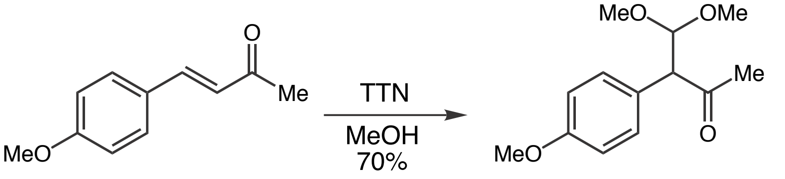


McKillop and Taylor, *TL*, **1977**, 1827.

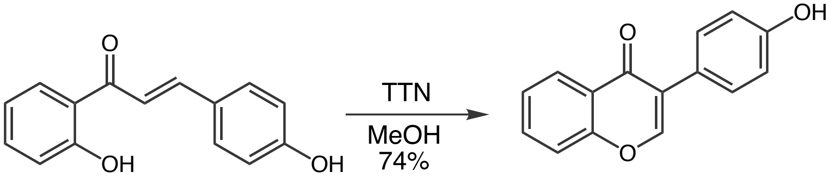


McKillop and Taylor, *TL*, **1977**, 1827.

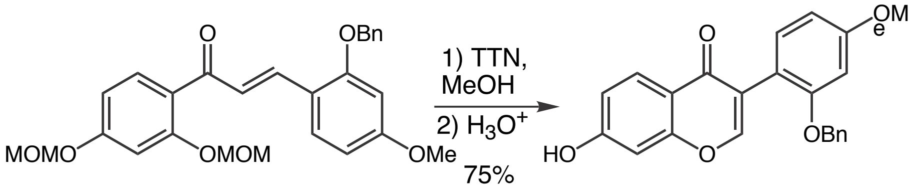
Oxidative Rearrangements of Chalcones



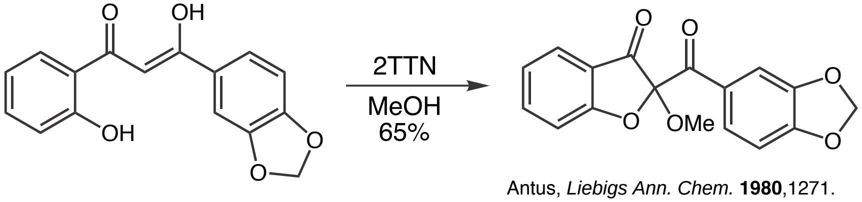
Antus, *Liebigs Ann. Chem.* **1980**, 1283.



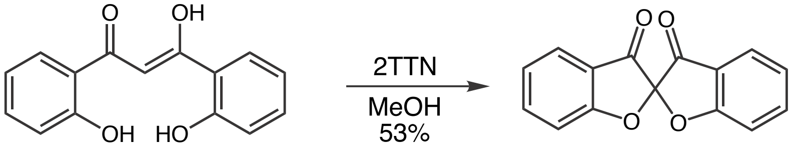
Eade,*Aust. J. Chem.* **1978**, *31*, 2699.



van Heerden *JCSPT1* **1980**, 2463.



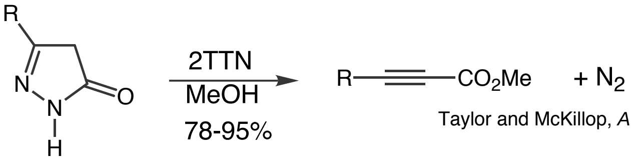
Antus, *Liebigs Ann. Chem.* **1980**,1271.



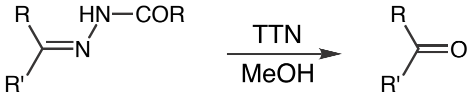
Antus, *Liebigs Ann. Chem.* **1980**,1271.

Oxidation of Nitrogen Compounds

TTN = $Tl(NO_3)_3$

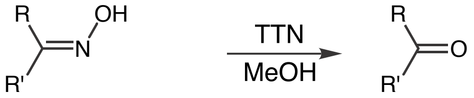


Taylor and McKillop, *ACIEE* **1972**, *11*, 48.



R and R' alkyl or aryl, yields 82-95%

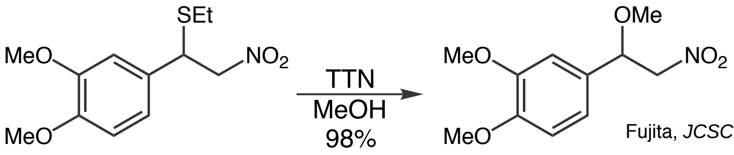
McKillop and Taylor, *JACS* **1971**, *93*, 4918.



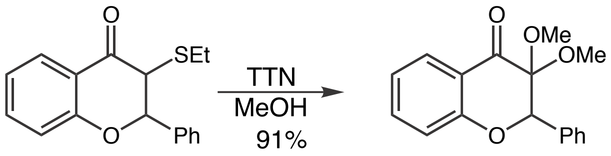
R and R' alkyl or aryl, yields 72-96%

McKillop and Taylor, *JACS* **1971**, *93*, 4918.

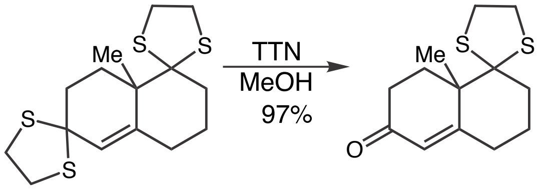
Oxidation of Sulfur Compounds



Fujita, *JCSCC*, **1976**, 202.



Fujita, *TL*, **1978**, 4115.



Smith, *Synth. Commun.* **1979**, *9*, 301.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 11

Pericyclic Reactions–1

- Introduction to Pericyclic Reactions
- Electrocyclic Reactions
- Sigmatropic Reactions
- Cycloaddition Reactions

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4
Thermal Pericyclic Reactions

Travis Dunn

Wednesday,
October 7, 2003

Other Reading Material:

- Woodward-Hoffmann Theory
  R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.

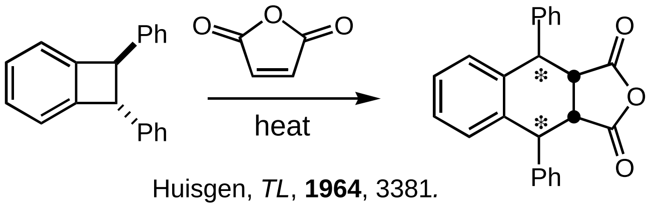
- Frontier Molecular Orbital Theory
  I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.

- Dewar-Zimmerman Theory
  T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, Harper & Row, New York, 1987.

- General Reference
  R. E. Lehr and A. P. Marchand, *Orbital Symmetry: A Problem Solving Approach*, Academic Press, New York, 1972.

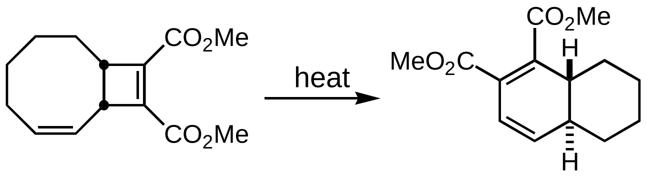
Problems of the Day:

Predict the stereochemical outcome of this reaction.



Huisgen, *TL*, **1964**, 3381.

Suggest a mechanism for the following reaction.



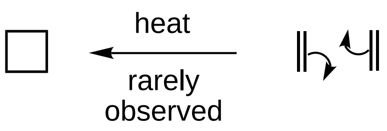
Bloomfield, *TL*, **1969**, 3719.

Pericyclic Reactions - Introduction/Definitions

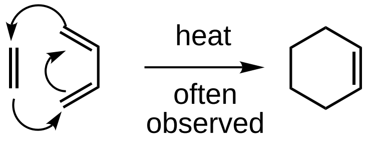
A pericyclic reaction is characterized as a change in bonding relationships that takes place as a ***continuous, concerted reorganization of electrons***.
The term "***concerted***" specifies that there is ***one single transition state*** and therefore ***no intermediates*** are involved in the process. To maintain ***continuous electron flow***, pericyclic reactions occur through ***cyclic transition states***.
More precisely: The cyclic transition state must correspond to an arrangement of the ***participating orbitals*** which has to ***maintain a bonding interaction*** between the reaction components throughout the course of the reaction.

Some factors to consider in our analysis:

The number of electrons involved has a profound influence on reactivity:

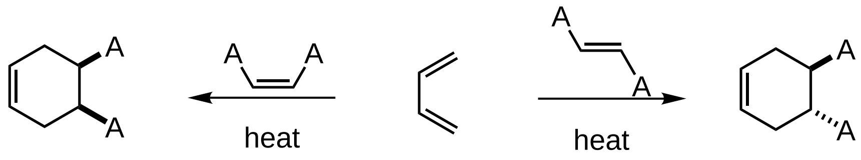


4 electrons

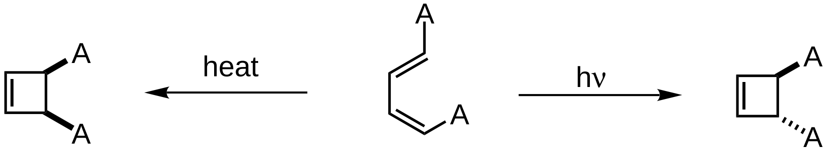


6 electrons

Pericyclic reactions are stereospecific:



Reactions behave differently depending on the conditions used (i.e. thermal versus photochemical conditions):



The Theories:

Three theories are commonly used to explain and predict pericyclic reactions. We will only concern ourselves with two of these theories.

1) Fukui: Frontier Molecular Orbital Interactions

- Much easier to use than the original orbital symmetry arguments
- HOMO/LUMO interactions

2) Dewar-Zimmerman: Aromatic Transition States

- The easiest to apply for all reaction types, but it is not as easy to understand why it it valid
- Aromatic or antiaromatic transition states

3) Woodward-Hoffmann: Conservation of Orbital Symmetry

- First theory to explain and predict the outcome of many reactions
- Correlation diagrams

On the three methods:

> "There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three of which are used more frequently than others. Of these three, we will discuss two: the frontier-orbital method and the Möbius-Hückel method. The third, called the correlation diagram method, is less convenient to apply than the other two."
> Jerry March in "Advanced Organic Chemistry"

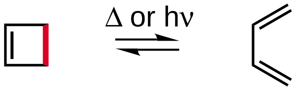
The Five Major Categories of Pericyclic Reactions

(1) ELECTROCYCLIC RING CLOSURE/RING OPENING:

An electrocyclic ring closure is the creation of a new sigma bond at the expense of the terminal p orbitals of a conjugated pi system. There is a corresponding reorganization of the conjugated pi system. We usually classify the reaction according to the number of electrons involved.

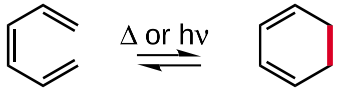
Examples:

A 4 e$^-$ electrocyclic reaction



Cyclobutene Butadiene

A 6 e$^-$ electrocyclic reaction



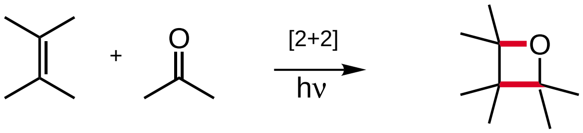
1,3,5-Hexatriene 1,3-Cyclohexadiene

Pericyclic Reactions: Major Classes

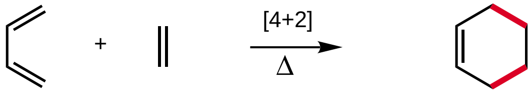
(2) CYCLOADDITION REACTIONS/CYCLOREVERSION REACTIONS:

A cycloaddition reaction is the union of two smaller, independent pi systems. Sigma bonds are created at the expense of pi bonds. A cycloaddition can occur in an intramolecular sense, but it must be between two **independent** pi systems. Cycloaddition reactions are referred to as [**m + n**] additions when a system of **m** conjugated *atoms* combines with a system of **n** conjugated *atoms*. A cycloreversion is simply the reverse of a cycloaddition.

Examples:



A 2+2 cycloaddition. The Paterno-Büchi reaction.

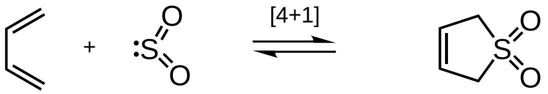


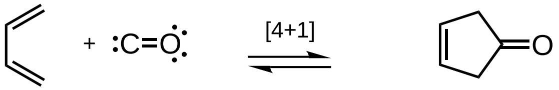
A 4+2 cycloaddition. The Diels-Alder reaction.

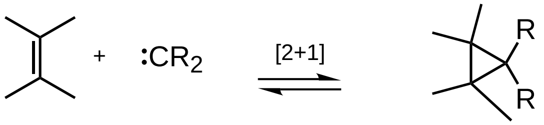
(3) CHELETROPIC REACTIONS:

Cheletropic reactions are a special group of cycloaddition/cycloreversion reactions. Two bonds are formed or broken at a single atom. The nomenclature for cheletropic reactions is the same as for cycloadditions.

Examples:



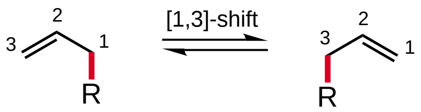


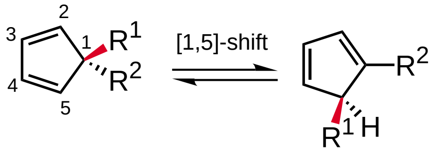


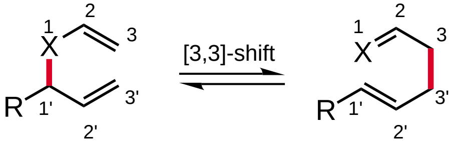
(4) SIGMATROPIC REARRANGEMENTS:

A sigmatropic rearrangement is the migration of a sigma bond from one position in a conjugated system to another position in the system, accompanied by reorganization of the connecting pi bonds. The number of pi and sigma bonds remains constant. The rearrangement is an [**m,n**] shift when the sigma bond migrates across **m** atoms of one system and **n** atoms of the second system.

Examples:







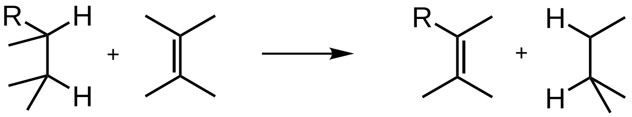
$X=CR_2$, Cope rearrangement
X=O, Claisen rearrangement

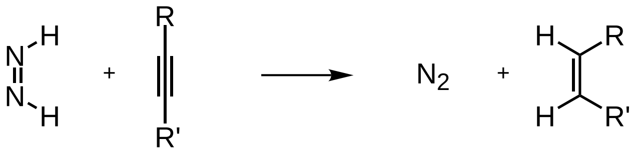
(5) GROUP TRANSFER REACTIONS:

In a group transfer reaction one or more groups get transferred to a second reaction partner.

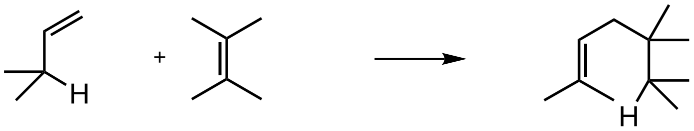
Examples:

Hydrogen Transfer:





Ene Reaction:



Electrocyclic Reactions

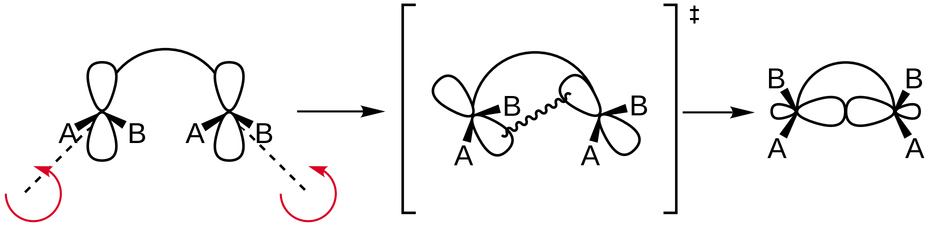
ELECTROCYCLIC RING CLOSURE/RING OPENING:

The Stereochemical issues:

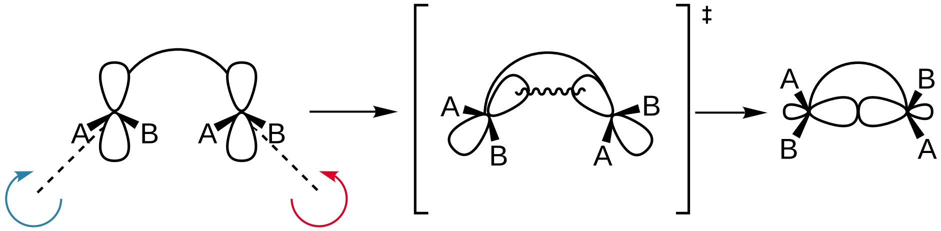
Ring closure can occur in two distinct ways. This has consequences with regard to:

- The orbital lobes that interact
- The disposition of substituents on the termini

Conrotatory Closure: The termini rotate in the **same direction**



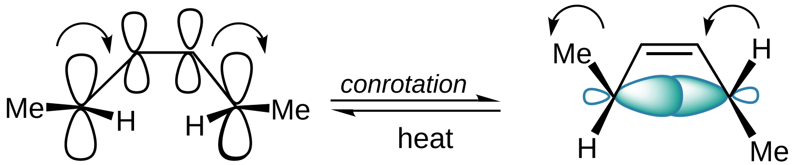
Disrotatory Closure: The termini rotate in **opposite directions**

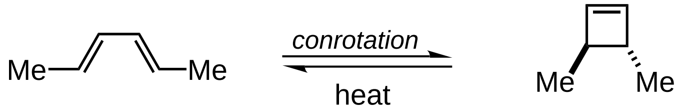


Empirical Observations:

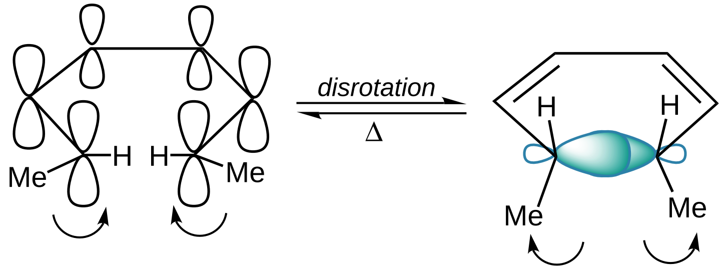
It was noted that butadienes undergo conrotatory closure under thermal conditions, while hexatrienes undergo disrotatory closure under thermal conditions. The microscopic reverse reactions also occur with the same rotational sense (i.e. cyclobutenes open in a conrotatory sense when heated, and cyclohexadienes open in a disrotatory sense when heated.)

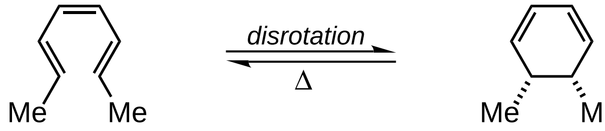
Butadiene to cyclobutene: A 4-electron (4q) system



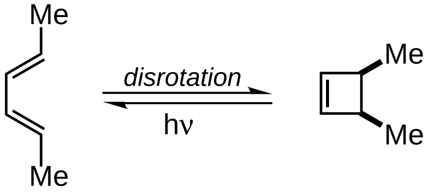


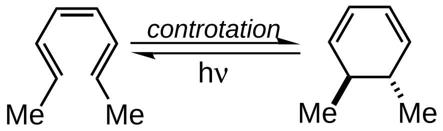
Hextriene to cyclohexadiene: A 6-electron (4q+2) system



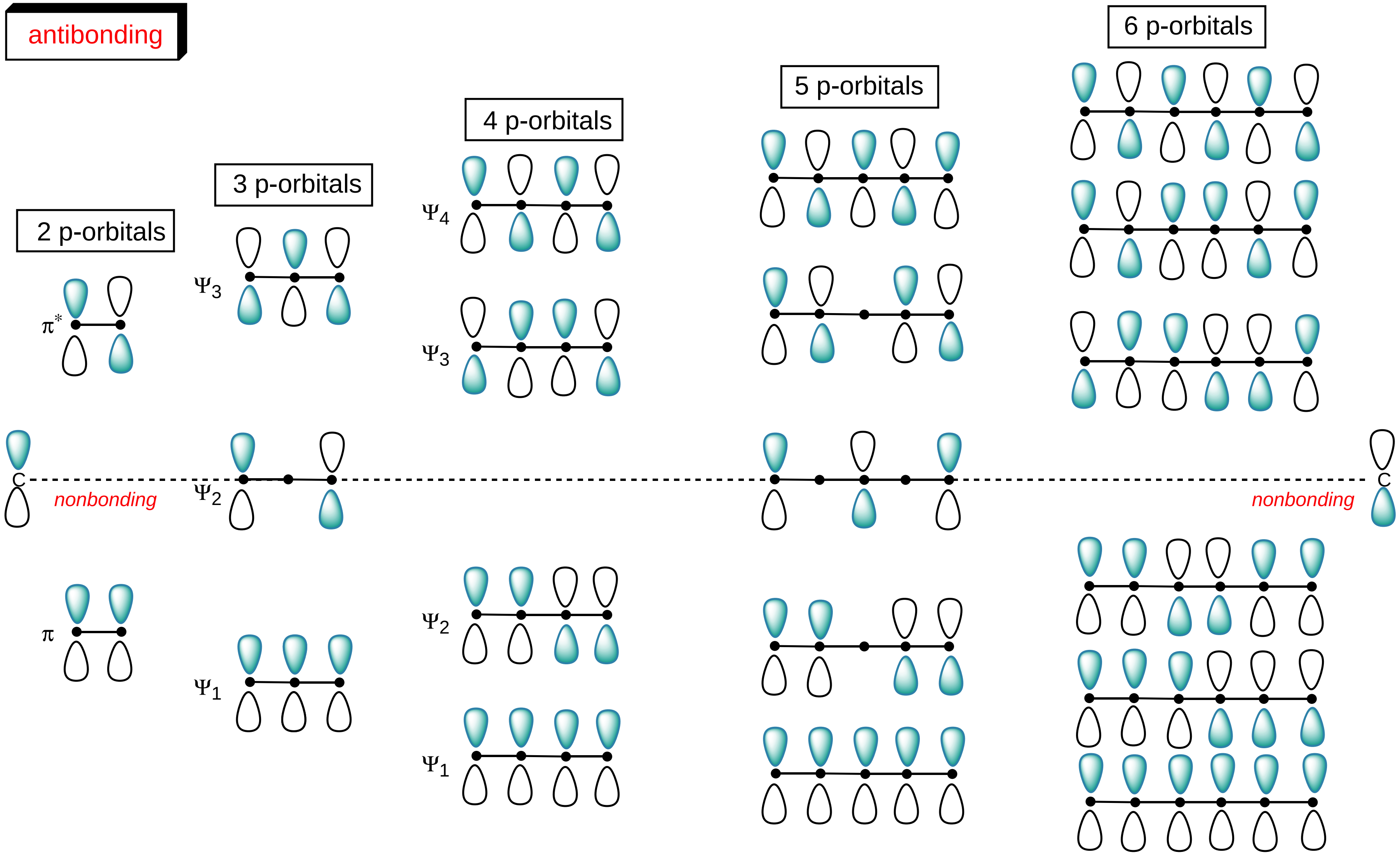


It was also noted that changing the "reagent" from heat to light reversed this reactivity pattern. Under photochemical conditions 4 electron systems undergo disrotatory motion, while 6 electron systems undergo conrotatory motion.





Conjugated pi systems



bonding

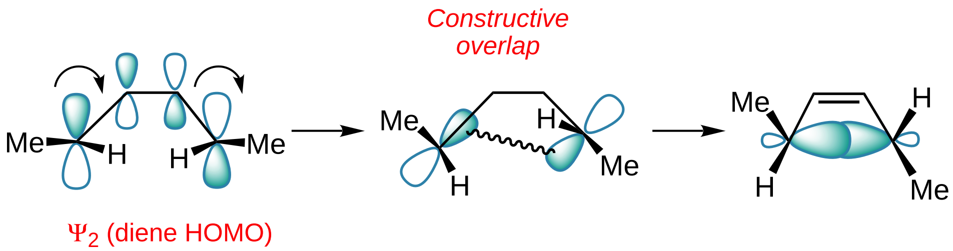
There are no nodal planes in the most stable bonding MO. With each higher MO, one additional nodal plane is added. The more nodes, the higher the orbital energy.

■ FMO Treatment of Electrocyclic reactions.

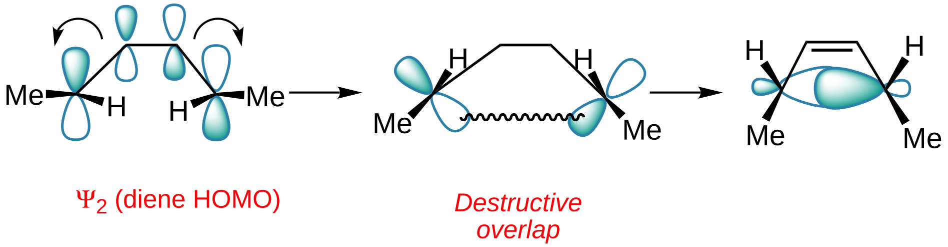
- ■ Examine the interactions that occur in the HOMO as the reaction proceeds.
- ■ If the overlap is constructive (i.e. of the same phase) then the reaction is "allowed."
- ■ If the overlap is destructive (i.e. of different phases) then the reaction is "forbidden."

Thermal Activation:

Conrotatory Closure: (Allowed and observed)



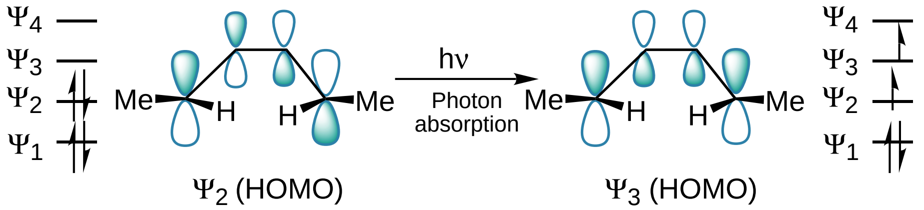
Disrotatory Closure: (Forbidden and not observed)



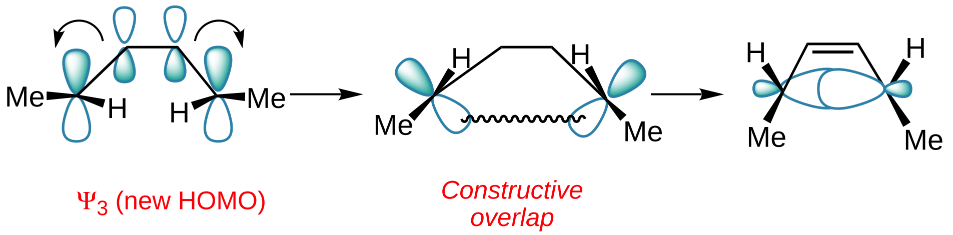
A similar analysis for the hexatriene system proves that under thermal conditions, disrotation is allowed and conrotation is forbidden.

Photochemical Activation:

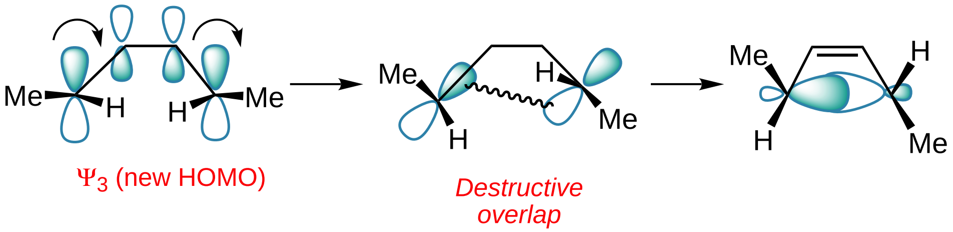
When light is used to initiate an electrocyclic reaction, an electron is excited from Ψ_2 to Ψ_3. Treating Ψ_3 as the HOMO now shows that disrotatory closure is allowed and conrotatory closure is forbidden.



Disrotatory Closure: (Allowed and observed)



Conrotatory Closure: (Forbidden and not observed)



We have so far proven which *ring closures* are allowed and which are forbidden. Do we now have to go back and examine all the *ring openings*?

NO!

The principle of microscopic reversiblity says that if the reaction is allowed in one direction, it must be allowed in the other direction.

Electrocyclic Reactions: Dewar-Zimmerman

The Dewar-Zimmerman analysis is based on identifying transition states as aromatic or antiaromatic. We will not go into the theory behind why this treatment works, but it will give the same predictions as FMO or Orbital Symmetry treatments, and is fundamentally equivalent to them.

Using the Dewar-Zimmerman model:

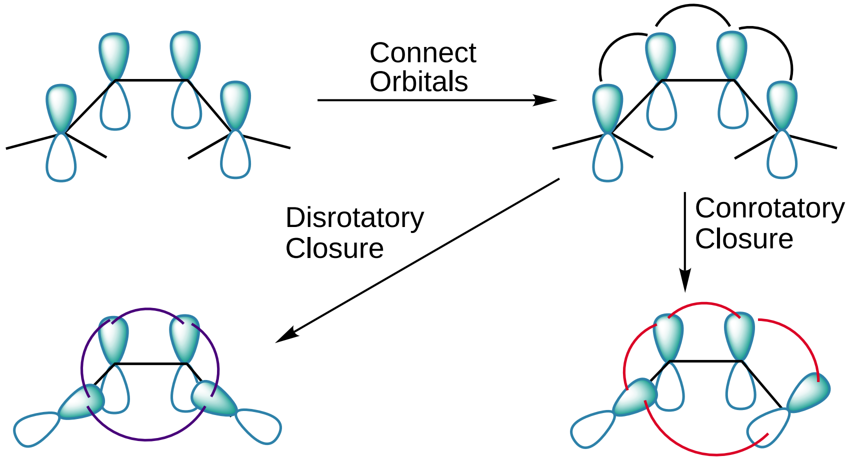
- Choose a basis set of 2p atomic orbitals for all atoms involved (1s for hydrogen atoms).
- Assign phases to the orbitals. Any phases will suffice. It is **not** important to identify this basis set with any molecular orbital.
- Connect the orbitals that interact in the starting material, before the reaction begins.
- Allow the reaction to proceed according to the geometry postulated. Connect those lobes that begin to interact that were not interacting in the starting materials.
- Count the number of phase inversions that occur as the electrons flow around the circuit. Note that a phase inversion **within** an orbital **is not counted**.
- Based on the phase inversions, identify the topology of the system.

Odd number of phase inversions:	Möbius topology
Even number of phase inversions:	Hückel topology

- Assign the transition state as aromatic or antiaromatic, based on the number of electrons present.

System	Aromatic	Antiaromatic
Hückel	4q + 2	4q
Möbius	4q	4q + 2

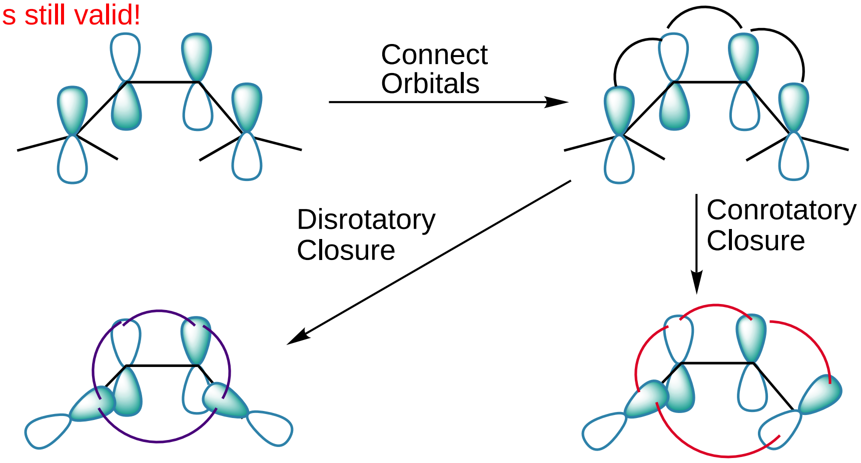
- If the transition state is aromatic, then the reaction will be allowed thermally. If the transition state is antiaromatic, then the reaction will be allowed photochemically.



Zero Phase Inversions
∴Hückel Topology
4 electrons in system
∴ Antiaromatic and
Forbidden

One Phase Inversion
∴Möbius Topology
4 electrons in system
∴ Aromatic and
Allowed

Note that I can change the phase of an abitrary orbital and the analysis is still valid!



Two Phase Inversions
∴Hückel Topology
4 electrons in system
∴ Antiaromatic and
Forbidden

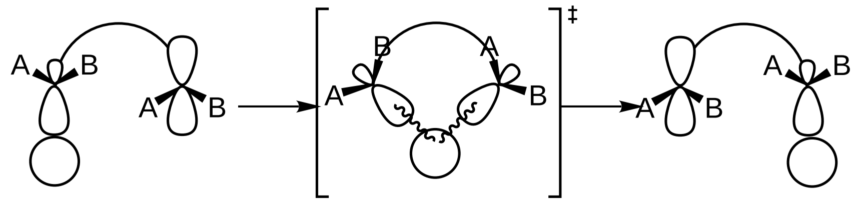
Three Phase Inversions
∴Möbius Topology
4 electrons in system
∴ Aromatic and
Allowed

[1,3]-Sigmatropic Rearrangements: FMO Analysis

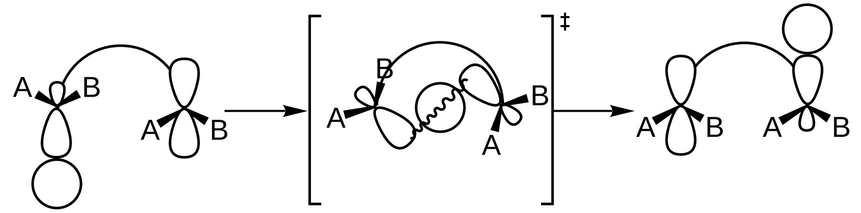
The Stereochemical issues:

The migrating group can migrate across the conjugated pi system in one of two ways. If the group migrates on the same side of the system, it is said to migrate **suprafacially** with respect to that system. If the group migrates from one side of the pi system to the other, it is said to migrate **antarafacially** with respect to that system.

Suprafacial migration: The group moves across the same face.



Antarafacial migration: The group moves from one face to the other.



■ Sigmatropic Rearrangements: FMO Analysis

■ Imagine the two pieces fragmenting into a cation/anion pair, (or a pair of radicals) and examine the HOMO/LUMO interaction.

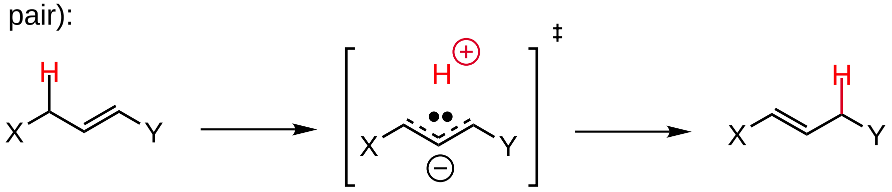
■ If the overlap is constructive at both termini then the reaction is allowed. If the overlap is destructive at either terminus then the reaction is forbidden.

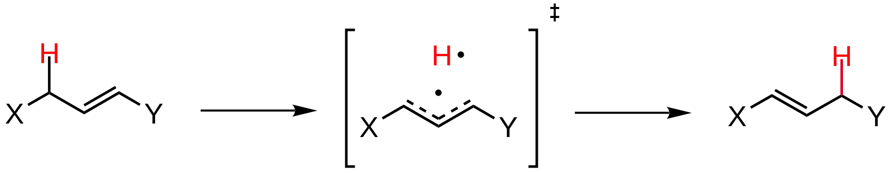
■ If the migrating atom is carbon, then we can also entertain the possiblity of the alkyl group migrating with inversion of configuration (antarafacial on the single atom).

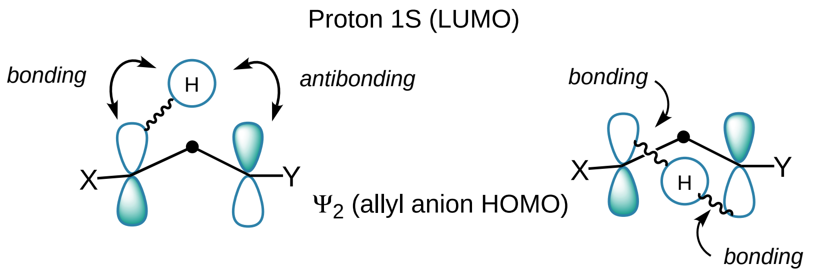
■ If the migrating atom is hydrogen, then it cannot migrate with inversion.

■ [1,3] Sigmatropic Rearrangements (H migration)

■ Construct TS by considering an allyl anion and the proton (or radical pair):







Suprafacial Geometry *Antarafacial Geometry*

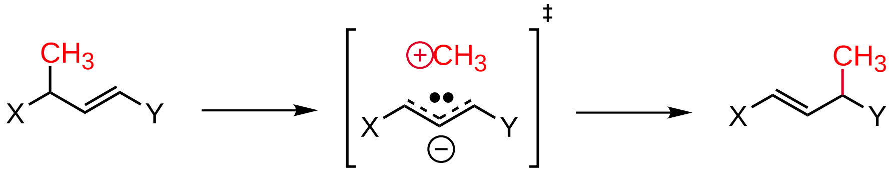
■ The analysis works if you consider the other ionic reaction, or consider a radical reaction. In each case it is the same pair of orbitals interacting.

■ The suprafacial migration is forbidden and the bridging distance too great for the antarafacial migration. Hence, [1,3] hydrogen migrations are not observed under thermal conditions.

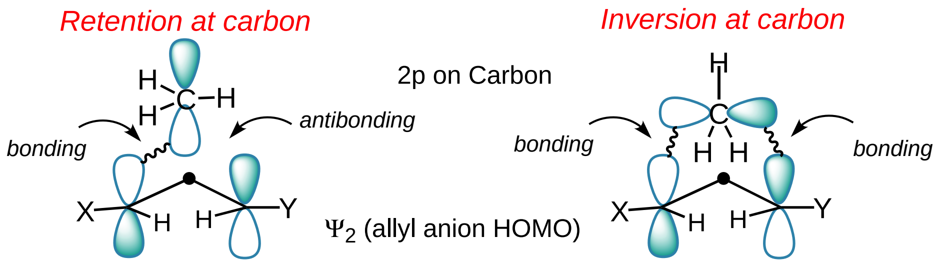
■ Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially. How would you predict this using FMO?

[1,3]-Sigmatropic Rearrangements

- [1,3] Sigmatropic Rearrangements (C migration)



- Construct TS by considering an allyl anion and the methyl cation:



Suprafacial on allyl fragment

Suprafacial on allyl fragment

- The analysis works if you consider the other ionic reaction, or consider a radical reaction. In each case it is the same pair of orbitals interacting.

- Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially with retention of stereochemistry.

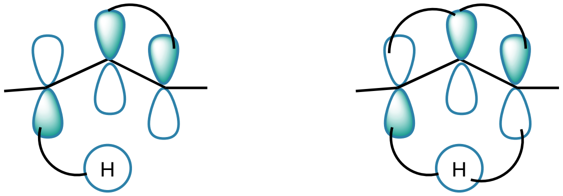
- The stereochemical constraints on the migration of carbon with inversion of configuration is highly disfavored on the basis of strain. Such rearrangements are rare and usually only occur in highly strained systems.

Using a similar analysis, one can prove that [1,5] hydrogen and alkyl shifts should be allowed when suprafacial on the pi component and proceeding with retention. Please refer to Fleming for more applications of FMO theory to [1,n] sigmatropic shifts.

■ Sigmatropic Rearrangements: Dewar-Zimmerman

Dewar-Zimmerman also predicts the [1,3] suprafacial migration to be forbidden.

The basis set of s and p orbitals with arbitrary phase:

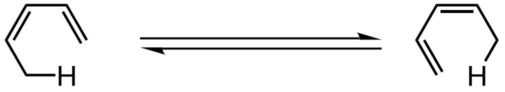


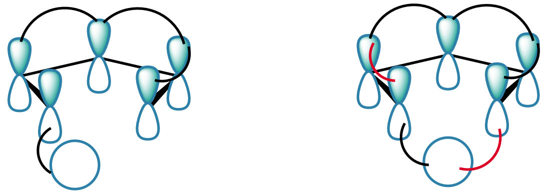
Orbital interactions in the parent system

Completing the circuit across the bottom face

Two Phase Inversions
Hückel Topology
Four Electrons
Forbidden thermally

The [1,5] shift of a hydrogen atom across a diene.





Orbital interactions in the parent system

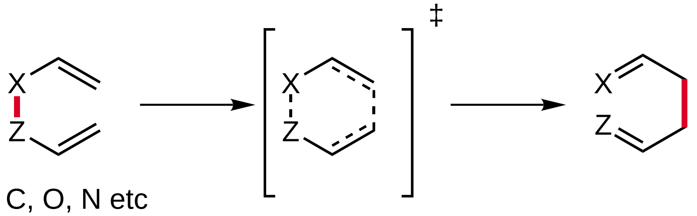
Completing the circuit across the bottom face

Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

[3,3]-Sigmatropic Rearrangements

[3,3] Rearrangements:

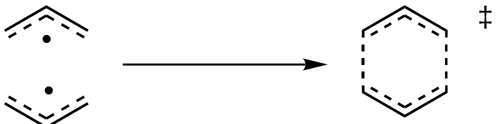
A thermally allowed reaction in either of two geometries, the "chair" or the "boat" geometry. Depicted below is the "chair" geometry. You should be able to work out the details of the "boat" geometry yourself.

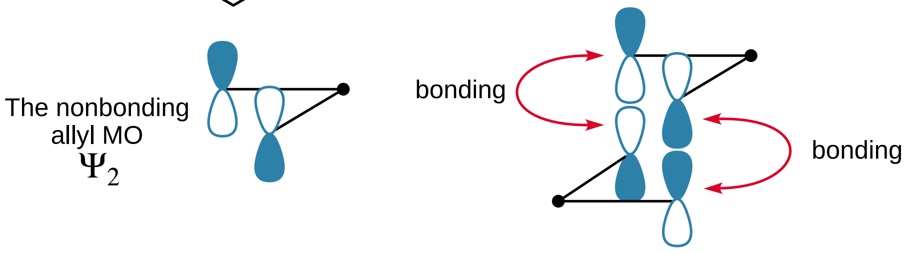


X & Z = C, O, N etc

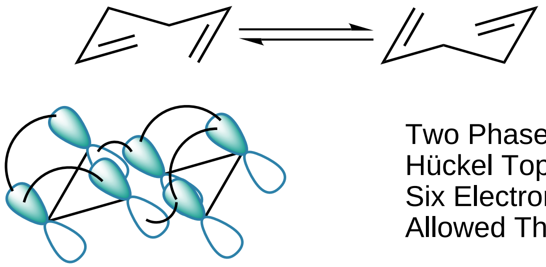
The FMO Analysis:

Bring two Allyl radicals together to access for a possible bonding interaction between termini.





The Dewar-Zimmerman Analysis:



Two Phase Inversions
Hückel Topology
Six Electrons
Allowed Thermally

The Toggle Algorithm:

The toggle algorithm is a simple way to take one reaction of each class that you remember is allowed (or forbidden) and derive if the reaction is allowed or forbidden under new conditions.

How does it work?

All of the various parameters of the pericyclic reaction are the input variables, the "switches."
The output is either "allowed" or "forbidden."
Write out all the relevant parameters of a reaction together with the known result.
Each time you change a parameter by one incremental value ("toggle a switch"), the output will switch.
This is the prediction of the reaction under the new parameters.

So it's nothing really new, is it?

No, its just a convenient way to rederive predictions without memorizing a table of selection rules.

An Example:

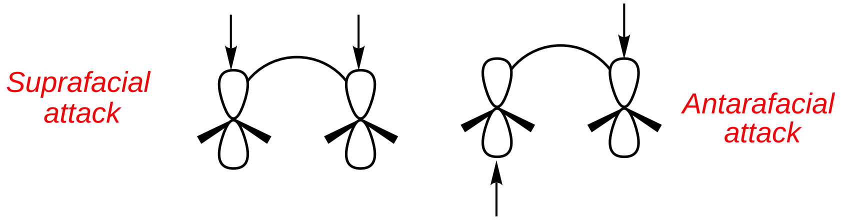
Take the [1,3] sigmatropic rearrangement of an alkyl group. We know this is forbidden under thermal conditions in a supra-supra manner, and so we make it the first entry in the table.

Rearrangement	Conditions	Component 1	Component 2	Output
[1,3]	Heat	Suprafacial	Suprafacial	Forbidden
[1,3]	Heat	Antarafacial	Suprafacial	Allowed
[1,3]	Light	Antarafacial	Suprafacial	Forbidden
[1,5]	Heat	Suprafacial	Suprafacial	?

Each incremental change in the "input" registers changes the "output" register by one. Multiple changes simply toggle the output back and forth. What is the prediction in the last line?

The Stereochemical issues:

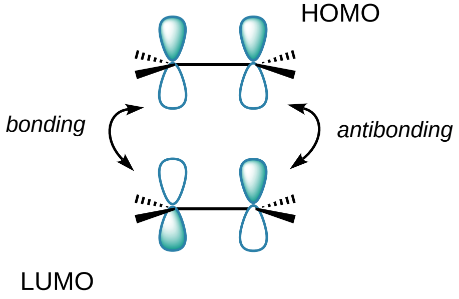
In a cycloaddition, a pi system may be attacked in one of two distinct ways. If the pi system is attacked from the same face, then the reaction is **suprafacial** on that component. If the system is attacked from opposite faces, then the reaction is **antarafacial** on that component.



The [2+2] Cycloaddition: FMO Analysis

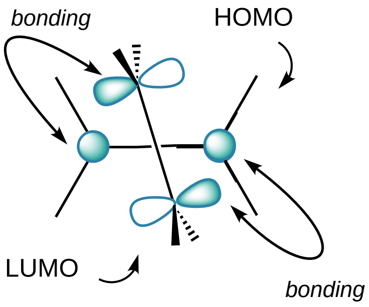
For the [2+2] cycloaddition two different geometries have to be considered.

Suprafacial/Suprafacial



Forbidden

Antarafacial/Suprafacial

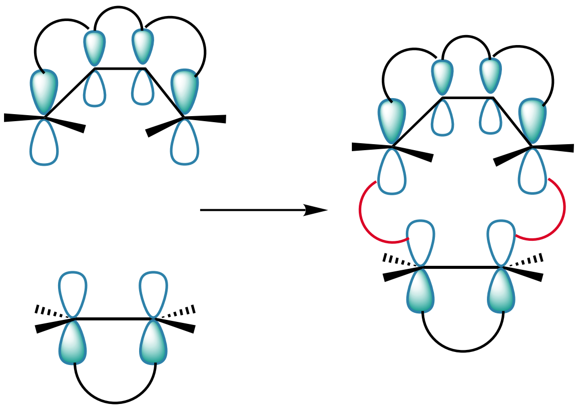


Allowed

The simplest approach (Supra/Supra) is forbidden under thermal activation. The less obvious approach (Antara/Supra) is allowed thermally but geometrically rather congested. It is believed to occur in some very specific cases (e.g. ketenes) where the steric congestion is reduced.

The [4+2] Cycloaddition: Dewar-Zimmerman

The most well known cycloaddition is the Diels-Alder reaction between a four pi component (the diene) and a two pi component (the dienophile). An exhaustive examination of this reaction is forthcoming, so we will limit ourselves to a simple examination.



Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

Summary:

- ■ There are three fundamentally equivalent methods of analyzing pericyclic reactions: Two are much simpler than the third.
  - ■ Fukui Frontier Molecular Orbital Theory
  - ■ Dewar-Zimmerman Hückel-Möbius Aromatic Transition States
  - ■ Woodward-Hoffmann Correlation Diagrams

- ■ Some methods are easier to use than others, but all are equally correct and no one is superior to another. Conclusions drawn from the correct application of one theory will not be contradicted by another theory.

- ■ The principle of microscopic reversibility allows us to look at a reaction from either the forward direction or the reverse direction.

- ■ There is a general trend that reactions will behave fundamentally different under thermal conditions and photochemical conditions.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 12

Pericyclic Reactions–2

- Electrocyclic Reactions
- Cheletropic Reactions

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

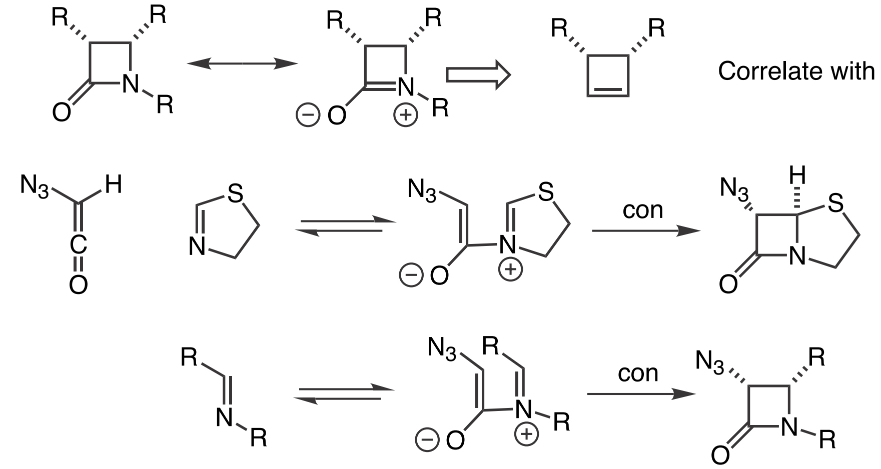
Fleming: Chapter 4
Thermal Pericyclic Reactions

D. A. Evans

Monday,
October 12, 2003

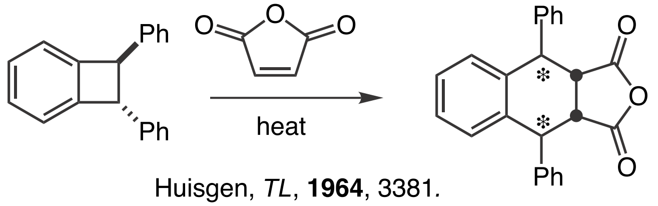
Other Reading Material:

C. Palomo, "Asymmetric Synthesis of β-Lactams by Stauginger Ketene-Imine Cycloaddition Reaction, Eur. *J. Org. Chem. 1999*, 3223-3235.



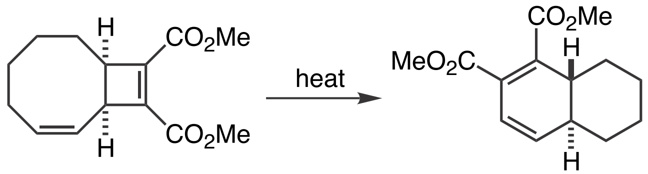
Problems of the Day:

Predict the stereochemical outcome of this reaction.



Huisgen, *TL*, **1964**, 3381.

Suggest a mechanism for the following reaction.

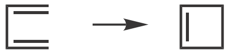
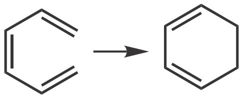
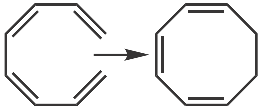
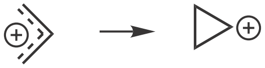
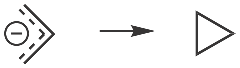
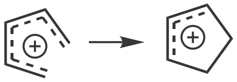
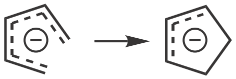


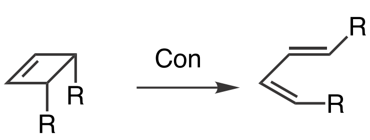
Bloomfield, *TL*, **1969**, 3719.

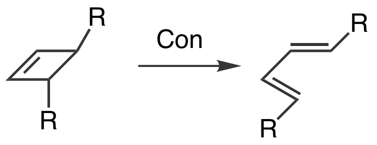
Electrocyclic Processes-1

Electrocyclic Reaction - Selection Rules

	Ground State (Thermal process)	Excited State (Photochemical Process)
4n π e^- (n = 1,2...)	conrotatory	disrotatory
4n+2 π e^- (n = 0,1,2...)	disrotatory	conrotatory

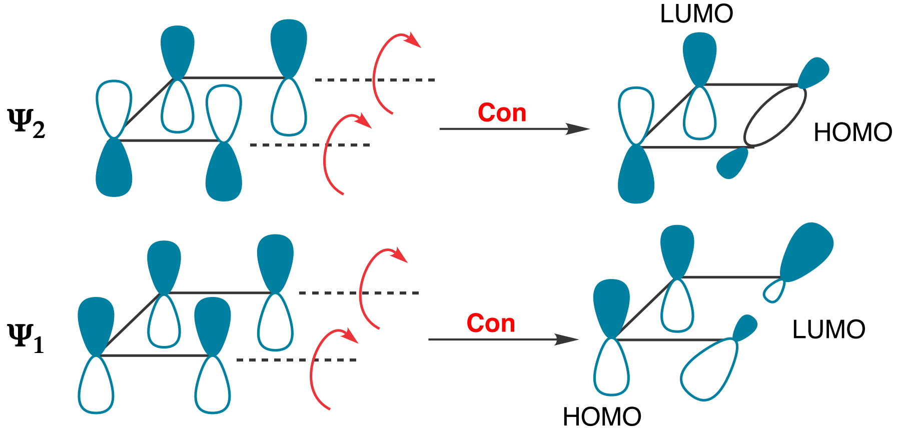
Examples	Ground State	Excited State
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory



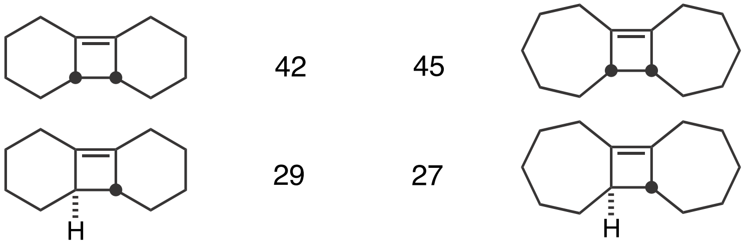


Sterically favored

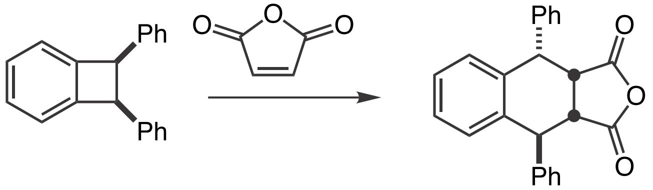
Controtation Ψ_1 and Ψ_2 on to the indicated bonding and anti-bonding orbitals of cyclobutene:

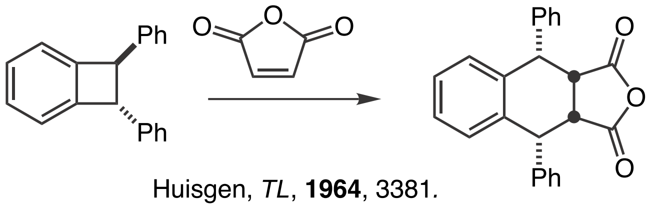


Activation Energy (kcal/mol)
for electrocyclic ring opening



Criegee, *Chem. Ber.* **1968**, *101*, 102.



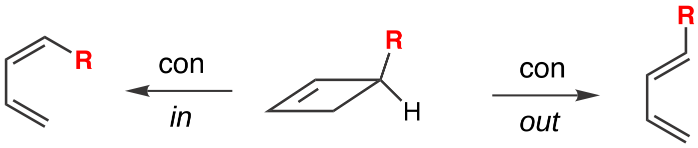


Huisgen, *TL*, **1964**, 3381.

Electrocyclic Processes-2: Torquoselectivity

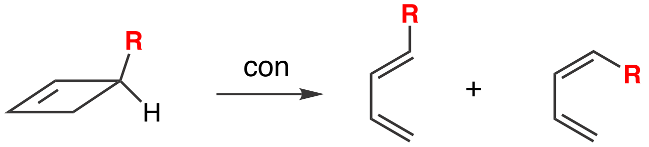
Torquoselectivilty is defined as the predisposition of a given R substituent for a given conrotatory motion

Houk et al. *Acc. Chem. Res* **1996**, 29, 471

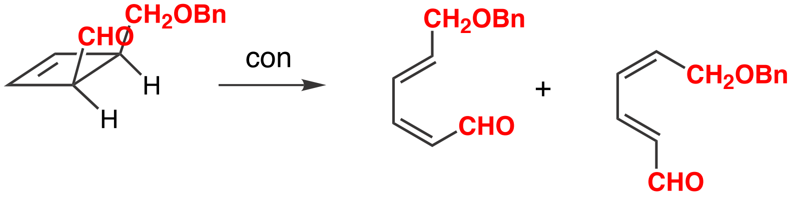


Examples: Donor substituents prefer con–out mode

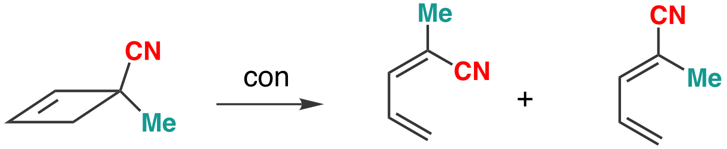
Pi acceptor substituents prefer con–in mode



R = Me	**only**	none
R = CHO	none	**only**



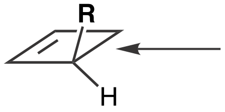
ratio: >20:1



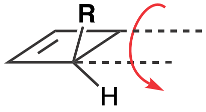
ratio: 4:1

How do we explain? Donor substituents prefer con–out mode

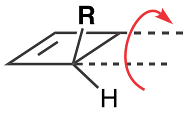
Pi acceptor substituents prefer con–in mode



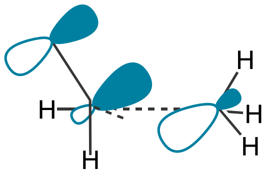
View the 2 conrotatory modes by looking at the breaking sigma bond from this perspective



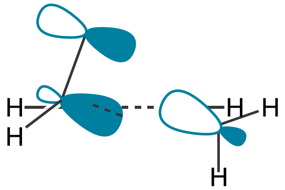
Outward Motion



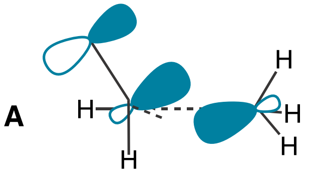
Inward Motion



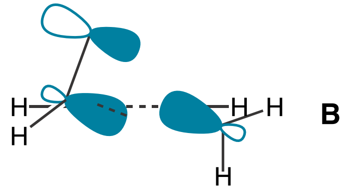
LUMO + p



LUMO + p



HOMO + p



HOMO + p

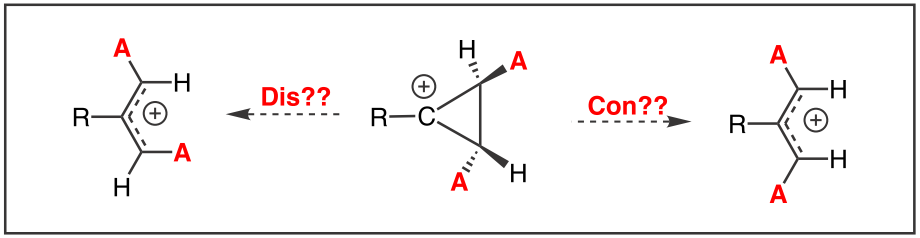
As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B**, is better in **B**. (Houk)

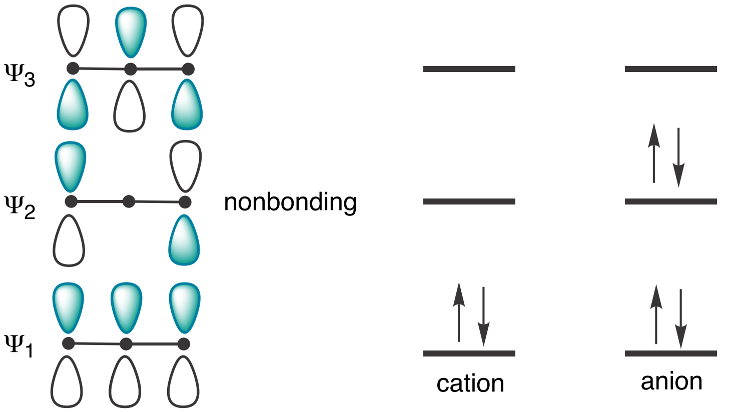
destabilizing 4 electron interation for donor substituents

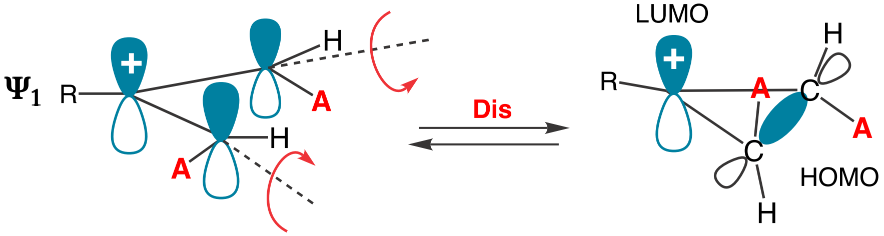
stabilizing 2 electron interation for acceptor substituents

Electrocyclic Processes-3: 3-Atom Electrocyclizations

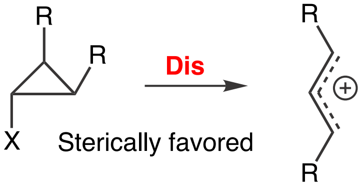
Three-Atom Electrocyclizations (2 electrons)

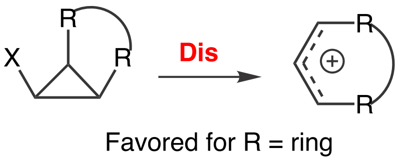






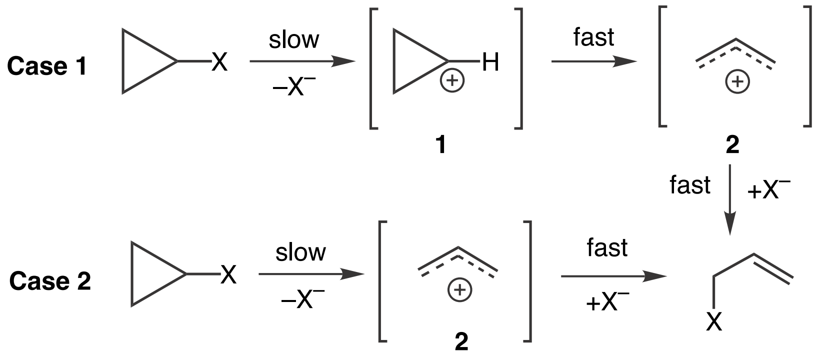
Note that there are two disrotatory modes

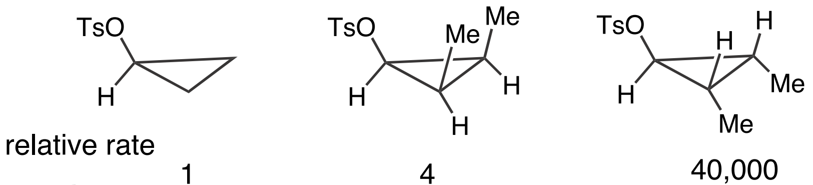




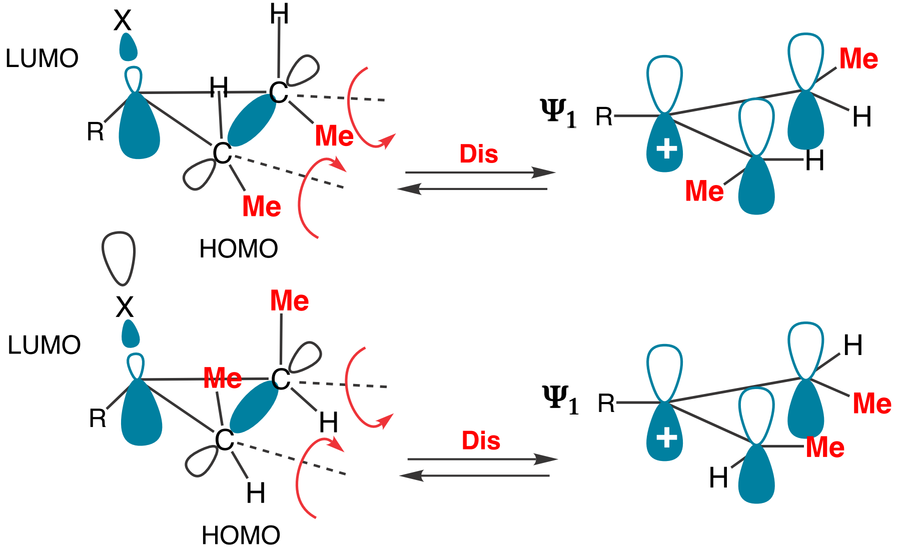
Solvolysis of Cyclopropyl Derivatives

Does solvolysis proceed via cation **1** followed by rearrangement to **2** (Case 1), or does it proceed directly to **2** (Case 2)?

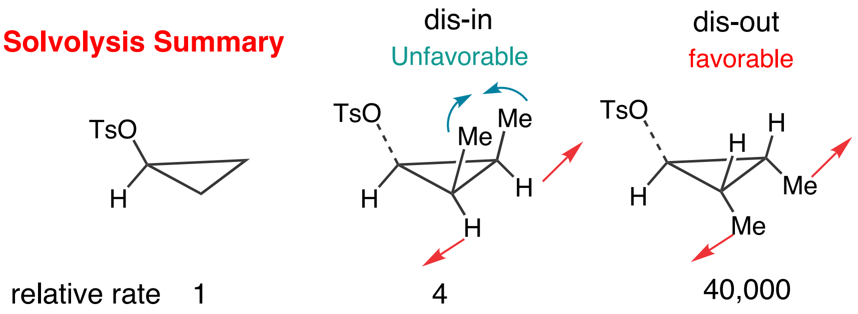




DePuy, *Accts. Chem. Res.* **1967**, *1*, 33

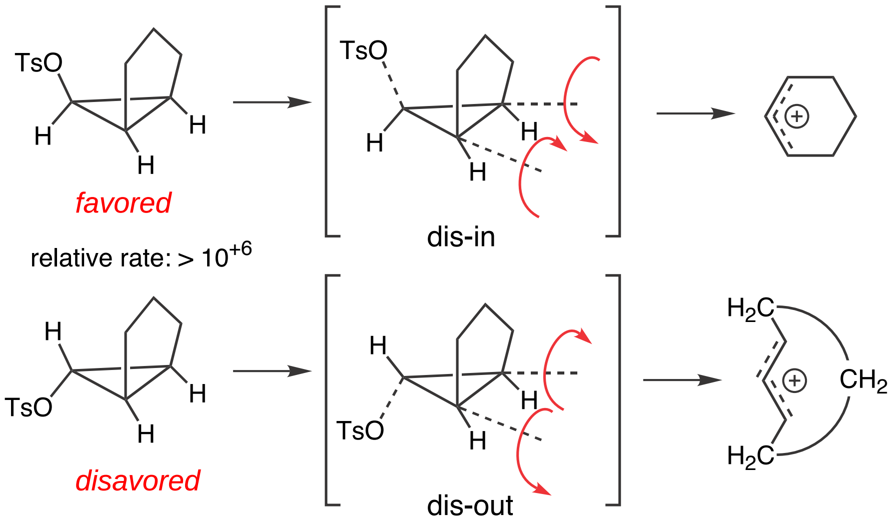


Solvolysis Summary

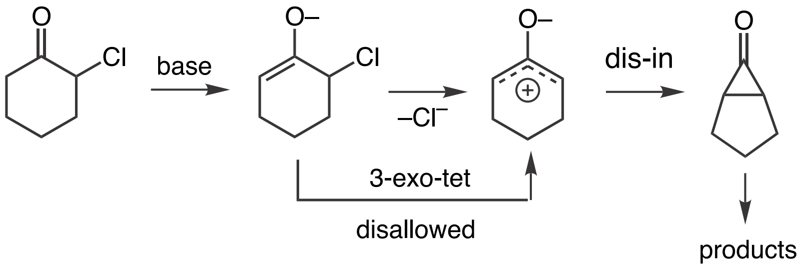


Ring-fused Cyclopropyl Systems

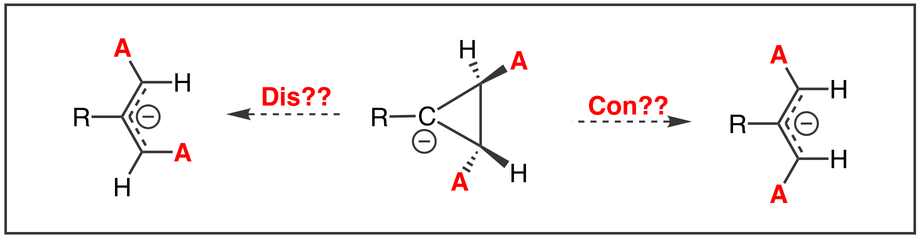
When the cis substiltutents on the cyclopropyl ring are tied together in a ring the following observsations have been made

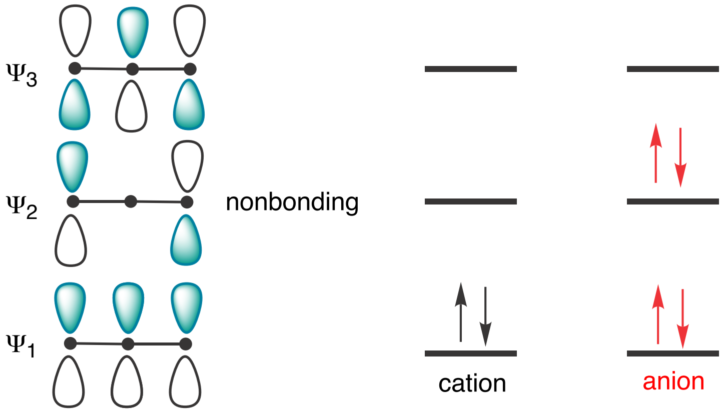


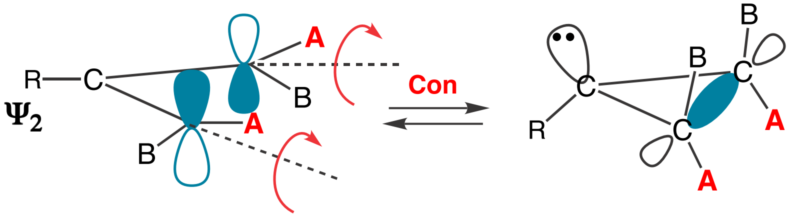
Revisiting the Favorski rearrangement: **(Carey, Part A, pp 506-8)**



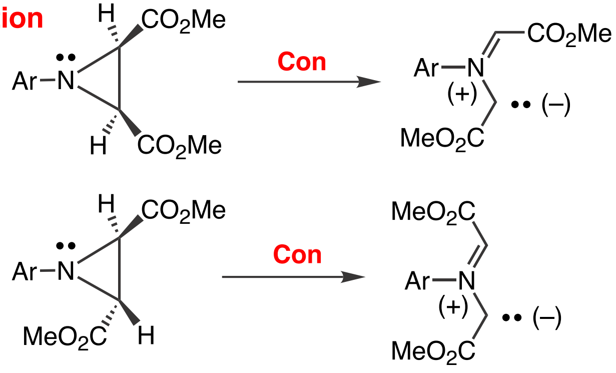
Three-Atom Electrocyclizations (4 electrons)





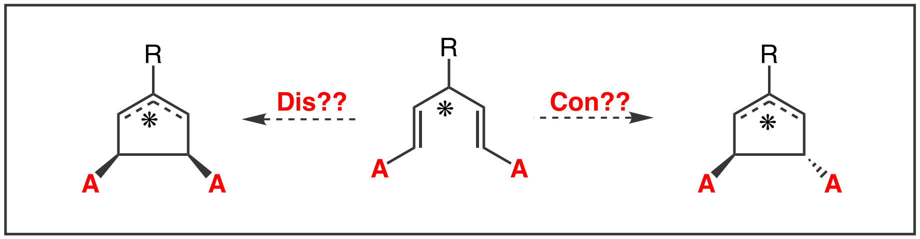


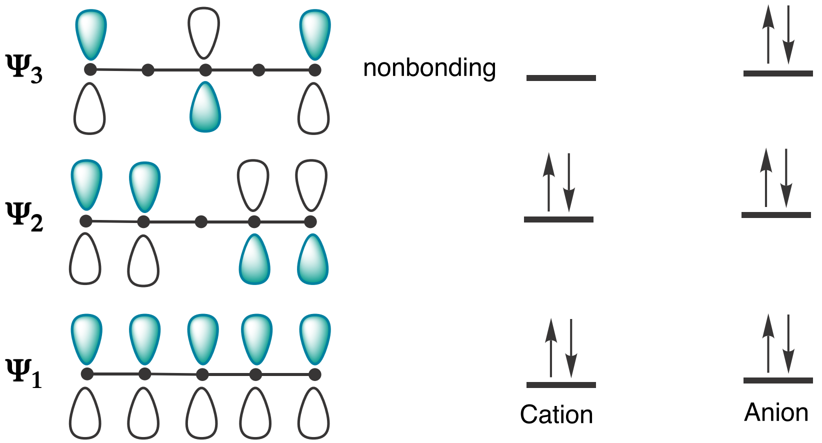
Observation



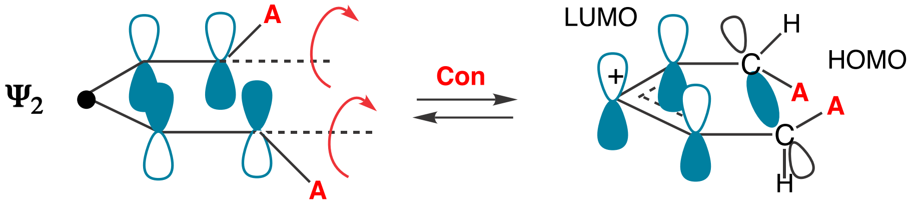
Electrocyclic Processes-3

Five-Atom Electrocyclizations (4 electrons)

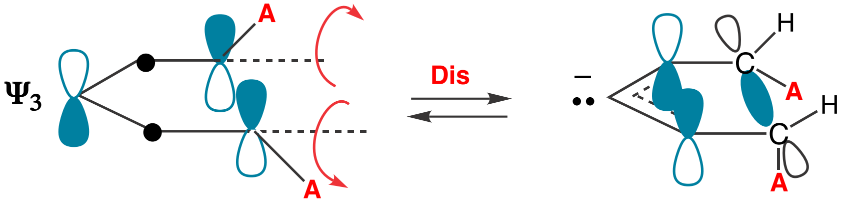




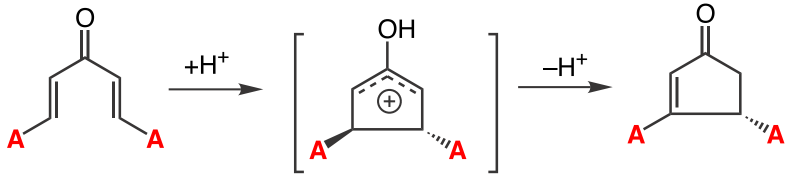
Pentadienyl Cation



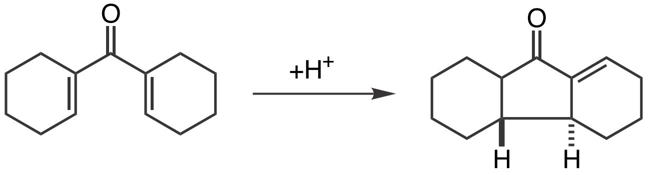
Pentadienyl Anion



The Nazarov Reaction

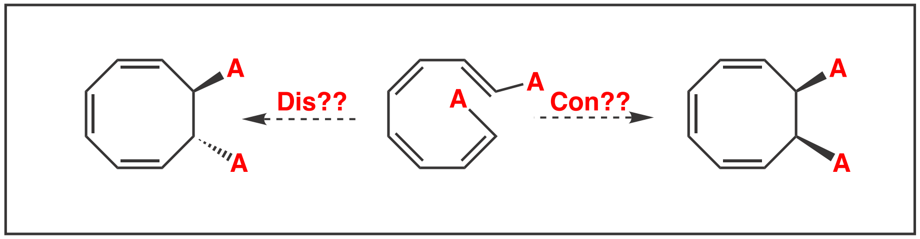


Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5; pp 751.

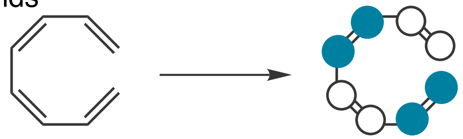


predict stereochemistry

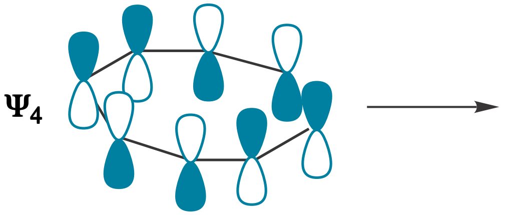
Eight-Atom Electrocyclizations (8 electrons)



Let's use the "Ready" shortcut to find the homo: Nodes will appear at single bonds



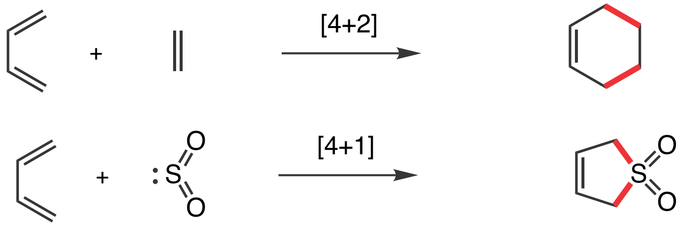
symmetry of homo



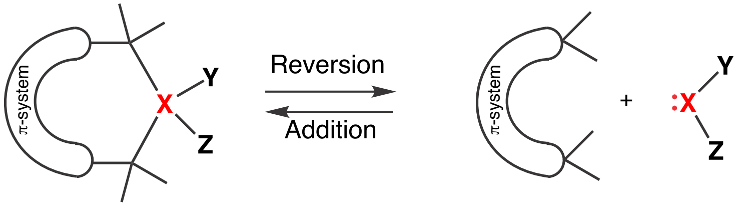
Closure should be conrotatory

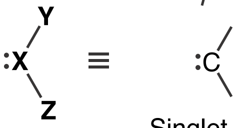
CHELETROPIC REACTIONS: [n+1] Cycloadditions (or Cycloreversions)

Concerted processes in which 2 σ-bonds are made (or broken) which terminate at a single atom.

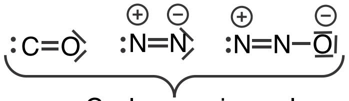


General





Singlet-Carbene Addition (and Reversion)

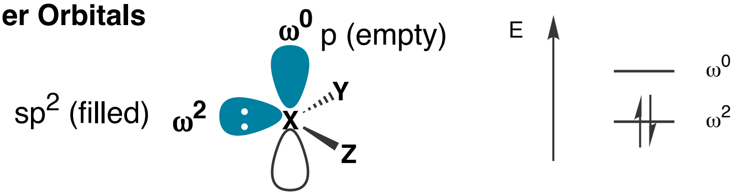


Cycloreversion only

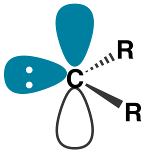
SO$_2$

Reversion and Addition

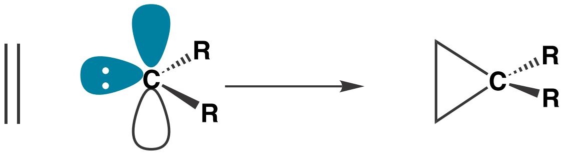
Frontier Orbitals



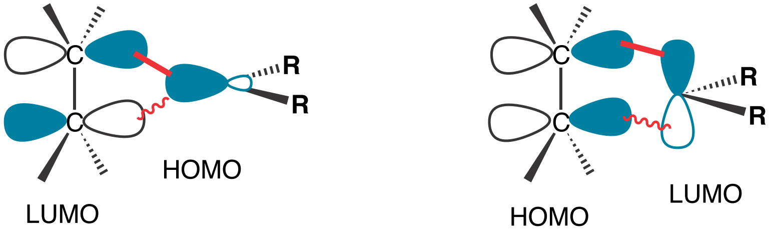
Question: what is orientation of carbene relative to attacking olefin??



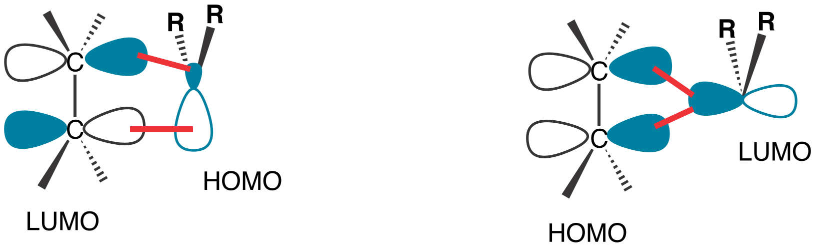
2 + 1 CheletropicReaction: Olefins + Singlet Carbene



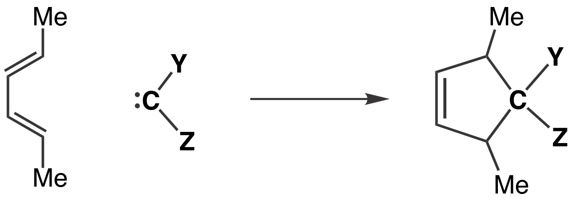
Linear Approach: 2 HOMO-LUMO Interactions



Nonlinear Approach: 2 HOMO-LUMO Interactions



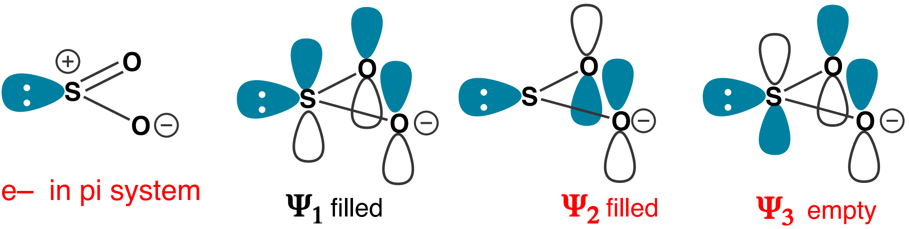
Carry out the analysis of the indicated hypothetical transformation



predict approach geometry of carbene

Cheletropic Processes-2

Let's now consider SO_2 as the one-atom component

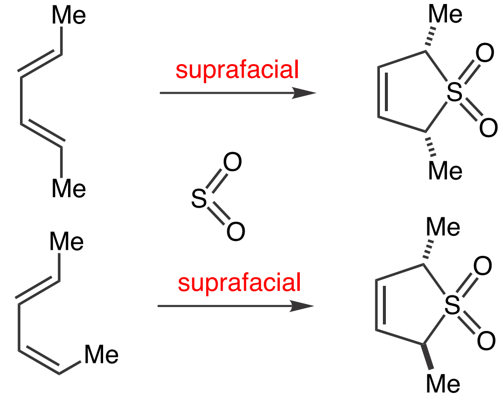


4e– in pi system

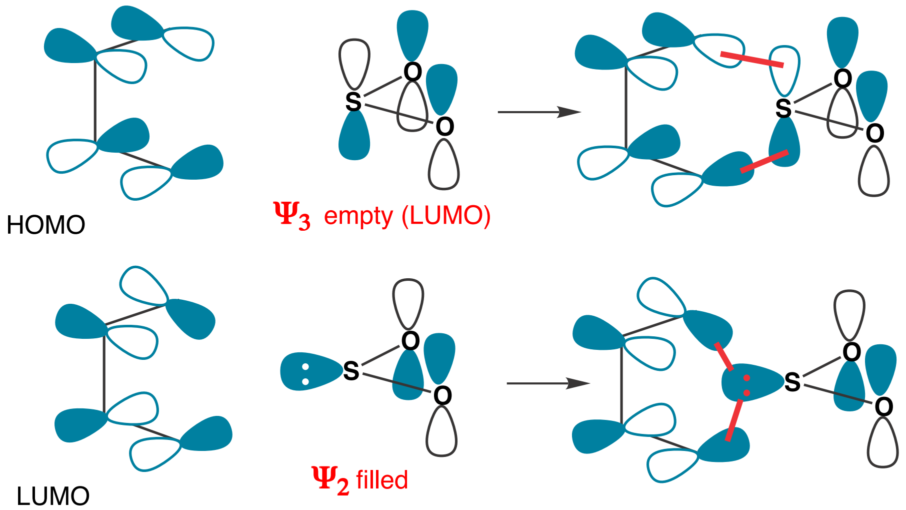
Ψ_1 filled

Ψ_2 filled

Ψ_3 empty



reactions are:
stereospecific & reversible



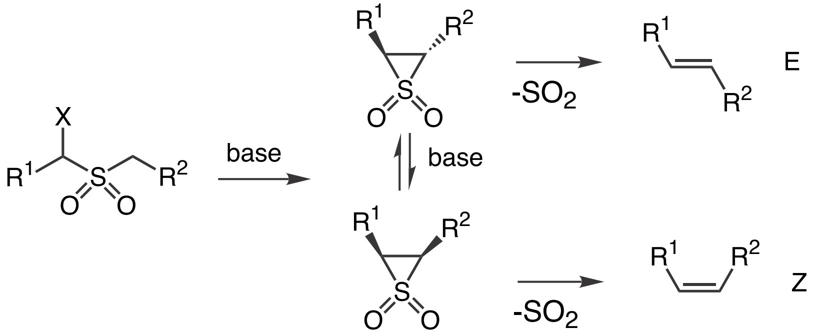
HOMO

Ψ_3 empty (LUMO)

LUMO

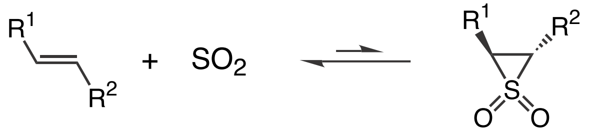
Ψ_2 filled

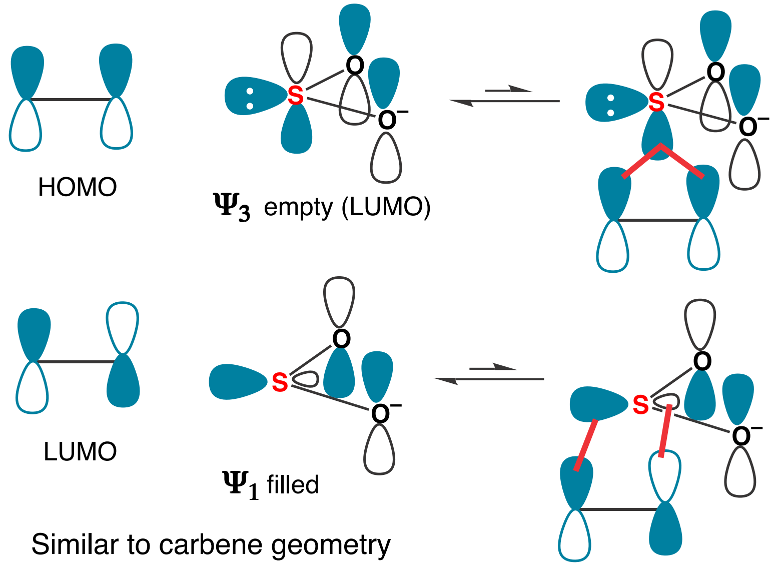
Key step in the *Ramberg Bäcklund* Rearrangement



Clough, J. M. *The Ramberg-Backlund Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861.
"The Ramberg-Backlund Rearrangement.", Paquette, L. A. *Org. React. (N.Y.)* **1977**, *25*, 1.

Analysis of the Suprafacial SO_2 Extrusion (nonlinear)





HOMO

Ψ_3 empty (LUMO)

LUMO

Ψ_1 filled

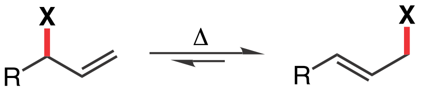
Similar to carbene geometry

Sigmatropic Rearrangements-1

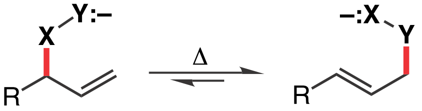
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

■ Examples:

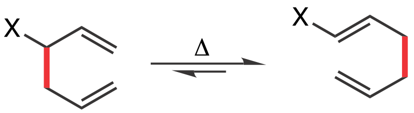
[1,3] Sigmatropic rearrangement



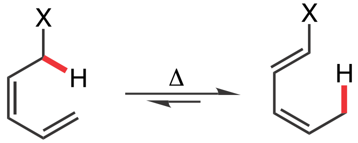
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

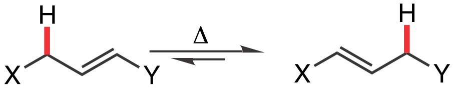


[1,5] Sigmatropic rearrangement

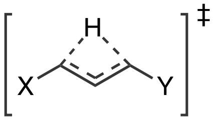


■ [1,3] Sigmatropic Rearrangements (H migration)

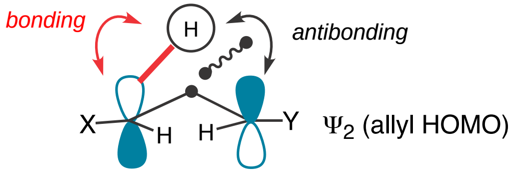
consider the 1,3-migration of H



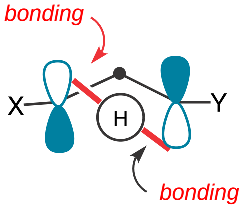
Consider the orbitals needed to contruct the transition state (TS).



■ Construct TS by uniting an allyl and H radical:



Suprafacial Geometry

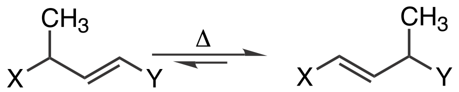


Antarafacial Geometry

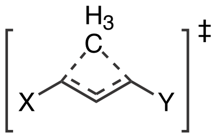
Bridging distance too great for antarafacial migration.

■ [1,3] Sigmatropic Rearrangements (C migration)

consider the 1,3-migration of Carbon

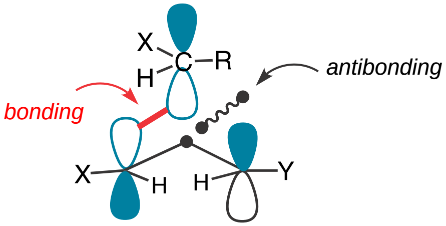


Consider the orbitals needed to contruct the transition state (TS).



❐ Construct TS by uniting an allyl and Me radicals:

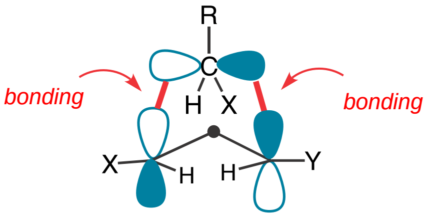
Retention at carbon



Suprafacial on allyl fragment

Sychronous bonding to both termini cannot be achieved from this geometry

Inversion at carbon



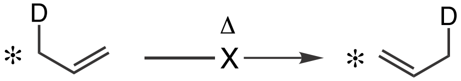
Suprafacial on allyl fragment

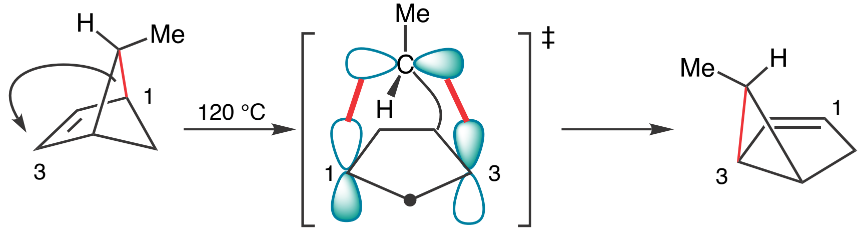
Sychronous bonding to both termini is possible from this geometry

❐ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

no observed scrambling of labels

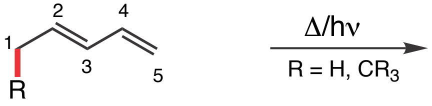




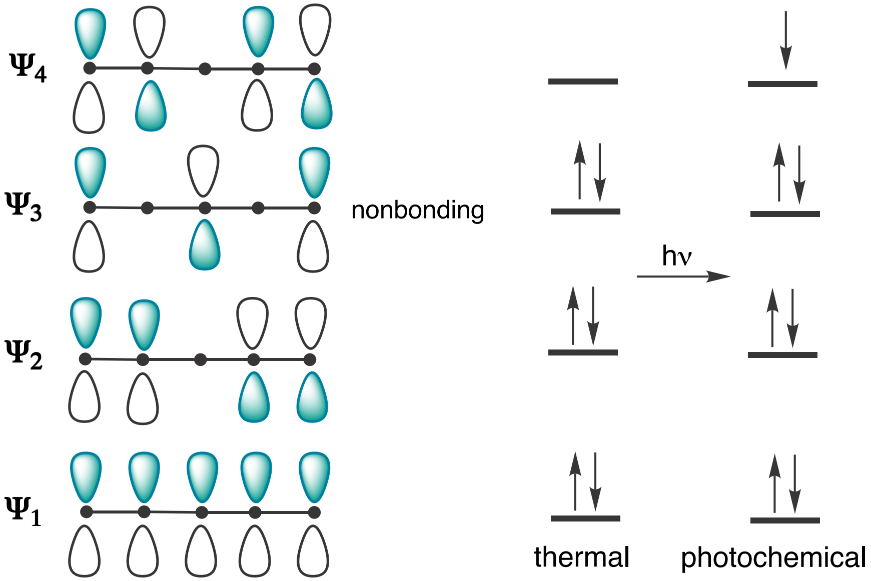
These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

Sigmatropic Rearrangements-2

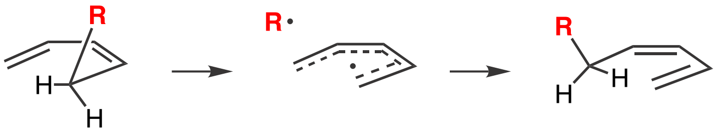
SIGMATROPIC REACTIONS - FMO-Analysis

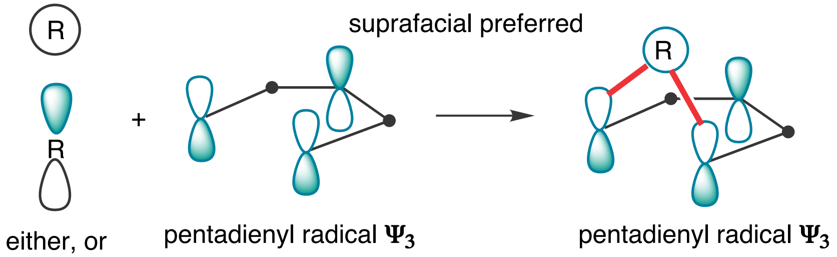


[1,5] Sigmatropic Rearrangements (H migration)

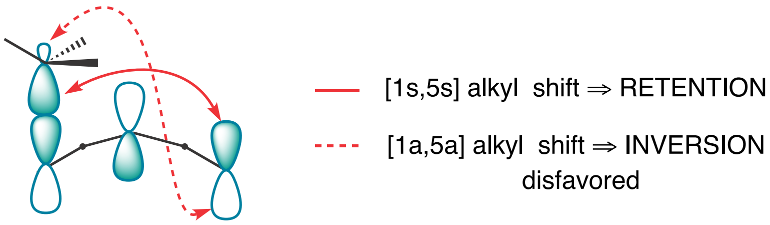


View as cycloadditon between following species:

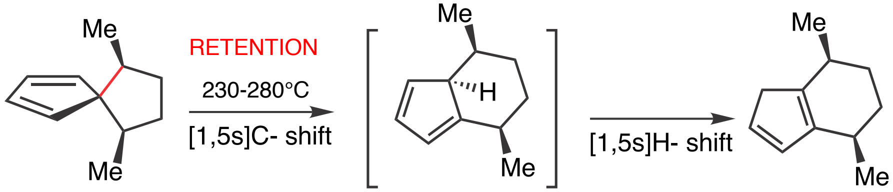




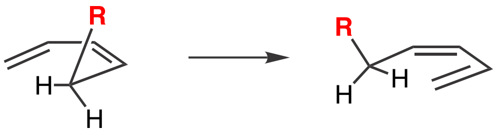
[1,5] Sigmatropic Rearrangements (C migration)

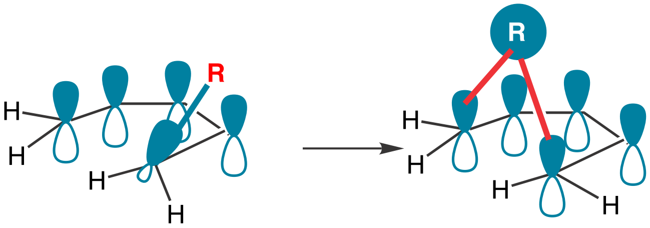

[1s,5s] alkyl shift ⇒ RETENTION
[1a,5a] alkyl shift ⇒ INVERSION
disfavored

[1,5] (C migration): Stereochemical Evaluation



Dewar–Zimmerman Analysis: Retention

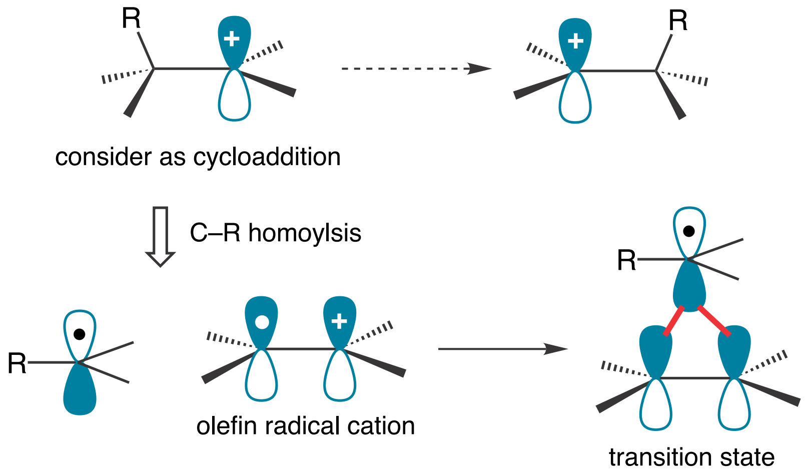




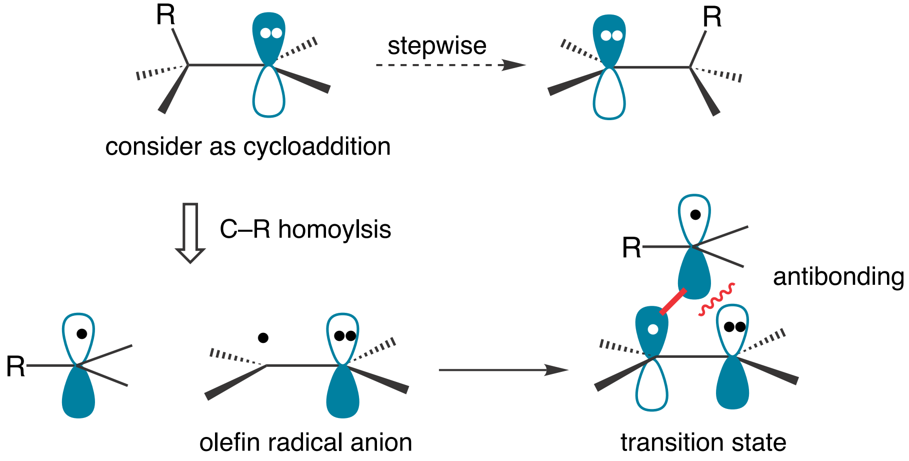
0 phase inversions ⇒ Huckel toplogy
6 electrons
therefore, allowed thermally

■ [1,2] Sigmatropic Rearrangements: Carbon

[1,2] Concerted sigmatropic rearrangements to cationic centers allowed



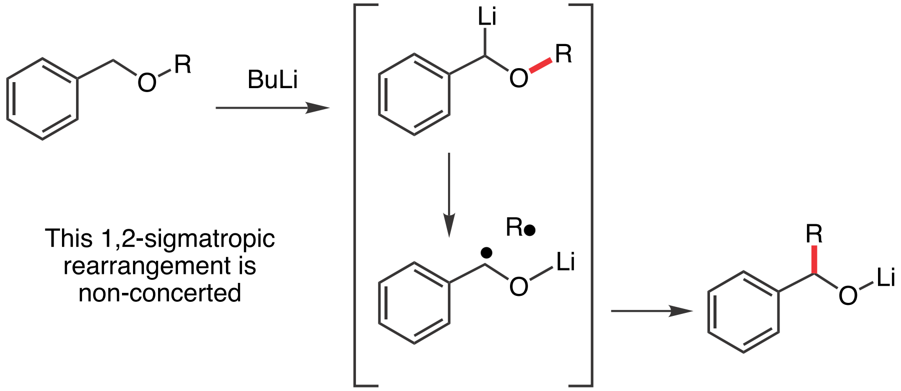
[1,2] Concerted sigmatropic rearrangements to carbanionic centers not observed



The Wittig Rearrangement [1,2]

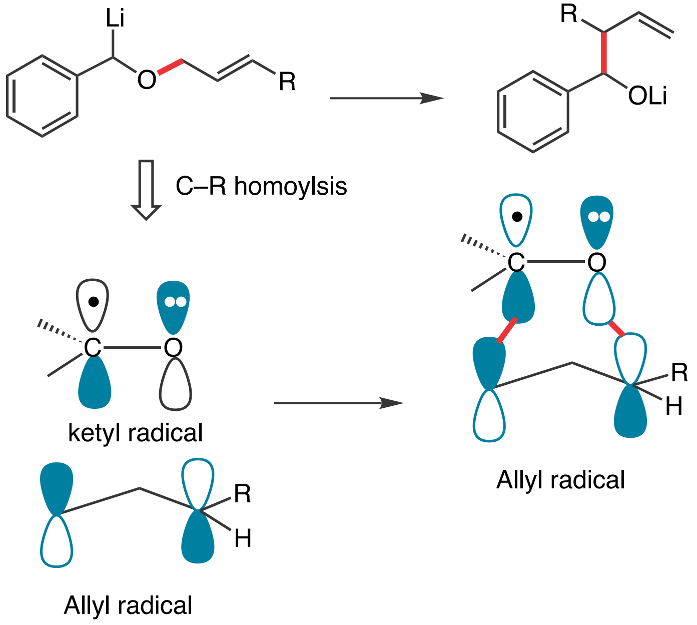
"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

Marshall, J. A. *The Wittig Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.



This 1,2-sigmatropic rearrangement is non-concerted

The Wittig Rearrangement [2,3]



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 13

Pericyclic Reactions–3

- Introduction to Sigmatropic Rearrangements
- [2,3] Sigmatropic Rearrangements

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4
Thermal Pericyclic Reactions

D. A. Evans

Wednesday,
October 14, 2003

Other Reading Material:

[2,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapter 4.6:

Nakai, T.; Mikami, K. *Org. React. (N.Y.)* **1994**, *46*, 105-209.

Hoffmann, *Angew. Chem. Int. Ed.* **1979**, *18*, 563-572 (Stereochemistry of)

Nakai, *Chem. Rev.* **1986**, *86*, 885-902 (Wittig Rearrangement)

Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55 (Sulfoxide Rearrangement)

Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358-364 (Sulfur Ylilde Rearrangements)

[3,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)

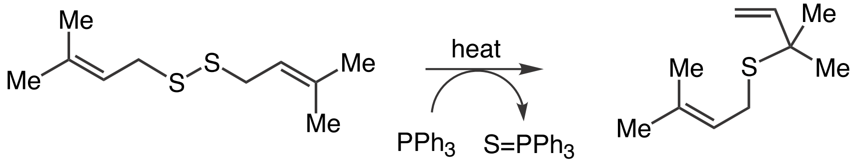
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)

Paquette, L. A. (1990). "Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement." Angew. Chem., Int. Ed. Engl. 29: 609.

Problems of the Day:

Provide a mechanism for this transformation.



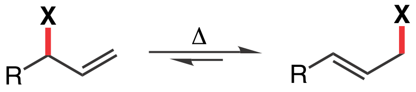
For study on this [2,3] rxn See Baldwin *JACS* **1971**, *93*, 6307

Sigmatropic Rearrangements-1

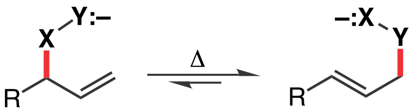
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

Examples:

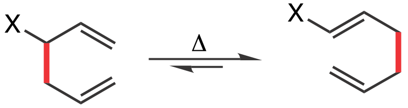
[1,3] Sigmatropic rearrangement



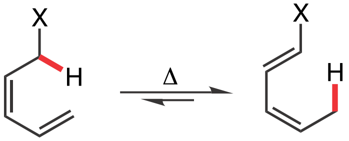
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

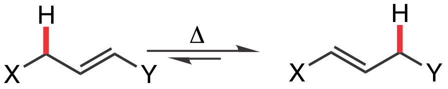


[1,5] Sigmatropic rearrangement

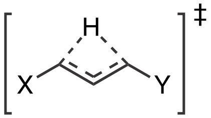


[1,3] Sigmatropic Rearrangements (H migration)

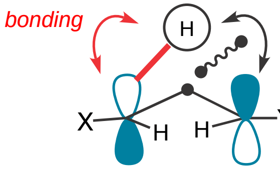
consider the 1,3-migration of H



Consider the orbitals needed to contruct the transition state (TS).

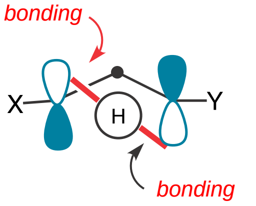


Construct TS by uniting an allyl and H radical:



Ψ_2 (allyl HOMO)

Suprafacial Geometry

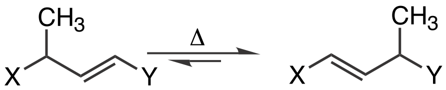


Antarafacial Geometry

Bridging distance too great for antarafacial migration.

[1,3] Sigmatropic Rearrangements (C migration)

consider the 1,3-migration of Carbon



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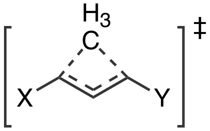
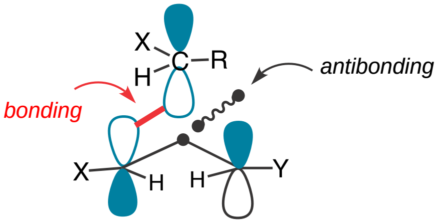


❒ Construct TS by uniting an allyl and Me radicals:

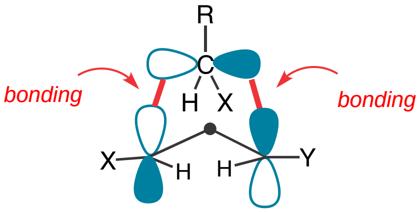
Retention at carbon



Suprafacial on allyl fragment

Sychronous bonding to both termini cannot be achieved from this geometry

Inversion at carbon



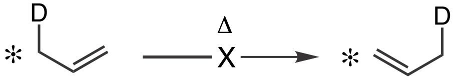
Suprafacial on allyl fragment

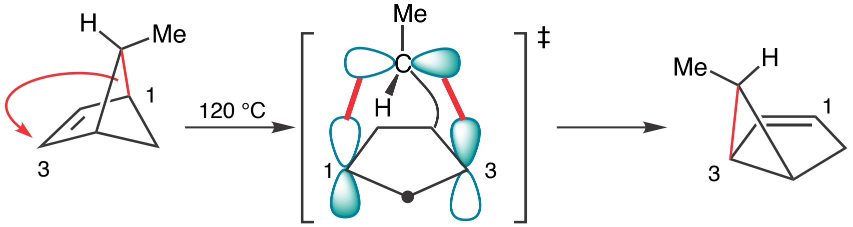
Sychronous bonding to both termini is possible from this geometry

❒ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

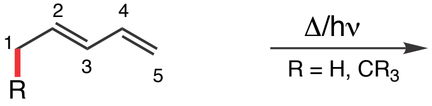
no observed scrambling of labels



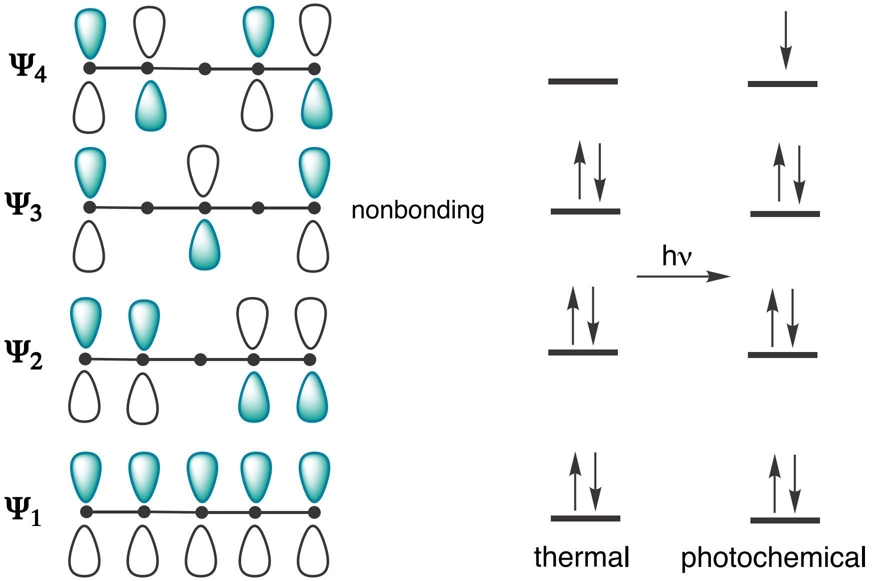


These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

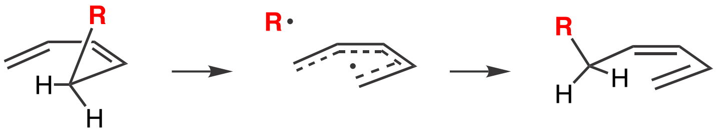
SIGMATROPIC REACTIONS - FMO-Analysis



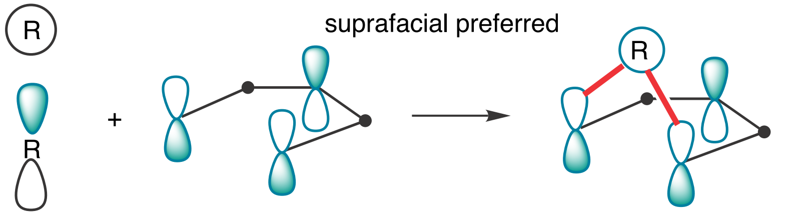
■ [1,5] Sigmatropic Rearrangements (H migration)



View as cycloadditon between following species:

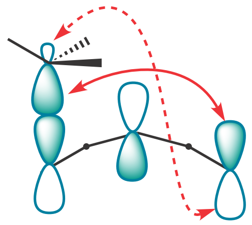


suprafacial preferred



either, or pentadienyl radical Ψ_3 the transiton structure

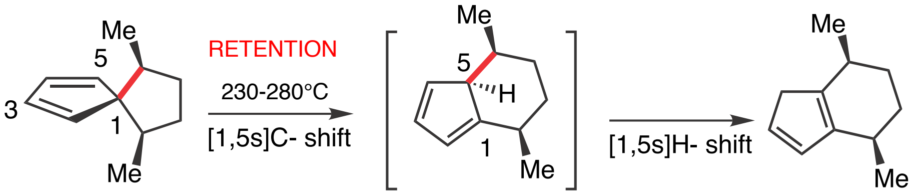
■ [1,5] Sigmatropic Rearrangements (C migration)



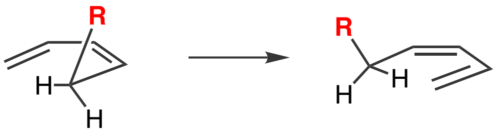
—— [1s,5s] alkyl shift ⇒ RETENTION

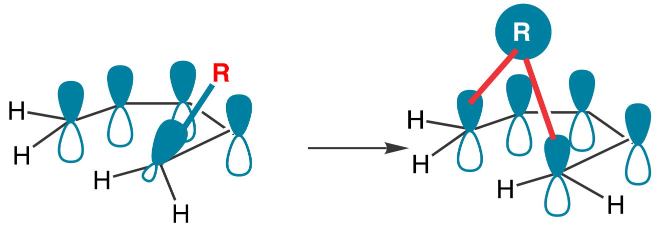
---- [1a,5a] alkyl shift ⇒ INVERSION disfavored

■ [1,5] (C migration): Stereochemical Evaluation



Dewar–Zimmerman Analysis: Retention





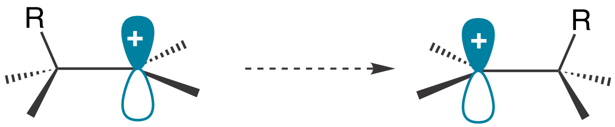
0 phase inversions ⇒ Huckel toplogy
6 electrons
therefore, allowed thermally

Sigmatropic Rearrangements: An Overview

[1,2] Sigmatropic Rearrangements: Carbon

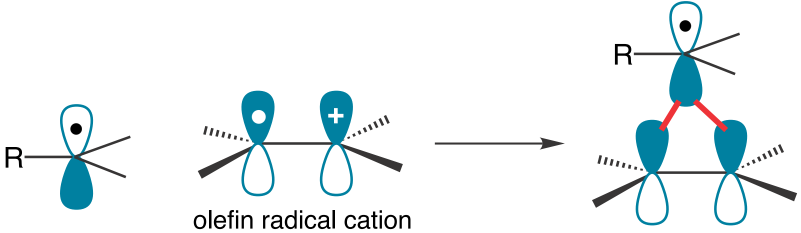
[1,2]-Sigmatropic rearrangements to cationic centers allowed.

Wagner-Meerwein Rearrangement



consider as cycloaddition

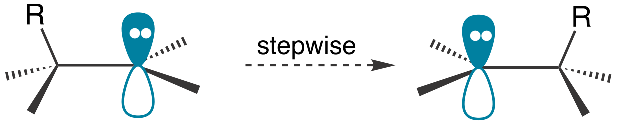
FMO analysis



olefin radical cation

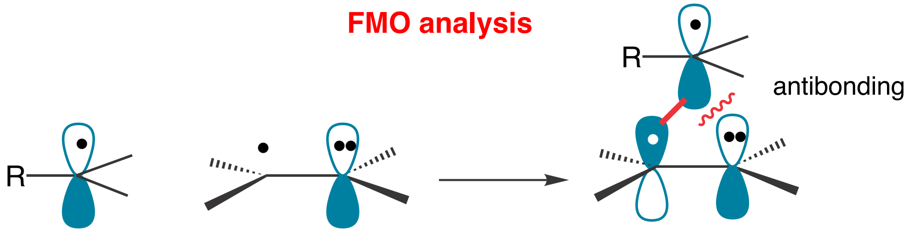
transition state

[1,2]-Sigmatropic rearr to carbanionic centers not observed



consider as cycloaddition

FMO analysis



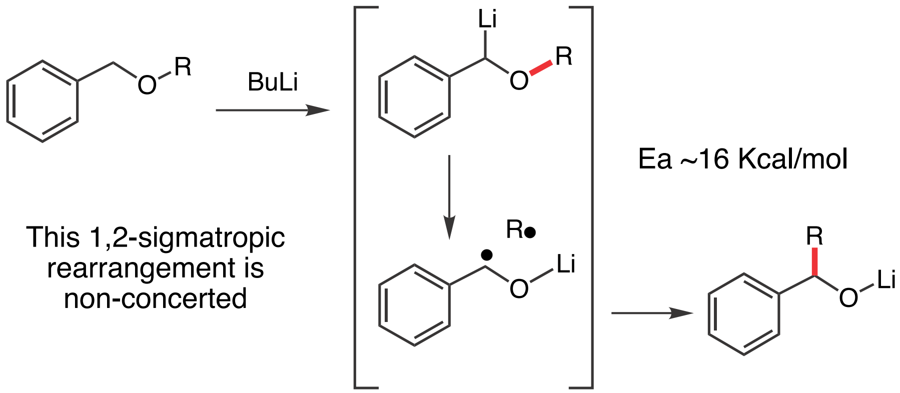
olefin radical anion

transition state

The Wittig Rearrangement [1,2]

"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

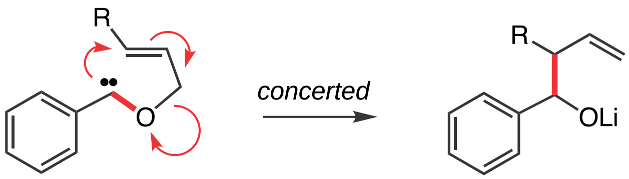
Marshall, J. A. *The Wittig Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.



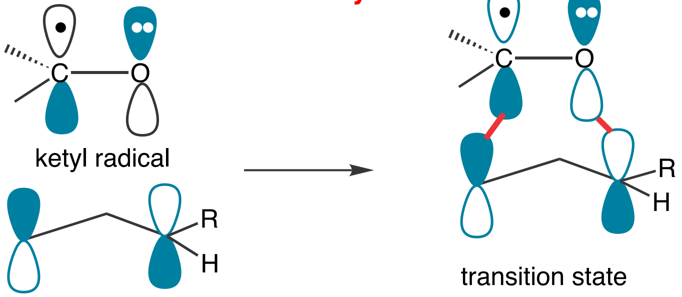
This 1,2-sigmatropic rearrangement is non-concerted

Ea ~16 Kcal/mol

The Wittig Rearrangement [2,3]



FMO analysis



ketyl radical

Allyl radical

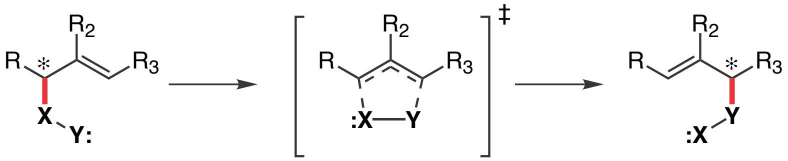
transition state

The ΔΔG‡ between concerted and non-concerted pathways can be quite small

[2,3]-Sigmatropic Rearrangements: An Introduction

[2,3] Sigmatropic Rearrangements

■ The basic process:



X & Y = permutations of C, N, O, S, Se, P; however X is usually a heteroatom

Attributes: Stereoselective olefin construction & chirality transfer

■ Representative X-Y Pairs:

N–O (amine oxides)
S–C (sulfur ylids)
O–C (Wittig rearrangement)
N–C (nitrogen ylids)
S–S (disulfides)

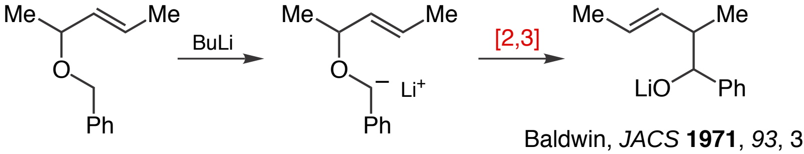
S–P, S–N, S–O (sulfoxides)
O–P (phosphites)
N–N, Cl^+–C (haloium ylids)
P–C, C–C (homoallylic anions).

An important early paper: Baldwin, *J. Chem. Soc., Chem. Comm.* **1970**, 576

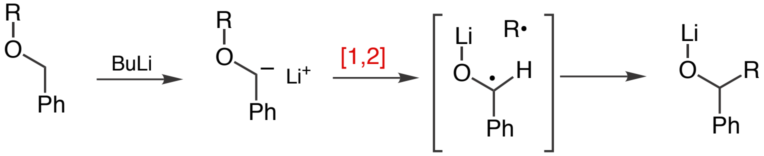
■ General Reviews:

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapter 4.6:
Nakai, T.; Mikami, K. *Org. React. (N.Y.)* **1994**, *46*, 105-209.
Hoffmann, *Angew. Chem. Int. Ed.* **1979**, *18*, 563-572 (Stereochemistry of)
Nakai, *Chem. Rev.* **1986**, *86*, 885-902 (Wittig Rearrangement)
Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55 (sulfoxide Rearrangement)
Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358-364 (Sulfur Ylilde Rearrangements)

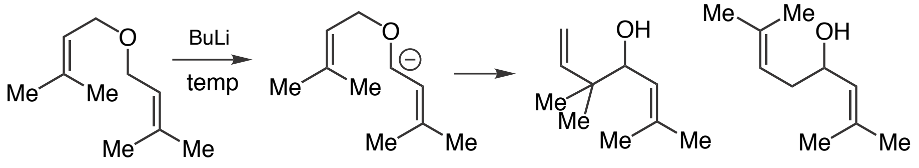
■ X - O, Y = C; Wittig Rearrangement:



Baldwin, *JACS* **1971**, *93*, 3556



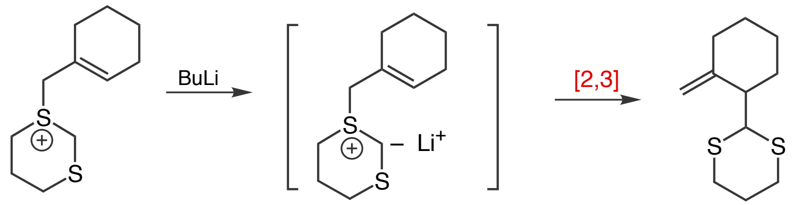
Garst, *JACS* **1976**, *98*, 1526



Rautenstrauch, *Chem Commun*. **1979**, 1970

–25 °C ~70% ~30%

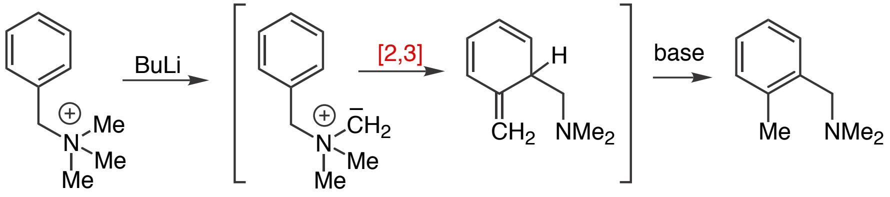
■ X - S, Y = C; Sulfonium Ylide Rearrangement:



Lythgoe, *Chem Commum* **1972**, 757

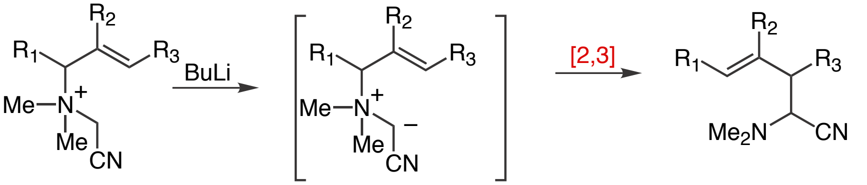
■ X - N, Y = C; Ammonium Ylide Rearrangement:

Sommelet-Hauser:



Review, Pines, *Org. Rxns* **1970**, *18*, 416

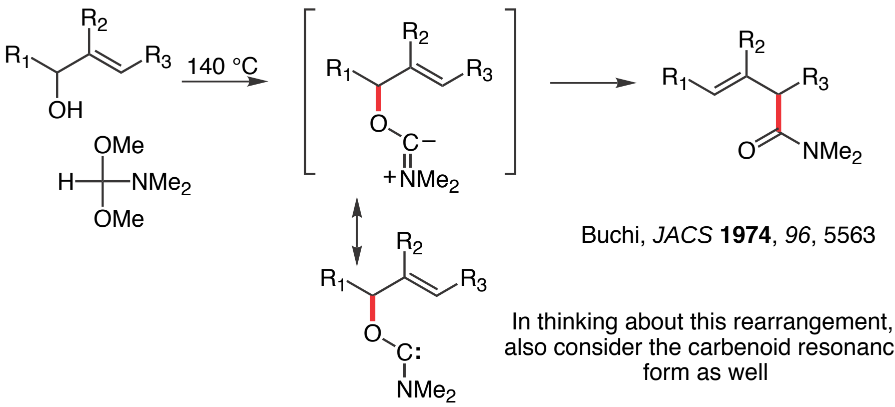
Modern versions of Stevens:



Buchi, *JACS* **1974**, *96*, 7573
Mander, *JOC* **1973**, *38*, 2915
important extension lacking CN FG; Sato, *JACS* **1990**, *112*, 1999

[2,3]-Sigmatropic Rearrangements: Introduction-2

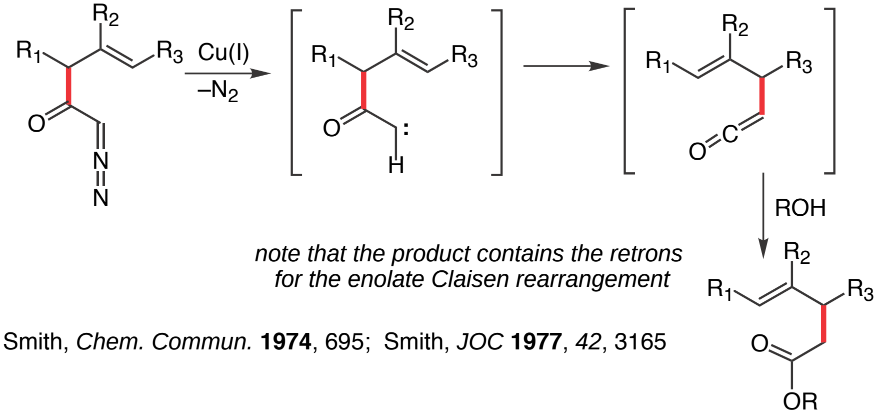
■ X - O, Y = C; Wittig-like Rearrangements



Buchi, *JACS* **1974**, *96*, 5563

In thinking about this rearrangement, also consider the carbenoid resonance form as well

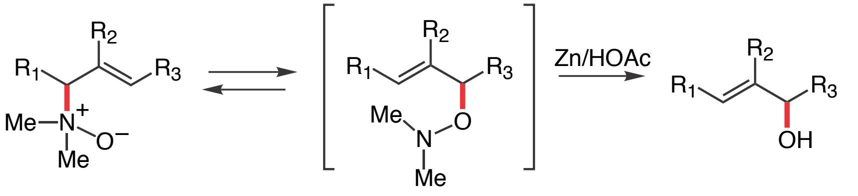
■ X - O, Y = C; An all-carbon Rearrangement



note that the product contains the retrons for the enolate Claisen rearrangement

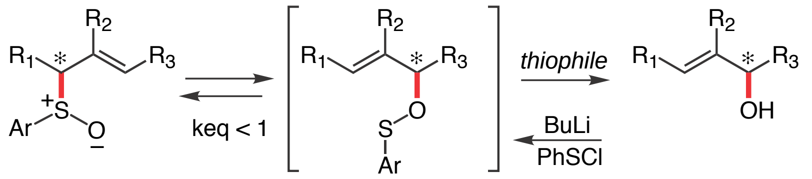
Smith, *Chem. Commun.* **1974**, 695; Smith, *JOC* **1977**, *42*, 3165

■ X - N, Y = O; Meisenheimer Rearrangement



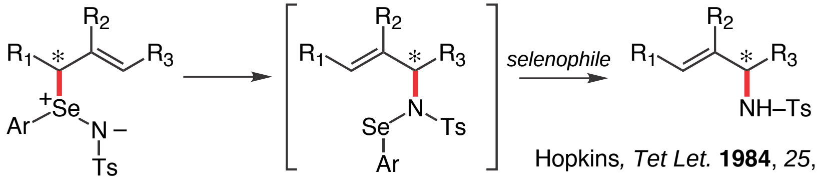
Tanabe, *Tet Let.* **1975**, 3005

■ X - S, Y = O; Sulfoxide Rearrangement



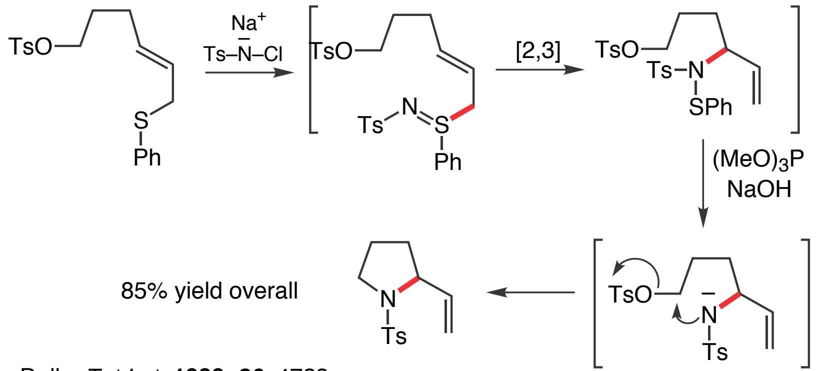
Evans, *Accts. Chem. Res.* **1974**, *7*, 147

■ X - Se, Y = N; Related Rearrangement



Hopkins, *Tet Let.* **1984**, *25*, 15
Hopkins, *JOC* **1984**, *49*, 3647
Hopkins, *JOC* **1985**, *50*, 417

■ X - S, Y = N; Related Rearrangement



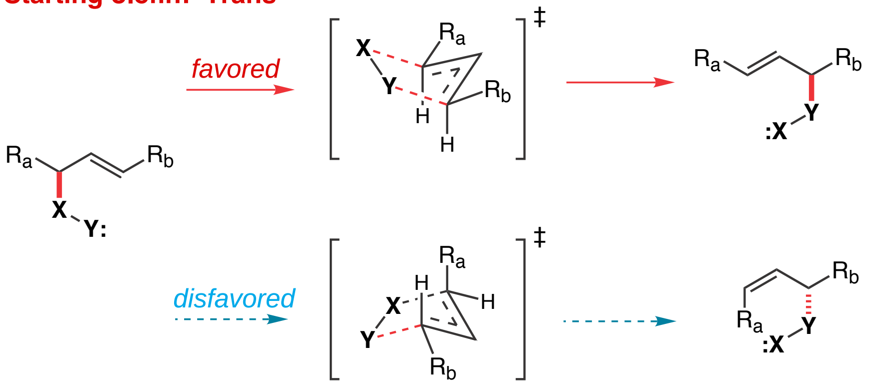
85% yield overall

Dolle, *Tet Let.* **1989**, ***30***, 4723

[2,3]-Sigmatropic Rearrangements: Olefin Geometry

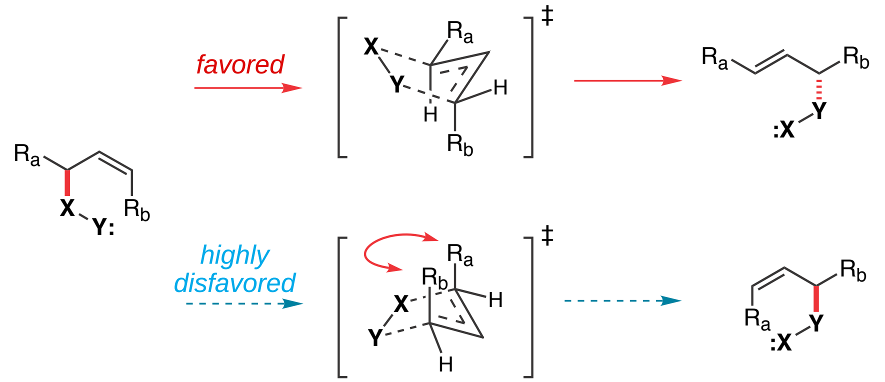
■ 1,2-Disubstitution: Good Trans Olefin Selectivity

Starting olefin: Trans



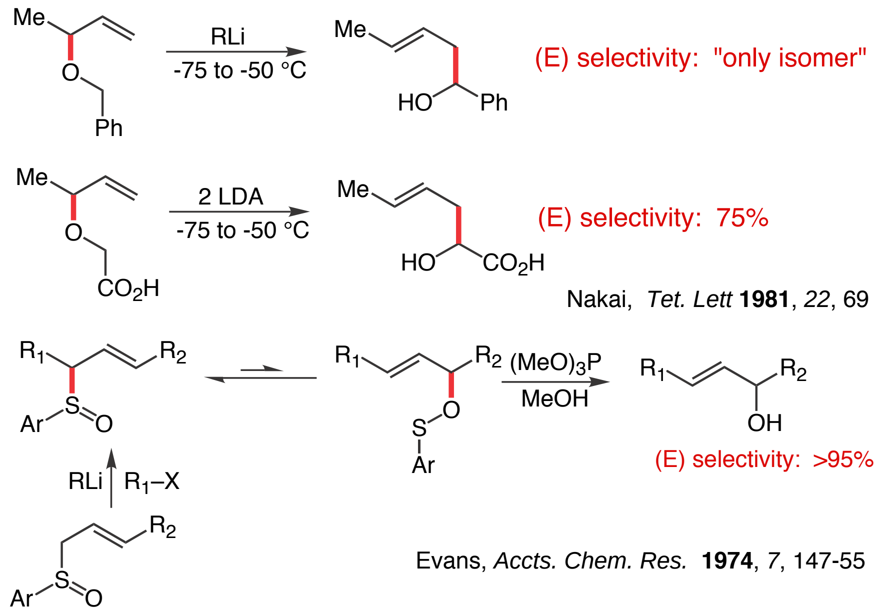
R_a & R_b prefer to orient in pseudo-equatorial positions during rearrangement; nevertheless, this is a delicately balanced situation

Starting olefin: Cis



Conclusions

- ❏ Olefin geometry dictates sense of asymmetric induction in rearrangement
- ❏ (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction
- ❏ Product olefin geometry can be either (E) or (Z) from (E) starting material
- ❏ Product olefin geometry will be (E) from (Z) starting material

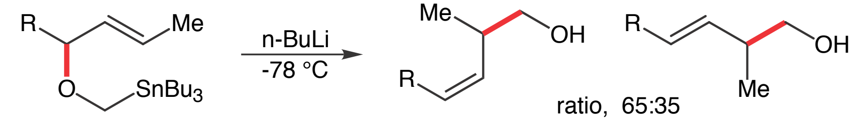


Nakai, *Tet. Lett* **1981**, *22*, 69

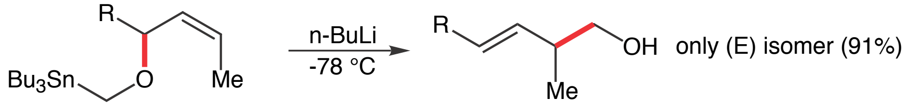
Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55

The preceeding transition state models do not explain some of the results:

❏ Cis selectivity has been observed: Still JACS **1978**, *100*, 1927.



❏ However, Cis selectivity is dependent on starting olefin geometry

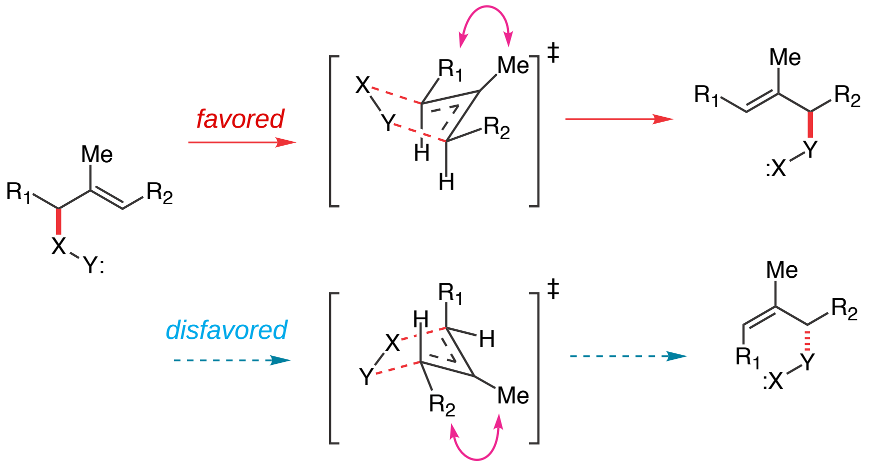


Several theoretical studies have been published: Good reading

Houk JOC **1991**, *56*, 5657 (Sulfur ylide transition states)

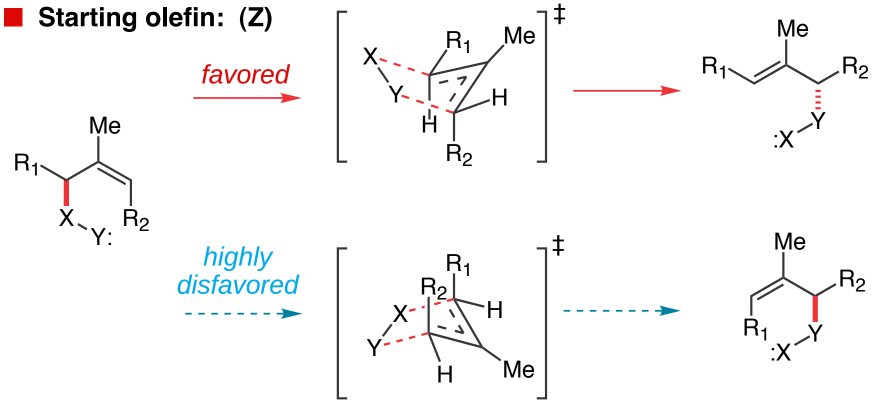
Houk JOC **1990**, *55*, 1421 (Wittig transition states)

Starting olefin: (E) Trisubstituted



R_1–Me interaction can destabilize the (E) transition state while (Z) TS might be destabilized by R_1 interactions with both X-Y and allyl moiety.

Starting olefin: (Z)



Conclusions

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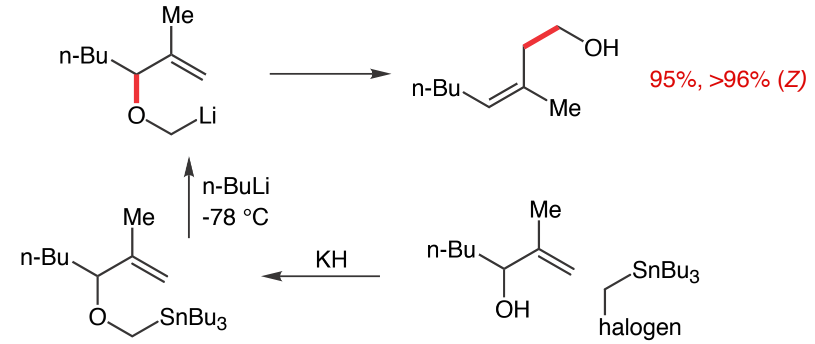
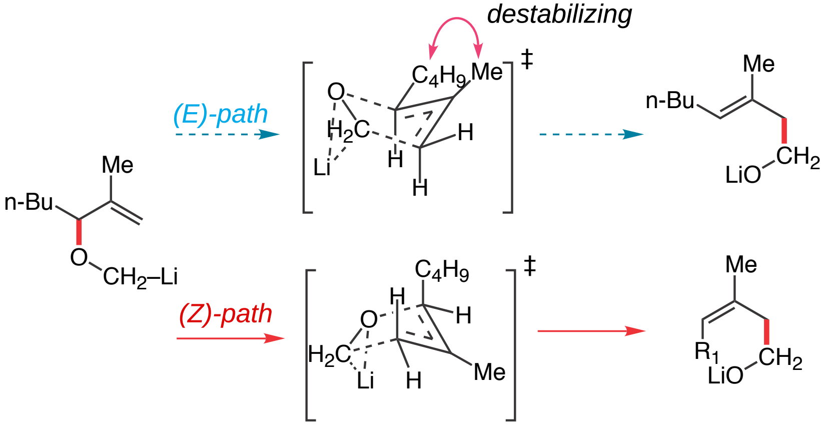
- ❏ (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction
- ❏ Product olefin geometry can be either (E) or (Z) from (E) starting material
- ❏ Product olefin geometry will be (E) from (Z) starting material

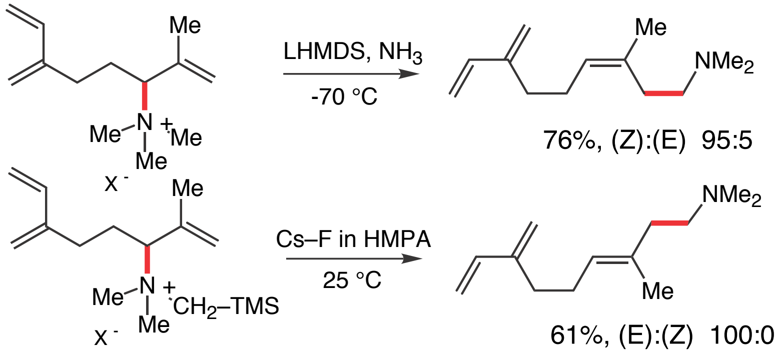
- (Z) selectivity has been observed: Still JACS **1978**, *100*, 1927.



Still says that the TS is early, so that the 1,2 interactions in the TS are most important.

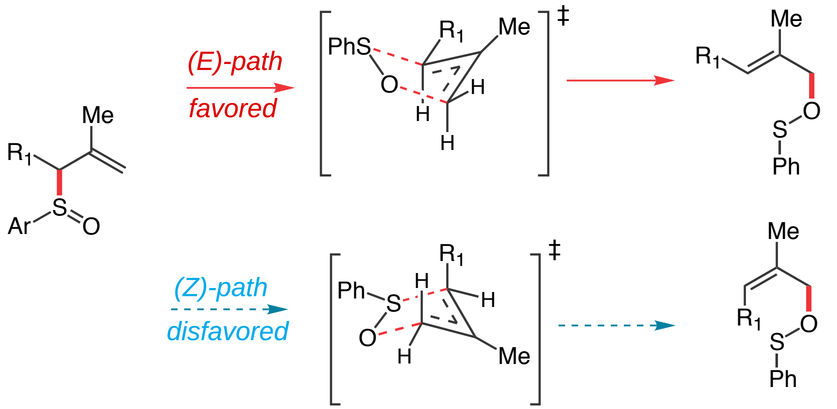


- (Z) selectivity has also been observed by others: Sato JACS **1990**, *112*, 1999.

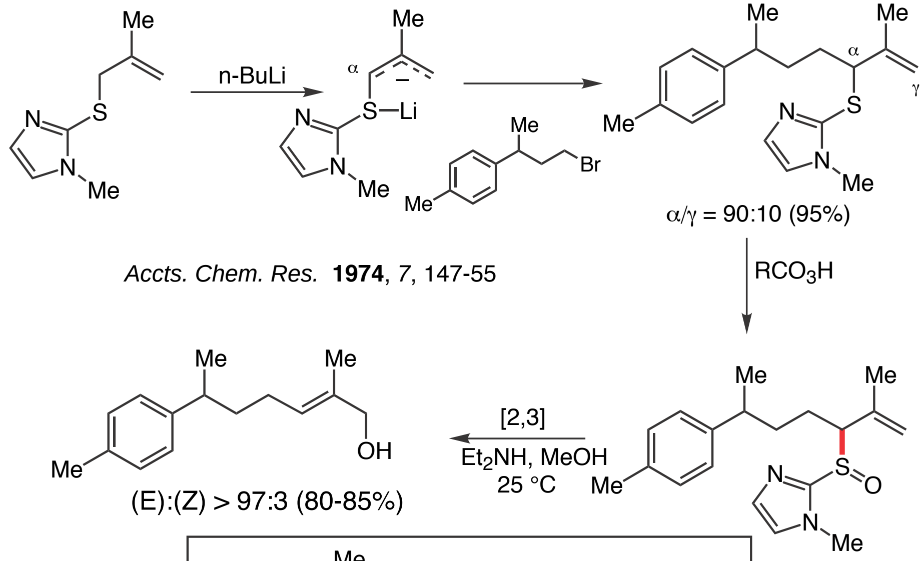


[2,3]-Sigmatropic Rearrangements: Olefin Geometry

Trisubstituted olefins via [2,3]-rearrangement of sulfoxides:

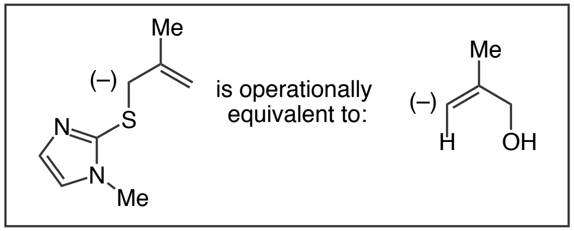


- In contrast to the previous cases exhibiting (Z) selectivity rearrangements (E)-selective rearrangments has been observed:

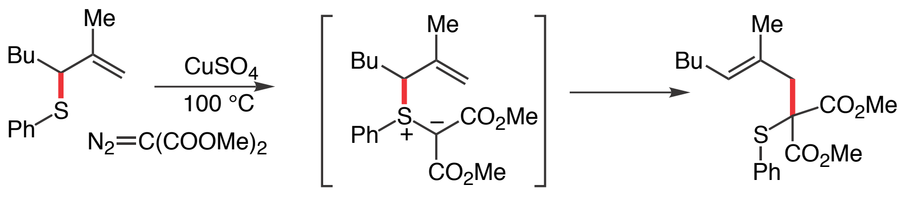


Accts. Chem. Res. **1974**, *7*, 147-55

(E):(Z) > 97:3 (80-85%)



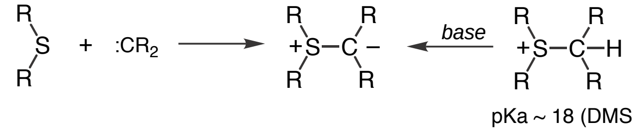
Trisubstituted olefins via [2,3]-rearrangement of sulfonium ylides:



Grieco, *JOC* **1973**, *38*, 2572

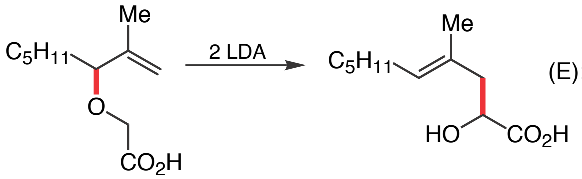
(E):(Z) > 90:10 (70%)

A general procedure for the direct synthesis of sulfur ylides:



pKa ~ 18 (DMSO

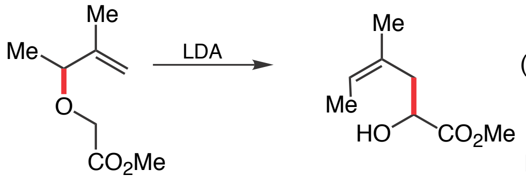
Trisubstituted olefins via Wittig [2,3]-rearrangement:



(E):(Z) > 95:5 (74%)

Nakai, *Tet Let* **1981**, *22*, 69

However, this reaction is not general:

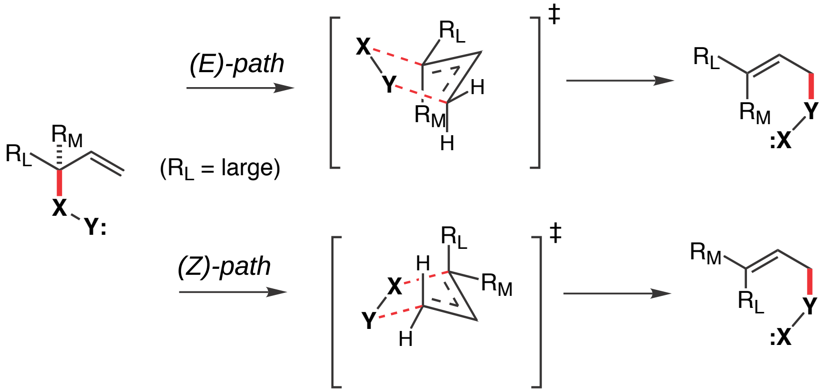


(E):(Z) 31:69

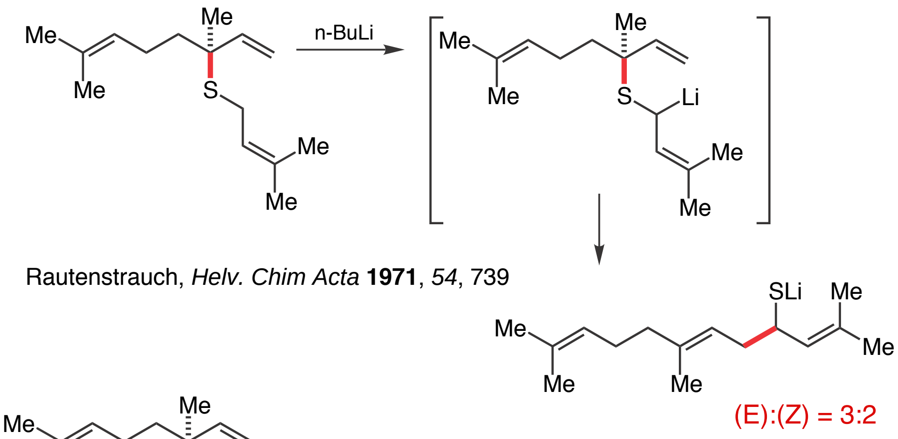
Nakai, *Tet Let* **1986**, *27*, 4511

[2,3]-Sigmatropic Rearrangements: Olefin Geometry

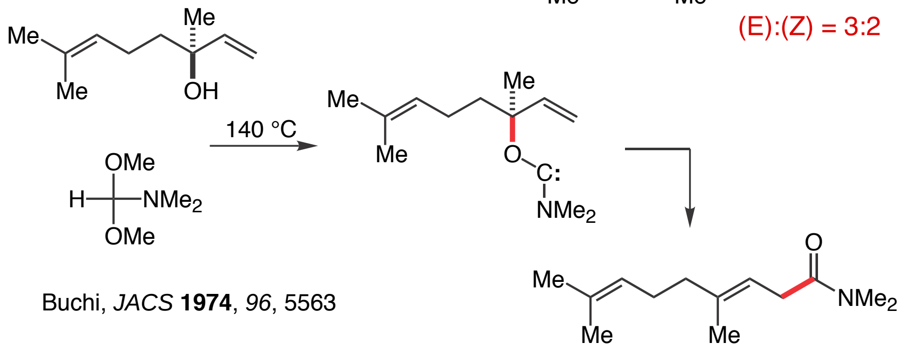
- Trisubstituted olefins via [2,3]-rearrangement:



One might project that the (E) path will be moderately favored with selectivity depending on size difference between R_L & R_M



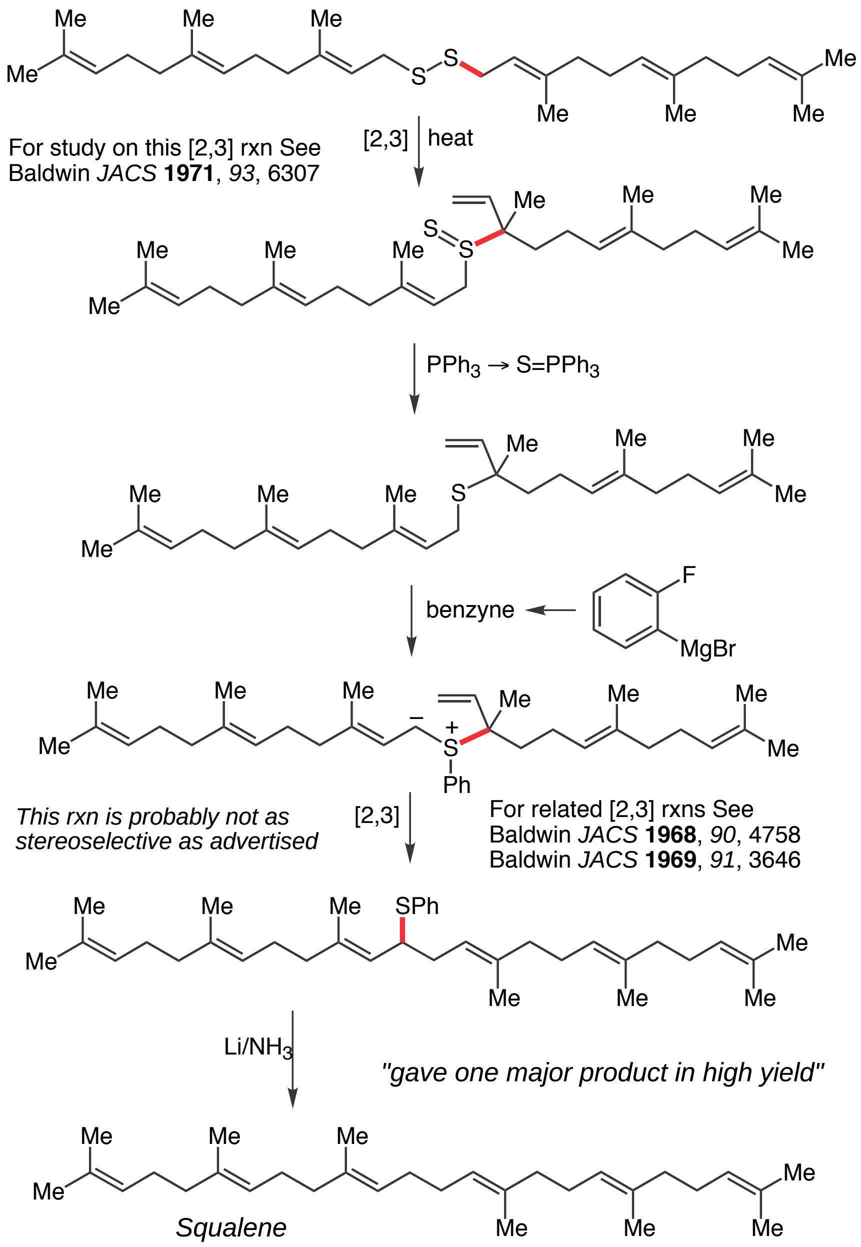
Rautenstrauch, *Helv. Chim Acta* **1971**, *54*, 739



Buchi, *JACS* **1974**, *96*, 5563

poorly selective

An elegant squalene synthesis ***Ollis, Chem. Commun*** **1969, 99**



For study on this [2,3] rxn See
Baldwin *JACS* **1971**, *93*, 6307

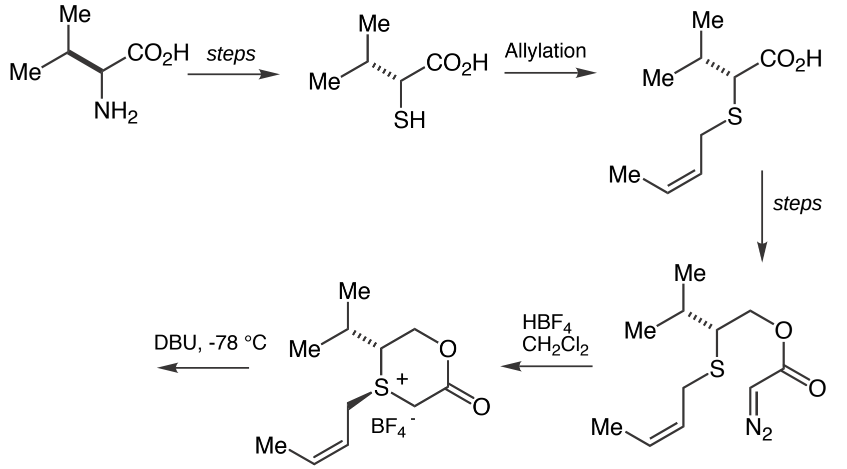
This rxn is probably not as stereoselective as advertised

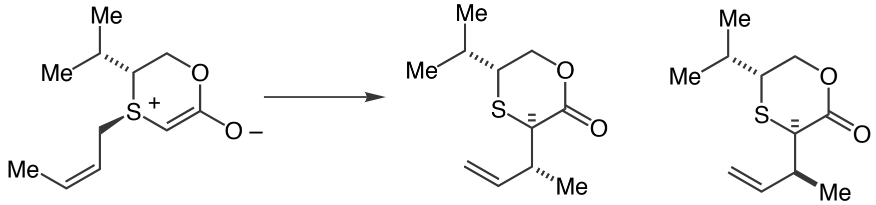
For related [2,3] rxns See
Baldwin *JACS* **1968**, *90*, 4758
Baldwin *JACS* **1969**, *91*, 3646

"gave one major product in high yield"

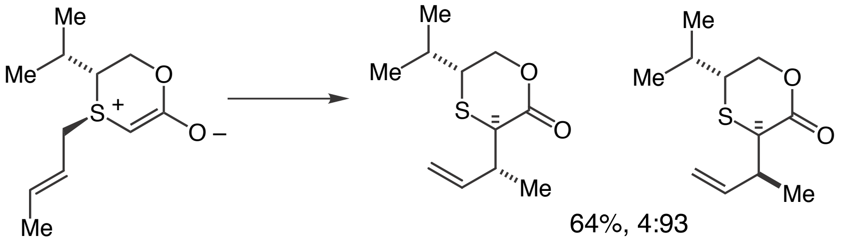
[2,3] Sulfur Ylide Rearrangement Using a Chiral Auxiliary

Kurth JOC **1990**, *55*, 2286 and TL **1991**, *32*, 335



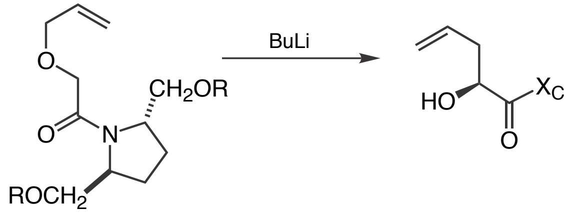


66%, 94:4

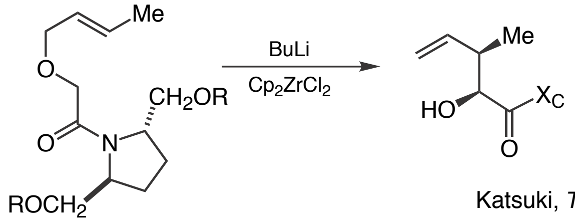


64%, 4:93

Chiral Auxiliaries can also be used in the Wittig Rearrangement



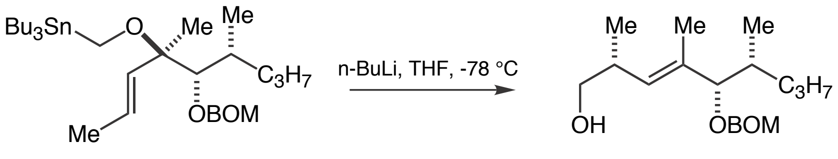
96% de (61%)



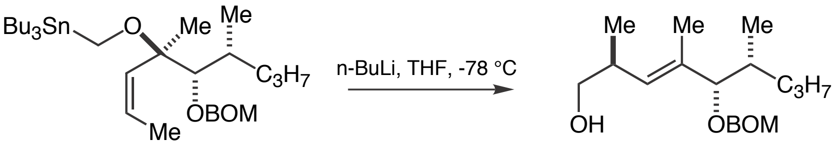
97% syn; 96% de (43%)

Katsuki, *Tet Lett* **1986**, *27*, 4577

Internal Relay of Stereochemistry in C–C Constructions



diastereoselection > 100:1 (57%)



Kallmerten TL **1988**, *29*, 6901.

diastereoselection > 100:1 (64%)

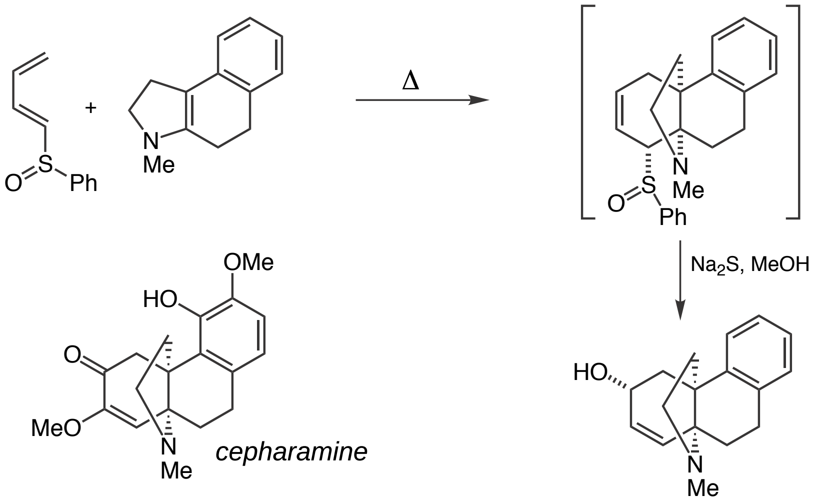
See these papers for other applications

- Kallmerten TL **1993**, *34*, 753.
- Kallmerten TL **1993**, *34*, 749.
- Kallmerten SynLet **1992**, 845.

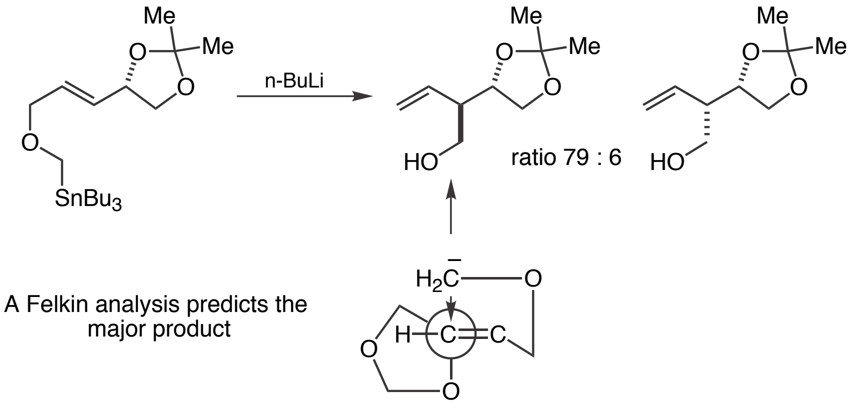
[2,3]-Sigmatropic Rearrangements: Chirality Transfer

Internal Relay of Stereochemistry in C–O Constructions

Tandem [4+2] & [2,3] Process: Evans, Bryan, Sims *J. Am. Chem. Soc.* **1972**, 2891.

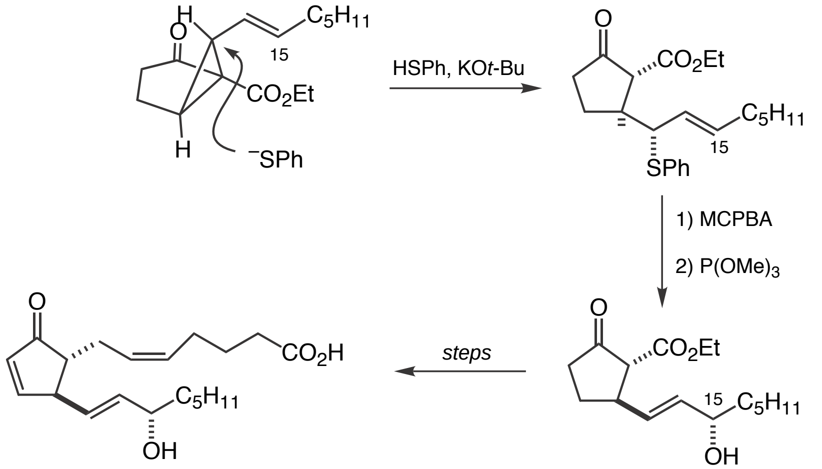


Cases where the chirality is exocyclic to the rearrangement



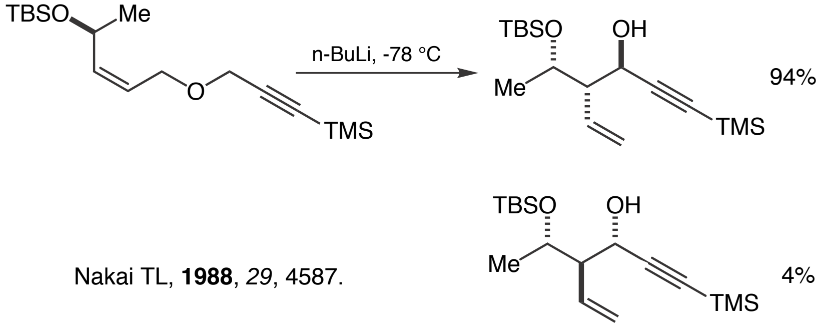
A Felkin analysis predicts the major product

Bruckner, *Angew. Chem. Int. Ed.* **1988**, *27*, 278



Taber *J. Am. Chem. Soc.* **1977**, *99*, 3513.
Kondo *Tet. Lett.* **1978**, 3927.

Allylic Ethers to Make Three Contiguous Stereocenters

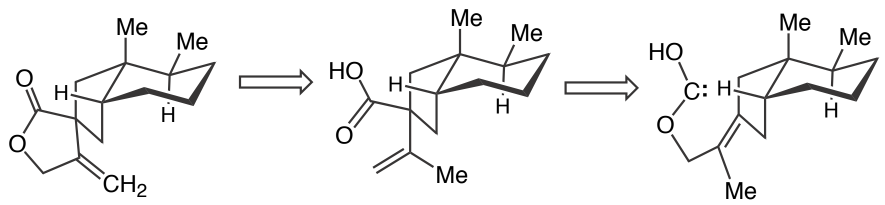


Nakai TL, **1988**, *29*, 4587.

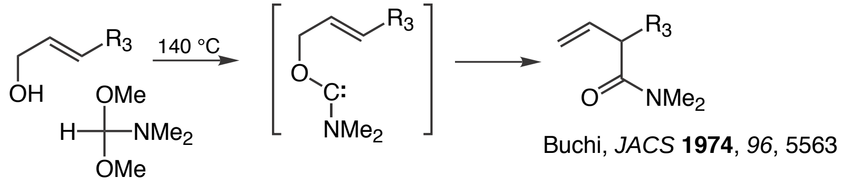
Can you rationalize the stereochemical outcome of this reaction?

[2,3]-Sigmatropic Rearrangements: Chirality Transfer

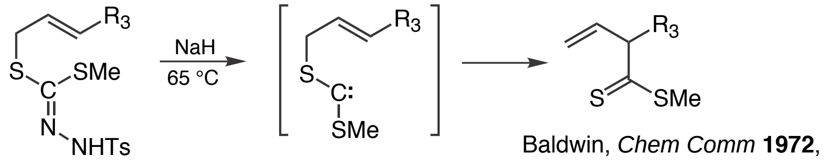
The Synthesis of Bakkenolide-A *(Evans JACS **1977**, 99, 5453)*



- Candidate processes:

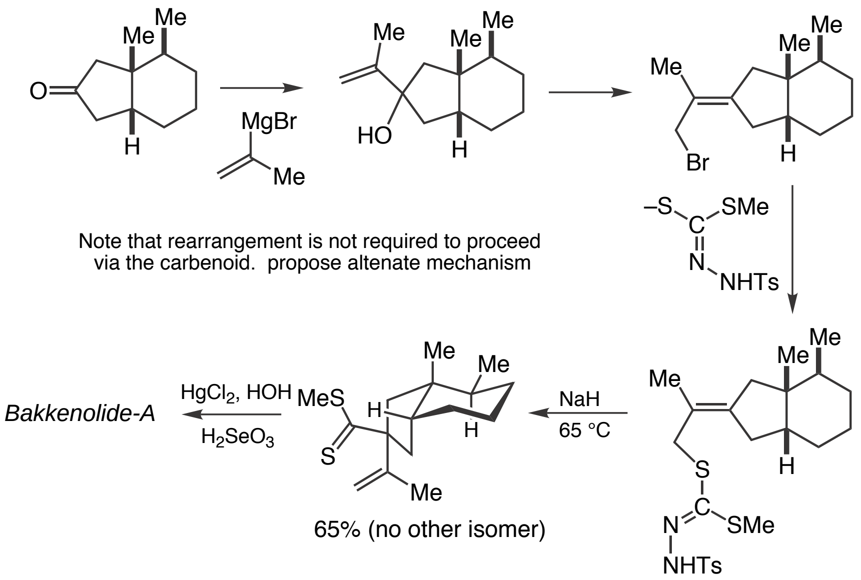


Buchi, *JACS* **1974**, *96*, 5563



Baldwin, *Chem Comm* **1972**, 354

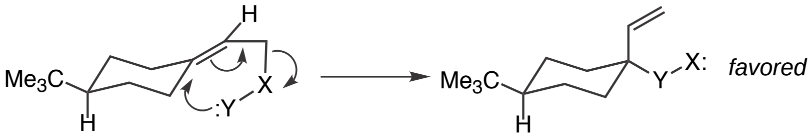
- The synthesis:

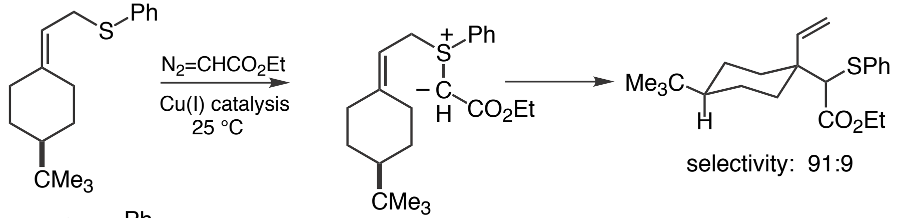


Note that rearrangement is not required to proceed via the carbenoid. propose altenate mechanism

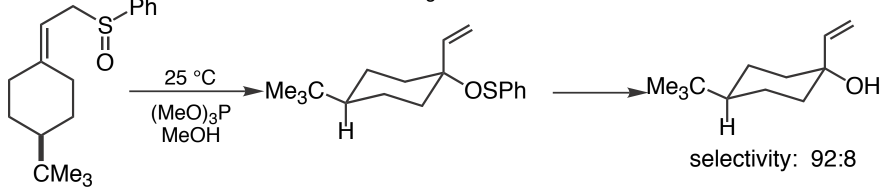
65% (no other isomer)

[2,3] Sigmatropic rearrangements respond to subtile steric effects



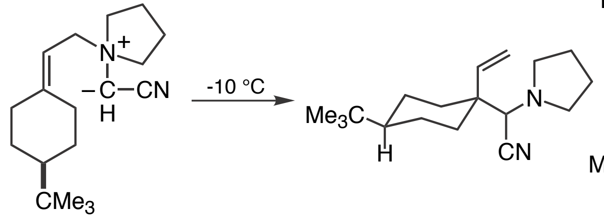


selectivity: 91:9



selectivity: 92:8

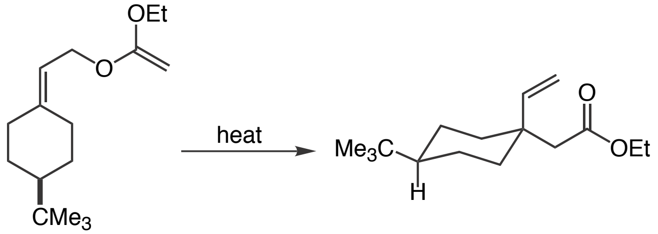
Evans, *JACS*, **1972**, *94*, 3672



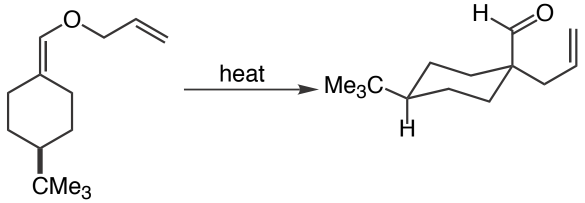
selectivity: 90:10

Mander, *JOC*, **1973**, *38*, 2915

- The comparison of analogous [2,3] & [3,3] rearrangements:



selectivity: 52:48



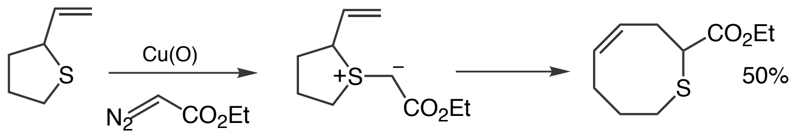
selectivity: 75:25

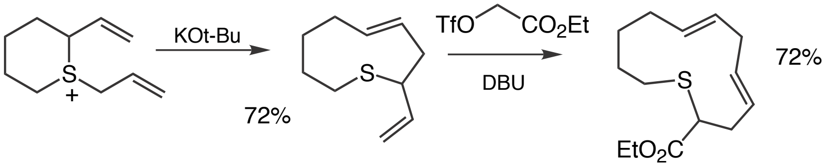
House, *JOC* **1975**, *40*, 86

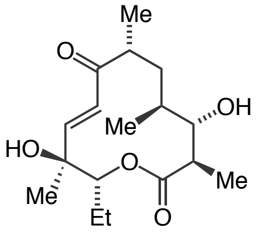
[2,3]-Sigmatropic Rearrangements: Ring Expansion & Contraction

Ring expansion reactions have been investigated

Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res*. **1984**, *17*, 358



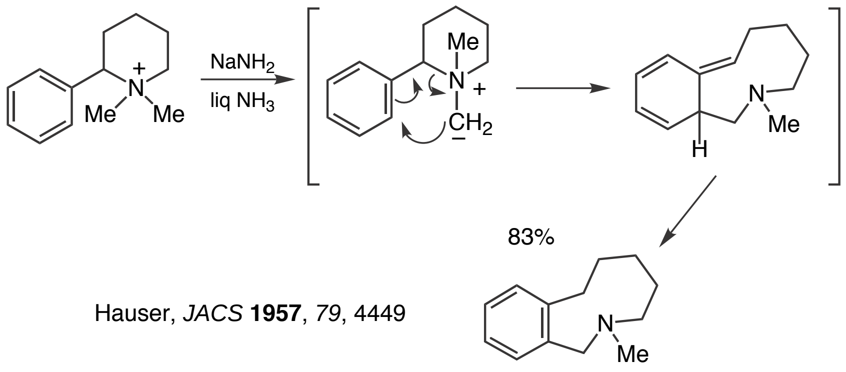




Methynolide has been synthesized by Vedejs using this ring-expansion methodology

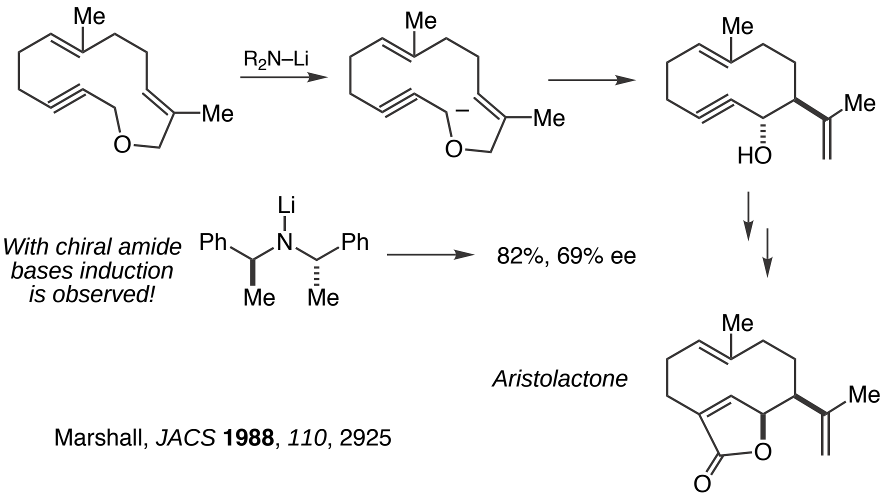
Vedejs, *JACS* **1989**, *111*, 8430

An early ring expansion using the Sommelet-Hauser Rearrangement



Hauser, *JACS* **1957**, *79*, 4449

A ring contraction using the Wittig Rearrangement



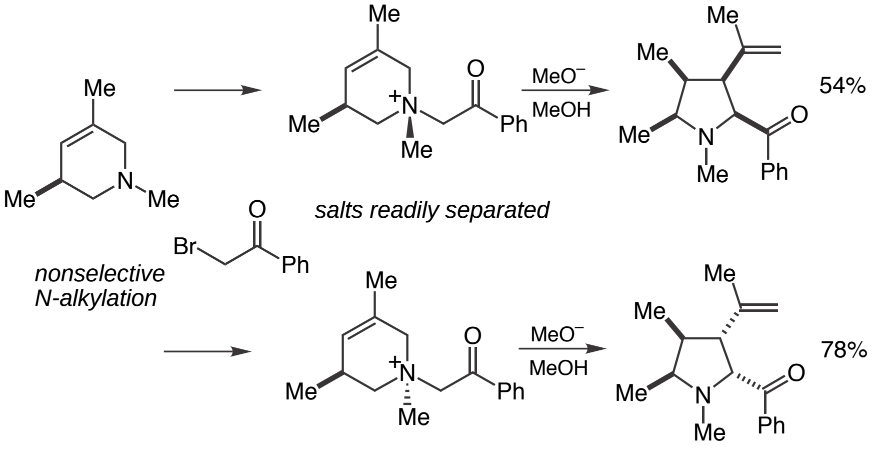
With chiral amide bases induction is observed!

82%, 69% ee

Aristolactone

Marshall, *JACS* **1988**, *110*, 2925

A ring contraction using the Stevens Rearrangement



salts readily separated

nonselective N-alkylation

Both rearrangements afford a single isomer

Stevenson, *Tet. Lett* **1990**, *31*, 4351

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 14

Pericyclic Reactions–4

- [3,3] Sigmatropic Rearrangements: Introduction
- Cope Rearrangements & Variants
- Claisen Rearrangements & Variants

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4: *Thermal Pericyclic Reactions*

K. Houk, *Transition Structures of Hydrocarbon Pericyclic Rxns*
Angew Chem. Int. Ed. Engl. **1992**, *31*, 682-708

K. Houk, *Pericyclic Reaction Transition States: Passions & Punctilios, Accts. Chem. Res.* **1995**, *28,* 81-90
Angew Chem. Int. Ed. Engl. **1992**, *31*, 682-708

D. A. Evans

Friday,
October 16, 2003

Other Reading Material:

[3,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)

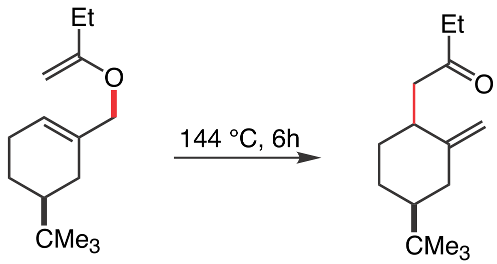
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)

Paquette, L. A. (1990). "Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement." Angew. Chem., Int. Ed. Engl. 29: 609.

Problems of the Day:

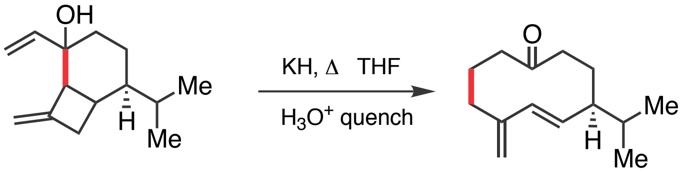
Predict the stereochemical outcome of this Claisen rearrangement



diastereoselection
>87:13

Ireland, *JOC* 1983, *48*, 1829

Provide a mechanism for the indicated transformation

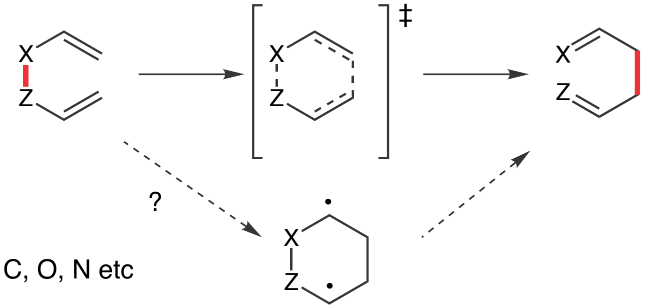


Schreiber, *JACS* **1984**, *106,* 4038

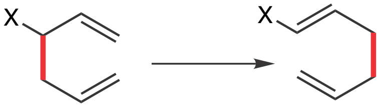
Introduction to [3, 3]-Sigmatropic Rearrangements

General Reviews:

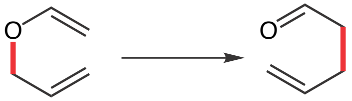
S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)
T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen



X & Z = C, O, N etc

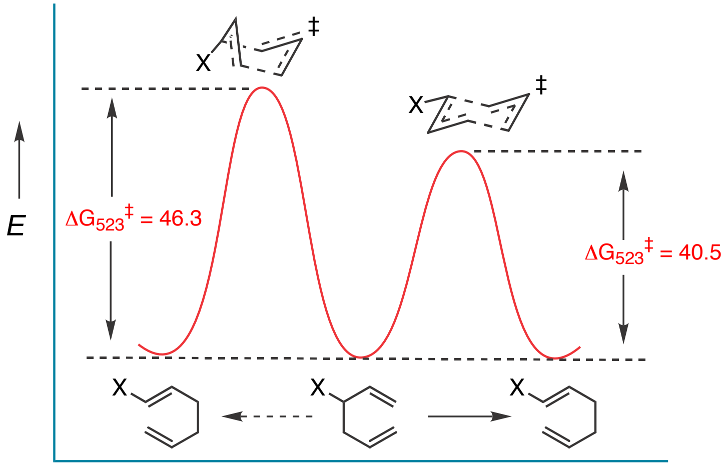


Cope Rearrangement, Ea = 33.5 kcal/mol

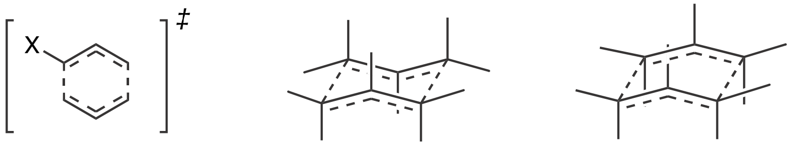


Claisen Rearrangement Ea = 30.6 kcal/mol

The Reaction Energetics Goldstein, *JACS* **1972**, *94*, 7147

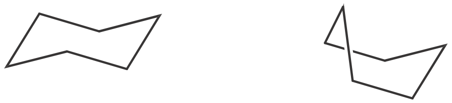


The CopeTransition States



CHAIR *BOAT*

Relative Energy $\Delta\Delta G^{\ddagger}$: 0 + 5.8 kcal/mol



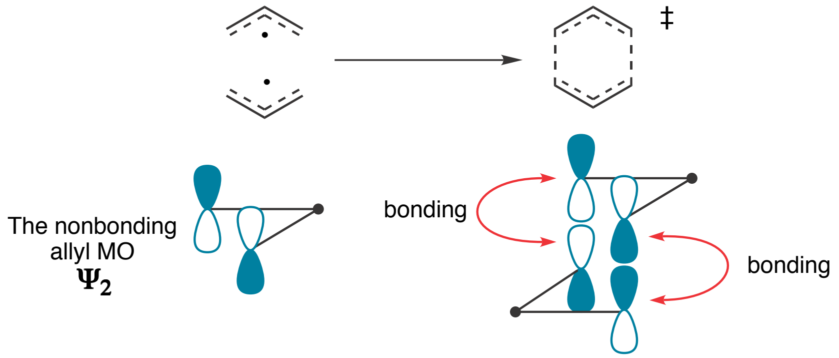
CHAIR *BOAT*

Relative Energy $\Delta G°$: 0 + 5.3 kcal/mol

The Boat and Chair geometries for these transition structures are well defined.

The FMO Analysis (Fleming page 101)

Bring two allyl radicals together to access for a possible bonding interaction between termini.

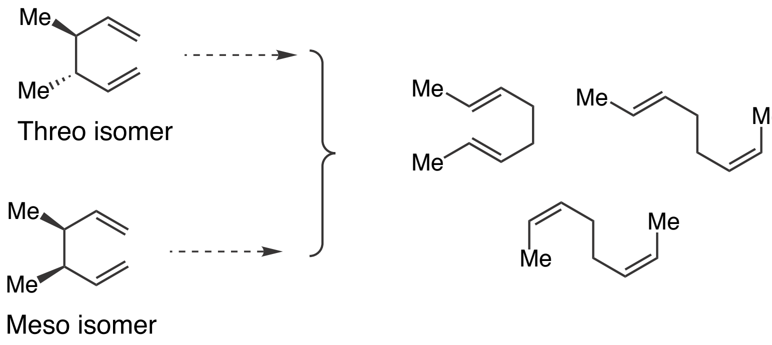


It is evident that synchronous bonding is possible in this rearrangement

The Doering–Roth Experiments

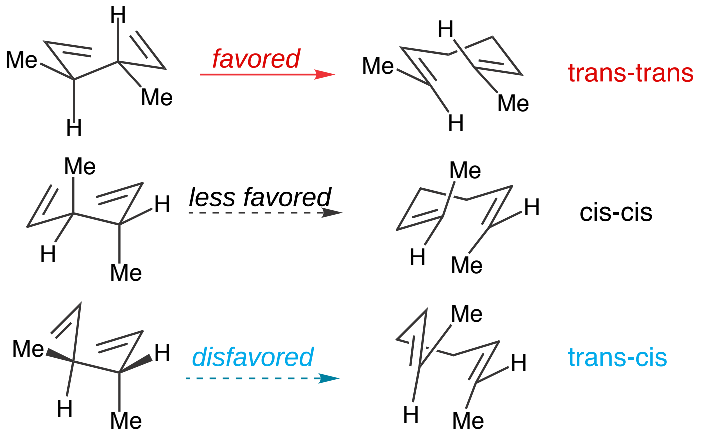
Doering/Roth Experiments: *Tetrahedron* 18, 67, (1962):

The Geometry of the transltion state (boat vs chair) can be analyzed via the rearrangement of substituted 1,5-dienes:

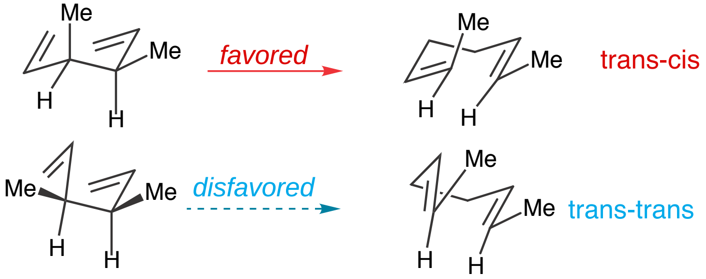


- Measure product composition from rearrangement of each diene isomer

Predictions: *Threo isomer*

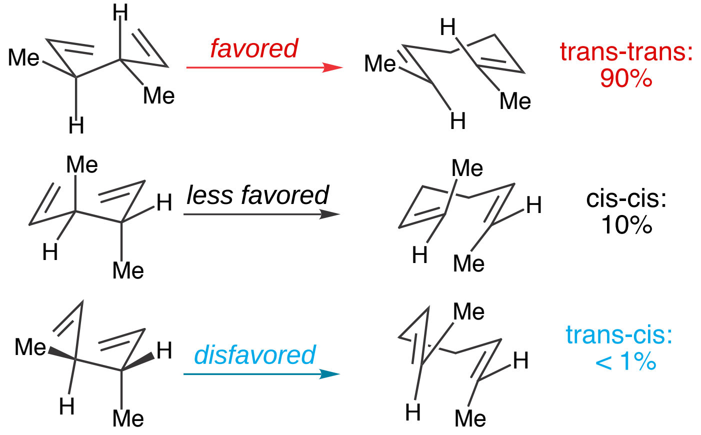


Predictions: *Meso isomer*

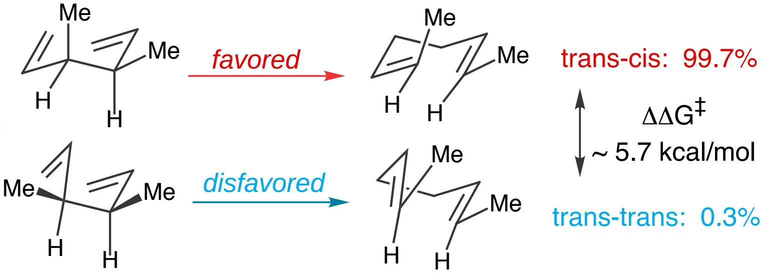


The Results

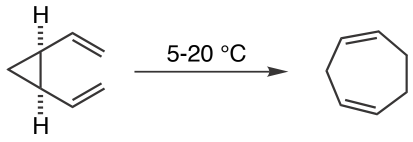
Results: *Threo isomer*



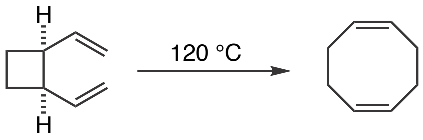
Results: *Meso isomer*



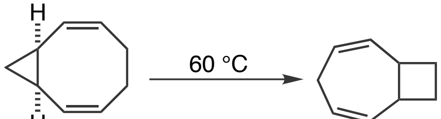
Ring Strain can be employed to drive the Cope process:



Brown *Chem. Commun.* **1973**, 319



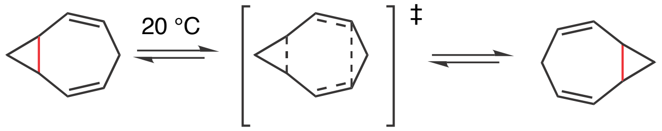
Vogel *Annalen* **1958**, *615*, 1



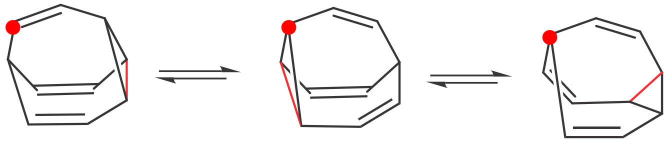
Reese *Chem. Commun.* **1970**, 1519

equilibrium stongly favors this isomer

Ring Strain can be employed to drive the Cope process:



W. von E. Doering's Bullvalene

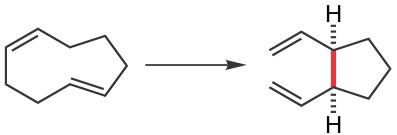


Bullvalene: Ea = 13.9 kcal/mol

At 100 °C one carbon is observed in nmr spectrum

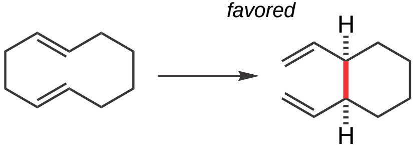
Carey, Vol 1, page 630-630

Position of Equilibrium dictated by ring strain issues:



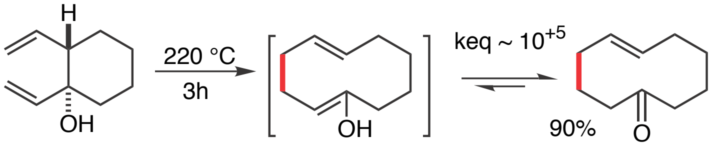
Vogel *Angew. Chem. Int. Ed.* **1963**, *2*, 739

favored



Wharton *J. Org. Chem.* **1973**, *38*, 4117

However, tautomerism can shift the equilibrium:



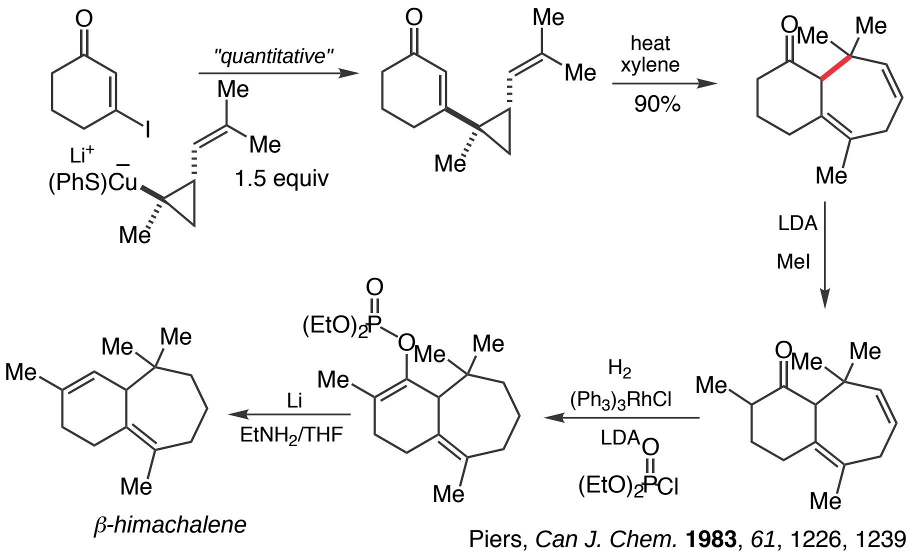
Marvell, *Tet. Lett.* **1970**, 509

Energetically, how much does tautomerization give you?

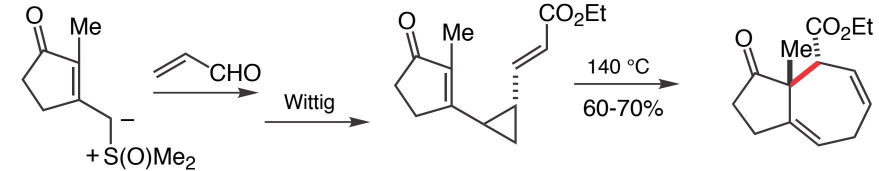
keq ~ 10^{+5}

$\Delta G = 1.4(\text{pKeq}) = 1.4 \times (-5) = -7$ kcal/mmol

Ring extension via divinylcyclopropane rearrangement

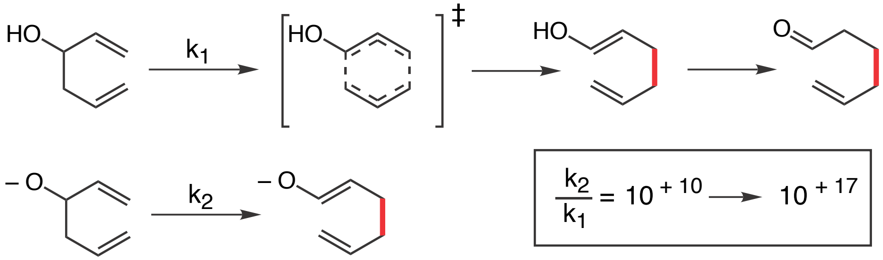


Piers, *Can J. Chem.* **1983**, *61*, 1226, 1239



Marino, *J. Org. Chem.* **1974**, *39*, 3175

Accelerated Cope Rearrangements



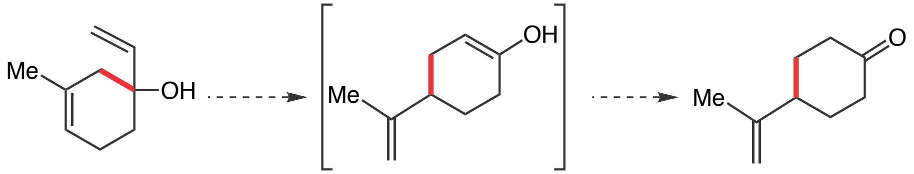
$$\boxed{\frac{k_2}{k_1} = 10^{+10} \longrightarrow 10^{+17}}$$

Evans, Golob, *JACS* **1975**, *97*, 4765.

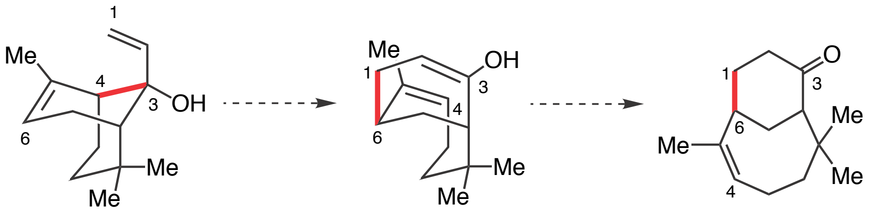
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
"Recent applications of anionic oxy-Cope rearrangements."
Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971-14020

The Aborted Oxy-Cope Reaction (circa 1969)

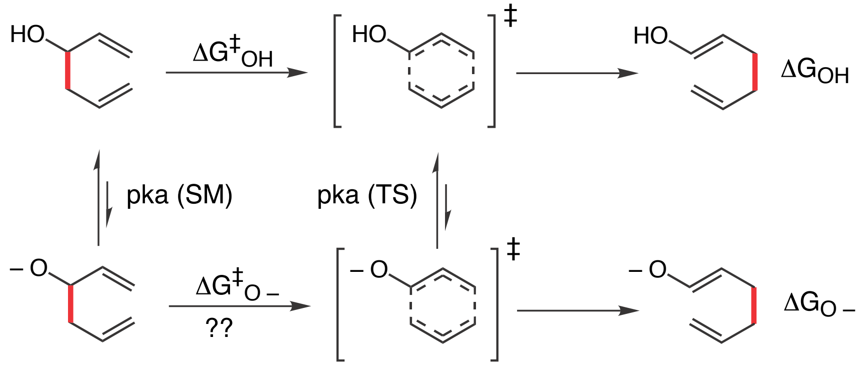
- *The basic reaction*



- *Actual case studied:*



Prediction of Substituent Effect (circa 1969)



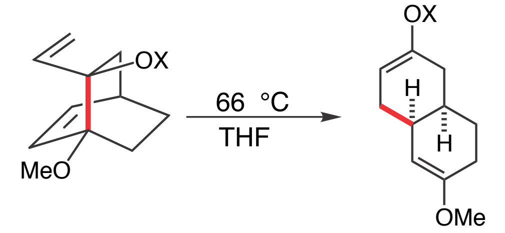
$$\boxed{\Delta G^{\ddagger}_{O^-} = \Delta G^{\ddagger}_{OH} + 2.3RT\,[\,pka_{TS} - pka_{SM}]}$$

$\Delta G^{\ddagger}_{O^-} = \Delta G^{\ddagger}_{OH} + 2.3RT\,[18 - 29]$ (in DMSO)

$\Delta G^{\ddagger}_{O^-} = \Delta G^{\ddagger}_{OH} + 1.4\,[-11]$

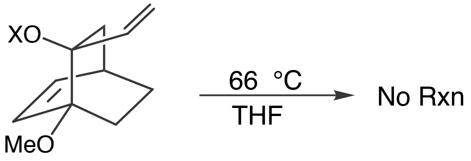
$\Delta G^{\ddagger}_{O^-} = \Delta G^{\ddagger}_{OH} - 15$ kcal/mol at 298 K (in DMSO)

Documentation of Alkoxy Substituent Effect



–OX	Half-life	
–OH	(66 yrs)	66 °C
–OLi	no rxn	
–ONa	1.2 hrs	
–OK	1.4 min	
–OK	11 hrs	10 °C
(HMPT) $–O^-\,{}^+K$	4.4 min	

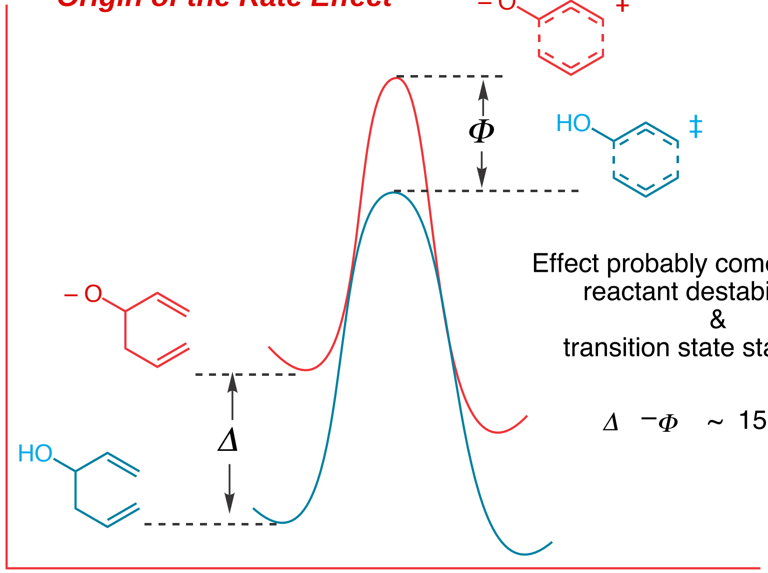
$\boxed{10^{+12} \text{ rate acceleration}}$



$$\boxed{\begin{array}{l} \Delta\Delta G^{\ddagger}_{estimate} = 15 \text{ kca mol}^{-1} \\ \Delta\Delta G^{\ddagger}_{experiment} = 13 \text{ kca mol}^{-1} \end{array}}$$

with A. M. Golob, JACS. **1975**, *97*, 4765.

Origin of the Rate Effect



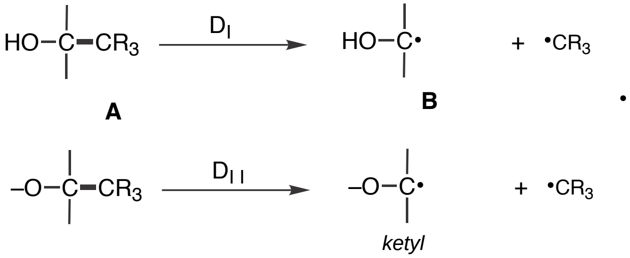
Effect probably comes from both
reactant destabilization
&
transition state stabilization

$\Delta - \Phi \sim 15$ kcal/mol

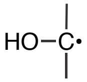
Maximal rates are observed under conditions where reactant is maximally destabilized

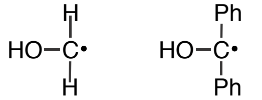
Anionic Substituent Effects: Bond Homolysis

Substituent Effects in Bond Homolysis



$$D_I - D_{II} = 2.3\,RT[\text{pka}\,(\mathbf{A}) - \text{pka}\,(\mathbf{B})]$$

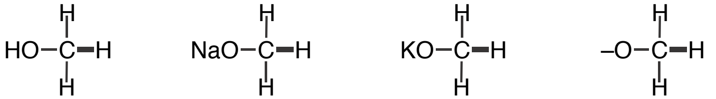

Acidities of these radicals are known in H_2O
Hayon, *Accts. Chem. Res.* **1974**, *7*, 114


(H$_2$O) pKa = 10.7 pKa = 9.2

In DMSO: $\Delta D = 2.3\,RT[29 - \text{pka } 18] = \sim 15$ kcal/mol

- Substituent Effect based on ab initio calculations

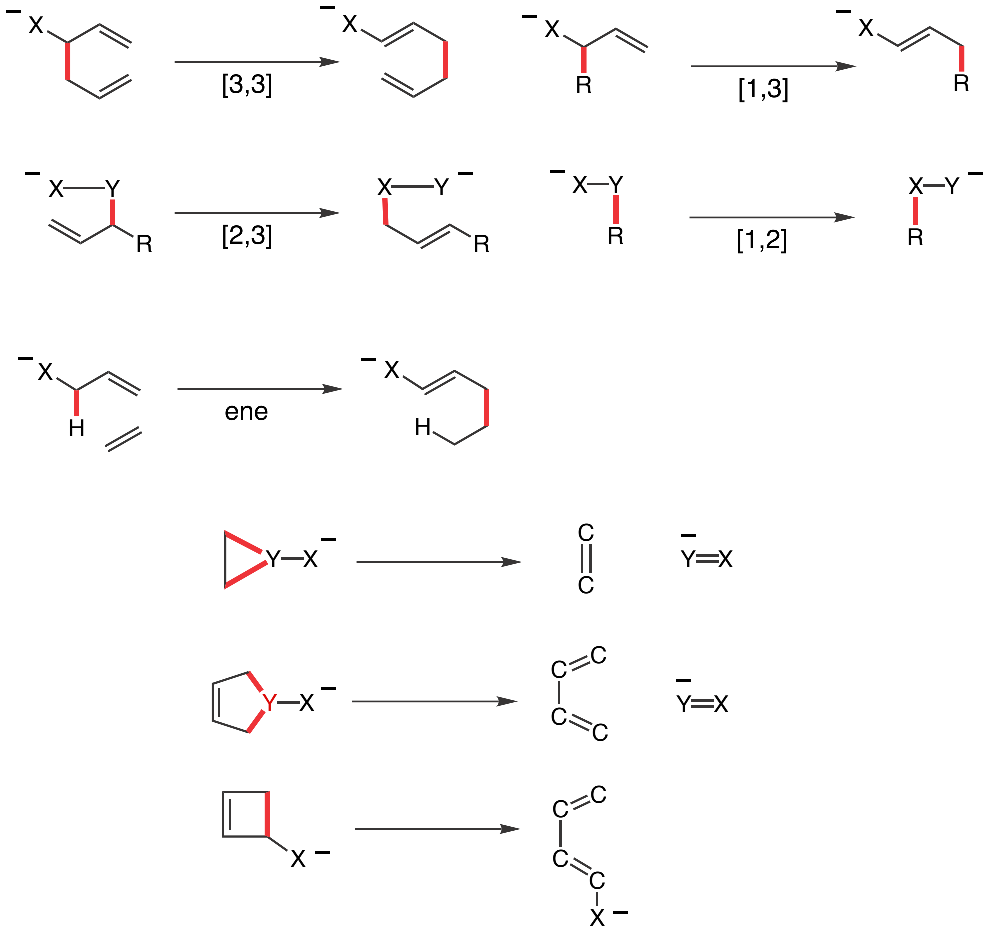
(Evans, Goddard, *JACS* **1979**, *101*, 1994)

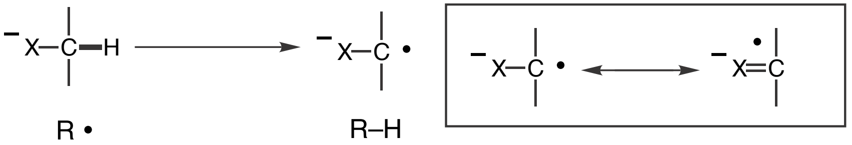

BDE = 90.7 (BDE = 91.8 expt) BDE = 80.6 BDE = 79.0 BDE = 74.2

ΔD
+16.5 kcal/mol

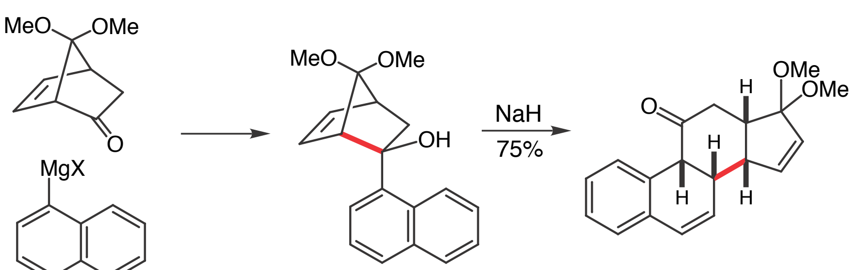
Related papers: Evans, Baillargeon, *Tet Lett*. **1978**, *36*, 3315, 3319

Substituent Effects in Molecular Rearrangements

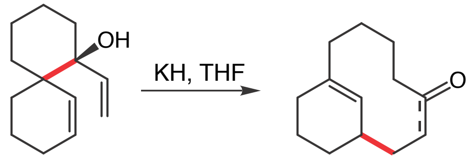




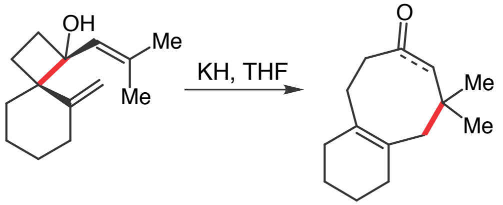
Anionic Oxy-Cope Rearrangement: Applications



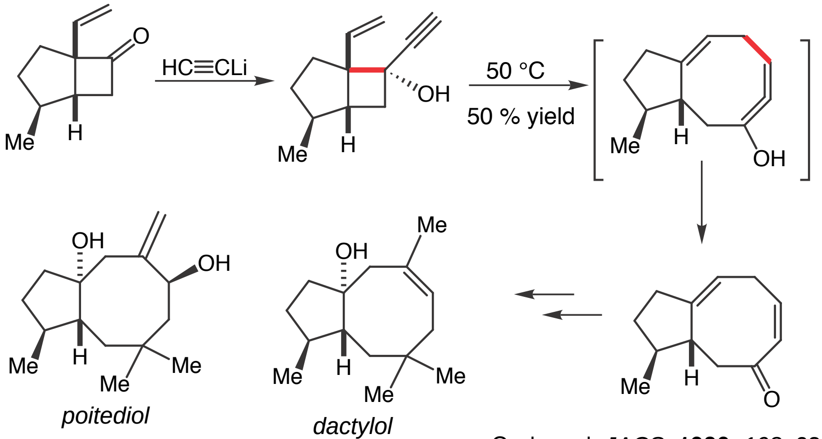
Jung, JACS **1978**, *100*, 4309
Jung, JACS **1980**, *102*, 2463



Levine, JOC **1981**, *46*, 2199

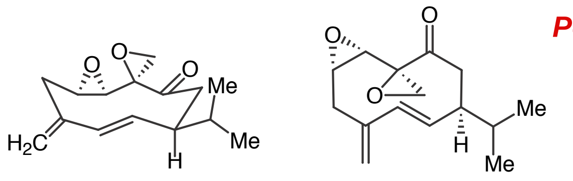


Gadwood, *JOC*, **1982**, *47*, 2268

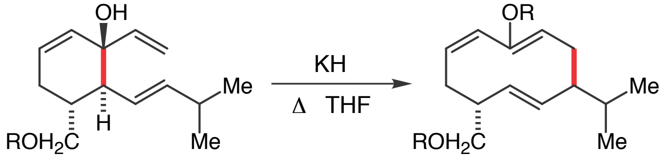


Gadwood, *JACS*, **1986**, *108*, 6343

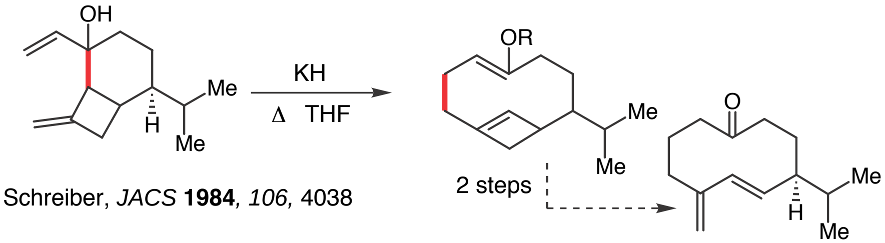
Periplanone-B Synthesis



200 µg from 75,000 virgin female cockroaches

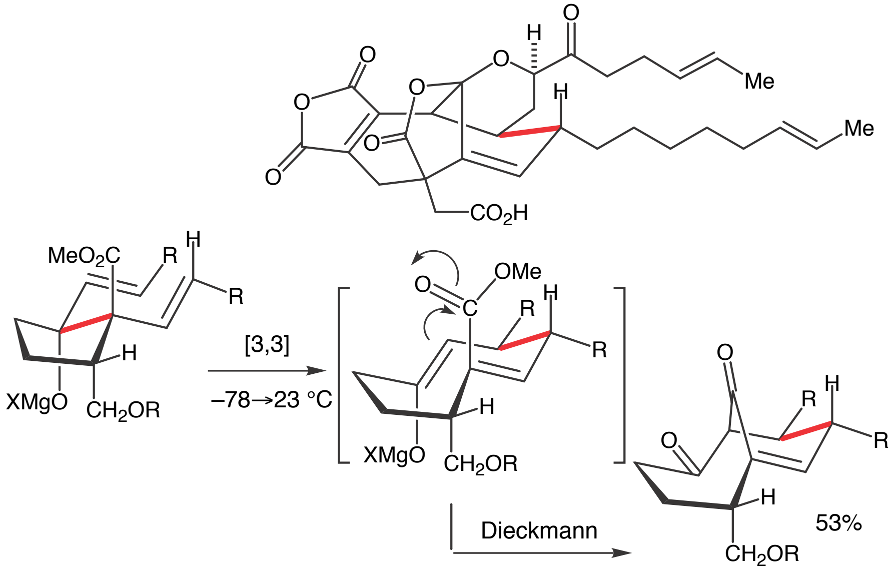


Still, *JACS* **1979**, *101*, 2493

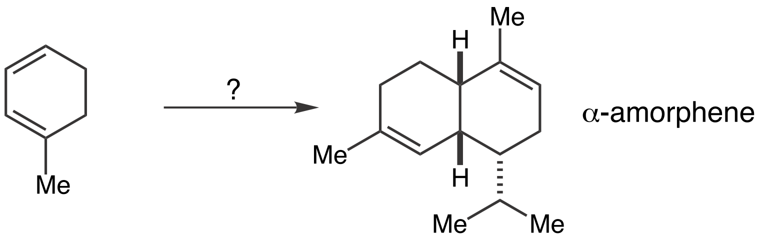


Schreiber, *JACS* **1984**, *106*, 4038

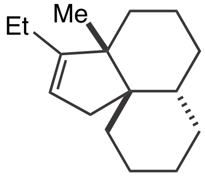
Synthesis of (+)-CP-263,114: Shair, *JACS* **2000**, *122*, 7424-7425.



Propose a synthesis of α-amorphene using 1-methyl-1,3-cyclohexadiene.

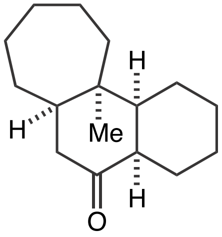


Gregson, R. P.; Mirrington, R. N. *J. Chem. Soc., Chem. Commun.* **1973**, 598.



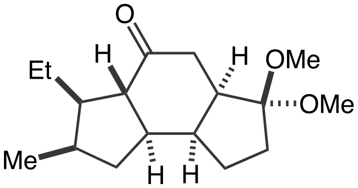
By incorporating a carbonyl group into this structure generate all possible oxy-Cope retrons.
Which is (are) the most reasonable?

Bérubé, G.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 4045.



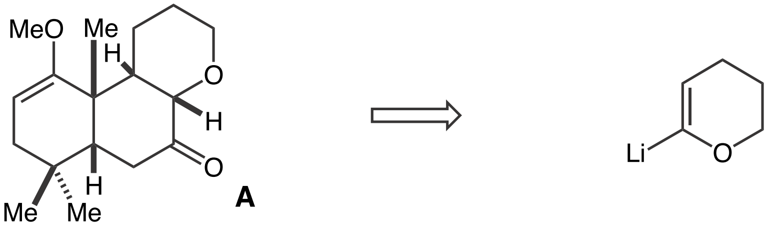
By incorporating a double bond into this structure generate all possible oxy-Cope retrons.
Which is (are) the most reasonable?

Ireland, et al. *J. Org. Chem.* **1981**, *46*, 4863.



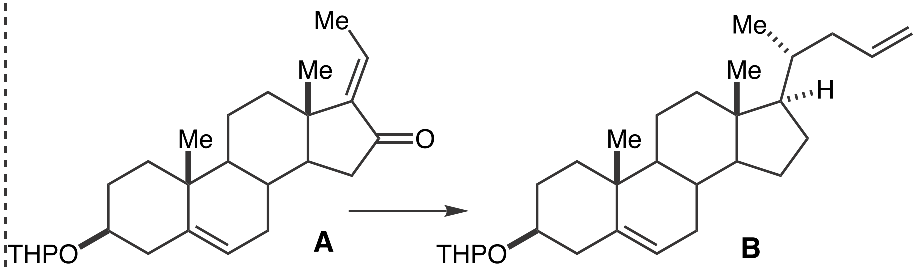
By incorporating a double bond into this structure generate all possible oxy-Cope retrons. Which is (are) the most reasonable?

Paquette, L. A. et al. *Tetrahedron Lett.* **1987**, *28*, 31.



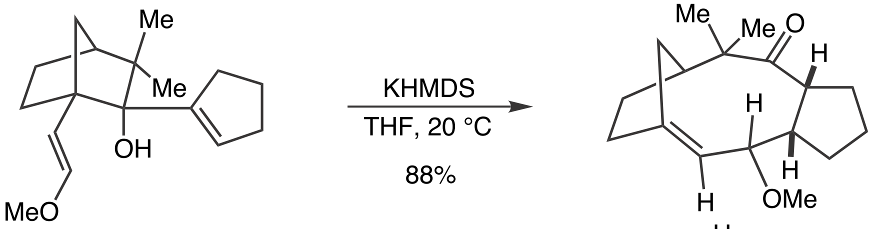
Propose a synthesis of **A** using the illustrated dihydropyran synthon.

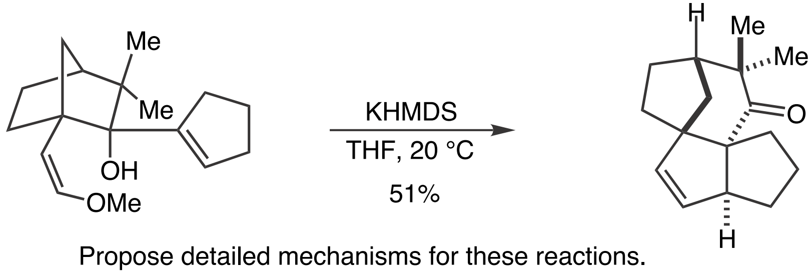
Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 5441.



Propose a three step synthesis of **B** from **A**.

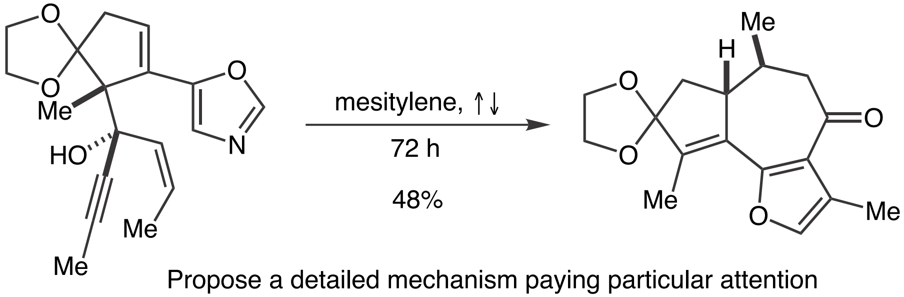
Koreeda, et al. *J. Org. Chem.* **1980**, *45*, 1172.





Propose detailed mechanisms for these reactions.
Rationalize the different behavior of these enol ether isomers.

Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331-2332.



Propose a detailed mechanism paying particular attention to issues of chemo- and stereoselectivity.

Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, *55*, 202.

General Reviews:

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Ch 7.2
Ziegler, *Accts. Chem. Res.* **1977**, *10*, 227 (Claisen)
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Blechert, *Synthesis* **1989**, 71 (HeteroCope)
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)
Ziegler, *Chem Rev.* **1989**, *89*, 1423 (Claisen)

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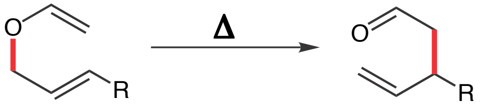

$\Delta H \sim -20$ kcal mol^{-1}

There is good thermodynamic driving force for this reaction.

Bonds Broken: C-C$_\pi$ (65 kcal mol^{-1}) & C-O$_\sigma$ (85 kcal mol^{-1})

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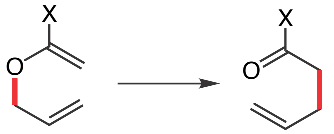
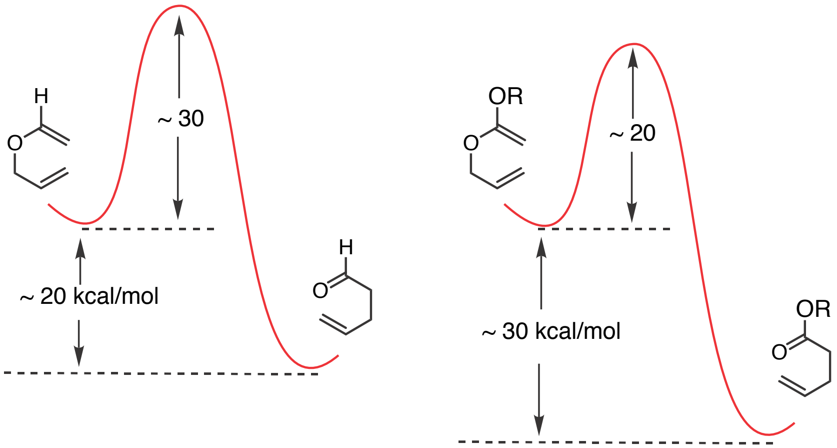


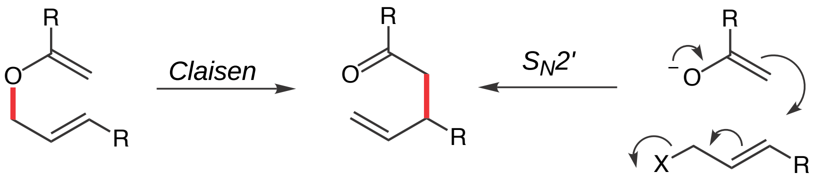
Substituent	ΔH (kcal mol^{-1})
X = H	–16
X = OH	–31
X = NH_2	–30

(Benson estimates)

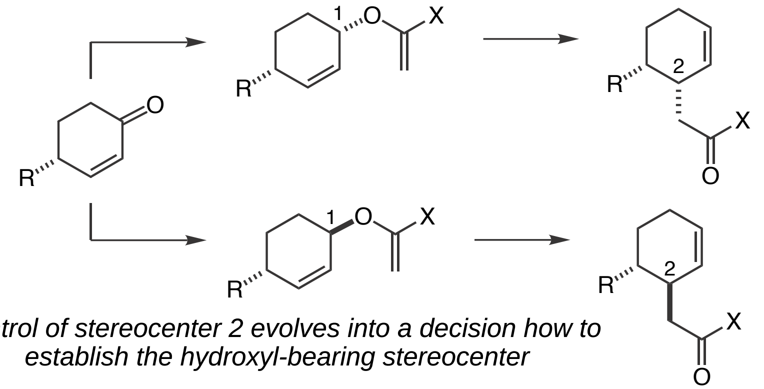


Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

Recognition Pattern for Organic Synthesis: An Enforced SN2'

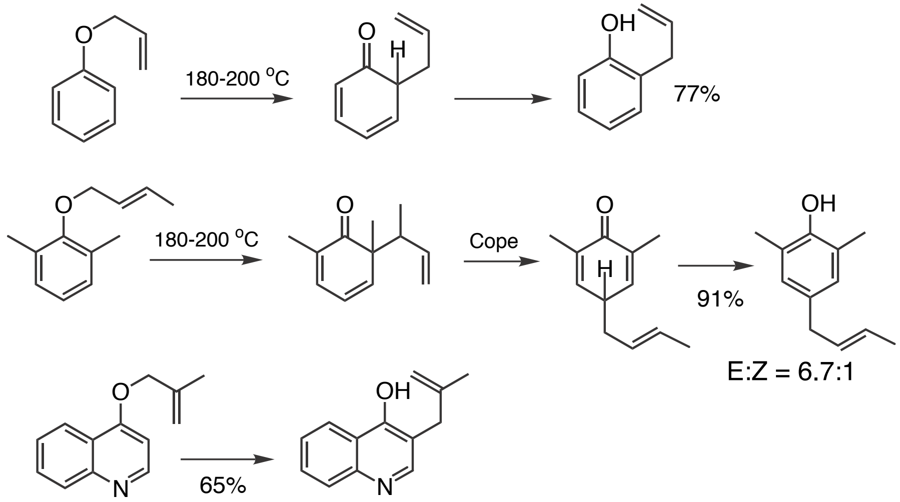


Stereochemical outcome is syn and controlled by hydroxyl stereocenter



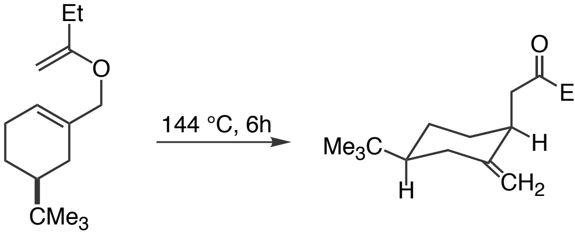
Control of stereocenter 2 evolves into a decision how to establish the hydroxyl-bearing stereocenter

Rearrangements of Aryl Allyl Ethers: Traditional Applications



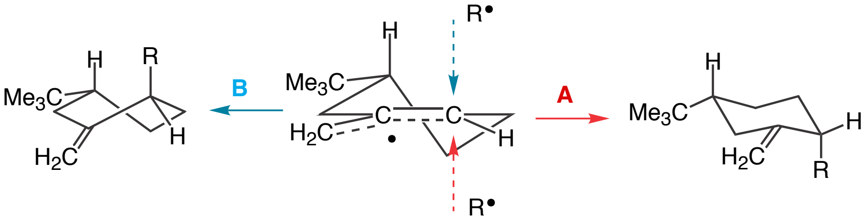
Stereoelectronic & steric constraints

■ Endocyclic Olefins: Ireland, *JOC* 1983, *48*, 1829

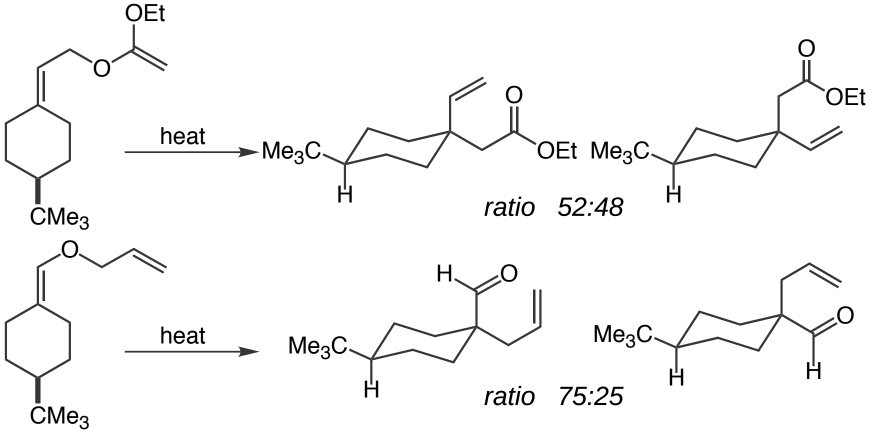


diastereoselection >87:13

for endocyclic olefins, overlap between developing sigma and pi bonds required. Best overlap for forming chair geometry. As shown below, bring a radical up to either face of the allylic radical. As the bond is formed, overlap must be maintained. **Parh A** evolves into a **chair** conformation while **Path B** evolved into a **boat** conformation.

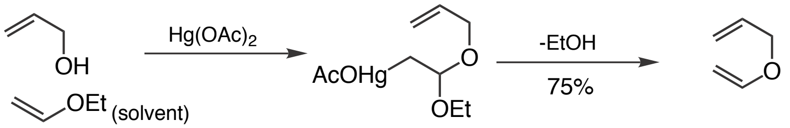


■ Exocyclic Olefins: House, *JOC* 1975, *40*, 86

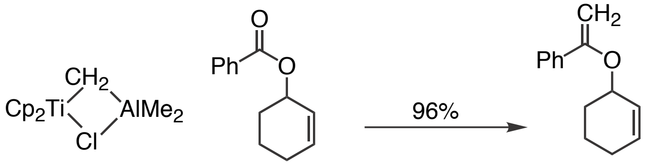


for exoocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack." A related case is provided below.

Synthesis of Allyl Vinyl Ethers

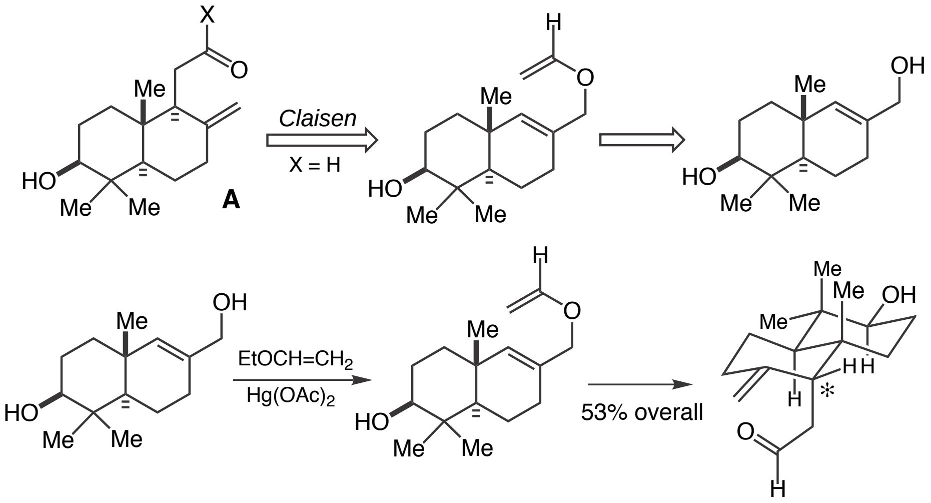


Watanabe, Conlon, *JACS* **1957**, *79*, 2828
Bronsted acids can also serve as catalysts



Use of Tebbe's Reagent: Evans, Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3272.
(review) S. H. Pines, *Organic Reactions* **1993**, *43*, 1

The Ireland approach to the bicyclic acid A: *JOC* **1962**, *27*, 1118

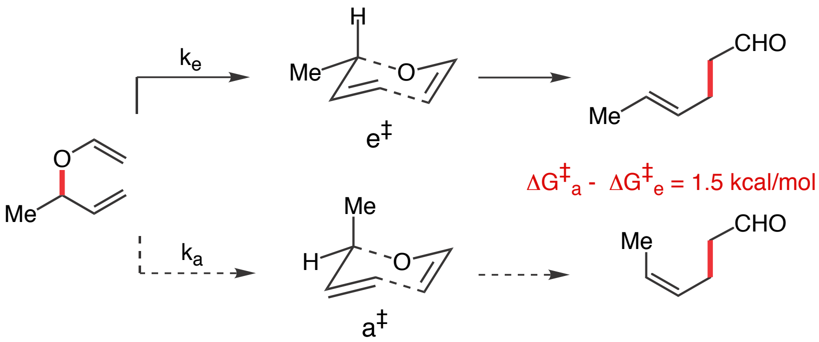


The new stereocenter (✻) introduced via the rearrangement had the wrong configuration!

The Claisen Rearrangement: Stereoselective Olefin Synthesis

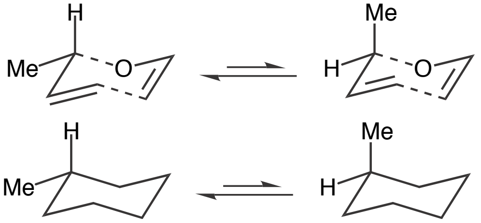
Claisen Rearrangement as vehicle for stereoselective olefin synthesis

Consider the following rearrangement:



$\Delta G^‡_a$ - $\Delta G^‡_e$ = 1.5 kcal/mol

Faulkner & Perrin (Tet. Lett. 2783 (**1969**) have made the correlation between $\Delta\Delta G^‡$ for rearrangement & ΔG° for the corrresponding cyclohexane[#] equilibria:

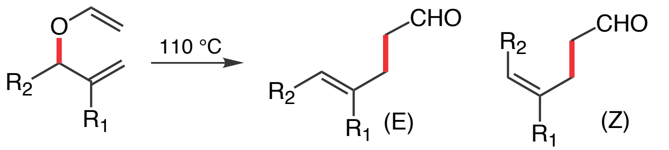


$\Delta\Delta G^‡$ = +1.5 kcal/mol

ΔG° = +1.75 kcal/mol

[#]Note: The A-value of 2-methyl-tetrahydropyran is +2.86 kcal/mol (LectureNo. 6)

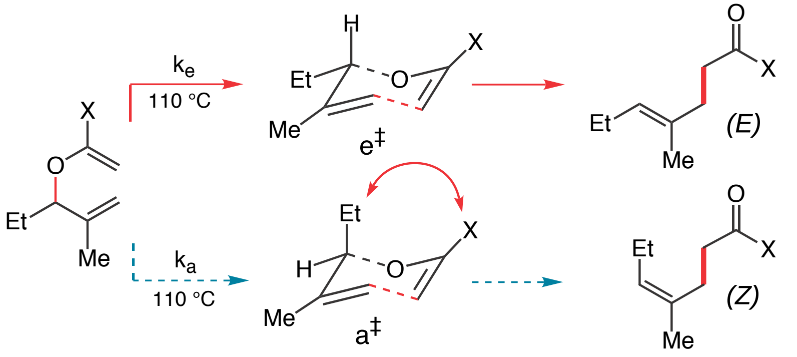
They then suggest that there is a good correlation between cyclohexane "A-values" & $\Delta\Delta G^‡$ for the rearrangement process. Their case is fortified by the following expamples:



R_1	R_2	(E):(Z) found	(E):(Z) predicted
Me–	Et–	90:10	91:9
Me–	iPr–	93:07	94:6
Et–	Et–	90:10	91:9

Faulkner, *JACS* **1973**, *95*, 553

Faulkner suggests that the installation of other substituents on Claisen transition states will lead to enhanced reaction diastereoselection:

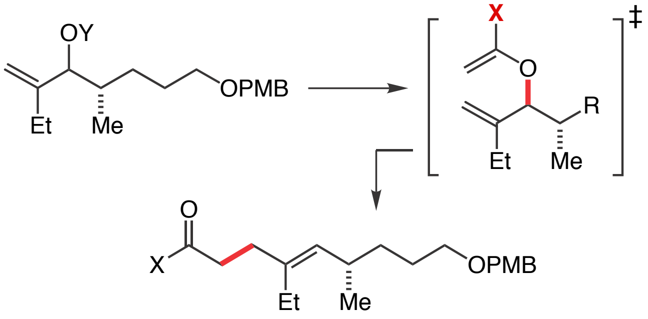


The $R_2 \leftrightarrow X$ interaction should destabilize $a^‡$ as X gets progressively larger.

X	(E):(Z) found
H–	90:10
Me–	>99:1
MeO–	>99:1
Me_2N–	>98:2

Faulkner, *Tet Let* **1969**, 3243
Faulkner, *JACS* **1973**, *95*, 553
Johnson, *JACS* **1970**, *92*, 741

■ Another comparison: (DAE) M. DiMare, Ph. D. Harvard University, 1988



procedure	conditions	X	T, °C	(E):(Z) ratio
Y = Ac, Ireland	LDA, TMSCl	TMSO–	-78→+55	97:3
Y = H, Johnson	$HC(OMe)_3$, H^+	MeO–	130	94:6
Y = H, Eschenmoser	$MeC(OMe)_2NMe_2$	Me_2N–	80	97.5:2.5

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 15

Pericyclic Reactions–5

- Claisen Rearrangements & Variants

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Fleming: Chapter 4
Thermal Pericyclic Reactions

Wipf, P. *Claisen Rearrangements.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 827.

New Aspects of the Ireland and Related Rearrangements, *Tetrahedron* **2002**, *58*, 2905–2928 **(handout)**

D. A. Evans

Wednesday,
October 20, 2003

Other Reading Material:

Enders, D.; Knopp, M.; Schiffers, R. "Asymmetric [3.3]-sigmatropic rearrangements in organic synthesis." *Tetrahedron: Asymmetry* **1996**, *7*, 1847-1882

Ziegler, F. E. "The Thermal Aliphatic Claisen Rearrangement." *Chem. Rev.* **1988**, *88*, 1423.

Gajewski, J. J. "The Claisen rearrangement. Response to solvents and substituents: The case for both hydrophobic and hydrogen bond acceleration in water and for a variable transition state." *Acc. Chem. Res.* **1997**, *30*, 219-225.

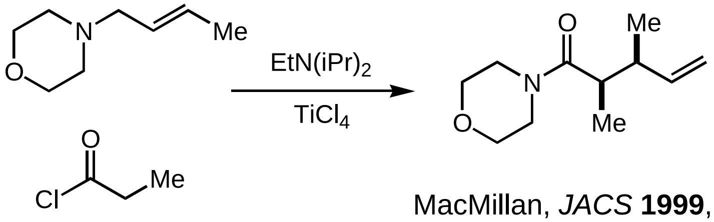
Tietze, L. F. "Domino reactions in organic synthesis." *Chem. Rev.* **1996**, *96*, 115-136.

Parsons, P. J.; Penkett, C. S.; Shell, A. J. "Tandem reactions in organic synthesis: Novel strategies for natural product elaboration and the development of new synthetic methodology." *Chem. Rev.* **1996**, *96*, 195-206.

Pereira, S.; Srebnik, M. "The Ireland-Claisen rearrangement." *Aldrichimica Acta* **1993**, *26*, 17.

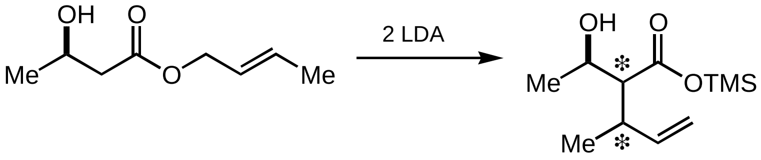
Problems of the Day:

Propose a mechanism for this transformation



MacMillan, *JACS* **1999**, *121*, 9726

Predict the stereochemical outcome of this reaction



Kurth, *JOC* **1985**, *50*, 1840

General Reviews:

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Ch 7.2
Ziegler, *Accts. Chem. Res.* **1977**, *10*, 227 (Claisen)
Bennett, *Synthesis* **1977**, 589 (Claisen)
Blechert, *Synthesis* **1989**, 71 (HeteroCope)
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)
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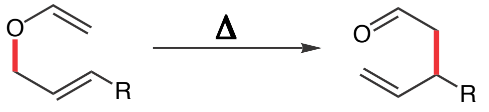

ΔH ~ –20 kcal mol^{-1}

There is good thermodynamic driving force for this reaction.

Bonds Broken: C-C$_\pi$ (65 kcal mol^{-1}) & C-O$_\sigma$ (85 kcal mol^{-1})

Bonds Made: C-O$_\pi$ (85 kcal mol^{-1}) and C-C$_\sigma$ (85 kcal mol-^{1})

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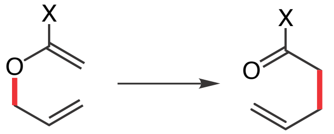

Substituent	ΔH (kcal mol^{-1})
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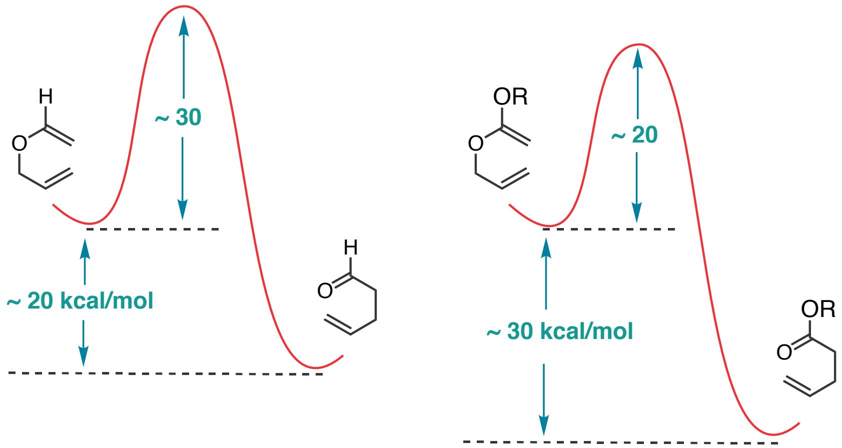
X = NH$_2$	–30

(Benson estimates)



Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

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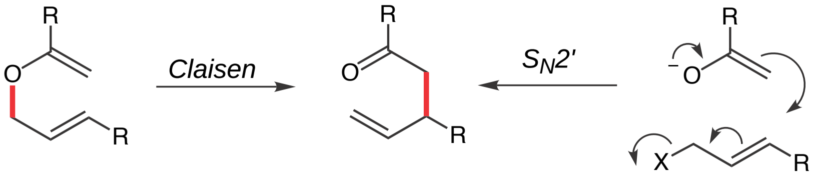
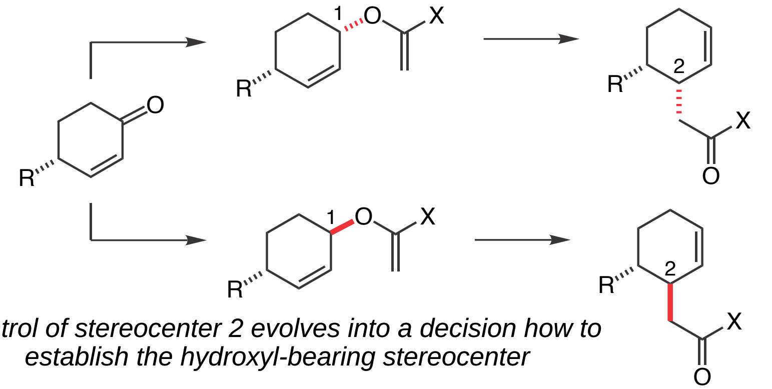


Stereochemical outcome is syn and controlled by hydroxyl stereocenter



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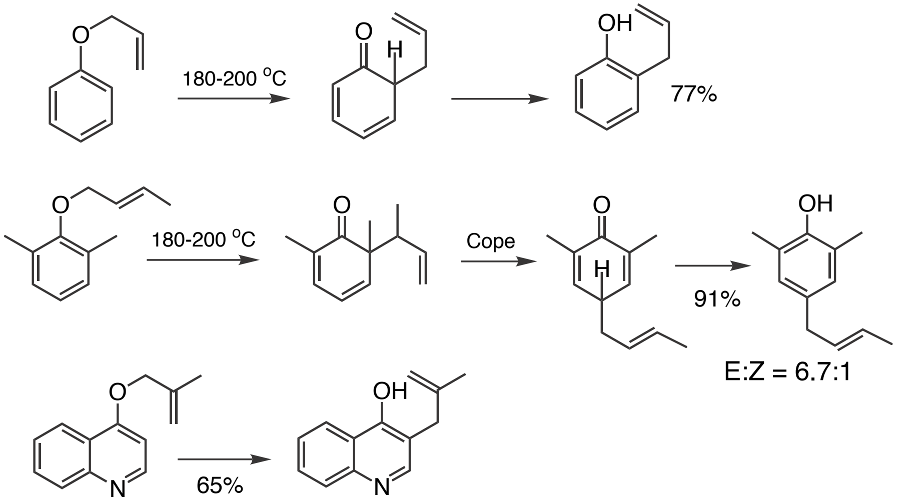

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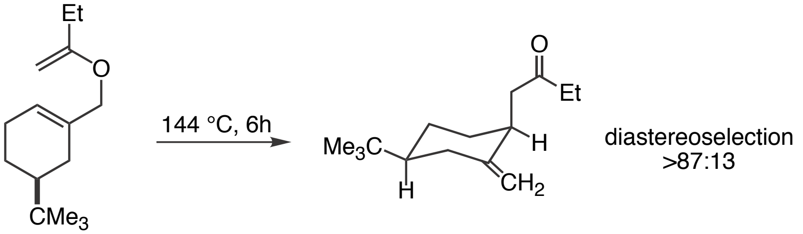

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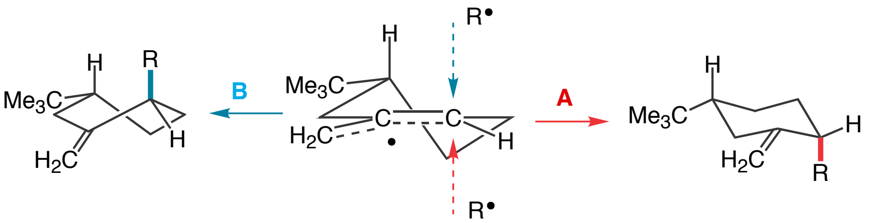

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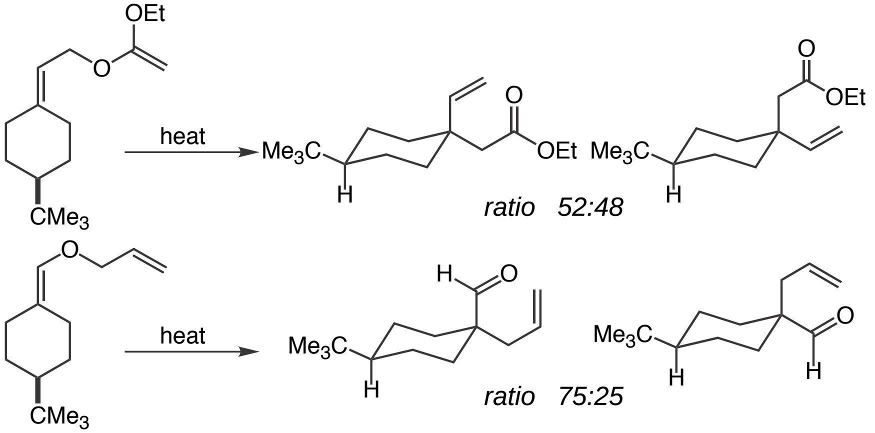

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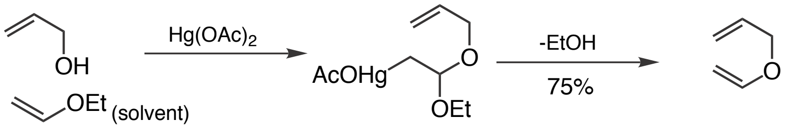

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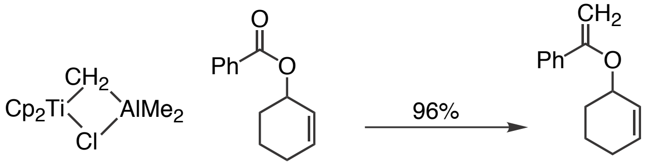

Use of Tebbe's Reagent: Evans, Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3272.
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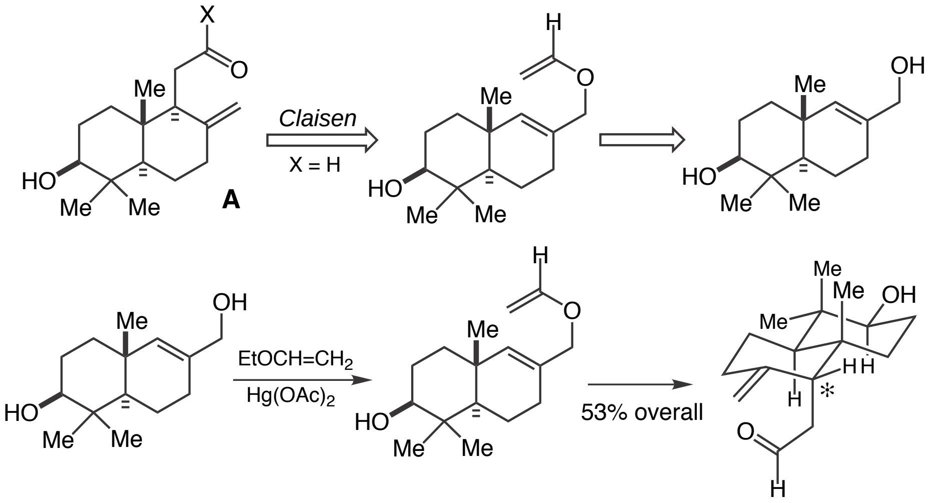

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Claisen Rearrangement as vehicle for stereoselective olefin synthesis

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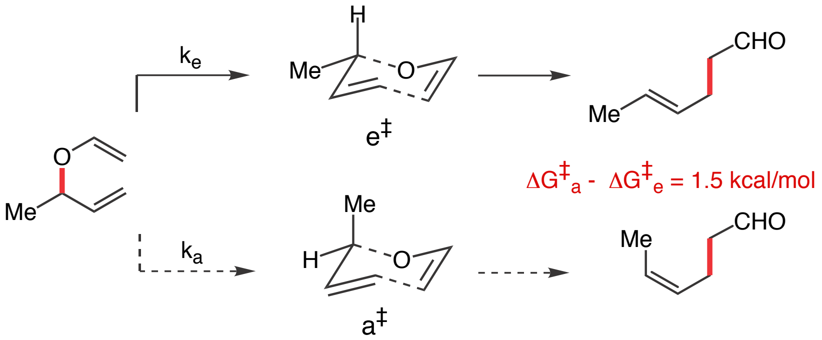

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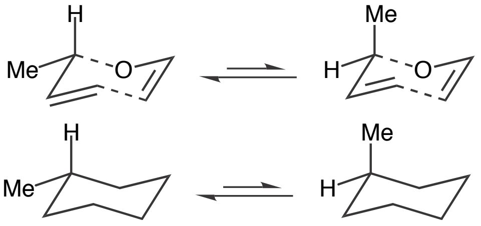
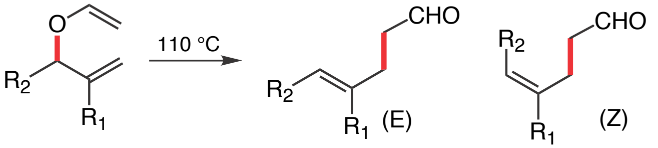


$\Delta\Delta G^‡$ = +1.5 kcal/mol

ΔG° = +1.75 kcal/mol

#Note: The A-value of 2-methyl-tetrahydropyran is +2.86 kcal/mol (Lecture No. 6)

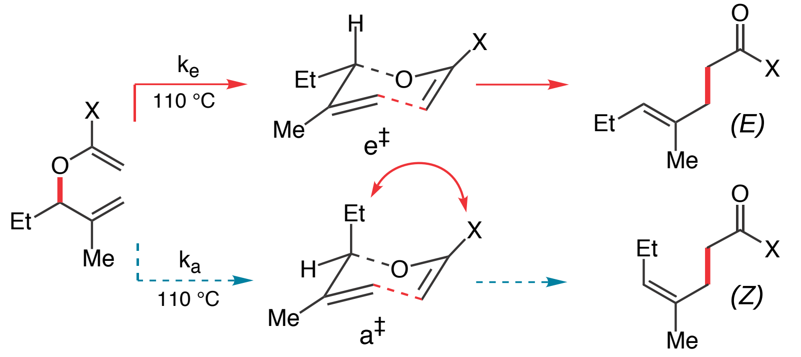
They then suggest that there is a good correlation between cyclohexane "A-values" & $\Delta\Delta G^‡$ for the rearrangement process. Their case is fortified by the following expamples:



R_1	R_2	(E):(Z) found	(E):(Z) predicted
Me–	Et–	90:10	91:9
Me–	iPr–	93:07	94:6
Et–	Et–	90:10	91:9

Faulkner, *JACS* **1973**, *95*, 553

Faulkner suggests that the installation of other substituents on Claisen transition states will lead to enhanced reaction diastereoselection:

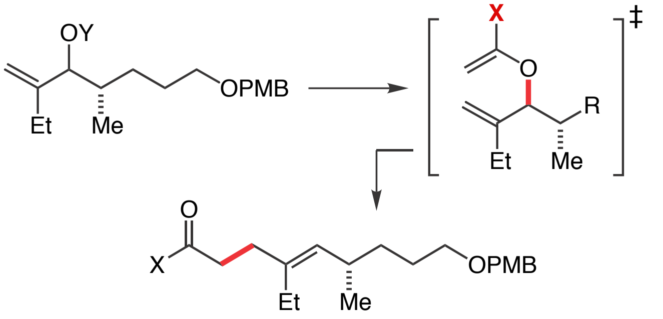


The $R_2 \leftrightarrow X$ interaction should destabilize a‡ as X gets progressively larger.

X	(E):(Z) found
H–	90:10
Me–	>99:1
MeO–	>99:1
Me_2N–	>98:2

Faulkner, *Tet Let* **1969**, 3243
Faulkner, *JACS* **1973**, *95*, 553
Johnson, *JACS* **1970**, *92*, 741

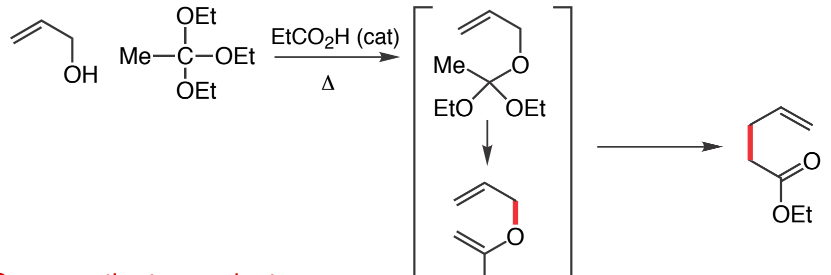
■ Another comparison: (DAE) M. DiMare, Ph. D. Harvard University, 1988



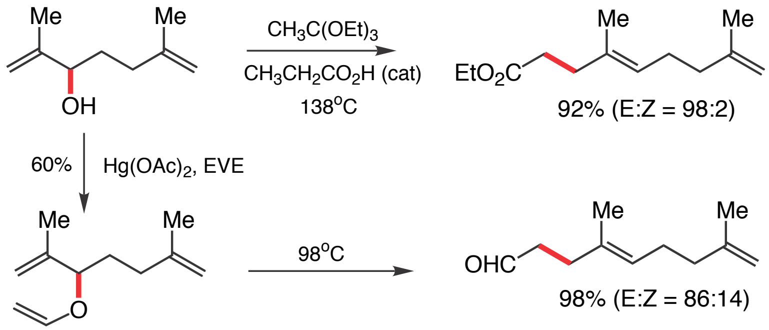
procedure	conditions	X	T, °C	(E):(Z) ratio
Y = Ac, Ireland	LDA, TMSCl	TMSO–	-78→+55	97:3
Y = H, Johnson	$HC(OMe)_3, H^+$	MeO–	130	94:6
Y = H, Eschenmoser	$MeC(OMe)_2NMe_2$	Me_2N–	80	97.5:2.5

Johnson Orthoester Claisen

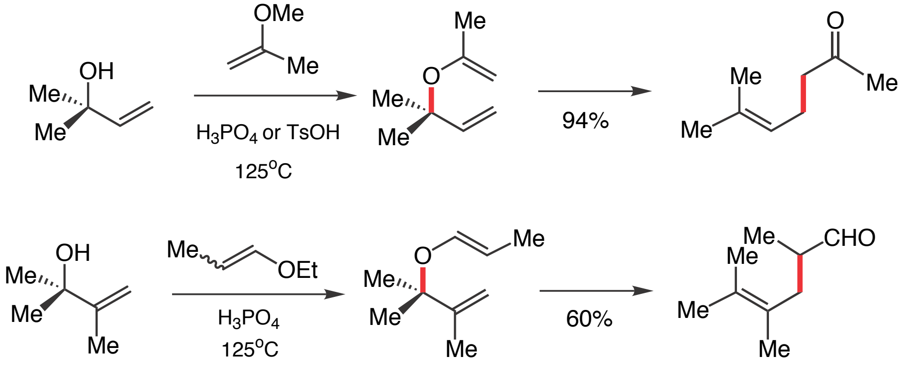
- Lead paper: Johnson, Faulkner, Peterson, *JACS* **1970**, *92*, 741



- Compare the two variants:



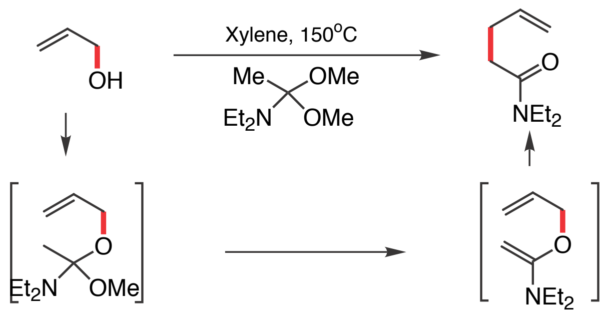
The Saucy Marbet Alternative

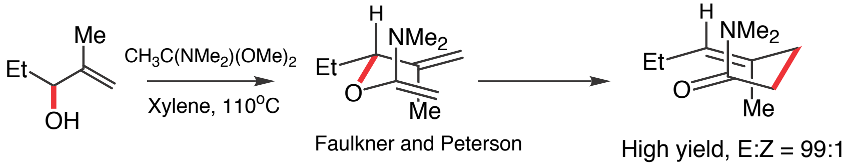


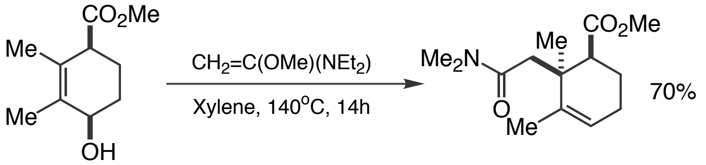
Saucy, Marbet, *Helv. Chim. Acta* **1967**, *50*, 2091,2095

Eschenmoser-Claisen

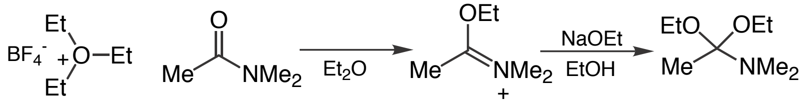
Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425; *Helv. Chim.Acta* **1969**, *52*, 1030.



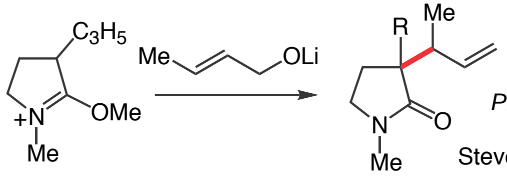




- Synthesis of Amide Acetals

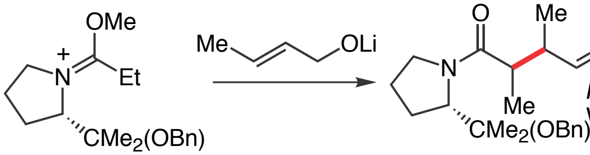


- Reactions to ponder:



diastereoselection 6:1
Predict the major diastereomer

Stevenson, *Tet. Let.* **1991**, *32*, 4199



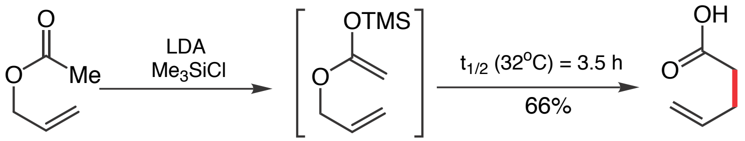
Predict the major diastereomer

Welch, *JACS* **1987**, *109*, 6716

Ireland-Enolate Claisen

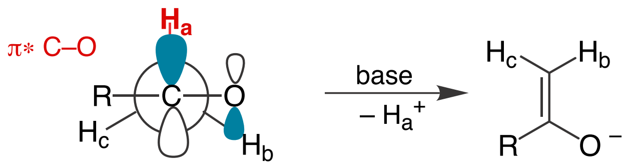
Reviews New Aspects of the Ireland and Re;ated Rearrangements, *Tetrahedron* **2002**, *58*, 2905–2928 **(handout)**

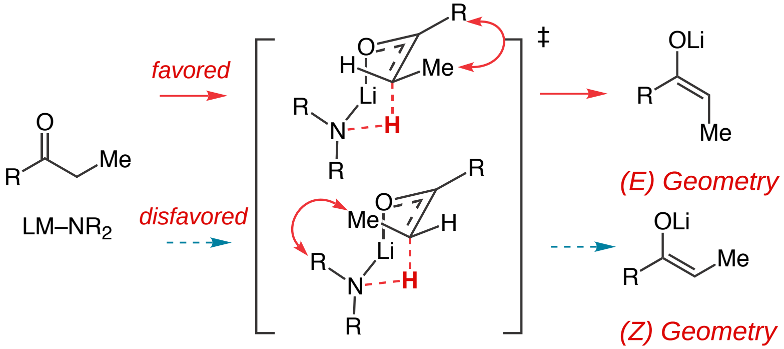
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868



Enolization: Amide Bases & Ireland Enollization Model

Stereoelectronic Requirements: α-C-H bond must be able to overlap with π* C–O

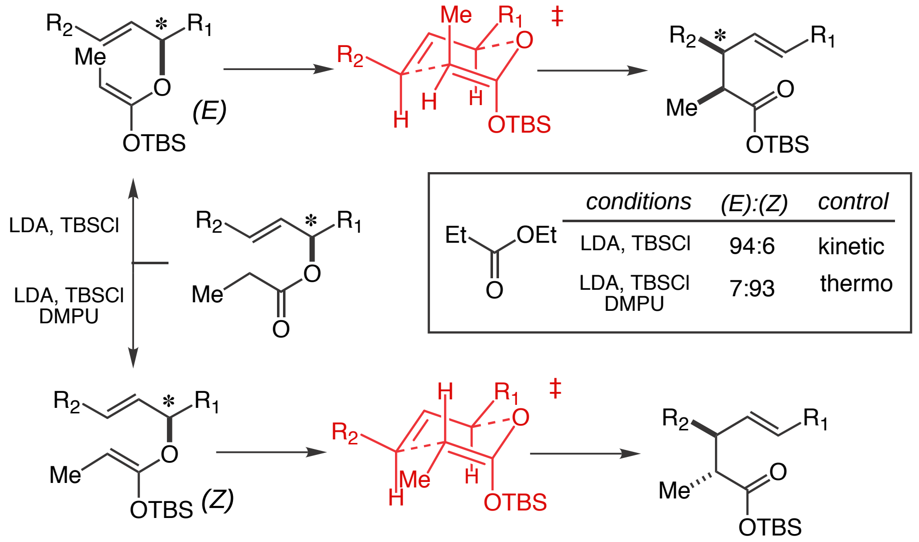




The Ireland Model (*JACS* **1976**, *98*, 2868); *Narula, Tetrahedron Lett.* **1981**, *22*, 4119; more recent study: Ireland, *JOC* **1991**, *56*, 650

For a recent study on the effect of amide base structure on (E)/(Z) selectivity in the cont3ext of the Ireland enolization model see: *JOC* **1997**, *62*, 7516.

Substituted enolates afford an additional stereocenter

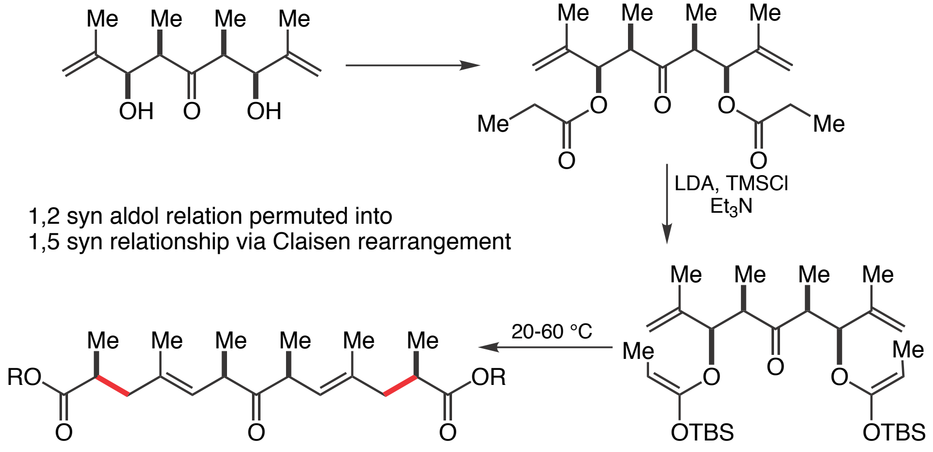


conditions	(E):(Z)	control
LDA, TBSCl	94:6	kinetic
LDA, TBSCl DMPU	7:93	thermo

key study: Ireland, *JOC* **1991**, *56*, 650 and earlier cited papers

Double Claisen Rearrangements are also possible

Paterson, *Tet Lett* **1991**, *32*, 7601

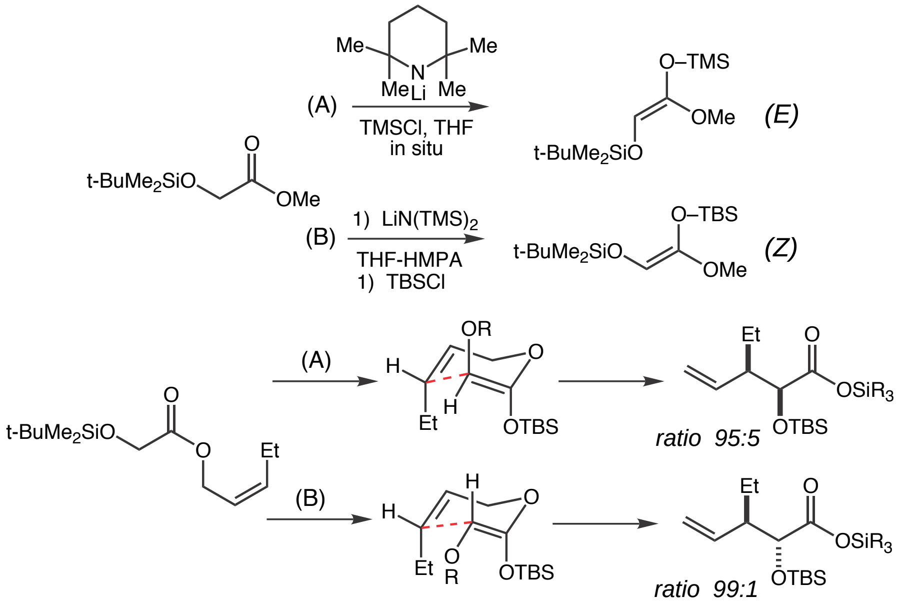


1,2 syn aldol relation permuted into
1,5 syn relationship via Claisen rearrangement

63% yield (diastereoselection 86%)

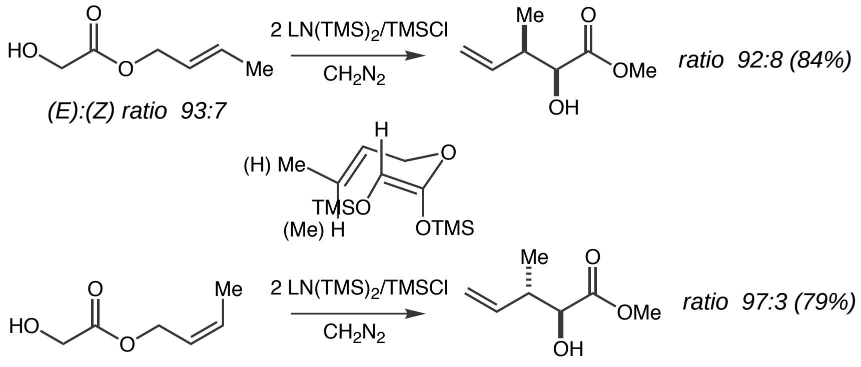
Recent studies on controlling enolization condiltions have apeared

Yamamoto, *JOC* **1993**, *58*, 5301



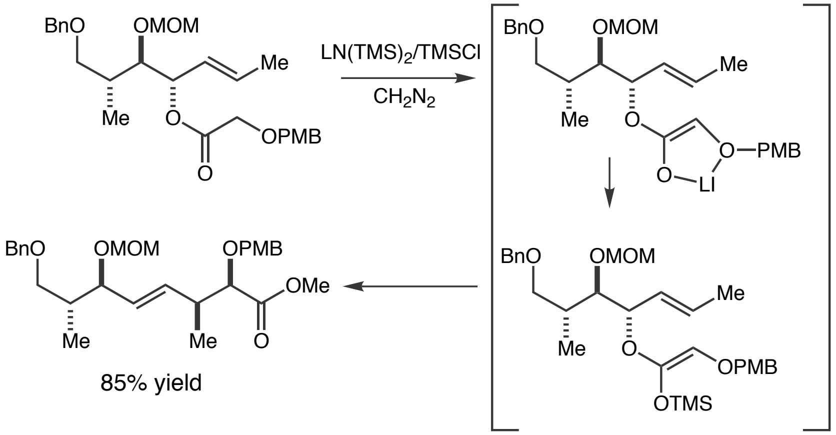
Chelating substituents on α-carbon afford (Z)-enolates

Fujisawa, *Tet Lett* **1983**, *24*, 729



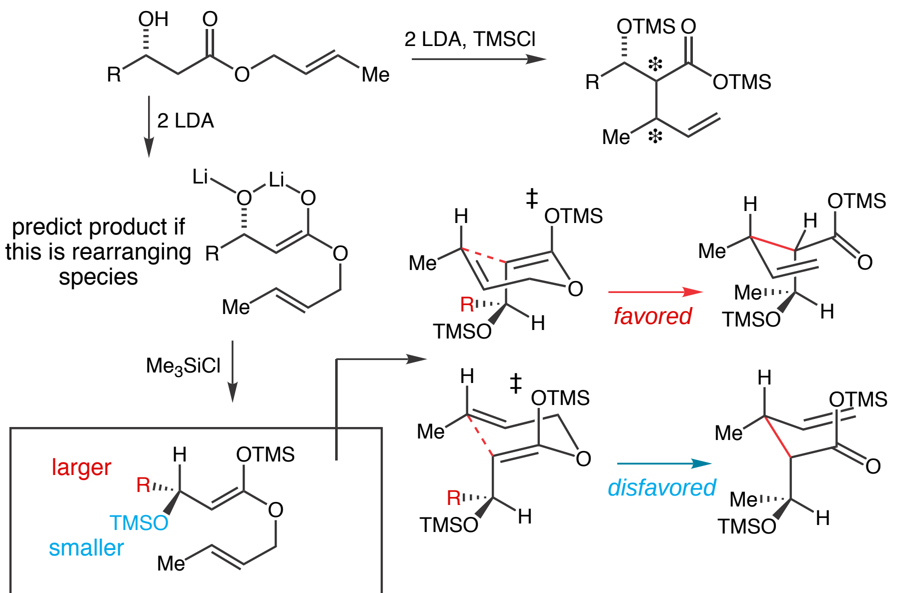
These Chelating substituents can be benzyl ethers as well

Kalmerton, *Tet Lett* **1993**, *34*, 1103



A Problem to consider

Predict the stereochemical outcome of this reaction

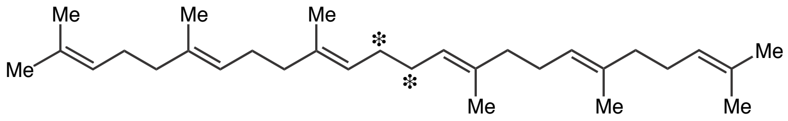


A(1,3) strain orients stereocenter relative size of carbon & oxygen substituents dictate relative face selectivity

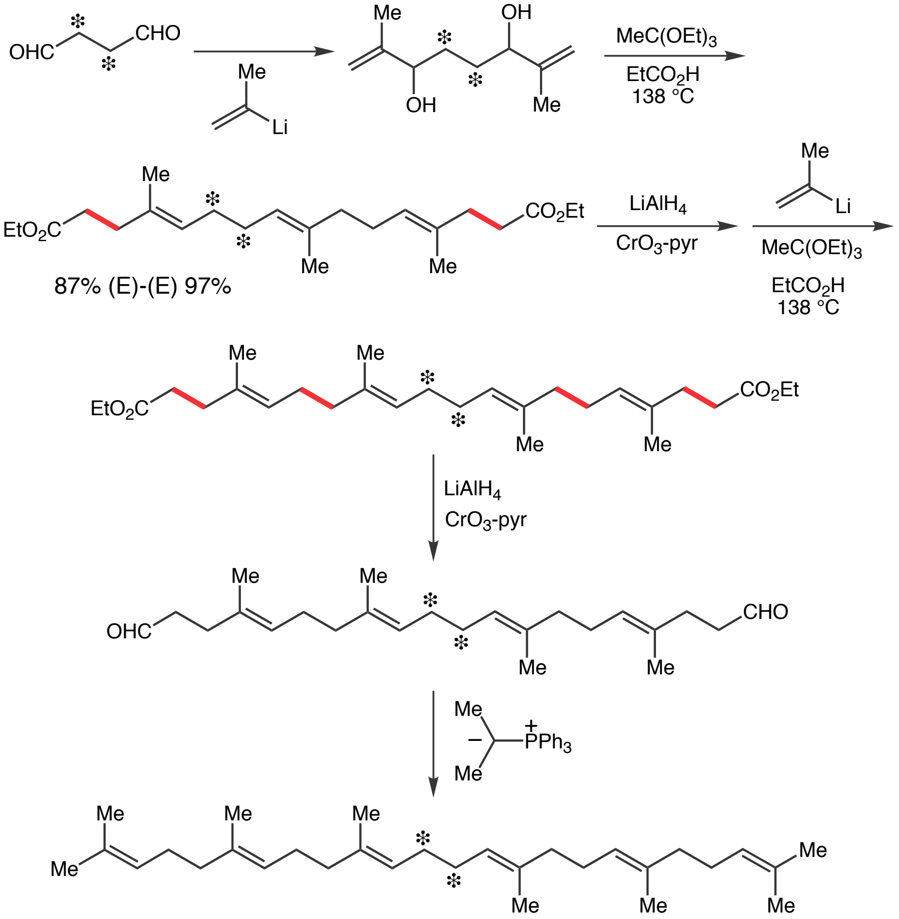
Kurth, *JOC* **1985**, *50*, 1840

Applications of the Claisen Rearrangement

Johnson Squalene Synthesis: JACS 1970, 92, 741

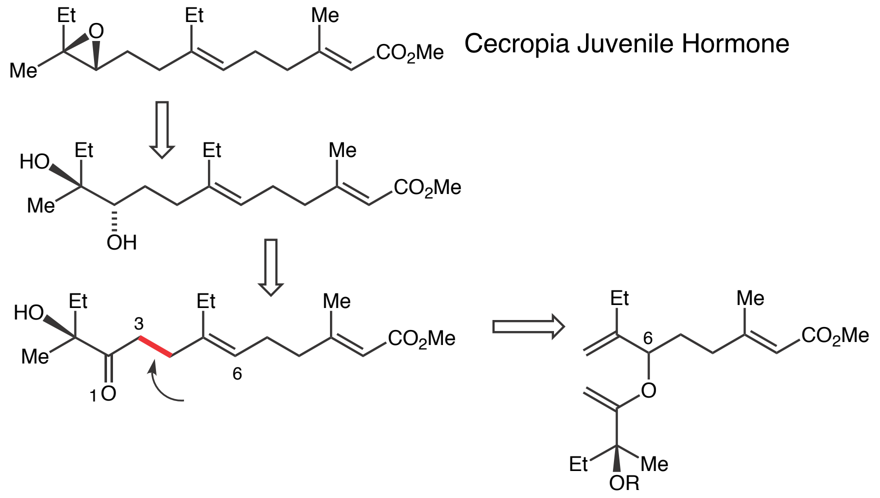


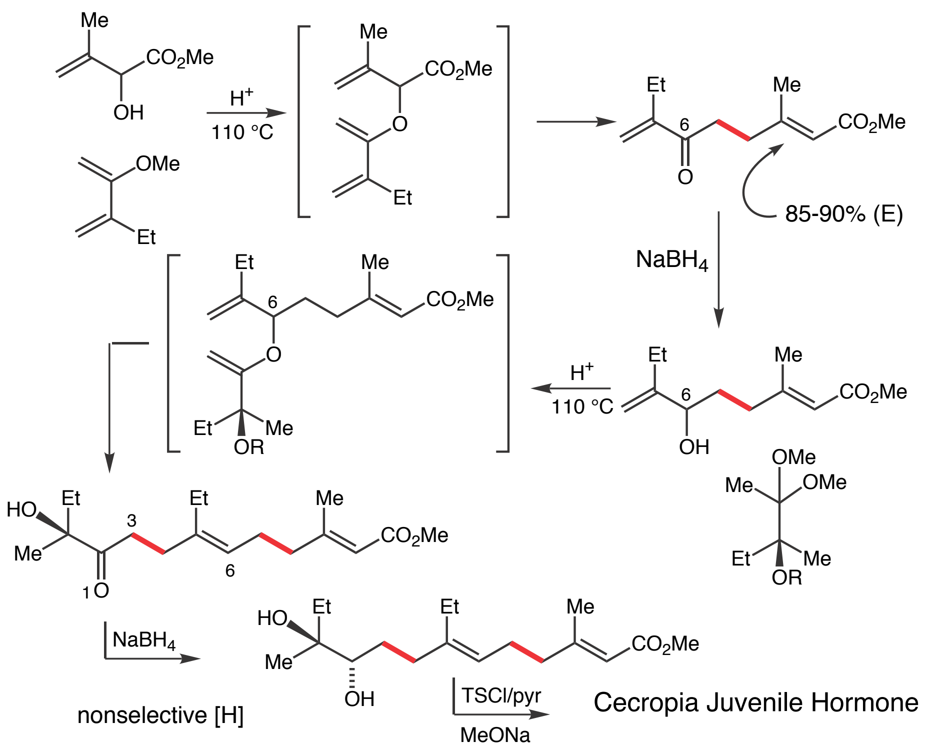
Observations: Molecule contains an obvious symmetry plane
The trisubstituted C=C's are the issue



Isomeric purity is Ca 95%

Faulkner Juvenile Hormone Synthesis: JACS 1973, 95, 553

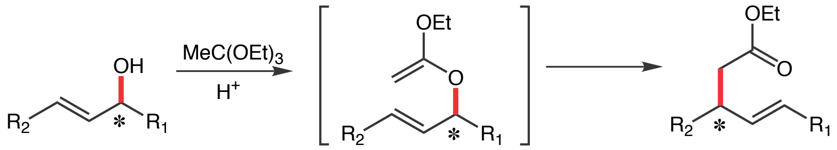




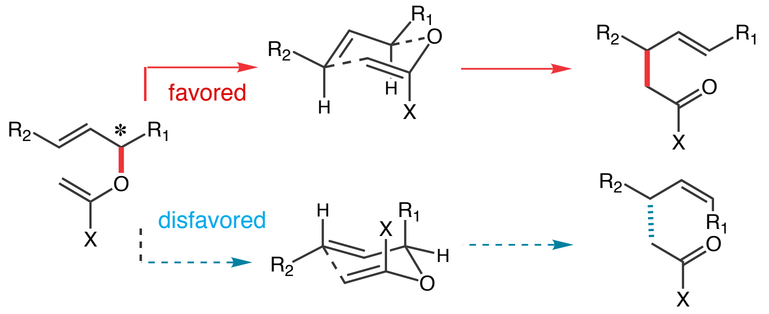
Claisen Rearrangement & Chirality Transfer

Chirality transfer via the Claisen rxn is an integral aspect of the general utility of process

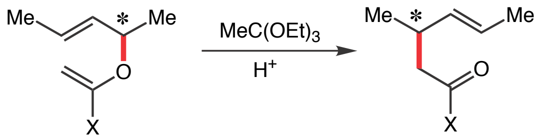
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)



Such chirality permutation processes are only as stereoselective as the energy difference between diastereomeric chair transiltion states:

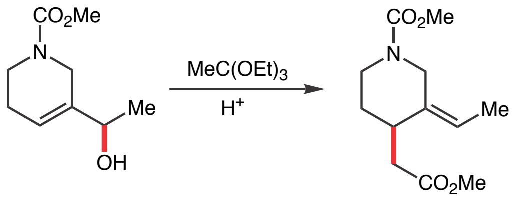


Note that chirality transfer is coupled to olefin geometry in product. Prior arguments (Faulkner) imply that the X substituent will play significant role in promoting selectivity.



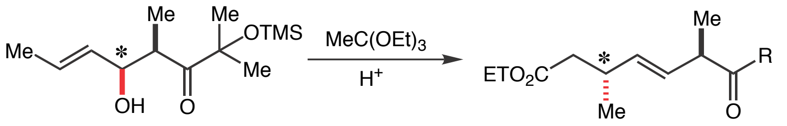
ee > 90%
(E)-selection > 90%

R. K. Hill
JOC **1972**, *37*, 3737



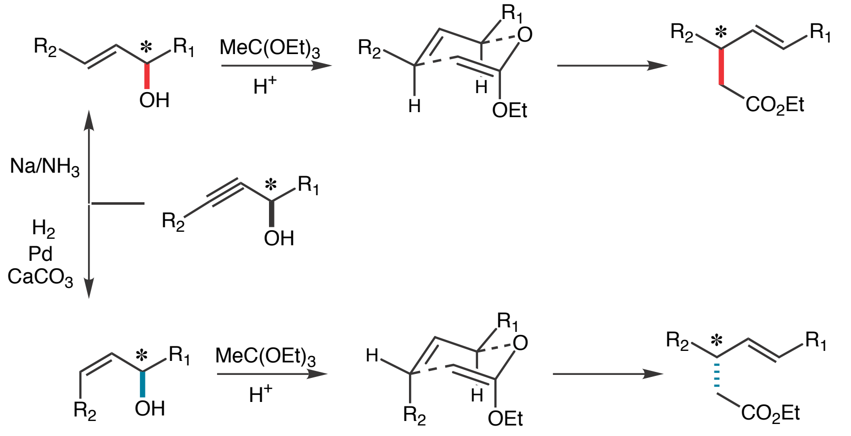
68% enantiomerically pure

Uskokovic,
JACS **1979**, *101*, 6742



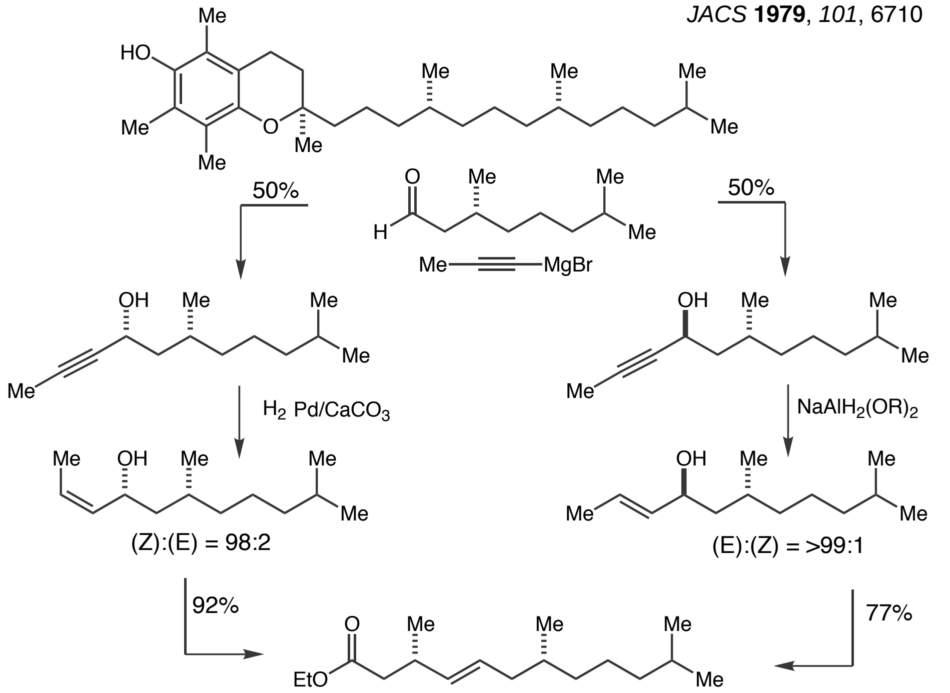
Heathcock
JOC **1988**, *53*, 1922

Sense of Asymmetric induction may be controlled by olefin geometry



Since stereoselection in reduction of acetylenes is >98%, either product accessible

tocopherol (Vitamin E) Cohen *JOC* **1976**, *41*, 3497
JACS **1979**, *101*, 6710



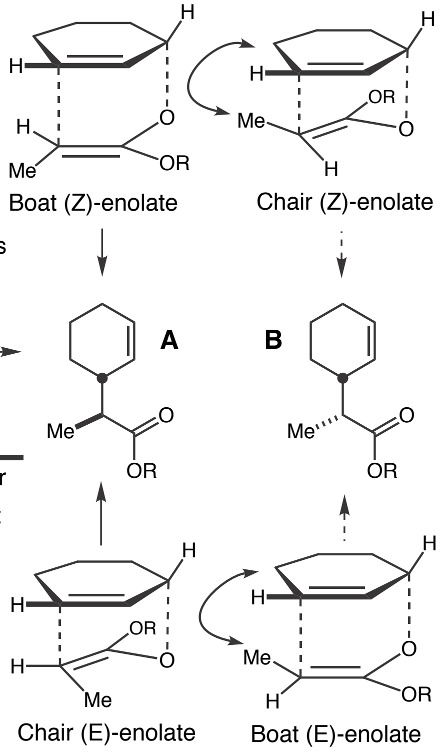
diastereoselection ~ 99% from both routes

Boat transition states more accessible in Claisen than in Cope rearrangements

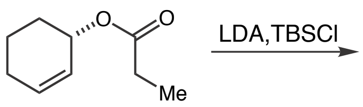
- A case where the chair-boat preference depends on enol geometry

Factors controlling diastereoselection
Enolate geometry
Chair vs Boat transition states

Bartlett, *JOC* **1981**, *46*, 3896
Ireland, *JACS* **1991**, *56*, 3572



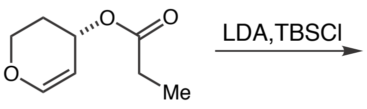
Ireland study supports Bartlett's conclusions

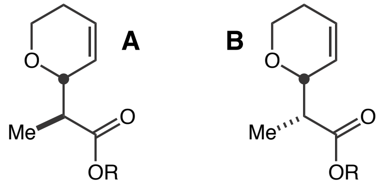


conditions	(E):(Z)	A:B	TS
LDA,THF	83:17	84:16	(E)-chair
LDA,THF DMPU	04:96	72:28	(Z)-boat

Boat geometies can be favored in these and related systems

- In this case the boat geometry is preferred from either enol geometry

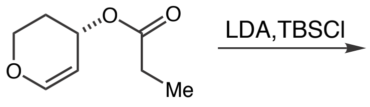


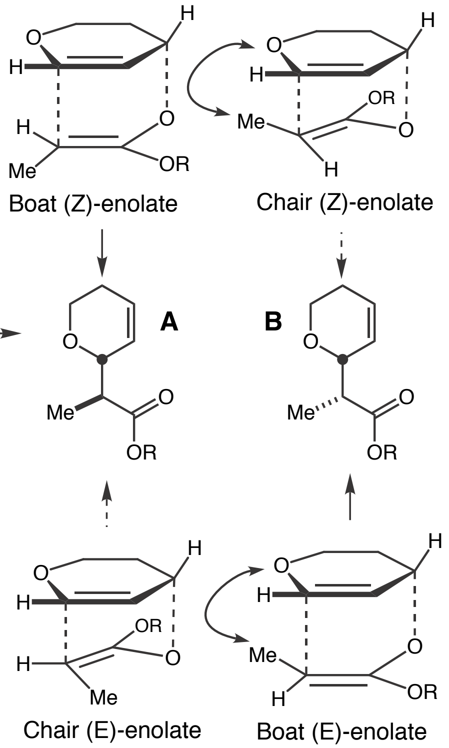


conditions	A:B	TS
LDA,THF	29:71	(E)-boat
LDA,THF DMPU	86:14	(Z)-boat

- The analysis:

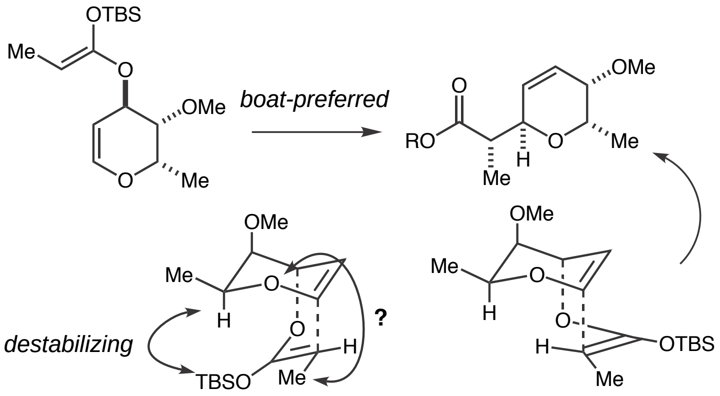
Ireland, *JACS* **1991**, *56*, 3572





conditions	A:B	TS
LDA,THF	29:71	(E)-boat
LDA,THF DMPU	86:14	(Z)-boat

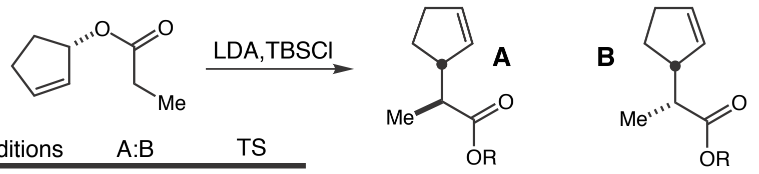
- A further example:



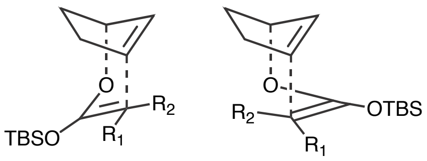
It appears that both of the indicated interactions contribute to the destabilization of chair geometry

Claisen Rearrangement & Chirality Transfer

- In this case the chair geometry is preferred from either enol geometry

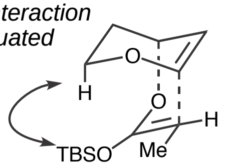


conditions	A:B	TS
LDA,THF	75:25	(E)-chair
LDA,THF DMPU	40:60	(Z)-chair

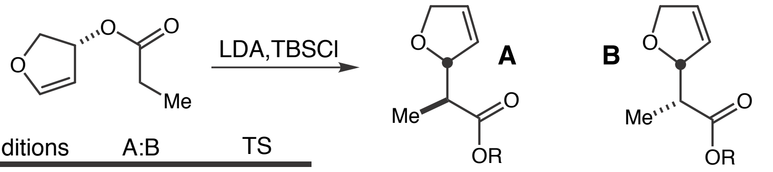


favored *disfavored*

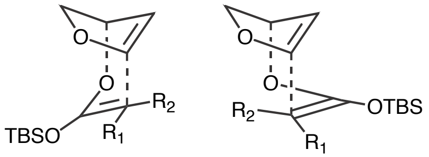
This destabilizing interaction has been attenuated



- In this case the boat geometry is preferred from either enol geometry

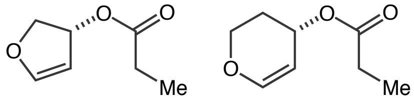


conditions	A:B	TS
LDA,THF	43:57	(E)-boat
LDA,THF DMPU	80:20	(Z)-boat

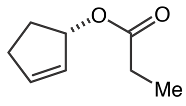


disfavored *favored*

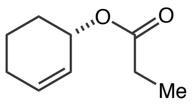
- Summary:



boat-preferred TS from either geometry

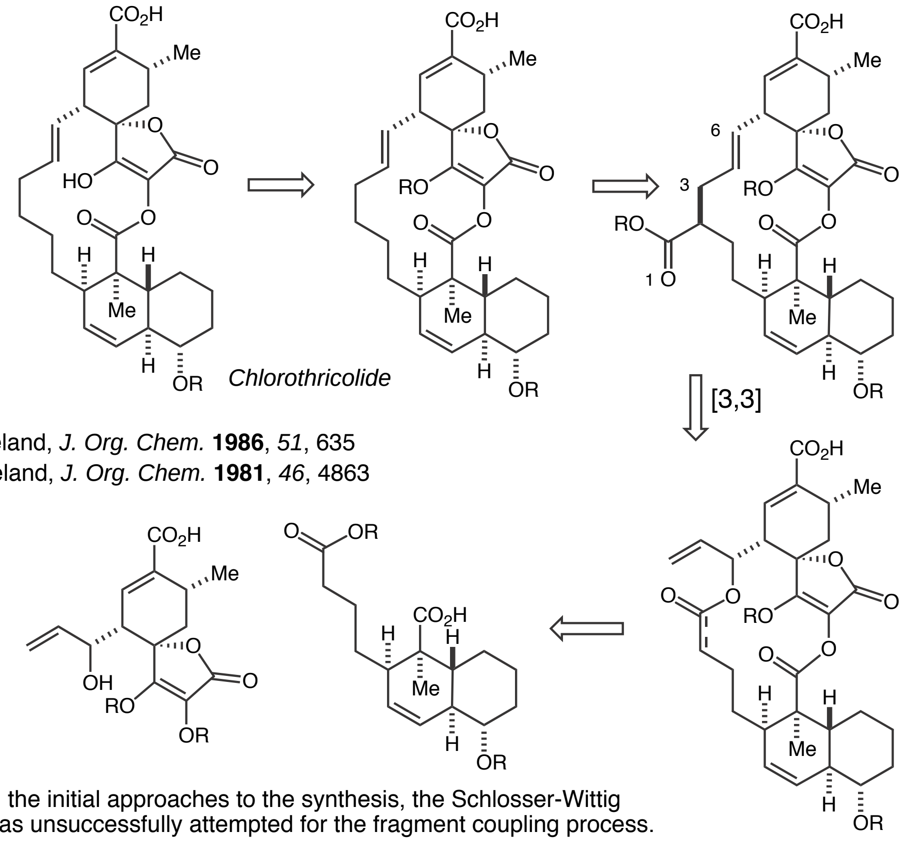


chair-preferred TS from either geometry



boat/chair TS dependant on enol geometry

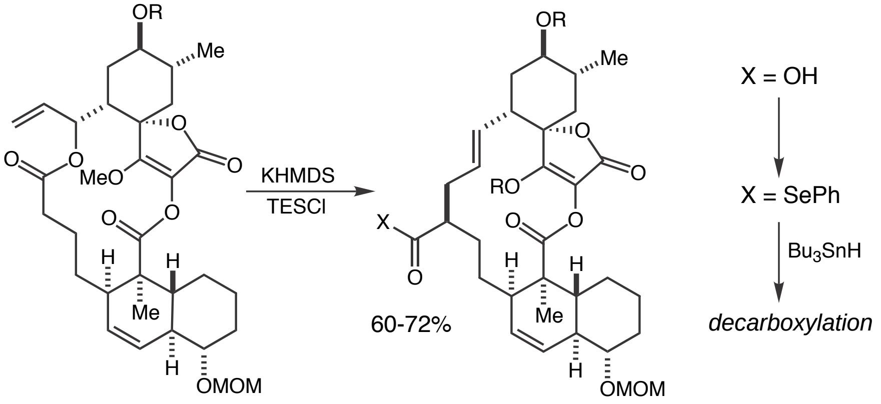
The Claisen Rearrangement has been used in fragment coupling



Chlorothricolide

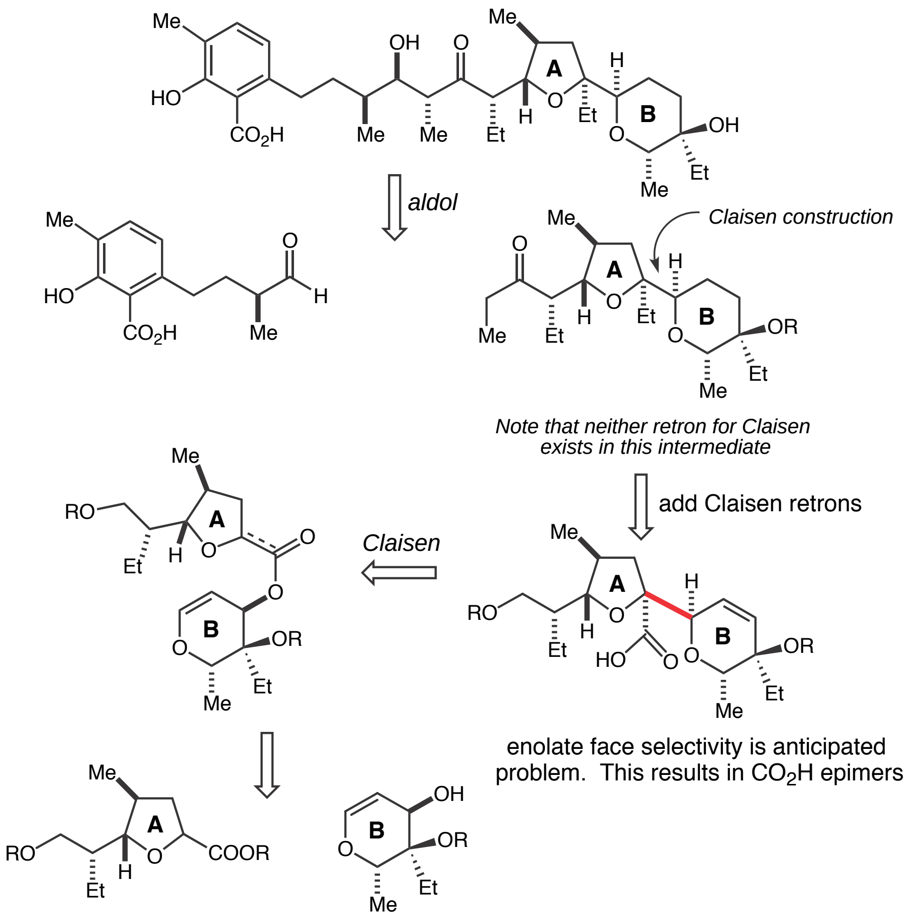
Ireland, *J. Org. Chem.* **1986**, *51*, 635
Ireland, *J. Org. Chem.* **1981**, *46*, 4863

In the initial approaches to the synthesis, the Schlosser-Wittig was unsuccessfully attempted for the fragment coupling process.



key paper for decarboxylation: Ireland, *JACS* **1985**, *107*, 3285

The Ireland lasalocid synthesis: JACS **1983**, *105,* 1988



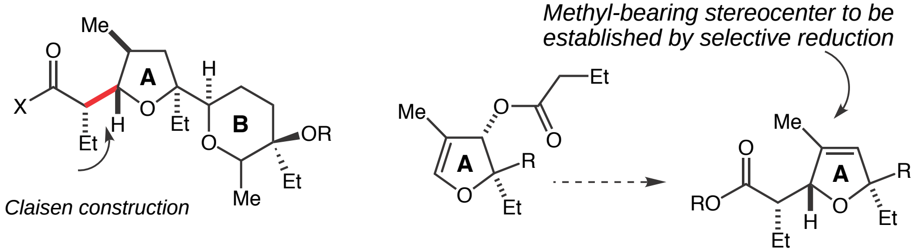
Claisen construction

Note that neither retron for Claisen exists in this intermediate

add Claisen retrons

enolate face selectivity is anticipated problem. This results in CO$_2$H epimers

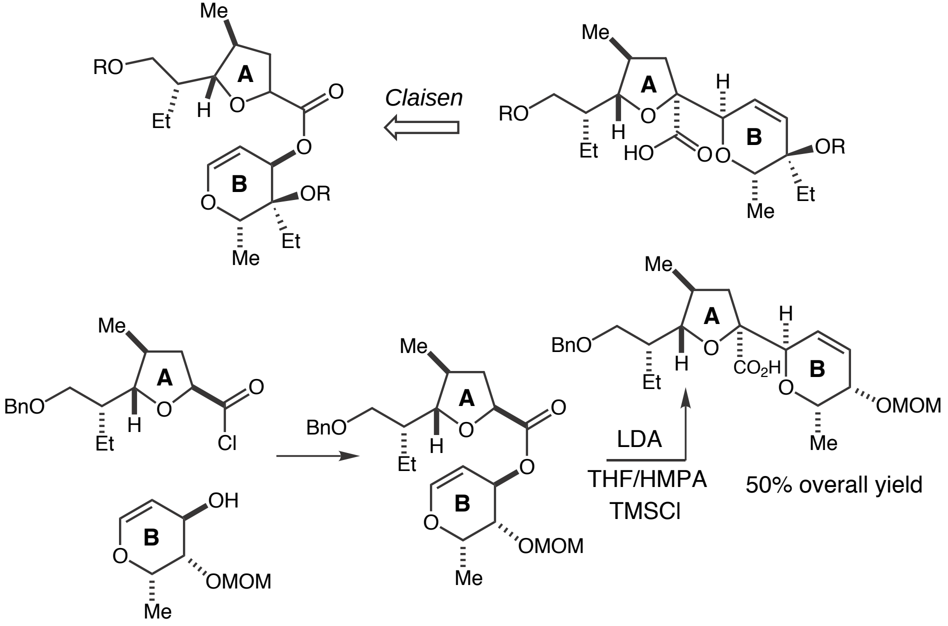
- Here is another potential Claisen construction



Claisen construction

Methyl-bearing stereocenter to be established by selective reduction

- The relevant rearrangements:



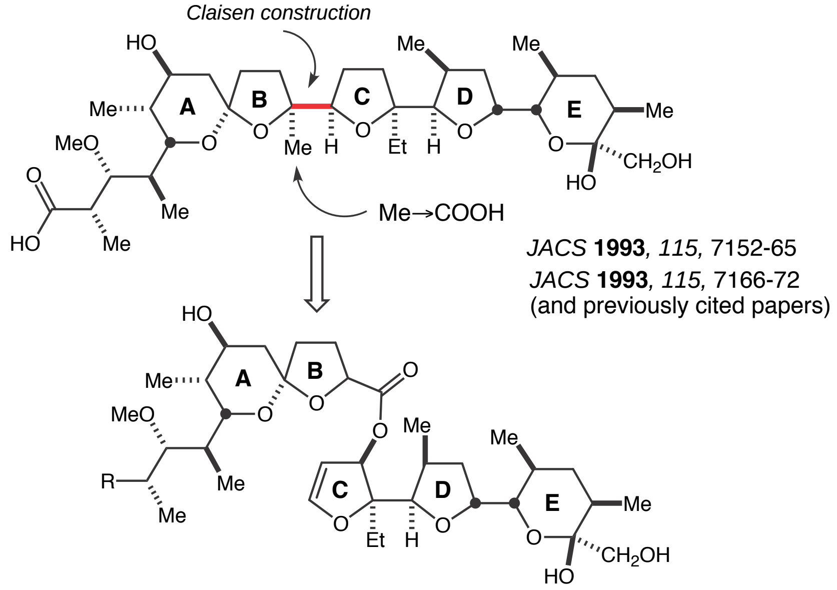
LDA

THF/HMPA

TMSCl

50% overall yield

The Ireland monensin synthesis:



Claisen construction

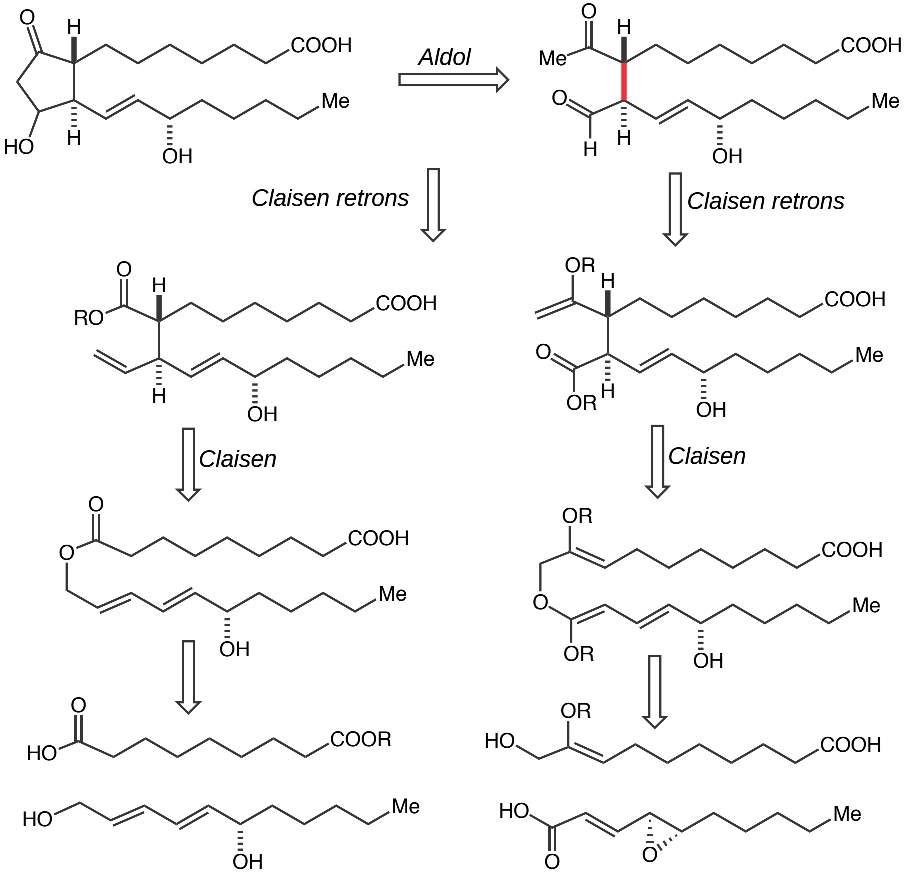
Me→COOH

JACS **1993**, *115*, 7152-65

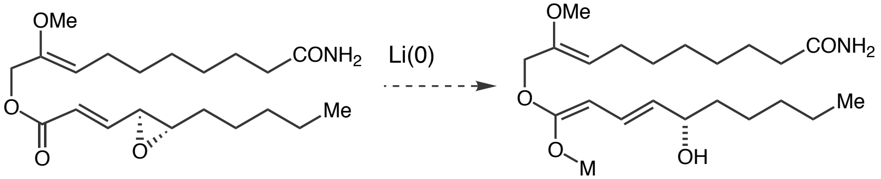
JACS **1993**, *115*, 7166-72

(and previously cited papers)

Consider the prostaglandin nucleus

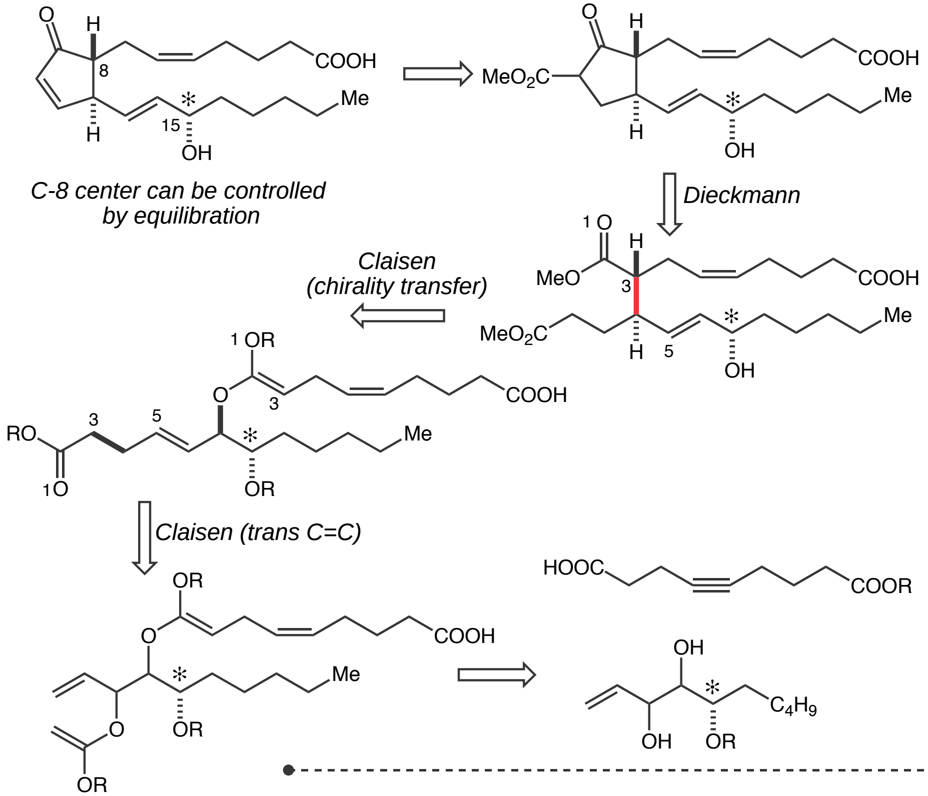


- Unrealized plan to generate the required enolate

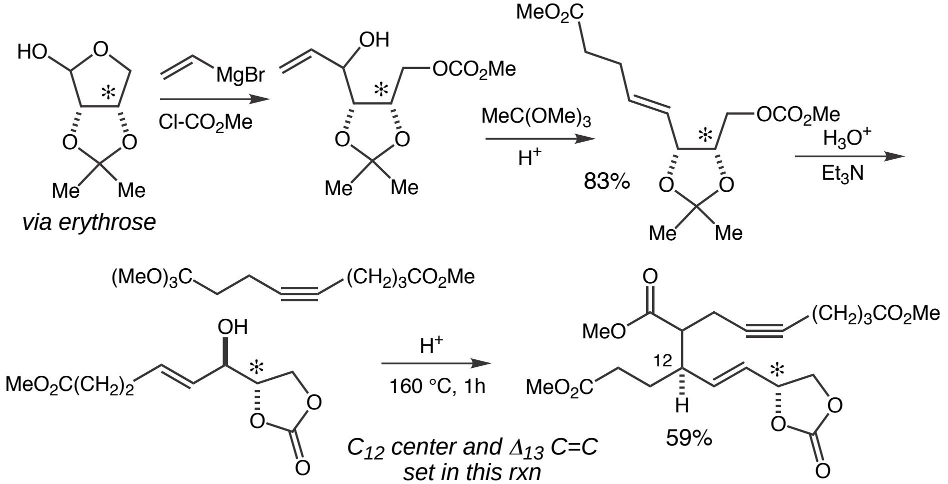


An Application PGA$_1$: Ireland *JOC* **1976**, *41*, 986; *Aldrichimica Acta* **1988**, *21*, 59

Prostaglandin A$_2$ Synthesis, G. Stork, JACS **1976**, *98*, 1583



C-8 center can be controlled by equilibration

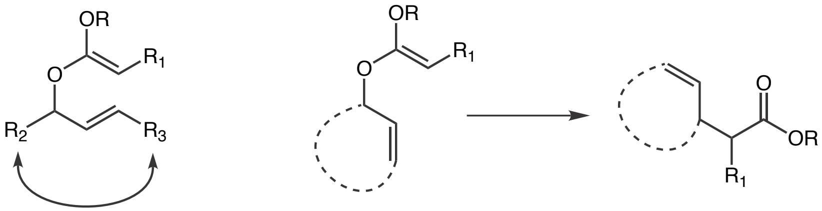


via erythrose

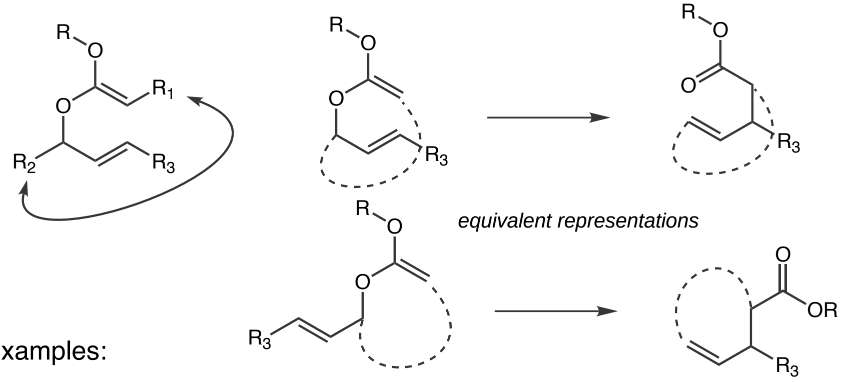
C$_{12}$ center and Δ$_{13}$ C=C set in this rxn

Ireland Claisen Rearrangements: Cyclic Enolates

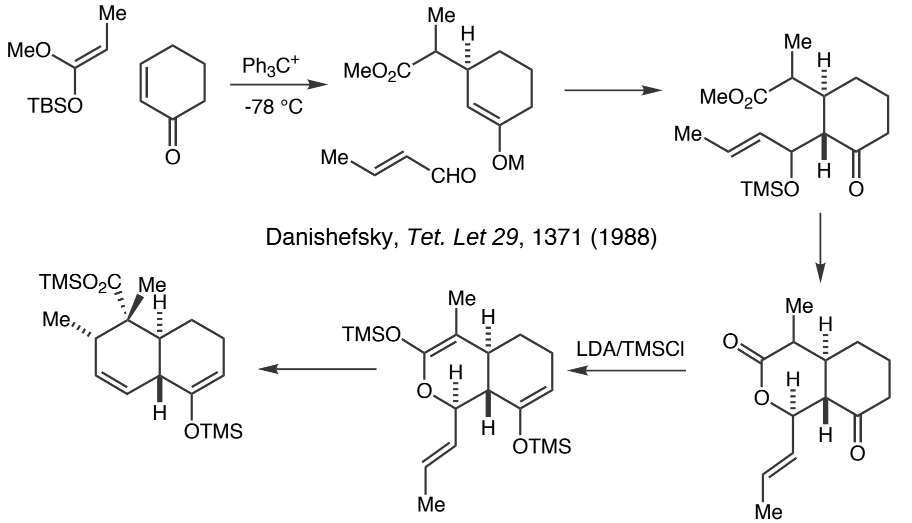
- The previous cases were derived from a connection between R_2 &R_3



- Consider consequence of connecting R_1 &R_2



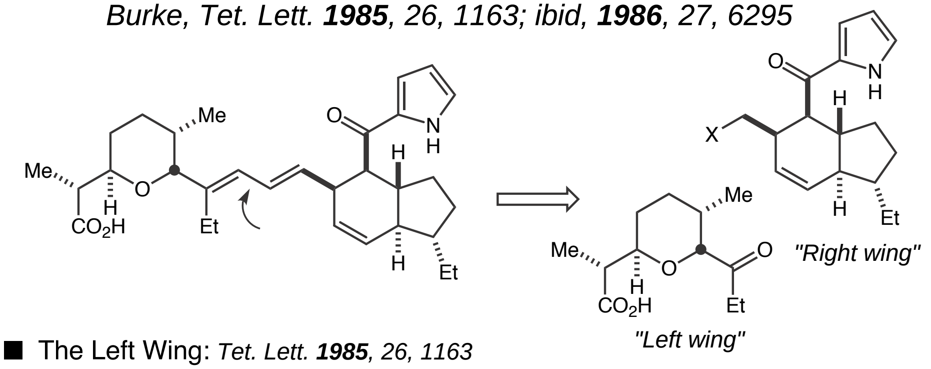
- Examples:



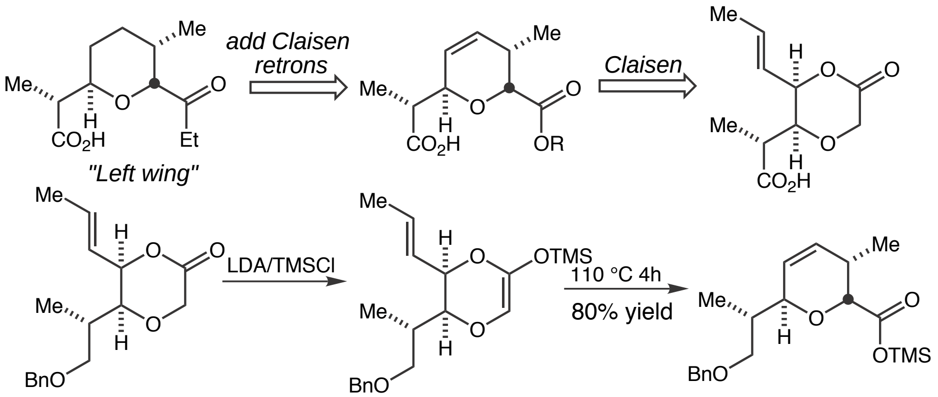
Danishefsky, *Tet. Let 29*, 1371 (1988)

see also Danishefsky, *JACS* **1980**, *102*, 6889, 6891

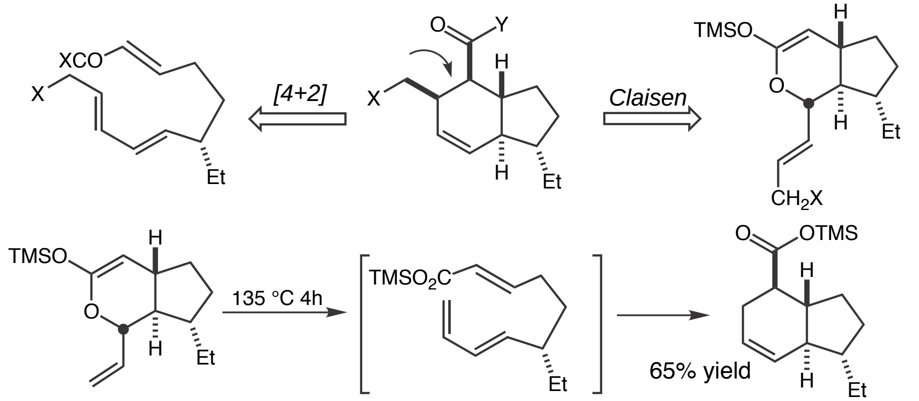
The Indanomycin Synthesis,
Burke, Tet. Lett. ***1985****, 26, 1163; ibid,* ***1986****, 27, 6295*



- The Left Wing: *Tet. Lett.* ***1985****, 26, 1163*



- The Right Wing: *Tet. Lett.* ***1986****, 27, 6295*

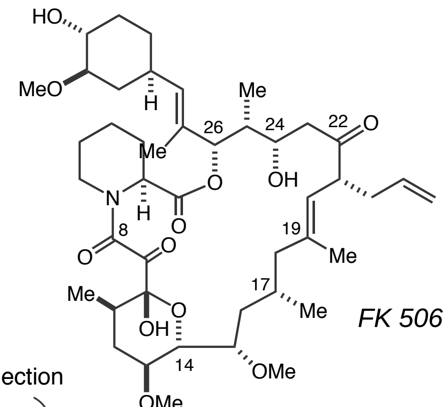


The "apparent" Claisen process is more complicated than anticipated.

Ireland Claisen Rearrangements: Cyclic Enolates

The FK 506 application

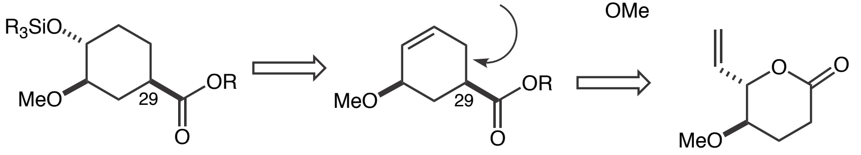
Schreiber Synthesis *JACS* **1990**,*112*, 5583

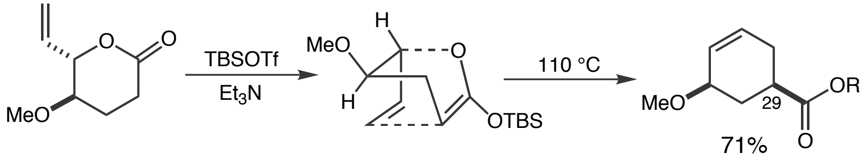


FK 506

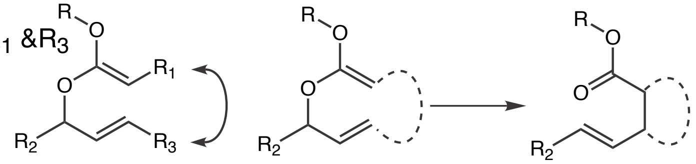
- The Schreiber Route:

Claisen disconnection

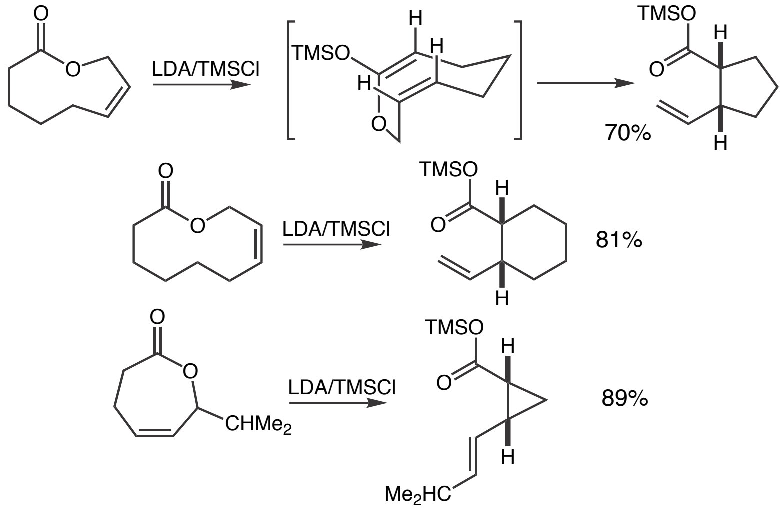




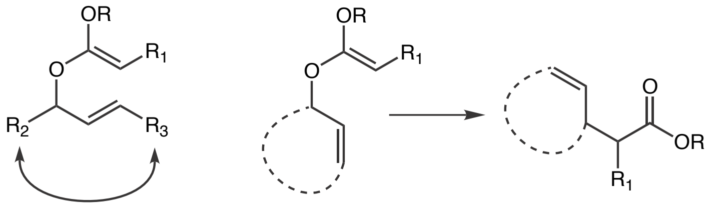
- Now connect R_1 &R_3



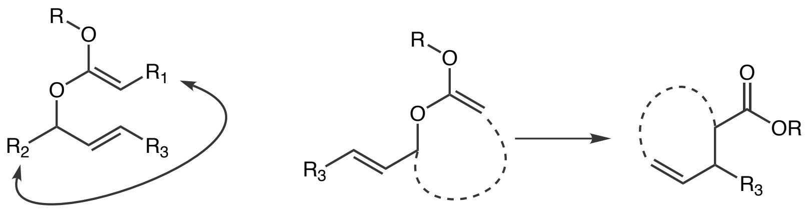
- Examples: Funk, *JACS* **1982**, *104*, 4030



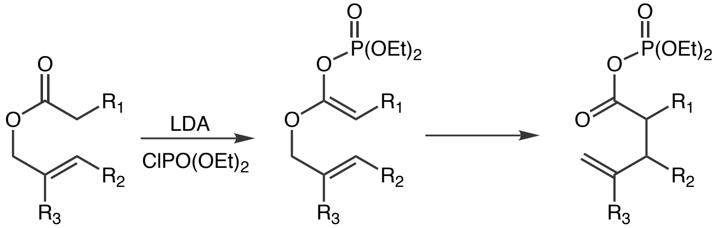
- The previous cases were derived from a connection between R_2 &R_3



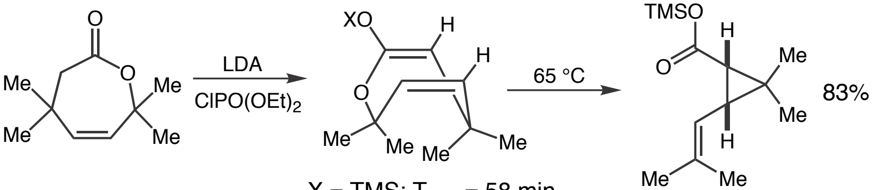
- and R_1 &R_2



- Recent improvments: Funk, *JACS* **1993**, *115*, 8847



chrysanthemic acid application

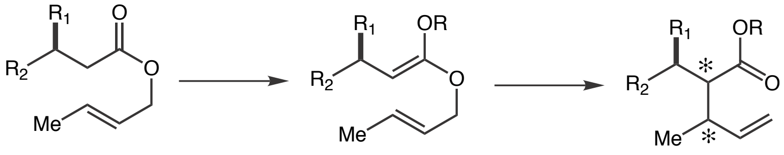


X = TMS; $T_{1/2}$ = 58 min

X = $PO(OEt)_2$; $T_{1/2}$ = 10 min

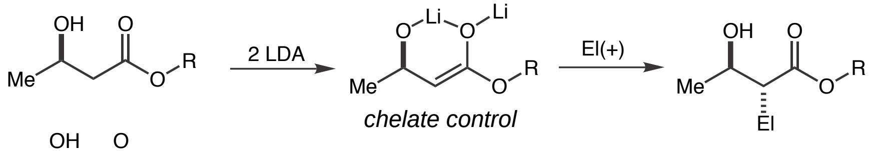
Claisen Rearrangements: Acyclic Cases with Stereoinduction

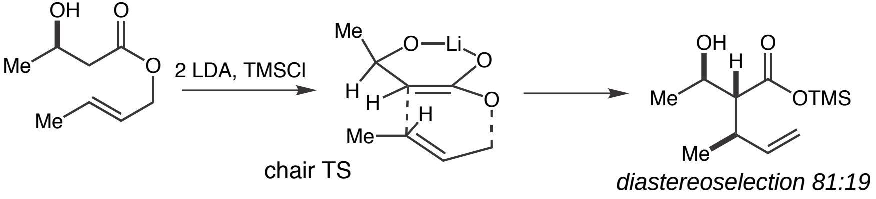
Exocyclic Stereochemical Issues



These rearrangements present many of the same issues which were encountered during our discussion of carbonyl addition with regrad to assymmetric induction.

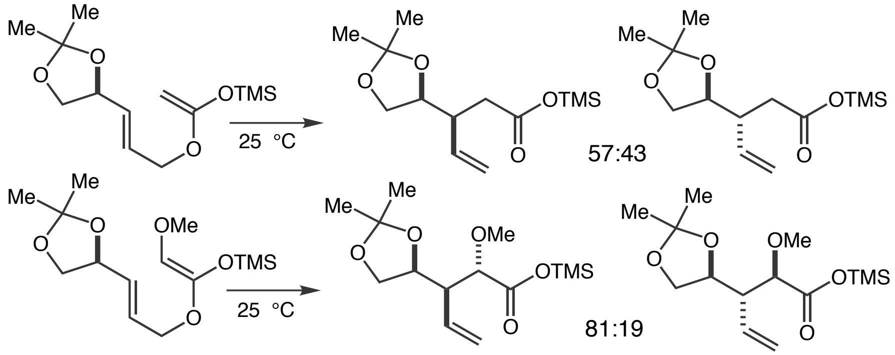
■ Chelate Control: β-Hydroxy ester enolates: Kurth, *JOC* **1985**, *50*, 1840

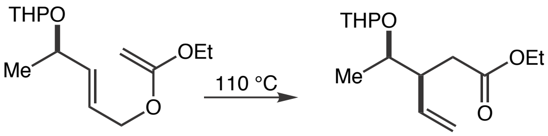




We again see the consequence of chelate-organized asymmetric induction

■ Felkin Control ?: Cha, *Tet. Lett.* **1984**, *25*, 5263

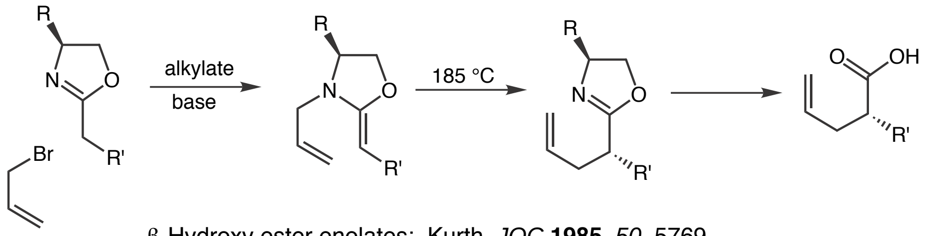




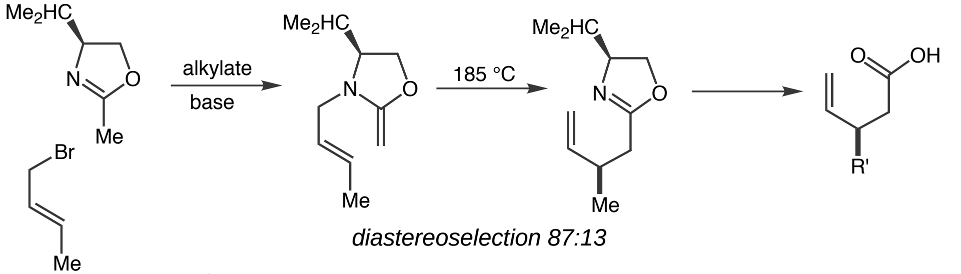
75:25
(Felkin model, RO = large)

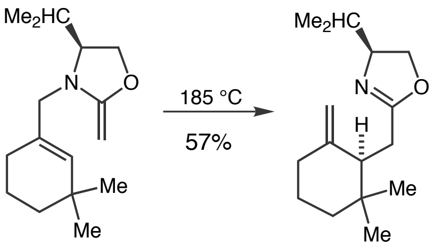
Takano, *Tet. Lett.* **1985**, *26*, 865

N-Allylketene-N-O-Acetals: Kurth, *JACS* **1985**, *107*, 443



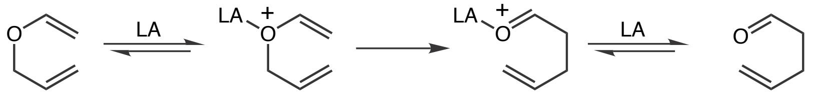
β-Hydroxy ester enolates: Kurth, *JOC* **1985**, *50*, 5769





diastereoselection 94:6

The Claisen Rearrangement is subject to acid catalysis



BF$_3$-HOAc: Bryusova, *J. Gen. Chem. (USSR)* **1941**, *11*, 722

BCl$_3$: Gerrard, *Proc. Chem. Soc.* **1957**, 19;
Schmid, Helv. Chem. Acta 1973. 56, 14

Et$_2$AlCl: Sonnenberg, *J. Org. Chem.* **1970**, *35*, 3166

TiCl$_4$: Mukaiyama, *Chem. Lett.* **1975**, *35*, 1041

(RO)$_2$AlMe: Yamamoto, *JACS.* **1988**, *110*, 7922

(RO)$_2$AlMe: Yamamoto, *Tet. Lett.* **1989**, *30*, 1265

(RO)$_2$AlMe: Yamamoto, *JACS.* **1990**, *112*, 316

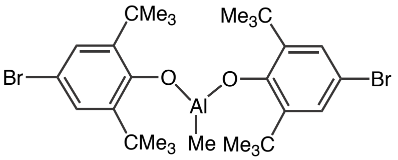
LiClO$_4$: Reetz, *Tetrahedron.* **1993**, *49*, 6025

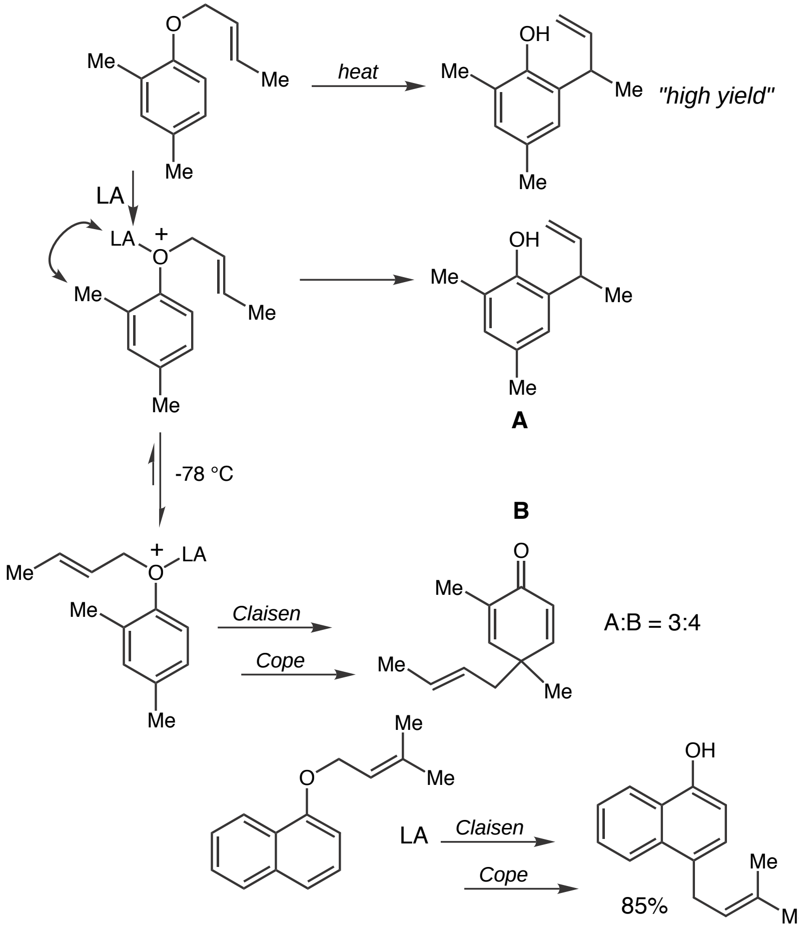
Lewis Acid Catalyzed Claisen Rearrangements

Catalyzed Claisen Rearrangement of Allyl-phenyl Ethers

$(RO)_2AlMe$: Yamamoto, *Tet. Lett.* **1990**, *31*, 377

The Lewis Acid (LA)



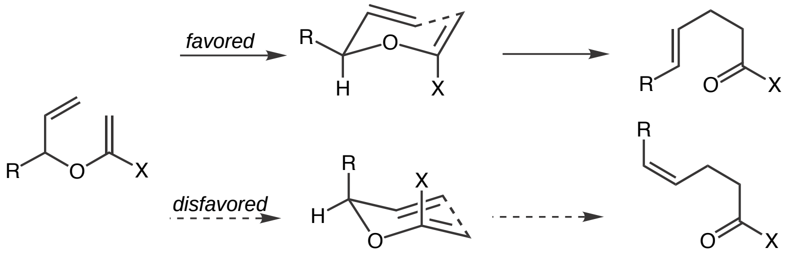


The hindered Lewis acid will alter the partitioning of the Claisen process to the two ortho positions

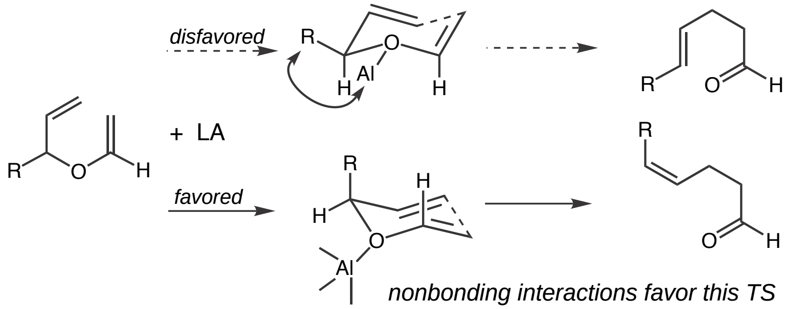
Catalyzed Claisen Rearrangement of Allyl-vinyl Ethers

$(RO)_2AlMe$: Yamamoto, *JACS.* **1990**, *112*, 316

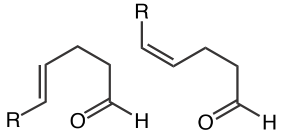
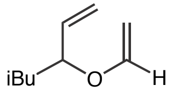
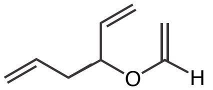
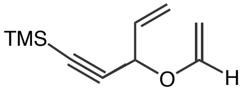
- The thermal process



- The catalyzed process



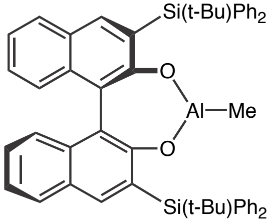
nonbonding interactions favor this TS

		
	43%	19:81
	40%	07:93
	94%	03:97

Chiral Lewis Acid Promoted Claisen Rearrangements

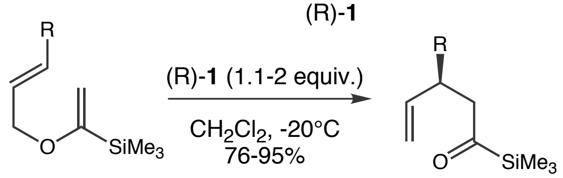
Yamamoto, *JACS.* **1990**, *112*, 7791

Yamamoto, *Tet. Asymmetry* **1991**, *2*, 647-662



(R)-**1**

Note that these reactions are not catalytic

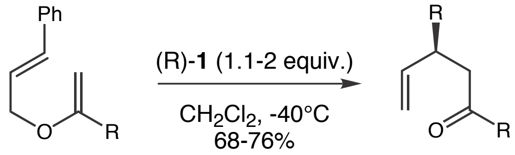


(R)-**1** (1.1-2 equiv.)

CH_2Cl_2, -20°C

76-95%

R	**% ee**
Ph	88%
C_6H_{11}	71%



(R)-**1** (1.1-2 equiv.)

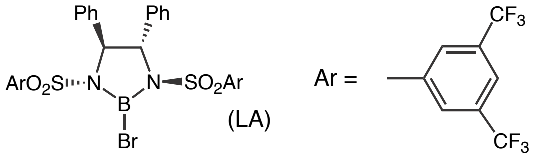
CH_2Cl_2, -40°C

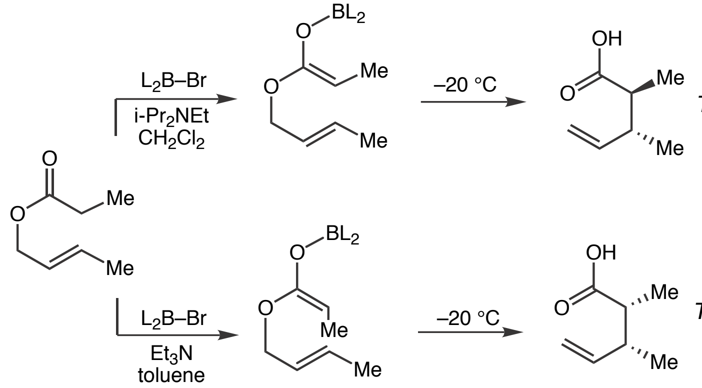
68-76%

R	**% ee**
$SiMe_2Ph$	90%
$GeMe_3$	93%

Enantioselective Claisen Rearrangements: Metal-Centered Chirality

Corey, *JACS.* **1991**, *113*, 4026





Threo: erythro 99:1

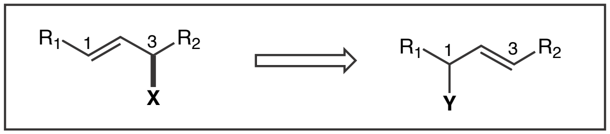
>97% ee (75%)

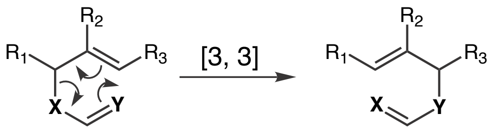
Threo: erythro 10:90

96% ee (65%)

8 cases reported

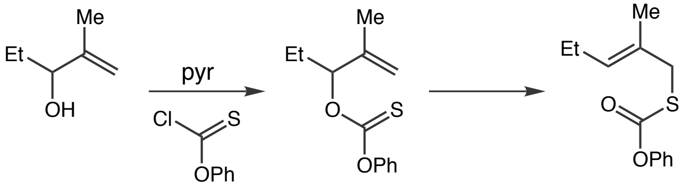
Allylic rearrangements may be included as a subset of other sigmatropic processes:





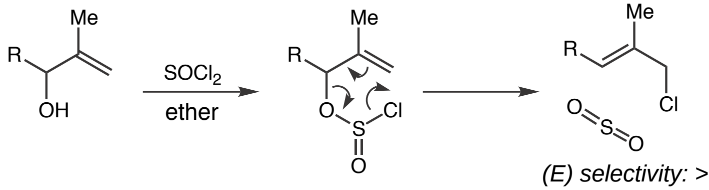
X = C, N, O, S

- ■ X = O; Y = S Faulkner, *Synthesis* **1971** 175 (see pg 183)



(E) selectivity: 96.5%

- ■ A stereochemically related case Johnson, *JACS* **1970** *92*, 735

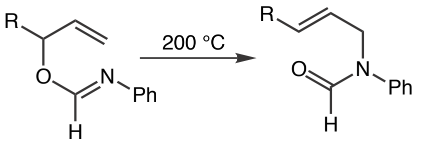


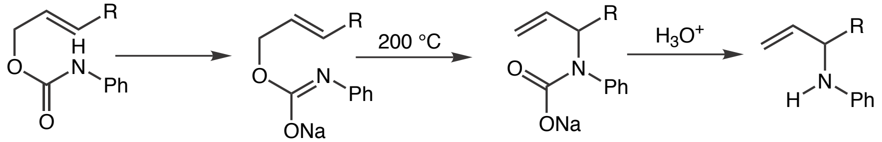
(E) selectivity: >98%

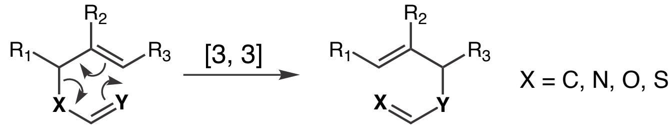
- ■ X = O; Y = N

Roberts, *JACS* **1960** *82*, 1950

Hill, *JOC* **1968** *33*, 1111



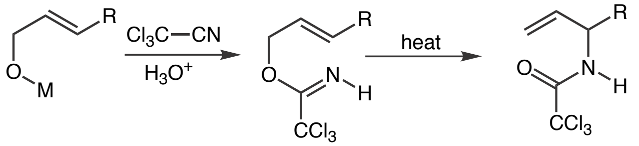




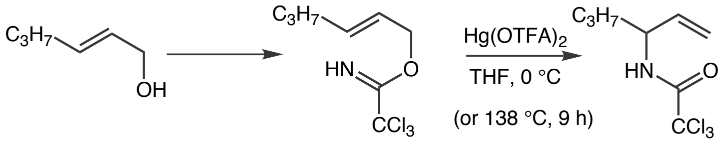
X = C, N, O, S

■ X = O; Y = N:

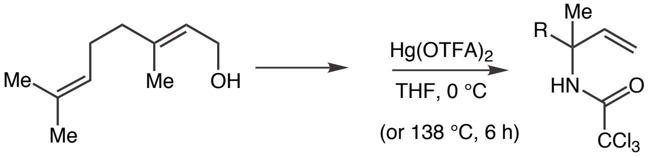
The Trichloroacetimidate Rearrangement, Overman, *JACS* **1974**, *96*, 597



This reaction is also catalyzed by Hg(II) ion

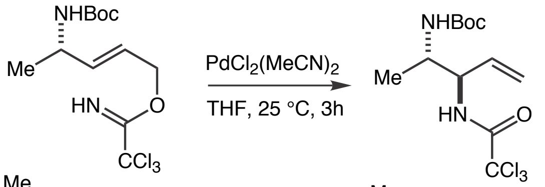


79%



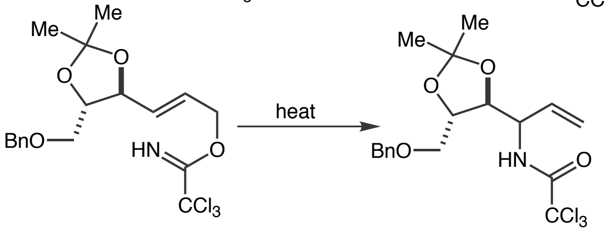
79%

For an excellent review see: Overman, *Angew. Chem. Int. Ed.* **1984**, *23*, 579



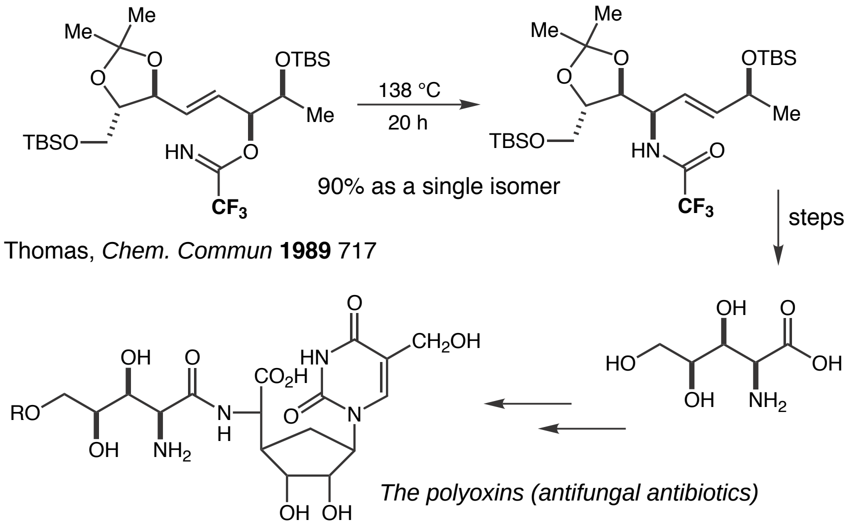
99% anti (45-62%)

Gonda, *Synthesis* **1993** 729



a 1:1 mixture was obtained

Saksena, *JOC* **1986** *51*, 5024



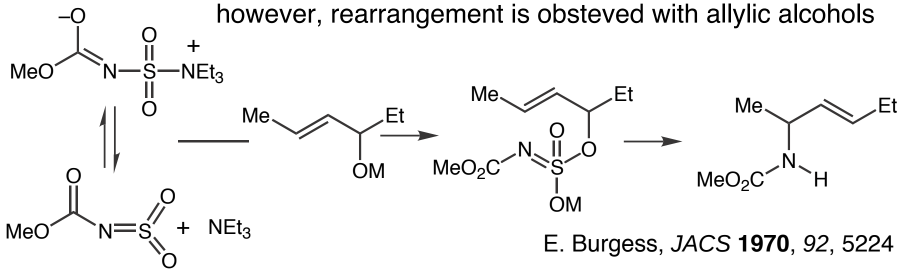
90% as a single isomer

Thomas, *Chem. Commun* **1989** 717

The polyoxins (antifungal antibiotics)

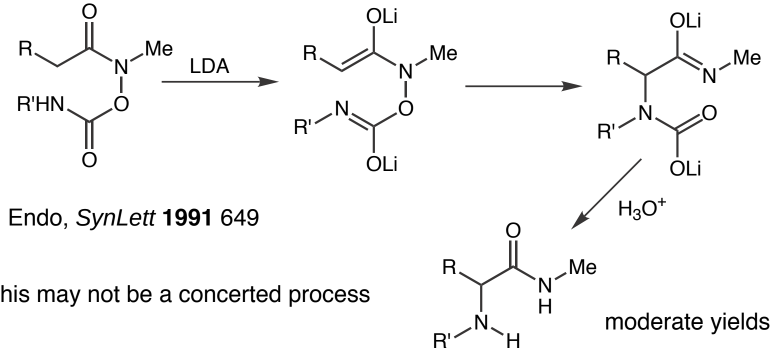
■ The "Burgess Reagent" is normally used for alcohol dehydration

however, rearrangement is obsteved with allylic alcohols



E. Burgess, *JACS* **1970**, *92*, 5224

■ A new approach to the synthesis of α-amino acids



Endo, *SynLett* **1991** 649

This may not be a concerted process

moderate yields

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 16

Cycloaddition Reactions-1

- Cycloadditions: Introduction
- Ketene Cycloadditions
- The Diels-Alder Reaction

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Fleming: Chapter 4
Thermal Pericyclic Reactions

D. A. Evans

Wednesday,
October 22, 2003

The Diels-Alder Cycloaddition Reactions

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(electronic handout)**

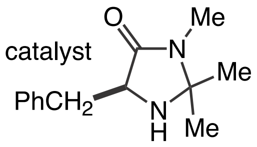
The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, *41*, 1668-1698 **(electronic handout)**

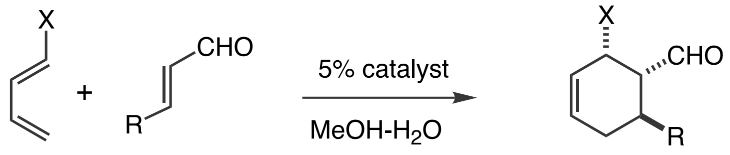
Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, *41*, 1650-1667 **(electronic handout)**

Chemistry and Biology of Biosynthetic Diels–Alder Reactions Emily M. Stocking and Robert M. Williams, *Angew Chem. Int. Ed.* **2003**, *42*, 3078-3115 **(electronic handout)**

Problem of the Day:

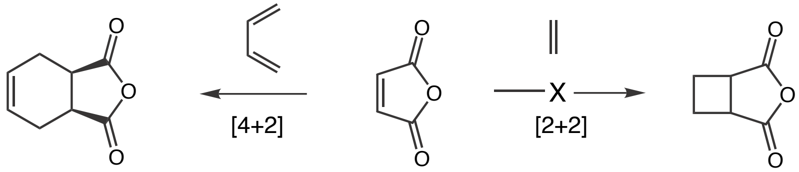
Rationalize the sense of asymmetric induction for this Diels-Alder Reaction reported by MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**



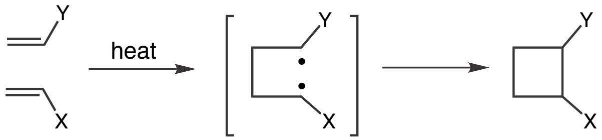


Cycloaddition Reactions-1

Why does maleic anhydride react easily with 1,3-butadiene, but not with ethylene? So what are the "rules"?



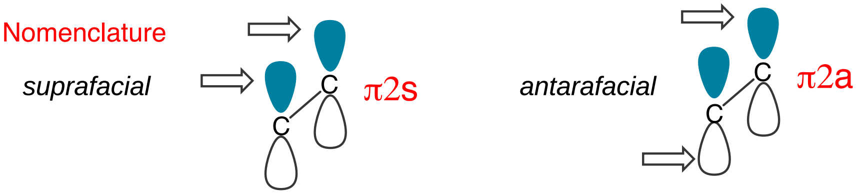
■ The related reaction of 2 ethylenes is nonconcerted: [2 + 2] cycloaddition



■ We also know that the photochemical variant is concerted

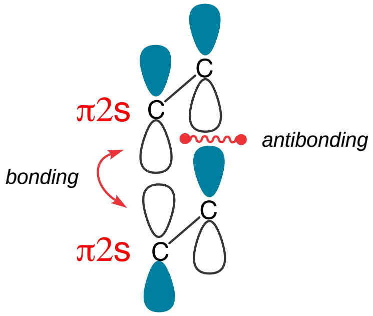
The frontier orbitals of the reacting species must have the proper symmetries

■ Nomenclature

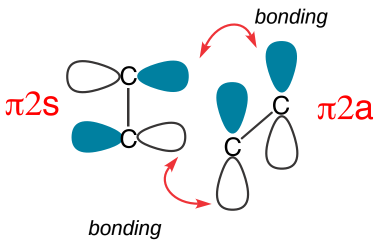


Using this nomenclature, the Diels-Alder reaction is a $\pi 4s + \pi 2s$ cycloaddition

■ Consider [2 + 2] cycloaddition: Thermal activation [$\pi 2s + \pi 2s$]

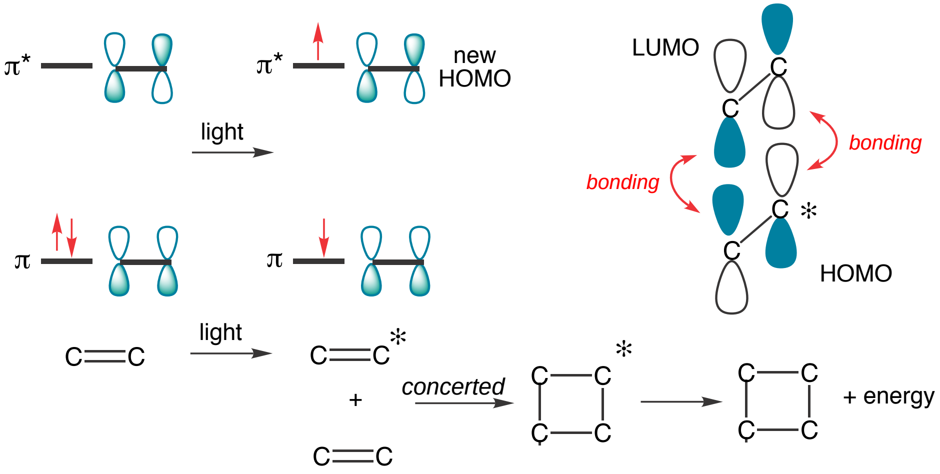


[$\pi 2s + \pi 2s$] "forbidden"

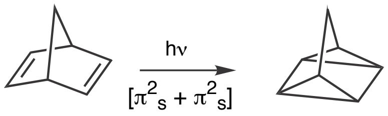


[$\pi 2s + \pi 2a$] "allowed"

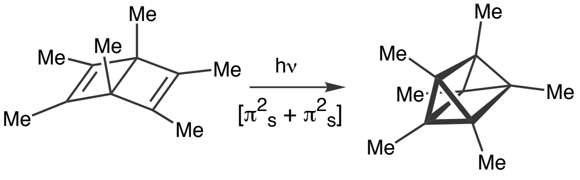
■ Consider [2 + 2] cycloaddition: Photochemical activation [$\pi 2s + \pi 2s$]



[2+2] Cycloaddition - Examples

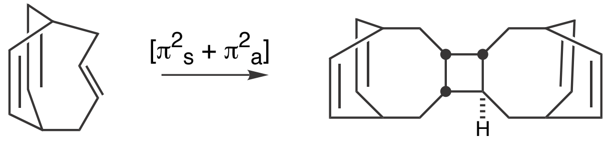


Quadricyclane Dauben, *Tet.* **1961**, *15*, 197.



Dewarbenzene-Derivative Prismane-Der.

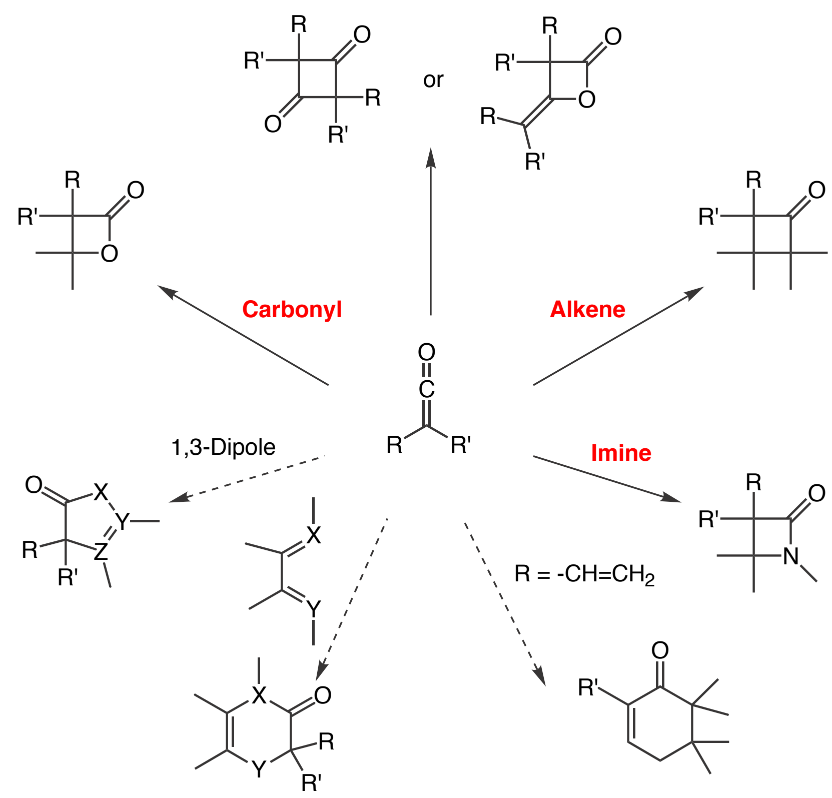
Schäfer, *AC* **1967**, *79*, 54.



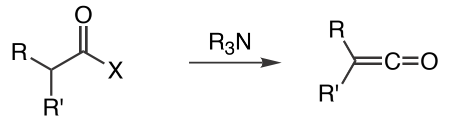
must be antarafical for indicated stereochem

TL **1967**, 4357, 4723.

Summary of Ketene Cycloadditions



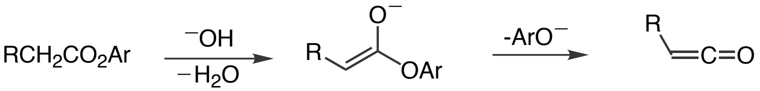
Ketene Preparation

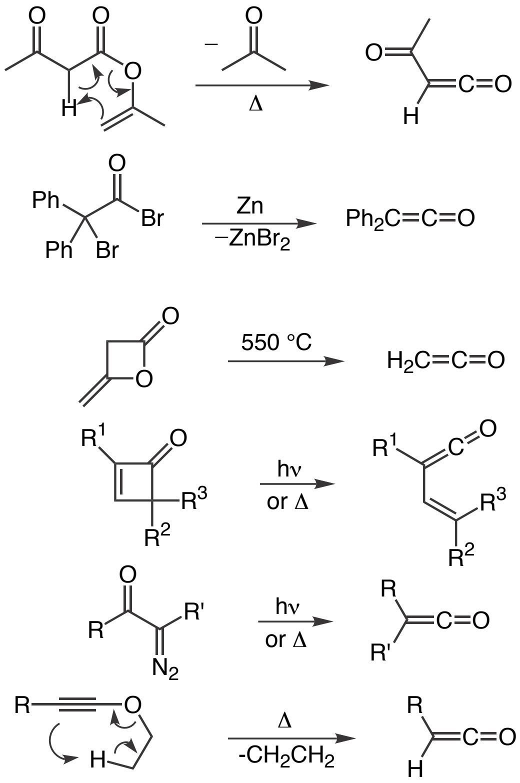


Staudinger Reaction (very general)

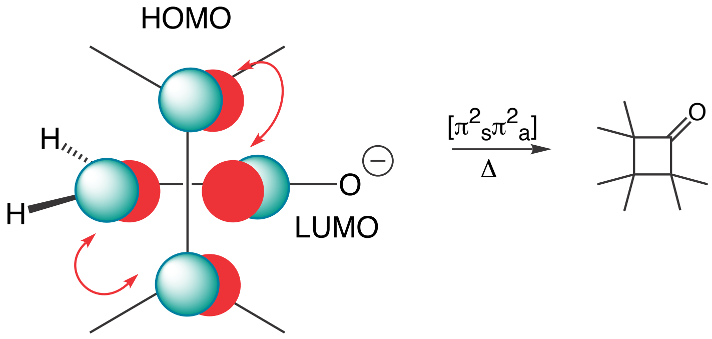
X = Cl, Ts, AcO, DCC, etc...

$(CH_3CO)_2O \xrightarrow{\Delta} H_2C{=}C{=}O + AcOH$



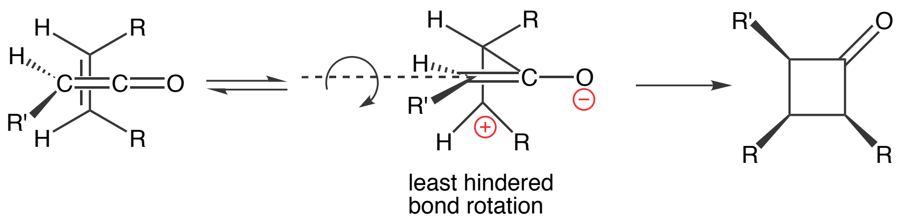


FMO Analysis



Cycloaddition Reactions-3

[2+2]: Stepwise Versus Concerted



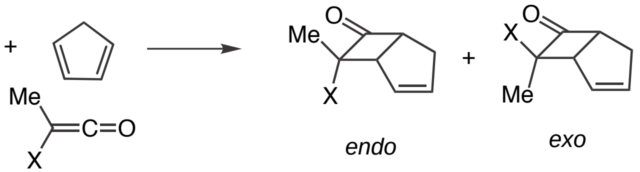
Stepwise

- Very large polar effects
- E olefins yield a mixture of *cis* and *trans* products
- Solvent effects observed, but it could merely be a ground state effect
- KIE seen for many reactions support stepwise mechanism
- Calculations (Wang and Houk) show a highly asynchronus transition state in the gas phase reaction
- All stereochemical outcomes can be rationalized assuming a stepwise mechanism

Concerted

- Ketenes add stereoselectively to Z alkenes
- Z olefins are much more reactive than E

Solvent Effects

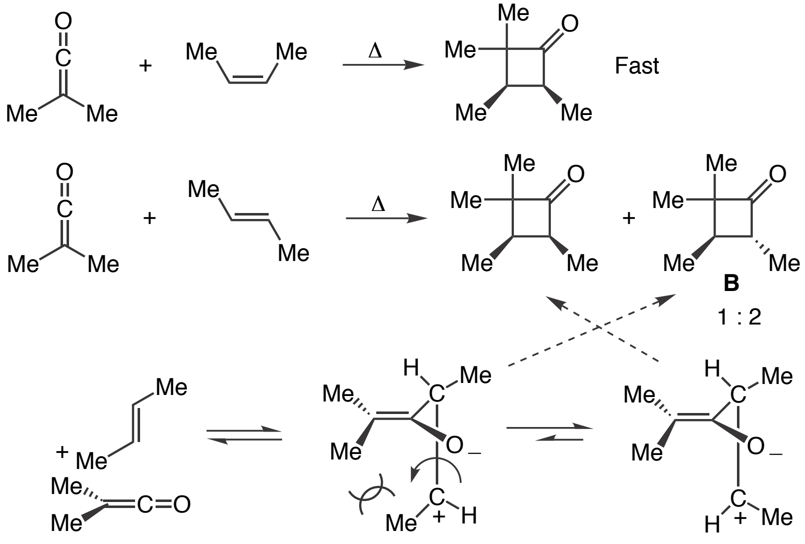


X	Solvent	*endo / exo*	X	Solvent	*endo / exo*
Cl	hexane	4.3 / 1	Br	hexane	0.71 / 1
Cl	Et_3N	2.2 / 1	Br	Et_3N	0.28 / 1
Cl	$CHCl_3$	1.6 / 1	Br	CH_3CN	0.14 / 1
Cl	CH_3CN	0.59 / 1			

- Solvent effects implicate a zwitterionic intermediate

Brady,et. al, *JACS* **1970**, *92*, 146-148.

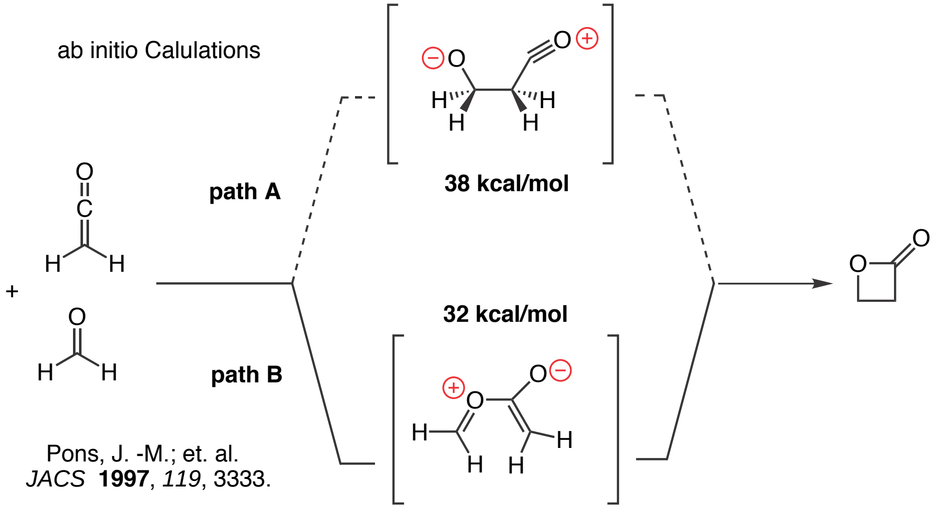
Ketene-Alkene [2+2]



Frey, H. M.; Isaacs, N. J. *J. Chem Soc. B*, **1970**, 830-832.

Ketenes + Aldehydes Afford β-Lactones

ab initio Calulations

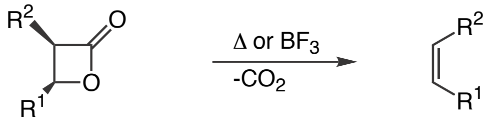


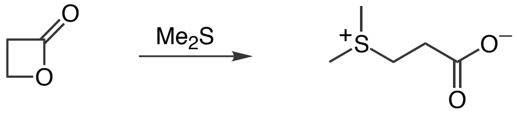
Pons, J. -M.; et. al.
JACS **1997**, *119*, 3333.

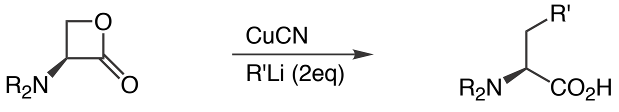
Mechanism and Origin of Stereoselectivity in Lewis Acid Catalyzed [2 2] Cycloadditions of Ketenes with Aldehydes, Singleton, *Angew. Chem. Int. Ed.* **2002**, *41*, 1572

Cycloaddition Reactions-4

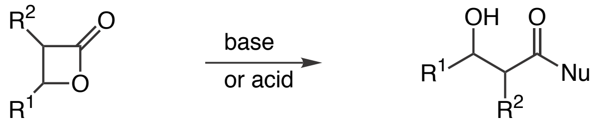
Transformations of β-Lactones





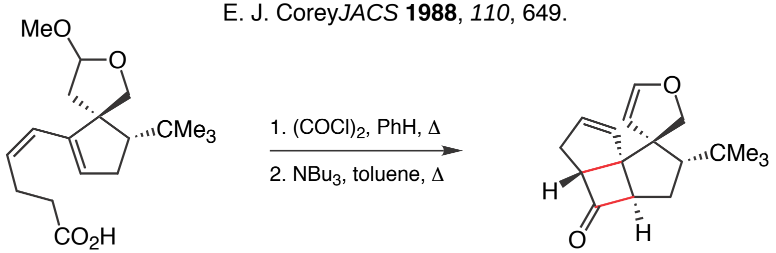


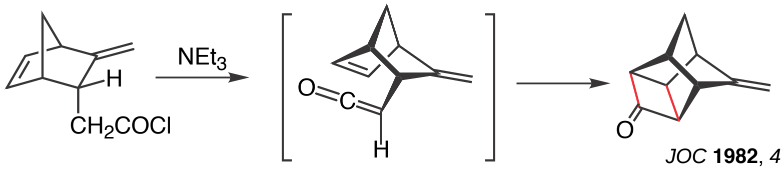
Vederas et al *JACS* **1987**, *107*, 4649.



Nu = OH_2, ROH, R_2NH

Application in Natural Product Synthesis: Ginkolide B,
E. J. Corey *JACS* **1988**, *110*, 649.

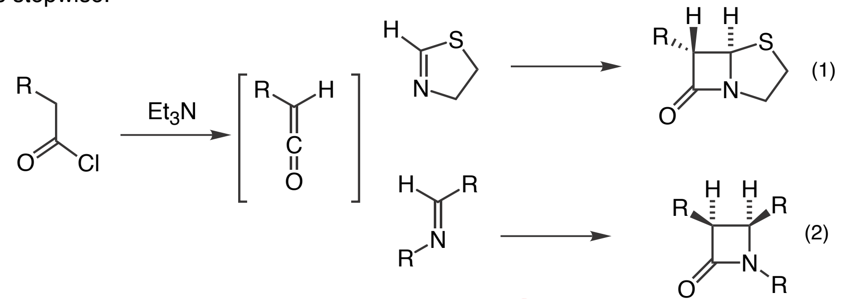




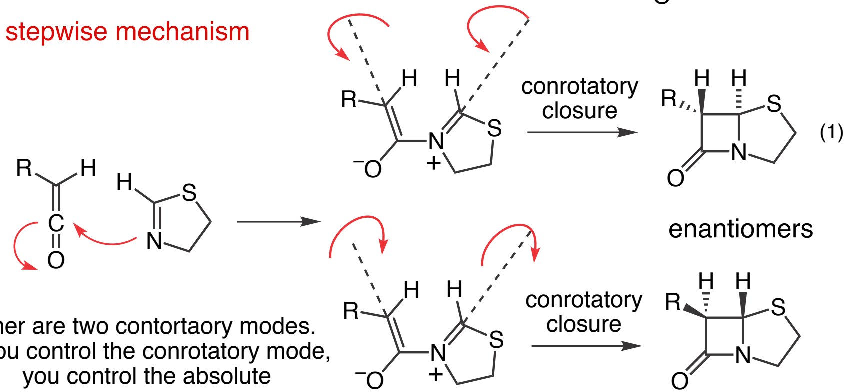
JOC **1982**, *47*, 3470.

The Staudinger Reaction

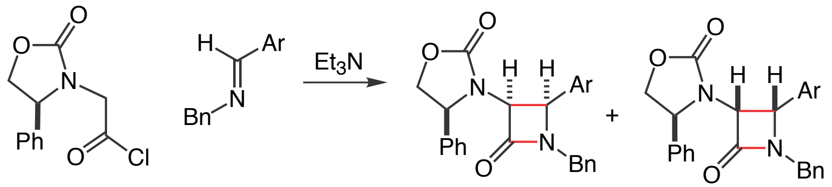
In this process, the illustrated ketene, generated *in situ* from an acid chloride, undergoes reaction with the indicated substrates to form β-lactams in a stereoselective process. When the azo-methine (RN=CHR) geometry in the reactant is (Z) the product stereochemistry is trans (eq 1). In a complementary fashion, the (E) imine affords the cis-substituted product (eq 2). While this transformatlion could be viewed as a [2s+2a] cycloaddition, it is felt that this reaction is stepwise.



The stepwise mechanism



There are two contortaory modes.
If you control the conrotatory mode,
you control the absolute
stereochemistry of the reaction:



Evans, Sjogren *Tet. Lett.* **1985**, *26*, 3783, 3787.

See also Evans, Williams, *Tet. Lett.* **1988**, *29*, 5065.

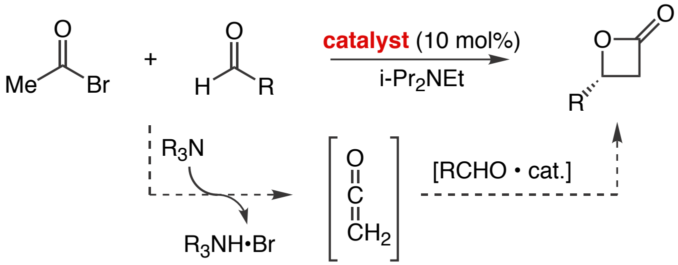
diastereoselection > 95:5
80-90% yields

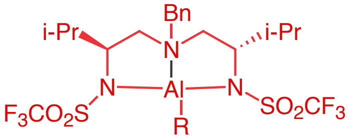
"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.

"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683.

Cycloaddition Reactions-4

Enantioselective Ketene-Aldehyde Cycloaddiitons

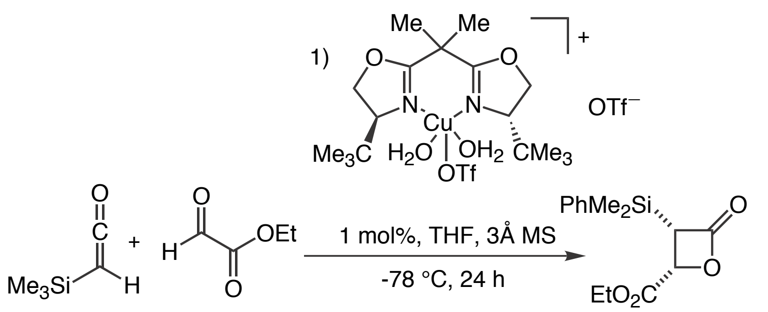




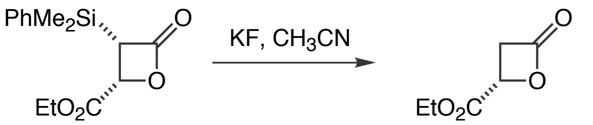
cat. = **5a**: R = Me
5b: R = Cl

entry	Aldehyde **2** (R)	catalyst [time (h), temp (°C)]	% yield	% ee **3** (configuration)
a	BnOCH$_2$—	**5b** (8, -40)	91	92 (*R*)
b	PhCH$_2$CH$_2$—	**5a** (16, -50)	93	92 (*S*)
	PhCH$_2$CH$_2$—	**5a** (72, -78)	89	95 (*S*)
c	CH$_2$CH(CH$_2$)$_8$—	**5b** (16, -50)	91	91 (*S*)
d	Me$_2$CHCH$_2$—	**5a** (24, -50)	80	93 (*S*)
e	BnOCH$_2$CH$_2$—	**5b** (16, -40)	90	91 (*S*)
f	TBDPSOCH$_2$—	**5b** (16, -40)	74	89 (*R*)
g	BnOCH$_2$—≡—	**5a** (16, -50)	86	93 (*R*)
h	Me$_3$C—≡—	**5a** (16, -50)	91	85 (*R*)
i	C$_6$H$_{11}$—	**5b** (24, -40)	56	54 (*R*)

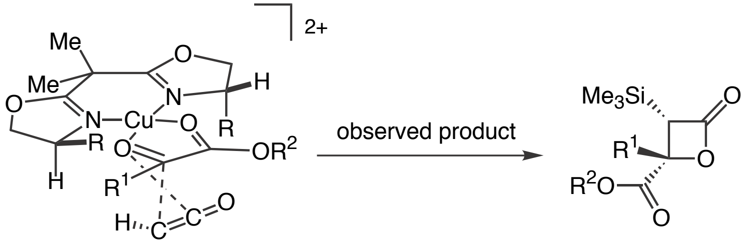
Nelson, S. G.; Peelen, T. J.; Wan, Z. *JACS*, **1999**, 121, 9742-9743

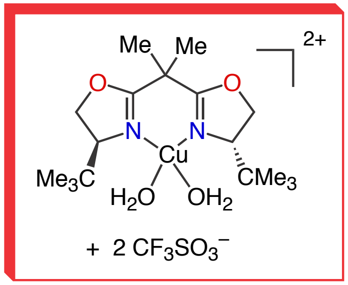


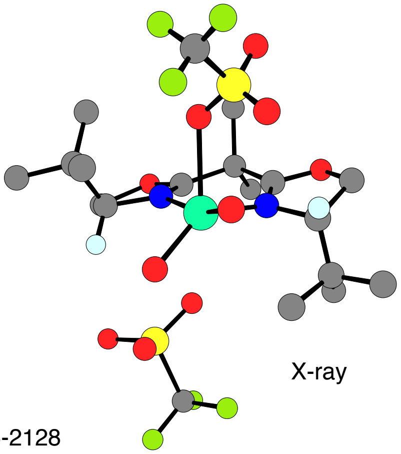
77% yield, 93% ee



3: >99% yield, 92% ee







with J. Janey, *Org. Lett.* **2001**, *3*, 2125-2128

Articles and monographs of Significance

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer
4.2 Heterodienophile Additions to Dienes, S. M. Weinreb
4.3 Heterodiene Additions, D. L. Boger
4.4 Intramolecular Diels-Alder Reactions, W. R. Roush
4.5 Retrogade Diels-Alder Reactions, R. W. Sweger, A. W. Czarnik

> *The Diels-Alder Reaction in Total Synthesis,* K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, *41*, 1668-1698 **(handout)**
>
> *Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications*, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, *41*, 1650-1667 **(handout)**

Hetero Diels-Alder Methodology in Organic Synthesis
Boger, D.L. and Weinreb, S.N., Academic Press, 1987

Natural Products Synthesis Through Pericyclic Reactions
Desimoni, Tacconi, Barco, Polini, ACS Monograph 180, 1983, Chapter 5,

Asymmetric Diels-Alder Reactions with Chiral Enoates as Dienophiles
Modern Synthetic Methods **1986**, Scheffold, Ed. Springer-Verlag,

Intramolecular Diels-Alder and Alder Ene Rxns, D. F. Taber, Springer-Verlag, **1984**

Synthetic Aspects of D-A Cycloadditions with Heterodienophiles
Weinreb, *Tetrahedron*, **1982**, *38*, 3087-3128

The Intramolecular DA Rxn: recent advances and synthetic applications
Fallis, *Can. J. Chem.*, **1984**, *62*, 183-234

Intramolecular [4 +2] & [3 + 2] Cycloadditions in Organic Synthesis
Oppolzer, *Angew. Chem. Int. Ed.*, **1977**, *16*, 10-23

Preparation & DA Reactions of Heterosubstituted 1, 3-Dienes
Petrzilka, *Synthesis*, **1981**, 753-786

DA Reactions of Azadienes
Boger, *Tetrahedron*, **1983**, *39*, 2869-2939

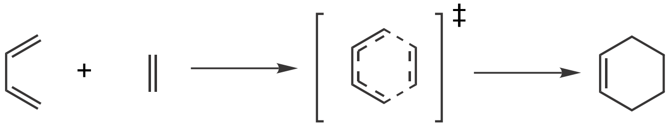
Silyloxydienes in Organic Synthesis
Danishefsky, *Acct. Chem. Res.*, **1981**, *14*, 400-406

DA Reactions Part I: New Preparative Aspects
Sauer, *Angew. Chem. Int. Ed.*, **1966**, *5*, 211-230

DA Reactions Part II: The Reaction Mechanism
Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

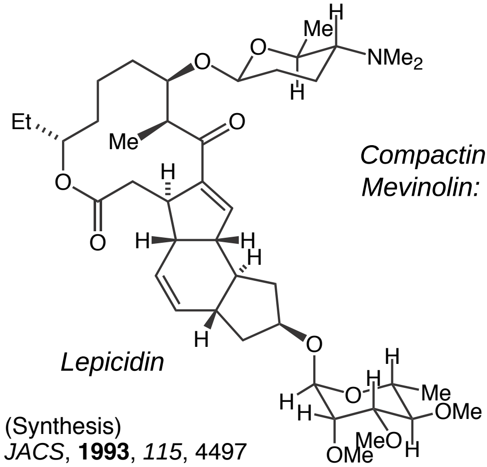
Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey
Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

■ The Reaction:



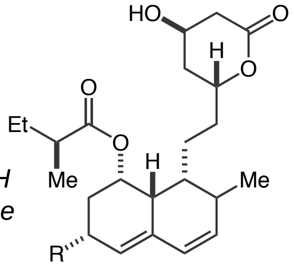
■ Representative natural products displaying the Diels-Alder retron:

These natural products could well have incorporated the DA rxn into the biosynthesis



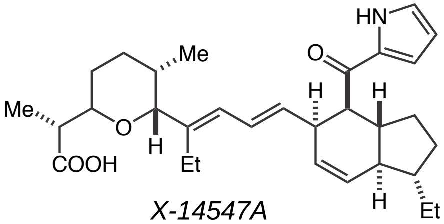
Lepicidin

(Synthesis)
JACS, **1993**, *115*, 4497



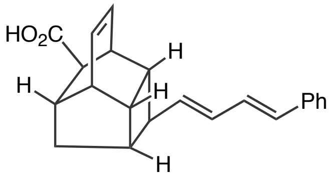
Compactin: R = H
Mevinolin: R = Me

(Biosynthesis) *JACS* **1985**, *107*, 3694
Clive, *JACS* **1988**, *110*, 6914
Kozikowski, *JOC* **1987**, *52*, 3541
Keck, *JOC* **1986**, *51*, 2487
Grieco, *JACS* **1986**, *108*, 5908
Heathcock, *JACS* **1985**, *107*, 3731
Girotra, *Tet. Let.* **1983**, *24*, 3687
Hirama, *JACS* **1982**, *104*, 4251

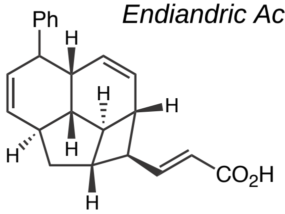


X-14547A

Roush *JOC* **1984**, *49*, 3429
Nicolaou *JOC* **1985**, *50*, 1440
Ley *Chem. Commun.* **1983**, 630



Endiandric Acid C



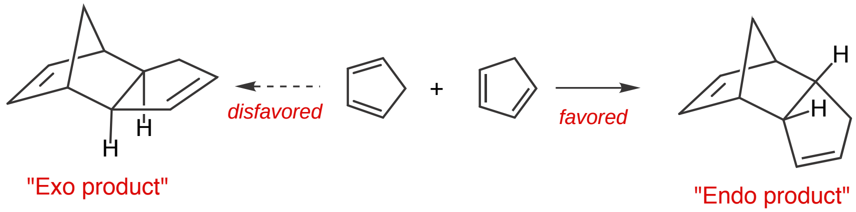
Endiandric Acid B

(Syntheses)
Nicolaou, *JACS* **1982**, *104*, 5555-5562

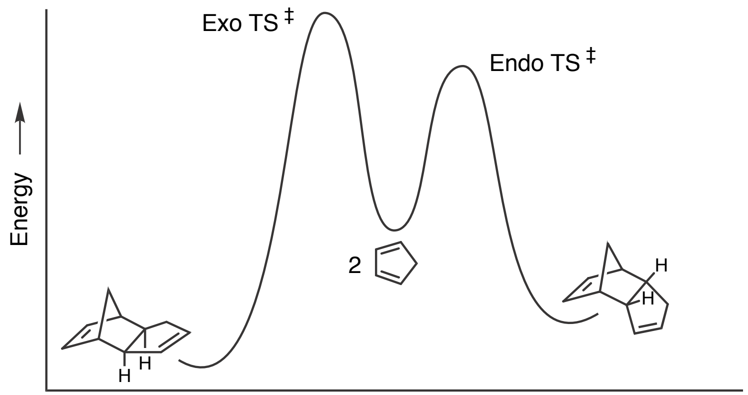
Diels-Alder Reaction-Orbital Symmetry Considerations

The Alder Endo Rule

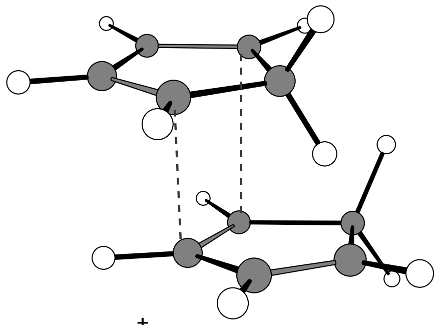
The following observation illustrates an example of the Alder Rule which will be defined below.



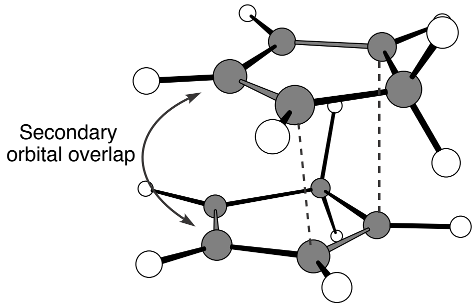
Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.



- Of the two possible transition states, the one having the "greatest accumulation of interacting double bonds will be preferred" (the Alder Endo Rule). Secondary orbital overlap is noted below.



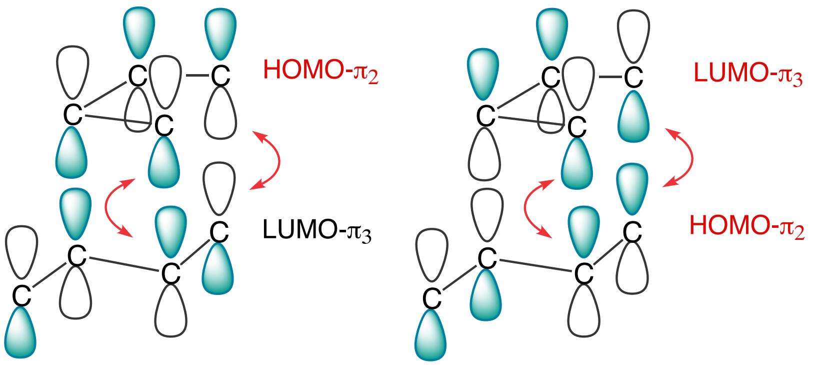
Exo TS ‡



Endo TS ‡

Orbital Symmetry Considerations for Diels Alder Reaction

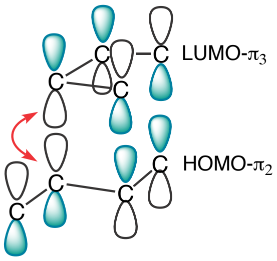
If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



- Primary orbital overlap leads directly to the formation of new chemical bonds.

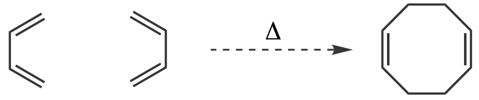
Frontier MO Explanation for the Endo Rule

- Secondary (transient) orbital overlap can also occcur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

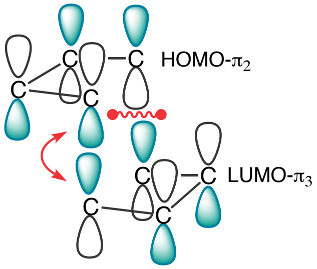


The Other Dimerization Possibility for Butadiene

Does the possibility for the following concerted dimerization exist?



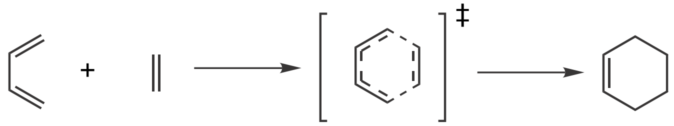
- Note that the termini only match at one end for the HOMO-LUMO pairing. Hence we say that the symmetry requirements for the reaction in question are not met. This does not mean that the reaction will not occur, only that the reaction will not be concerted. Such reactions are called "symmetry-forbidden".



Additional Reading: Lowry & Richardson,
Chapter 10, theory of Pericyclic Rxns pp 839-900

Diels-Alder Reaction: The Transition Structure

Transition State Modelling is Coming of Age

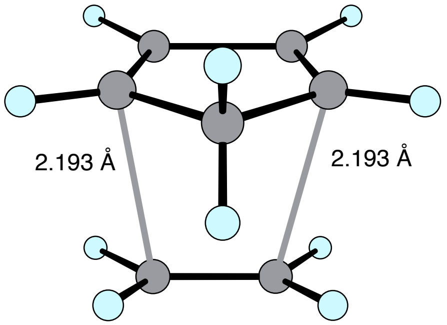


- The lengths of the forming C–C bonds are Ca. 1.5 times the normal bond distance. This factor comes out of the *ab initio* work of Jorgensen & Houk

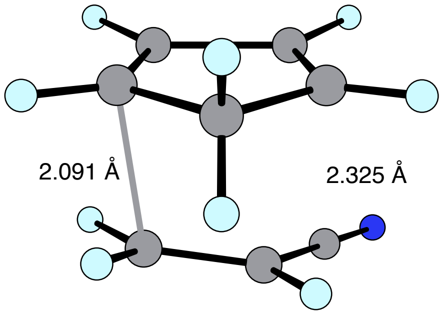
leading references: Jorgensen, *JACS* **1993**, *115*, 2936-2942
Houk, Jorgensen, *JACS* **1989**, *111*, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
Houk *Angew. chem. Int. Ed.* **1992**, *31*, 682-708

- Bond formation is not synchronus with substituted dienophiles (Jorgensen)

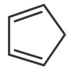


exptl $\Delta H^{\ddagger}$ = 22.5 kcal/mol
$\Delta S^{\ddagger}$ = -32.1 eu
rel rate = 1

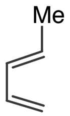


$\Delta H^{\ddagger}$ = 14.0 kcal/mol
$\Delta S^{\ddagger}$ = -38.3 eu
rel rate = 10^{+5}

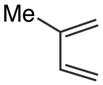
- Diene Reactivity as measured against Maleic anhydride



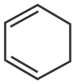
log k = 4.96



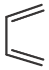
log k = 2.36



log k = 2.19



log k = 2.12



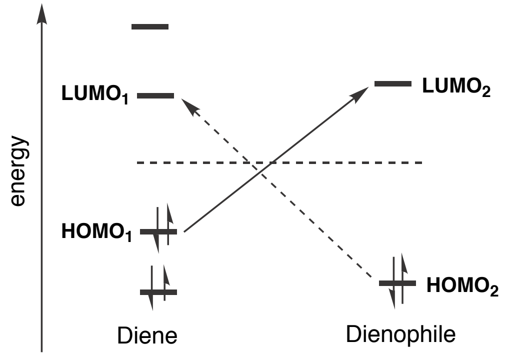
log k = 1.83

Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

16-08-DA transtion structure 10/22/03 6:52 AM

- Lewis Acid Catalysis of the reaction is possible:

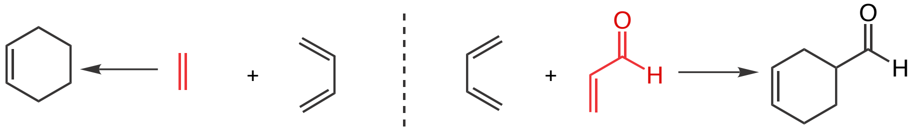
Yates & Eaton,
JACS **1960**, *82*, 4436

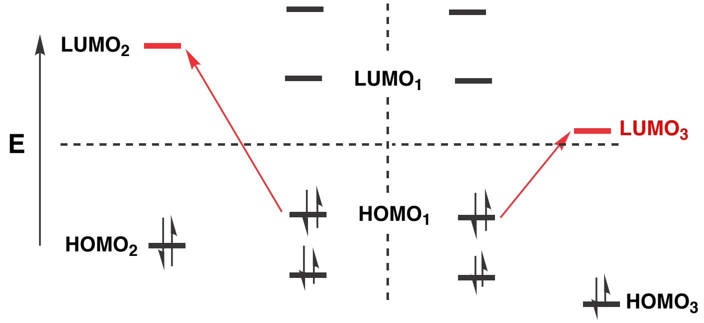


The Critical Energy Difference:
E(LUMO$_1$) - **E**(HOMO$_2$)
or
E(LUMO$_2$) - **E**(HOMO$_1$)

- The closer the two orbitals are in energy, the better they interact
- As ΔE decreases for the relevant ground state FMOs, rxn rates increase

Ethylene & Butadiene Vs Butadiene & Acrolein



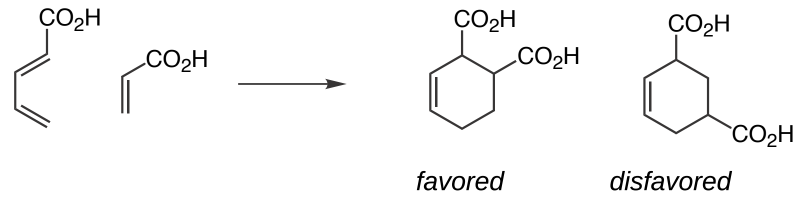


ΔE (LUMO$_3$-HOMO$_1$) < ΔE (LUMO$_2$-HOMO$_1$) ⟹ *Rate Acceleration*

Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

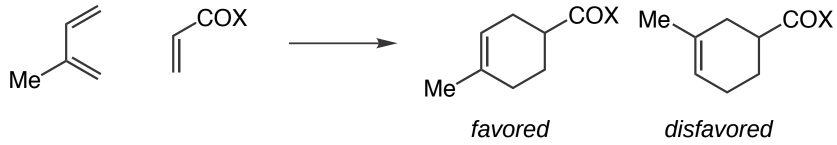
Diels-Alder Reaction: Regiochemistry

Orientation of Reacting Partners



4.5 : 01 @ 100 °C

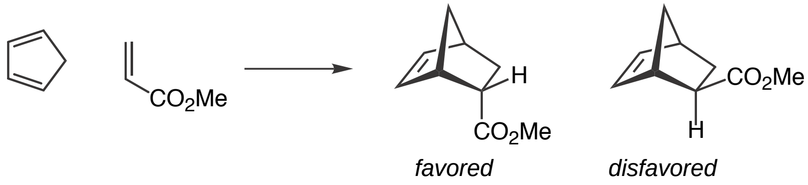
Lewis acid catalysis improves orientation



toluene, 120 °C	59 : 41
C_6H_6, $SnCl_4$, 25 °C	96 : 04

In general, 1-substituted dienes are more regioselective than their 2-substituted counterparts: Sauer, Angew. Chem. Int. Ed., ***1967****, 6, 16-33*

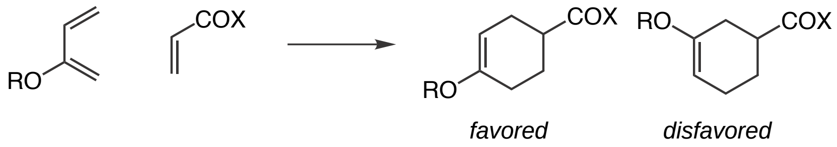
Lewis acid catalysis improves endo diastereoselection



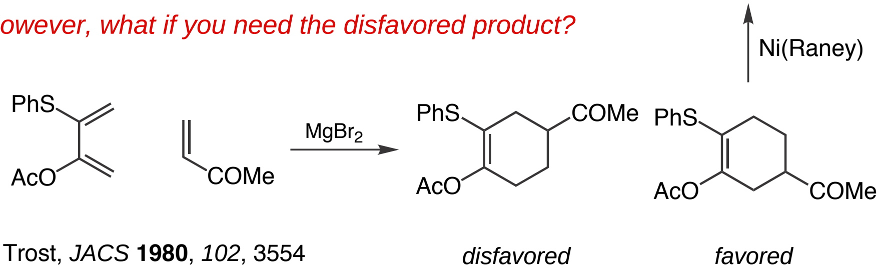
CH_2Cl_2, 0 °C	80 : 20
C_6H_6, $SnCl_4$, 25 °C	95 : 05

DA Reactions Part II: The Reaction Mechanism, Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

Here is an interesting problem in reaction design

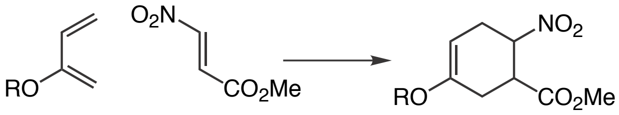


However, what if you need the disfavored product?



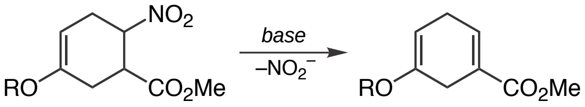
Trost, *JACS* **1980**, *102*, 3554

By employing a removable substituent, it is possible to access the normally disfavored product diastereomer

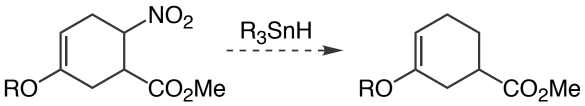


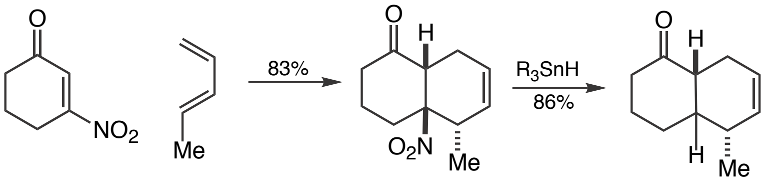
Danishefsky, *JACS* **1978**, *100*, 2918: The NO_2 FG completely dominates directivity

It then can be removed by elimination



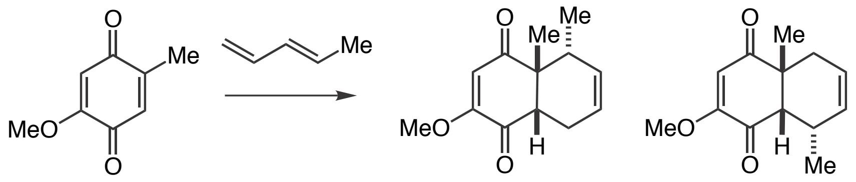
or by reduction
Ono, *Tet.* **1985**, 4013





Ono, *Chem. Commun.* **1982**, 33-34

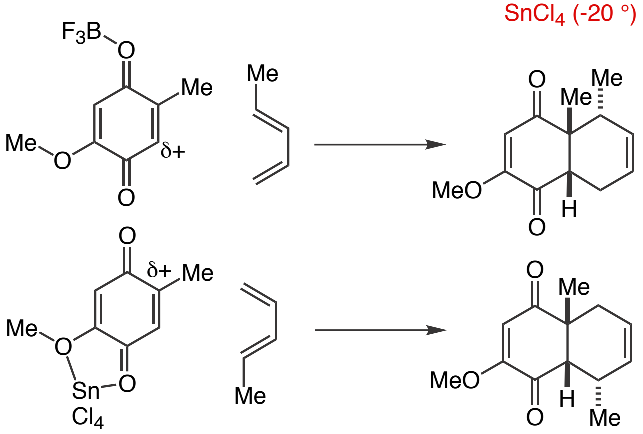
Instructive Issues of Regiocontrol with Quinone Dienophiles



Orientation of Reacting Partners controlled by Lewis acid structure

Reusch *JOC* **1980**, *45*, 5013

Conditions	Ratio
thermal (100 °)	50 : 50
BF_3•OEt_2 (-20 °)	80 : 20
$SnCl_4$ (-20 °)	<5 : 95

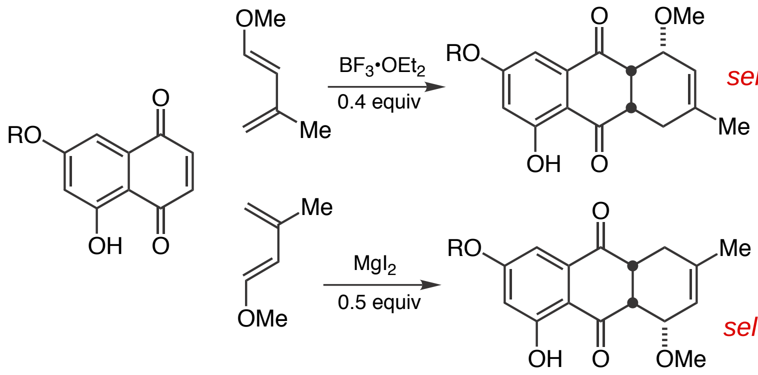


selection 80 : 20

selection >95 :5

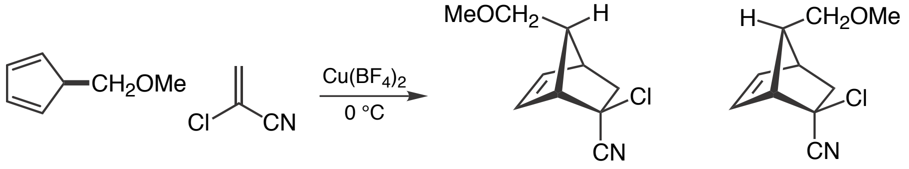
Similar results provided by Stoodley *Chem. Comm.* **1982**, 929

Kelly *Tet. Let.* **1978**, 4311



selection >95 :5

selection >95 :5



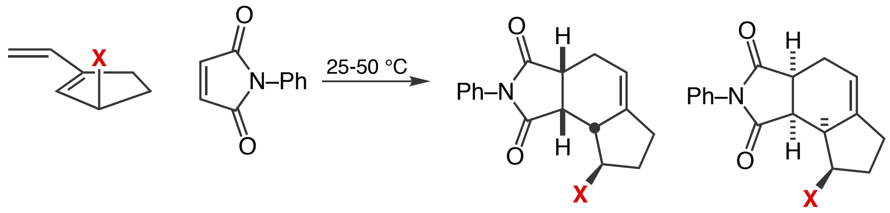
Corey, *JACS* **1969**, *91*, 5675

Ratio: 90 : 10

Diels-Alder Reactions with Chiral Dienes

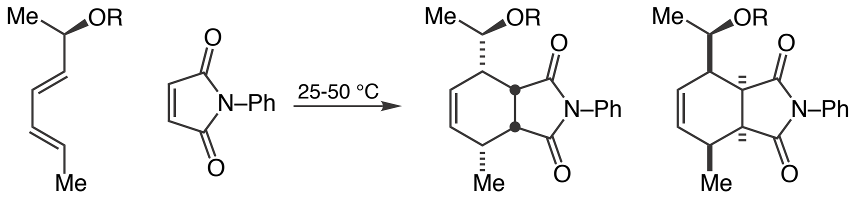
Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347



Overman, *JACS* **1988**, *110*, 4625

X =	Ratio
–OH	36 : 64
–Me	83 : 17
–OMe	>97 : 3



Franck, *Tet. Lett.* **1985**, *26*, 3187

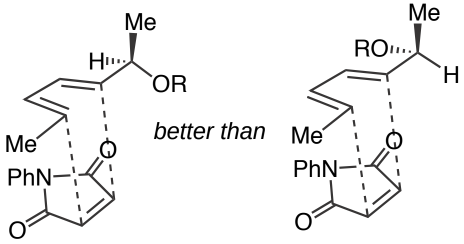
Franck, *JACS* **1988**,*110*, 3257

R = Me: Ratio; 83 : 17

R = Me_3Si: Ratio; 88 : 12

Comments on the Transition State

- Avoid Eclipsing allylic substituents
- better donor (Me) anti to forming bond
- avoid gauche OR interaction



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 17

Cycloaddition Reactions-2

- The Diels-Alder Reaction

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Fleming: Chapter 4
Thermal Pericyclic Reactions

D. A. Evans

Friday,
October 24, 2003

The Diels-Alder Cycloaddition Reactions

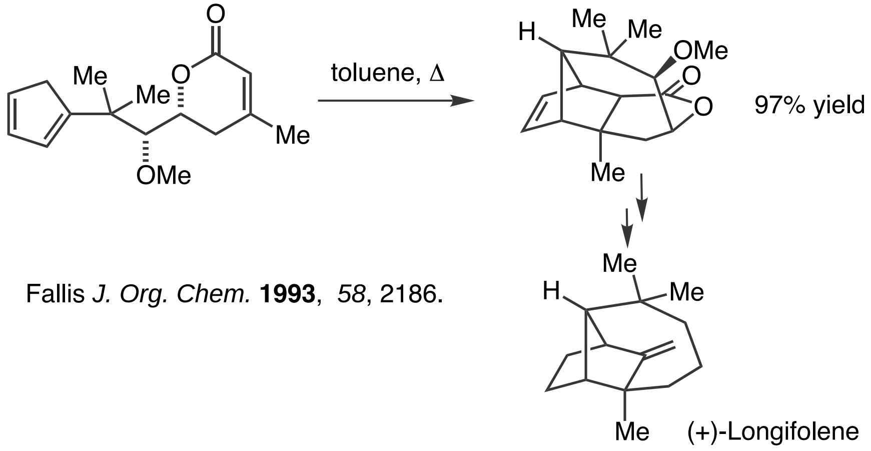
"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(pdf)**

"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325-335. **(pdf)**

"New Strategies for Organic Catalysis: The first Highly Selective Organocatalytic Diels-alder Reaction", MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**

"New Strategies for Organic Catalysis: The first Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition", MacMillan, *JACS*, **2000**, 122, 9874. **(pdf)**

Problem of the Day:

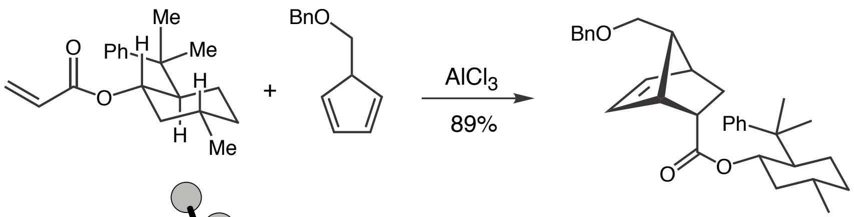


Fallis *J. Org. Chem.* **1993**, *58*, 2186.

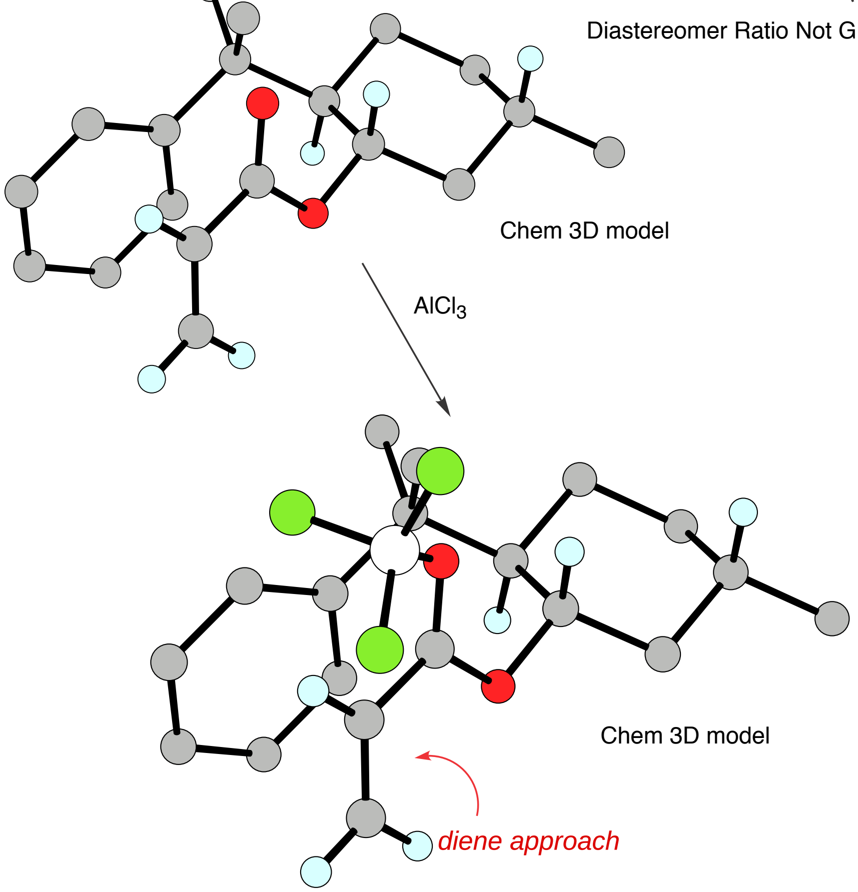
Chiral Auxiliary Controlled Diels-Alder Reactions

Review: Oppolzer in *Comprehensive Organic Synthesis* **1992**, *Vol. 4*, 315-399.

■ Ester-Type Chiral Auxiliaries Corey *JACS* **1975**, *97*, 6908.

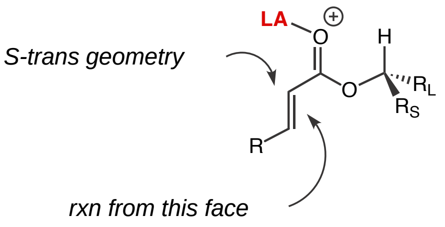


Diastereomer Ratio Not Given

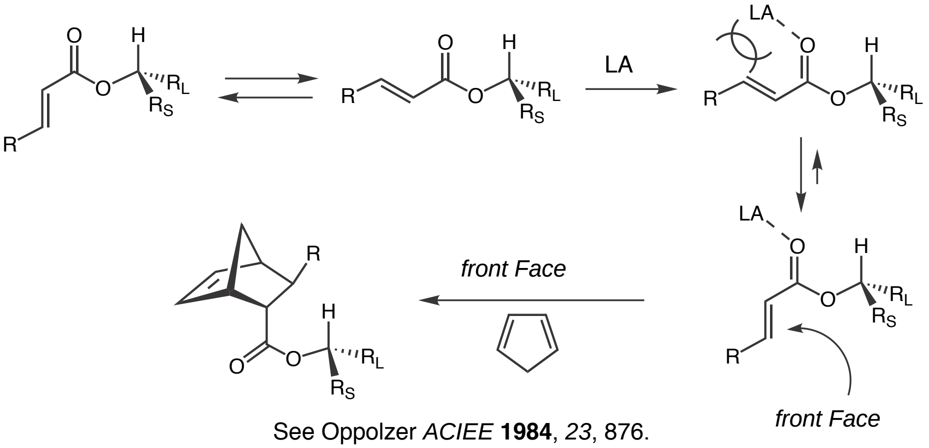

Chem 3D model

Chem 3D model

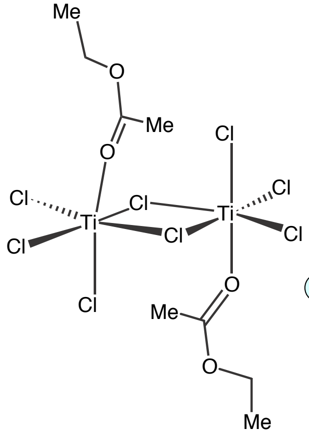
■ Non-Chelate Ester-Type Chiral Auxiliaries

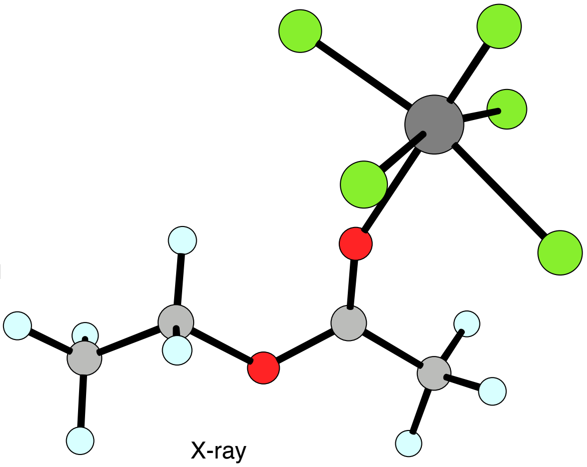


Lewis Acid-Ester Complex Conformation Dictates Diastereoselection



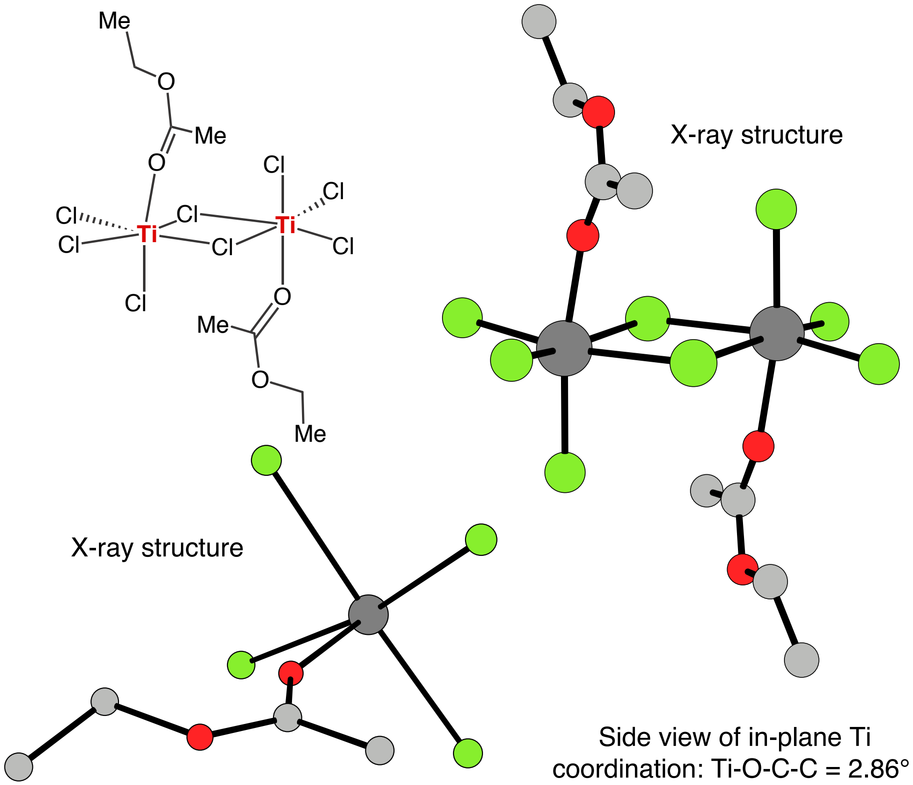
See Oppolzer *ACIEE* **1984**, *23*, 876.




X-ray

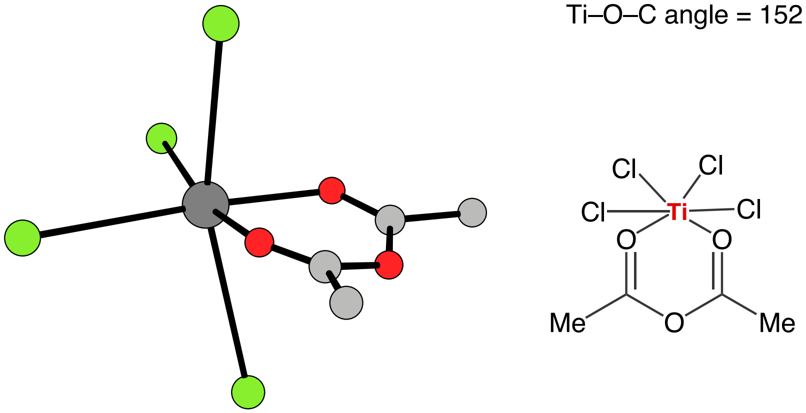
Lewis Acid–Carbonyl Complexes-3

Representative η1–titanium complexes with organic compounds

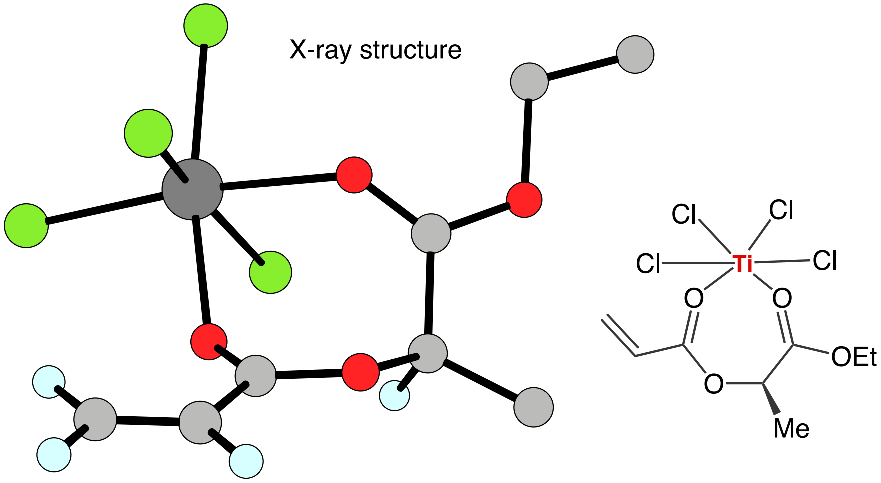


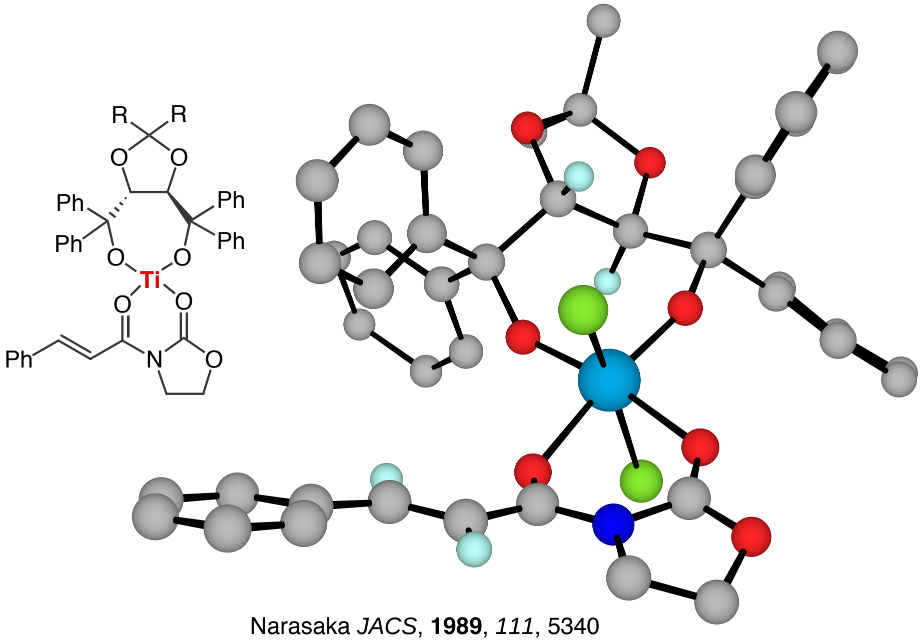
Side view of in-plane Ti coordination: Ti-O-C-C = 2.86°

Ti–O–C angle = 152 °



Representative η1–titanium complexes with organic compounds





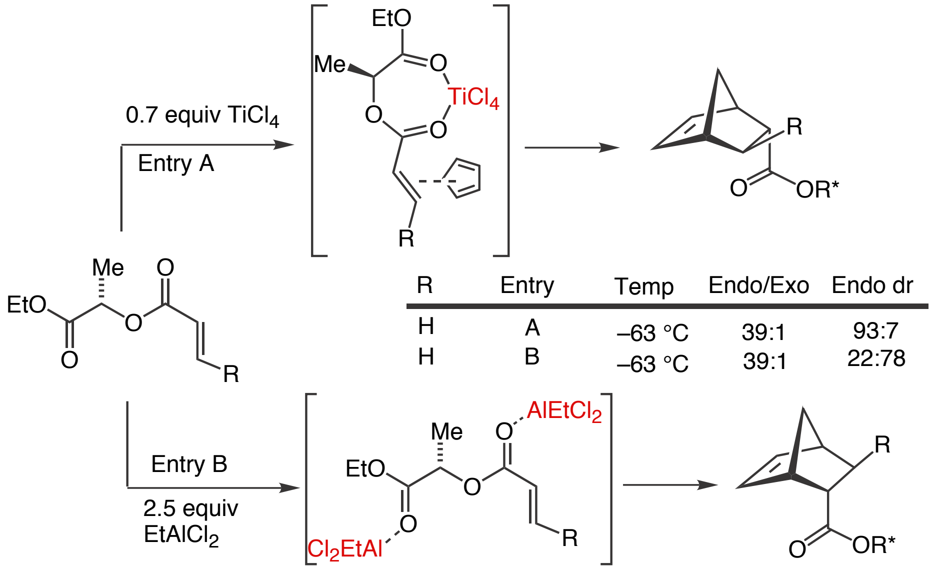
Narasaka *JACS*, **1989**, *111*, 5340

A. Jorgensen, *JACS*, **1995**, *117*, 4435

X-ray structure

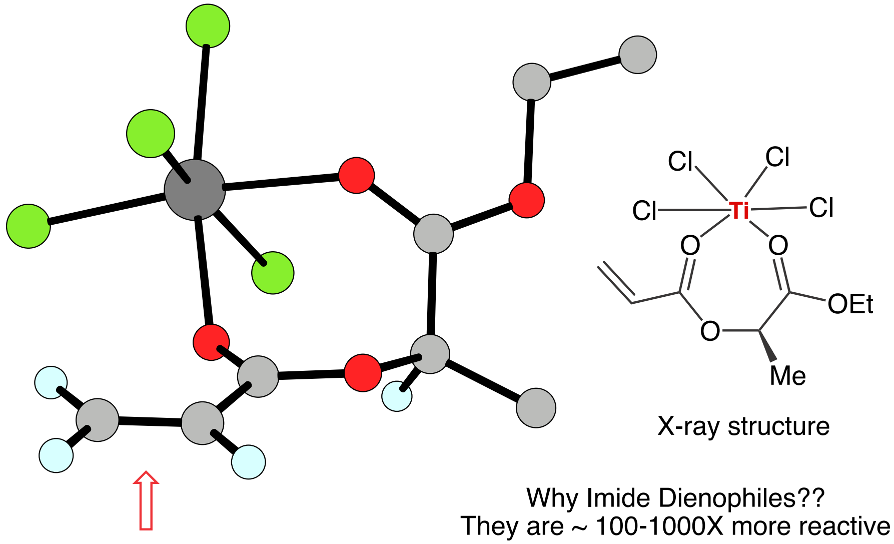
Chiral Auxiliary Controlled Diels-Alder Reactions-2

Ester-Type Chiral Auxiliaries: Chelating Dienophiles



R	Entry	Temp	Endo/Exo	Endo dr
H	A	–63 °C	39:1	93:7
H	B	–63 °C	39:1	22:78

Helmchen *Tetrahedron Lett.* **1984**, *25*, 2191.
ACIEE **1985**, *24*, 112.
Tetrahedron Lett. **1985**, *26*, 3095.

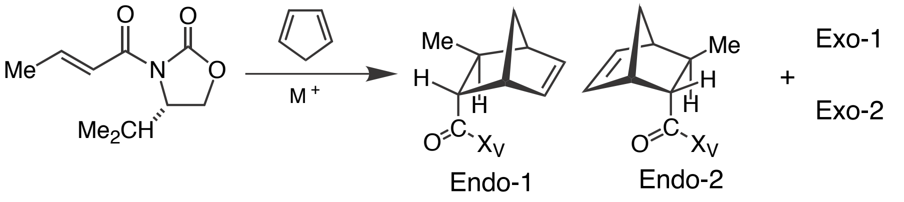


X-ray structure

Why Imide Dienophiles??
They are ~ 100-1000X more reactive

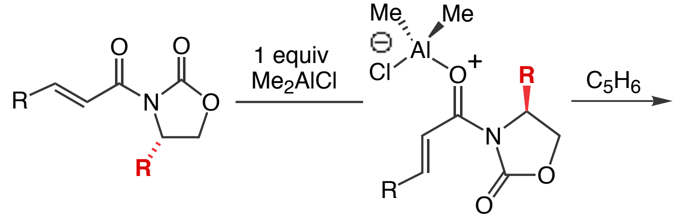
Chelating Imide-type Chiral Auxiliaries
Metal ion Dependent Diastereoselection

Evans *JACS*, **1984**, *106*, 4261.
Evans *JACS*, **1988**, *110*, 1238.



Lewis Acid (1.2 equiv)	Temp.	Endo-1 / Endo-2	Σ Endo / Exo
$SnCl_4$	25	2.7	92 : 8
$SnCl_4$	–78	3.1	93 : 7
$TiCl_4$	–78	2.6	91 : 9
$AlCl_3$	–78	1.5	80 : 20
(2.0 equiv) **Et_2AlCl**	–78	**15.7**	**>99 : 1**
(0.7 equiv) **Et_2AlCl**	–78	**4.4**	**92 : 8**

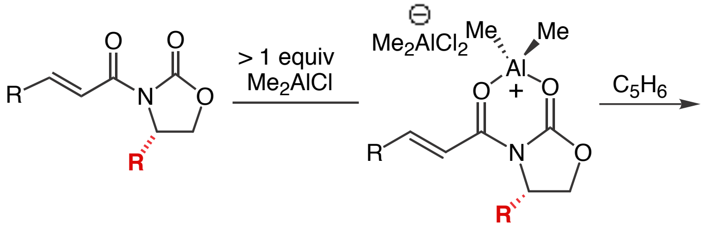
Binding Mode Dictates Diastereoselectivity



1 Point Binding

⇩

Endo/Exo = 4 :1
Rel. Rate = 1



2 Point Binding

⇩

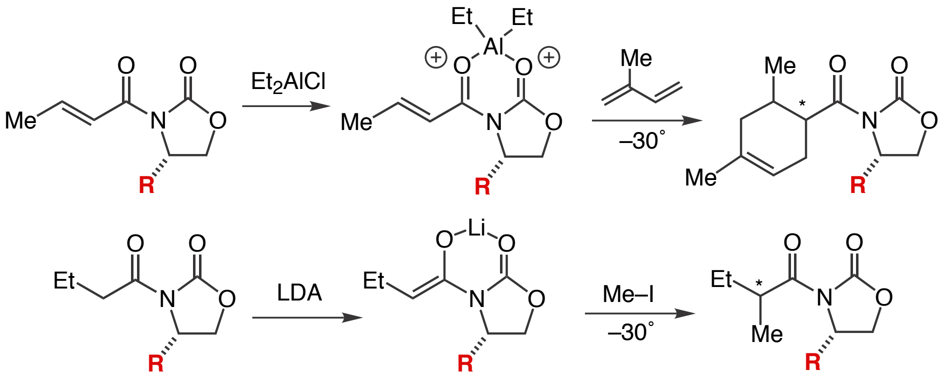
Endo/Exo = >20:1
Rel. Rate = 100

R = CH_2Ph much more stereoselective than R = $CHMe_2$

Chiral Auxiliary Controlled Diels-Alder Reactions-2

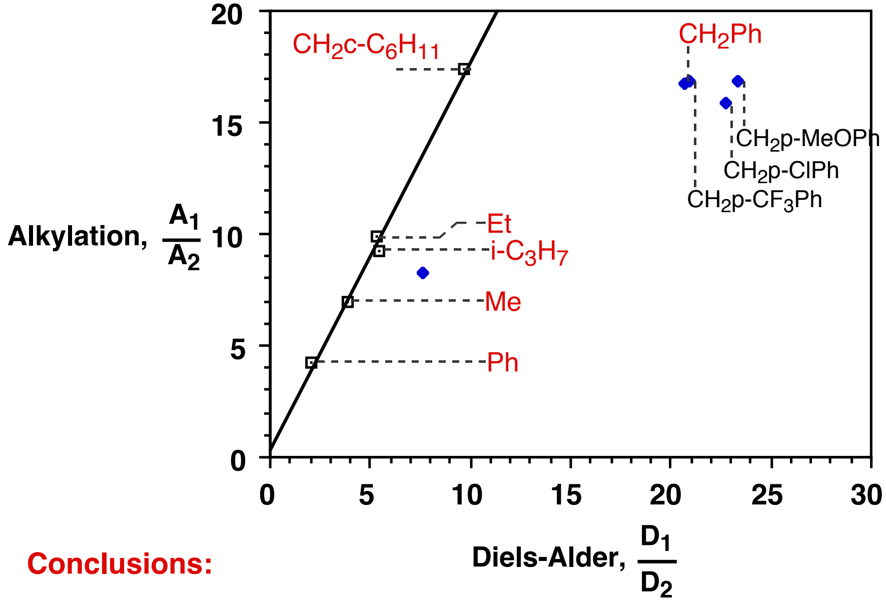
A Case for Π-Stacking: *Angew Chem, Int Ed.* **1987**, *26*, 1184

Compare the alkylation rxn which is dominated by steric effects with the DA rxn which may be controlled by both steric and electronic effects



$$\Delta\Delta G^{\ddagger} = 2.3\ RT\ \mathrm{Log}\ P_1/P_2$$

PLOT $\Delta\Delta G^{\ddagger}$ FOR EACH RXN AS A FUNCTION OF THE SUBST., R.

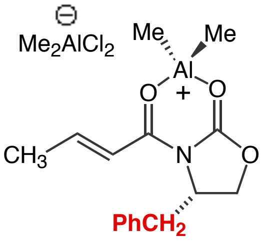


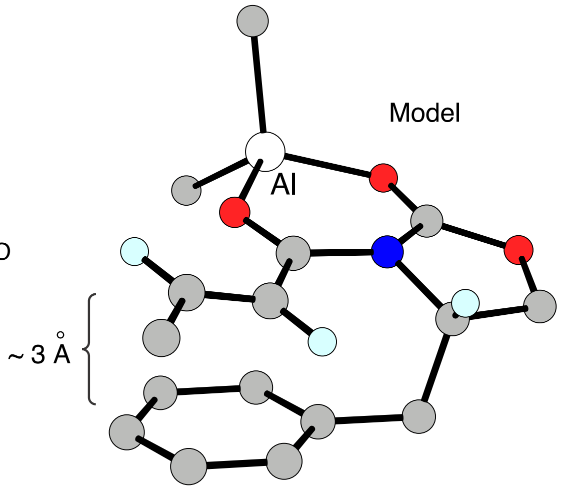
Conclusions:

Steric effects correlate well for the two reactions

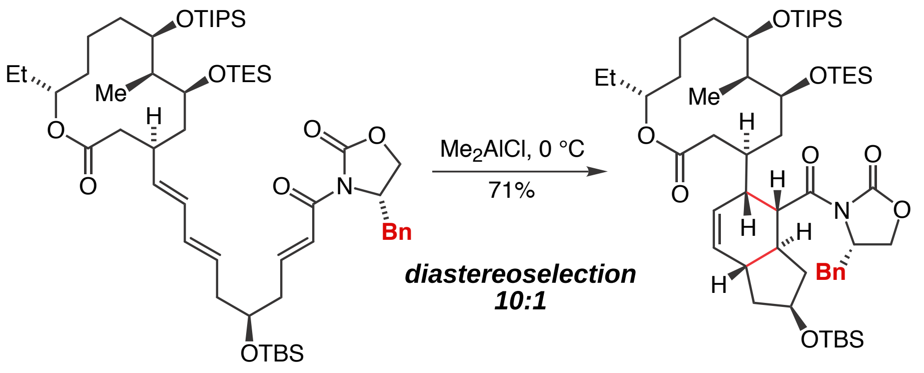
Added electronic effects from Bn group enhance facial bias

The Chiral Dienophile



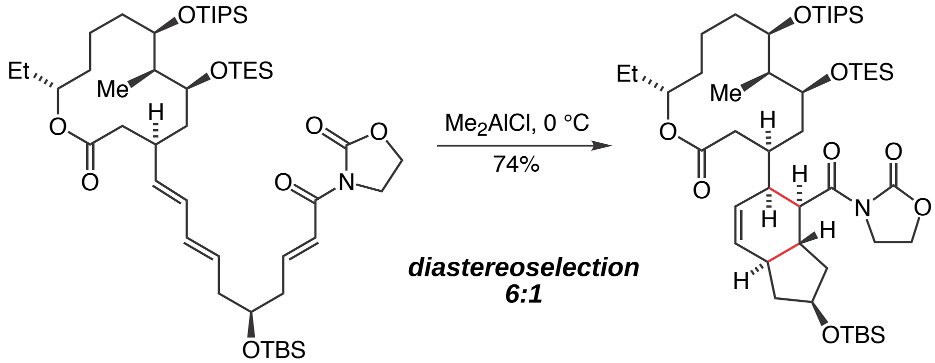


A Complex Application



diastereoselection 10:1

The control experiment with no chiral auxiliary:

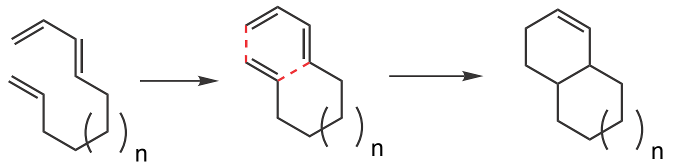


diastereoselection 6:1

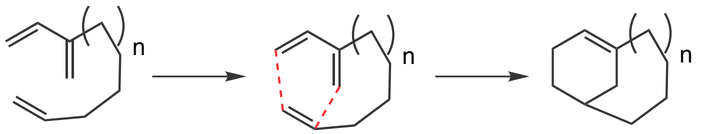
Evans, BlackLepicidin Synthesis, *JACS*, **1993**, *115*, 4497

Diels-Alder Reaction: Intramolecular Reactions

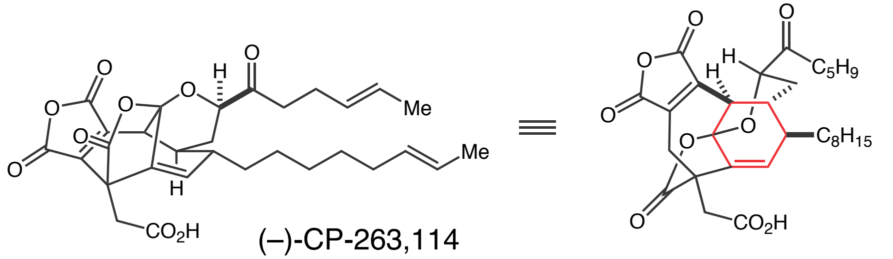
Type I intramolecular Diels-Alder Reaction:



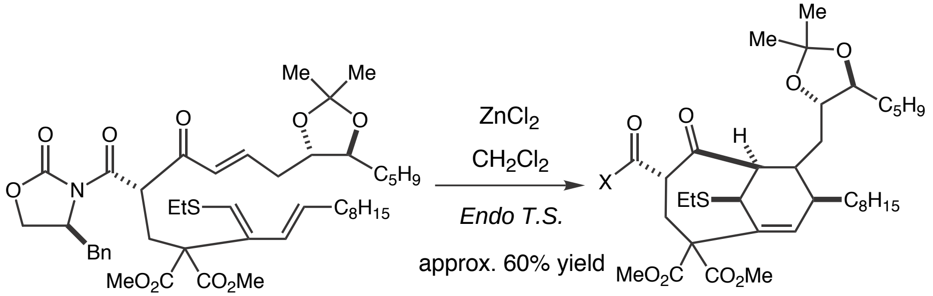
Type II intramolecular Diels-Alder Reaction:



A Type II Intramolecular Diels-Alder:



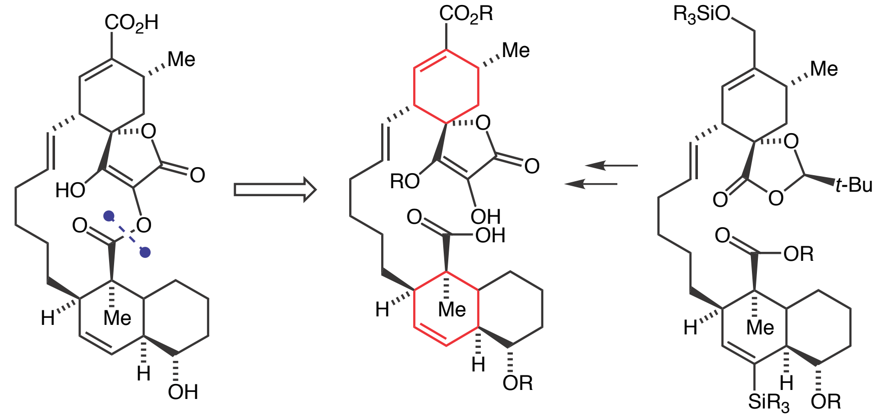
(–)-CP-263,114



Fukuyama et al *JACS* **2000**, *122*, 7825-7826.

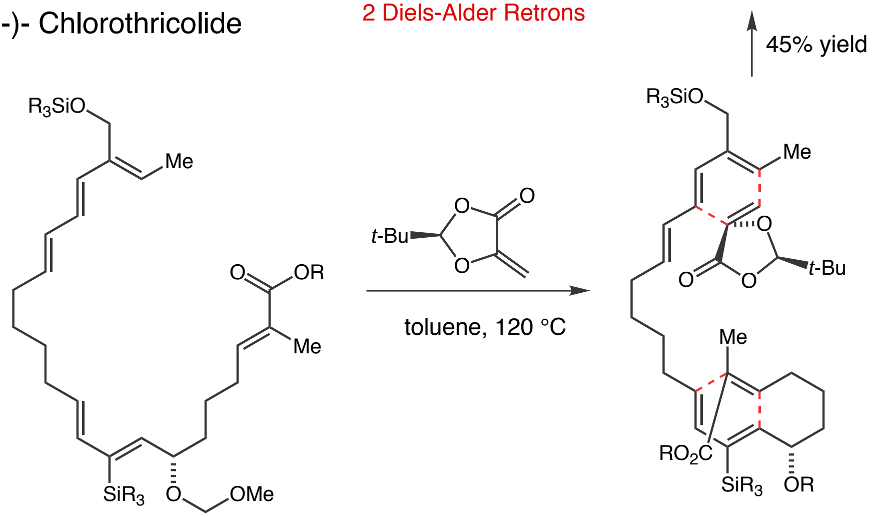
The concept: Evans, et al *Angew. Chem. Int. Engl.* **1997**, *36*, 2119-2121.

A Type I Intramolecular Diels-Alder:



(-)- Chlorothricolide

2 Diels-Alder Retrons



Roush, Sciotti *J. Am. Chem. Soc.* **1998**, *120*, 7411-7419.

Some Intramolecular Diels-Alder Reviews:

Shea *Angew. Chem. Int. Ed.* **2001**, *40*, 820.

Fallis *Acc. Chem. Res.* **1999**, *32*, 464-474.

The Diels-Alder Reaction: Enantioselective Catalysis

Articles and monographs of Significance

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, 1999; Vol III, 1178-1235.

Review: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer
4.2 Heterodienophile Additions to Dienes, S. M. Weinreb
4.3 Heterodiene Additions, D. L. Boger
4.4 Intramolecular Diels-Alder Reactions, W. R. Roush
4.5 Retrogade Diels-Alder Reactions, R. W. Sweger, A. W. Czarnik

Catalytic Asymmetric Synthesis, I. Ojima, Ed. **1993**

Chapter 9, *Asymmetric Rxns with Chiral Lewis Acid Catalysts*

Chiral Lewis Acids in Catalytic Asymmetric Reactions
Narasaka, *Synthesis*, **1991**, 1-11

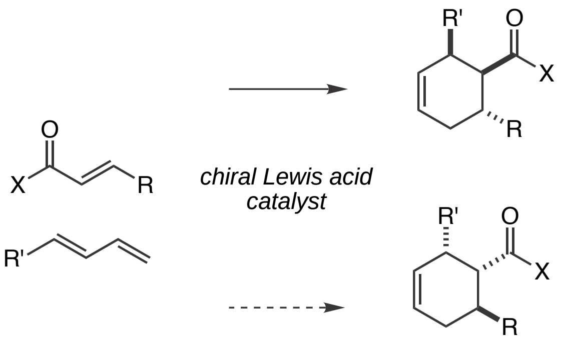
(Carbonyl-Lewis Acid Complexes)
Schreiber, *Angew. Chem. Int. Ed.*, **1990**, *29*, 256-272

Rotational barriers in Aldehydes & Ketones Coordinated to Neutral Lewis Acids
Wiberg, *JACS*, **1988**, *110*, 6642

Theoretical Studies on Conformations of Acrolein, Acrylic Acid, Methyl Acrylate & their Lewis Acid Complexes Houk, *JACS*, **1987**, *109*, 14-23

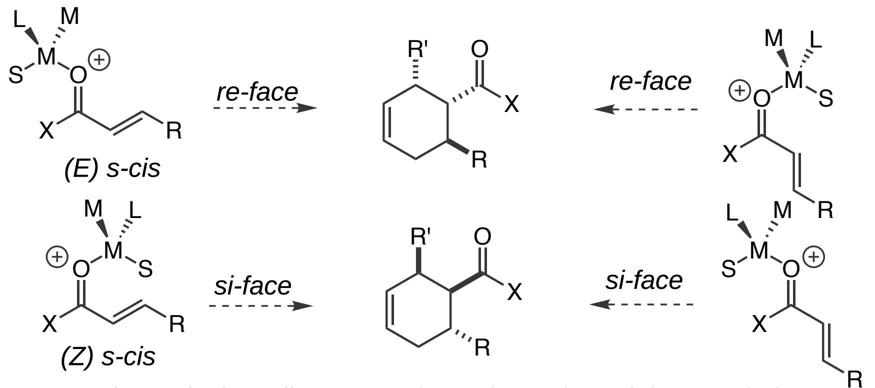
C_2 Symmetry and Asymmetric Induction, Whitesell, *Chem. Rev.*, **1989**, *89*, 1581-1590

The Design of Enantioselective Diels-Alder Catalysts



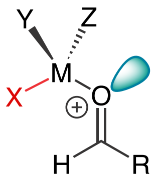
The conformation of the dienophile is also an issue

The S-cis versus S-trans dienophile conformation is coupled to the geometry of the Lewis acid-dienophile complex & both issues determine face selection



Theoretical Studies on Conformations of Acrolein & Methyl Acrylate & their Lewis Acid Complexes
Houk, *JACS*, **1987**, *109*, 14-23

Stereoelectronic Effects (?) in Lewis acid-C=O Complexes

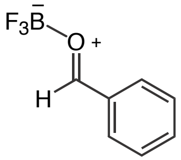


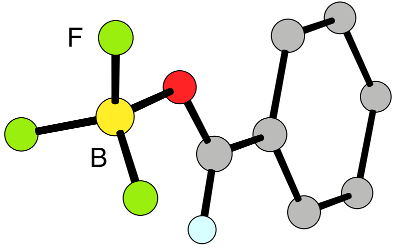
Let X be the most electronegative ligand in the Lewis acid

The stabilizing hyperconjugative interaction between the O-lone pair and σ* M–X will provide a stabilizing interaction for the illustrated conformation.

J. M. Goodman, *Tet. Lett.* **1992**, *33*, 7219

However, there is no evidence for this orienting effect in this X-ray structure reported by Reetz, *JACS*, **1986**, *108*, 2405



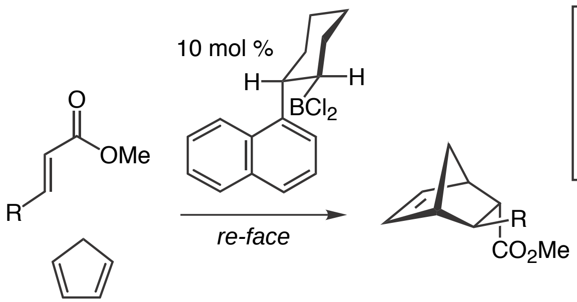


However pi-bonding to coordinated C=O-Al complexes has been reported Barron, *JACS*, **1990**, *112*, 3446, *JACS*, **1990**, *112*, 2950

Theory predicts a small rotational barrier about B–O bond: Wiberg *JACS*, **1988**, *110*, 6642

The Diels-Alder Reaction: Enantioselective Catalysis-2

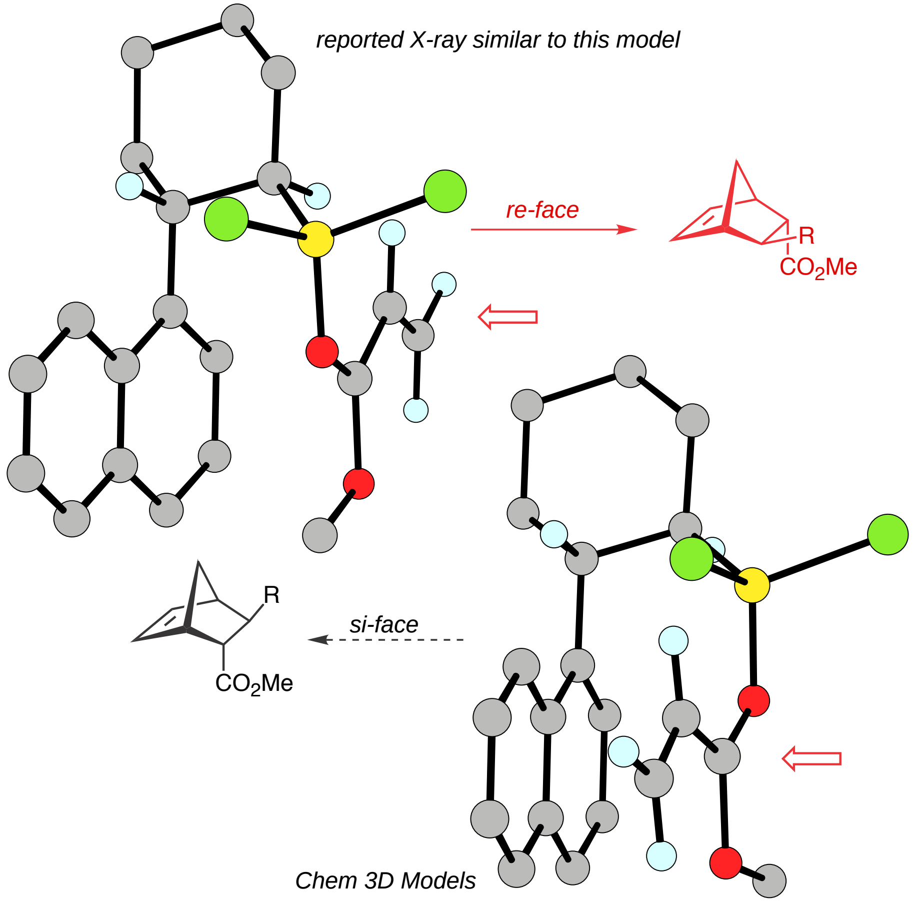
Boron-Based Catalysts: Hawkins *JACS* 1991, *113*, 7794



R	Temp (°C)	Endo ee
H	-78	97 %
Me	-20	91 %
CO_2Me	-78	92 %

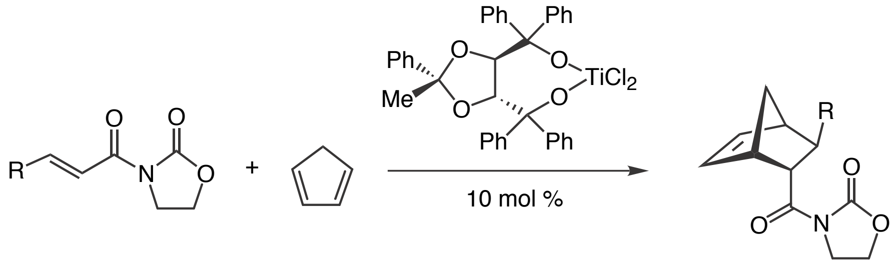
Endo/Exo Ratios not provided.

reported X-ray similar to this model

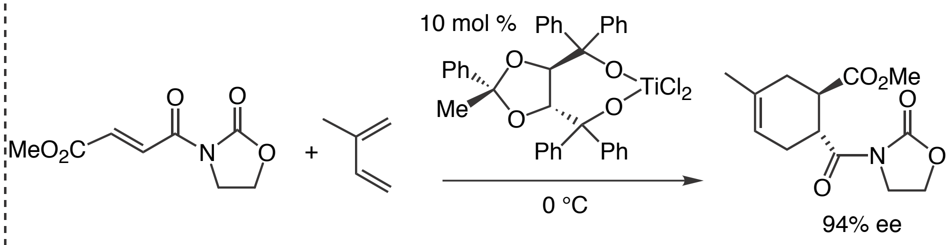


Chem 3D Models

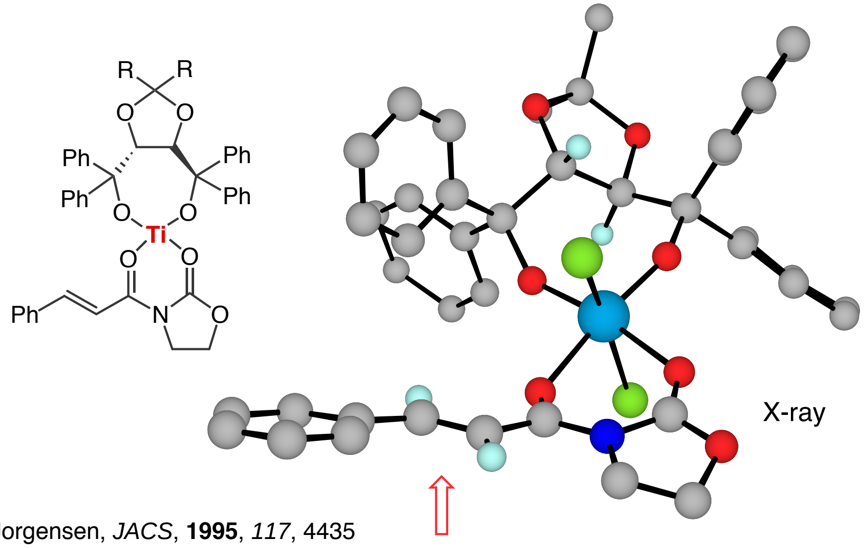
Titanium-Based Catalysts: Narasaka *JACS* 1989, *111*, 5340.



R	Temp (°C)	Endo/Exo	Endo ee
H	-40	96:4	64 %
Me	0	92:8	91 %
Ph	25	88:12	64 %



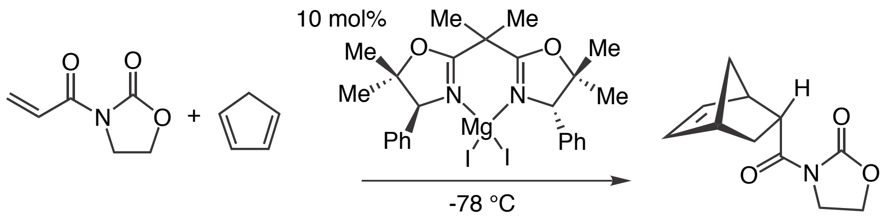
94% ee



A. Jorgensen, *JACS*, **1995**, *117*, 4435

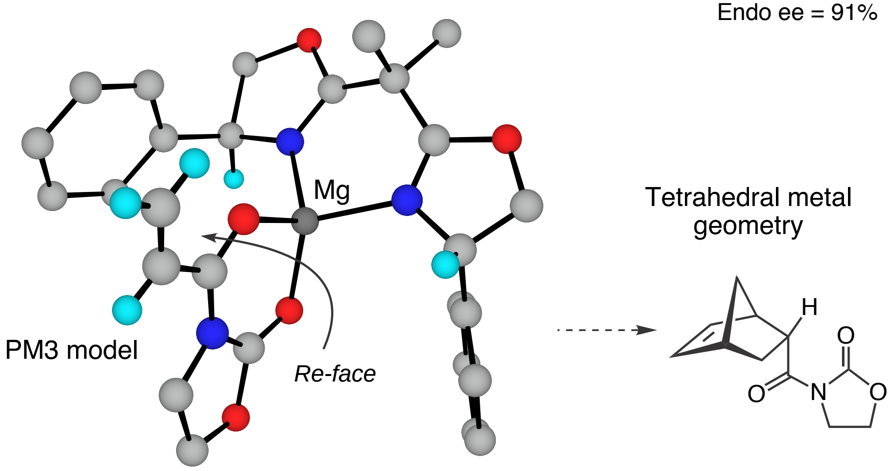
The Diels-Alder Reaction: Enantioselective Catalysis-2

Mg(2+)-Based Catalysts: Corey *Tetrahedron Lett*. 1992, *33*, 6807.



Endo/Exo = 98:2
Endo ee = 91%

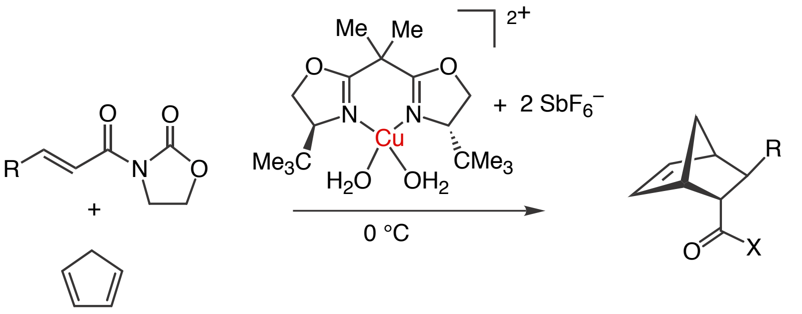
Stereochemical Model:

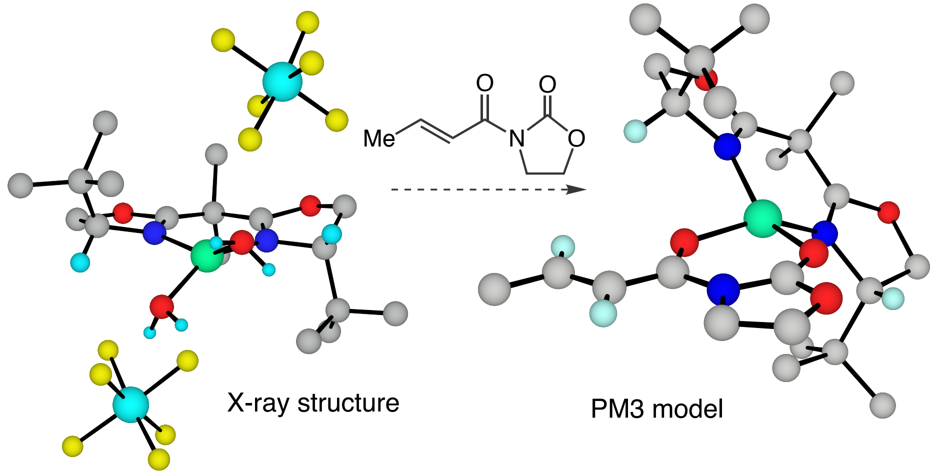


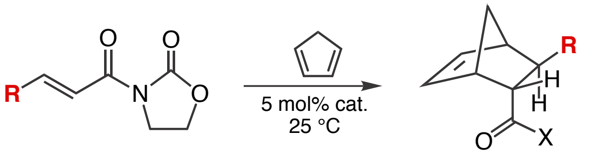
Limitations: Scope limited to illustrated reaction

Cu(2+)-Based Catalysts:

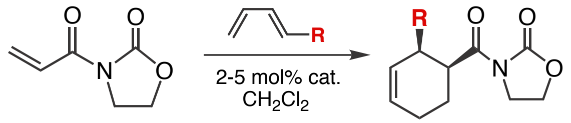
Evans, Miller, Lectka *JACS* **1993**, *115*, 6460.
Angew. Chem. Int. Engl. **1995**, *34*, 798-800.
JACS **1999**, *121*, 7559-7573.
JACS **1999**, *121*, 7582-7594



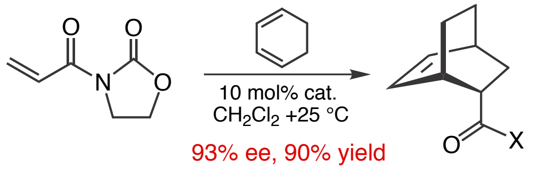




R	time	endo ee	yield
R = Me	8 h	96% ee	98%
R = Ph	8 h	96% ee	95%
R = Cl	8 h	94% ee	95%



R	temp	endo ee	yield
R = Me	25 °C	94% ee	89%
R = Ph	-20 °C	97% ee	95%
R = OAc	0 °C	97% ee	100%

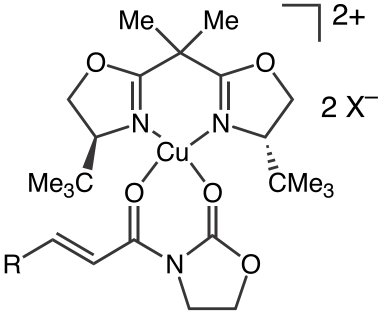


93% ee, 90% yield

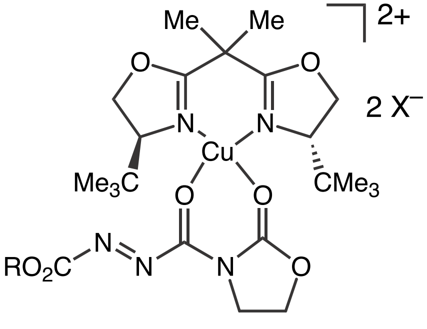
Chiral Cu(2+) Complexes as Chiral Lewis Acids

Cu(box) and Cu(pybox) catalyst-substrate complexes implicated in enantioselective reactions.

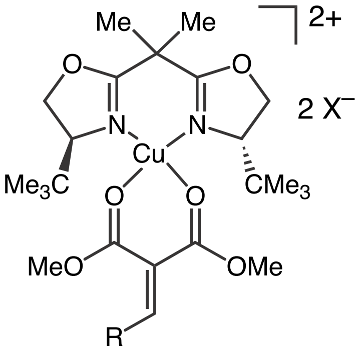
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res*. **2000**, *33*, 325-335. **(pdf)**



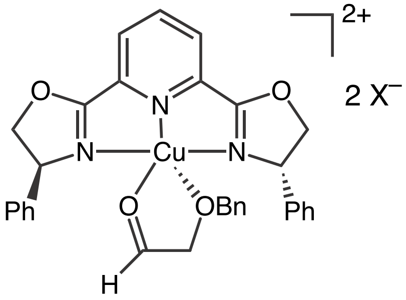
Cycloaddition Reactions
Michael Reactions



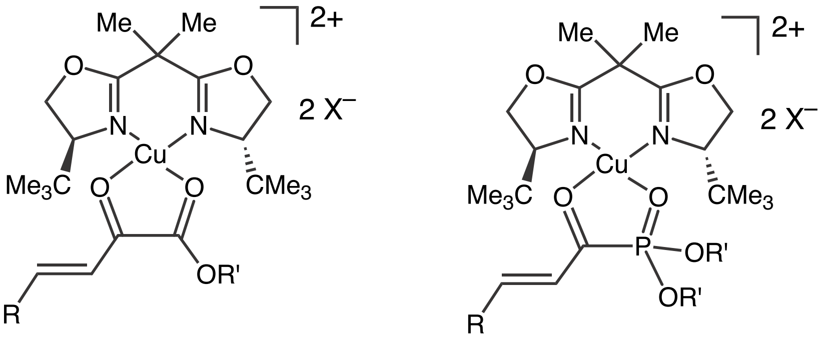
Enol Amination Reactons



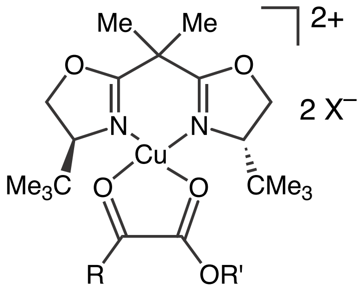
Michael Reactions



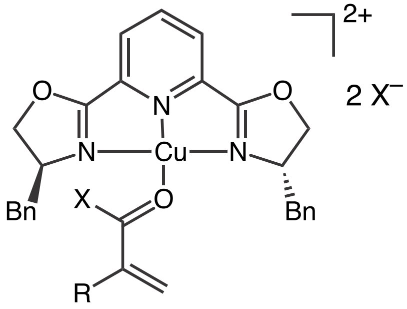
Aldol Reactions



Hetero Diels-Alder Reactions

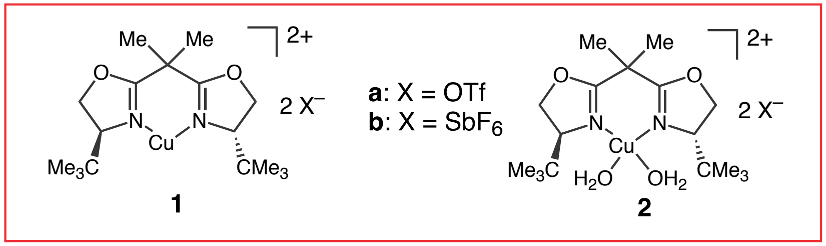


R = H, Cycloaddition Reactions
Ene Reactions
R = Alkyl, Cycloaddition Reactions
Aldol Reactions



Diels-Alder Reactions

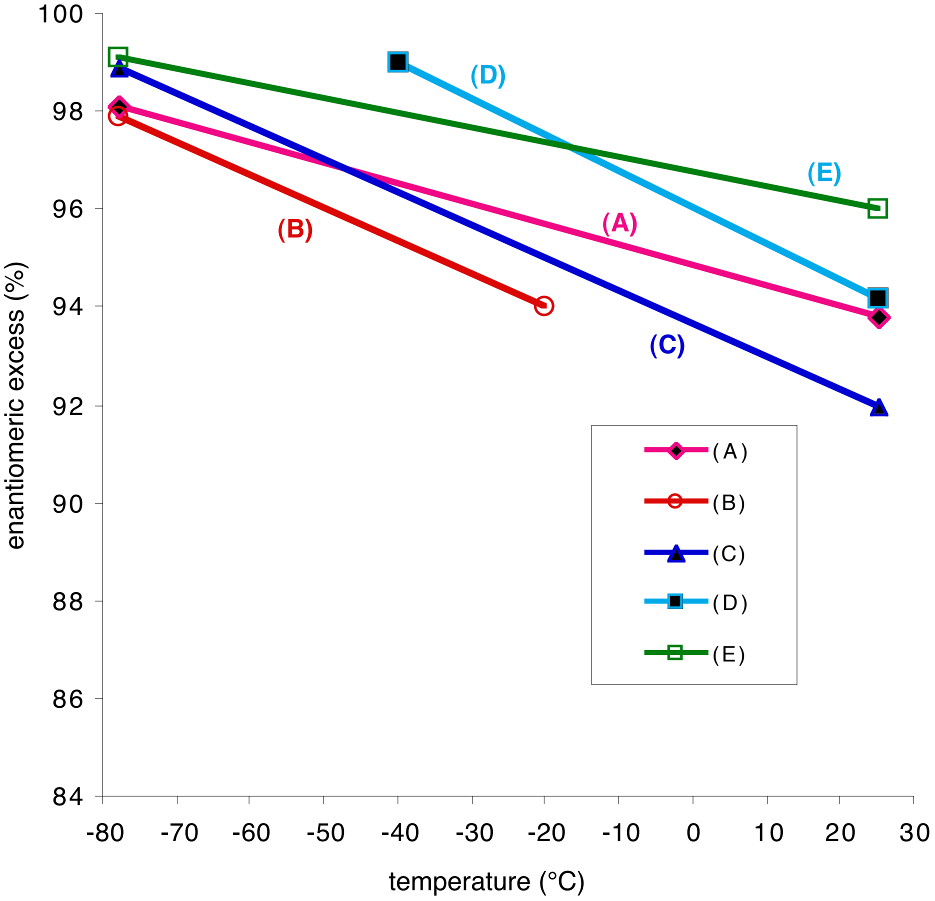
Temperature–Enantioselection Profile for [Cu((S,S)-t-Bu-box)](X)$_2$ Catalysts



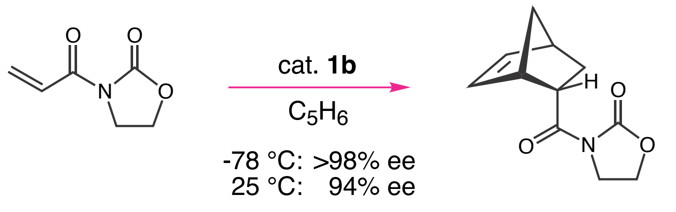
1

2

a: X = OTf
b: X = SbF$_6$



(A)

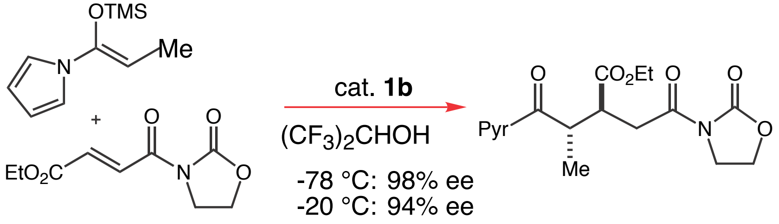


cat. **1b**

C_5H_6

-78 °C: >98% ee
25 °C: 94% ee

(B)

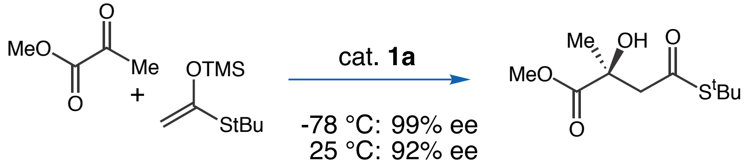


cat. **1b**

$(CF_3)_2CHOH$

-78 °C: 98% ee
-20 °C: 94% ee

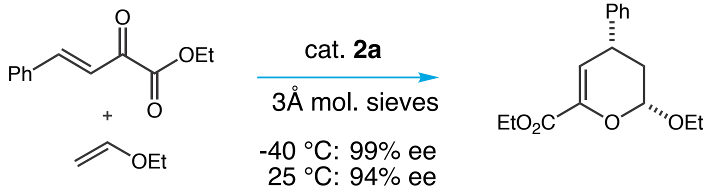
(C)



cat. **1a**

-78 °C: 99% ee
25 °C: 92% ee

(D)

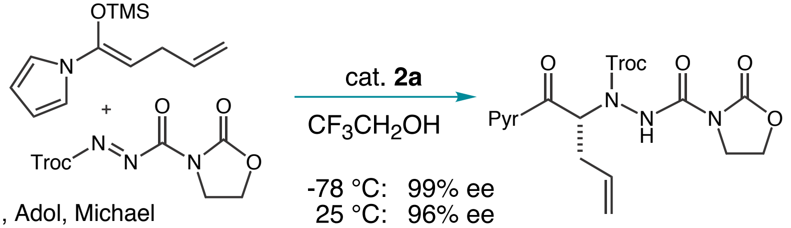


cat. **2a**

3Å mol. sieves

-40 °C: 99% ee
25 °C: 94% ee

(E)



cat. **2a**

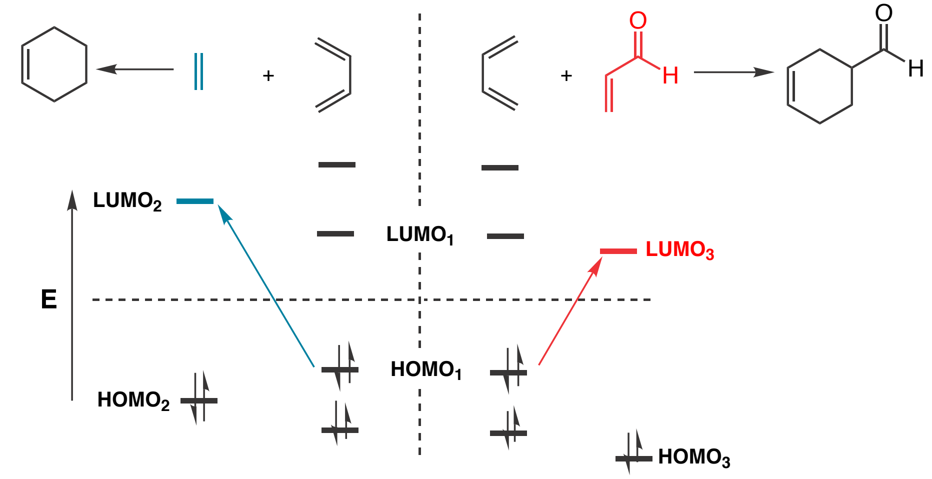
CF_3CH_2OH

-78 °C: 99% ee
25 °C: 96% ee

"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335. **(electronic pdf)**

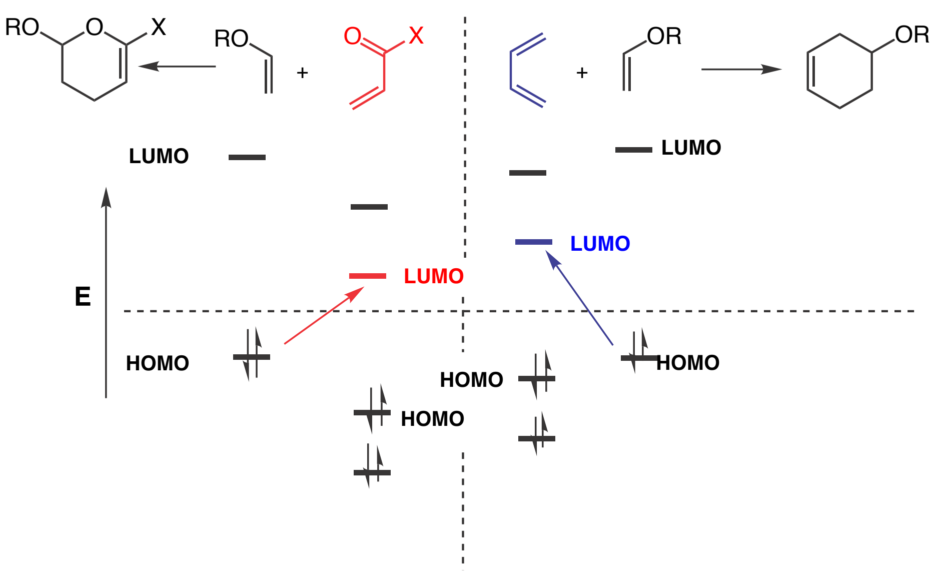
Diels-Alder Reaction: Molecular Orbital Analysis

Ethylene & Butadiene Vs Butadiene & Acrolein

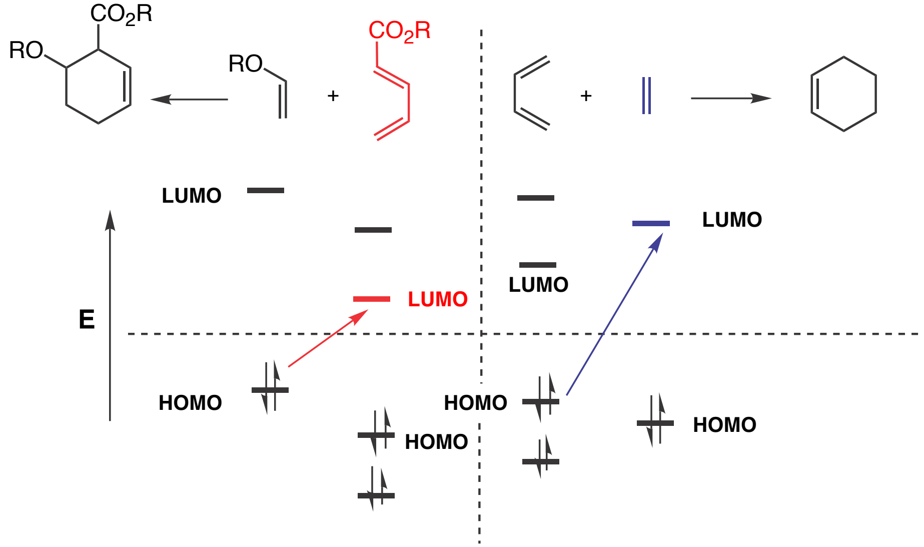


ΔE ($LUMO_3$-$HOMO_1$) < ΔE ($LUMO_2$-$HOMO_1$) ⟹ *Rate Acceleration*

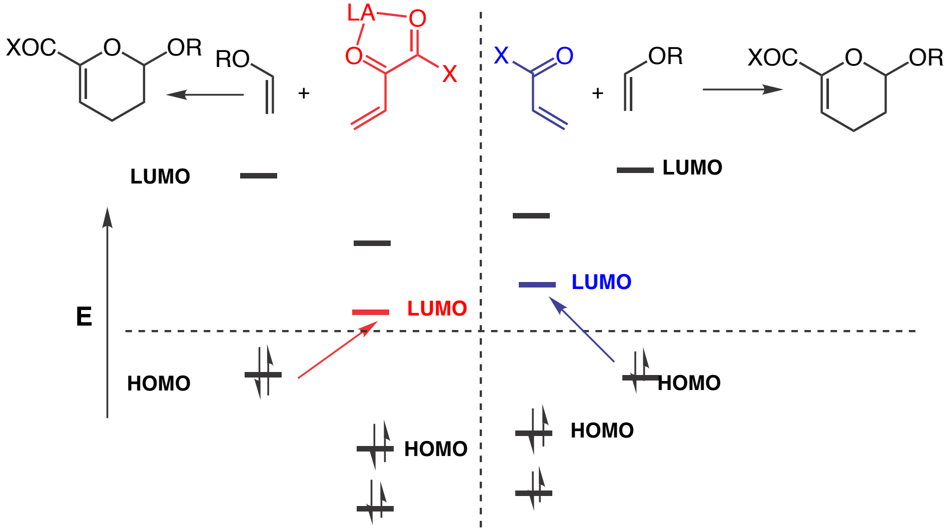
"Inverse-Electron Demand" Hetero-Diels-Alder Reactions



"Inverse-Electron Demand" Diels-Alder Reactions

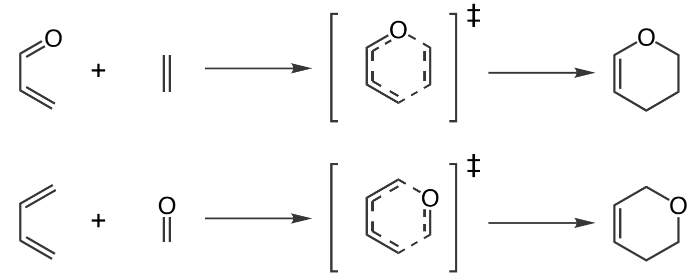


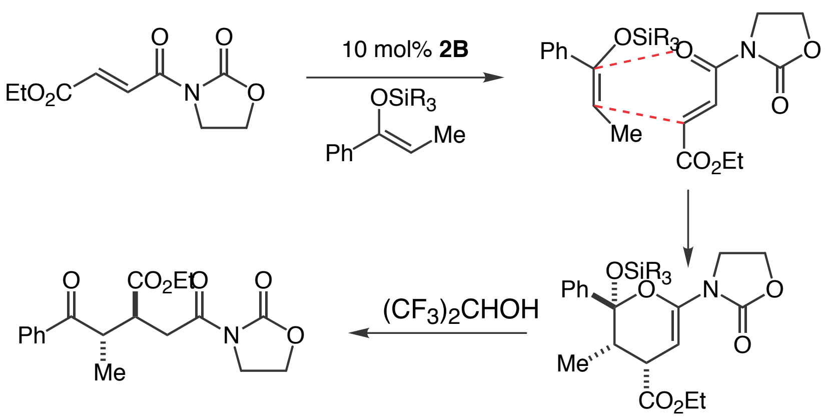
■ **Lewis Acid Catalysis of the reaction is possible:**



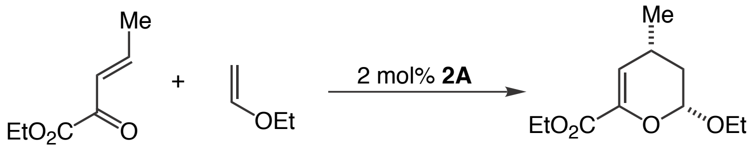
Hetero-Diels-Alder Reactions – Chiral Catalysis

•Heteroatom-substituted reactions are also possible:

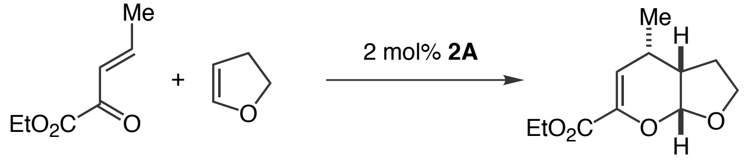




Evans, Scheidt, Johnston, Willis *J. Am. Chem. Soc.* **2001**, *123*, 4480.



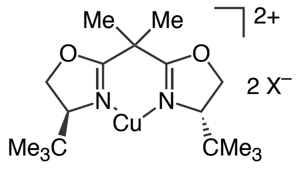
24:1 Endo:Exo
87% yield
97% ee



16:1 Endo:Exo
96% yield
97%ee

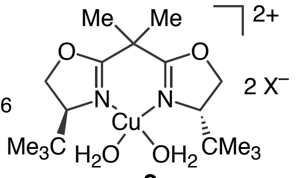
Evans, Johnson, Olhava *J. Am. Chem. Soc.* **2000**, *122*, 1635.

Chiral Copper Lewis Acids:

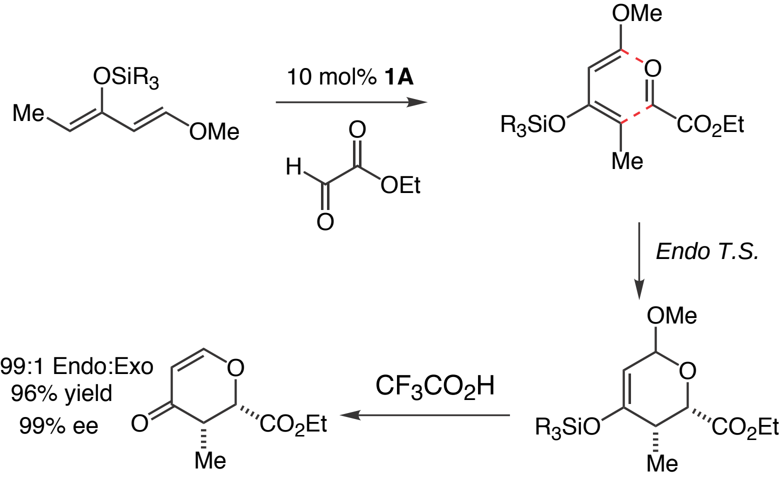


1

A: X = OTf
B: X = SbF$_6$

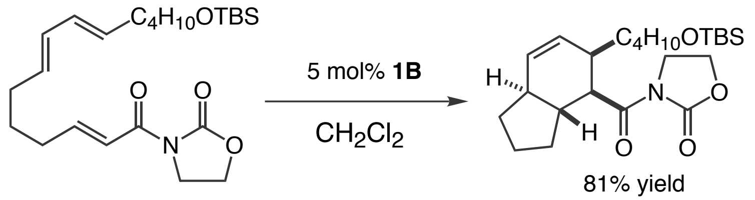


2



>99:1 Endo:Exo
96% yield
99% ee

Jorgensen *J. Am. Chem. Soc.* **1998**, *120*, 8599.

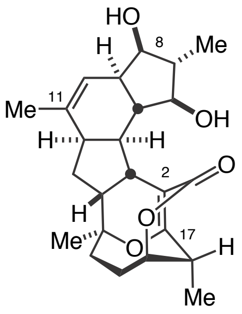


81% yield
96% ee, 99:1 dr

Evans, Johnson *J. Org. Chem.* **1997**, *62*, 786-787.

Diels-Alder Reactions: **Synthesis of FR182877**

Structures of FR182877 & Hexacyclinic acid



(—)-FR182877

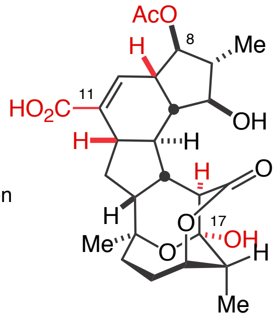
Structural Differences:

Acylation at C_8 hydroxyl

Oxidation at C_{11}

endo vs. *exo* Diels-Alder retron

Hydration across C_2-C_{17} double bond

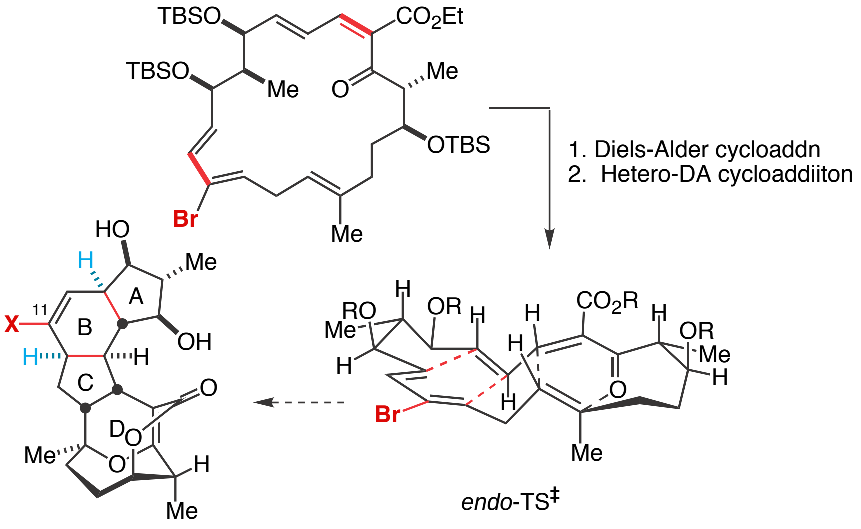


Hexacyclinic Acid

Sato, B. *J. Antibiot.* **2000**, 123, 204, 615.
Corrected Structure: *J. Antibiot.* **2002**, C-1.

Hofs, R., et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 3258.

Hypothesis: A Transannular Diels-Alder Cycloaddition Cascade



1. Diels-Alder cycloaddn
2. Hetero-DA cycloaddiiton

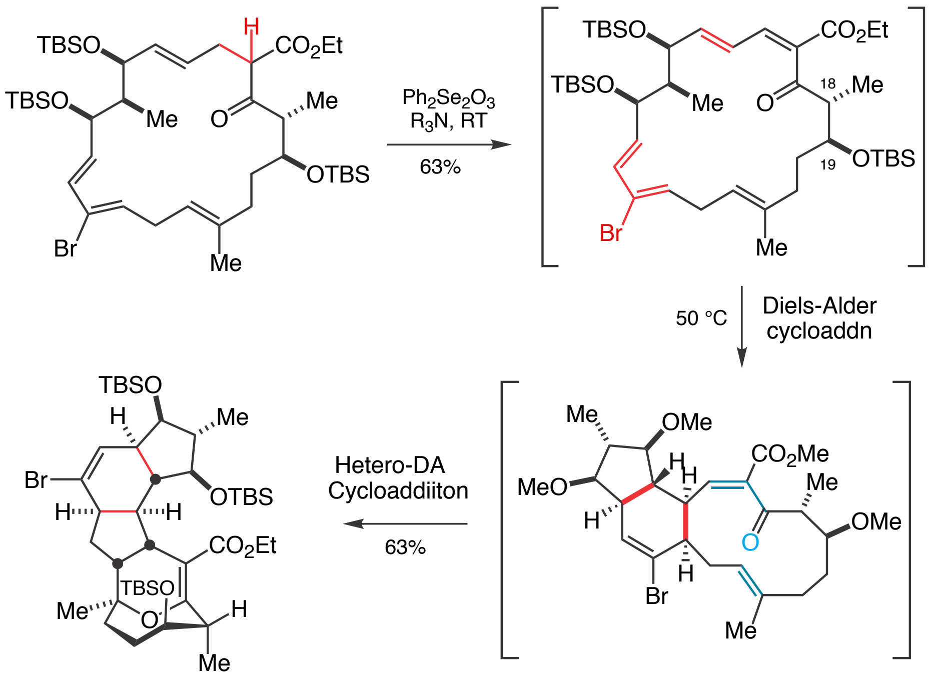
endo-TS‡

FR182877

Evans & Starr, *JACS*, **2003**, *125*, ASAP

Sorensen et al, *JACS*, **2003**, *125*, 5393

The Transannular Diels-Alder Step

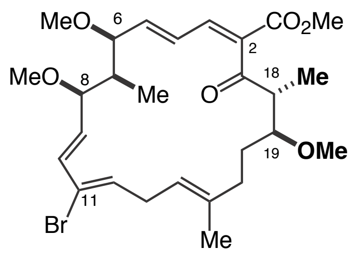


$Ph_2Se_2O_3$
R_3N, RT
63%

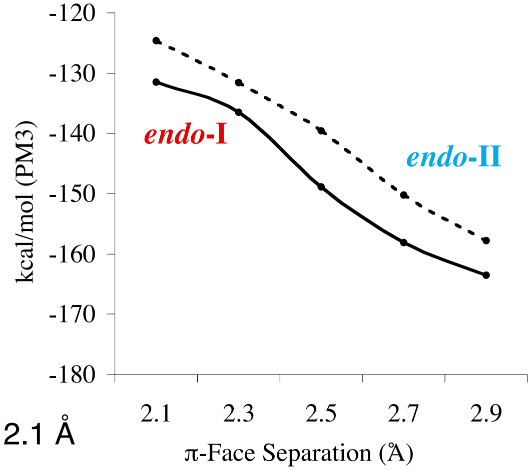
50 °C
Diels-Alder cycloaddn

Hetero-DA Cycloaddiiton
63%

C_{18} & C_{19} stereocenters exert complete control over the first cycloaddition (Evans)

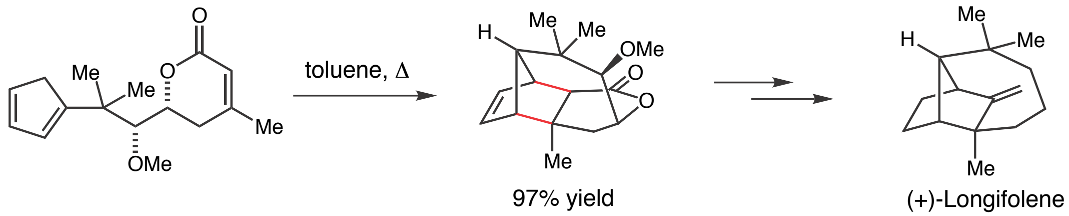


(natural configuration)

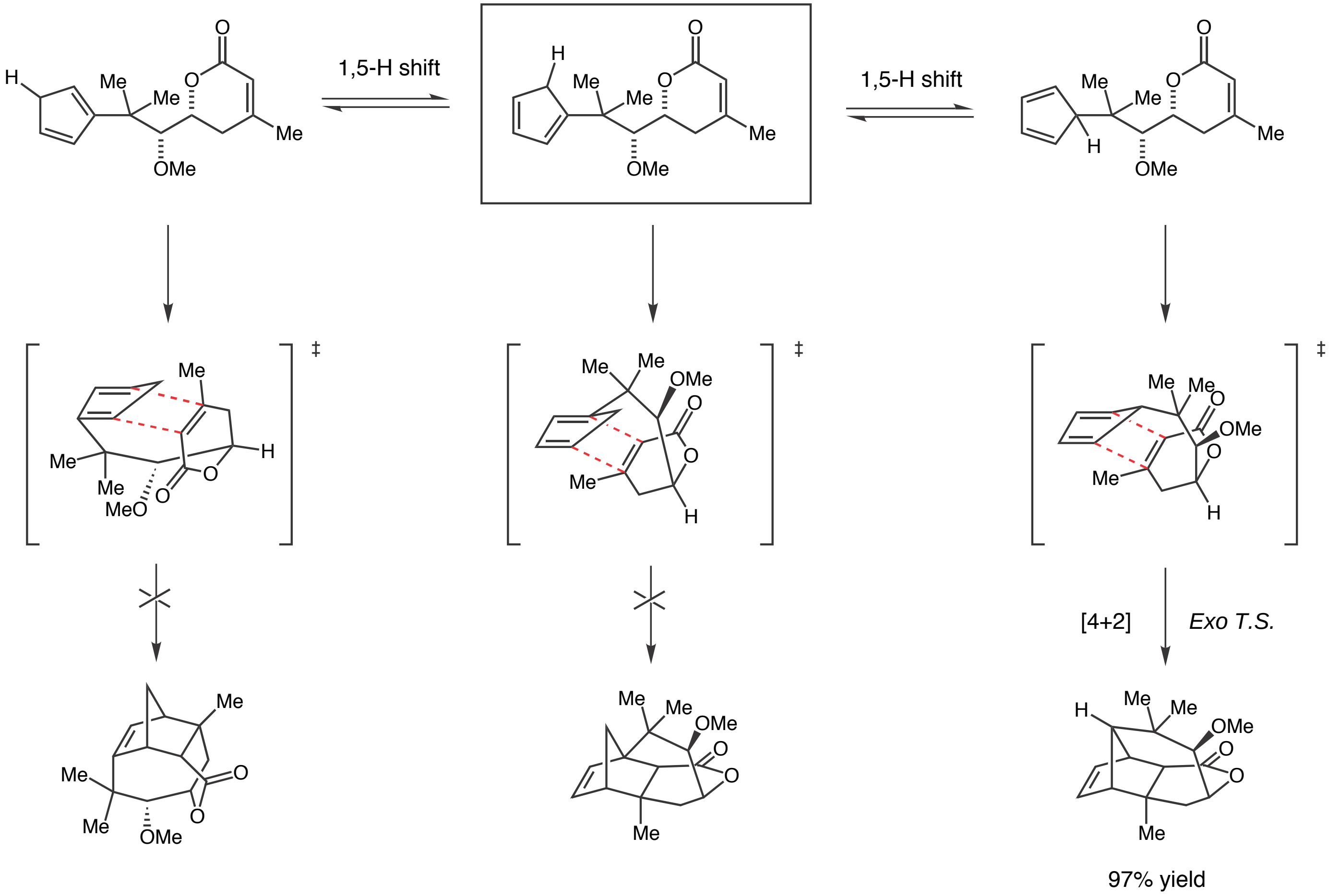


$\Delta\Delta E^{\ddagger}$ = 5–9 kcal/mol @ 2.1 Å

■ Problem of the Day:



Fallis *J. Org. Chem.* **1993**, *58*, 2186.



17-14-Fallis Longifolene 10/22/01 8:06 AM

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 17

Dipolar cycloaddition Reactions

- Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11, p 647-648
Concerted Pericyclic Reactions

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.pp 294-331 **(Handout)**

D. Ripin, W. *Use of Isoxazoles as 1,3-Dicarbonyl equivalents in Organic synthesis*; Evans Group Seminar **1997** **(ElectronicHandout)**

D. A. Evans

Monday,
October 27, 2003

Dipolar Cycloaddition Reactions

General References

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.

Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley, **1984,** Volumes 1 & 2,

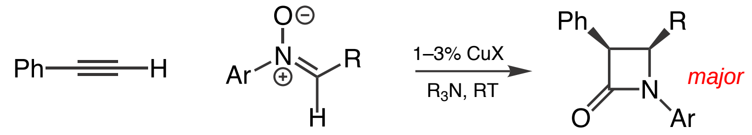
Jorgensen, *Asymmetric 1,3-Dipolar cycloadditions*, *Chem Rev*. **1998**, *98*, 863-909

Padwa, A. Generation and utilization of carbonyl ylides via the tandem cyclization-cycloaddition method." *Acc. Chem. Res.* **1991**, *24*, 22. **(handout)**

Confalone, P. N.; Huie, E. M. *The [3+2] Nitrone-Olefin Cycloaddition Reaction Org. React. (N.Y.)* **1988**, *36*, 1.
S. Kanemasa, *Metal Assisted 1,3-Dipolar Cycloaddition Reactions,* SynLett **2002**, 1371-1387 **(handout)**

Problem of the Day

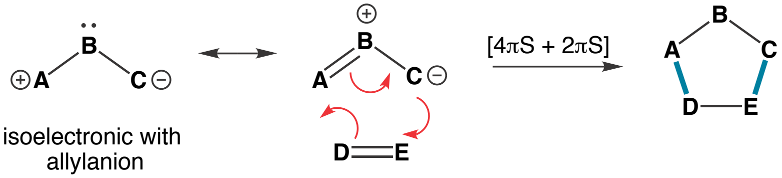
Provide a plausible mechanism for this transformation in the space below. *In attacking this question, it is important that you are aware of the transformation that transpires when terminal acetylenes are treated with Cu(I) or Ag(I) in the presence of an amine base.*



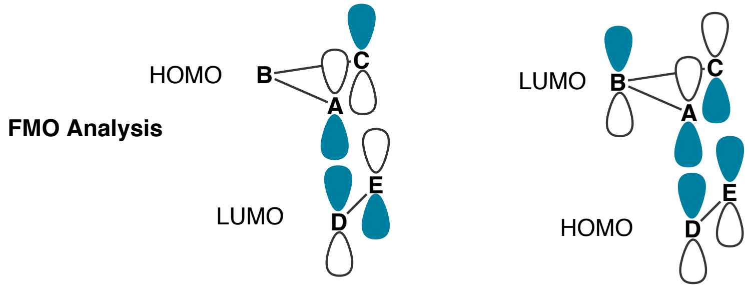
In 1995 Miura and co-workers reported the remarkable reaction illlustrated below (*J. Org. Chem.* **1995**, *60*, 4999). Recently, Fu has reported an enantioselective variant of this transformation (*J. Am. Chem. Soc.* **2002**, *124*, 4572). In most instances, the cis adduct is formed in large excess (>90%). There is really no thoughtful mechanism in the literature for this transformation. You will be graded on "reasonability"

Dipolar Cycloaddition Reactions: An Introduction

The General Reaction Family

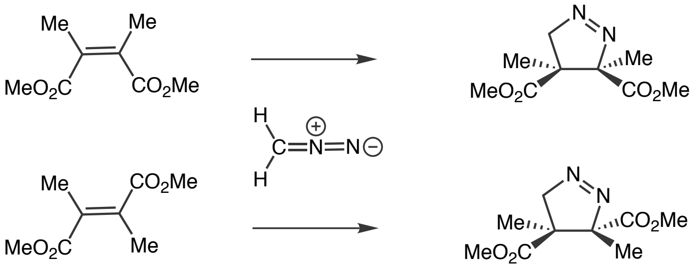


isoelectronic with allylanion

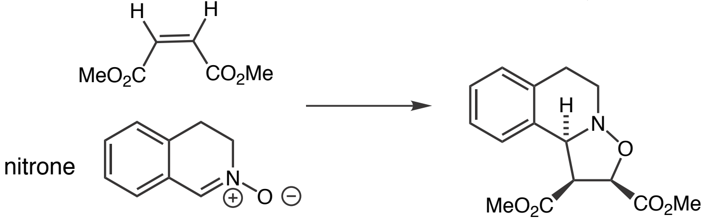


The specific set of reaction partners, will define the dominant frontier orbitals

Reaction Stereospecificity: The Dipolariphile (Padwa, Vol 1, pp 61-90)



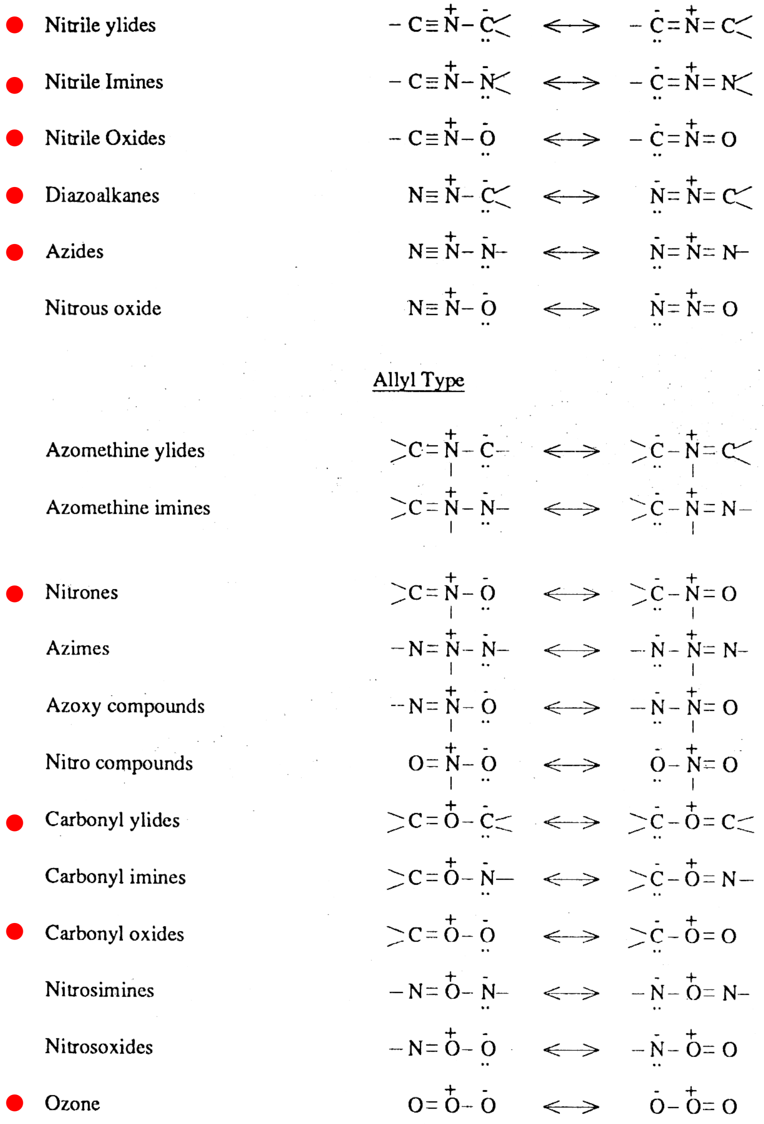
Rinehart, *JACS* **1962**, *84*, 3736



Fumarate gives trans cycloadduct

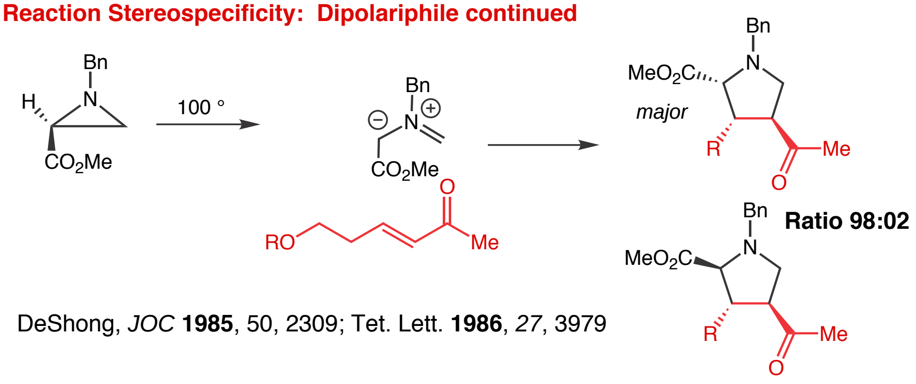
Huisgen, *Chem. Ber.* **1969**, *102*, 736

Classification of 1,3-Dipoles Containing C, N, & O Atoms



(After R.Huisgen, J.Org.Chem., 1976, 41, 403.)

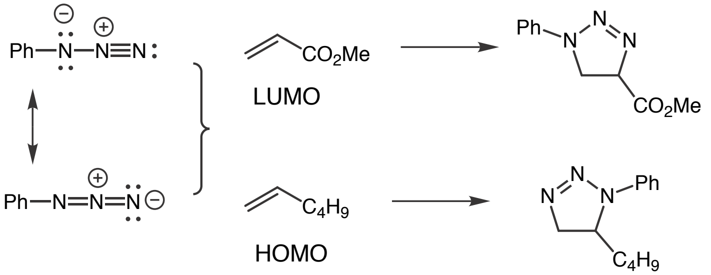
Reaction Stereospecificity: Dipolariphile continued



DeShong, *JOC* **1985**, 50, 2309; Tet. Lett. **1986**, *27*, 3979

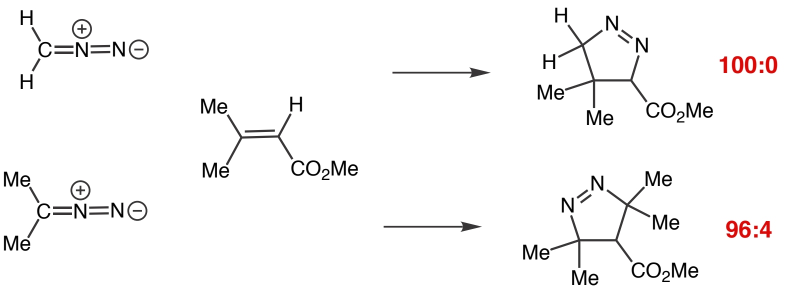
We will return to the other stereochemical element of this reaction shortly

Reaction Regiochemistry (Padwa, Vol 1, pp 135)



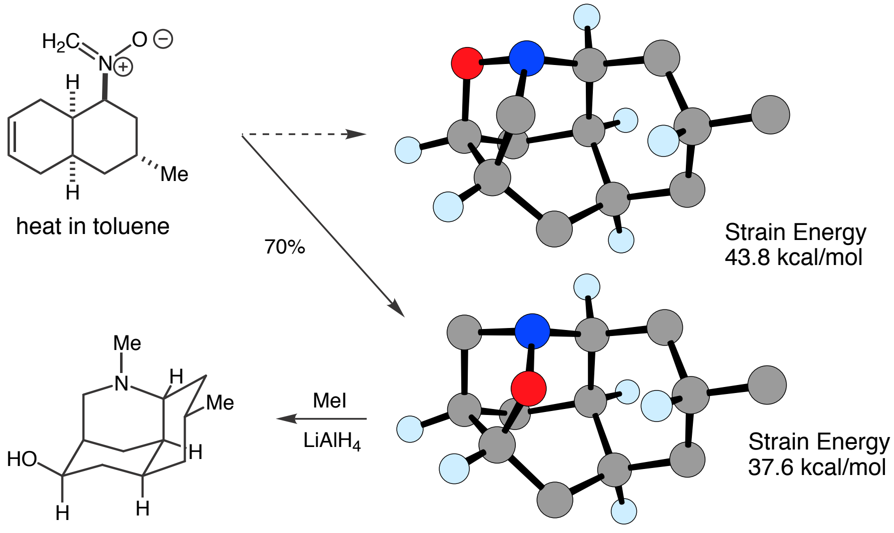
The specific set of reaction partners, will define the dominant frontier orbitals

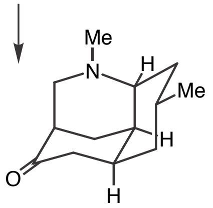
Steric Effects will frequently alter regioselectivity (Padwa, Vol 1, pp 144)



Steric effects are also important considerations in reaction regiochemistry

Rng strain factors may control regioselectivity



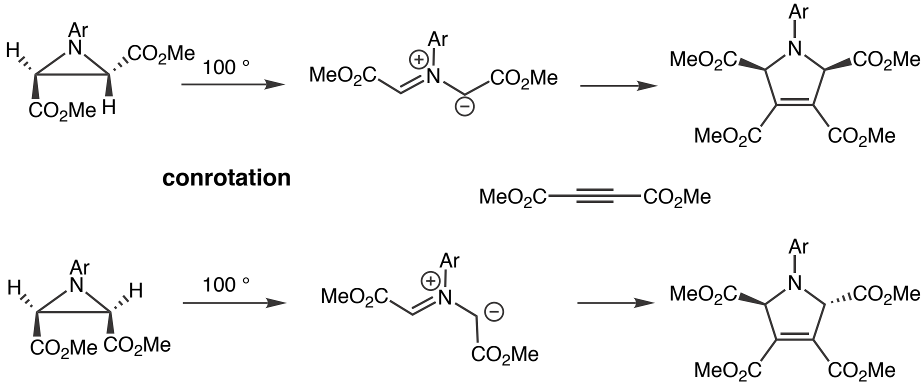


Here is an elegant example of regiochemical control. While the authors offer no explanation for the outcome, it appears that the reaction is being governed by transition state steric strain factors.

Oppolzer, *JACS* **1978**, *98*, 6722

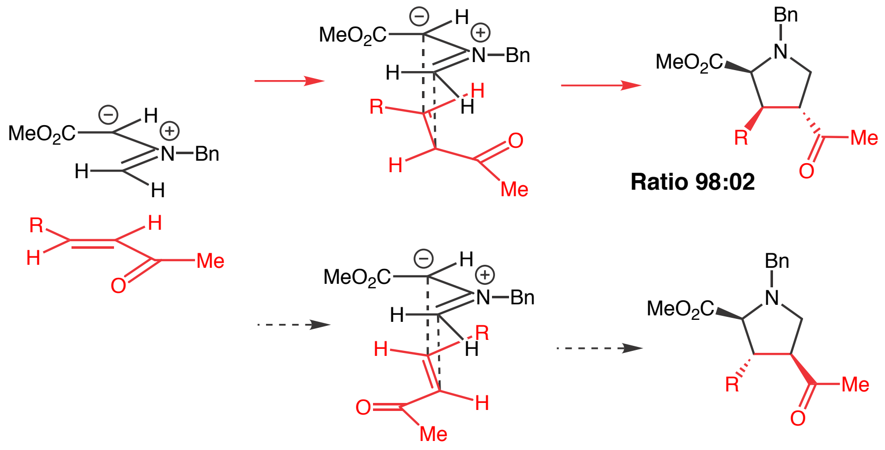
Reaction Diastereoselectivity

Huisgen et al, *Angew.Chem. Int. Ed*. **1969**, *8*, 604



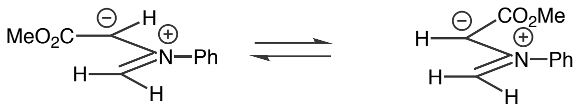
Relative Orientation of Reaction Partners

DeShong, *JOC* **1985**, 50, 2309; Tet. Lett. **1986**, *27*, 3979



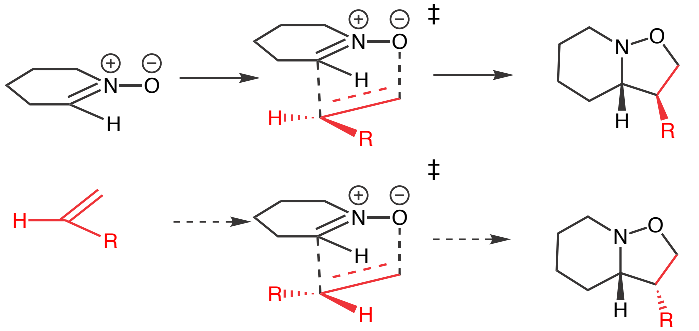
Ratio 98:02

The above analysis is clouded by the fact that the geometry of the 1, 3-dipole is not fixed.



Monosubstituted Olefins.

In the following study, 1,3-dipole isomerism is not an issue

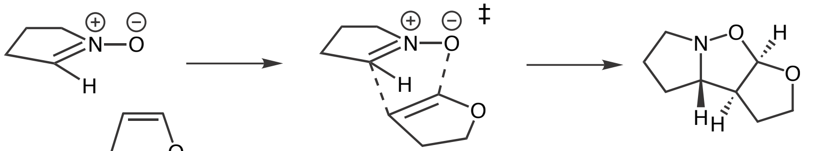


Ph	Me	CO$_2$Me
78%	100%	82%
22%	0%	18%

Diastereoselection appears to be dictated by steric effects

Tufariello, *Accounts. Chem. Res.* **1979**, *12*, 396-1403

Cis Disubstituted Olefins.



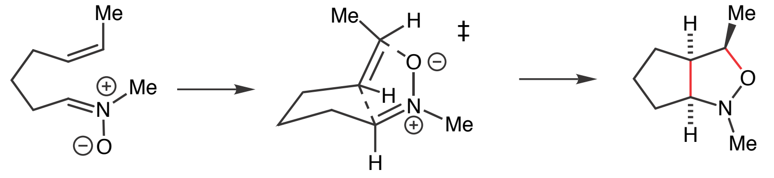
Major cycloadduct (30:1)

The preceding trend appears to be reinforced by cis disubstitution

I. Washita et al, *Chem lett* **1979**, 1337

Intramolecular Reaction Variants

N. LeBel et al, *JACS* **1964**, *86*, 3759

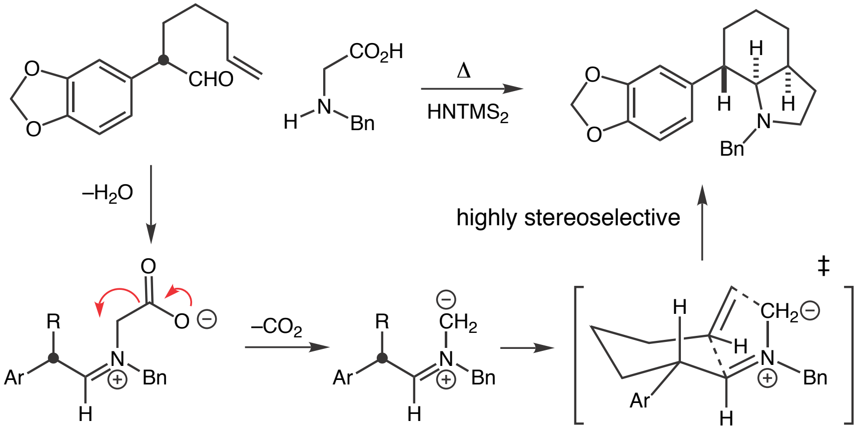


Orientation probably driven by ring strain as in Oppolzer case (previous page)

"highly diastereoselective"

Intramolecular Reaction Variants

P. Confalone et al, Tet. Lett. **1984**, *25*, 4613



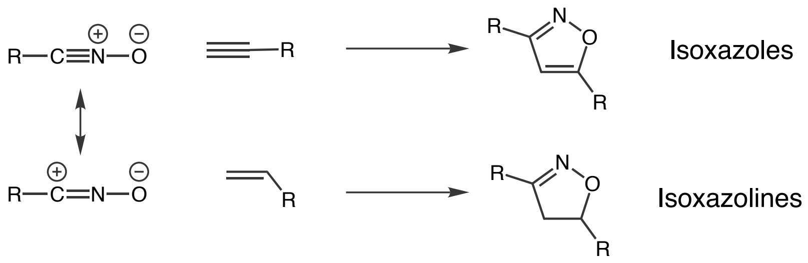
Conclusions on Reaction Diastereoselection

In general reaction diastereoselection appears to be dictated by steric and torsional rather than electronic factors

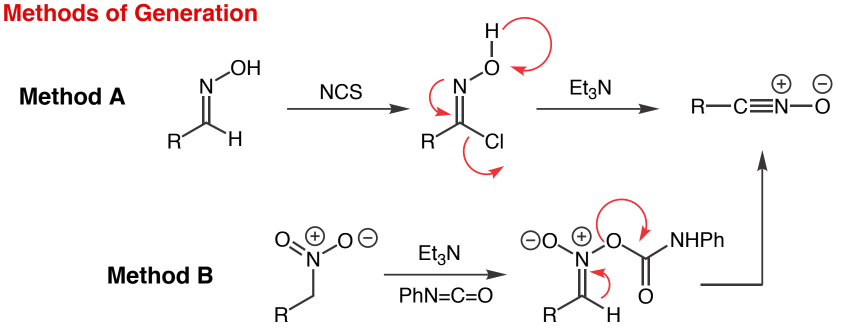
Dipolar Cycloaddition Reactions: Nitrile Oxide Cycloadditions

The Basic Reactions

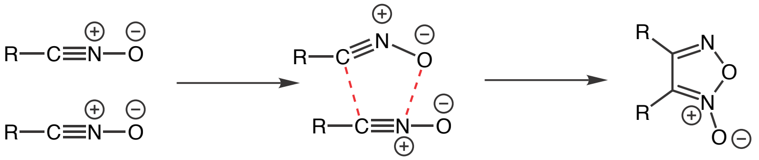
Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley, **1984,** Vol 1, Chapter 3



Methods of Generation



Stability Nitrile oxides are usually prepared in the presence of the olefin or acetylene acceptor. These intermediates are generall unstable and will dimerize if not given an alternative reaction course

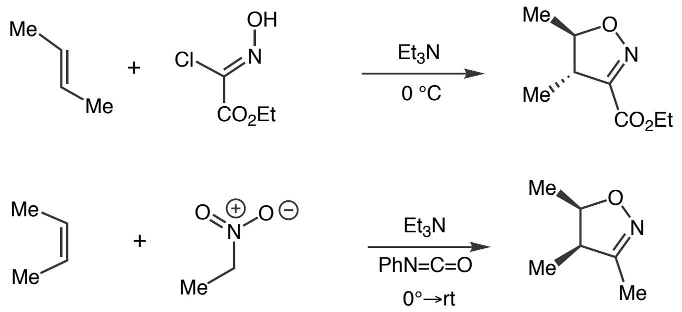


Regioselectivity Nitrile oxide cycloadditions with olefins and acetylenes are usually quite regioselective and in the direction as illustrated above.

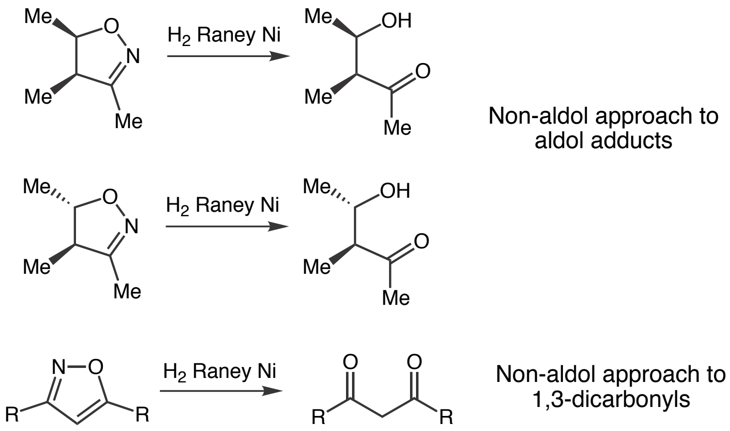
DeShong, *JOC* **1985**, 50, 2309; Tet. Lett. **1986**, *27*, 3979

Reactions with olefins are stereospecific

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.Chapter 6, pp2 69–298

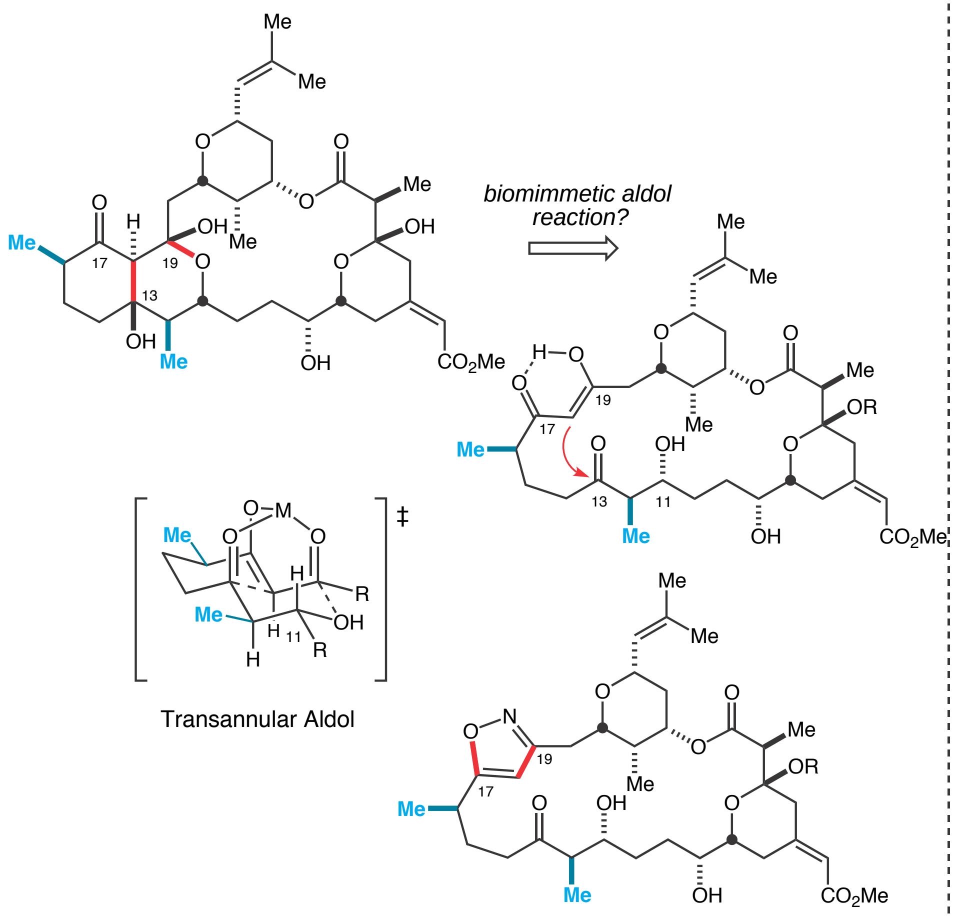


Oxazoline Cleavage

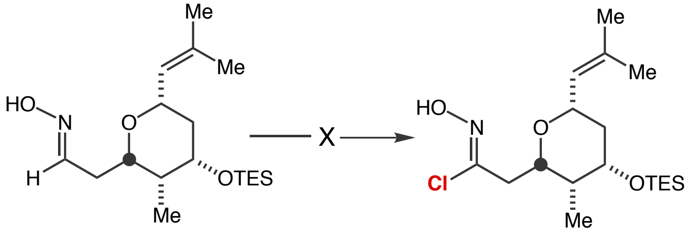

H2 Raney Ni
Non-aldol approach to aldol adducts
H2 Raney Ni
H2 Raney Ni
Non-aldol approach to 1,3-dicarbonyls

Preferred method for reducing oxazoles and oxazolines:
Nittta et al, *Chem. Comm.* **1982**, 877-878: $Mo(CO)_6$ MeCN

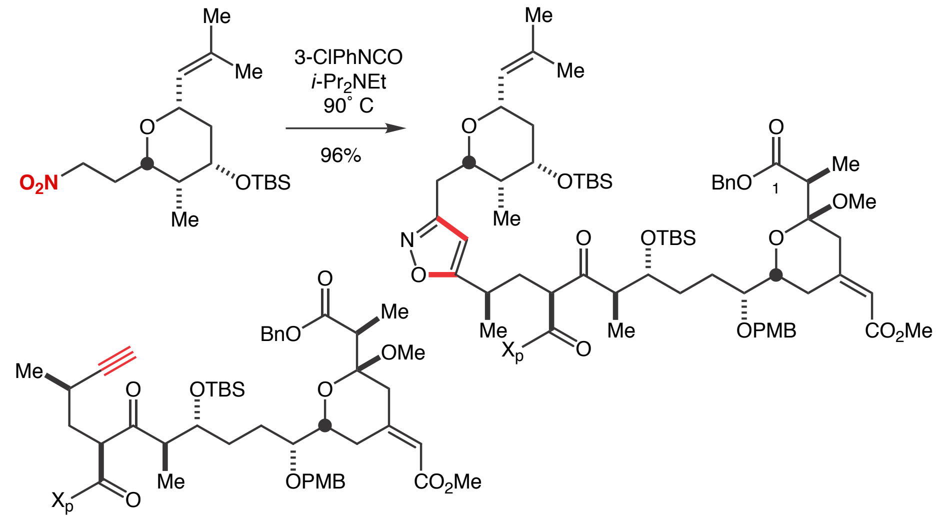
Miyakolide Synthesis: with David Ripin & David Halstead, *JACS* **1999**, *121*, 6816-6826



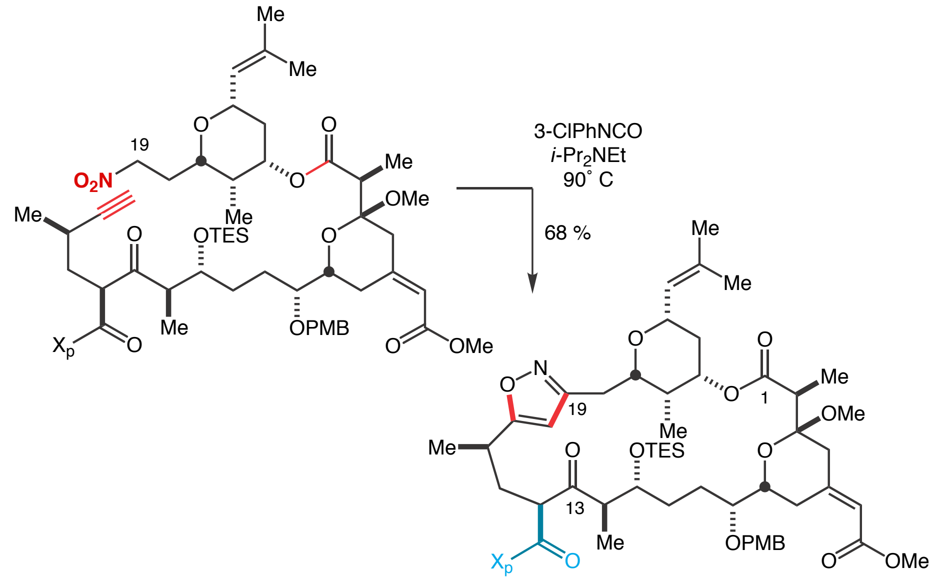
Competing olefin chlorination eliminated this approach to the nitrile oxide precursor



The Intermolecular Case



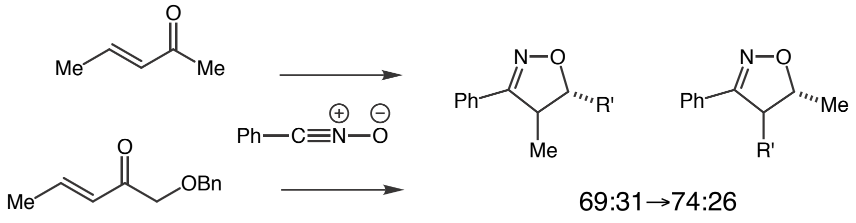
The Intramolecular Case



Nitrile Oxide Cycloadditions: Applications in Synthesis

Development of Directed Cycloadditions

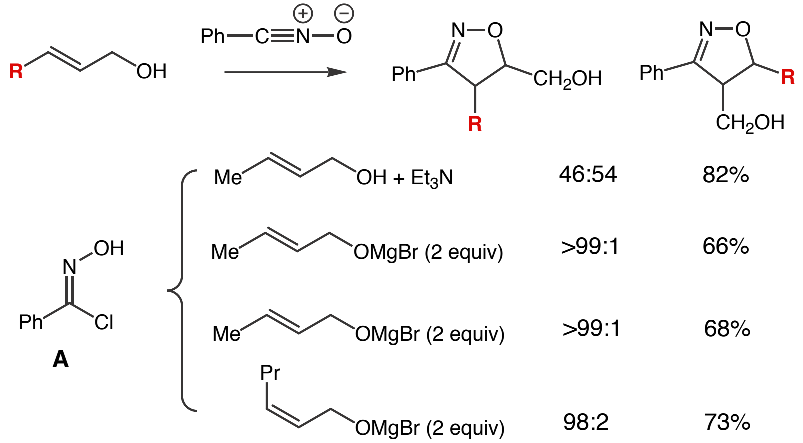
Kanemasa at al, *JACS* **1994**, *116*, 2324-2339 **(electronic handout)**
Kanemasa at al, Metal-Assisted Stereocontrol of 1,3-Dipolar Cycloaddition Reactions
SynLett 2002, 1371-1387 **(electronic handout)**

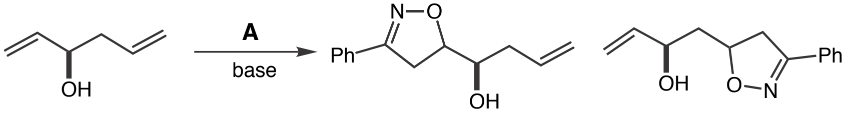


conditions; no cat, ZnI_2, $Ti(OiPr)_4$

While lewis acid activation is known, no change in regiochemistry was noted under above connditions

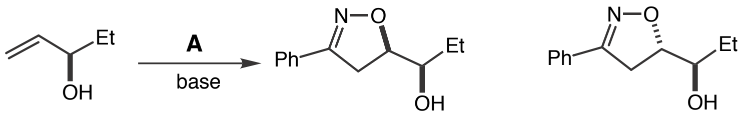
Magnesium alkoxides found to effect regiochemical control



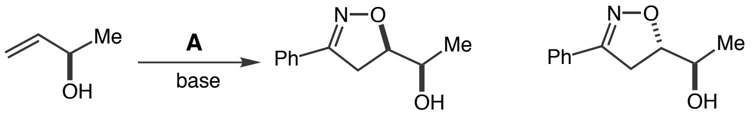


Et_3N	**67:33**
EtMgBr	**100:0**

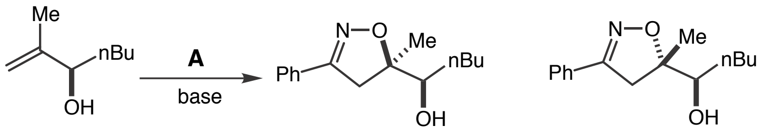
Reaction Diastereoselectivities



Et_3N	**67:33**	**60%**
EtMgBr	**95:5**	**75%**

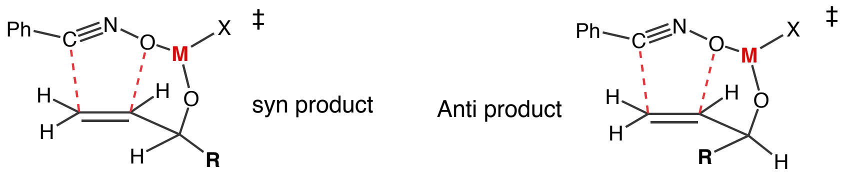


Et_3N	**61:39**	**60%**
EtMgBr	**96:4**	**75%**

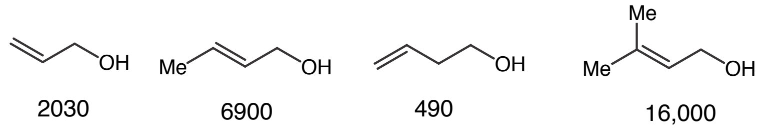


Et_3N	**60:40**	—
EtMgBr	**96:4**	**85%**

Stereochemical Rationale

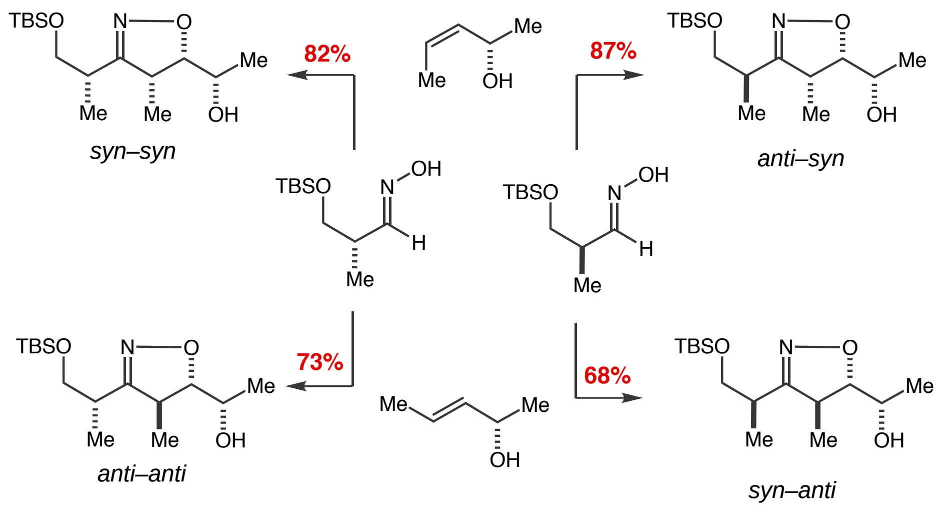


Rate acceleratons



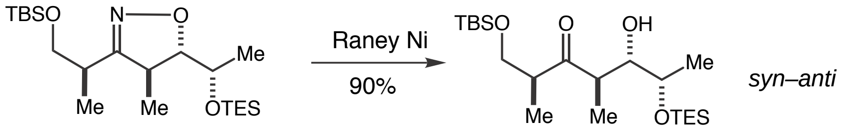
Applications in Polypropionate Synthesis

Carreira at al, *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085

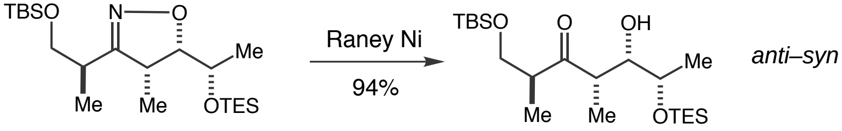


a, Oxime Chlorination: t-BuOCl; b, 3 Equiv EtMgBr, room temp, 12 h

Oxazoline Reduction



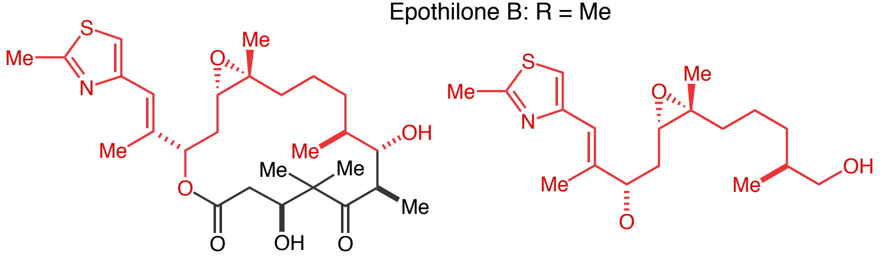
Lit Conditions: Curran, *JACS* **1983**, *105*, 5826; *JOC* **1984**, *49*, 3474

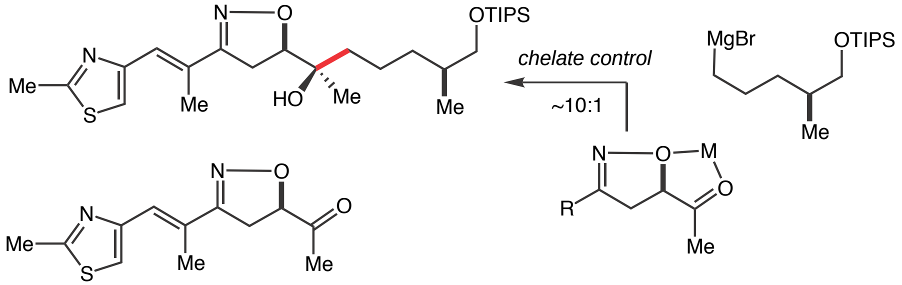


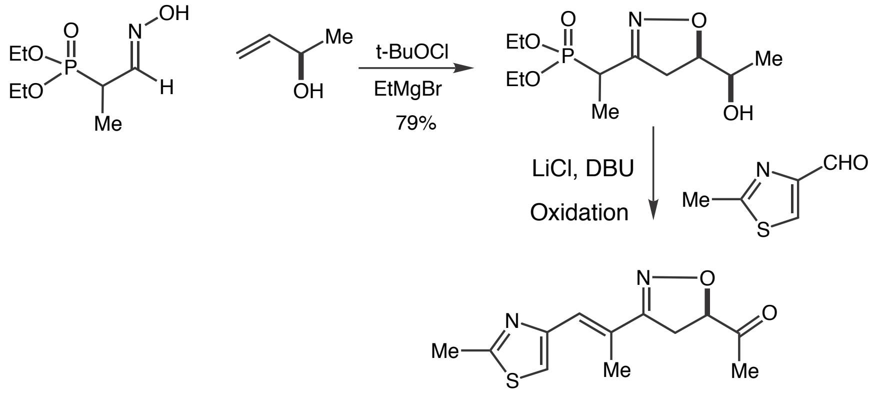
Applications to the Synthesis of Epothilones A, B

Carreira & Bode *JACS* **2001**, *123*, 2082–2085

Epothilone A: R = H
Epothilone B: R = Me



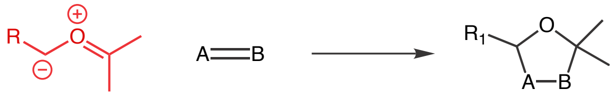




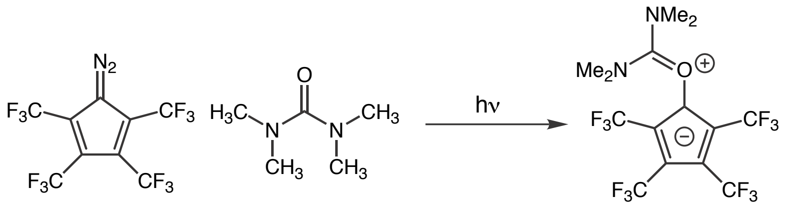
The Basic Reactions

Reviews - Ylides

Padwa, A.; Hornbuckle, S. F. *Chem. Rev*. **1991**, *91*, 263-309.
Padwa, A.; Krumpe, K. E. *Tetrahedron*. **1992**, *48*, 5385-5483.
Padwa, A. *Acc. Chem. Res*. **1991**, *24*, 22-28.

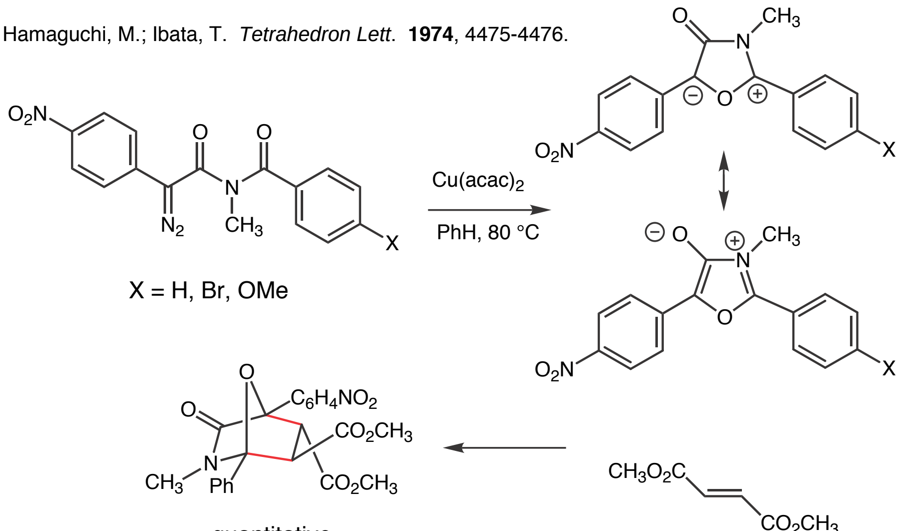


Stabilized (Isolable) Carbonyl Ylides



Arduengo, A. J., III; Janulis, E. P., Jr. *J. Am. Chem. Soc*. **1983**, *105*, 5929-5930

Hamaguchi, M.; Ibata, T. *Tetrahedron Lett*. **1974**, 4475-4476.

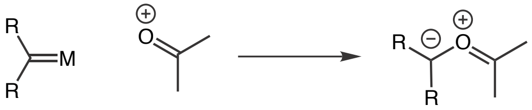


X = H, Br, OMe

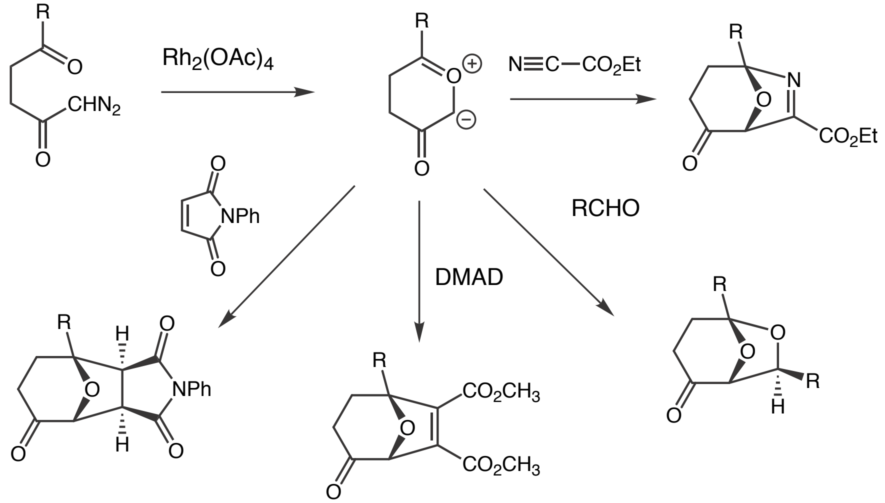
quantitative

Hamaguchi, M.; Ibata, T. *Chem. Lett*. **1975**, 499-502.

Carbenes Plus Carbonyl Groups

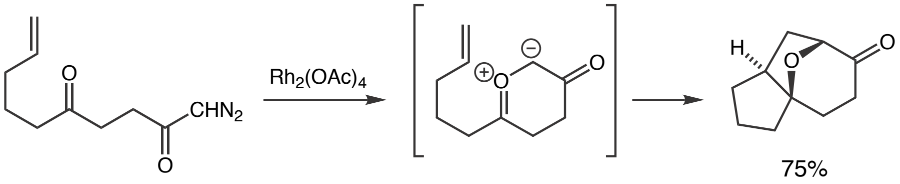


Tandem Intramolecular Cyclization–Intermolecular Cycloaddition



Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem*. **1989**, *54*, 817-824.

Intramolecular Variants

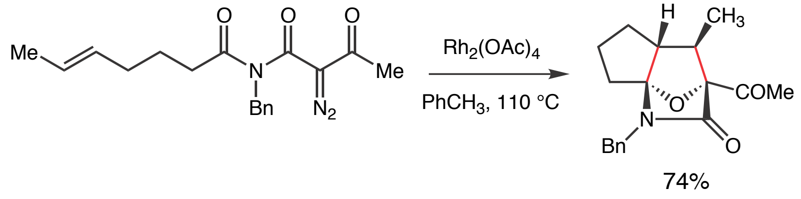


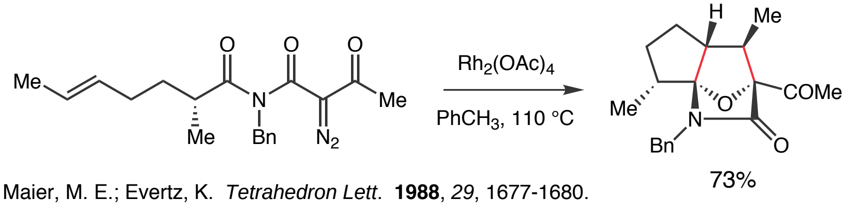
75%

Can make 5-7 membered rings

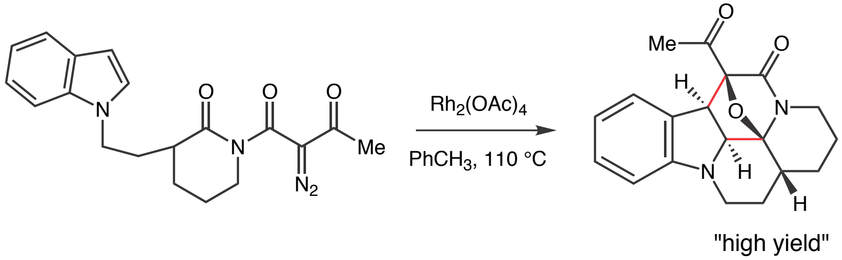
Carbonyl Ylides: Applications

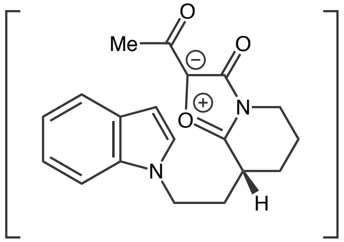
Carbonyl Ylide Cycloadditions of Diazoimides





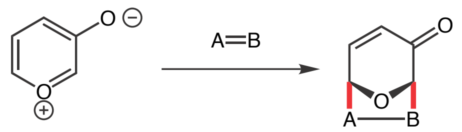
Maier, M. E.; Evertz, K. *Tetrahedron Lett*. **1988**, *29*, 1677-1680.

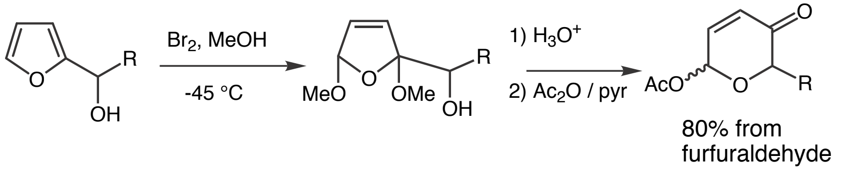


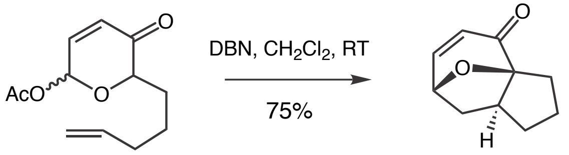


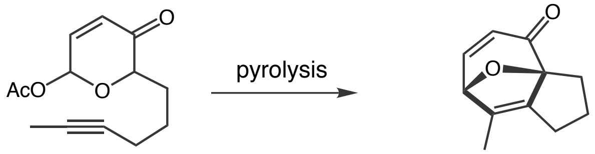
Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett*. **1992**, *33*, 4731-4734.

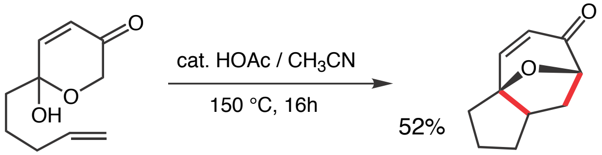
Cycloadditions with Oxidopyrylium Ylides





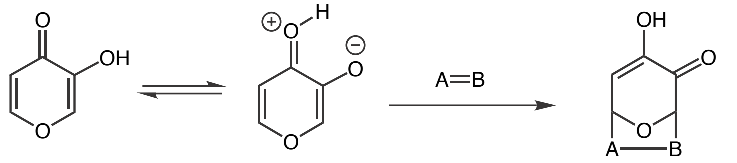


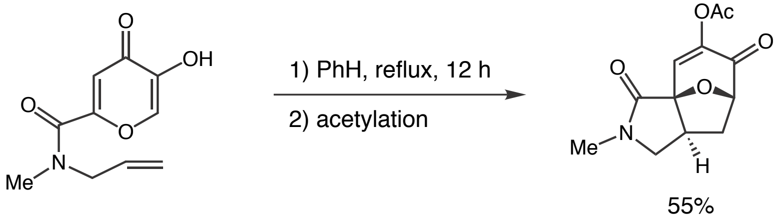


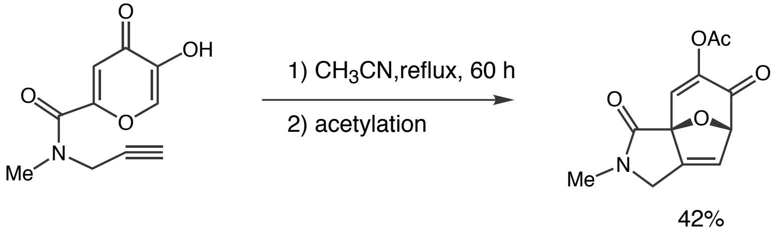


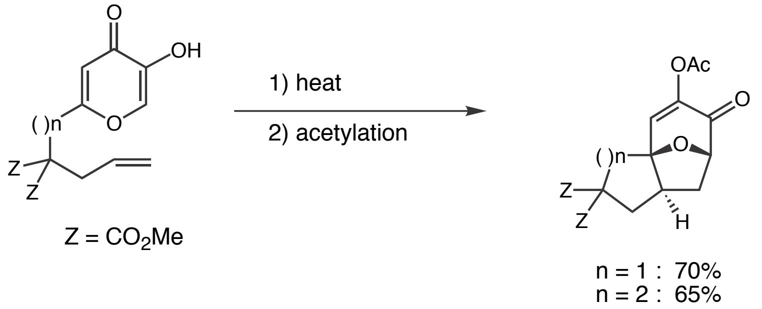
Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun*. **1982**, 1056-1057

Cyclizations with 5-Hydroxy-4-Pyrones





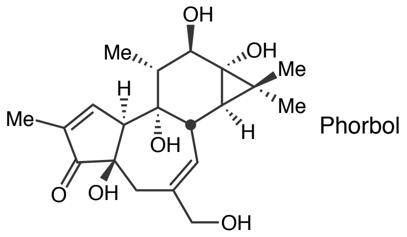


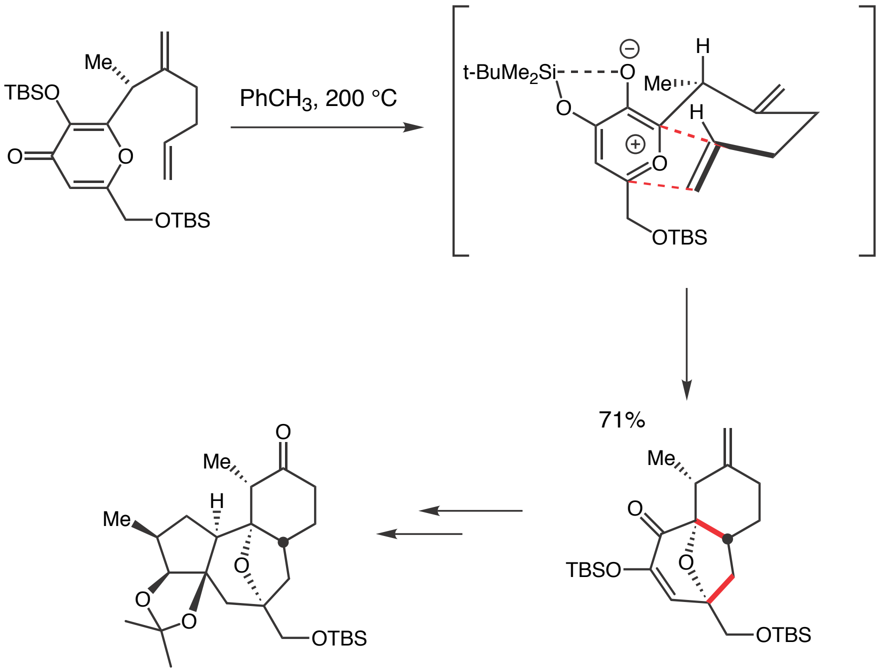


Z = CO_2Me

Garst, M. E.; McBride, B. J.; Douglass, J. G. III. *Tetrahedron Lett.* **1983**, *24,* 1675-1678.

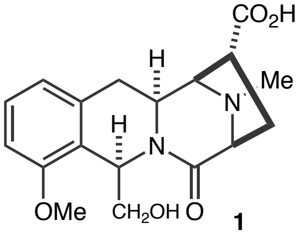
Phorbol: The Hydroxypyrone Approach



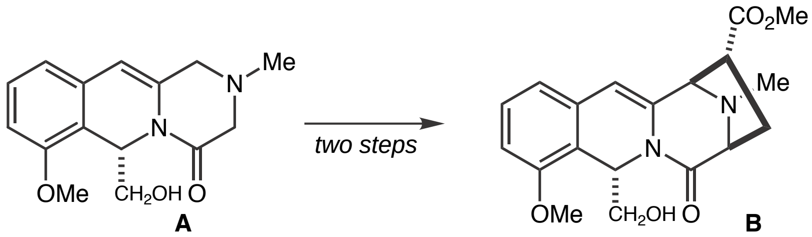


Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956-4958

Problem 53. Williams recently reported an approach to the synthesis of quinocarcinamide (**1**) (*J. Org. Chem.* **1995**, *60*, 6791). The pivotal process that establishes the tetracyclic nucleus is the two-step transformation shown below (eq 1).



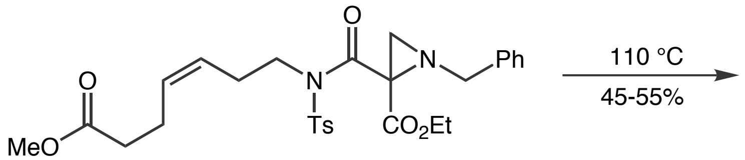
1



(1)

Devise a strategy for transforming A into B and clearly illustrate your answer in the space below. Full credit will be awarded to concise answers.

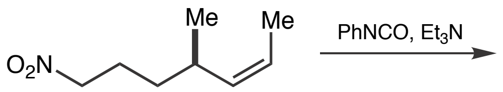
Problem 55. The following transformation was recently reported by Heathcock during studies directed toward the synthesis of sarain A
(*Tetrahedron Lett.* **1995**, *6*, 2381). From your knowledge of the functionality present in the starting material, deduce the structure (including stereochemistry) of the reaction product which has the same molecular weight as the starting material. Hint. the 1H NMR spectrum of the product reveals that the olefinic resonances have disappeared.



Your mechanism for the transformation

product structure

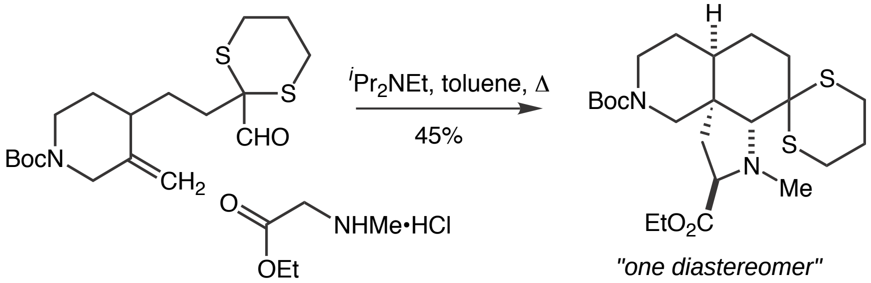
Problem 65. The following stereoselective nitrile oxide cycloaddition has been reported by Kozikowski (*Tetrahedron Lett.* **1982**, 23, 2081;
J. Org. Chem. **1984**, 49, 2762). Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.

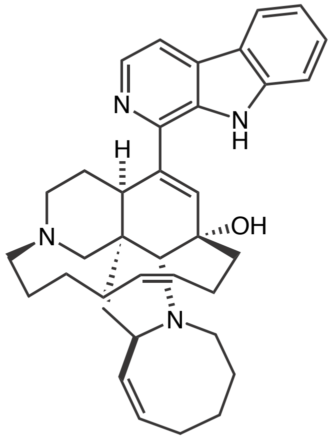


The product ?
Stereoselection: 16/1

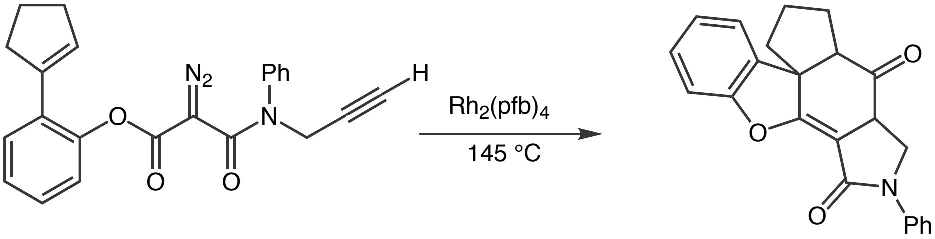
product structure

Problem 87. The illustrated transformation has been utilized by Coldham (*Chem. Commun.* **1999**, 1757) to construct the core ring system of the manzamines.



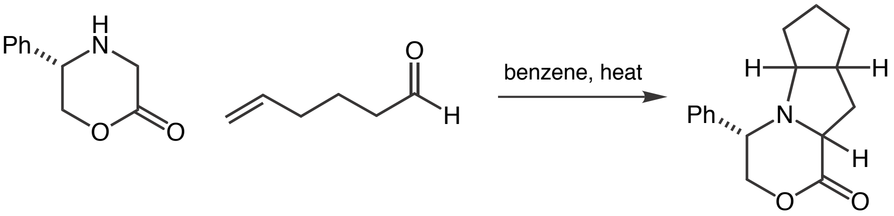


Problem 90. Padwa and co-workers recently disclosed the illustrated multistep polycyclisation as a possible route to the strychnine core (*Org. Lett.* **2001**, ASAP)



In the space below, provide a mechanism for the indicated transformation. *Hint: The management suggests that a carefull bidirectional analysis might help you to arrive at a sollution of this question.*

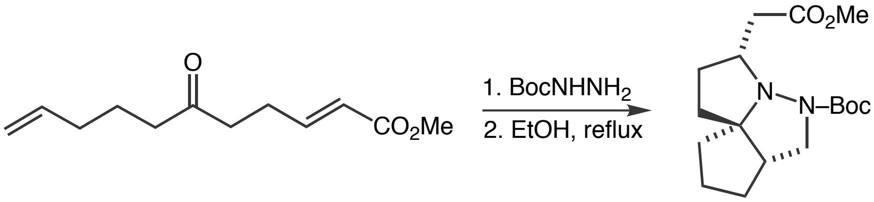
Problem 136. A recent paper by Harwood and Park highlights the rapidity which whch one may assemble complex architecture in a single chemical operation (*Tetrahedron Lett.* **1999**, *40*, 2907 and earlier cited references). The transformation in question is illustrated below. You are asked to address two aspects of this transformation.



Part A. Provide a concise mechanism for the indicated transformation. For now, ignore the stereochemical aspects of the reaction.

Part B. Predict the stereochemical outcome of the reaction at the three new stereocenters, and provide a three-dimensional drawing of the transition state wherein these centers are produced.

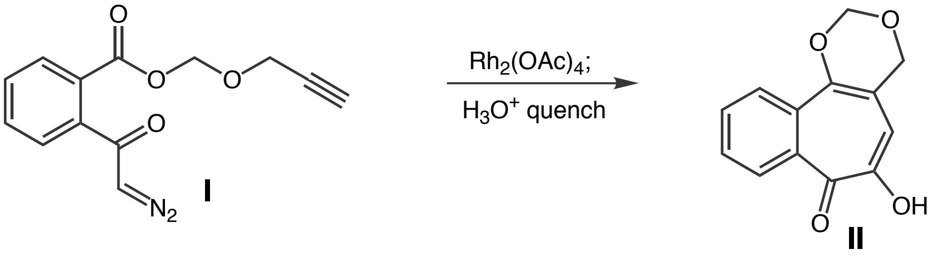
Problem 171. A recent paper by Dolle (*Tetrahedron Lett.* **1999**, *40*, 2907) highlights the rapidity which whch one may assemmble complex architecture in a single chemical operation. The transformation in question is illustrated below.



75% yield, one diastereomer

Provide a concise mechanism for the indicated transformation. In that step where the complex stereochemical relationships are established, a carefully rendered three dimensional illustration is requested.

Problem 189. This question is taken from recent work reported by Jack Baldwin (*Org. Lett.*, **1999**, 1933 and 1937). Provide a mechanism for the conversion of **I** to **II**.



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 19

Acid-Base Properties of Organic Molecules

- Bronsted Acidity Concepts in the Activation of Organic Structures
- Medium Effects on Bronsted Acidity
- Substituent & Hybridization Effects on Bronsted Acidity
- Kinetic & Thermodynamic Acidity of Ketones
- Kinetic Acidity: Carbon vs. Oxygen Acids
- Tabulation of Acid Dissociation Constants in DMSO

Reading Assignment for this Lecture:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

"Equilibrium acidities in DMSO Solution", F. G. Bordwell. *Acc. Chem. Res*. **1988**, *21*, 456-463. (**handout**)

D. A. Evans

Wednesday,
October 29, 2003

Articles on the Acidities of Organic Molecules

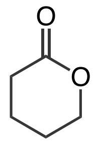
Lowry & Richardson: 3rd Edition, Chapter 3
Acids and Bases

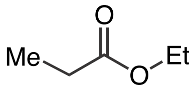
Here is a web site containing Brodwell pKa data

http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

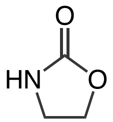
Problems of the Day:

Explain why **1** and **3** are ~4 pKa units more acidic than their acyclic counterparts **2** and **4**. (*J. Org. Chem.* **1994**, *59*, 6456)

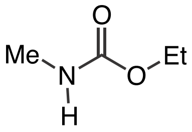

1



2

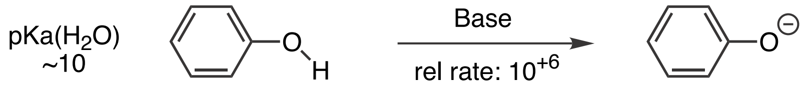


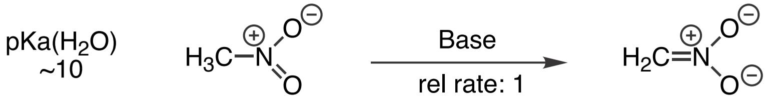
3



4

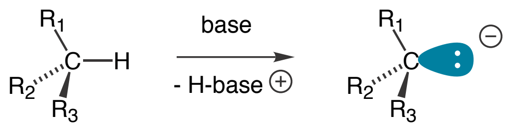
The thermodynamic acidities of phenol and nitromethane are both ~10; however, using a common base, phenol is deprotonated 10^{+6} times as fast. Rationalize





Activation of Organic Molecules

■ Base Activation

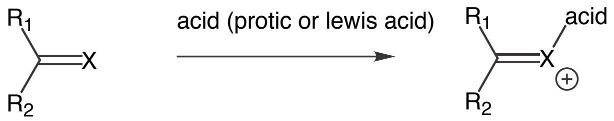


Nucleophile

pK$_a$, describes quantitatively a molecule's propensity to act as an acid, i.e. to release a proton.

- Medium effects
- Structural effects (influence of substituents R$_1$)

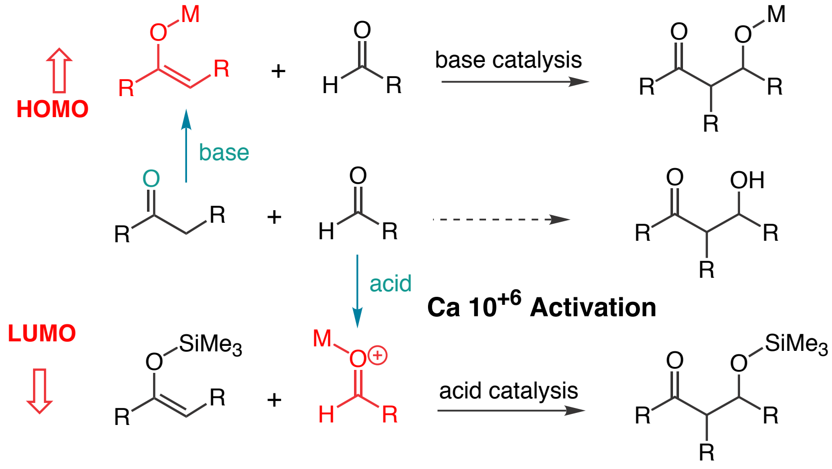
■ Acid Activation



Electrophile

X = e.g. O, NR ...

■ The Aldol Example



■ Definition of Ka

Let H–X be any Bronsted acid. In water ionization takes place:

$$H{-}X + HOH \rightleftharpoons H_3O^+ + X{-}$$

where $$K_{eq} = \frac{[H_3O^+]\,[X^-]}{[H{-}X]\,[HOH]}$$ where [HOH] = 55.5 mol L^{-1} (A)

Since [HOH] is, for all practical purposes, a constant value, the acid dissociation constant K$_a$ is defined wilthout regard to this entity. e.g.

$$H{-}X \rightleftharpoons H^+ + X{-} \qquad \text{where } H^+ = H_3O^+$$

Hence $$\mathbf{K_a = \frac{[H^+]\,[X^-]}{[H{-}X]}} \qquad \textbf{(B)}$$

From the above definitions, K$_a$ is related to K$_{eq}$ by the relation:

$$\mathbf{K_a(H{-}X) = 55.5\ K_{eq}(H{-}X)} \qquad \textbf{(C)}$$

■ Autoionization of water

$$HOH + HOH \rightleftharpoons H_3O^+ + HO^-$$

$K_{eq} = 3.3 \times 10^{-18}$

From Eq C: $K_a = 55.5\ K_{eq} = 55.5(3.3 \times 10^{-18})$

Hence $K_a = 1.8 \times 10^{-16}$

Since pK$_a$ is defined in the following equation:

$\mathbf{pK_a = -\log_{10}\,[K_a]}$ The pK$_a$ of HOH is + 15.7

Keep in mind that the strongest base that can exist in water is HO$^-$.

Lets now calculate the acid dissociation constant for hydronium ion.

$$H_3O^+ + H_2O \rightleftharpoons H_3O^+ + H_2O$$

obviously: $K_{eq} = 1$

$K_a = [HOH] \times K_{eq}$ hence $K_a = 55.5$

$pK_a = -\log_{10} K_a = -1.7$

The strongest acid that can exist in water is H$_3$O$^+$.

Acidity Trends for Carbonyl & Related Compounds

■ The Gibbs Relationship

$$\Delta G° = -RT \ln K$$

or $$\Delta G° = -2.3\,RT \log_{10} K$$

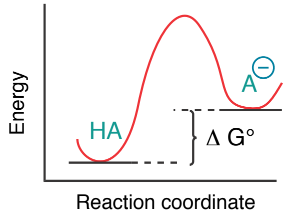
2.3 RT = 1.4
at T = 298 K
in kcal · mol^{-1}

$$\Delta G°_{298} = -1.4 \log_{10} K_{eq}$$

$$\boxed{\Delta G°_{298} = 1.4\, pK_{eq} \approx 1.4\, pK_a}$$ with $pK = -\log_{10} K$

Hence, pK_a is proportional to the free energy change

K_{eq}	pK_{eq}	ΔG°
1	0	0
10	- 1	–1.4
100	- 2	–2.8 kcal/mol

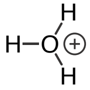
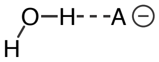
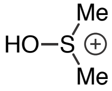


■ Medium Effects

Consider the ionization process:

$$H{-}A \;+\; \text{solvent} \;\rightleftharpoons\; A:^{-} \;+\; \text{solvent}(H^{+})$$

In the ionization of an acid in solution, the acid donates a proton to the medium. The more basic the medium, the larger the dissociation equilibrium. The ability of the medium to stabilize the conjugate base also plays an important role in the promotion of ionization. Let us consider two solvents, HOH and DMSO and the performance of these solvents in the ionization process.

	The Protonated Solvent	Conjug. Base Stabiliz.
Water		
DMSO		No H-bonding Capacity

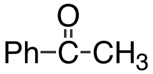
As shown above, although HOH can stabilize anions via H-bonding, DMSO cannot. Hence, a given acid will show a greater propensity to dissociate in HOH. As illustrated below the acidity constants of water in HOH, DMSO and in a vacuum dramatically reflect this trend.

■ Medium Effects on the pKa of HOH

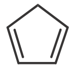
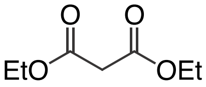
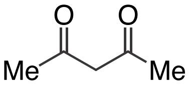
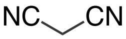
** The gas phase ionization of HOH is endothermic by 391 kcal/mol !!!

HOH pKa	Medium
15.7	HOH
31	DMSO
279 (est)**	Vacuum

■ Representative pKa Data

Substrate	DMSO	HOH	Δ pKa
HOH	31.2	15.7	15.5
HSH	14.7	7.0	7.7
MeOH	29.0	15.3	13.7
C_6H_5OH	18.0	9.9	8.1
$O_2N{-}CH_3$	17.2	10.0	7.2
 $Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_3$	24.6	17	7.6

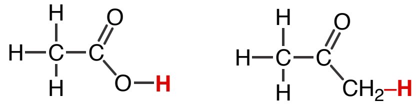
The change in pKa in going from water to DMSO is increasingly diminished as the conjugate base becomes resonance stabilized (Internal solvation!).

Substrate	DMSO	HOH	Δ pKa
	18.1	16.0	2.1
	16.4	13.3	3.1
	13.3	8.9	4.5
	11.1	11.2	0

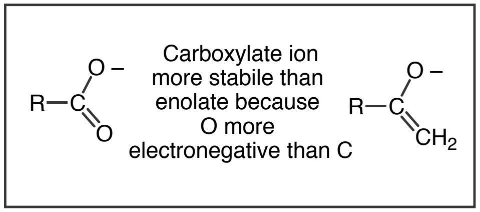
Acidity Trends for Carbonyl & Related Compounds

Substituent Effects

Electronegativity e.g. Compare Carboxylic Acids vs. Ketones



(H_2O)	$pK_A = 4.8$	$pK_A \approx 19$
(DMSO)	$pK_A = 12.3$	$pK_A \approx 26.5$



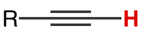
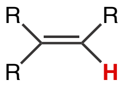
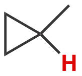
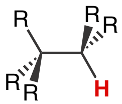
Carboxylate ion more stabile than enolate because O more electronegative than C

Hybridization - S-character of carbon hybridization

Remember:

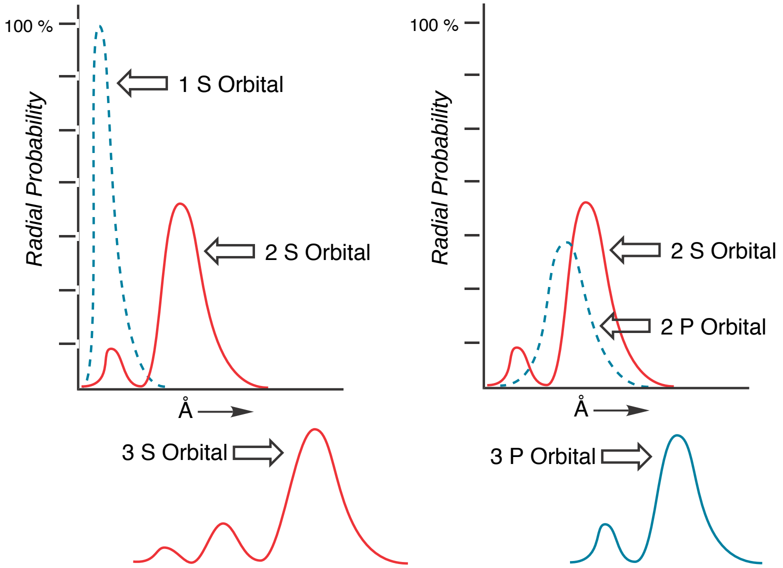
sp^3-orbitals	25% s-character
sp^2-orbitals	33% s-character
sp-orbitals	50% s-character

Carbon Acids

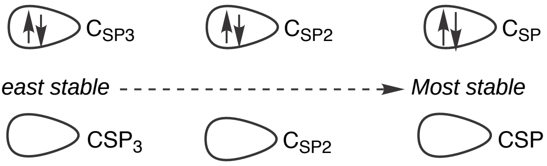
				
Hybridization	sp	sp^2	$\approx sp^2$	sp^3
Bond Angle	180°	120°	≈ 120	109°
pK_a(DMSO)	23	≈ 44	≈ 39	≈ 60

Electrons in 2S states "see" a greater effective nuclear charge than electrons in 2P states.

This becomes apparent when the radial probability functions for S and P-states are examined: The radial probability functions for the hydrogen atom S & P states are shown below.



S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in s states see a higher nuclear charge. The above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital.



Carbanions C_{SP3} C_{SP2} C_{SP}

Least stable --------→ *Most stable*

Carbenium ions CSP_3 C_{SP2} CSP

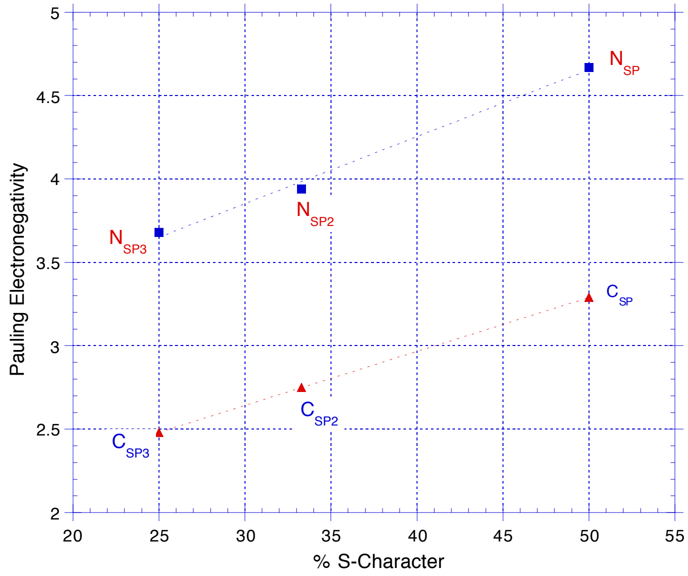
Most stable ←-------- *Least stable*

The above trends indicate that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

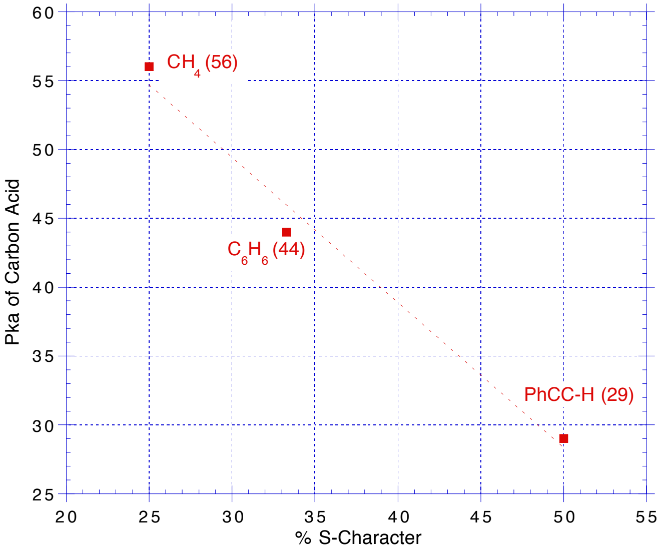
Acidity Trends for Carbonyl & Related Compounds

Hybridization vs Electronegativity

There is a linear relationship between %S character & Pauling electronegativity



There is a direct relationship between %S character & hydrocarbon acidity

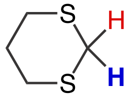
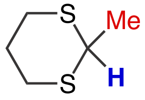


Substituent Effects

Alkyl Substituents on Localized Carbanions are Destabilizilng:

Steric hinderance of anion solvation

Compare: (*JACS* **1975**, *97*, 190)

	pK_A (DMSO)		pK_A (DMSO)
$PhSO_2\text{-}\underset{H}{CH}\text{–}H$	29		31.1
$PhSO_2\text{-}\underset{H}{CH}\text{–}Me$	31		38.3

Heteroatom-Substituents: - 1st row elements of periodic table

	pK_A (DMSO)	
$PhSO_2\text{-}\underset{H}{CH}\text{-}OCH_3$	30.7	Inductive Stabilization versus Lone Pair Repulsion (-I vs +M -Effect)
$PhSO_2\text{-}\underset{H}{CH}\text{-}OPh$	27.9	
$PhSO_2\text{-}\underset{H}{CH}\text{-}\overset{\oplus}{N}Me_3$	19.4	Inductive Stabilization

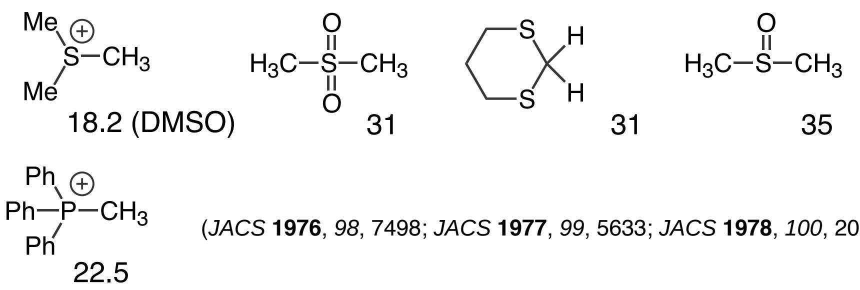
Heteroatom-Substituents: - 2nd row elements of periodic table

Strong carbanion stabilizing effect

	pK_A (DMSO)		pK_A (DMSO)
$PhSO_2\text{-}\underset{H}{CH}\text{-}H$	29	$PhSO_2\text{-}\underset{H}{CH}\text{-}SO_2Ph$	12.2
$PhSO_2\text{-}\underset{H}{CH}\text{-}SPh$	20.5	$PhSO_2\text{-}\underset{H}{CH}\text{-}PPh_2$	20.5

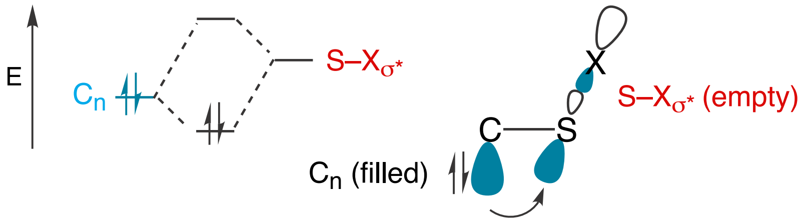
Acidity Trends for Carbonyl & Related Compounds

■ Carbanion Stabilization by 2rd–Row Atoms: SR, SO_2R, PR_3 etc



(*JACS* **1976**, *98*, 7498; *JACS* **1977**, *99*, 5633; *JACS* **1978**, *100*, 200).

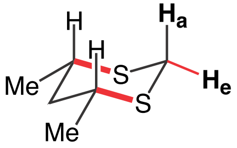
The accepted explanation for carbanion stabilization in 3rd row elements is delocalization into vicinal antibonding orbitals



This argument suggests a specific orientation requirement. This has been noted:

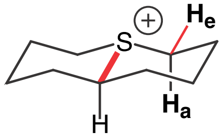
Anti (or syn) periplanar orientation of Carbanion-orbital and σ* orbital mandatory for efficient orbital overlap.

Rates for deprotonation with *n*-BuLi



$H_e : H_a = 8.6$

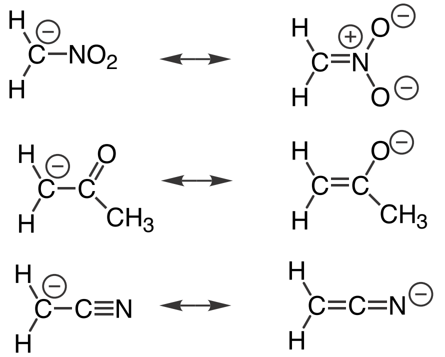
(*JACS* **1974**, *96*, 1811)



$H_e : H_a = 30$

(*JACS* **1978**, *100*, 200)

■ Conjugative Stabilization of Conjugate Base



17.2 pK_A (DMSO)

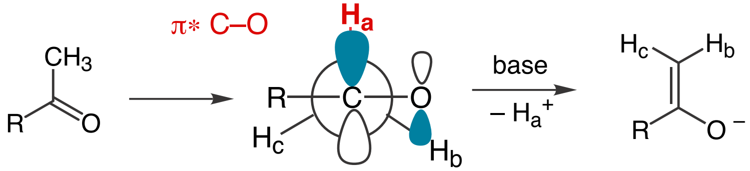
26.5

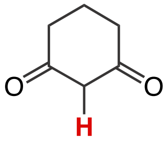
31.5

For efficient conjugative stabilization, rehybridization of carbanion orbital from n_{sp3} to n_p is required for efficient overlap with low-lying π*-orbital of stabilizing group. However, the cost of rehybridization must be considered.

■ Stereoelectronic Requirement for Carbanion Overlap: Enolization of Carbonyl Compounds

Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π* C–O





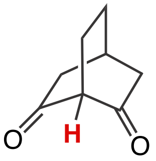
pK_A

5.2

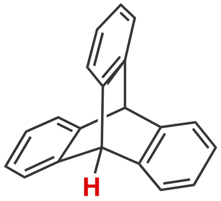
pK_A (DMSO)

Ph_3C-**H**

31.5



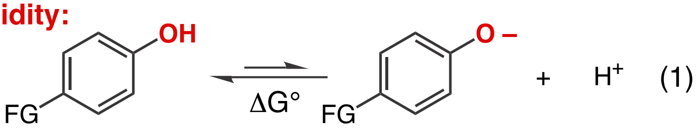
C-H acidity not detectable



47.7

Phenol Acidity: An Analysis of Resonance & Inductive Effects

■ Phenol Acidity:

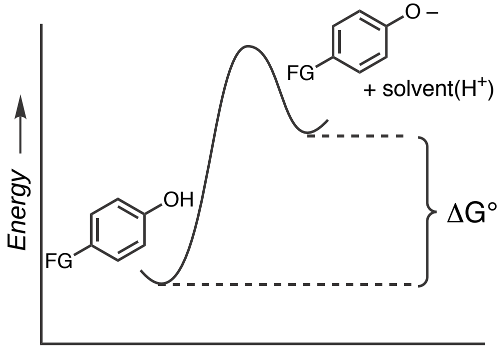


This topic has a number of take-home lessons. Most importantly, is is a useful construct on which to discuss the role of FG's in influencing the acidity of this oxygen acid.

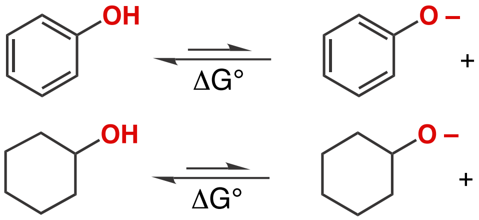
■ How does one analyze the impact of structure on pKa of a weak acid (pKa > 0) ?

■ The Approach:

For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.



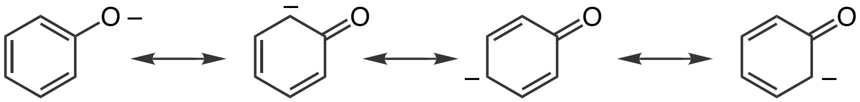
■ Why is phenol so much more acidic than cyclohexanol?



H^+ pKa (H_2O) = 10

H^+ pKa (H_2O) = 17

Loudon (pg 730): "The enhanced acidity of phenol is due largely to stabilization of its conjugate base by resonance."

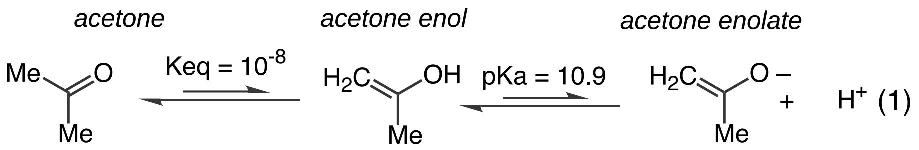


from previous discussion, $\Delta G^\circ_{298} = -1.4 \ \mathrm{Log}_{10}\ \mathrm{Keq} = 1.4\ \mathrm{pKeq}$

ΔG° (stab) = $1.4(\mathrm{Pka}_{phenol} - \mathrm{pKa}_{cyclohenanol}) = 1.4(-7) = 9.8$ kcal/mol

■ Is the benzene ring somehow special. i.e "larger resonance space."

■ Acetone enol:



The surprising facts is that the acetone enol has nearly the same pKa as phenol. Hence, the answer to the above question is no!

■ How important are inductive effects in the stabilization of $C_6H_5O^-$?

Consider the following general oxygen acid X–OH where X can only stabilize the conjugate base through induction:

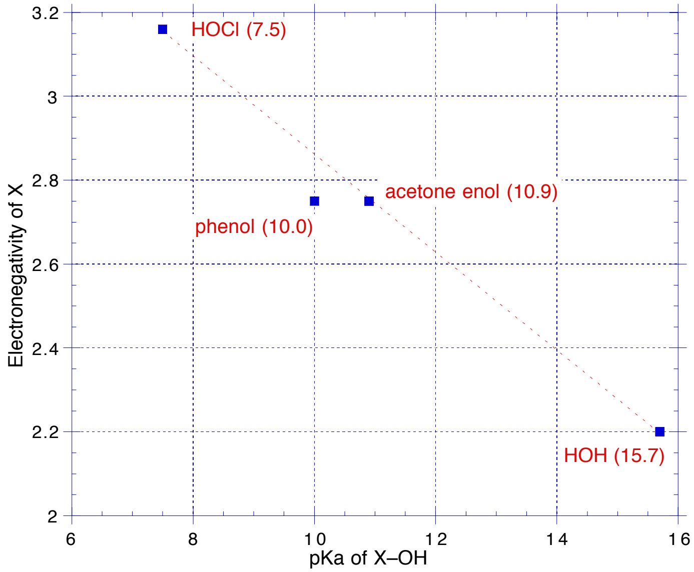
$$X\text{—}OH \rightleftharpoons X\text{—}O^- + H^+$$

As the electronegativity of X increases the acidity of X–OH increases.

X—OH	pKa(H_2O)
CH_3—OH	15.5
CF_3CH_2—OH	12.4
Cl—OH	7.5

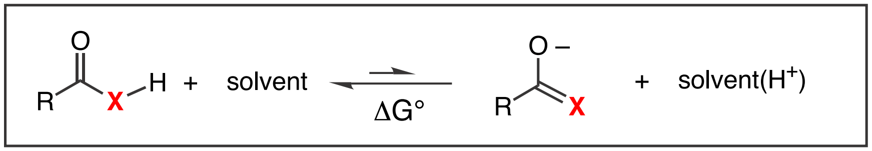
If you take the calculated electronegativity of an SP_2 carbon (2.75) you can see that there is a linear correlation between the electronegativity of X and the pKa of X–OH.

This argument suggests that the acidity of acetone enol is largely due to inductive stabilization, not resonance.



Weak Acids: Impact of Structure on Acidity

■ The General Reaction: Ionization of a weak acid (pKa > 0)



Variables:

X = O (carboxylic acid)

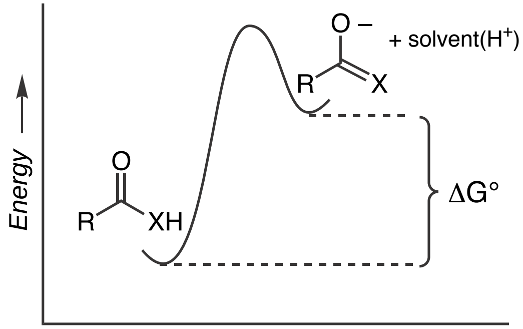
X = NH (amide)

X = CH_2 (Ketone/ester)

$R = CR_3$

R = OR

$R = NR_2$

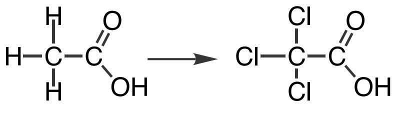


■ The Question: How does one analyze the impact of structure on pKa ?

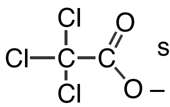
■ The Approach:

For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.

Case I: Carboxylic Acids: Inductive Effects

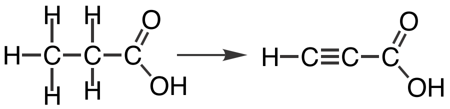


pKa = 4.8 pKa = 0.6

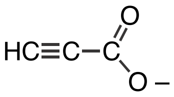


Carboxylate ion stabilized by increased electron-withdrawing CCl_3 group.

Case II: Carboxylic Acids: Inductive Effects & Carbon Hybridization

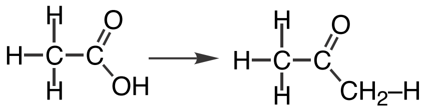


pKa = 4.9 pKa = 1.9

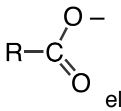


Carboxylate ion stabilized by increased electron-withdrawing SP-hybridized carbon

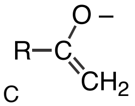
Case III: Carboxylic Acids vs Ketones:



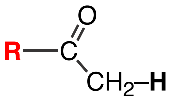
pKa = 4.8 pKa ~ 19

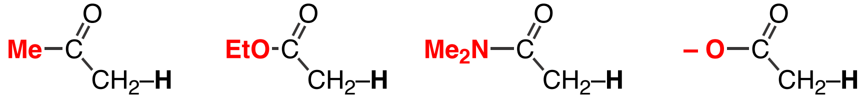


Carboxylate ion more stabile than enolate because O more electronegative than C



Case IV: Carboxylic Acids, Esters, Amides & Ketones:





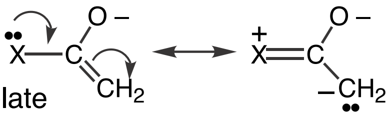
Me–C(O)CH₂–H	EtO–C(O)CH₂–H	Me₂N–C(O)CH₂–H	–O–C(O)CH₂–H
pKa ~ 26	pKa ~ 30	pKa ~ 34	pKa > 34 < 40

The Analysis:

In this series of compounds, there are two variables to consider:

■ Inductive Effect: OEt > Me_2N > H_3C but (O–?)

■ Resonance Effect:

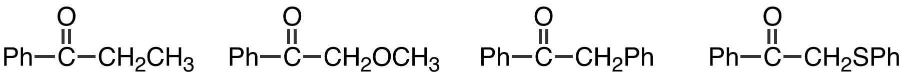


The degree to which substituent X: "contributes" electron density into enolate represents a destabilizing interaction:

Trend: O– > Me_2N > OEt

■ Resonance donation dominates inductive electron withdrawal as indicated by the data.

Substituents on the α-carbon: Stabilization by either resonance, induction, or both is observed:



$Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_3$ pKa = 24.4

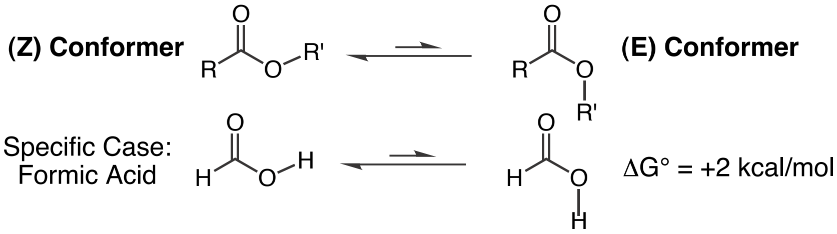
$Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2OCH_3$ pKa = 22.9

$Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2Ph$ pKa = 17.7

$Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2SPh$ pKa = 17.1

Acidity of Carboxylic Acids, Esters, & Lactones: Anomeric Effects Again?

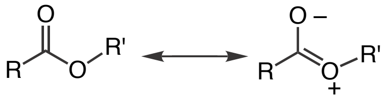
■ Conformations: There are 2 planar conformations.



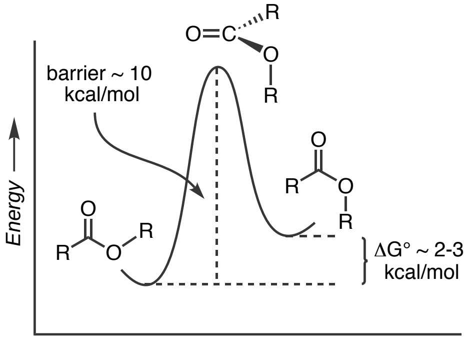
The (E) conformation of both acids and esters is less stable by 2-3 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must also be considered. These effects will be introduced shortly.

■ Rotational Barriers: There is hindered rotation about the =C–OR bond.

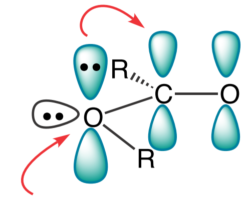
These resonance structures suggest hindered rotation about =C–OR bond. This is indeed observed:



Rotational barriers are ~ 10 kcal/mol
This is a measure of the strength of the pi bond.



■ Lone Pair Conjugation: The oxygen lone pairs conjugate with the C=O.

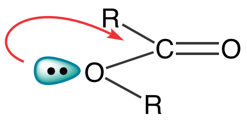


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

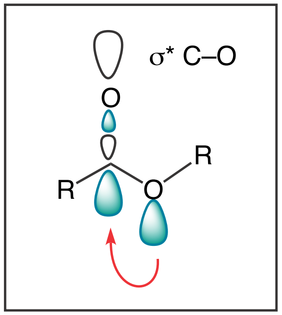
■ Oxygen Hybridization: Note that the alkyl oxygen is Sp2. Rehybridization is driven by system to optimize pi-bonding.

■ Hyperconjugation: Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

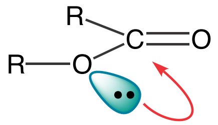
(Z) Conformer



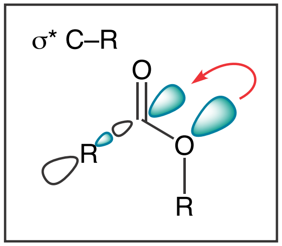
In the (Z) conformation this lone pair is aligned to overlap with σ^* C–O.



(E) Conformer



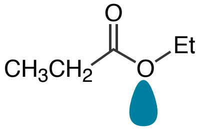
In the (E) conformation this lone pair is aligned to overlap with σ^* C–R.



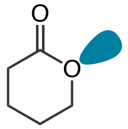
Since σ^* C–O is a better acceptor than σ^* C–R (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

Lone pair orientation & Impact on pKa (DMSO)

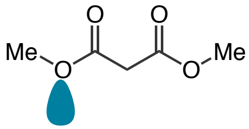
See Bordwell, *J. Org. Chem.* **1994,** *59*, 6456-6458



pKa ~ 30

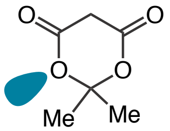


pKa = 25.2

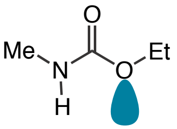


pKa = 15.9

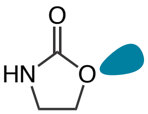
Meldrum's Acid



pKa = 7.3



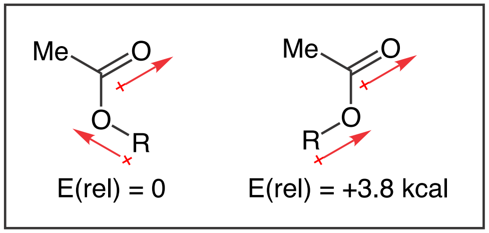
pKa = 24.5



pKa = 20.6

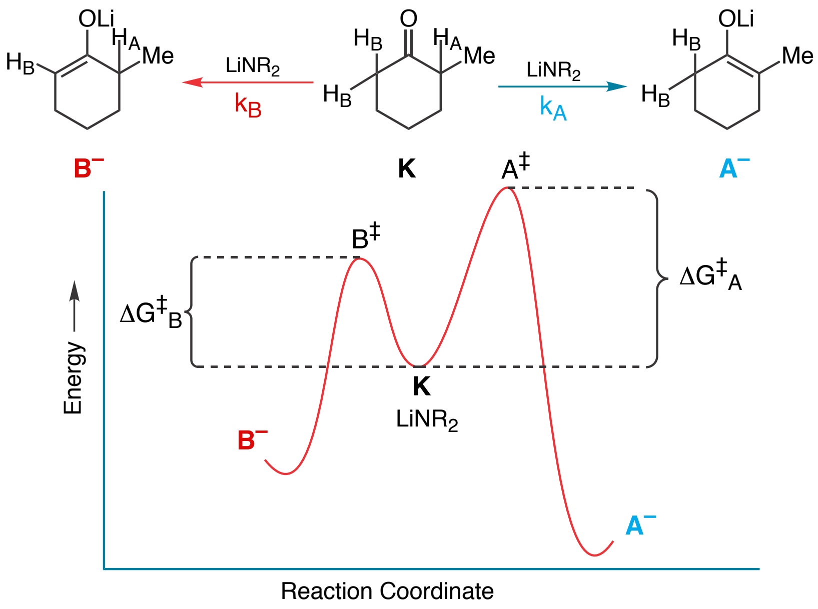
Houk, *JACS* **1988**, *110*, 1870
supports the dipole argument

Is this a dipole effect? See Bordwell

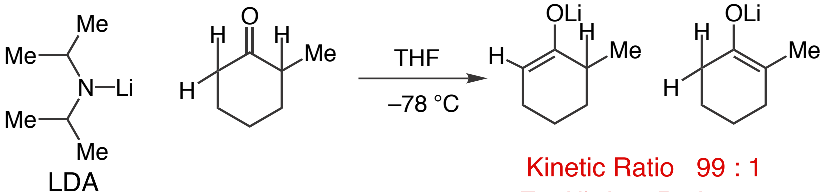


■ Kinetic Acidity: Rates of proton removal

Consider enolization of the illustrated ketone under non-equilibrating conditions:

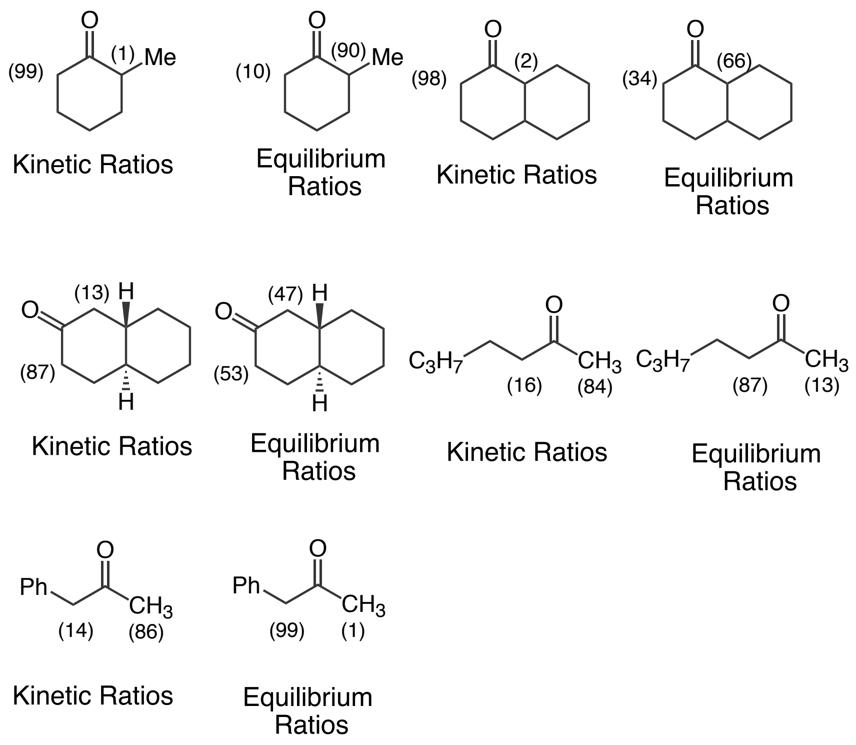


Kinetic acidity refers to the rate of proton removal. e.g. k_A vs k_B. For example, in reading the above energy diagram you would say that H_A has a lower kinetic acidity than H_B. As such, the structure of the base (hindered vs unhindered) employed plays a role in determining the magnitude of k_A and k_B. For the case shown above, $\Delta G^‡_A$ will increase more than $\Delta G^‡_B$ as the base becomes more hindered since the proton H_A resides in a more sterically hindered environment. The example shown below shows the high level of selectivity which may be achieved with the sterically hindered base lithium diisopropylamide (LDA).



Kinetic Ratio 99 : 1
Equilibrium Ratio 10 : 90

Kinetic & Equilibrium Ratios of Enolates Resulting from Enolization with LDA & Subsequent Equilibration



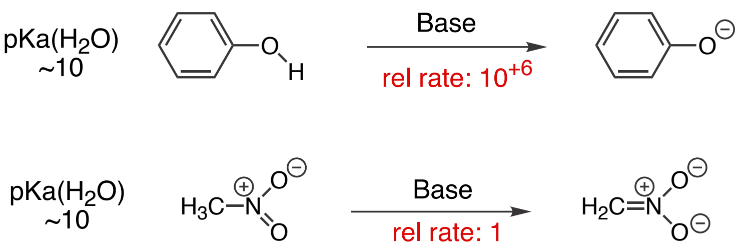
■ Note that alkyl substitution stabilizes the enolate (Why??). This effect shows up in the equilibrium ratios shown above.

■ Hence, enolization under "kinetic control with LDA allows you to produce the less-substituted enolate while subsequent equilibration by simply heating the enolate mixture allows equilibration to the more substituted enolate.

Kinetic Acidity: Carbon versus Oxygen Acids

■ Kinetic Acidity

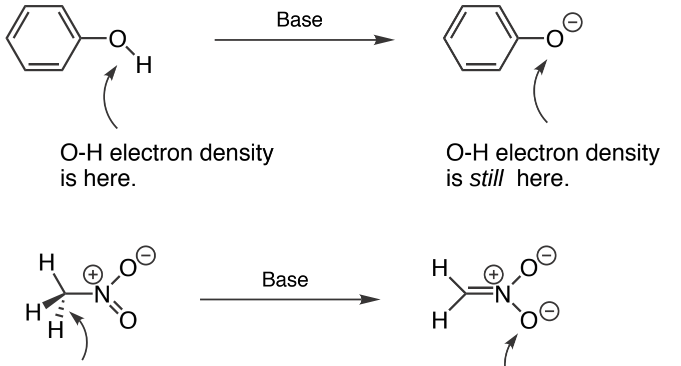
Observation: The thermodynamic acidities of phenol and nitromethane are both approximately 10; however, using a common base, phenol is deprotonated 10^{+6} times as fast.



Proton transfers from C-H Bonds are slow.

■ Why???

Most carbon acids are stabilized by resonance. Hence significant structural reorganization must accompany deprotonation.



O-H electron density is here.

O-H electron density is *still* here.

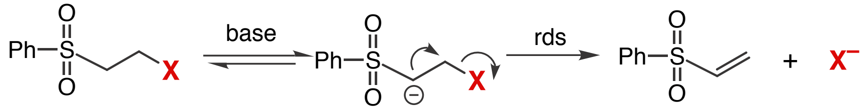
C-H electron density is here.

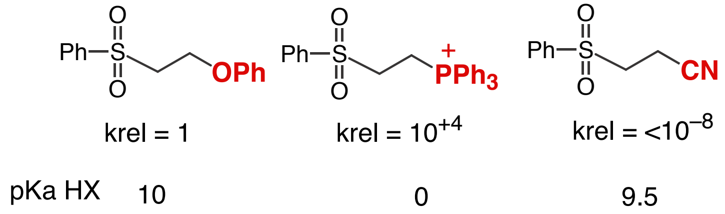
electron density now resides here, and nuclei have moved to accomodate rehybridization.

The greater the structural reorganization during deprotonation, the lower the kinetic acidity

■ Kinetic Acidity vs. Leaving Group Ability: E1cb Elimination Reactions

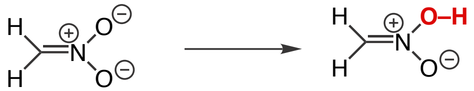
Stirling, *Chem. Commun.* **1975**, 940



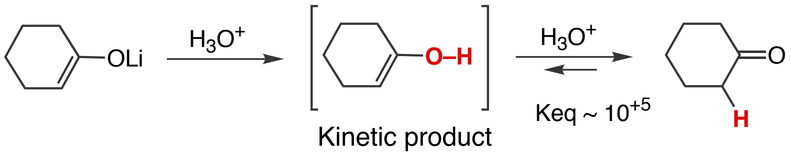


The greater the structural reorganization of the leaving group during E1cb elimination, the slower the rate of elimination.

■ Protonation of Conjugate bases



Kinetic product



Kinetic product

Jack Hine: Least Motion Principle (*Adv. Phys. Org. Chem*. **1977**, *15*, 1)
Lowry & Richardson, 3rd Edition, pp 205-206

Those elementary reactions that involve the least change in atomic posiitons will be favored

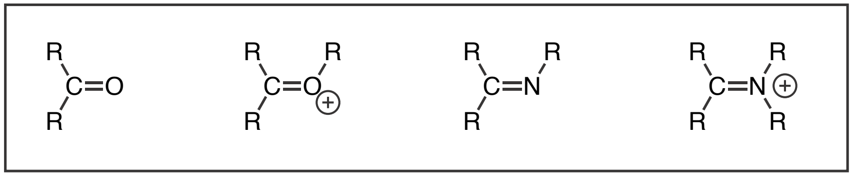
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 20

Carbonyl and Azomethine Electrophiles-1



- Reactivity Trends
- C=X Stereoelectronic Effects
- Carbonyl Addition: Theoretical Models
- The Felkin-Anh-Eisenstein Model for C=O Addition
- Diastereoselective Ketone Reduction

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

D. A. Evans

Friday,
October 31, 2003

Additional Reading Material Provided

Additions to 5- & 6-Membered oxocarbenium Ions:

Woerpel etal. *JACS* **1999**, *121*, 12208 **(Handout)**
Woerpel etal. *JACS* **2000**, *122*, 168 **(Handout)**
Woerpel etal. *JACS* **2003**, *125*, ASAP **(Handout)**

"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153. **(Electronic Handout)**
"Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, *1*, 61-70. **(Handout)**

"Around and Beyond Cram's Rule" A. Mengel & O. Reiser, Chem Rev. 1999, 99, 1191-1223 **(Electronic Handout)**

Relevant Dunitz Articles

"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

"Stereochemistry of Reaction Paths at Carbonyl Centers", *Tetrahedron* **1974**, *30*, 1563

"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153. **(Electronic Handout)**

"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.", Burgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460.

Chemistry Reviews Issue on Diastereoselection in C=O Addition

Chem Rev. **1999**, *99*, (5), 1069-1480

Mengel, A. and O. Reiser, "Around and beyond Cram's rule." *Chem. Rev.* **1999**, 1191-1223.

Reetz, M. T., "Synthesis and diastereoselective reactions of N,N-dibenzylamino aldehydes and related compounds." *Chem. Rev.* **1999**,1121-1162.

Dannenberg, J. J., "Using perturbation and frontier molecular orbital theory to predict diastereofacial selectivity." *Chem. Rev.* **1999**, 1225-1241.

Tomoda, S., "The exterior frontier orbital extension model." *Chem. Rev.* **1999**,1243-1263.

Cieplak, A. S., "Inductive and resonance effects of substituents on pi-face selection." *Chem. Rev.* **1999**,1265-1336.

Ohwada, T., "Orbital-controlled stereoselections in sterically unbiased cyclic systems." *Chem. Rev.* **1999**,1337-1375.

Gung, B. W., "Structure distortions in heteroatom-substituted cyclohexanones, adamantanones, and adamantanes: Origin of diastereofacial selectivity." *Chem. Rev.* **1999**,1377-1386.

Kaselj, M., W. S. Chung, et al., "Face selection in addition and elimination in sterically unbiased systems." *Chem. Rev.* **1999**, 1387-1413.

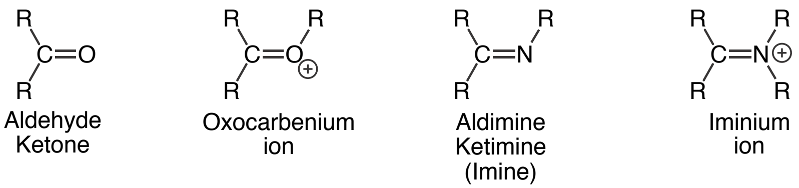
Adcock, W. and N. A. Trout, "Nature of the electronic factor governing diastereofacial selectivity in some reactions of rigid saturated model substrates." *Chem. Rev.* **1999**,1415-1435.

Mehta, G. and J. Chandrasekhar, "Electronic control of facial selection in additions to sterically unbiased ketones and olefins." *Chem. Rev.* **1999**,1437-1467.

Wipf, P. and J. K. Jung, "Nucleophilic additions to 4,4-disubstituted 2,5-cyclohexadienones: Can dipole effects control facial selectivity?." *Chem. Rev.* **1999**,1469-1480.

C=X Electrophiles: Carbonyls, Imines & Their Conjugate Acids

■ The Set of Functional Groups:



Aldehyde Ketone

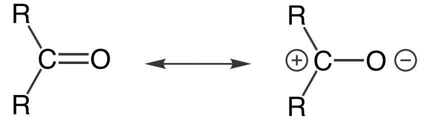
Oxocarbenium ion

Aldimine Ketimine (Imine)

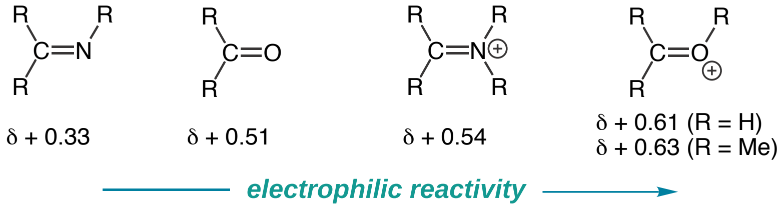
Iminium ion

These functional groups are among the most versatile sources of electrophilic carbon in both synthesis and biosynthesis. The ensuing discussion is aimed at providing a more advanced discussion of this topic.

■ C=X Polarization



Partial Charge: As the familiar polar resonance structure above indicates, the carbonyl carbon supports a partial positive charge due to the polarization of the sigma and pi system by the more electronegative heteroatom. The partial charges for this family of functional groups derived from molecular orbital calclulations (ab initio, 3-21(G)*, HF) are illustrated below:



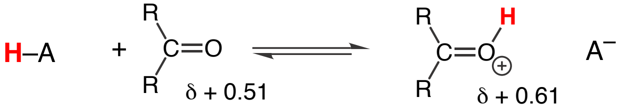
δ + 0.33

δ + 0.51

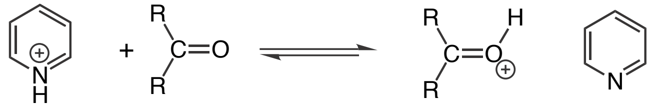
δ + 0.54

δ + 0.61 (R = H)
δ + 0.63 (R = Me)

■ Proton Activation of C=X Functional groups



The electrophilic potential of the C=O FG may be greatly increased by either Lewis acid coordination of by protonation. The magnitide of this increase in reactivity is ~ 10^{+6}. Among the weakest Bronsted acids that may be used for C=O actilvation (ketalization) is pyridinium ion (pKa = 5). Hence, the Keq below, while quite low, is still functional.



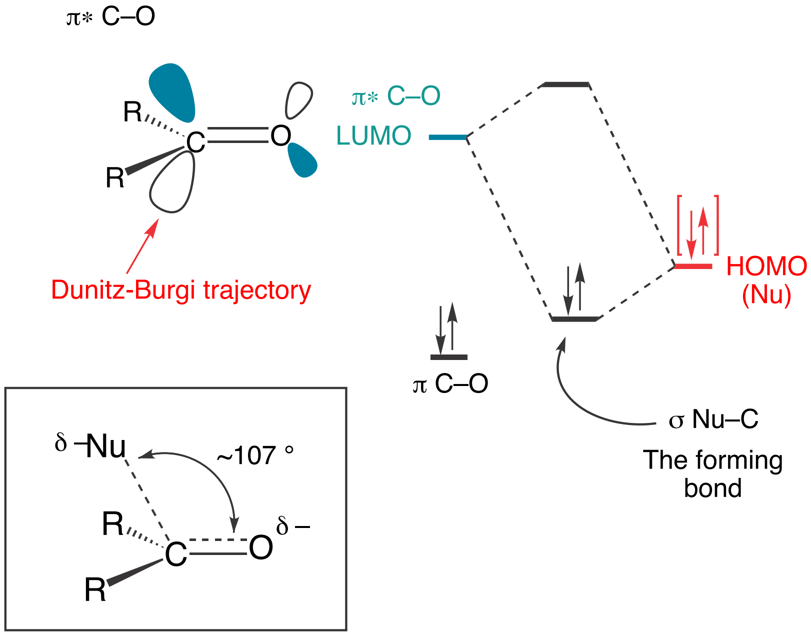
pka = +5

pka = –6

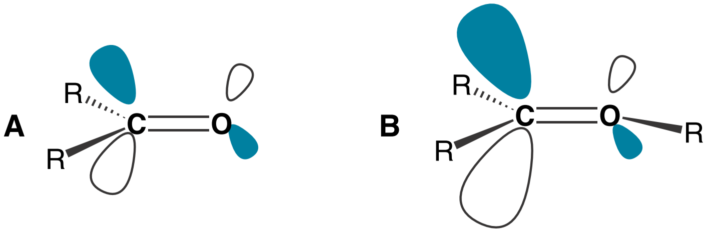
Keq ~ 10^{-11}

Stereoelectronic Considerations for C=O Addition

LUMO is π∗ C–O; **HOMO** Provided by Nu:



■ What about C=O vs C=O-R(+)?



The LUMO coefficient on carbon for **B** will be considerably larger than for **A.** Does this mean that there is a lower constraint on the approach angle for the attacking nucleophile? There is no experimental proof for this question; however, it is worthy of consideration

■ What was the basis for the Dunitz-Burgi analysis?

The Dunitz-Burgi Trajectory for C=O Addition

■ Relevant Dunitz Articles

"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

"Stereochemistry of Reaction Paths at Carbonyl Centers", *Tetrahedron* **1974**, *30*, 1563

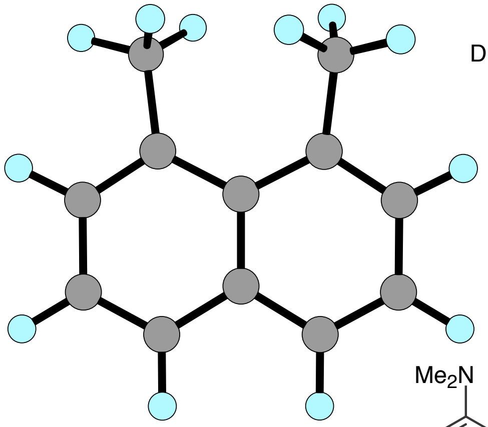
"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153.

"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.", Burgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460.

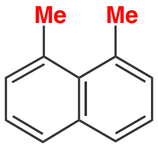
■ Dunitz Method of Analysis

A series of organic structures containing both C=O and Nu FG's disposed in a geometry for mutual interaction were designed. These structures positioned the interacting FGs an increasingly closer distances. The X-ray structures of these structures were determined to ascertain the direction of C=O distortion. The two families of structures that were evaluated are shown below.

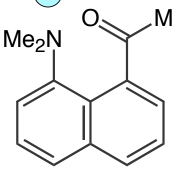
1,8-Disubstituted Naphthalenes. Substituents located at these positions are strongly interacting as illustrated by the MM2 minimized di-methyl-naphthalene structure shown below.



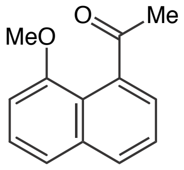
Dunitz, *Helv. Chem. Acta* **1978**, *61*, 2783



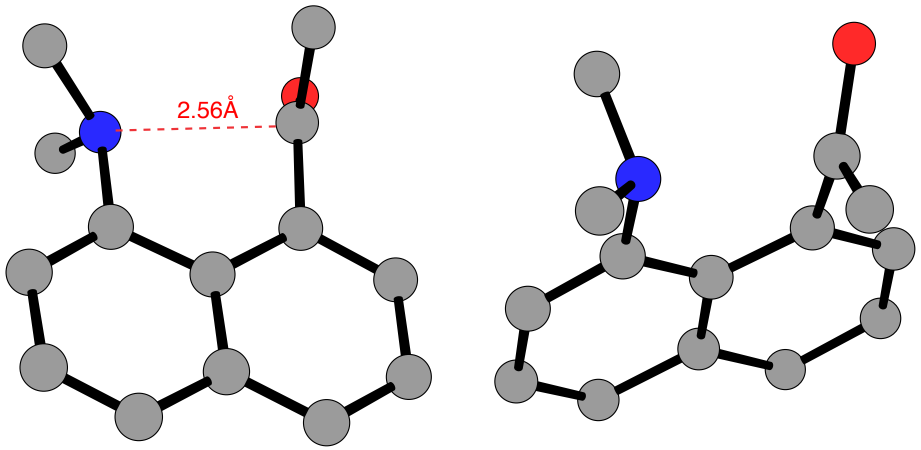
~ 7.6 kcal/moll
Lecture 5



A (shown)

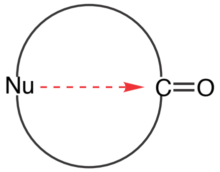


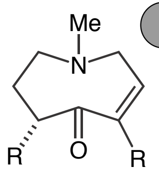
B



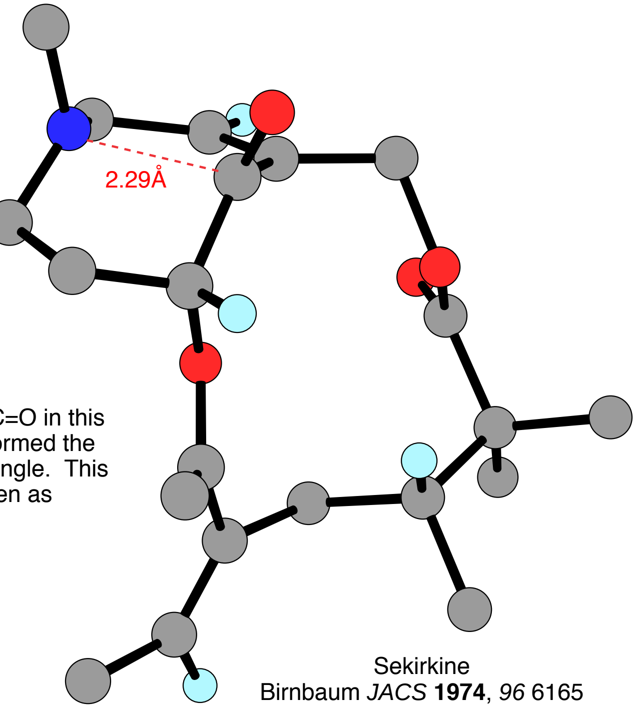
In this structure (**A**), at 2.56Å the C=O is starting to pyramidalize

Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine an C=O FGs. One example is shown below.





Analysis of distortion of C=O in this and related structures formed the basis of the 107° attack angle. This value should be taken as approximate.

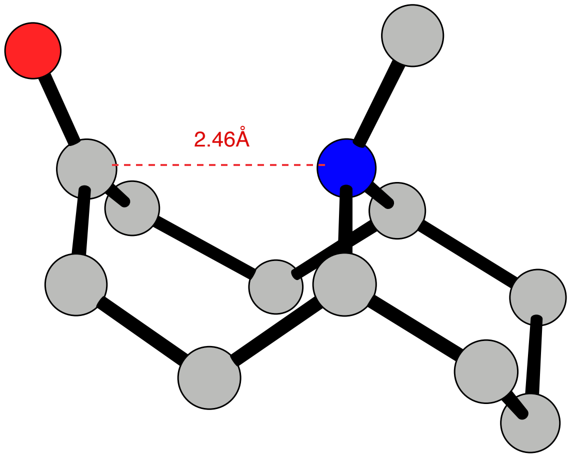


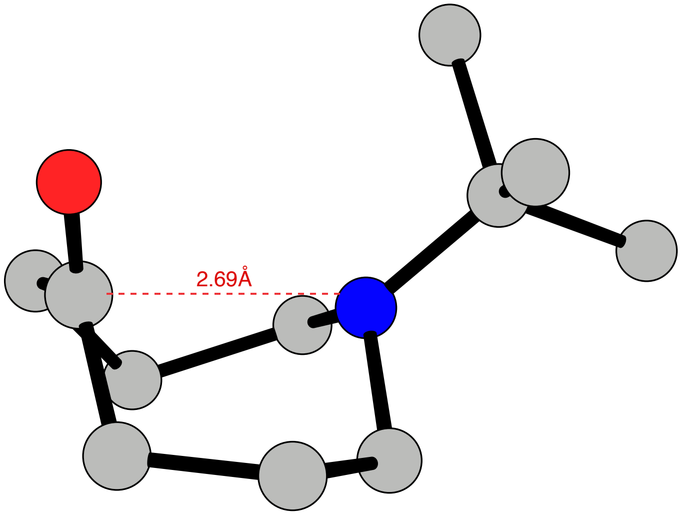
Sekirkine
Birnbaum *JACS* **1974**, *96* 6165

The Dunitz-Burgi Trajectory for C=O Addition

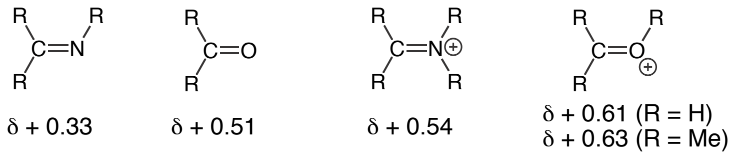
Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine an C=O FGs. Two examples are shown below.

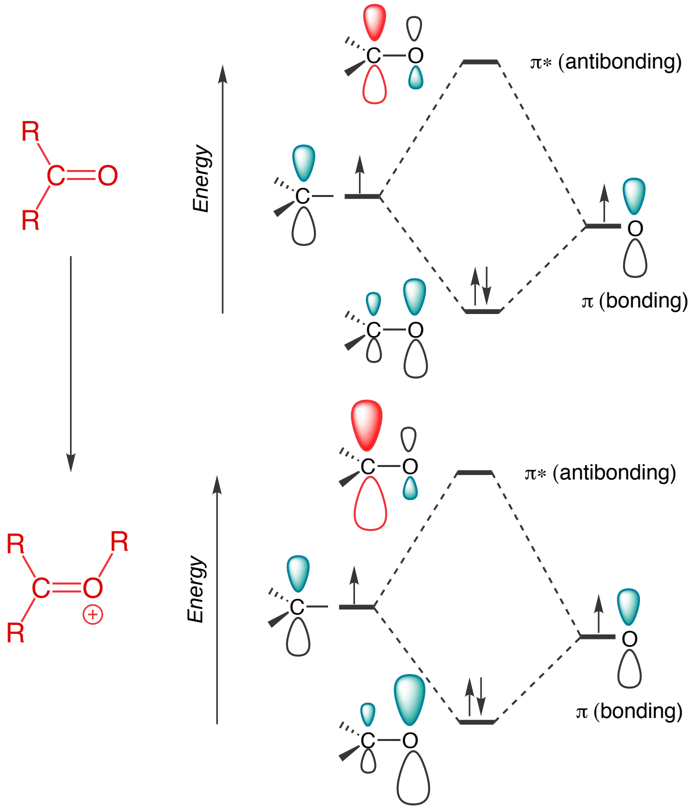
Sekirkine
Birnbaum *JACS* **1974**, *96* 6165

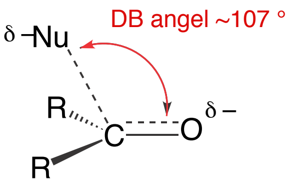


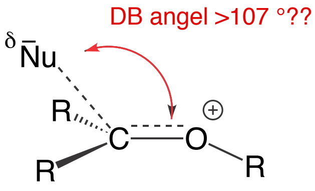


Should these crystallographic date be relevant to the addition to complexed C=O & Iminium Ions?









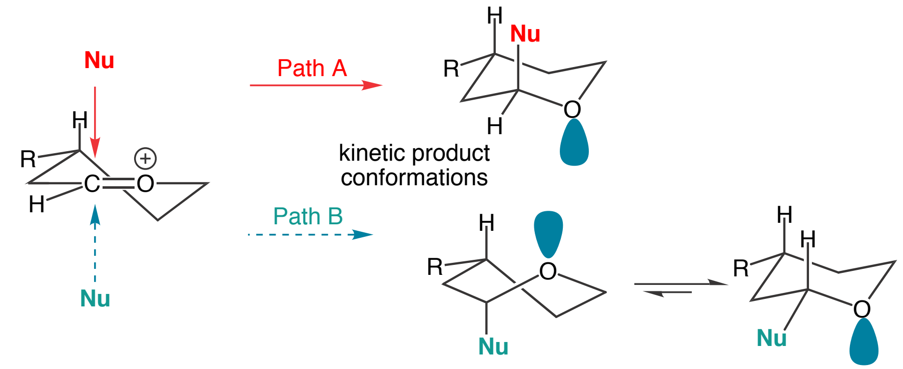
Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

■ Pivotal Articles

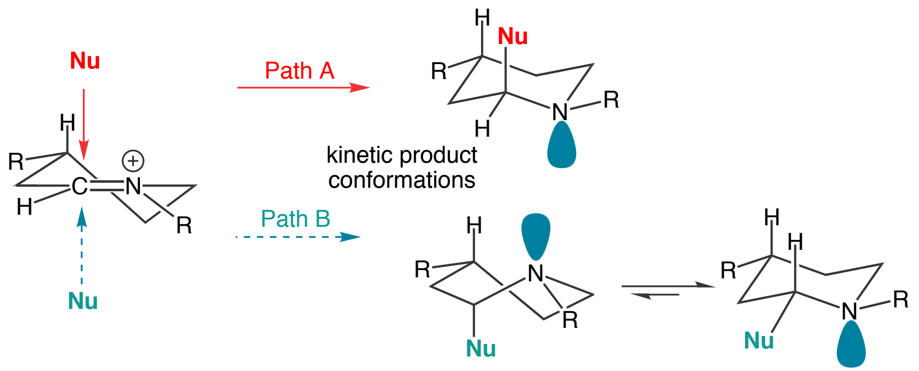
R. V. Stevens in
"Strategies and Tactics in Organic Synthesis", Vol. 1.
On the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts: a Powerful Heuristic Principle for the Stereorationale Design of Alkaloid Synthesis.;
Lindberg, T., Ed.; Academic Press, 1984;

Eliel etal. , *JACS* **1969**, *91*, 536
Kishi etal. , *JACS* **1982**, *104*, 4976-8

■ The Proposal for Oxo-carbenium Ions (Eliel, Kishi)

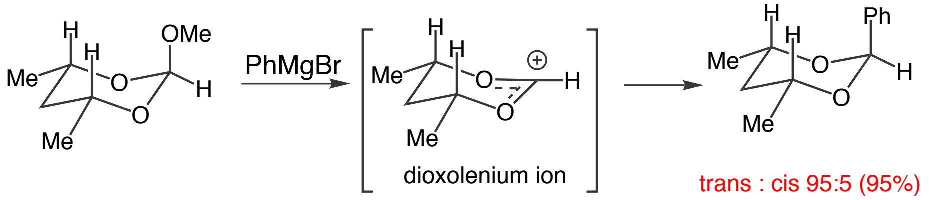


■ The Proposal for Iminium Ions (Stevens)



It was proposed that chair-axial addition would be preferred as a consequence of the intervention of a transition state anomeric effect (Path A). Attack through Path B would necessitate the generation of the twist-boat kinetic product conformation thus destabilizing attack from the equatorial diastereoface. While Stevens espoused this concept for iminium ions in the late 70's, his untimely death at the age of 42 significantly delayed his cited publication.

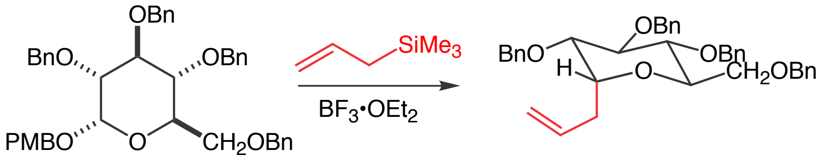
■ An early example from Eliel; *JACS* 1969, *91*, 536



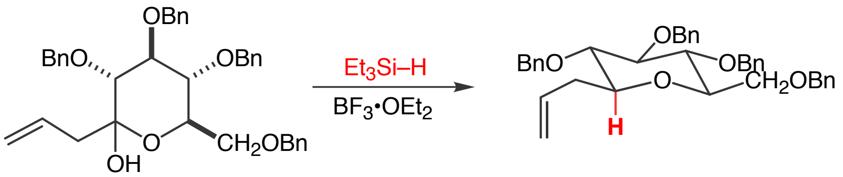
trans : cis 95:5 (95%)

Eliel was the first to attibute stereoelectronic factors to the addition of nucleophiles to cyclic oxo-carbenium ions.

■ Kishi Examples; *JACS* 1982, *104*, 4976-8



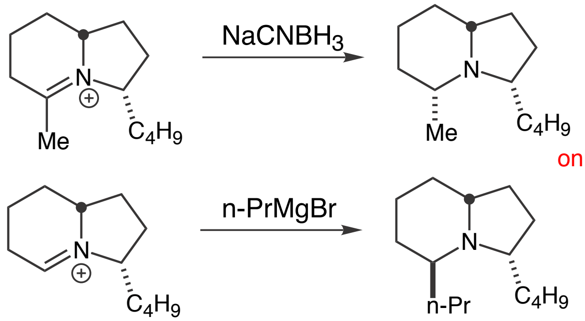
stereoselection 10:1 (55%)



stereoselection 10:1 (55%)

Chair-aixal attack on oxo-carbenium ion occurs for both carbon and hydride nucleophiles

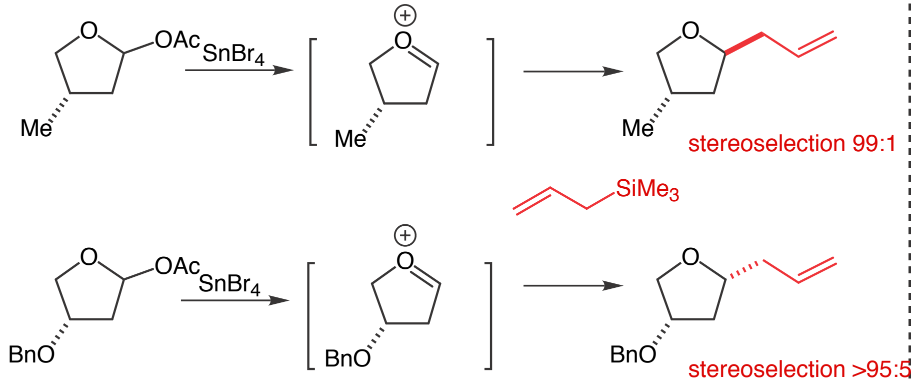
■ Iminium Ions (Stevens) *cited reference*



only one stereoisomer

Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

5-Membered oxocarbenium Ions: Woerpel etal. *JACS* 1999, 121, 12208.

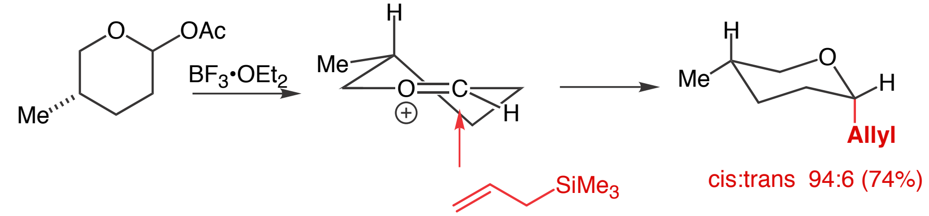


stereoselection 99:1

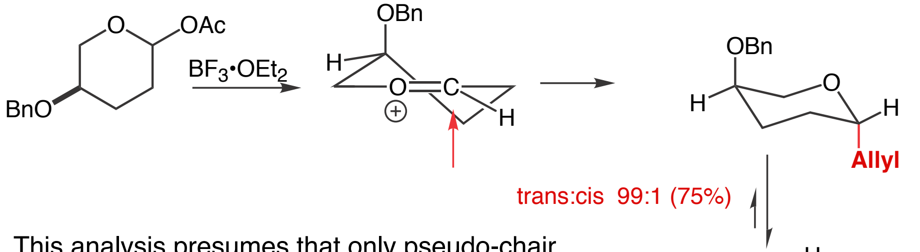
stereoselection >95:5

These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selecticity.

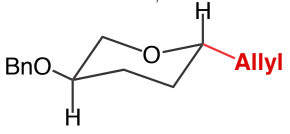
6-Membered oxocarbenium Ions: Woerpel etal. *JACS* 2000, 122, 168.



cis:trans 94:6 (74%)

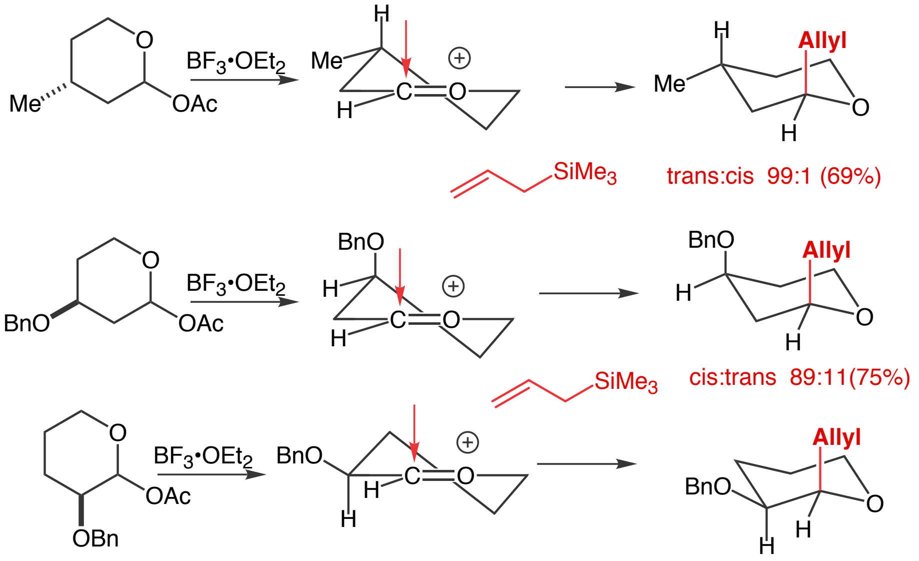


trans:cis 99:1 (75%)



This analysis presumes that only pseudo-chair transition states need be considered.

Woerpel's model states that axial attack from the most stable chair conformer predicts the major product.



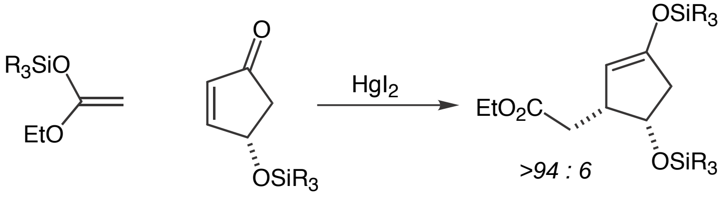
trans:cis 99:1 (69%)

cis:trans 89:11(75%)

cis:trans 83:17(84%)

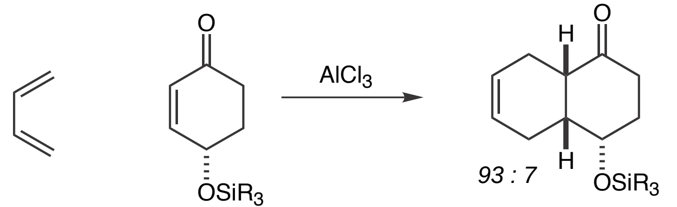
These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selecticity.

Are the preceding addition reactions somehow related to the apparently contrasteric reactions shown below??

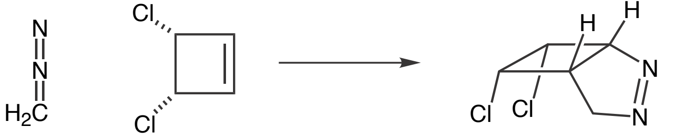


>94 : 6

JOC **1991**, *56*, 387



93 : 7

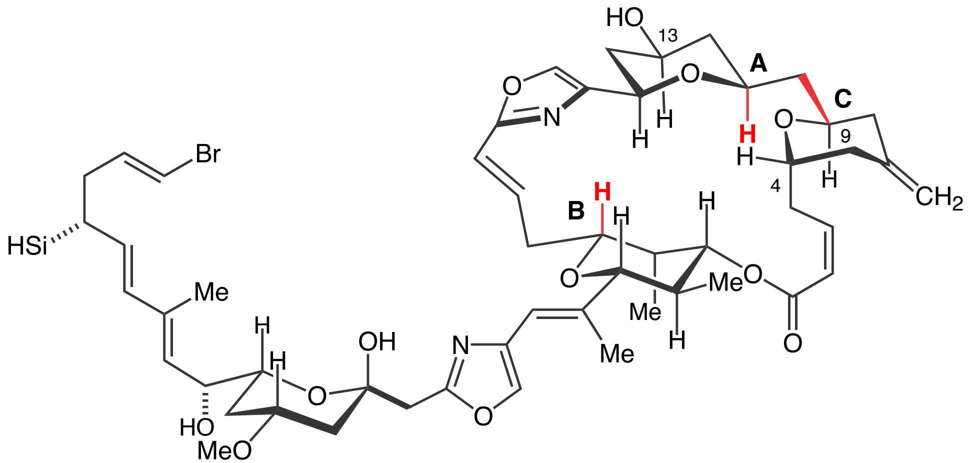


exclusive adduct

Tet. Lett. **1988**, *29*, 6593

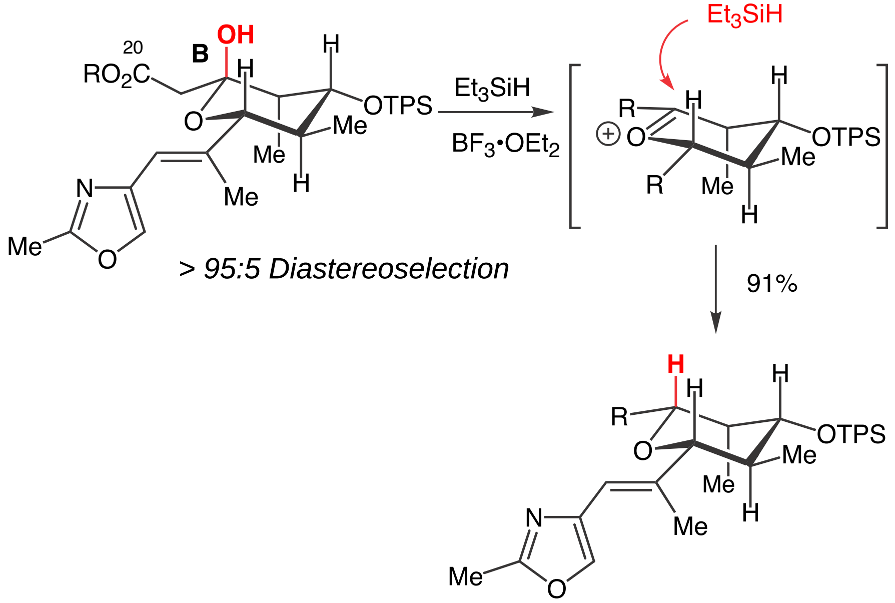
Phorboxazole B

Evans, Fitch, Smith, Cee, *JACS* ***2000****, 122, 10033*



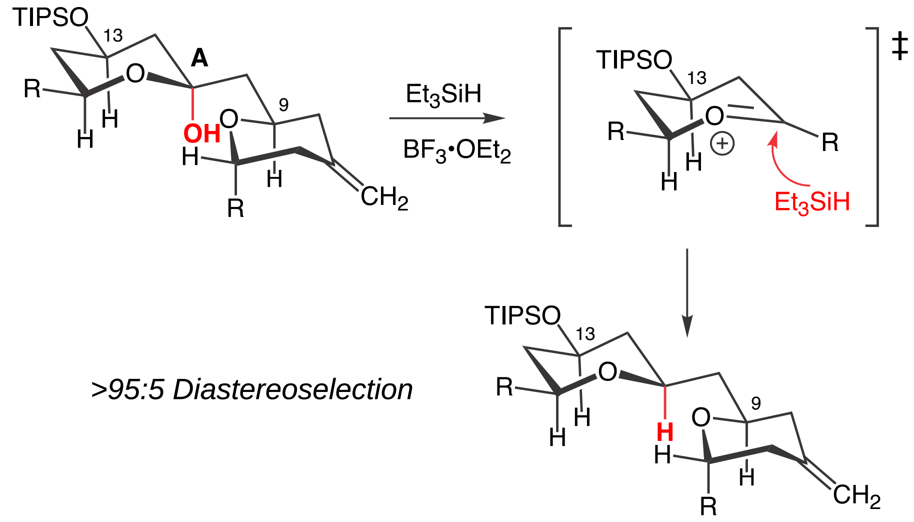
Stereochemical analogies:
Kishi et. al.: *JACS* **1982**, *104*, 4976-8

B: The C-22 Reduction



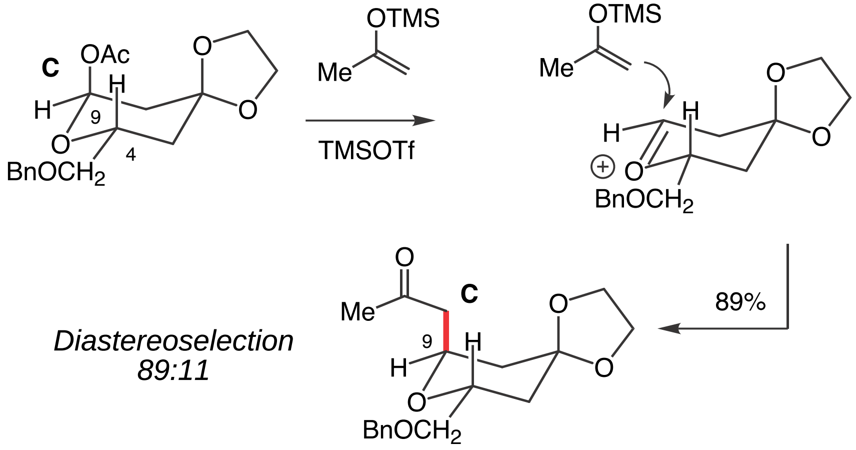
> 95:5 Diastereoselection

A: The C-11 Reduction



>95:5 Diastereoselection

C: The C-9 C–C Bond Construction



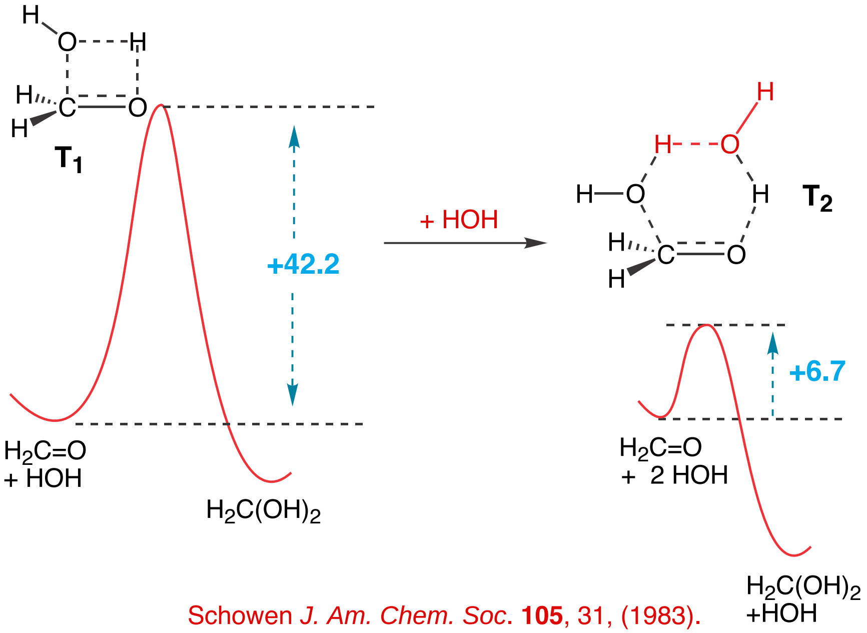
Diastereoselection
89:11

Carbonyl Addition Reactions: Transition State Geometry

4- vs 6-Membered Transition Structures for C=O Addition

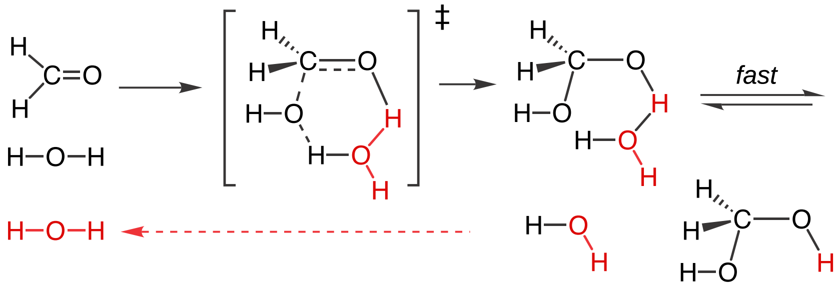
Consider carbonyl hydration:

$$H_2C{=}O \;+\; n\,HOH \longrightarrow H_2C(OH)_2 \;+\; (n\text{-}1)\,HOH$$



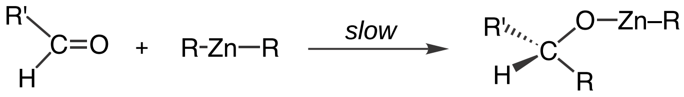
Schowen *J. Am. Chem. Soc.* **105**, 31, (1983).

Overall Process: The valure of the proton shuttle

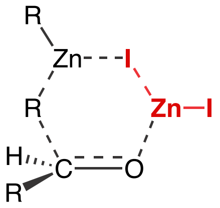


Transiton structure T_2 ~40 kcal/mol more stable than transition structure T_1.

Do these results relate to "real" reactions? Yes!



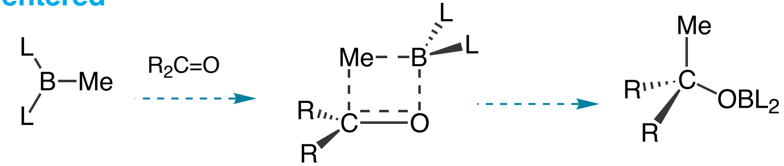
Observation: catalytic amounts of **ZnI_2** dramatically catalyze addition process.



bimetallic transition state

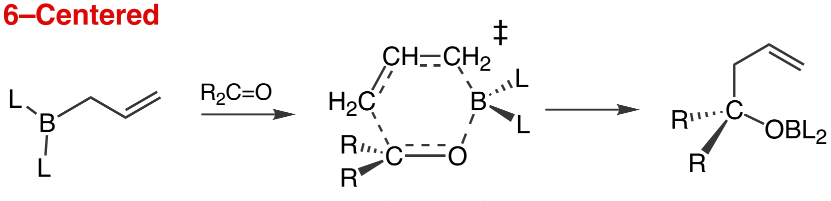
4– Versus 6–Center Transition States for Boron

4-Centered



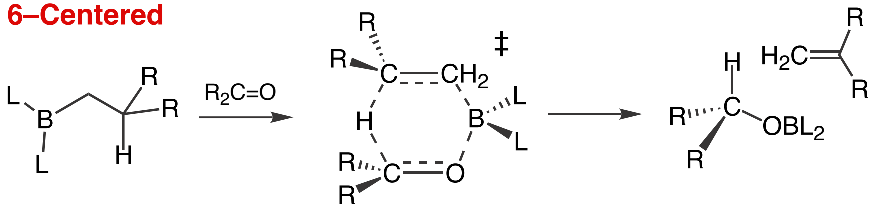
disfavored : rxn does not proceed!)

6–Centered



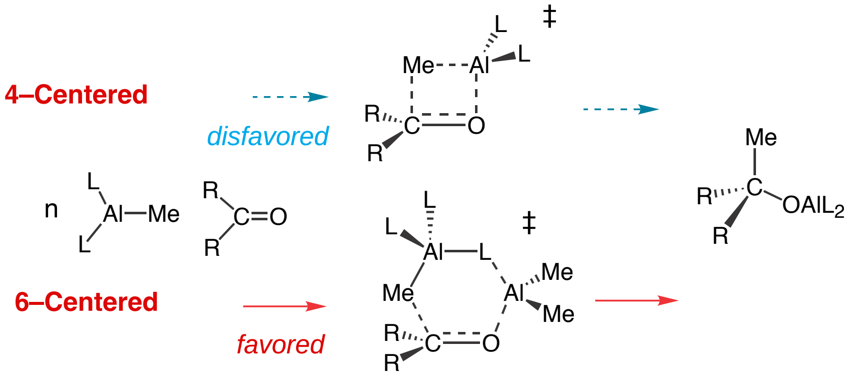
favored

6–Centered

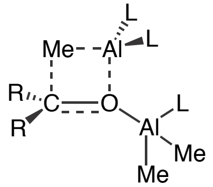


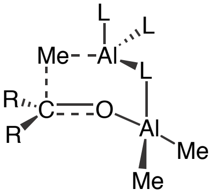
favored

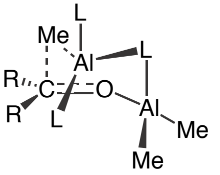
Carbonyl Addition: 4– Versus 6–Center Transition States for Aluminum



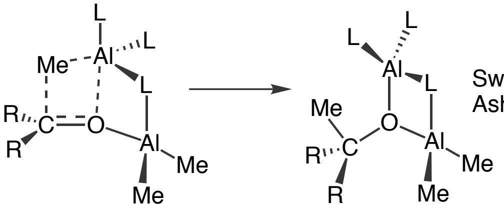
The Bimetallic Transition States are preferred


4-Centered


6-Centered Boat

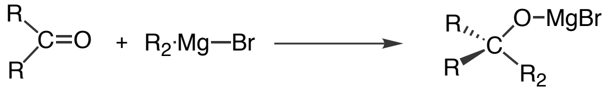

6-Centered Chair

Bicyclic TS



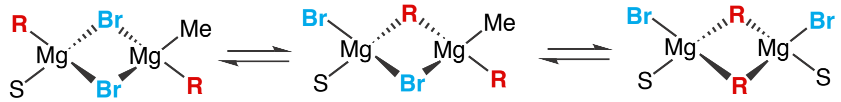
Swain *JACS* **1951**, *73*, 870
Ashby *JACS* **1974**, *89*, 1967

Grignard Reagents:



The molecularity and transition structure for this reaction have not been carefully elucidated. The fact that the Grignard reagent is not a single species in solution greatly complicates the kinetic analysis.

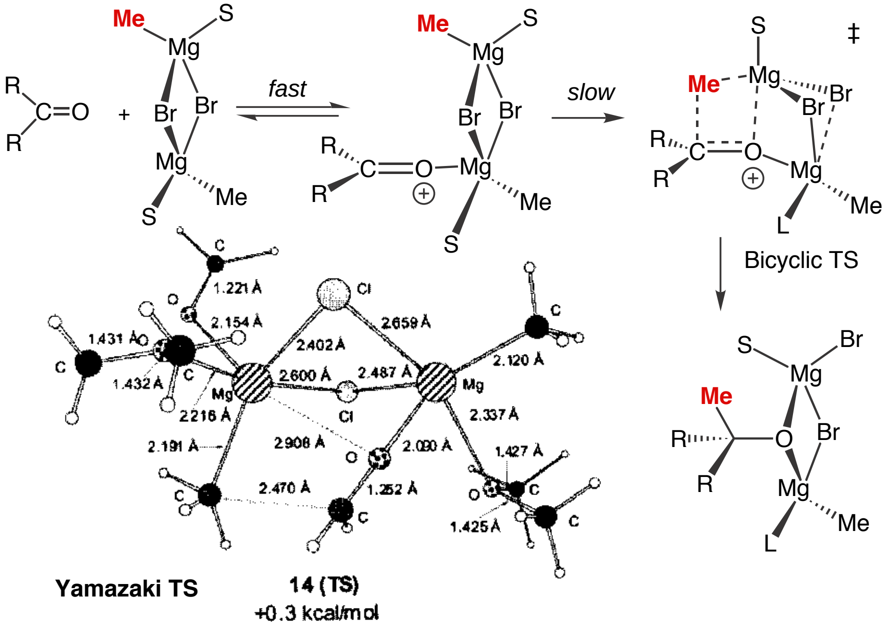
The Schlenk Equilibrium



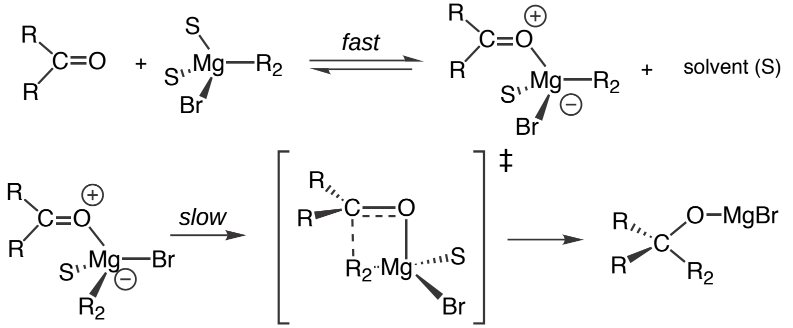
Solution structure of R–MgBr is in dynamic eqkuilibrium through Schlenck equilib

The Bimetallic (Binuclear) Mechanism for C=O Addition

Recent theoretical study: Yamazaki & Yambe, *J. Org. Chem.* **2002**, *67*, 9346

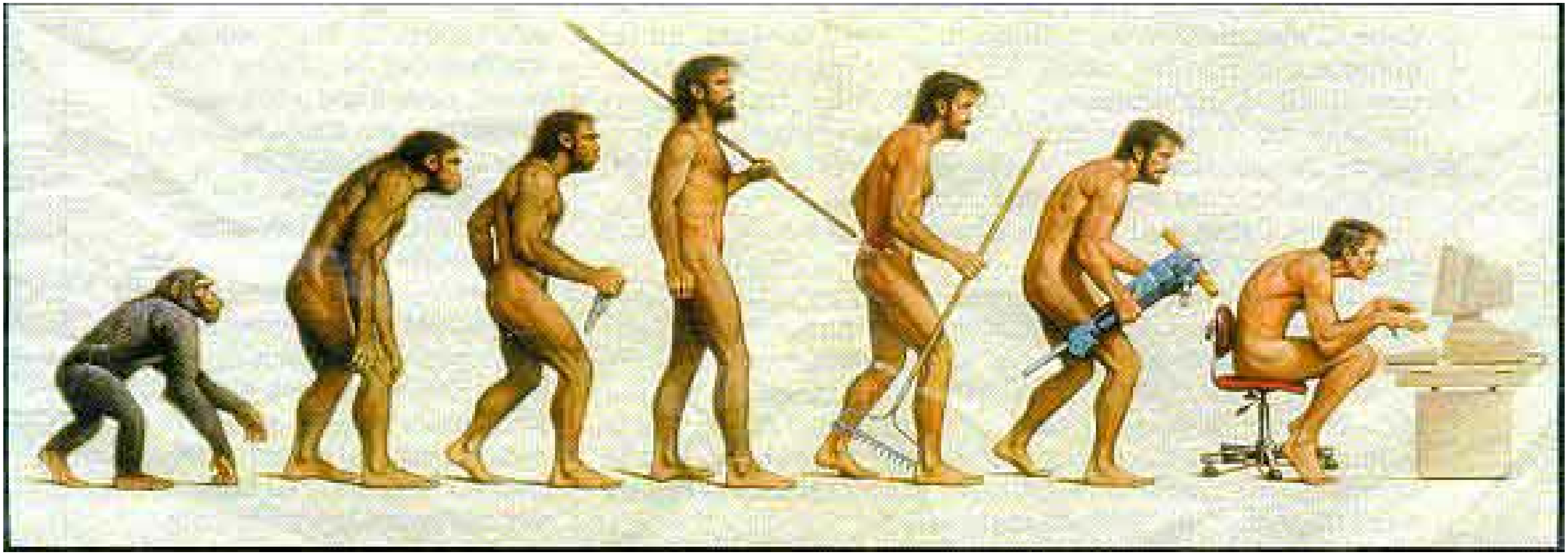


The Mononuclear) Mechanism is now in disfavor



The Evolution of Models for Carbonyl Addition

Mengel, A. and O. Reiser, “Around and Beyond Cram's Rule.”
Chem. Rev. **1999**, 1191-1223

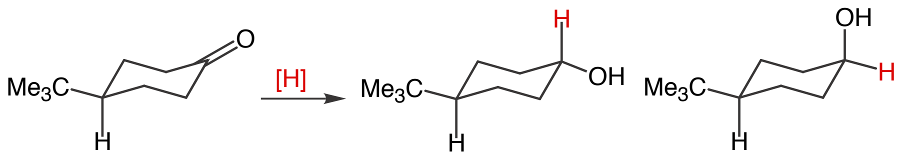


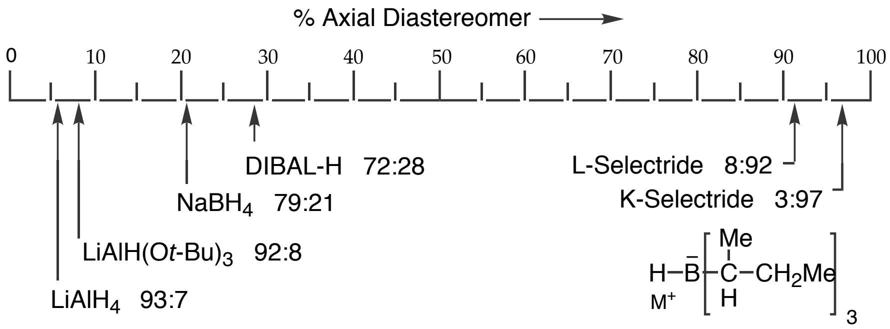
Humor provided by Sarah Siska

Evolution of a Model for C=O Addition

Product Development & Steric Approach Control:

Dauben, *JACS* **1956**, *78*, 2579



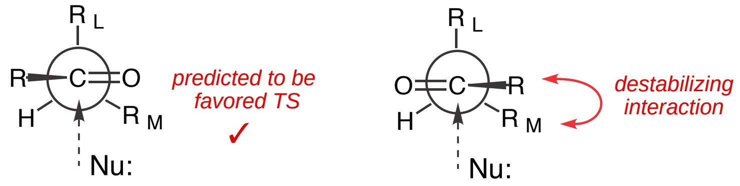


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

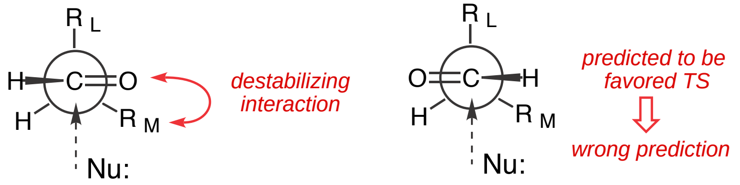
Assumption: Hindered reagents react through more highly developed transition states than unhindered reagents

Assumptions in Felkin Model:

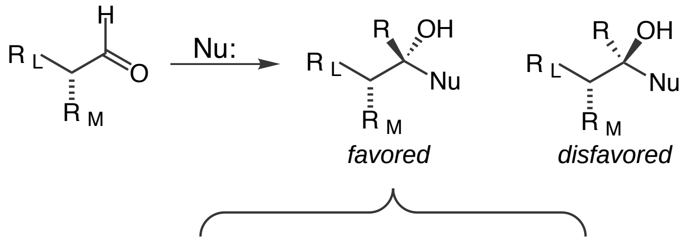
- Transition states are all reactant-like rather than product-like.
- Torsional strain considerations are dominant.
  Staggered TS conformations preferred
- The principal steric interactions are between Nu & R.

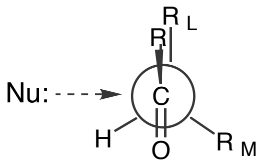


The flaw in the Felkin model: A problem with aldehydes!!

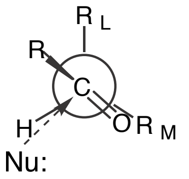


Carbonyl Addition: Evolution of Acyclic Models

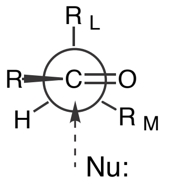




Cram
JACS **1952**, *74*, 5828

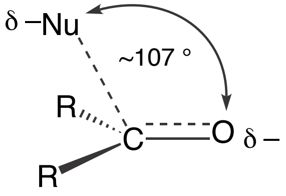


Karabatsos
JACS **1967**, *89*, 1367

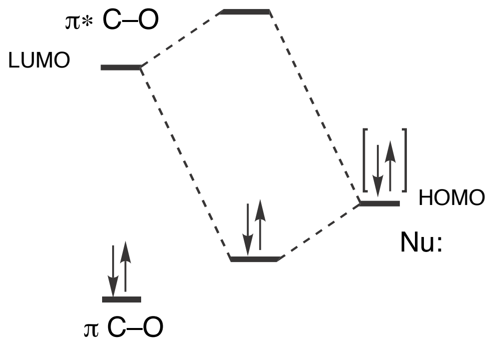


Felkin
TL. **1968**, 2199-2208

Stereoelectronic Effect: The HOMO-LUMO interaction dictates the following reaction geometry:



The Dunitz-Bürgi Angle

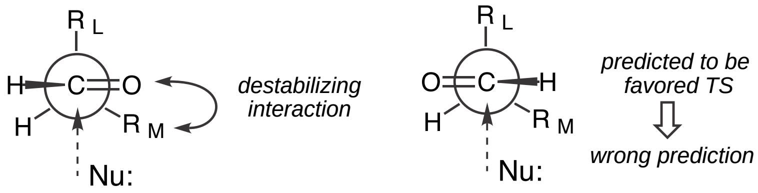


attack angle greater than 90 °; estimates place it in the 100–110 ° range

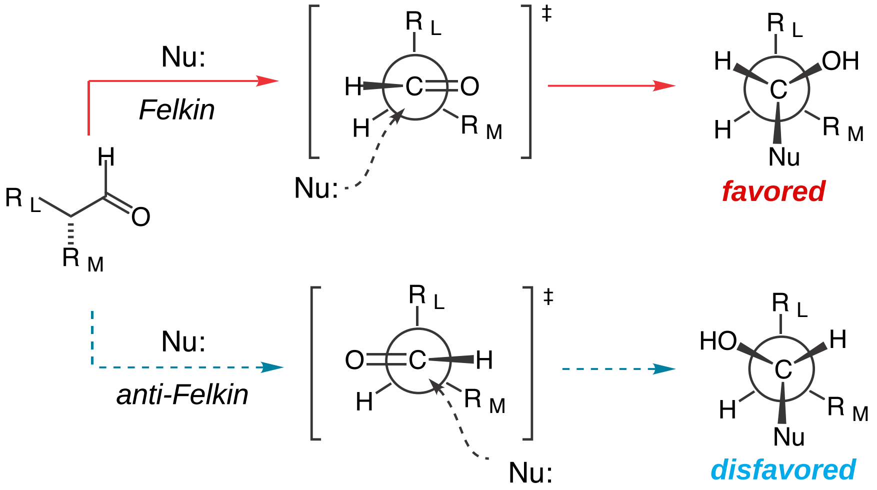
Burgi, Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153-161

The Felkin-Anh Eisenstein Model

The flaw in the Felkin model: A problem with aldehydes!!



Anh & Eisenstein *Noveau J. Chim.* **1977**, *1*, 61-70
Anh *Topics in Current Chemistry.* **1980**, ***No 88***, 146-162



New Additions to Felkin Model:

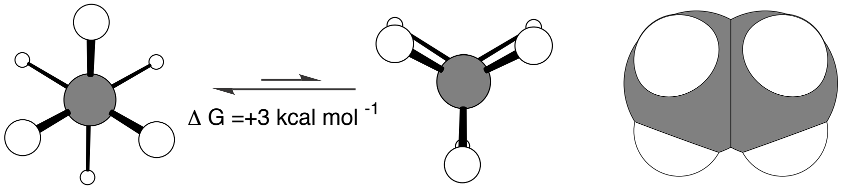
- ■ Dunitz-Bürgi C=O–Nu orientation applied to Felkin model.
- ■ The antiperiplanar effect:
Hyperconjugative interactions between C-R_L which will lower π*C=O will stablize the transition state.

Theoretical Support for Staggered Transition states (Lecture 7)

(Read this) Houk, *JACS* **1982**, *104*, 7162-6
(Read this) Houk, *Science* **1986**, *231*, 1108-17

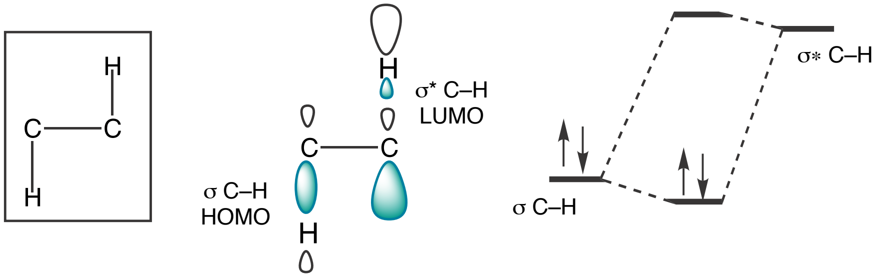
Houk: "The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds"
Lecture–7

Lets begin with ground state effects: Ethane Rotational Barrier

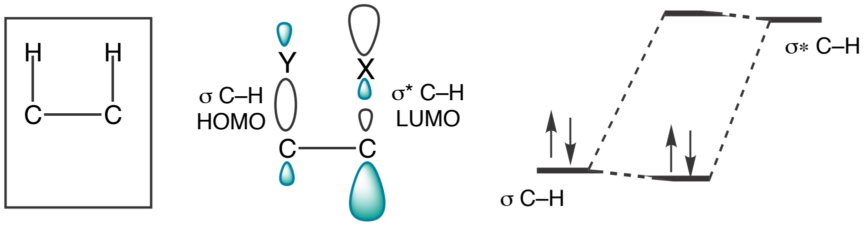


One explanation for the rotational barrier in ethane is that better overlap is achieved in the staggered conformation than in the eclipsed conformation.

In the staggered conformation there are 3 anti-periplanar C–H Bonds



In the eclipsed conformation there are 3 syn-periplanar C–H Bonds

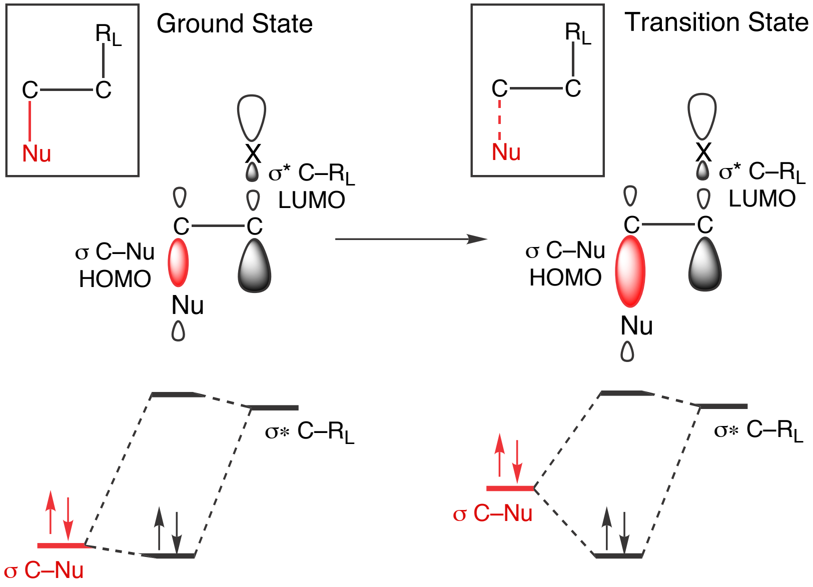


Following this argument one might conclude that:

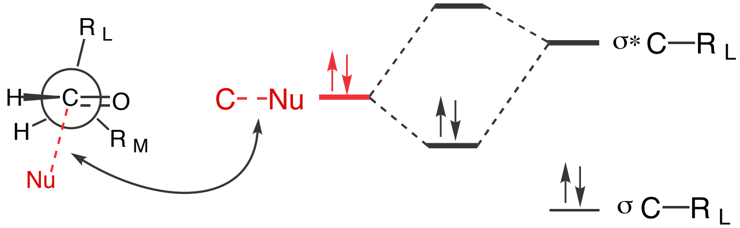
- ■ The staggered conformer has a better orbital match between bonding and antibonding states.
- ■ The staggered conformer can form more delocalized molecular orbitals.

The Felkin-Anh Eisenstein Model

The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds



Best acceptor σ* orbital is oriented anti periplanar to forming bond



Theoretical support:

Padden-Row, *Chem. Commun.* **1990**, 456; ibid **1991**, 327

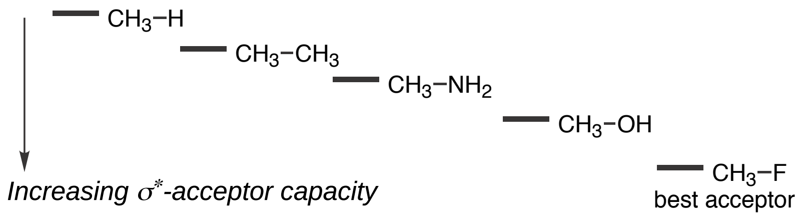
Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5018

Frenking & Reetz, *Tetrahedron* **1991**, *47*, 8091

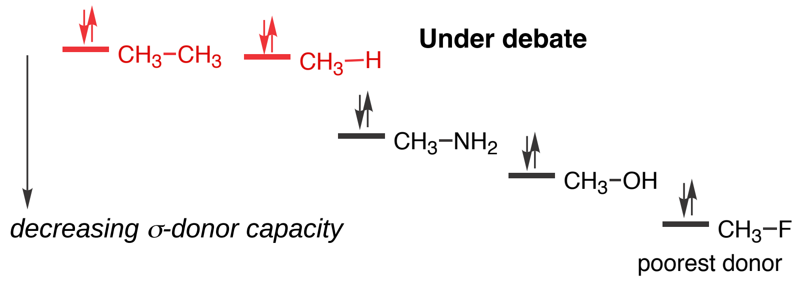
Hierarchy of Donor & Acceptor States

The following trends are made on the basis of comparing the bonding and antibonding states for the molecule CH_3-X where X = C, N, O, F, and H.

σ-anti-bonding States: (C–X)

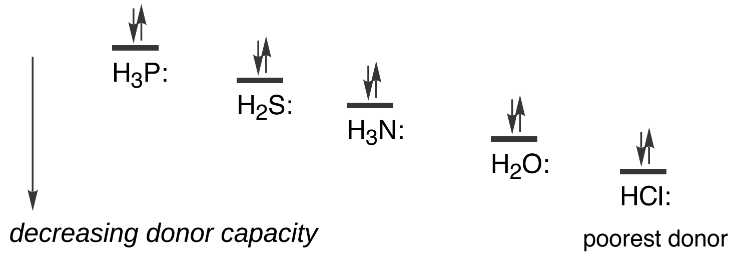


σ-bonding States: (C–X)



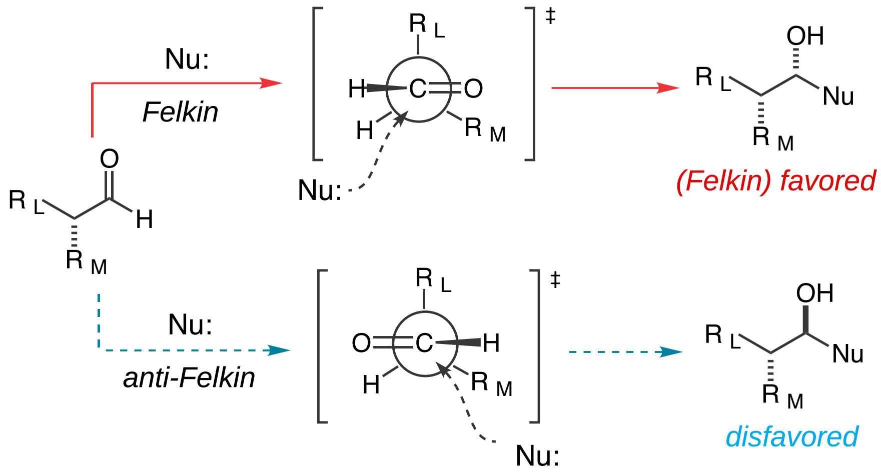
The following are trends for the energy levels of *nonbonding states* of several common molecules. The trend was established by photoelectron spectroscopy.

Nonbonding States

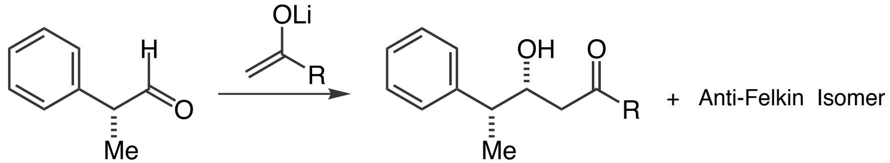


The Felkin-Anh Eisenstein Model: Verification

Addition of Enolate & Enol Nucleophiles

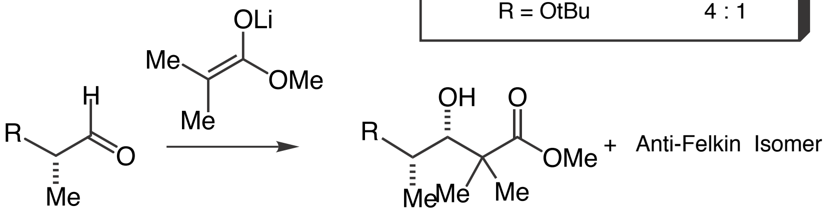


Trend-1: For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1

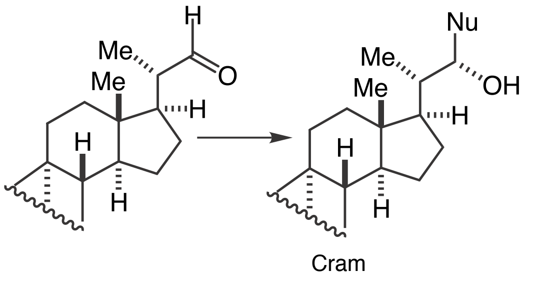
L. Flippin & Co-workers,
Tetrahedron Lett.. **1985**, *26*, 973.



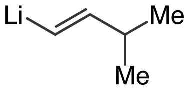
Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C_6H_{11}	9 : 1

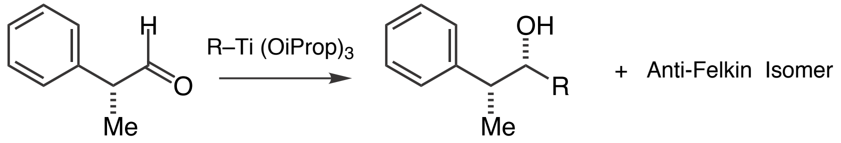
L. Flippin & Co-workers,
Tetrahedron Lett.. **1985**, *26*, 973.

■ This trend carries over to organometallic reagents as well



C. Djerassi & Co-workers,
J. Org, Chem. **1979**, 44, 3374.

Reagent	Ratio
ClMg—C≡CEt	1 : 1
	5 : 1

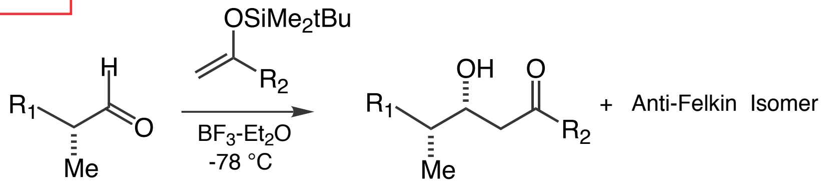


M. Reetz & Co-workers,
Angew Chemie Int. Ed.. **1982**, *21*, 135.

(R–MgX gives Ca 3:1 ratios)

R-Titanium	Ratio
R = Me	>90 : 10
R = n-Bu	>90 : 10

Trend-2: Lewis acid catalyzed reactions are more diastereoselective

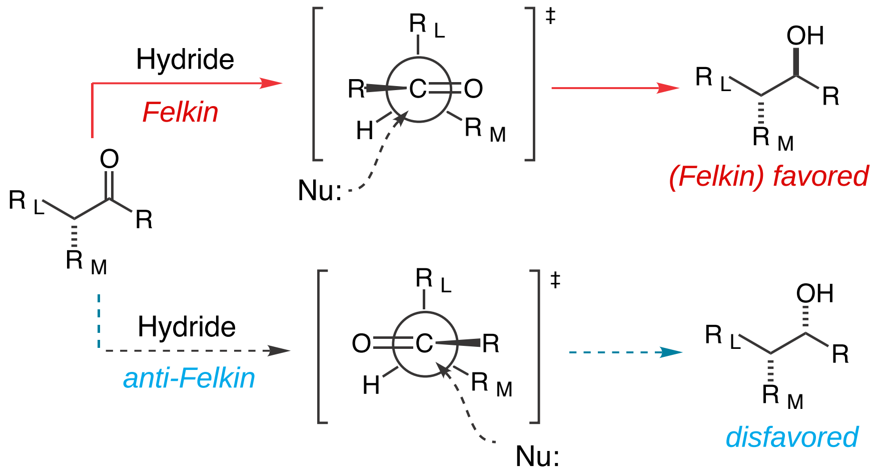


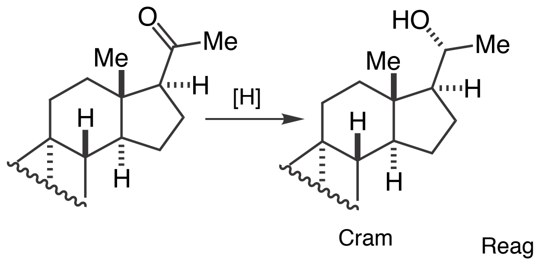
Ketone (R_1)	Enolate (R_2)	Ratio	Ratio Li enolate
R = Ph	R = Me	10 : 1	3 : 1
R = Ph	R = t-Bu	24 : 1	
R = Ph	R = OMe	15 : 1	
R = Ph	R = Ot-Bu	36 : 1	4 : 1
R = c-C_6H_{11}	R = Ot-Bu	16 : 1	

C. Heathcock & L. Flippin *J. Am. Chem. Soc.* **1983**, *105*, 1667.

The Felkin-Anh Eisenstein Model: Ketone Reduction

Addition of Hydride Nucleophiles



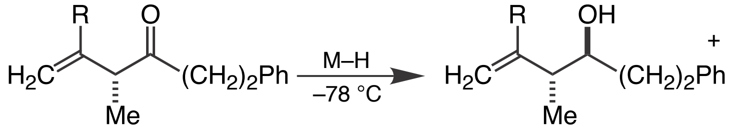


+ Anti-Felkin Isomer

M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

Reagent	Ratio	TS ‡
Li$^+$H–B$^-$(sec-Bu)$_3$	54 : 1	Felkin
NaBH$_4$	5 : 1	Felkin
LiAlH$_4$	3 : 1	Felkin
H–B(Sia)$_2$	1 : 10	Anti-Felkin

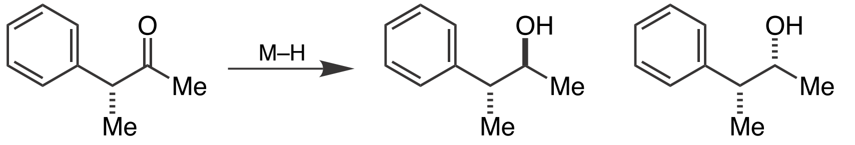
Note: Borane reducing agents do not follow the normal trend



+ Anti-Felkin Isomer

G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, *25*, 2479.

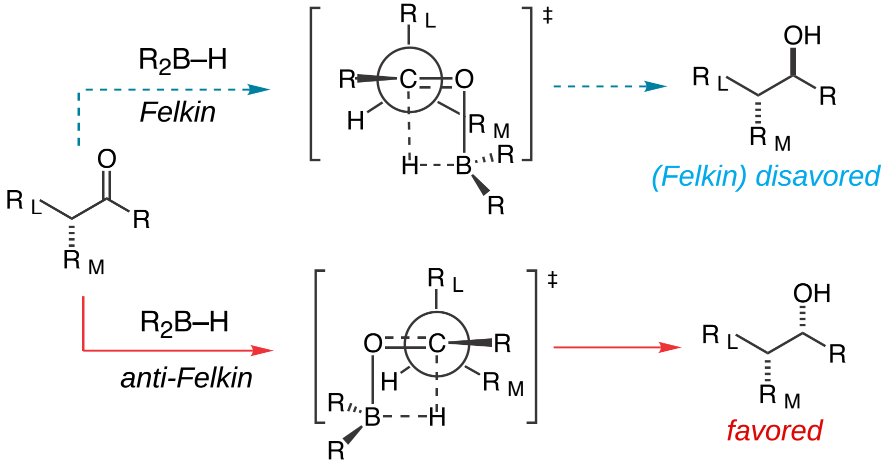
Ketone (R)	Reagent	Ratio
R = H	Li$^+$H–B$^-$(sec-Bu)$_3$	96 : 4
R = H	DIBAL	47 : 53
R = Me	Li$^+$H–B$^-$(sec-Bu)$_3$	>99 : 1
R = Me	DIBAL	88 : 12



M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

Reagent	Ratio	TS ‡
Li$^+$H–B$^-$(sec-Bu)$_3$	22 : 1	Felkin
H–B(Sia)$_2$	1 : 4	Anti-Felkin

Transition States for C=O-Borane Reductions



Nonspherical nucleophiles are unreliable in the Felkin Analysis

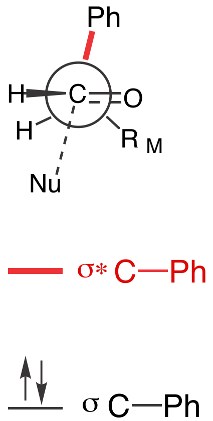
Exercise: Draw the analogous bis(R$_2$BH)$_2$ transition structures

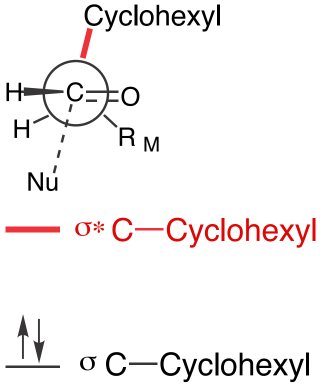
The Felkin-Anh Eisenstein Model: A Breakdown

Are there cases not handled by the Anh-Eisenstein Model?

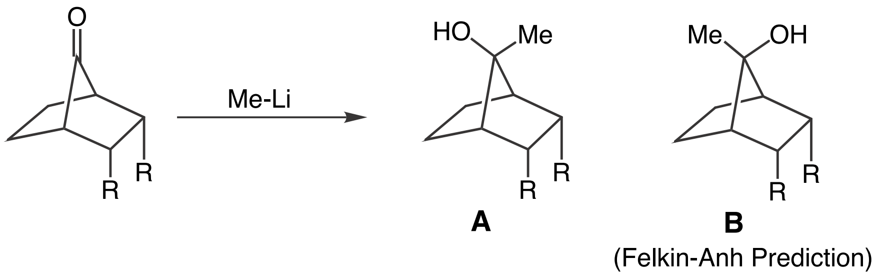
Anh-Eisenstein:
"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

σ* C_{SP3}–C_{SP2} is lower in energy than σ* C_{SP3}–C_{SP3} bond.





Felkin-Anh analysis predicts **B** for R = electronegative substituent.

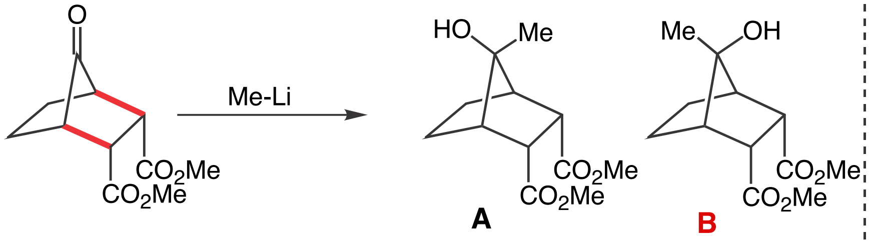


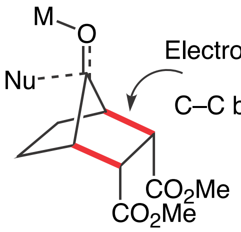
G. Mehta, *JACS* **1990**, *112*, 6140

Felkin-Anh analysis predicts the wrong product!

(R) Substituent	A/B Ratio
$-\overset{O}{\overset{\|}{C}}-OMe$	>90:10
$-CH_2OMe$	34:66
$-CH=CH_2$	27:73
$-CH_2-CH_3$	17:83

Case I:

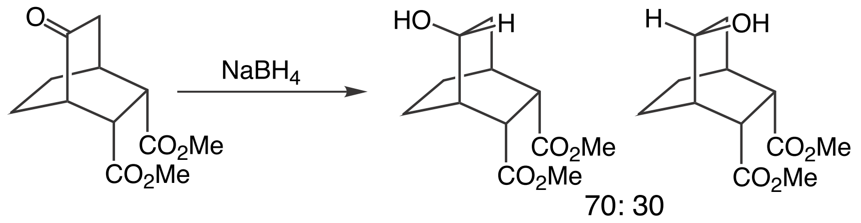


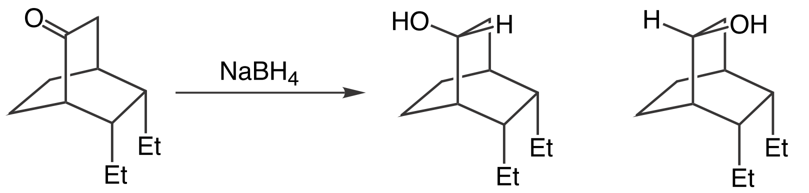


Electronegative -CO_2Me substituent will stabilize both C–C bonding & antibonding states

⇓

Felkin-Anh analysis predicts **B**





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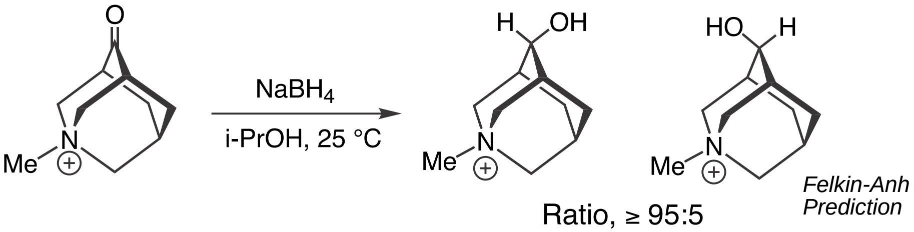
"These results can be reconciled in terms of the Cieplak model."

The Felkin-Anh Eisenstein Model: A Breakdown

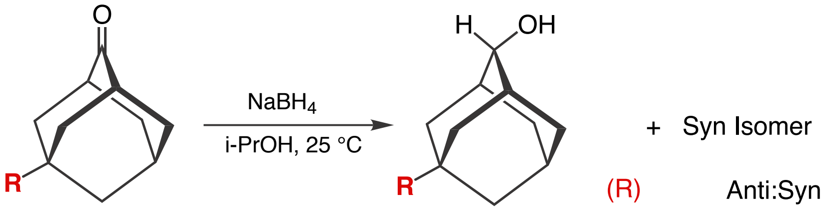
Case II: The Le Noble Examples

Le Noble, *JACS* 1992, *114*, 1916



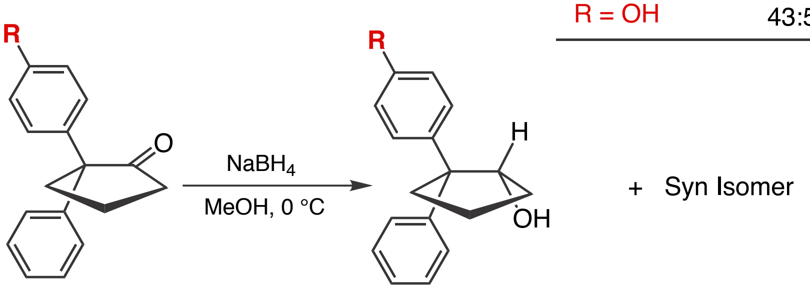
Ratio, ≥ 95:5

Pyramidally distorted C=O ruled out from inspection of X-ray structures.



(R)	Anti:Syn Ratio
R = F	62:38
R = CO_2Me	61:39
R = $SiMe_3$	45:55
R = OH	43:57

Le Noble, *J. Org. Chem*. **1989**, *54*, 3836

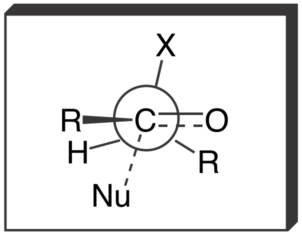


(R)	Anti:Syn Ratio
R = NO_2	79:21
R = Cl	63:37
R = OMe	43:57
R = NH_2	36:64

Halterman, *JACS* **1990**, *112*, 6690

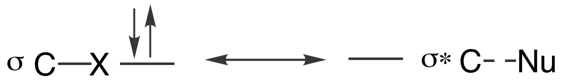
Cieplak Model for C=O Addition

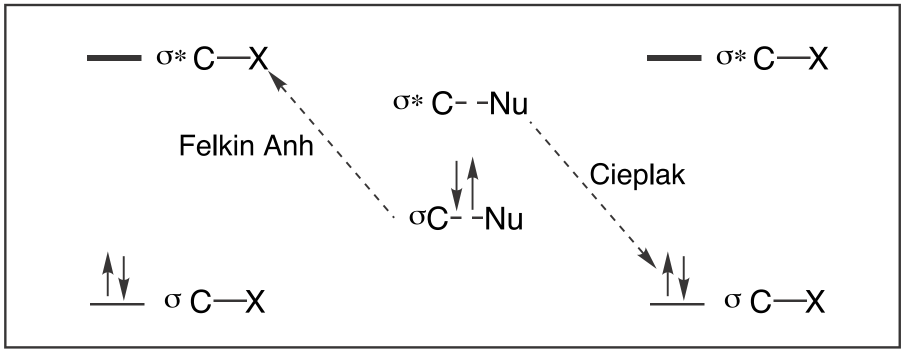
Cieplak, *JACS* **1981**,*103*, 4540; Cieplak/Johnson, *JACS* **1989**, *111*, 8447



Point A: TS is stabilized by antiperiplanar allylic bond, but....

Point B: Nature of the stabilizing secondary orbital interactions differ:





Point C: C–X Electron donating ability follows the order:
C–H > C–C > C–N > C–O
(Houk disputes the ordering of C–H, C–C)

Point D: Importance of torsional effects
(Felkin, Anh, Houk, Padden-Row) disputed.

"Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamendal assumptions in frontier molecular orbital theory." The Cieplak hypothesis is nonsense."

"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

The management

Quotes for the Day

"Every generation of scientists starts where the previous generation left off, and the most advanced discoveries of one age constitute elementary axioms of the next."

Aldous Huxley

“It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.”

(Sherlock Holmes, A Scandal in Bohemia)

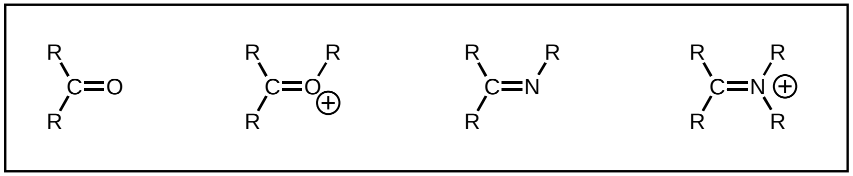
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 21

Carbonyl and Azomethine Electrophiles-2



- Breakdown in the Felkin-Anh Model
- Cyclohexanone Revisited
- Diastereoselective Additions to Cyclic Ketones
- Chelate Controlled Carbonyl Additions

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

D. A. Evans

Monday,
November 3, 2003

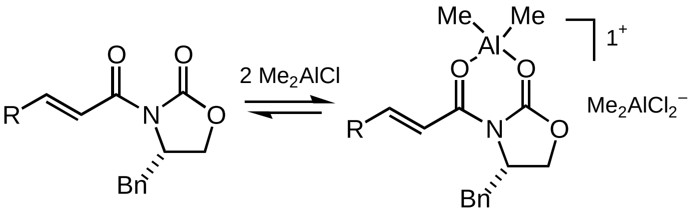
1. "Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, *1*, 61-70. **(pdf)**

2. "Structural, mechanistic, and theoretical aspects of chelation controlled carbonyl addition reactions."Reetz, Acc. Chem. Res. **1993** *26*: 462. **(pdf)**

3. "A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes." Evans, et. al. *JACS* **1996**, *118*, 4322-4343. **(pdf)**

4. "The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride. The Merged Stereochemical Impact of α- and β-Stereocenters in Chelate-Controlled Carbonyl Addition Reactions with Enolsilane and Hydride Nucleophiles". Evans, Allison,Yang, Masse, **2001**, *123*, 10840-10852. **(pdf)**

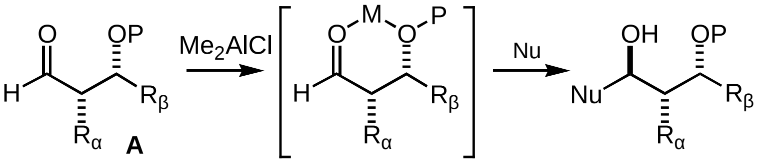
Me_2AlCl is the most powerful chelating Lewis acid yet documented



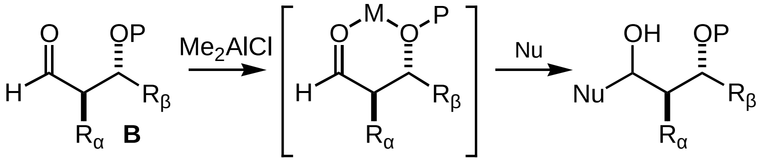
(1)

"Asymmetric Diels-Alder Cycloaddition Reactions with Chiral α,β-Unsaturated-*N* Acyloxazolidinones". Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

Syn Diastereomer: α & β Centers Reinforcing



(2)



(3)

Anti Diastereomer: α & β Centers Opposing

The Felkin-Anh Eisenstein Model: A Breakdown

Are there cases not handled by the Anh-Eisenstein Model?

Anh-Eisenstein:
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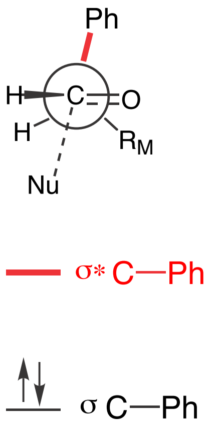
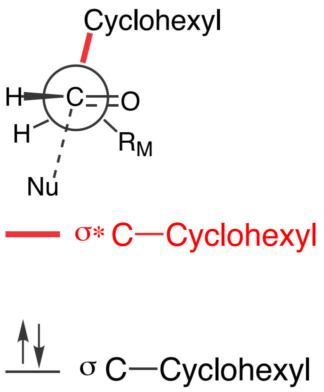
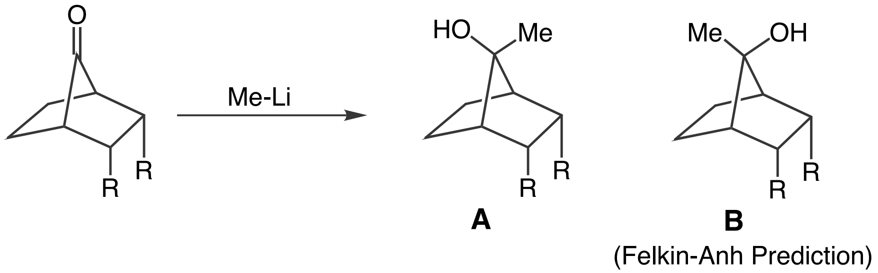
σ* C_{SP3}–C_{SP2} is lower in energy than σ* C_{SP3}–C_{SP3} bond.





Felkin-Anh analysis predicts **B** for R = electronegative substituent.



(Felkin-Anh Prediction)

G. Mehta, *JACS* **1990**, *112*, 6140

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Felkin-Anh analysis predicts the wrong product!

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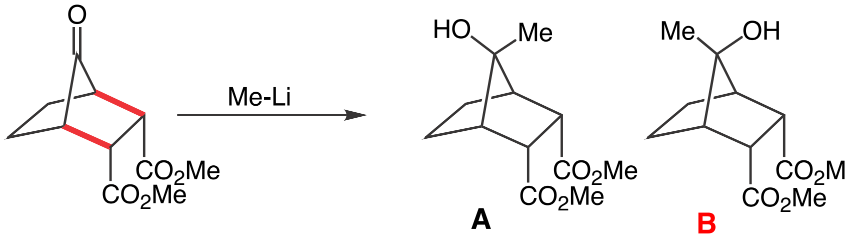

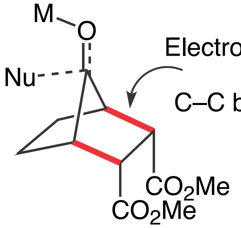

Electronegative -CO_2Me substituent will stabilize both C–C bonding & antibonding states

⇩

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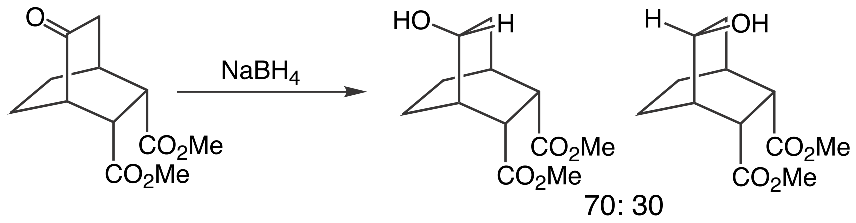

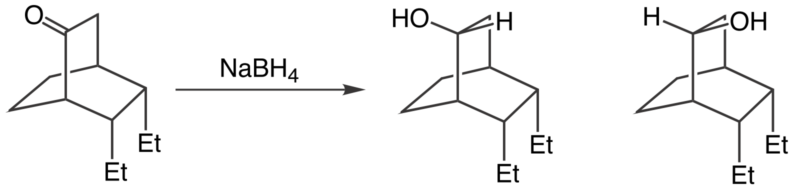

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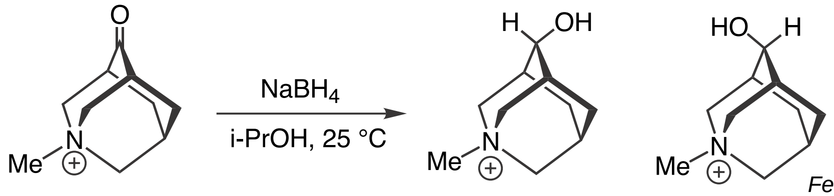

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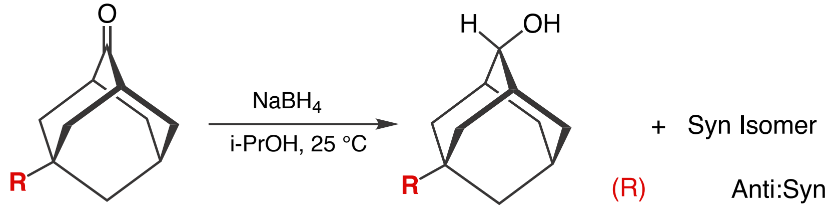

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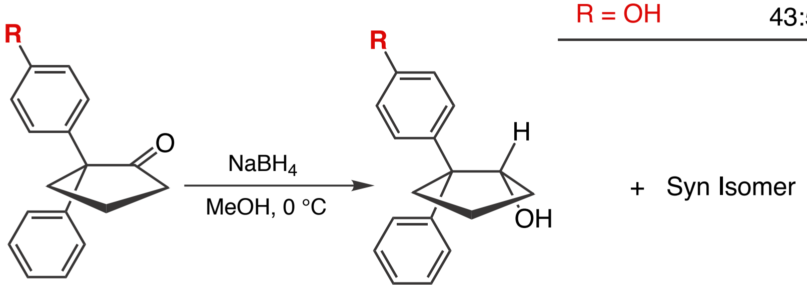

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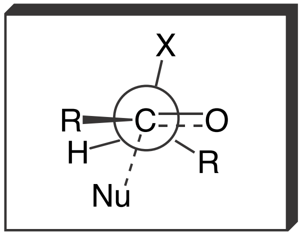

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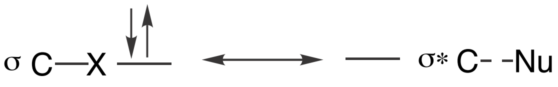
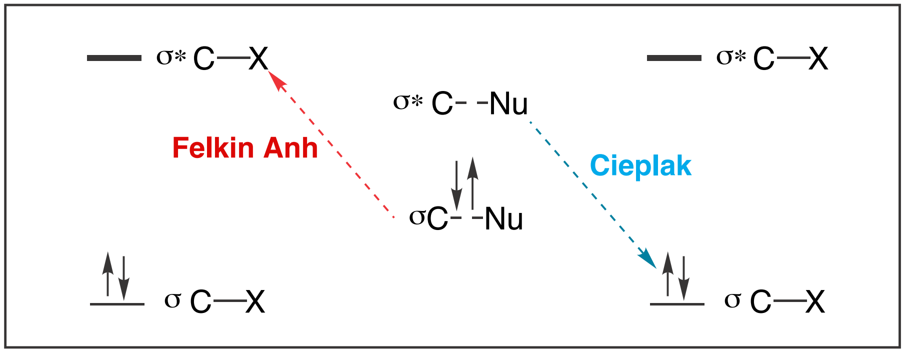
Point B: Nature of the stabilizing secondary orbital interactions differ:





Point C: C–X Electron donating ability follows the order:
C–H > C–C > C–N > C–O
(Houk disputes the ordering of C–H, C–C)

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(Felkin, Anh, Houk, Padden-Row) disputed.

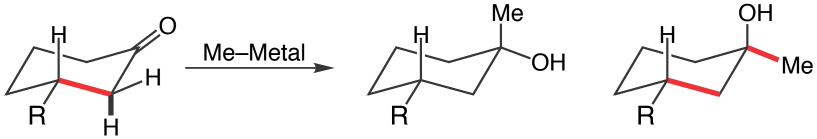
"Structures are stabilized by stabilizing their highest energy filled states. This one of the fundamendal assumptions in frontier molecular orbital theory." The Cieplak hypothesis is nonsense."

"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct." The management

“It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.”
(Sherlock Holmes, A Scandal in Bohemia)

The Cyclohexanone Case Revisited: Frenking & Houk

Observation As R becomes more electronegative, percentage of axial attack increases.



(R) Substituent	% Axial Attack Me-Li	 Me_2Cu-Li
R = H	21%	6%
R = C_6F_5	34%	21%
R = CF_3	50%	42%

Felkin-Anh predicts opposite trend.

Cieplak argument consistent with results.

The Frenking Position:

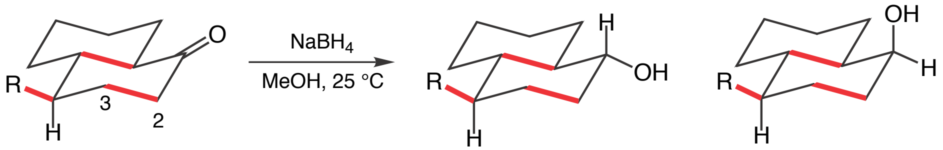
- Cieplak stabilizing interaction is "dubious." Why not stabilize the forming sigma bond?
- Enhanced rate of axial Nu attack on cyclohexanone is caused by better electrostatic interactions of the ketone with the attacking reagent and not by torsional considerations.
- Nonequivalence of the π*C=O LUMO with a greater extension on the axial face dictates stereoselection (Klein, 1973).

"Since interactions between the π C=O & π* C=O and the bonding & anti-bonding (β) C–H & (β) C–C orbitals are all symmetry allowed, it is difficult to predict a priori which interactions are dominant without carrying out quantum mechanical calculations."

Frenking & Reetz, *Angew. Chem.* Int. Ed. **1991**, *30*, 1146

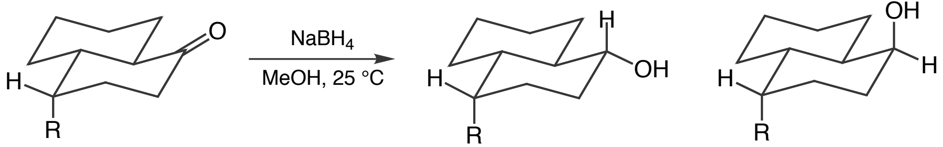
Houk: Electrostatic rather than covalent considerations may be dominant.

"Equatorial electronegative substituents should interact more strongly with the C(2-3) and C(9-10) bonds than axial substituents."



(R) Substituent	Product Ratio
R = H	60:40
R = OAc	71:29
R = Cl	71:29

"If nucleophilic addition occurs anti to the better donor bond (Cieplak), the equatorial isomers should have considerably more axial attack than the parent while the axial isomers should have only a slight increase in axial attack."

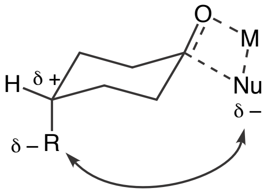


"Exactly the opposite is observed."

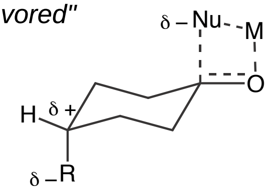
(R) Substituent	Product Ratio
R = OAc	83:17
R = Cl	88:12

Axial 4-substituents favor axial attack for electrostatic reasons:

"Disfavored"



"Favored"



(DAE: Bimetallic transition states were not considered)

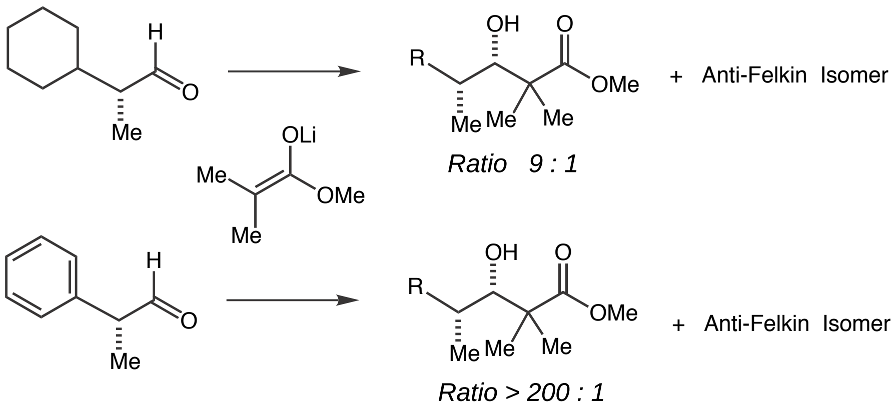
K. Houk & Co-workers, *J. Am. Chem. Soc.* **1991**, *113*, 5018

The Felkin-Anh Eisenstein Model: Electronic Effects

Are there electronic effects in the reaction?

Several cases have already been presented which may be relevant

L. Flippin & Co-workers, *Tetrahedron Lett.*. **1985**, *26*, 973.



Ratio 9 : 1

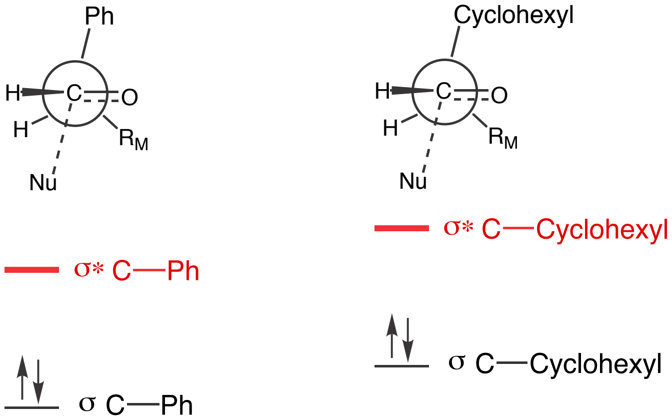
Ratio > 200 : 1

The molecular volume occupied by cyclohexyl acknowledged to be larger than that for phenyl. Because of shape phenyl "can get out of the way."

Anh-Eisenstein Explanation based on HOMO-LUMO Analysis:

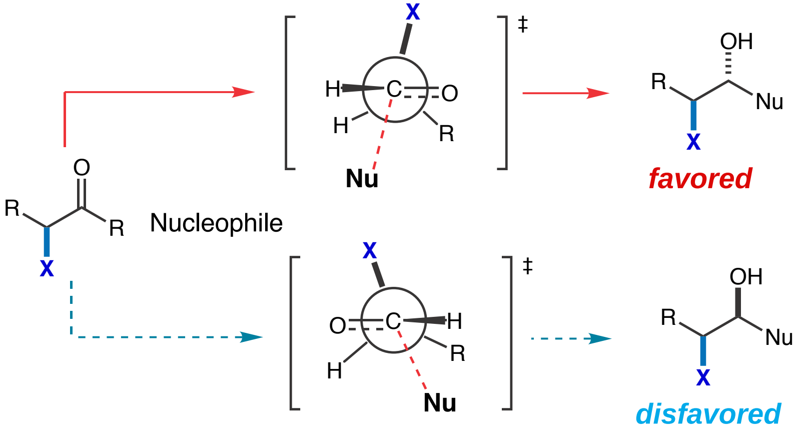
"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

$\sigma*$ C_{SP3}–C_{SP2} is lower in energy than $\sigma*$ C_{SP3}–C_{SP3} bond.



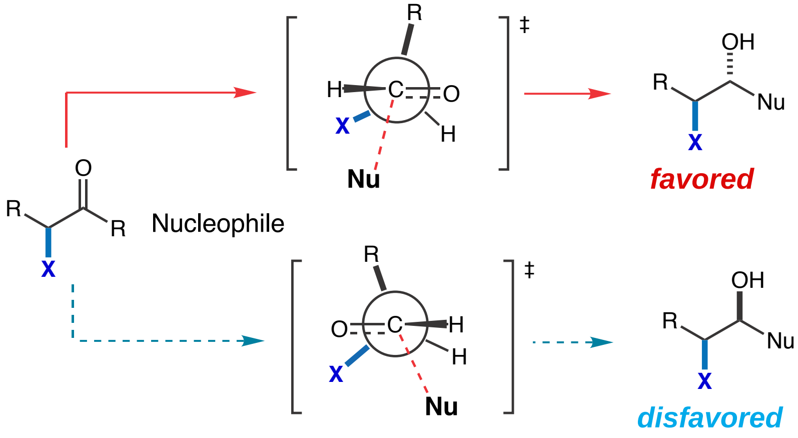
The Polar Felkin-Anh Model

Premise: Transition state **hyperconjugation** between forming bond (HOMO) and best antiperiplanar acceptor (σ* C–**X**, LUMO). Steric effects alre also considered; X = Halogen, OR, SR etc



Modified Cornforth Model

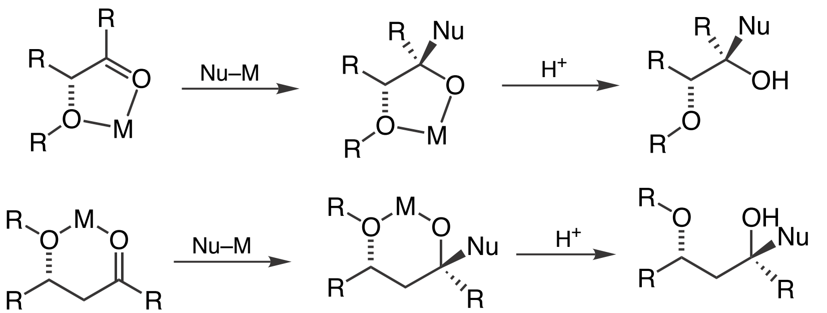
Premise: Transition State **dipole minimization** between polar C–X substituent and the transforming carbonyl function dictate preferred TS geometrics. Steric effects alre also considered; X = Halogen, OR, SR etc



Both models lead to the same stereochemical prediction.

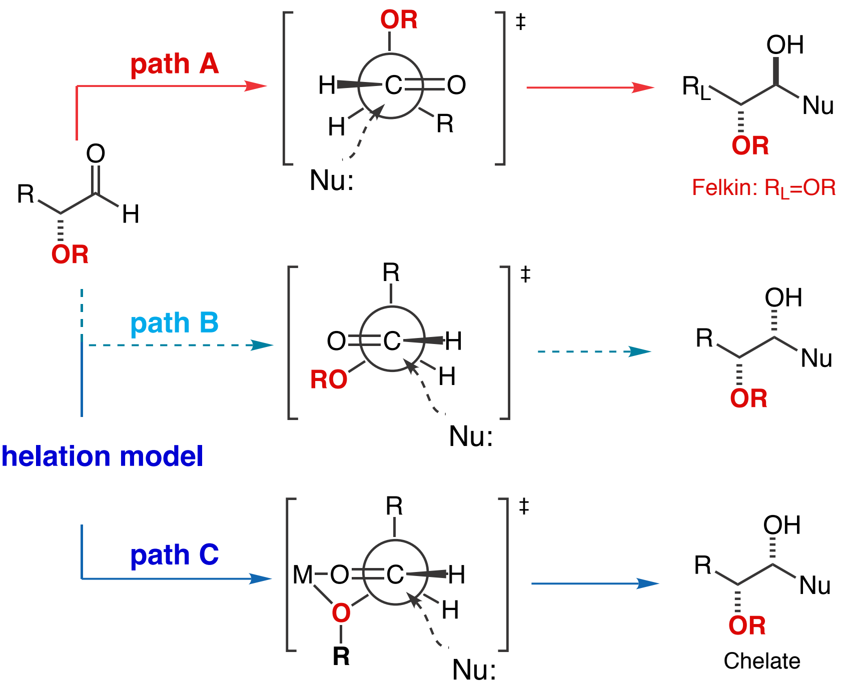
Carbonyl Addition Reactions: Chelate Organization

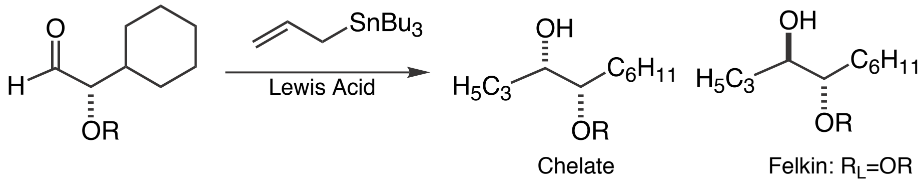
Chelate organization also provides a powerful control element in carbonyl addition reactions



Reviews Reetz, *Accts. Chem. Res*. **1993**, *26*, 462-468 **(pdf)**
Reetz, *Angew. Chem. Int. Ed*. **1984**, *23*, 556-569

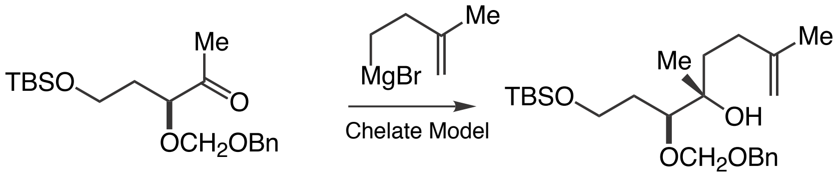
Addition of Carbon Nucleopiles



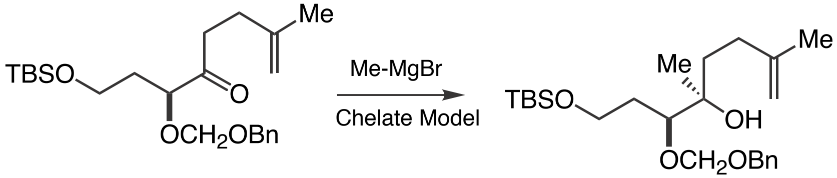


(OR)	Acid	Solv.	Ratio
R = CH_2OBn	$MgBr_2$	THF (0°)	20 : 80
R = CH_2OBn	$MgBr_2$	CH_2Cl_2 (-20°)	>99 : 1
R = CH_2OBn	$TiCl_4$	CH_2Cl_2 (-78°)	>99 : 1
R = $SiMe_2$(t)Bu	BF_3-Et_2O	CH_2Cl_2 (-78°)	5 : 95

G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 265

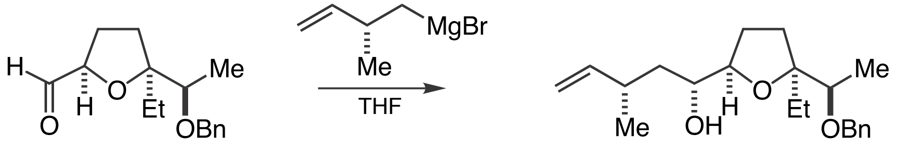


diastereoselection 50 : 1



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

diastereoselection >100 : 1

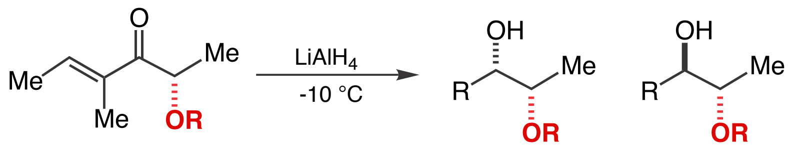


Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, *19*, 2745

"only one isomer"
Chelate Model

Chelate Organization in C=O Addition

Chelate organization provides a powerful control element in carbonyl addition reactions



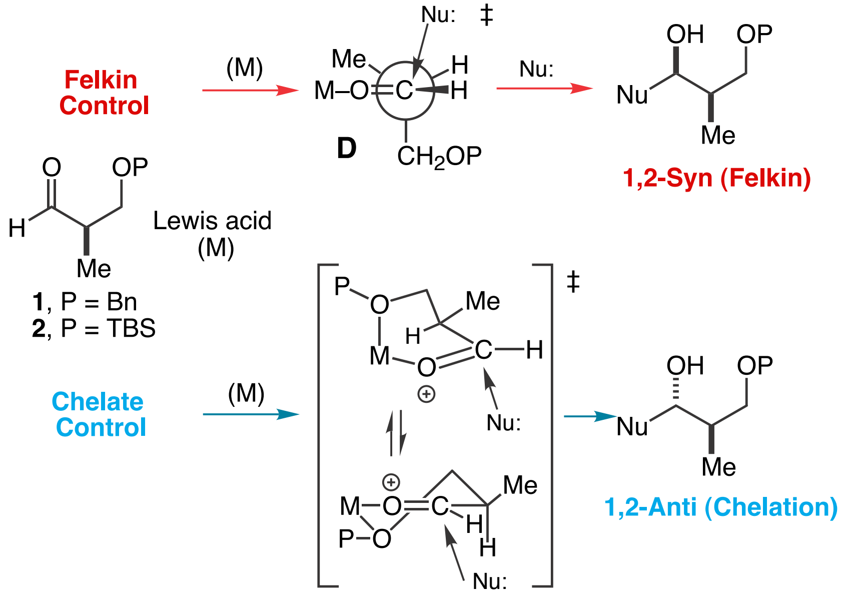
Polar Felkin Anh   Chelation

Overman
Tet Lett. **1982**, *23*, 2355

(OR)	Solv.	Ratio	Model
R = CH_2OBn	THF	30 : 70	Chelate
R = CH_2OBn	Et_2O	2 : 98	Chelate
R = $SiPh_2$(t)Bu	**THF**	**95 : 5**	**F–A: R_L=OR**

Degree of chelate organization may be regulated by choice of solvent and protecting group. Note that $SiPh_2$(t)Bu group prevents chelation.

Case Study



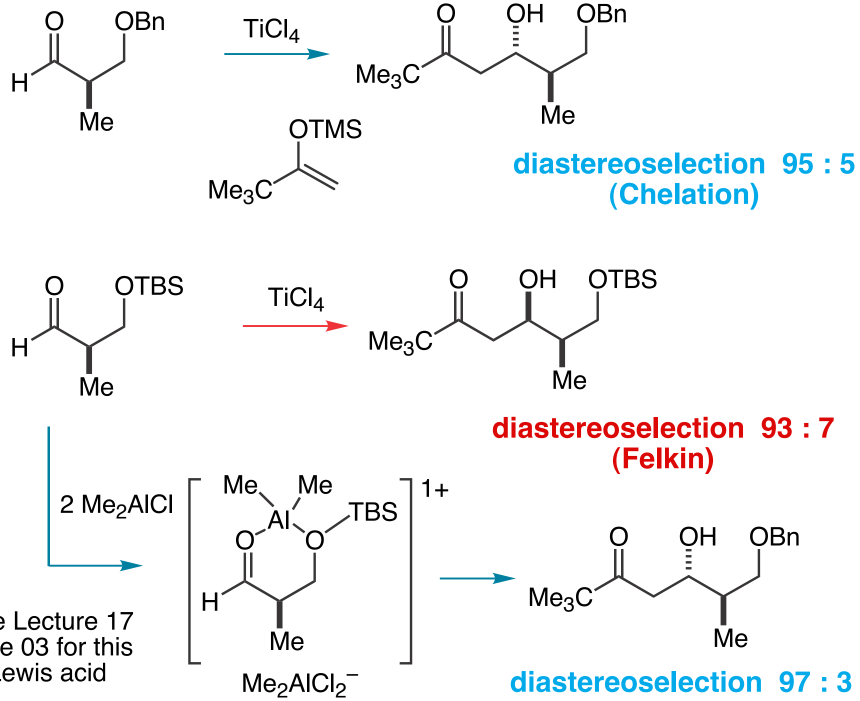
Felkin Control

1,2-Syn (Felkin)

1, P = Bn
2, P = TBS

Chelate Control

1,2-Anti (Chelation)



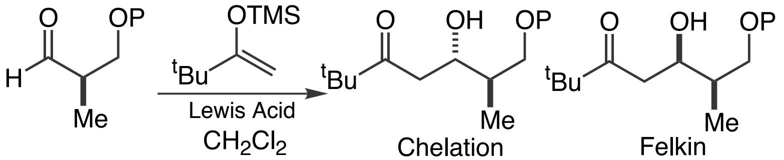
diastereoselection 95 : 5 (Chelation)

diastereoselection 93 : 7 (Felkin)

See Lecture 17 slide 03 for this Lewis acid

diastereoselection 97 : 3 (Chelation)

Me_2AlCl & $MeAlCl_2$ only Lewis acids that will chelate strongly to $OSiR_3$ Groups.
Evans, Allison, Yang, Masse, *JACS* **2001**, *123,* 10840–10852



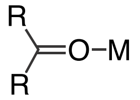
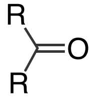
Chelation   Felkin

1 P = Bn   **9**   **10**
2 P = TBS   **11**   **12**

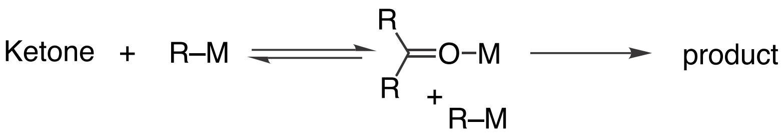
entry	Lewis acid[b]	**1** P = Bn **9** : **10** (%)	**2** P = TBS **11** : **12** (%)
A	BF_3•OEt_2	26 : 74 (76)	09 : 91 (55)
B	$SnCl_4$	50 : 50 (87)	07 : 93 (41)
C	$TiCl_4$	**97 : 03** (74)	07 : 93 (55)
D	Me_2AlCl	90 : 10 (45)	**97 : 03** (62)[c]
E	$MeAlCl_2$	78 : 22 (70)	77 : 23 (55)

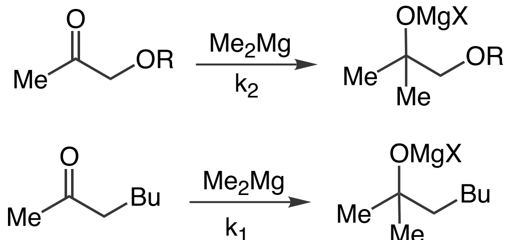
Carbonyl Addition Reactions: Chelate Organization

Kinetic Evidence for Chelate-Controlled C=O Additon

Since  much more reactive than 

Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.





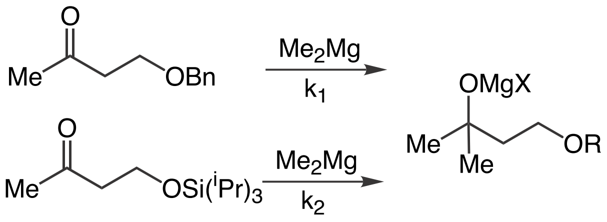
reference rxn

R	rel rate
–Me	213
–Bn	174
$–CMe_3$	9
$–SiMe_3$	7
$–Si\text{-}i\text{-}Pr_3$	1

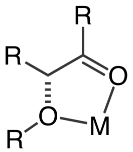
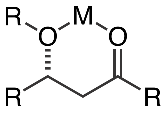
rxn run inTHF at - 78°C

Eliel, Frye, *JACS* **1992**, *114*, 1778-84 (read)

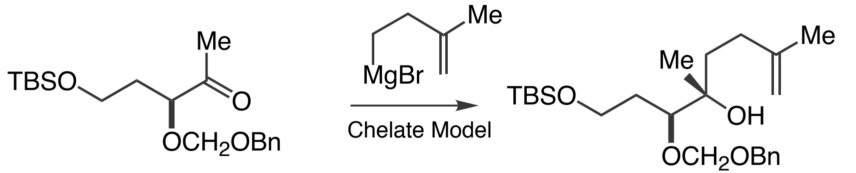
However, these trends are not transmitted strongly to β-chelation



$$\boxed{\frac{k_1}{k_2} = 2.5}$$

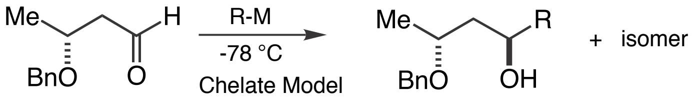
Hence, organization through  better than 

Alpha–Versus Beta-Chelation



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

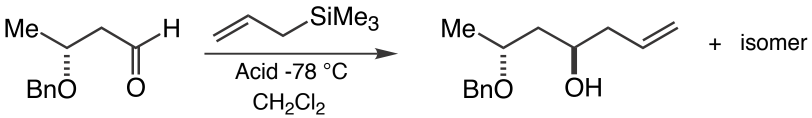
diastereoselection 50 : 1



M. T. Reetz & Co-workers
J. Am. Chem. Soc.. **1983**, 105, 4833.

Other nucleophiles reported

R-M	Solv.	Ratio
Me-MgCl	THF	40 : 60
$Me\text{-}TiCl_3$	CH_2Cl_2	90 : 10



Chelate Model

M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

Acid	Ratio
$TiCl_4$	95 : 5
$SnCl_4$	95 : 5
$BF_3\text{-}OEt_2$	85 : 15

- Note that beta chelation can be developed as a control element by varying solvent & Nu.
- Note BF_3 gives "apparent" chelate control

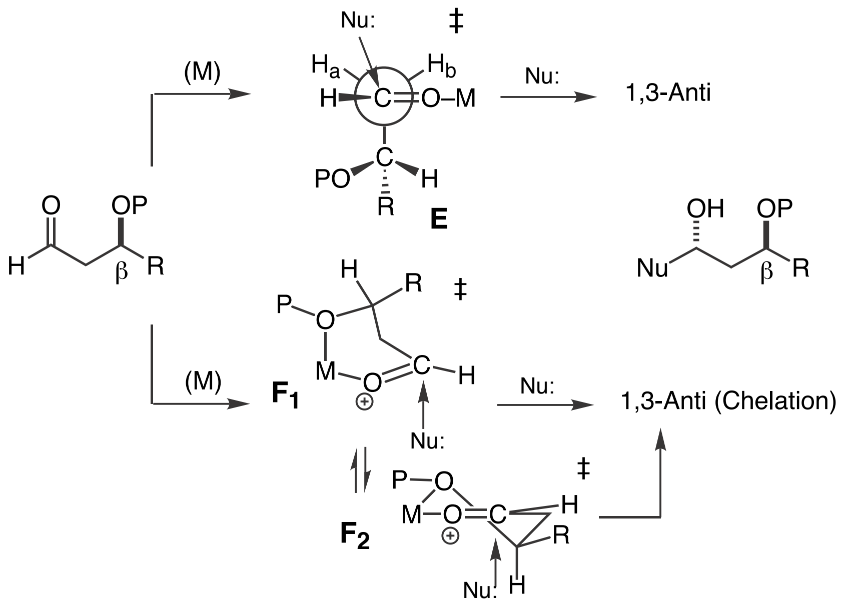
1,3-Stereoinduction Models for Chelate & non-Chelate Rxns

1,3-Stereoinduction Polar Model:

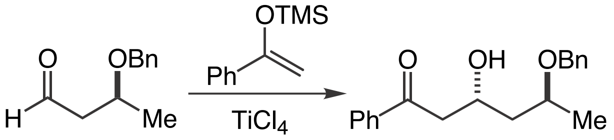
Evans, Dart, Duffy,Yang, *JACS* **1996**, *118,* 4322–4343

1,3-Stereoinduction Chelate Model:

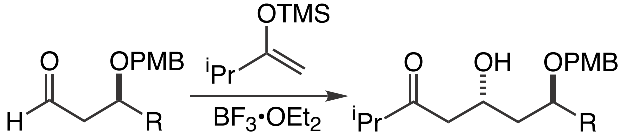
Evans, Allison, Yang,Masse, *JACS* **2001**, *123,* 10840–10852



1,3-Anti Relationship is favored by either polar or chelate models



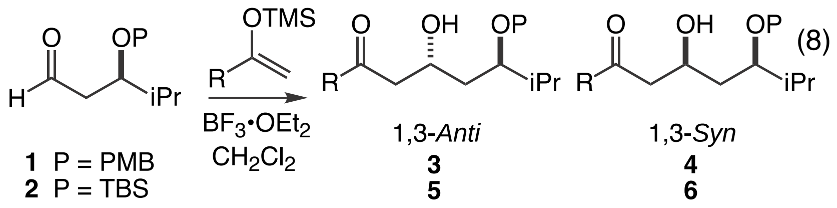
diastereoselection 92 : 8



R = $(CH_2)_2Ph$

diastereoselection 81 : 19

1,3-Stereoinduction Polar Model:



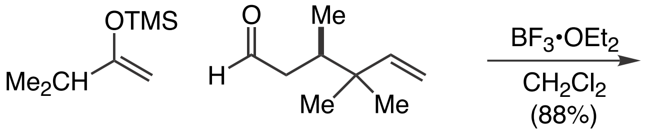
1 P = PMB
2 P = TBS

1,3-*Anti* **3** **5**

1,3-*Syn* **4** **6**

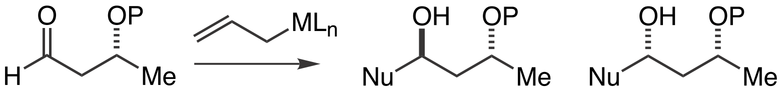
entry	R	**3** : **4** (P = PMB)	(%)	**5** : **6** (P = TBS)	(%)
A	t-Bu	89 : 11	(82)	84 : 16	(79)
B	i-Pr	92 : 08	(91)	80 : 20	(84)
C	Me	91 : 09	(89)	93 : 07	(87)

Steric effects appear to play a minor role in stereoinduction:



1,3-Anti (58%)

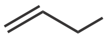
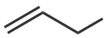
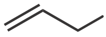
1,3-Syn (42%)



P = Bn (benzy)
P = MOM (methoxymethyl)

1,3-*Anti*

1,3-*Syn*

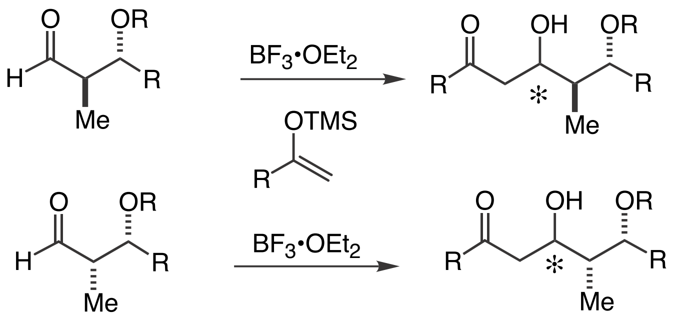
entry	conditions	(P = Bn) *anti* : *syn*	(P = MOM) *anti* : *syn*
A	 $SiMe_3$ $BF_3•OEt_2$	85 : 15	—
B	 $SnPh_3$ $BF_3•OEt_2$	79 : 29	—
C	 $SnMe_3$ $BF_3•OEt_2$	—	70 : 30

Carbonyl Addition Reactions: Chelate Organization

1,3-Stereoinduction Polar Model

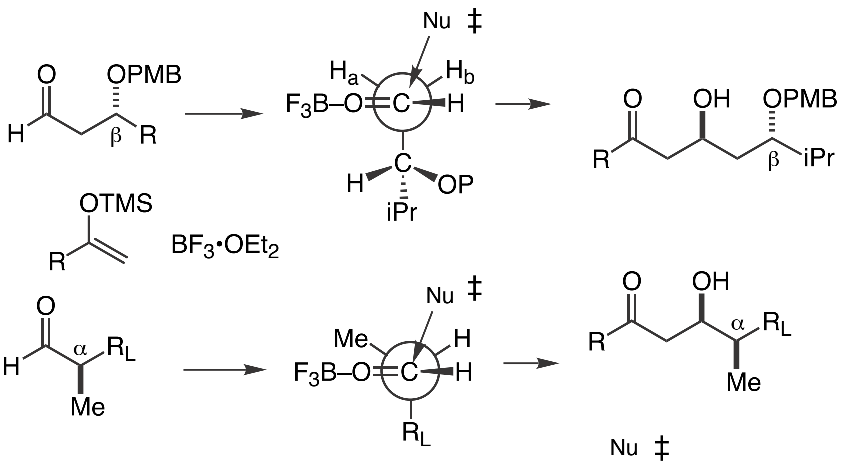
Evans, Dart, Duffy,Yang, *JACS* **1996**, *118,* 4322–4343

Can one develop a Rational model for α & β Stereocenters?

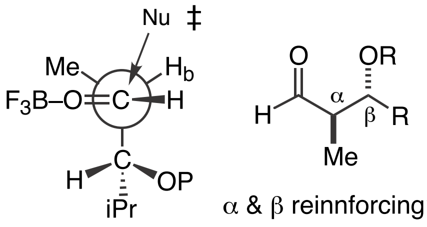


Which of the two stereochemical representations is reinforcing? Non-reinforcing?

Integration of 1,3- Polar Model & Felkin-Anh Model

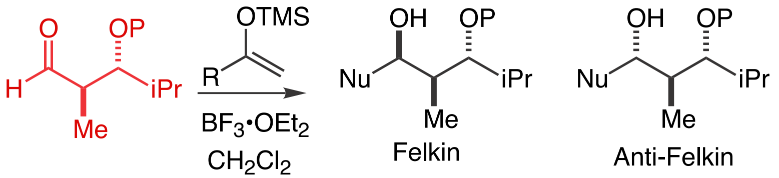


If both models are correct, they should integrate when the two stereocenters are reinforcing



α & β reinnforcing?

The Anti Diastereomer



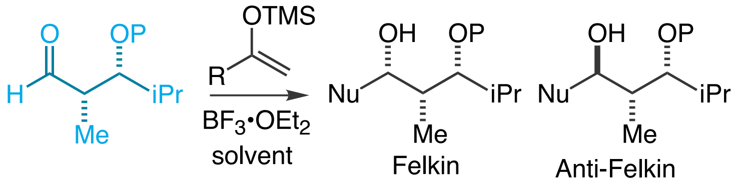
13 P = PMB
14 P = TBS

15
17

16
18

entry	R	**15** : **16** (P = PMB)	**17** : **18** (P = TBS)
A	t-Bu	99 : 01	99 : 01
B	i-Pr	98 : 02	95 : 05
C	Me	97 : 03	71 : 29

The Syn Diastereomer



19 P = PMB
20 P = TBS

21
23

22
24

entry	R	Solvent	**21** : **22** (P = PMB)	**23** : **24** (P = TBS)
A	t-Bu	CH_2Cl_2	96 : 04	96 : 04
B	t-Bu	toluene	88 : 12	94 : 06
C	i-Pr	CH_2Cl_2	56 : 44	87 : 13
D	i-Pr	toluene	32 : 68	75 : 25
E	Me	CH_2Cl_2	17 : 83	58 : 42
F	Me	toluene	06 : 94	40 : 60

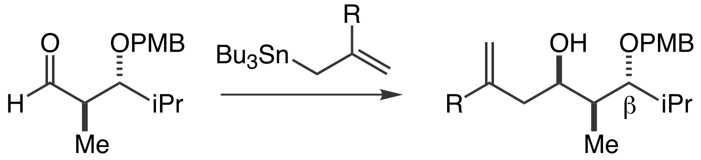
Conclusions

A: Anti diastereomer is reinforcing. Both models integrate.

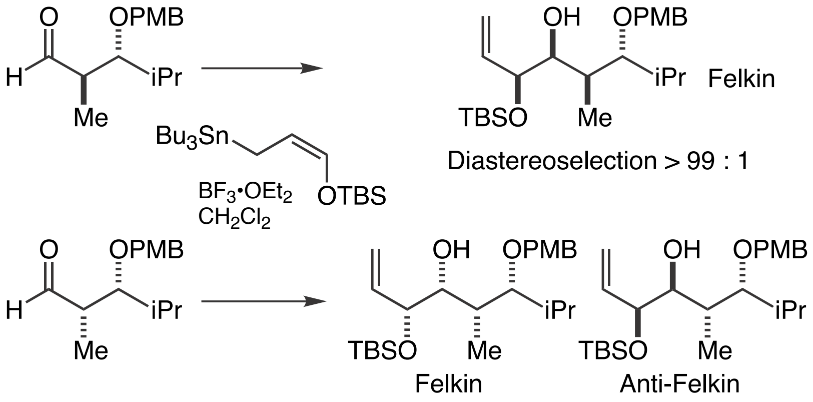
B: Syn diastereomer transitions from Felkin control (Large Nu) to 1,3-control (Small Nu).

Reinforcing & Non-reinforcing Relationsips

The Anti Diastereomer: Both Centers Reinforcing



entry	Conditions	R	Felkin : anti-Felkin
A	BF_3•OEt_2, toluene	Me	>99 : 1
B	BF_3•OEt_2, toluene	H	>99 : 1
C	Ph_3CClO_4, CH_2Cl_2	H	>99 : 1

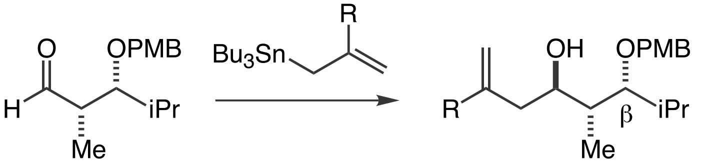


Diastereoselection > 99 : 1

Diastereoselection 59 : 32 : 9[a]

[a]The third unpictured product is the Felkin-3,4-*anti* diastereomer.

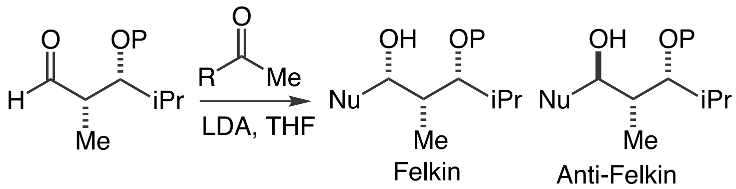
The Syn Diastereomer: Stereocenters are Non-reinforcing



entry	Conditions	R	Felkin : anti-Felkin
A	BF_3•OEt_2, toluene	Me	20 : 80
B	BF_3•OEt_2, toluene	H	13 : 87
C	Ph_3CClO_4, CH_2Cl_2	H	62 : 38

In this example, the OR substituent is the dominant stereo-control element

The Syn Diastereomer: Stereocenters are Non-reinforcing



19 P = PMB
20 P = TBS

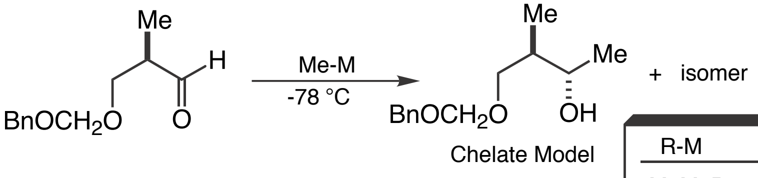
21 **23**

22 **24**

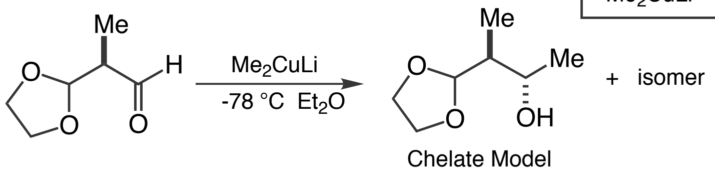
entry	R	**21** : **22** (P = PMB)	(%)	**23** : **24** (P = TBS)	(%)
A	t-Bu	11 : 89	(71)	08 : 92	(91)
B	i-Pr	14 : 86	(95)	13 : 87	(64)
C	Me	22 : 78	(73)	14 : 86	(88)

Carbonyl Addition Reactions: Chelate Organization

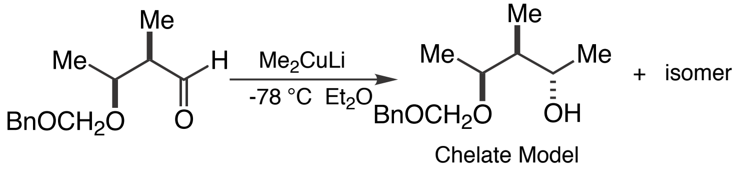
Beta Chelation with Organometals



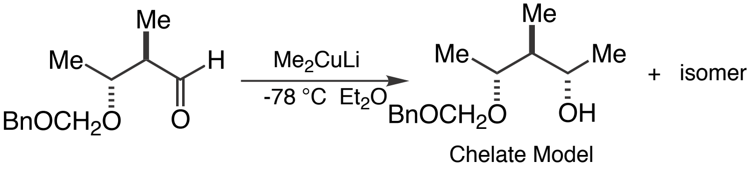
R-M	Ratio
MeMgBr	50 : 50
Me_2CuLi	97 : 3



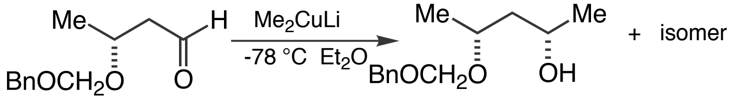
diastereoselection > 95 : 5



diastereoselection > 95 : 5

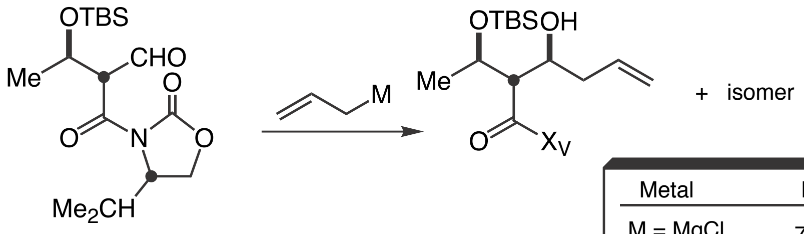


diastereoselection 70 : 30



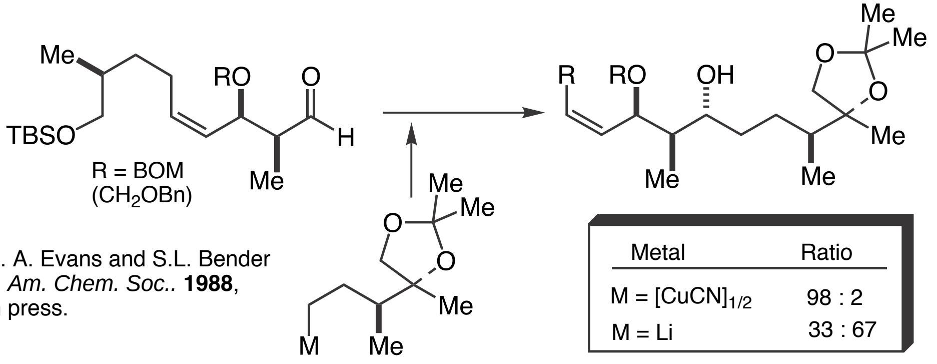
diastereoselection 50 : 50

W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1035.



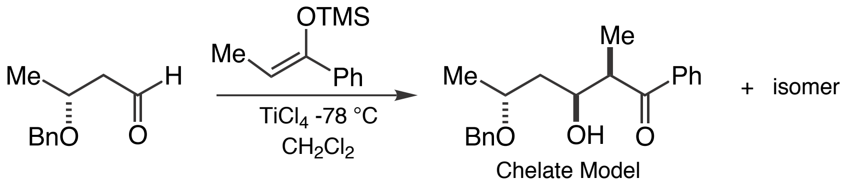
D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, *27*, 4961.

Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3



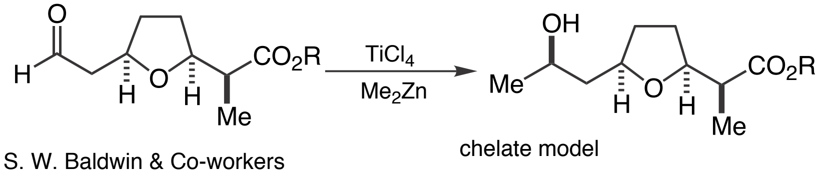
D. A. Evans and S.L. Bender
J. Am. Chem. Soc.. **1988**,
in press.

Metal	Ratio
M = $[CuCN]_{1/2}$	98 : 2
M = Li	33 : 67



M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

diastereoselection >92 %

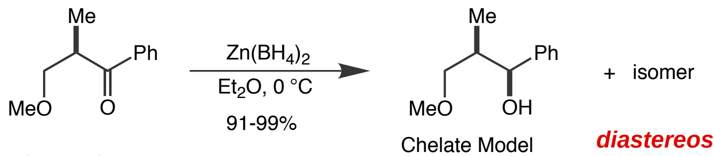


S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, *52*, 320.

diastereoselection 96 : 4

Carbonyl Addition Reactions: Chelate Organization

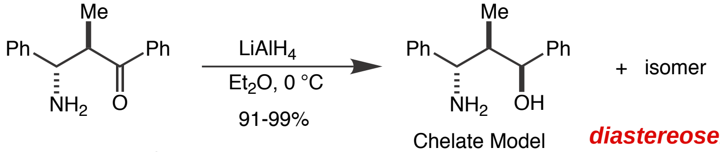
Beta Chelate-Controlled Reduction



Chelate Model

***diastereoselection* 97 : 3**

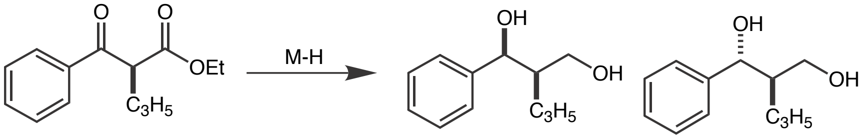
T. Oishi & Co-workers
Chem. Pharm Bull. **1984**, *32*, 1411.



Chelate Model

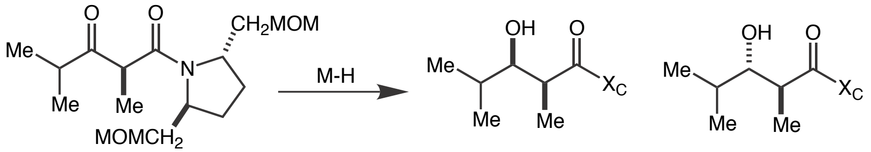
***diastereoselection* 88 : 12**

J. Barluenga & Co-workers
J. Org. Chem. **1985**, *50*, 4052.



G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

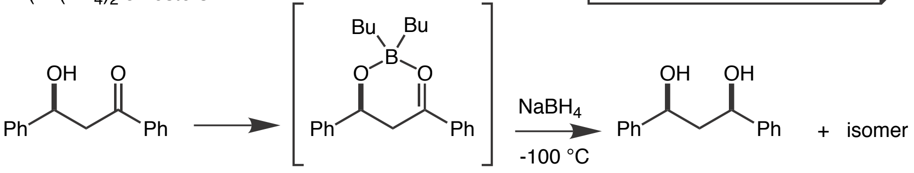
M-H	Ratio
Zn(BH$_4$)$_2$ Et$_2$O	100 : 0
LiAlH$_4$ THF	0 : 100



M. Yamaguchi & Co-workers
Tetrahedron Lett. **1985**, *26*, 4643.

T. Oishi & Co-workers
Tetrahedron Lett. **1980**, *21*, 1641
(Zn(BH$_4$)$_2$ on esters.

M-H	Ratio
Zn(BH$_4$)$_2$ Et$_2$O	100 : 0
KBH$_3$H THF	0 : 100

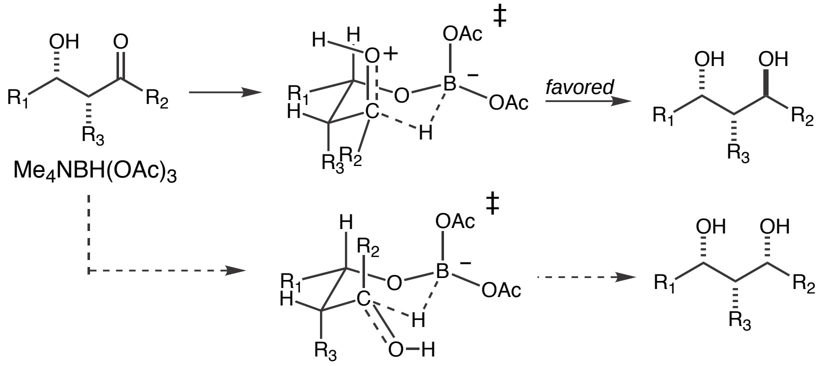


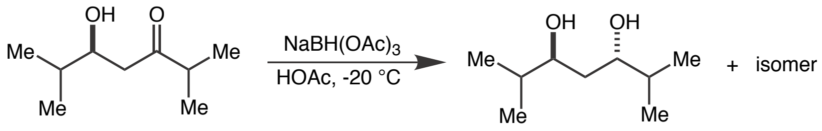
K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

***diastereoselection* 96 : 4**

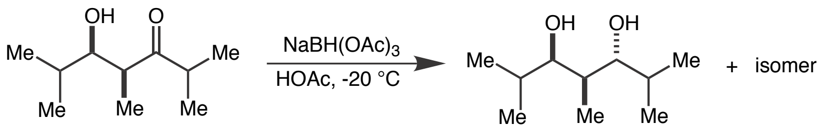
Directed reductions of β-hydroxyketones

Evans, Chapman, Carreira, JACS **110**, 3560 (1988)

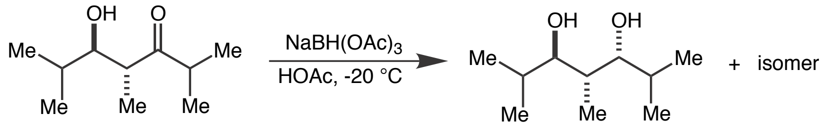




***diastereoselection* 96 : 4**

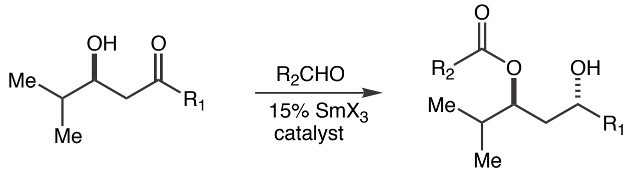


***diastereoselection* 98 : 2**



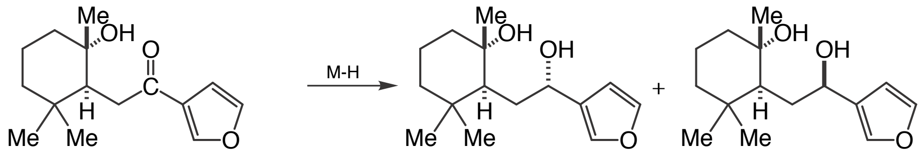
***diastereoselection* 98 : 2**

Propose a mechanism for tihs highly diastereoselective transformation, Evans, Hoveyda JACS **112**, 6447 (1990)



diastereoselection
> 100:1

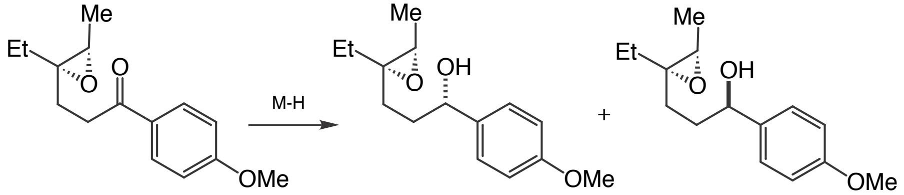
Remote Heteroatom Effects in Carbonyl Addition



Temp. & Solvent not specified in this study in first three cases

R. Baker & Co-workers
Chem. Commun. **1984,** 74

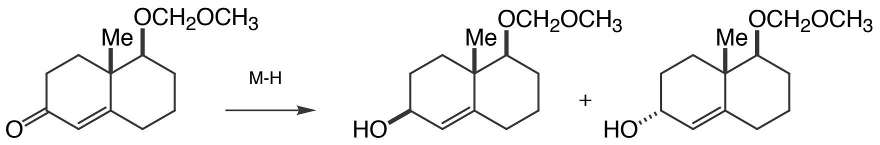
Reagent	Ratio
Li-AlH$_4$	40 : 60
Na-BH$_4$	50 : 50
Zn-BH$_4$	60 : 40
Li-BHEt$_3$, (THF, -78˚C)	100 : 0



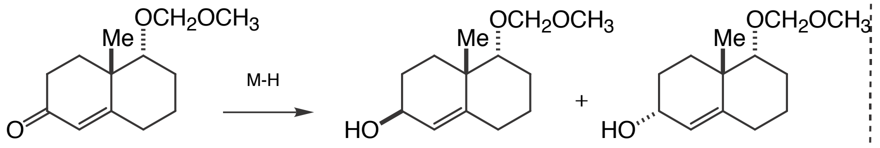
Y. Kishi & Co-workers
Tetrahedron Lett. **1978**, 2741.

Li-BH(R)$_3$, Et$_2$O, 25˚C	1 : 1
LiAlH$_4$, Et$_2$O, 25˚C	3 : 1
LiAlH$_4$-diamine,* -78˚C	11 : 1

** di-2-(o-toluidinomethyl)pyrrolidine*

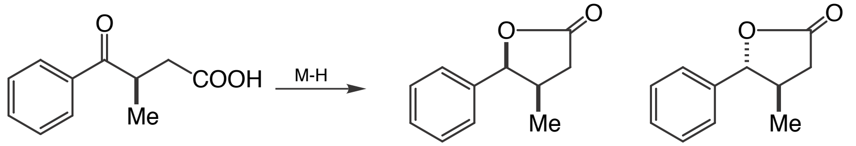


Li-BH(R)$_3$,	73 : 27
LiAlH$_4$	76 : 24



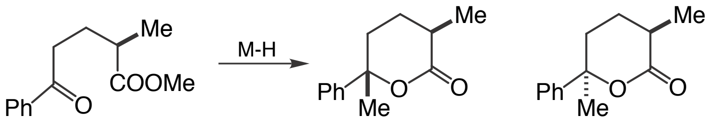
Li-BH(R)$_3$,	28 : 72
LiAlH$_4$	72 : 28

W. G. Dauben & Co-workers
Tetrahedron Lett. **1978**, 2741.



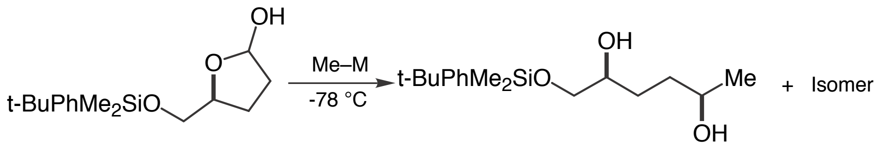
R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

Reagent	Ratio
NaBH$_2$(OR)$_2$	50 : 50
NaBH$_4$	70 : 30
DIBAL (2.4 equiv)	95 : 5
DIBAL (2.4 equiv) with ZnCl2	99 : 1



R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

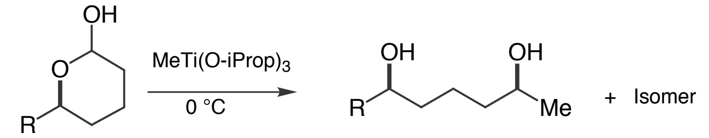
Solvent	Ratio
THF	50 : 50
C$_6$H$_6$	70 : 30



67-87% yields

G. Tsuchihashi & Co-workers
Tetrahedron Lett. **1987**,*28*, 6335.

Reagent	Solvent	Ratio
MeLi	Et$_2$O	1.7 : 1
MeMgBr	THF	1.3 : 1
Me$_3$Al	CH$_2$Cl$_2$	1.1 : 1
MeTiCl$_3$	CH$_2$Cl$_2$	8.4 : 1
MeTi(O-iProp)$_3$	CH$_2$Cl$_2$	12 : 1



R = Me, Ph(CH$_2$)$_2$

Ratio 4-5.5 : 1

Quote for the Day

Richard P. Feynman (as an undergraduate) in Surely you're Joking Mr. Feynman

"When I was an undergraduate student at MIT I loved it. I thought it was a great place, and I wanted to go to graduate school there too of course. But when I went to Professor Slater and told him of my intentions, he said,

'We won't let you in here.'

I said, "what"?

Slater asked, 'Why do you think that you should go to graduate school at MIT'?

"Because it is the best school for science in the country."

'You think *that*'?

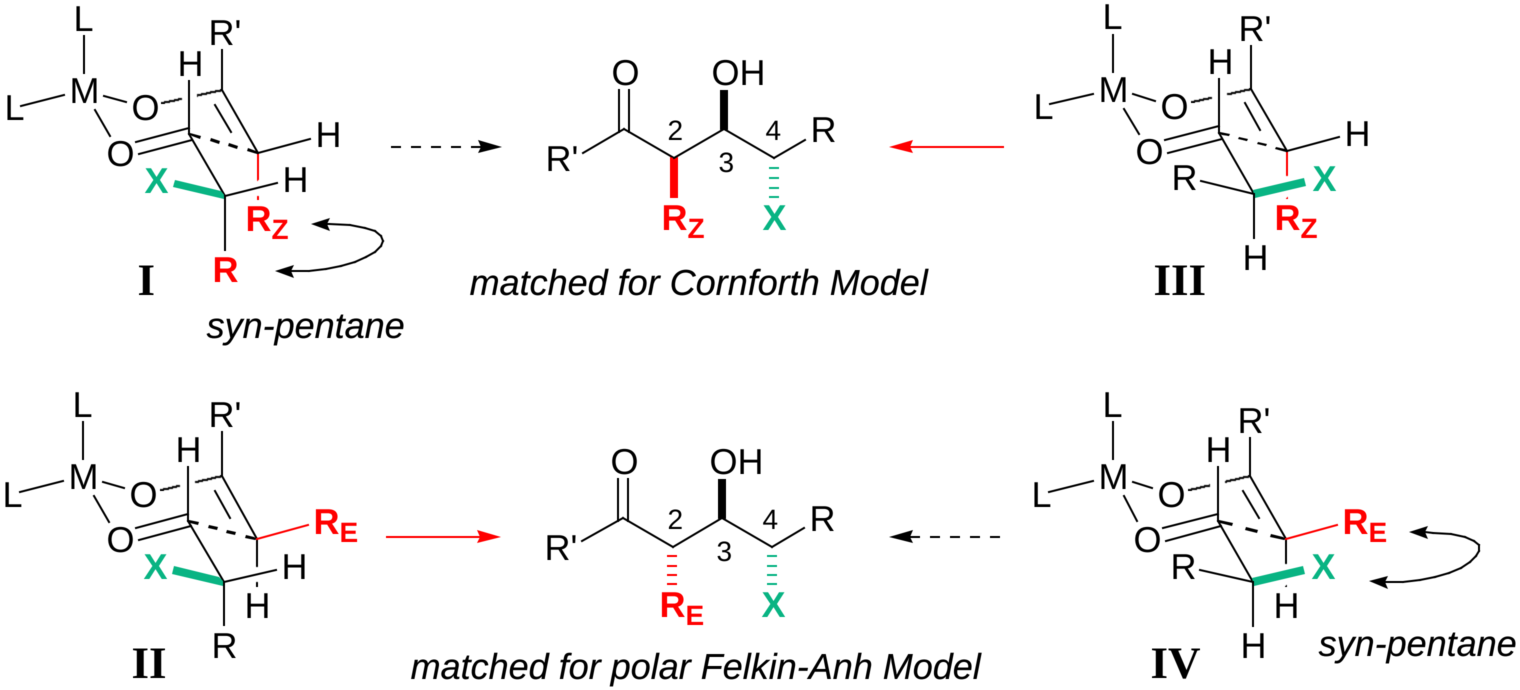
"Yeah."

'That's why you should go to some other school. You should find out how the rest of the world is.'

Experimental Support for Cornforth or Felkin–Anh Models

Polar Felkin-Anh Model

Cornforth Model



matched for Cornforth Model

matched for polar Felkin-Anh Model

PFA Model Prediction: The (*Z*) enolate substituent causes a destabilizing syn-pentane interaction (**I**), while the (*E*) enolate substituent experiences no such interaction (**II**). *Therefore, (E) enolates are predicted to give superior 3,4-anti selectivity relative to (Z) enolates.*

Cornforth Model Prediction: The (*E*) enolate substituent causes a destabilizing syn-pentane interaction (**IV**) while the (*Z*) enolate substituent experiences no such interaction (**III**). *Therefore, (Z) enolates are predicted to give superior 3,4-anti selectivity relative to (E) enolates.* Due to this dichotomy, the experimentally determined relationship between enolate geometry and aldehyde diastereofacial selectivity should validate a single model for asymmetric induction.

Angew. Chem. Int. Ed., **2003**, *42*, 1761-1765.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 22

Enantioselective Carbonyl Addition

- Enantioselective addition of R_2Zn to aldehydes
- Enantioselective Reduction of Ketones & Imines
- Introduction to Enolate-based Nucleophiles

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int Ed*. **1998**, *37*, 1986-2012 **(handout)**

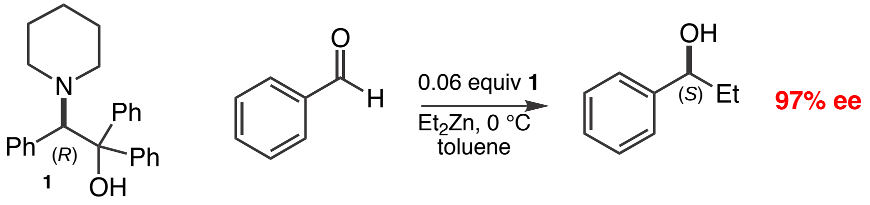
Enantioselective Carbonyl Addition (R_2Zn): Noyori *Angew. Chem. Int Ed*. **1991**, *30*, 49-69 **(handout)**

D. A. Evans

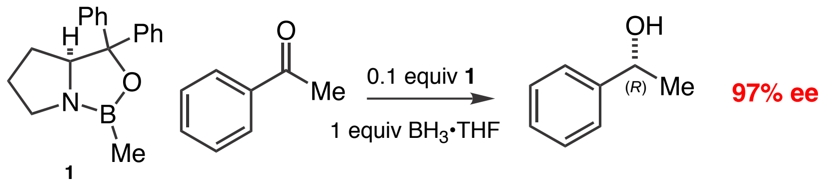
Wednesday,
November 5, 2003

Relevant Problems:

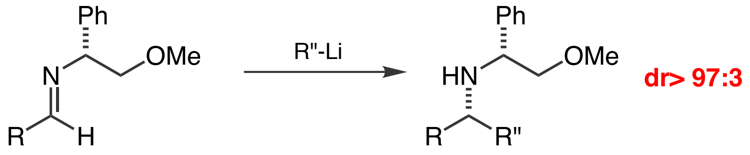
Database Problem 27: Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational investigation that addresses the preferred transition state geometry for this addition process (Pericas, et al. *J. Org. Chem.* **2000**, *65*, 7303 and references cited therein). It should be noted that, while **1** is not the actual catalyst, it is modified under the reaction conditions to the competent catalytic agent. Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



Cume Question, 2000: Corey's introduction of chiral oxazaborolidine catalysts **1** in the borane-mediated enantioselective reduction of ketones represents an important advance in asymmetric synthesis (Corey & Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012). Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.

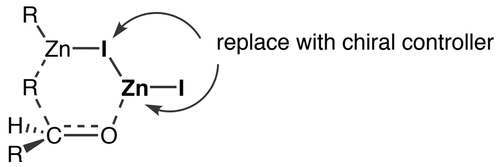


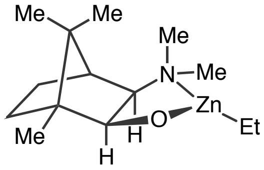
Database Problem 151: The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the structure of the product, rationalize the stereochemical outcome of the process.



Enantioselective C=O Addition: Noyori Catalyst

Catalytic Asymmetric Carbonyl Addition

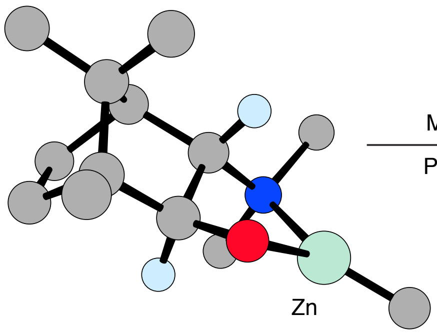




the catalyst

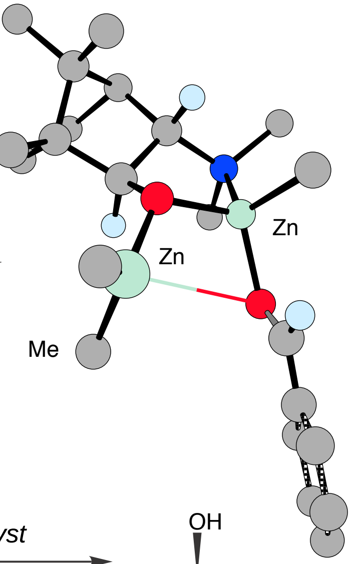
Noyori & co-workers, *J. Am. Chem. Soc.* **1986**, 108, 6072.
J. Am. Chem. Soc. **1989**, 111, 4028.

Review: Noyori *Angew. Chem. Int. Ed.* **1991**, *30*, 49
Review: L. Pu, *Chem. Reviews* **2001**, *101*, 757-824



(DAIB-Zn)

$\xrightarrow[PhCHO]{Me_2Zn}$

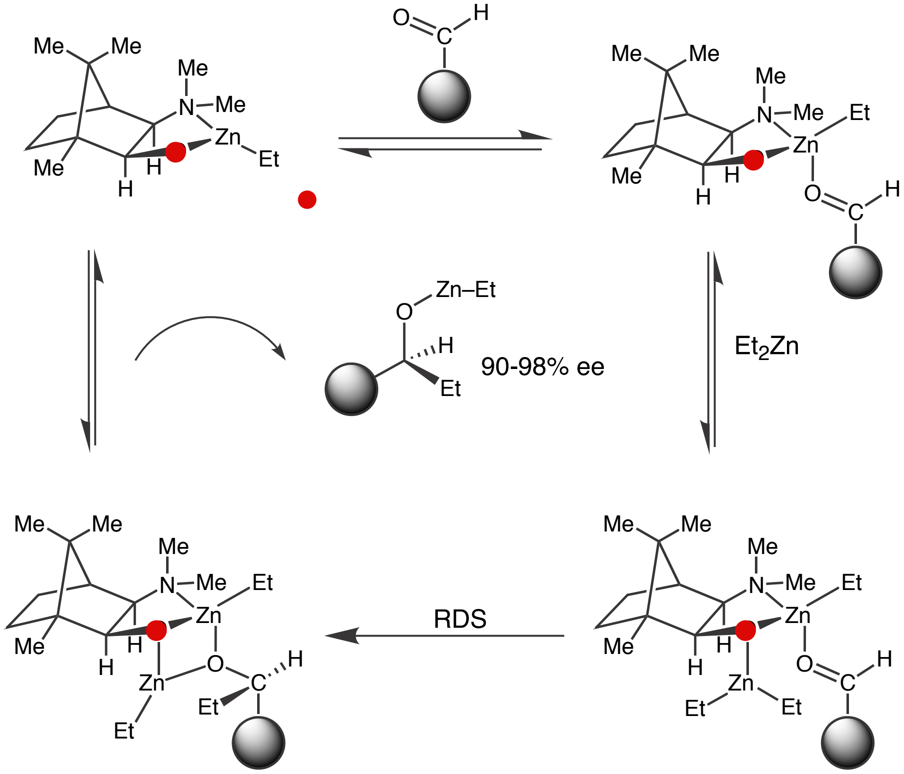


$$Ar–CHO \quad + \quad R_2'Zn \xrightarrow[\substack{0°C, toluene \\ 59 - 97\%}]{the\ catalyst} Ar–CH(OH)–R'$$

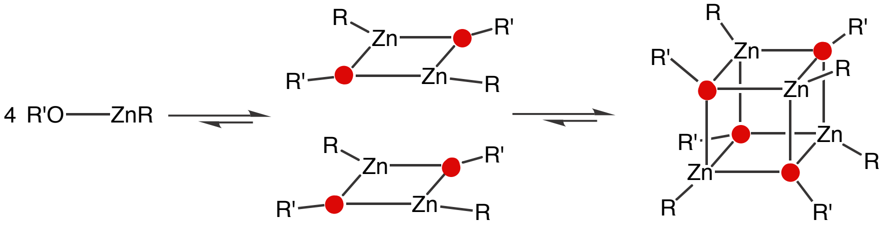
C_6H_5CHO	Et_2Zn	98% e.e.
"	Me_2Zn	91% e.e.
p-ClC_6H_4CHO	Et_2Zn	93% e.e.
p-$MeOC_6H_4CHO$	Et_2Zn	93% e.e.
Cinnamyl	Et_2Zn	96% e.e.
$PhCH_2CH_2CHO$	Et_2Zn	90% e.e.
n-$C_6H_{13}CHO$	Et_2Zn	61% e.e.

- *The method is catalytic in aminoalcohol.*
- *Two zinc species per aldehyde are involved in the alkylation step.*

The Catalytic Cycle



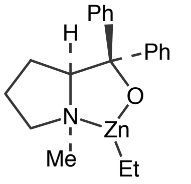
- *Catalyst must be sterically hindered so that association is precluded*



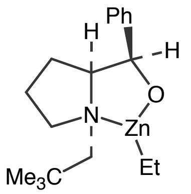
- *Product is taken out of the picture by aggregation*

Enantioselective C=O Addition: Noyori Catalyst-2

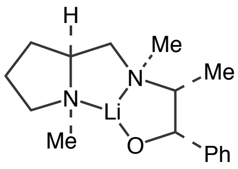
Other Catalysts for the R_2Zn Addition Process



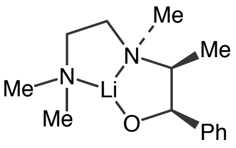
97% e.e. (S)



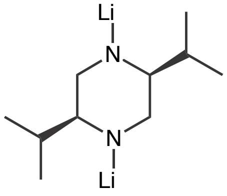
100% e.e. (R)



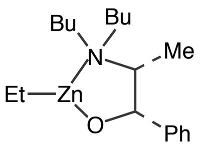
95% e.e. (S)



90% e.e. (R)



90% e.e. (R)



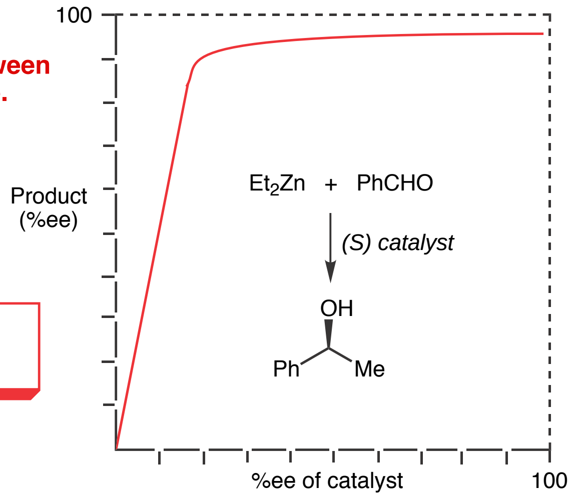
90% e.e. (R)

(Results are cited for the reaction of benzaldehyde and Et_2Zn)

Problem: Rationalize the stereochemical course of each of the catalysts

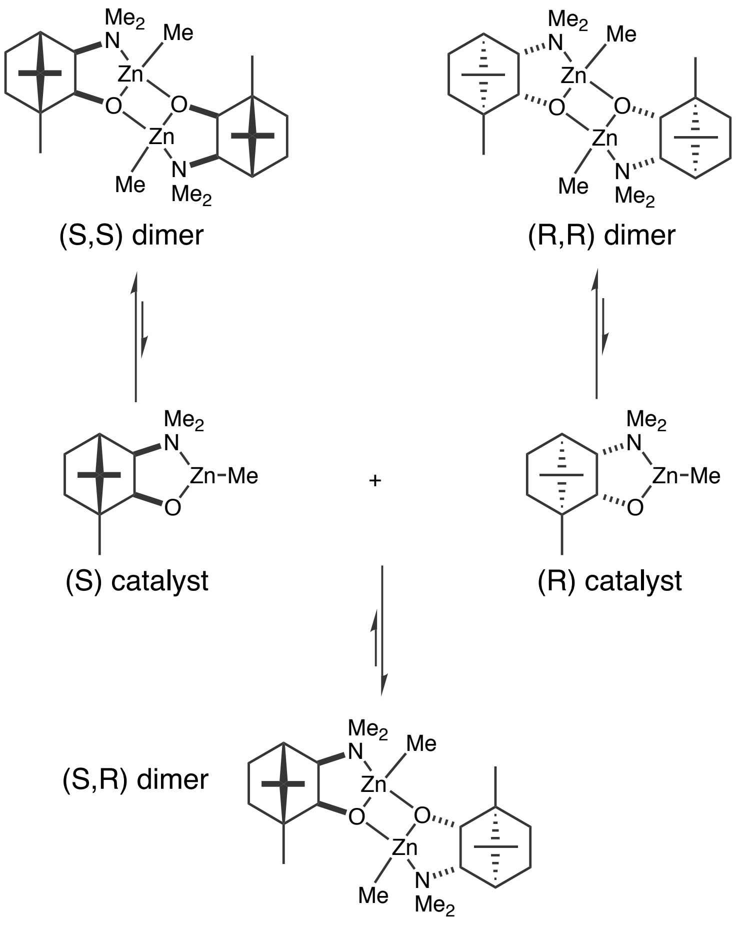
- ■ Non-linear effects observed with the Noyori Catalyst (DAIB-Zn)

There is no correlation between catalyst and product ee.



25% ee Catalyst affords product in 95% ee.

Explanation for Nonlinearity of DAIB Catalyst

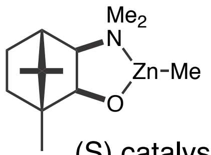


Observations

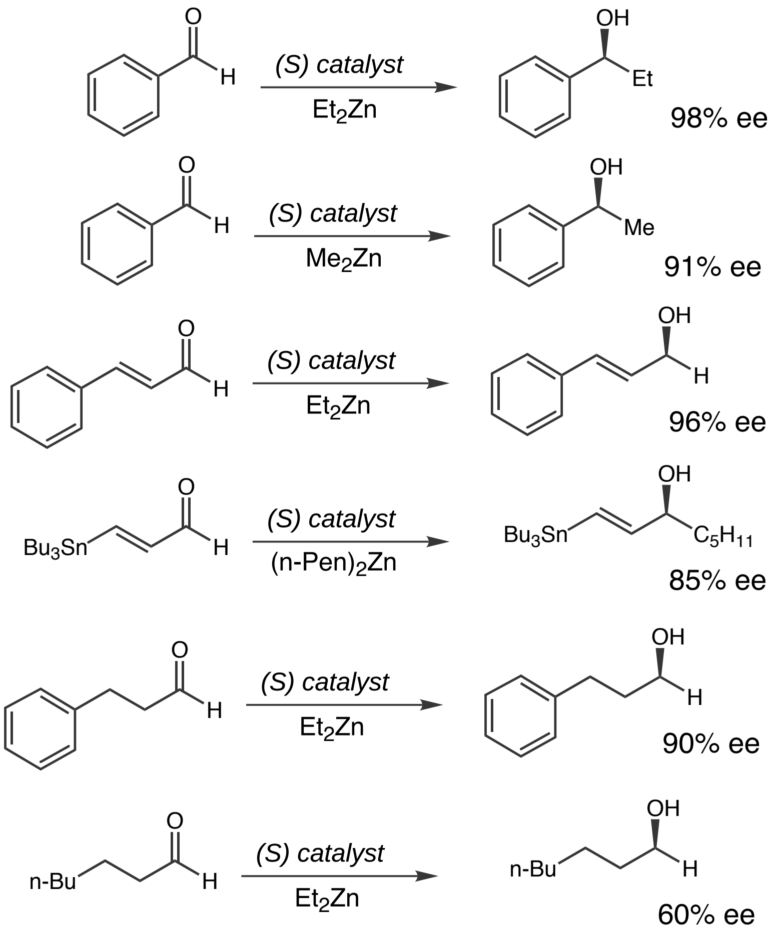
- ■ (S,S) dimer dissociates upon addition of RCHO & effects catalysis
- ■ (S,R) dimer is overwhelmingly more stable than (S,S) homodimer
- ■ (S,R) dimer is ineffective as a catalyst

Enantioselective C=O Addition: Dialkylzinc Addn Scope

Scope of the DAIB Catalyst



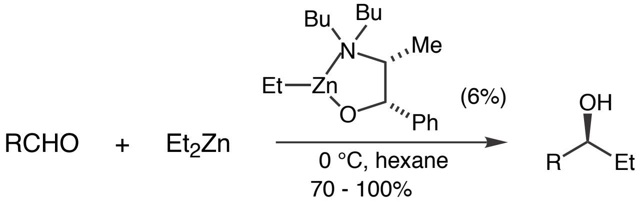
(S) catalyst

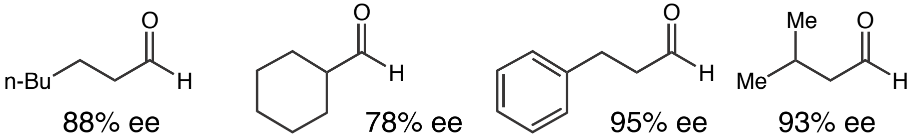


Review: Noyori *Angew. Chem. Int. Ed.* **1991**, *30*, 49

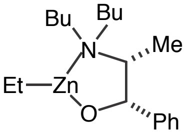
Improved Selectivity with Aliphatic Aldehydes

Soai, *J. Org. Chem.* **1991**, *56*, 4264



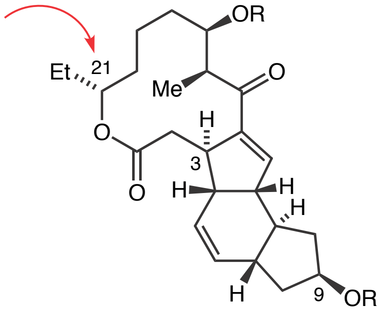


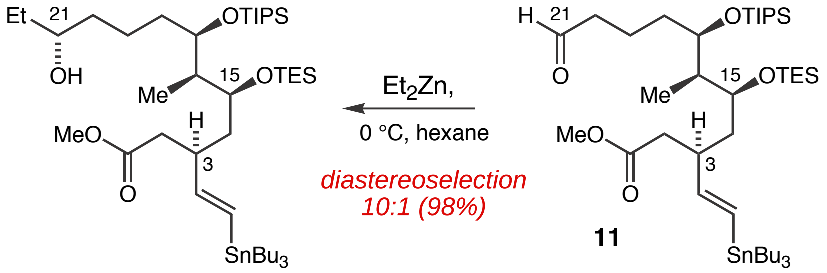
Lepicidin Application: The reaction functions in complex systems



the catalyst

Evans, Black, *JACS* **1993**, *115*, 44974513





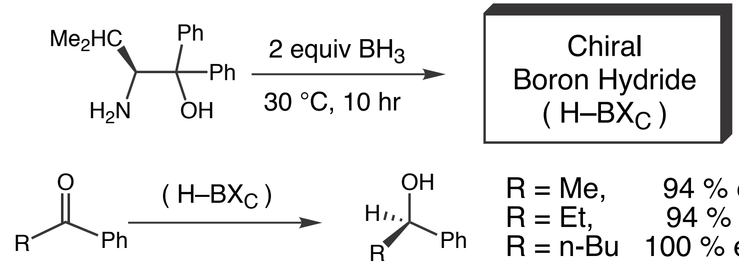
11

Enantioselective C=O Addition: Corey-Itsuno Catalyst

Discovery of a Catalytic Process

Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int Ed*. **1998**, *37*, 1986-2012 **(handout)**

■ The Stoichiometric Process: Itsuno, 1983-1985



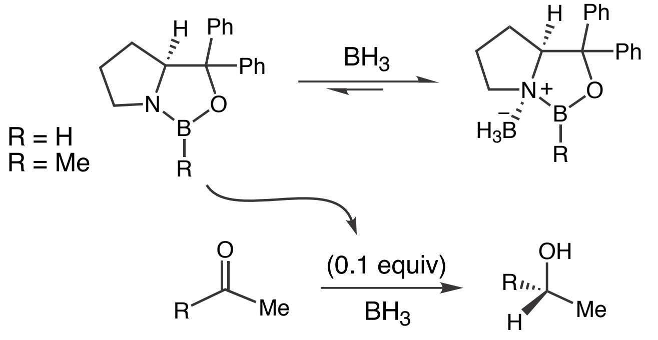
R = Me,	94 % ee
R = Et,	94 % ee
R = n-Bu	100 % ee

Itsuno, *Chem. Commun*. **1983**, 469

Itsuno, *J. Org. Chem.* **1984**, 49, 555

Itsuno, *J. Chem. Soc. Perkin Trans I*. **1985**, 2615

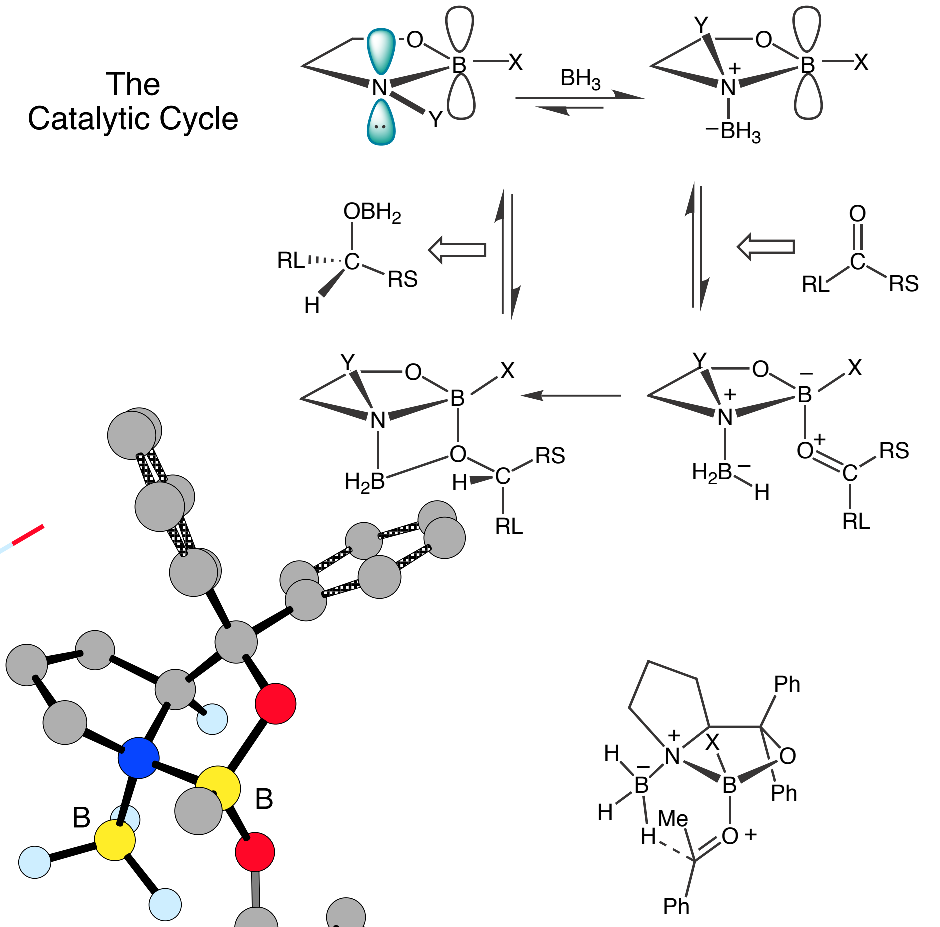
■ The Catalytic Process: Corey, 1987



R = Ph,	97 % ee
R = t-Bu,	97 % ee
R = c-C$_6$H$_{11}$	91 % ee

But how does it really work ?

The Catalytic Cycle



Corey, *JACS* **1987**, *109*, 5551

Corey, *JACS* **1987**, *109*, 7925

Corey, *JOC* **1988**, *53*, 2861

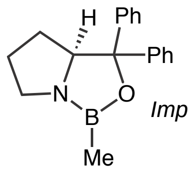
Catalyst X-ray, Corey, *Tet. Let* **1992**, *33*, 3429

Mathre, *JOC* **1993**, *58*, 2880

catalyst prep: Mathre, *JOC* **1993**, *58*, 799

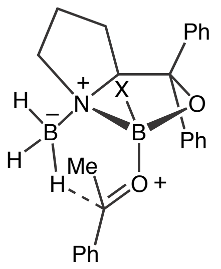
Mathre, *JOC* **1991**, *56*, 751

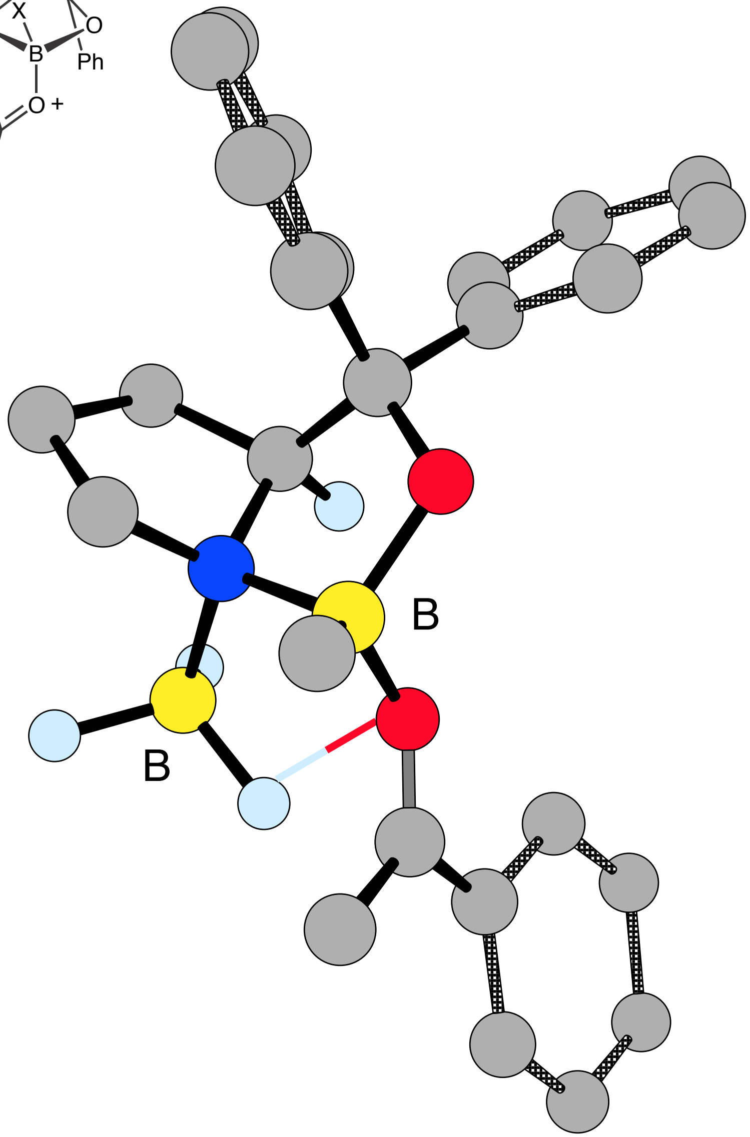
(Review) Martens, *Tertrahedron Asymmetry* **1992**, *3*, 1475

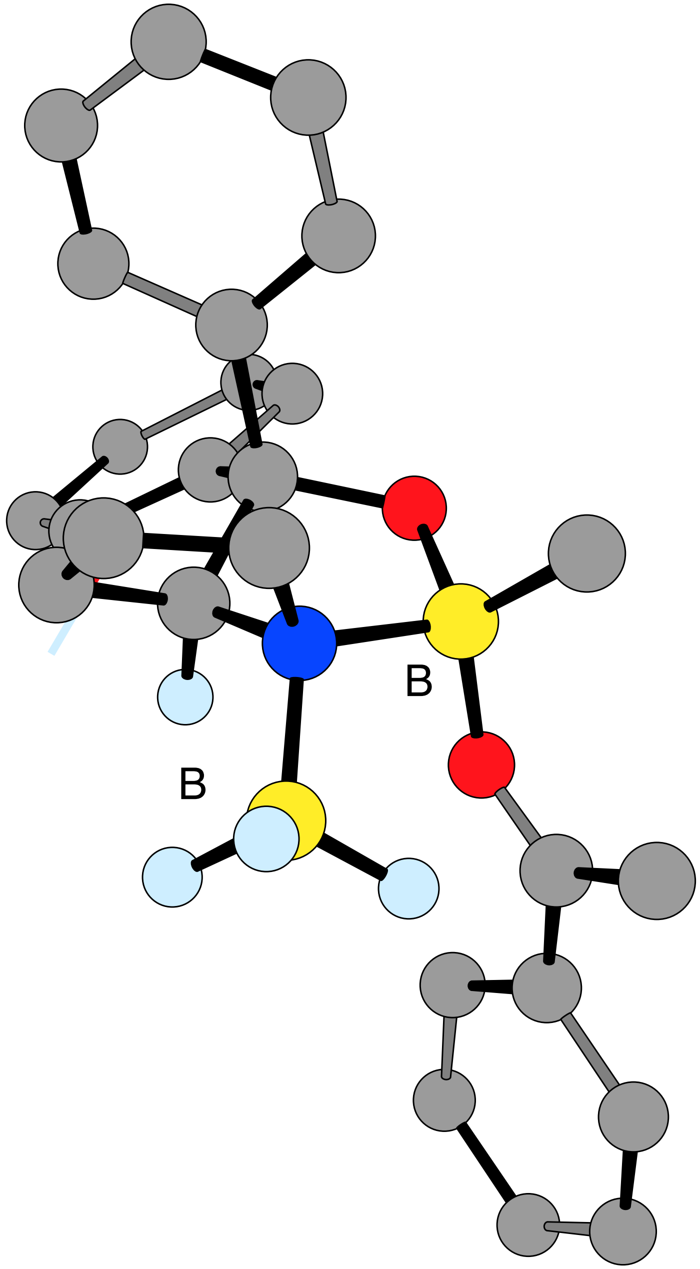


Improved version

Enantioselective C=O Addition: Corey-Itsuno Catalyst

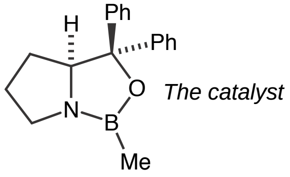


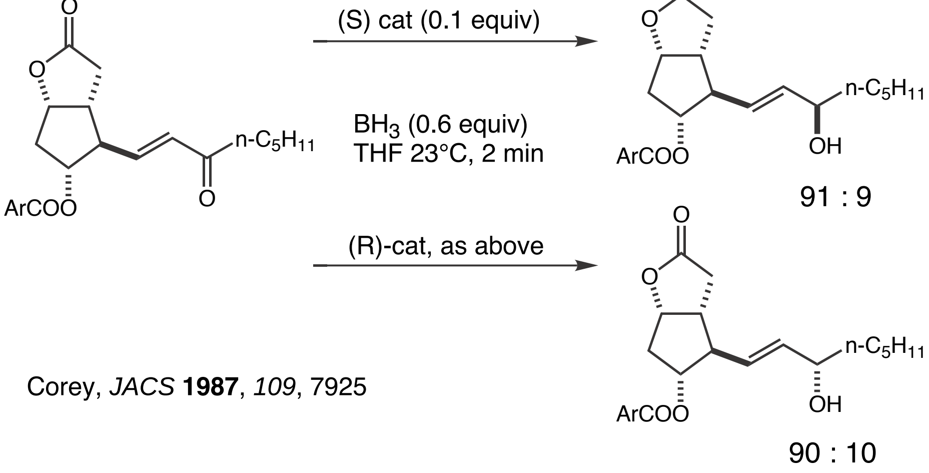




Enantioselective C=O Addition: Catalyst Scope

Representative Reductions

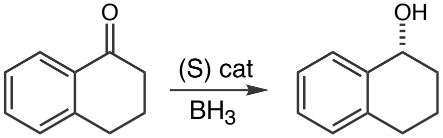




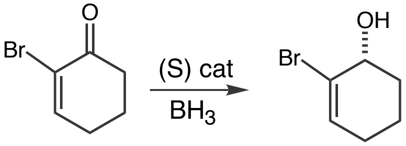
91 : 9

90 : 10

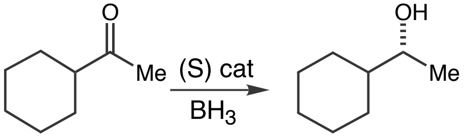
Corey, *JACS* **1987**, *109*, 7925



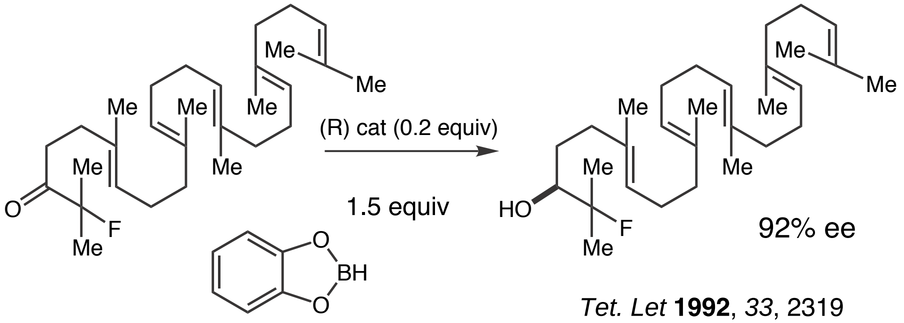
86% ee



91% ee



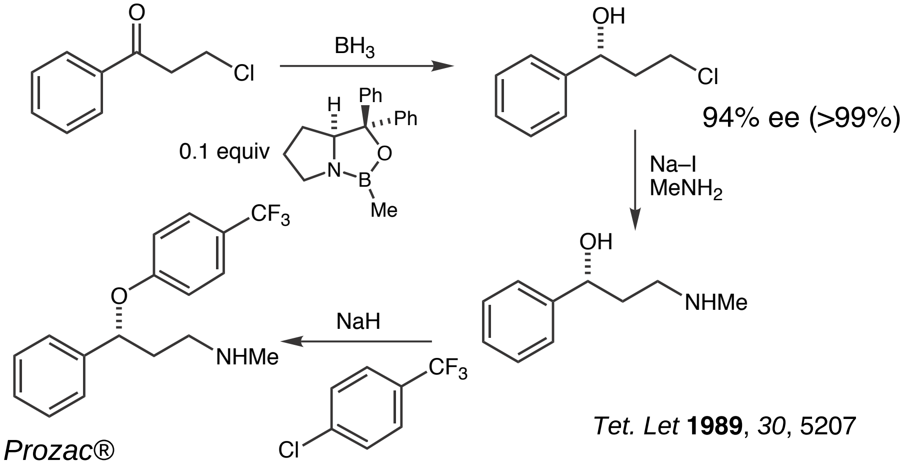
91% ee



92% ee

Tet. Let **1992**, *33*, 2319

Fluoxetine (Prozac®) Synthesis

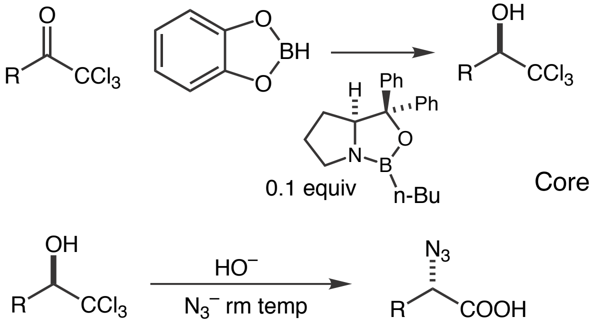


94% ee (>99%)

Tet. Let **1989**, *30*, 5207

Prozac®

An α-Amino Acid Synthesis

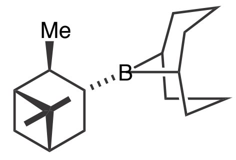


R	ee
n-C_5H_{11}	95%
c-C_6H_{11}	92%
t-C_4H_9	98%

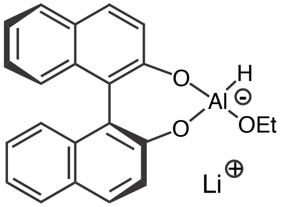
Corey, *JACS* **1992**, *114*, 1906
Tet. Let **1992**, *33*, 3435
Tet. Let **1992**, *33*, 3431

Enantioselective C=O Addition: Ketone Reduction

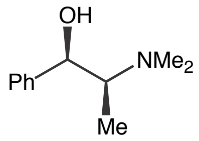
Enantioselective Reducing Agents



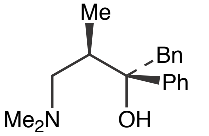
(R)-Alpine Borane



(S)-BINAL-H



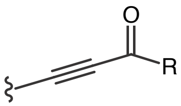
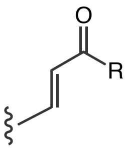
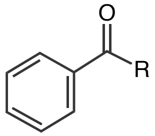
N-Methylephedrine, $LiAlH_4$, (3,5-xylenol)$_2$
[LiAl(lig)(OAr)$_2$H]



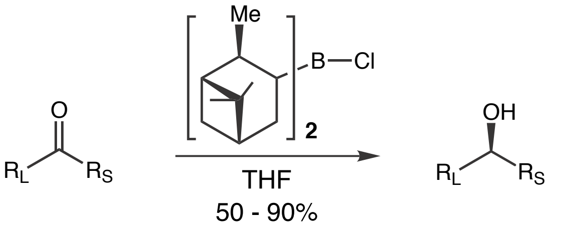
Darvon alcohol, $LiAlH_4$
[LiAl(lig)$_2$H]

Reviews: Midland, *Asymmetric Synthesis*, *Vol 2*, p 45-
Granbois, *Asymmetric Synthesis*, *Vol 2*, p 71-
Brown, *Accts. Chem. Res.* **1992**, *25*, 16-24
Singh, *Synthesis* **1992**, 605-617

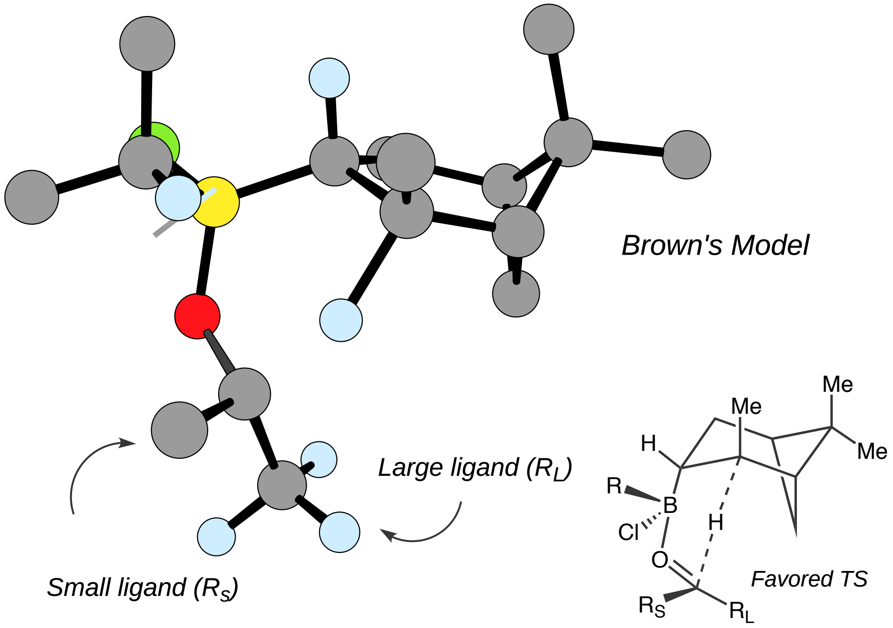
Reductions of Representative Carbonyl Compounds

Reagent			
Alpine-Borane	72 - 92% e.e.	59 - 89% e.e.	78% e.e. R=Me 90% e.e. R=CO_2Me
BINAL-H	84 - 96% e.e. (57% ee, R=i-Pr)	>95% e.e.	95 - 100% e.e. (71% ee, R=i-Pr)
Darvon-$LiAlH_4$	34 - 90% e.e.	25% e.e.	15 - 75% e.e.
N-Methylephedrine-$LiAlH_4$	75 - 90% e.e.	78 - 98% e.e. (cyclic ketones)	----

Stoichiometric Chloroborane Reducing Agents



Ketone	Reaction Conditions	% ee
acetophenone	–25 °C	98%
butyrophenone	–25 °C	98%
2,2-dimethylpropiophenone	–25 °C	79%
3,3-dimethyl-2-butanone	25°C, 12 days	95%
2,2-dimethylcyclohexanone	25°C, 2 days	91%



Brown's Model

Favored TS

Less hindered aliphatic ketones are not reduced with useful levels of enantioselectivity

Brown, *J. Org. Chem.* **1985**, *50*, 5446
Brown, *J. Org. Chem.* **1986**, *51*, 3394
Brown, *J. Org. Chem.* **1988**, *53*, 2916

Enolates & Metalloenamines: Introduction

Important References

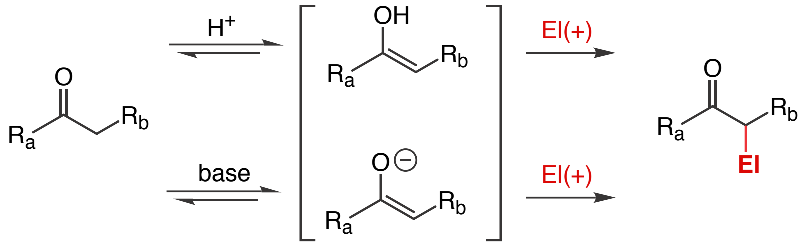
"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983).

"Stereoselective Alkylation Reactions of Chiral Metal Enolates". D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984).

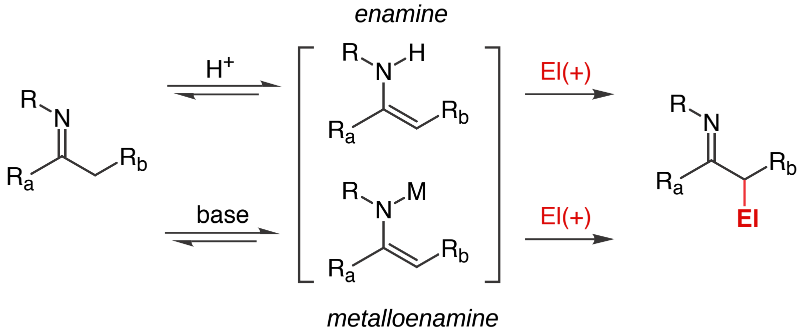
"Generation of Simple Enols in Solution". B. Capon, B.-Z. Guo, F. C. Kwok, A. K. Siddhanta, and C. Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Y. Chiang, A. J. Kresge, and Y. S. Tang *J. Am. Chem. Soc.* **106**, 460 (1984).

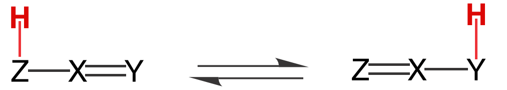
Enols & Enolates are the most important nucleophiles in organic & biological chemistry.



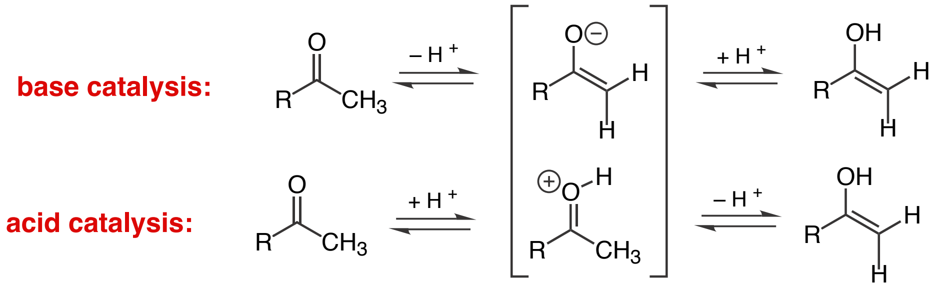
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



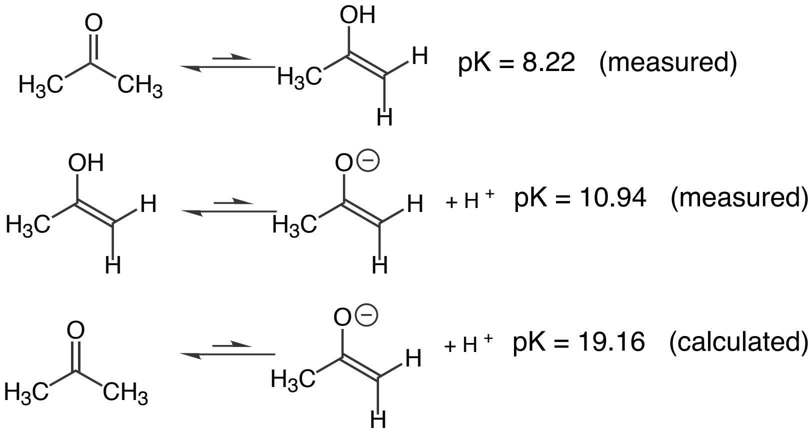
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



Acidity of Keto and Enol Tautomers: Consider Acetone:



pK = 8.22 (measured)

pK = 10.94 (measured)

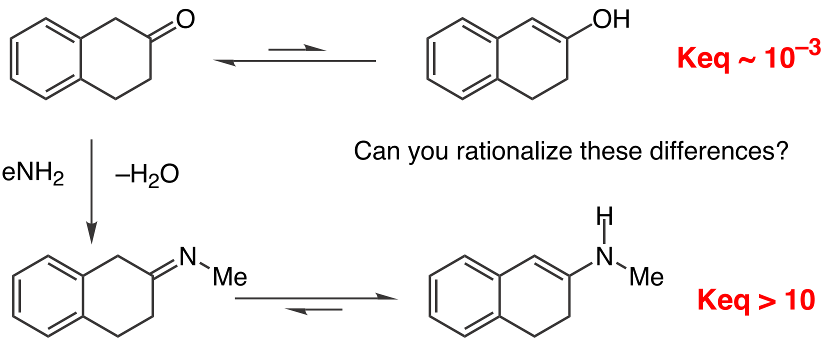
pK = 19.16 (calculated)

Kresge, *JACS* **1984**, *106*, 460

On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

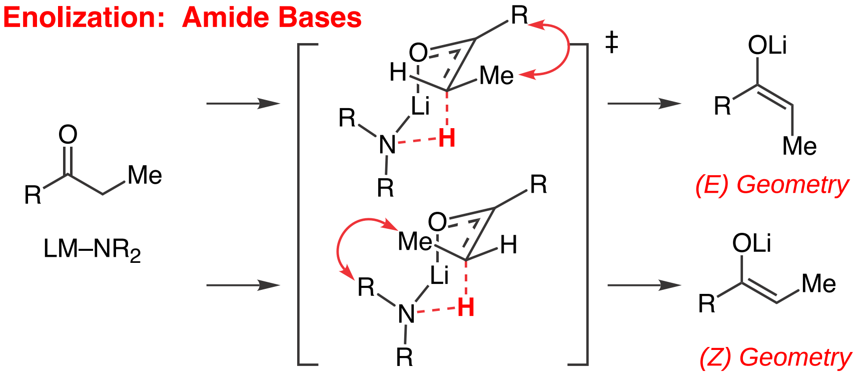
Enolization with Metal Amides bases

Tautomeric Equilibria: Ketones vs. Imines



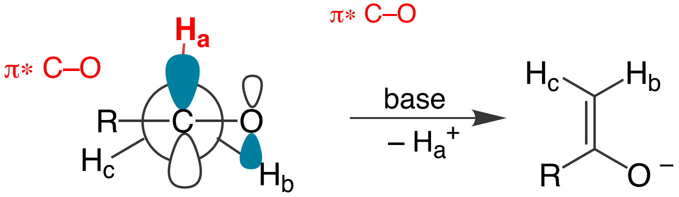
The enamine content in an analogous imine is invariably higher than its carbonyl counterpart. In the case above, ring conjugation now stabilizes the enamine tautomer as the major tautomer in solution.

Enolization: Amide Bases

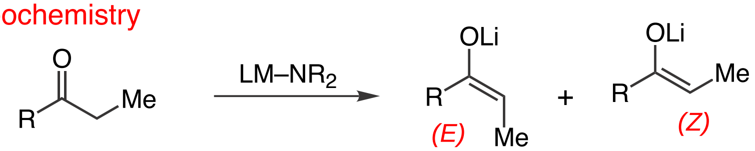


The Ireland Model (*J. Am. Chem. Soc*. **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650
For the latest word on this subject see: Xie, *JOC* 1997, *62*, 7516-9

Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π∗ C–O



■ Stereochemistry



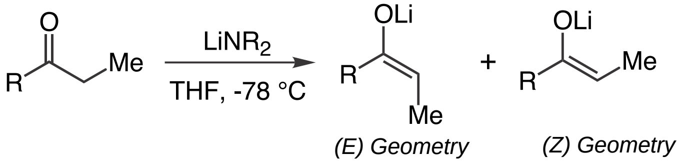
Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5
LDA (THF)	-Et	77 : 23
LDA (THF)	$-CHMe_2$	40 : 60
LDA (THF)	$-CMe_3$	0 : 100
LDA (THF)	$-C_6H_5$	0 : 100
LDA (THF)	$-NEt_2$	0 : 100
s-BuLi (THF)	$-NEt_2$	25 : 75

■ Solvent

Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe	95 : 5
LDA (THF, HMPA)	-OMe	16 : 84

■ Base Structure

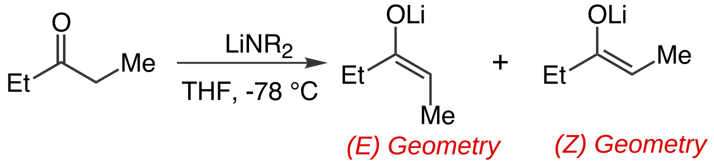
Masamune (*J. Am. Chem. Soc.* **1982**, *104*, 5526)



Base	R = Et, (E):(Z)	R = Cy, (E):(Z)
Li–N(i-Pr)$_2$	70 : 30	39 : 61
Li–N(SiMe$_3$)$_2$	30 : 70	15 : 85
Li–N(SiEt$_3$)$_2$	1 : 99	4 : 96
Li–N(SiMe$_2$Ph)$_2$	0 : 100	0 : 100
at equilibrium	16 : 84	—

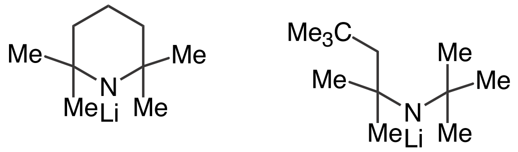
Base Structure

Corey & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 491, 495



$Li–N(i-Pr)_2$

(LDA) 77 : 23



(LiTMP) 86 : 14

(LOBA) 98 : 2

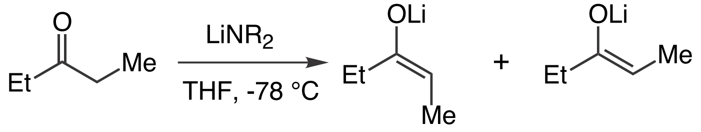
Lithium Halide Effects

Collum (*J. Am. Chem. Soc.* **1991**, *113*, 9572)

Collum (*J. Am. Chem. Soc.* **1991**, *113*, 9575)

Collum (*J. Am. Chem. Soc.* **1991**, *113*, 5053)

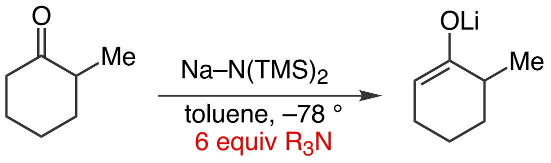
For the latest in the series of Column papers see: *JACS* **2000**, *122*, 2452-2458



	Ratio, (E):(Z)
LiTMP	86 : 14
LiTMP, 10% LiBr	98 : 2

Enolization in Non-Ethereal Solvents

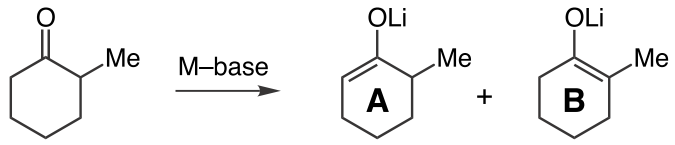
Collum (*JACS* **2003**, *125*, ASAP)



R_3N	none	Me_2NEt	$n-Bu_3N$	$1-Bu_3N$
k_{rel}	1	200	3000	1

Reaction kinetics suggest $(TMS_2NLi)_2(R_3N)(Ketone)^‡$

Regioselective Enolization

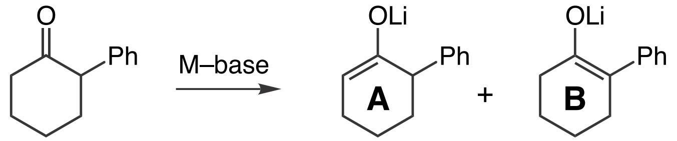


Base	temp	control	Ratio (A:B)
$LiN(i-Pr)_2$	–78 °	kinetic	99:1
$LiN(SiMe_3)_2$	–78 °	kinetic	95:5
$Ph_3C–Li$	–78 °	kinetic	90:10
$Ph_3C–Li$	heat	thermo	10:90
Na–H	heat	thermo	26:74
K–H	heat	thermo	38:62

A: Alkyl groups stabilize metal enolate

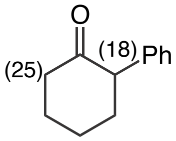
A: As M–O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure



ratio: 99:1

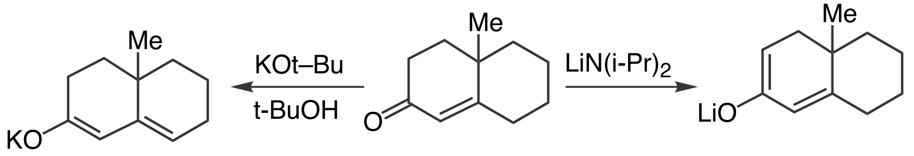
estimated pKa's (Bordwell)



$A \rightleftharpoons B$

pKeq est: 7 (10^{+7})

Unsaturated Ketones



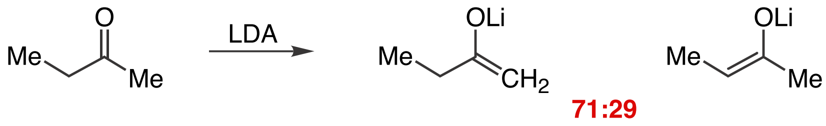
thermodynamic enolate

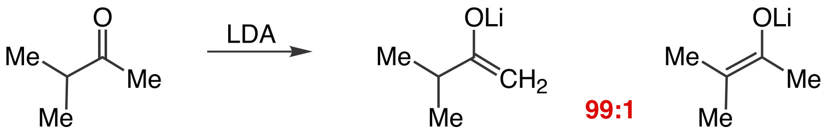
kinetic enolate

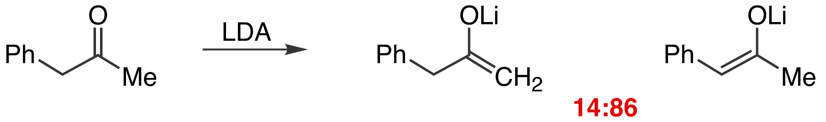
see kinetic acidity handout for an extensive compilation of cases.

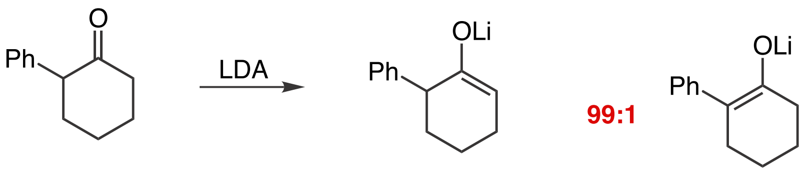
Enolization with Metal Amides bases

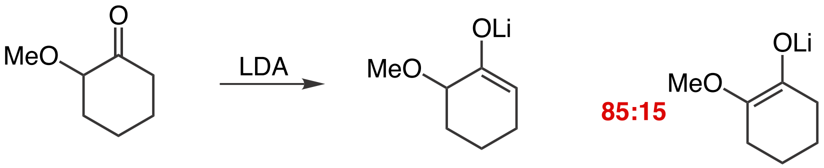
Kinetic Selection sensitive to structure

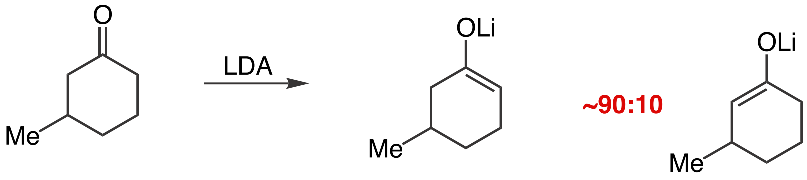


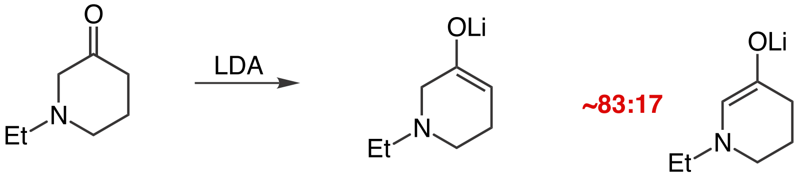




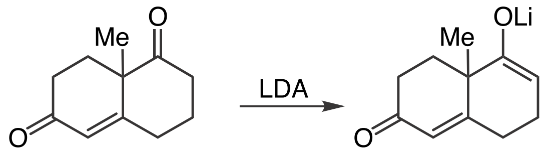




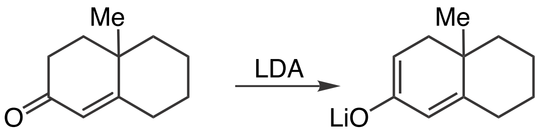




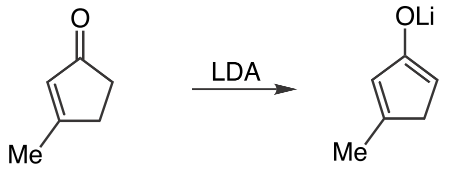
Kinetic Selection in Enolization of Unsaturated Ketones



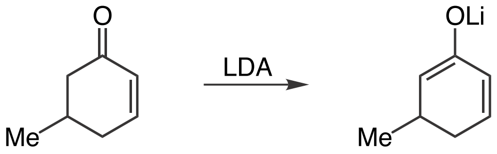
only enolate



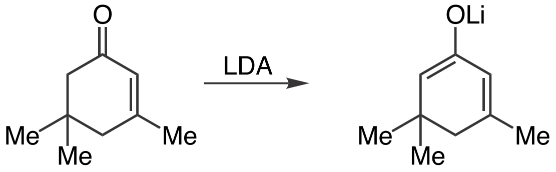
only enolate



only enolate



only enolate



only enolate

Quote for the Day

Professor Robert Milikan (1928), Nobel Laureate in Chemistry

"There is no likelihood man can ever tap the power of the atom. The glib supposition of utilizing atomic energy when our coal has run out is a completely unscientific Utopian dream, a childish bug-a-boo. Nature has introduced a few foolproof devices into the great majority of elements that constitute the bulk of the world, and they have no energy to give up in the process of disintegration."

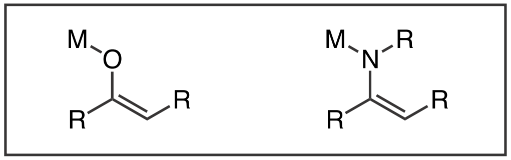
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 23

Enolates & Metalloenamines-1



- Tautomerism in C=O and C=NR Systems
- C=O Enolization with Metal Amide Bases
- C=O Enolization: Kinetic Acidities
- Mild Methods for Enolate Generation
- Enolate Structure: A Survey of X-ray Structures
- Metallo-Enamine X-ray Structures

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Friday,
November 7, 2003

Assigned Journal Articles

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983). **(handout)**

"Stereoselective Alkylation Reactions of Chiral Metal Enolates".
D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984). **(handout)**

Other Useful References

"Recent Advances in Dianion Chemistry". C. M. Thompson and D. L. C. Green *Tetrahedron*, **47**, 4223 (**1991**).

The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (**1982**).

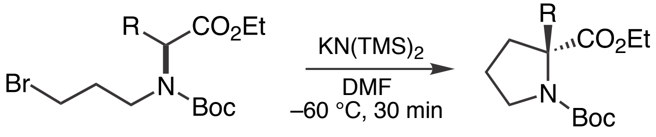
"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res*. **21**, 121 (**1988**).

"Keto-Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution". Keeffe, Kresge, and Schepp *JACS*, 112, 4862 (**1990**).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (**1984**).

Database Problem 314

Kawabata and co-workers recently reported the remarkable enolate alkylation illustrated below (*JACS* **2003,** *125*, 13012). When the indicated α-aminoacid ester is treated with KHMDS in DMF at —60 °C, the derived cyclic amino acid ester is formed in high yield and enantioselectivity. The stereochemical outcome represents a formal retention of configuration. This reaction exhibits some generality as the 4- 5-, 6-, and 7-membered lactams may be obtained in high ee.



R	ee
Bn	98 (S)
Me_2CH	94 (S)

Provide a rationalization of these results. Three-dimensional drawings are recommended.

Enolates & Metalloenamines: Introduction

Important References

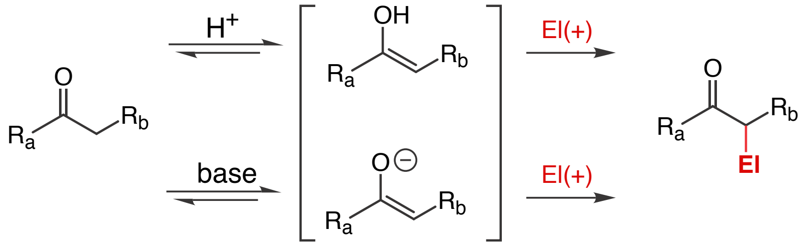
"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures". D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983).

"Stereoselective Alkylation Reactions of Chiral Metal Enolates". D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984).

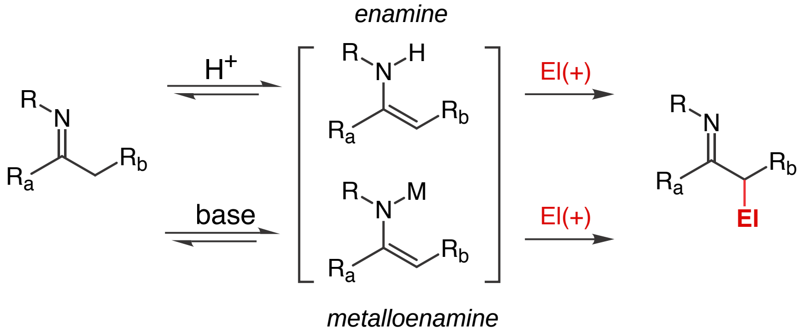
"Generation of Simple Enols in Solution". B. Capon, B.-Z. Guo, F. C. Kwok, A. K. Siddhanta, and C. Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Y. Chiang, A. J. Kresge, and Y. S. Tang *J. Am. Chem. Soc.* **106**, 460 (1984).

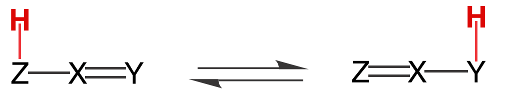
Enols & Enolates are the most important nucleophiles in organic & biological chemistry.



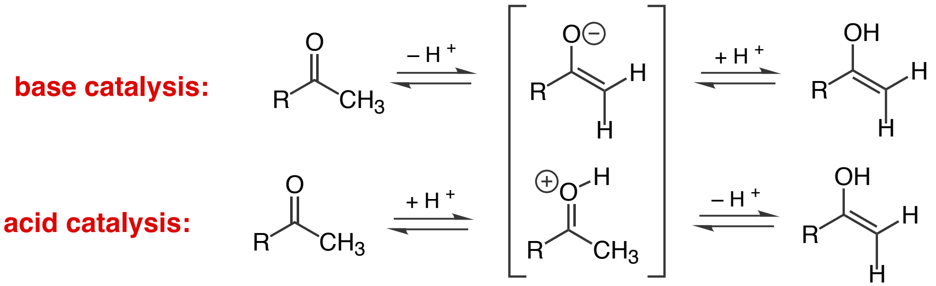
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



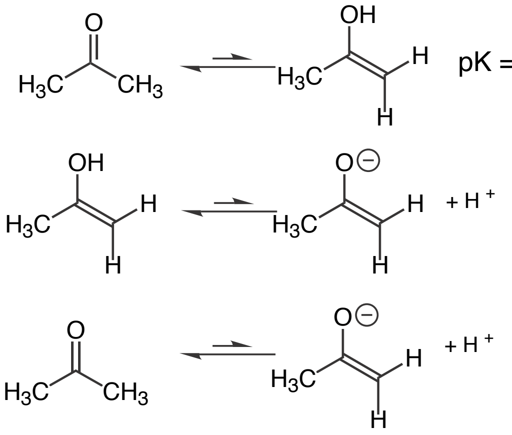
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



Acidity of Keto and Enol Tautomers: Consider Acetone:



pK = 8.22 (measured)

+ H + pK = 10.94 (measured)

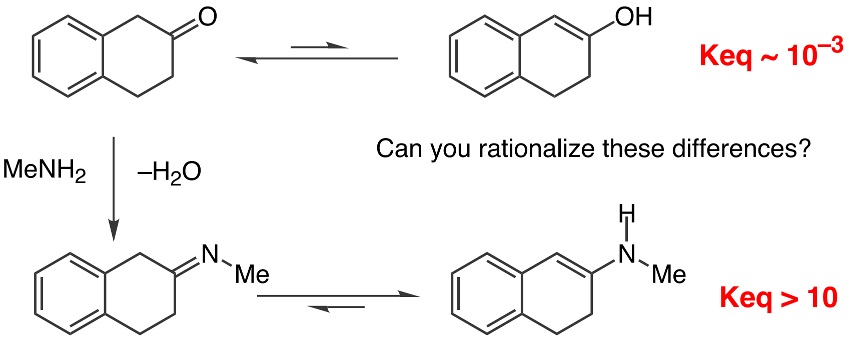
+ H + pK = 19.16 (calculated)

Kresge, *JACS* **1984**, *106*, 460

On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

Enolization with Metal Amides bases

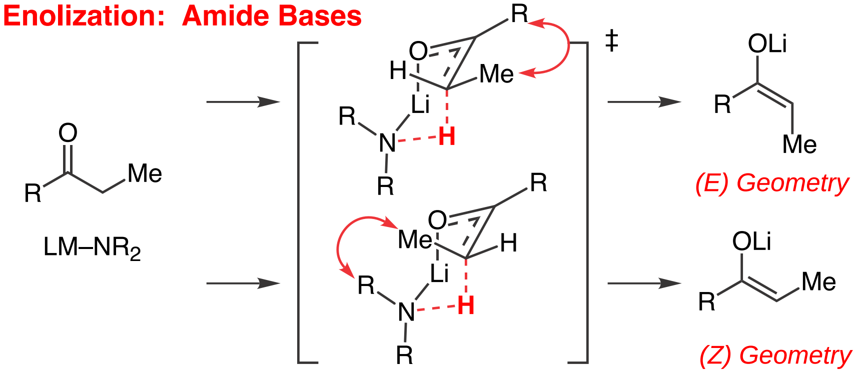
Tautomeric Equilibria: Ketones vs. Imines



Can you rationalize these differences?

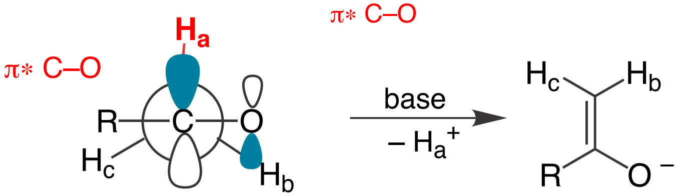
The enamine content in an analogous imine is invariably higher than its carbonyl counterpart. In the case above, ring conjugation now stabilizes the enamine tautomer as the major tautomer in solution.

Enolization: Amide Bases

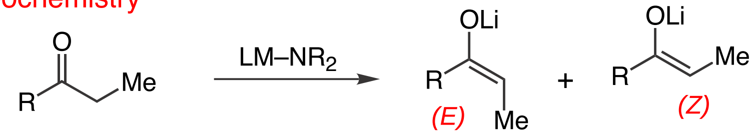


The Ireland Model (*J. Am. Chem. Soc*. **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650
For the latest word on this subject see: Xie, *JOC* 1997, *62*, 7516-9

Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π* C–O



■ Stereochemistry



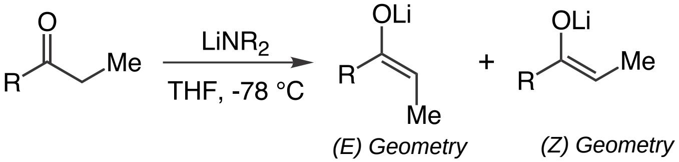
Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5
LDA (THF)	-Et	77 : 23
LDA (THF)	$-CHMe_2$	40 : 60
LDA (THF)	$-CMe_3$	0 : 100
LDA (THF)	$-C_6H_5$	0 : 100
LDA (THF)	$-NEt_2$	0 : 100
s-BuLi (THF)	$-NEt_2$	25 : 75

■ Solvent

Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe	95 : 5
LDA (THF, HMPA)	-OMe	16 : 84

■ Base Structure

Masamune (*J. Am. Chem. Soc.* **1982**, *104*, 5526)

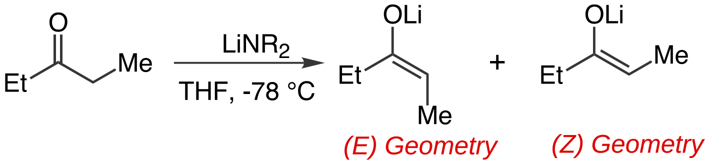


Base	R = Et, (E):(Z)	R = Cy, (E):(Z)
$Li–N(i-Pr)_2$	70 : 30	39 : 61
$Li–N(SiMe_3)_2$	30 : 70	15 : 85
$Li–N(SiEt_3)_2$	1 : 99	4 : 96
$Li–N(SiMe_2Ph)_2$	0 : 100	0 : 100
at equilibrium	16 : 84	—

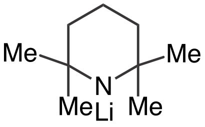
Enolization with Metal Amides bases

Base Structure

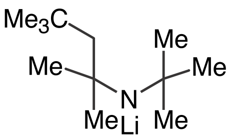
Corey & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 491, 495



Li–N(i-Pr)$_2$
(LDA) 77 : 23



(LiTMP) 86 : 14

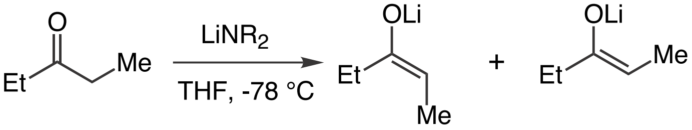


(LOBA) 98 : 2

Lithium Halide Effects

Collum (*J. Am. Chem. Soc.* **1991**, *113*, 9572)
Collum (*J. Am. Chem. Soc.* **1991**, *113*, 9575)
Collum (*J. Am. Chem. Soc.* **1991**, *113*, 5053)

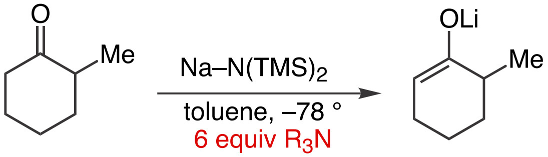
For the latest in the series of Column papers see: *JACS* **2000**, *122*, 2452-2458



	Ratio, (E):(Z)
LiTMP	86 : 14
LiTMP, 10% LiBr	98 : 2

Enolization in Non-Ethereal Solvents

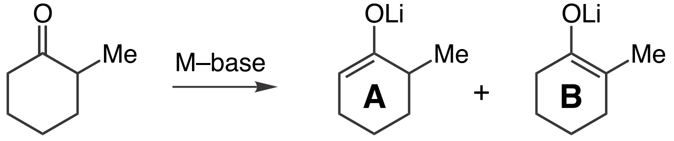
Collum (*JACS* **2003**, *125*, ASAP)



R_3N	none	Me_2NEt	n-Bu_3N	1-Bu_3N
k_{rel}	1	200	3000	1

Reaction kinetics suggest $(TMS_2NLi)_2(R_3N)(Ketone)^‡$

Regioselective Enolization

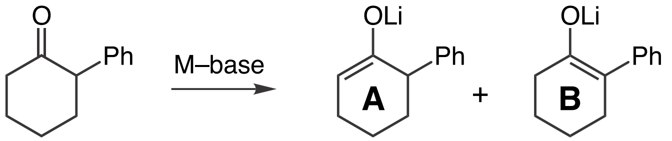


Base	temp	control	Ratio (A:B)
LiN(i-Pr)$_2$	–78 °	kinetic	99:1
LiN(SiMe$_3$)$_2$	–78 °	kinetic	95:5
Ph$_3$C–Li	–78 °	kinetic	90:10
Ph$_3$C–Li	heat	thermo	10:90
Na–H	heat	thermo	26:74
K–H	heat	thermo	38:62

A: Alkyl groups stabilize metal enolate

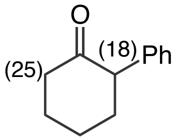
A: As M–O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure



ratio: 99:1

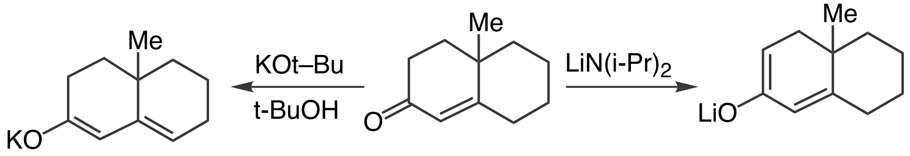
estimated
pKa's
(Bordwell)



$A \rightleftharpoons B$

pKeq est: 7 (10^{+7})

Unsaturated Ketones



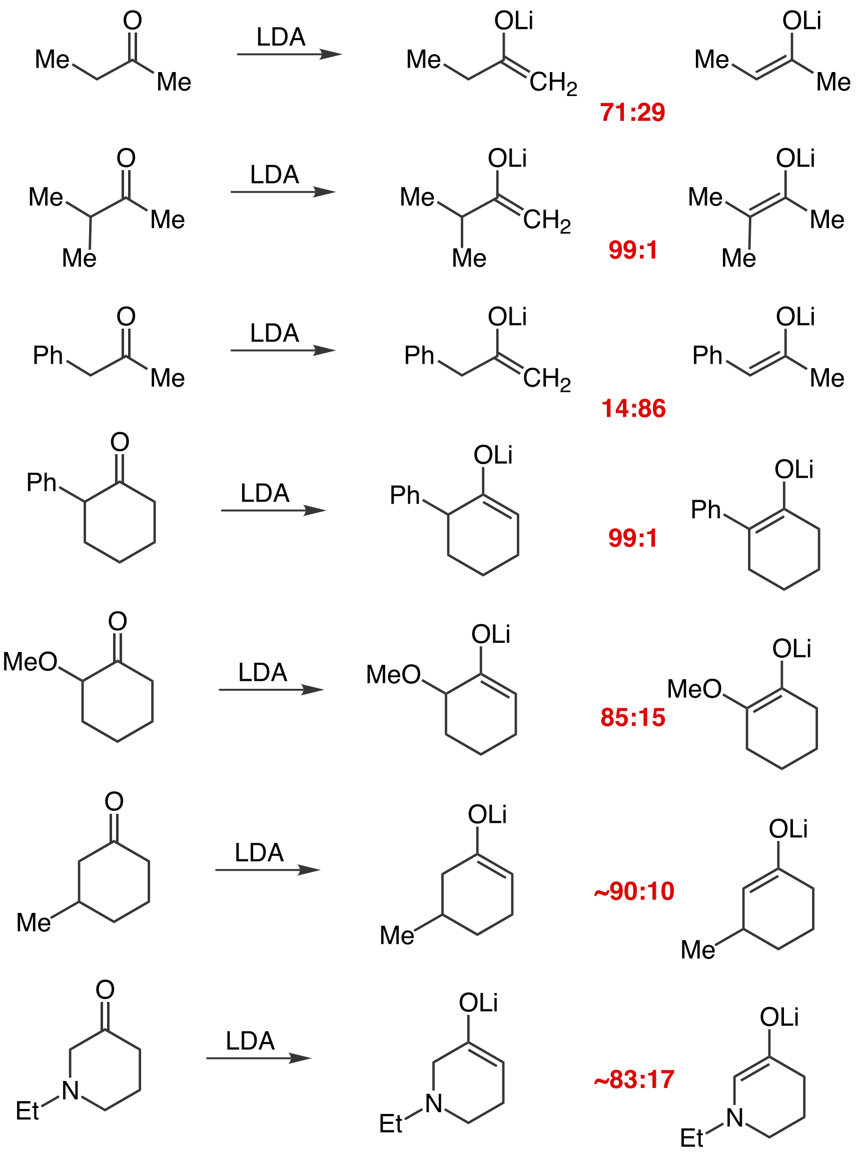
thermodynamic
enolate

kinetic enolate

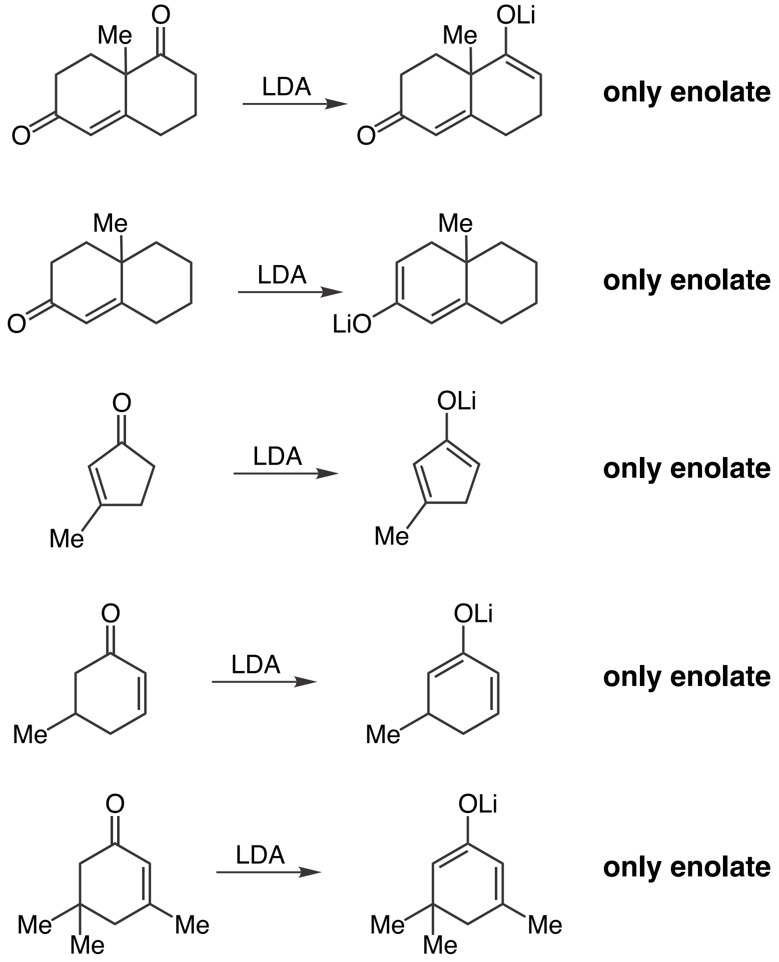
see kinetic acidity handout for an
extensive compilation of cases.

Enolization with Metal Amides bases

Kinetic Selection sensitive to structure

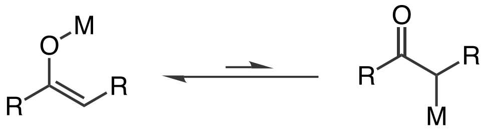


Kinetic Selection in Enolization of Unsaturated Ketones



Enolate Structures from X-ray Diffraction

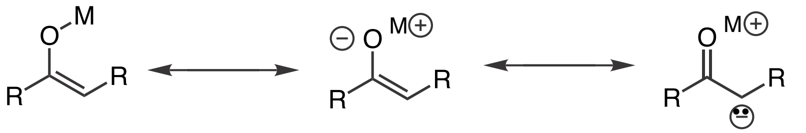
Metal Tautomerism



For alkali metal enolates (M = Li, Na, K etc.) the O-metal tautomer is strongly favored. This generalization holds for most alkaline earth enolates (Mg^{+2}) as well. These are the generally useful enolate nucleophiles

For certain metal enolates from heavy metals such as M = Hg^{+2} the C-metal tautomer is sometimes favored.

Resonance Structures



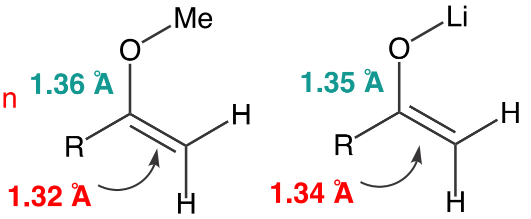
O^{-} resonance structure

C^{-} resonance structure

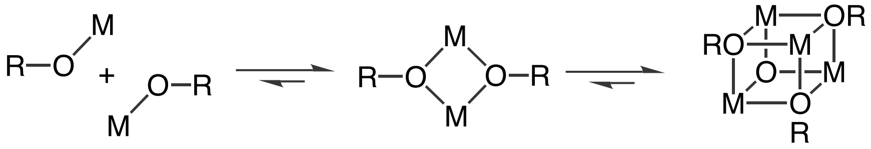
Since enolates usually function as carbon nucleophiles, it is therefore of some interest to assess the relative importance of the illustrated contributing polar resonance structures. Within the last decade good X-ray crystal structures of a number of metal enolates have been obtained.

One would predict that as the relative importance of the C^{-} structure increases, the C–O bond would shorten and the C–C bond would lengthen.

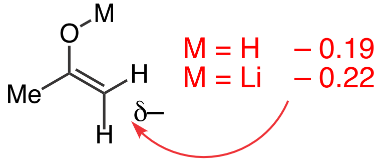
The prediction stated above does hold, but the net change in the C–C bond length is < 2 % !



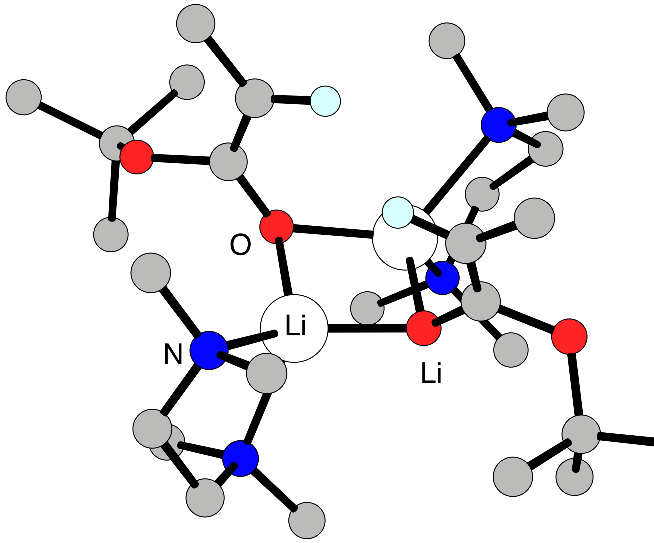
In solution and in the solid state metal enolates have a strong tendency to aggregate into dimers and tetramers to satisfy metal solvation requirements.

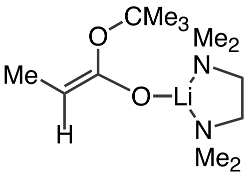


Ab initio calculations (Spartan) indicate that the partial negatilve charge on the alpha carbon is ~ – 0.22 for the Li enolate



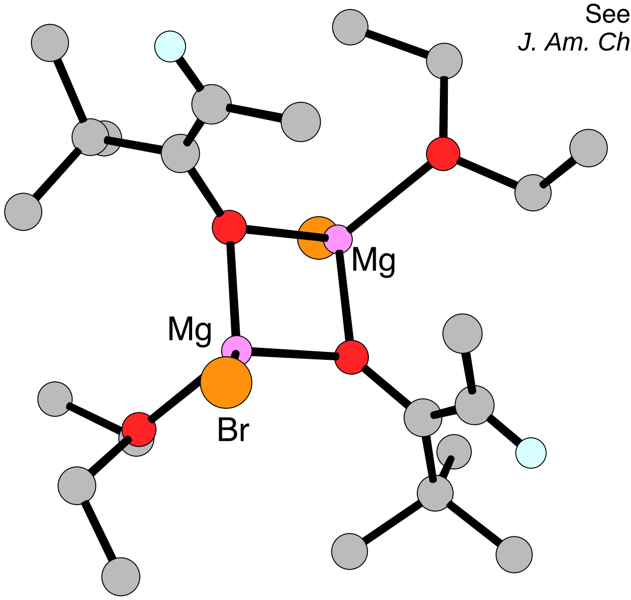
M = H – 0.19
M = Li – 0.22

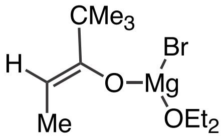




Crystallized as the dimer

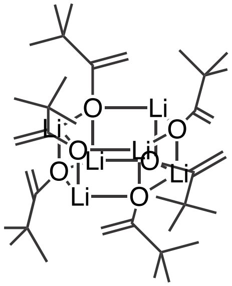
Seebach & co-workers,
J. Am. Chem. Soc. **1985**,*107*, 5403.

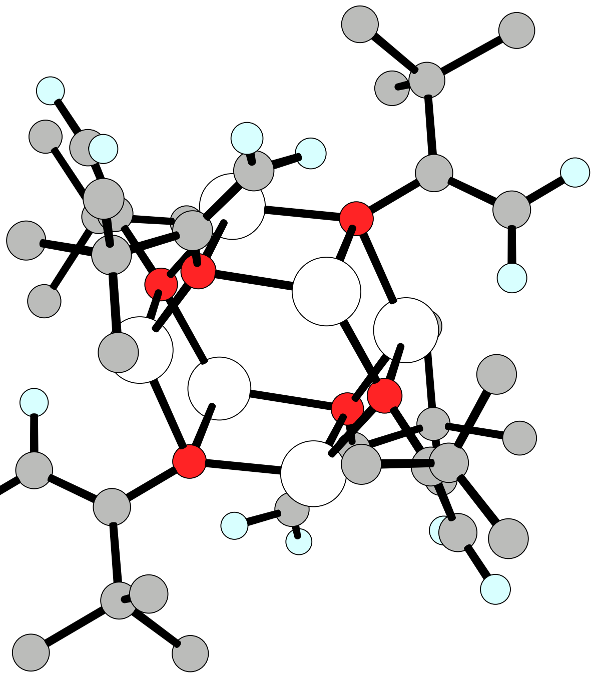


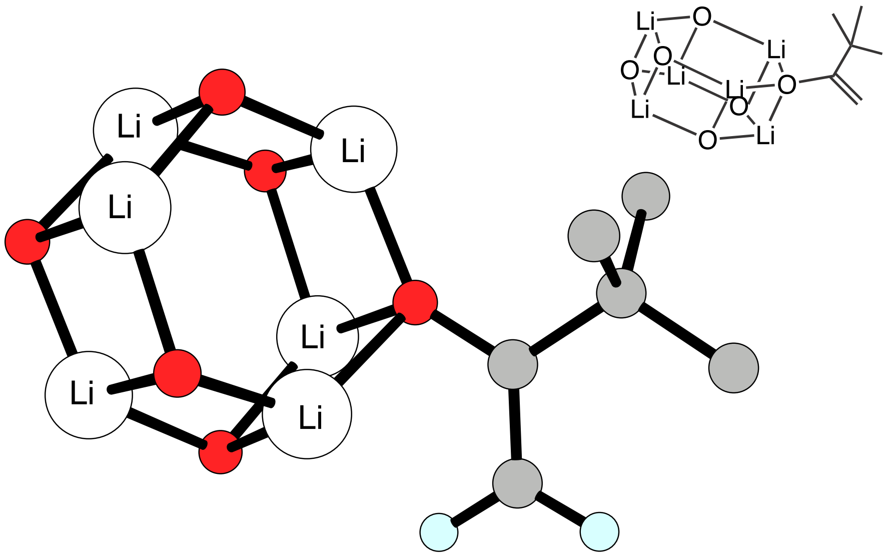


Crystallized as the dimer

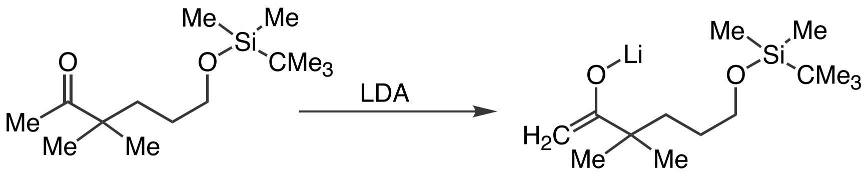
Li Enolates



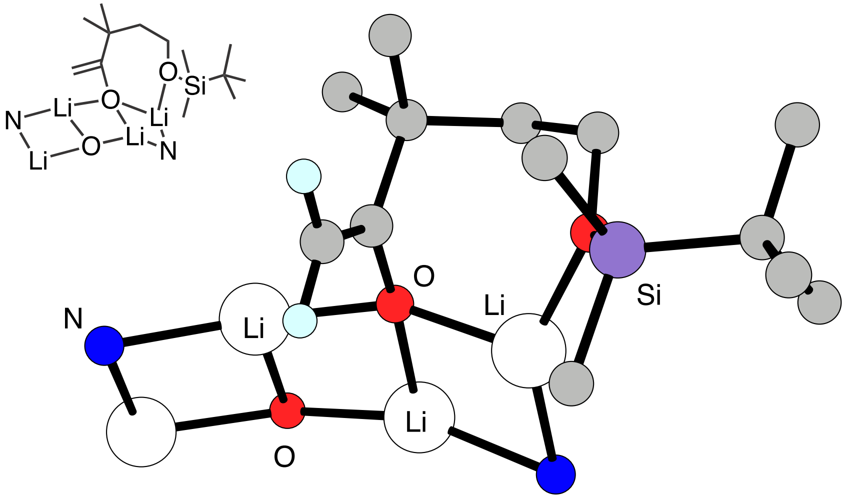


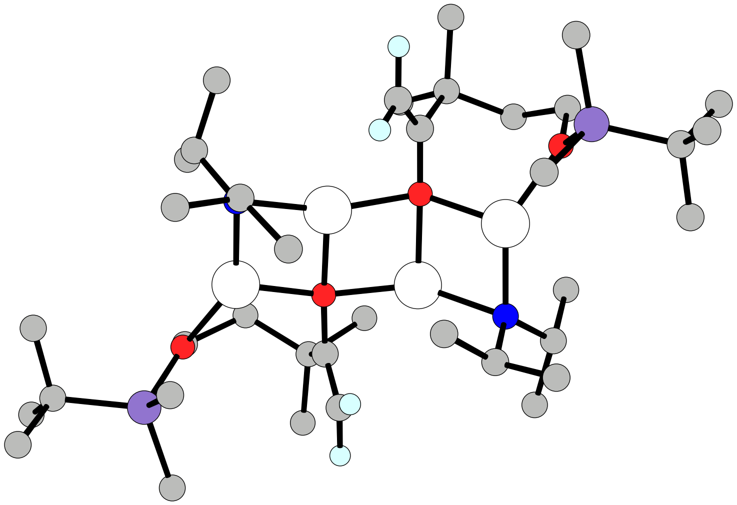


Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462-468.



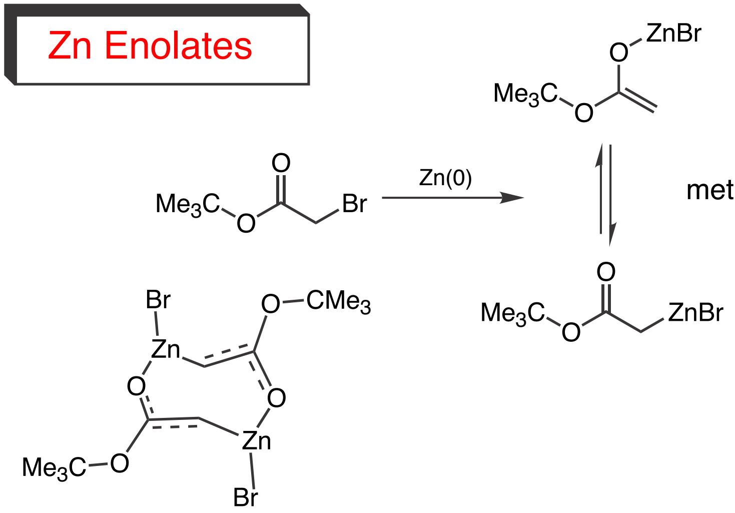
Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539-5541.



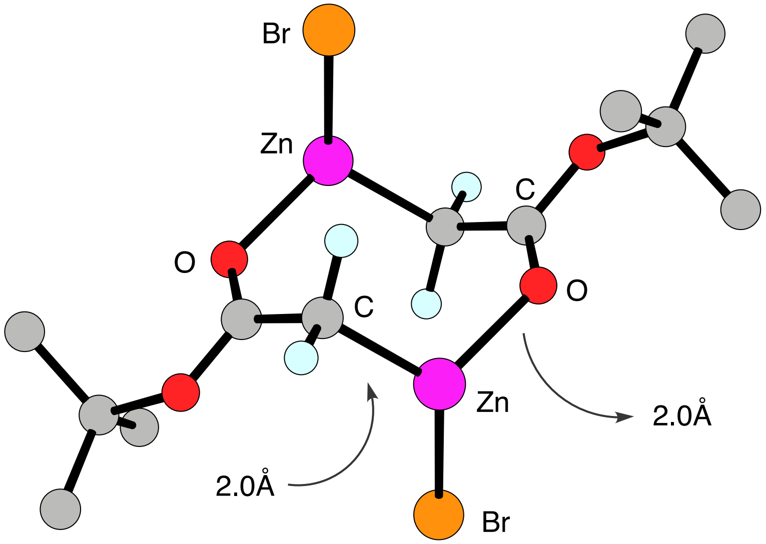


Enolate Structures: The Reformatsky Reagent

Zn Enolates

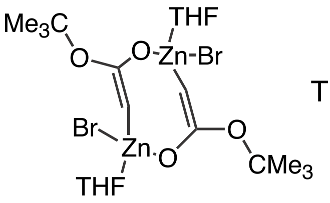


metal tautomers

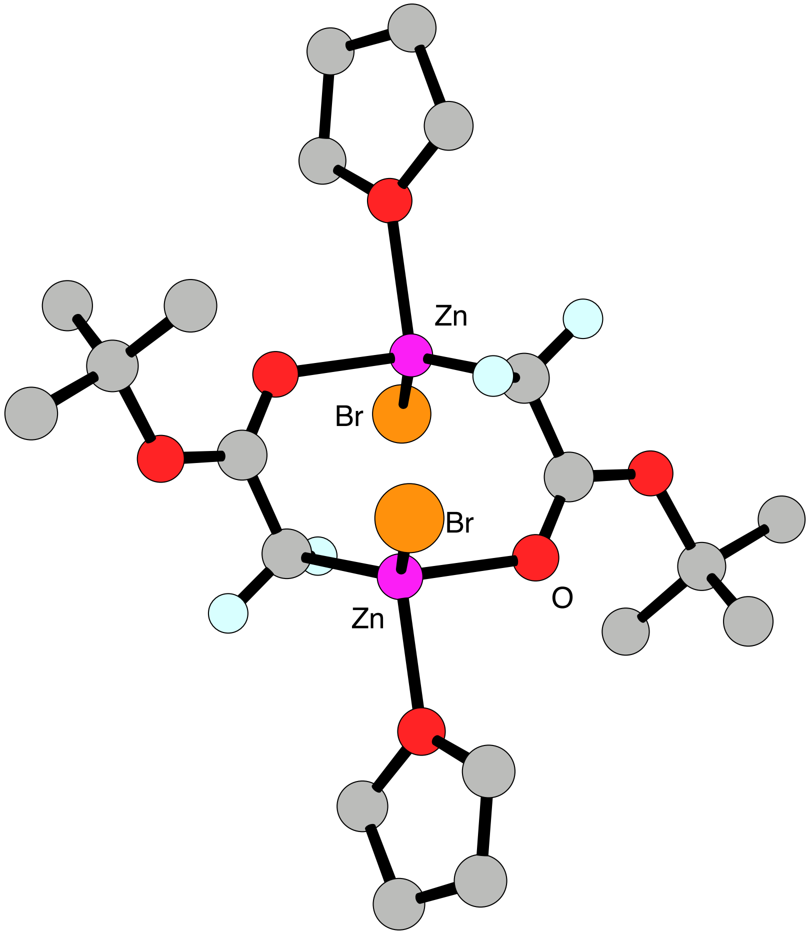


Dekker, J.; Boersma, J.; van der Kerk,
G. J. M. *J. Chem. Soc. Chem. Commun.* **1983**, 553.

Dekker, J.; Budzelaar, J.; Boersma, J.; van der Kerk, G. J. M.
Organometallics **1984**, *3*, 1403.

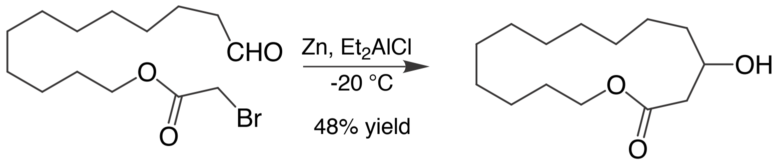


The THF Complex



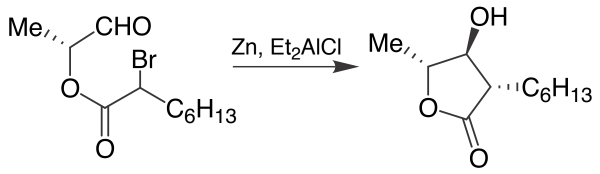
The "Classical" Reformatsky Process

Review: *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.8, pp 277-299
Fürstner, A. "Recent Advances in the Reformatsky Reaction." *Synthesis* **1989**, 571.



H. Nozaki & Co-workers,
J. Am. Chem. Soc. **197**, *99*, 7705

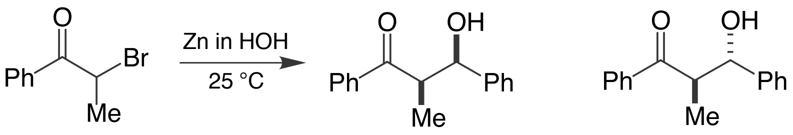
Both cyclic and acyclic cases studied (11 cases).



diastereoselection 10:1
55% yield

T. Nishida & Co-workers,
Tetrahedron **1991**, *47*, 6623.

Based on the Nozaki recipe *JACS* **1977**, *99*, 7705

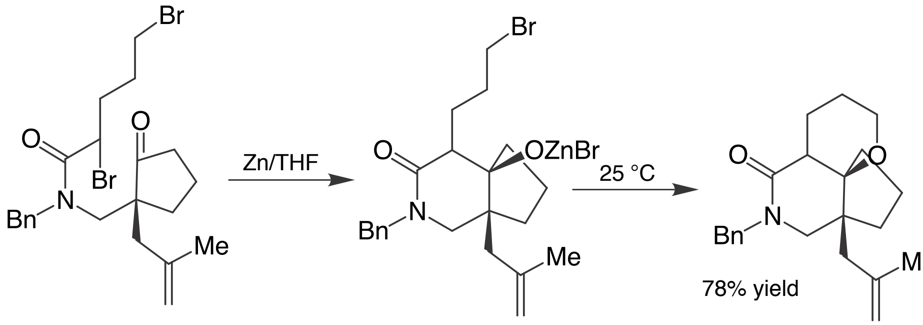


PhCHO

diastereoselection 60:40
87% yield

T. H. Chan & Co-workers,
Chem. Commun. **1990**, 505.

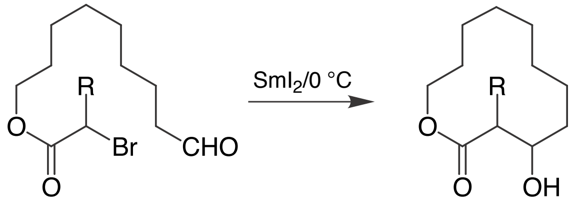
Rxns carried out in water with either activated Zn or Sn.
19 cases reported.



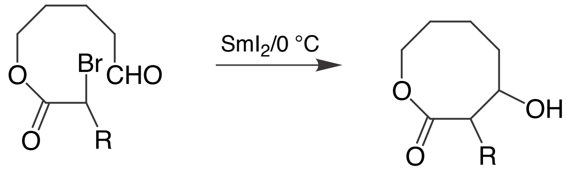
C. H. Heathcock & Co-workers,
J. Org. Chem. **1987**, *52*, 5745.

The Samarium(II) Variant

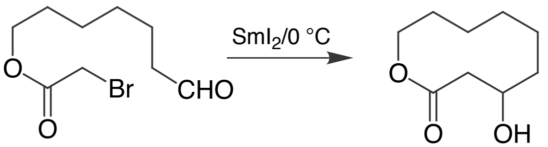
Molander, "Reductions with Samarium (II) Iodide." *Org. Reactions* **1994**, *46*, 211-367.



R = H: 85% yield
R = Me: 82% yield
aldol diastereoselection 70:30
no config assignment



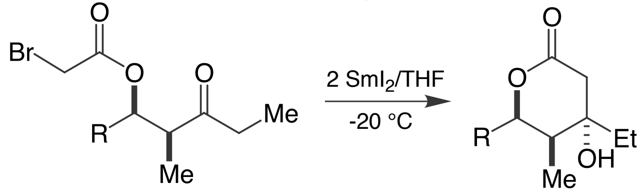
R = H: 76% yield
R = Me: 82% yield
aldol diastereoselection 62:38
no config assignment



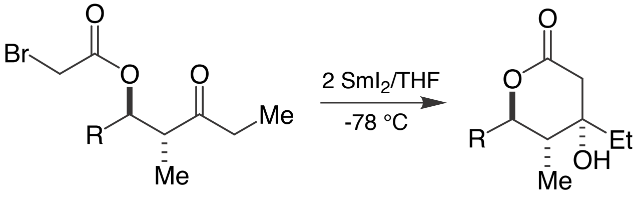
82% yield

Good entry into prior literature

T. Tabushi & Co-workers,
Tetrahedron Lett. **1986**, *27*, 3889.



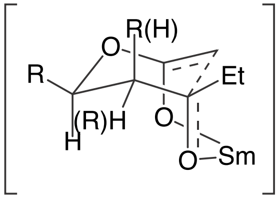
8: 1 diastereoselection
97% yield



one isomer? 86% yield

G. A. Molander & Co-workers,
J. Am. Chem. Soc. **1987**, *109*, 6556.

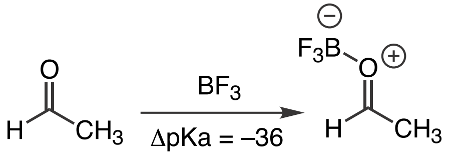
Proposed Transition
structure



Design of Soft Enolization Systems

Mild Methods for Forming Enolates

Lewis Acid C=O Complexation Enhances C–H Acidity (Computation)



$\Delta H_{\text{gas phase}}$ **+366** **+316**

pKa_{HOH} **+17** $\xrightarrow{BF_3}$ **–7**

ΔpKa = –24

ΔH_{gp} H_2SO_4 = 304

ΔH_{gp} H–I = 314

$\Delta\Delta H_{gp}$ = –50 kcal/mol

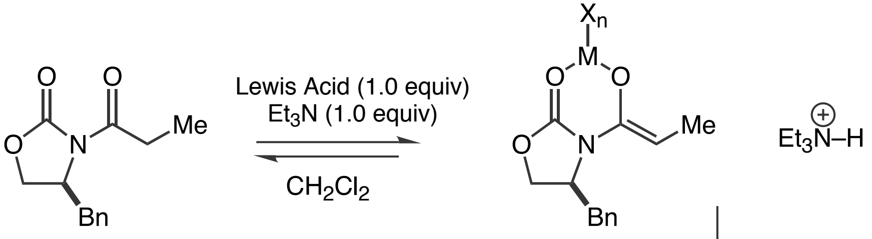
↓

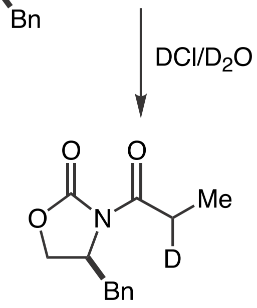
$\Delta\Delta H_{gp}$ = –24 kcal/mol

BF_3 complexation generates a "superacid" comparable to the acidity of H_2SO_4

Ren et al, *JACS* **1999**, *121*, 2633-2634 **(pdf)**

Some qualitative observations (Evans Group, Unpublished))



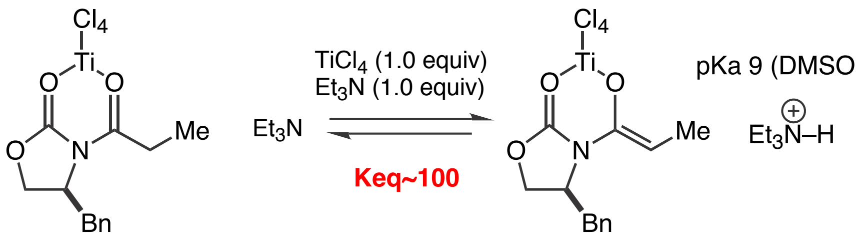


Lewis Acid (MX_n)	% deuterium
$TiCl_4$	100
$TiCl_3(Oi\text{-}Pr)$	100
$TiCl_4 \cdot (THF)_2$	80
$TiCl_2(Oi\text{-}Pr)_2$	70
$AlCl_3$	70
$MgBr_2 \cdot OEt_2$*	25
$TiCl(Oi\text{-}Pr)_3$	10
$SnCl_4$, Et_2AlCl, $ZrCl_4$	0

*2.0 equiv required

In these experiments, the Lewis acid was added first followed by the amine.

Some qualitative observations (Evans Group, Unpublished))

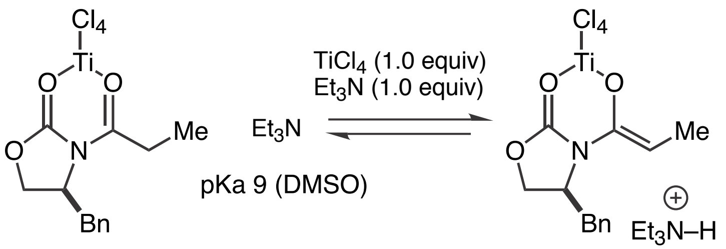


pKa 9 (DMSO)

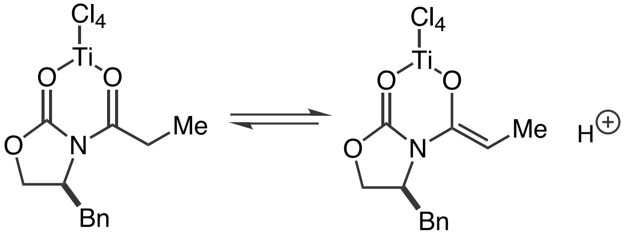
estimated pKa (DMSO)???

pK

$Et_3N\text{–}H^{\oplus} \rightleftharpoons H^{\oplus} + Et_3N$ **+9**



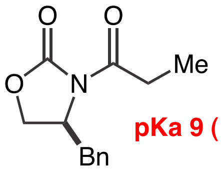
–2



pKa ~ +7

estimated pKa (DMSO) ~ +7

Hence $TiCl_4$ complexation lowers acidity by **~20 pka units.** this number is the same mgnitude as the BF_3–acetaldehyde case just discussed



pKa 9 (DMSO)~ +27

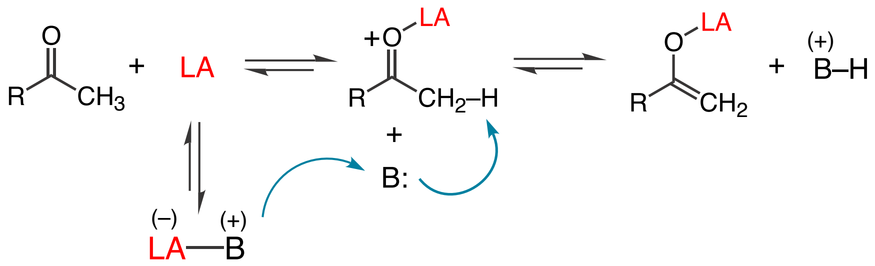
Design of Soft Enolization Systems

Strategy

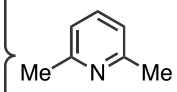
Choose Lewis Acid (LA) which can reversibly associate with amine base (B:).

$$LA + B: \rightleftharpoons \overset{(-)}{LA}-\overset{(+)}{B}$$

This system has the potential to enolize carbonyl functional groups:

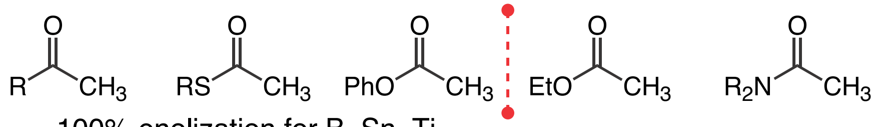


Useful Lewis Acid Pairs	Complexation
$MgBr_2$ + NEt_3	Reversible
Li–X + NR_3	Reversible
$Sn(OTf)_2$ + NR_3	Reversible (Et_3N, EtNi-Pr_2)
R_2B-OTf + NR_3	Reversible (Et_3N, EtNi-Pr_2)
R_2BCl + NR_3	Reversible (Et_3N, EtNi-Pr_2)
$PhBCl_2$ + NR_3	Reversible (Et_3N, EtNi-Pr_2)
$TiCl_4$ + NR_3	Irreversible (Et_3N, EtNi-Pr_2)
i-PrOTiCl_3 + NR_3	Reversible (Et_3N, EtNi-Pr_2)
(i-PrO)$_2TiCl_2$ + NR_3	Reversible (Et_3N, EtNi-Pr_2)
(i-PrO)$_3$TiCl + NR_3	Reversible (Et_3N, EtNi-Pr_2)



$^-OTf = {}^-OSO_2CF_3$

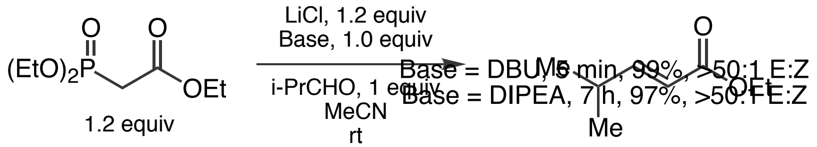
All of the above systems will enolize simple ketones to some extent.



100% enolization for B, Sn, Ti
partial enolization for Li, Mg

Lithium Enolates

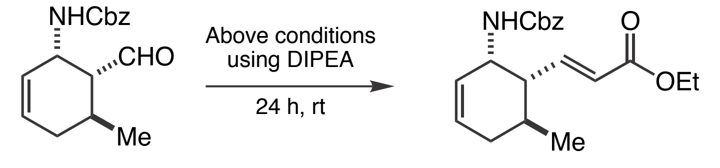
Horner-Wadsworth-Emmons Reaction.



Base = DBU, 5 min, 99%, >50:1 E:Z
Base = DIPEA, 7 h, 97%, >50:1 E:Z

pKa 19.2 (DMSO), K^+ counterion
pKa 12.2 (Diglyme), Li^+ counterion

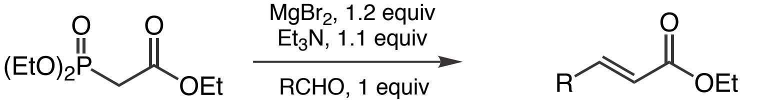
Roush & Masamune, Tet. Lett. 1984, 25, 2183-2186



85% + 10% recovered aldehyde

Conventional methods of deprotonation (NaH) resulted in epimerization (Overman *JACS* **1978**, 5179).

Magnesium Enolates



1 equiv

R= i-Pr, 40% yield
R= n-C_6H_{13}, 100% yield

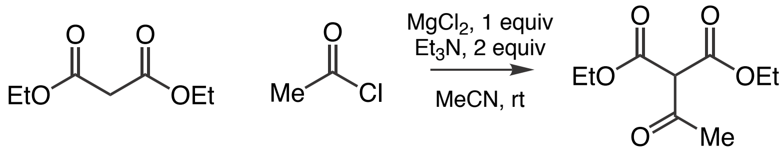
Rathke, Nowak *J. Org. Chem.* **1985**, *50*, 2624-2626.

A Survey of 'Soft' Enolization Techniques

Magnesium Enolates

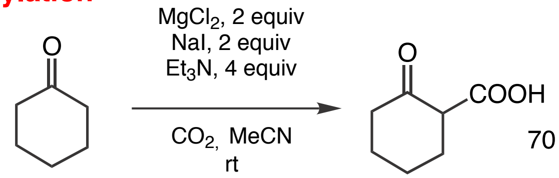
Rathke *J. Org. Chem.* **1985**, *50*, 2622-2624.
J. Org. Chem. **1985**, *50*, 4877-4879.
Syn. Comm. **1986**, *16*, 1133-1139.

Diethylmalonate acylations

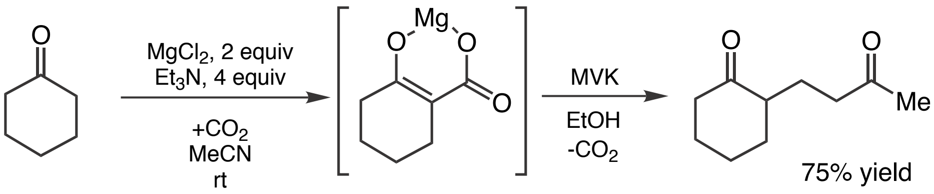


85% yield

Ketone Carboxylation

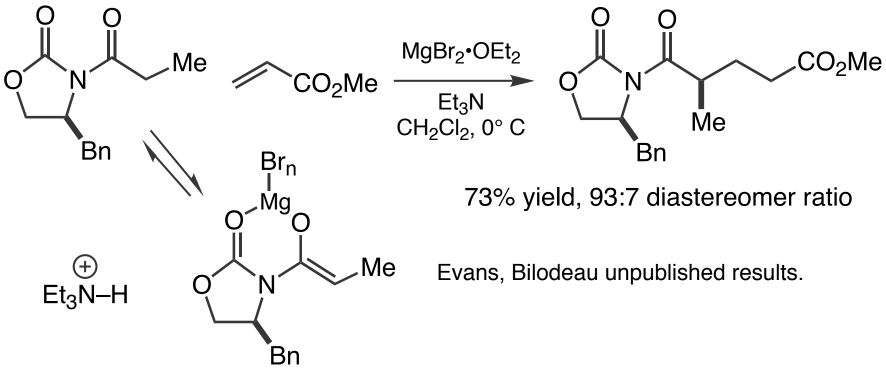


70 % yield



75% yield

Michael reaction



73% yield, 93:7 diastereomer ratio

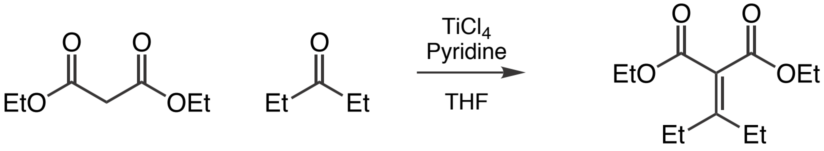
Evans, Bilodeau unpublished results.

Deuterium quench indicates 25% enolization of *N*-propionyloxazolidinone

Titanium Enolates

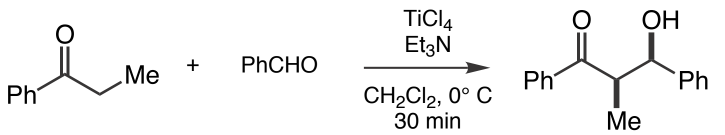
The Early Literature

Lehnert, W. *Tetrahedron Lett.* 1970, 4723-4724.



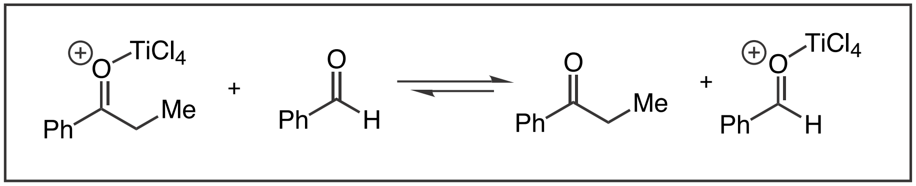
75% yield

Harrison, C. R. *Tetrahedron Lett.* 1987, *28*, 4135-4138.

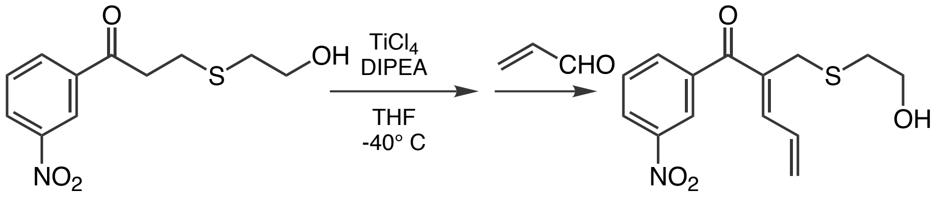


91% yield
95:5 syn/anti

Ketone and aldehyde combined followed by sequential addn of $TiCl_4$ and then amine



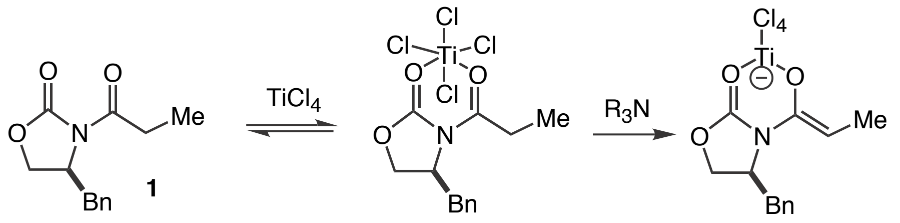
Brocchini, Eberle, Lawton *J. Am. Chem. Soc.* 1988, *110*, 5211-5212.



10-15:1 Z/E

A Survey of 'Soft' Enolization Techniques

Titanium Enolates



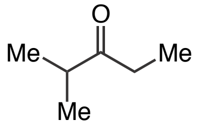
- Enolization process not responsive to tertiary amine structure
- DIPEA, Et_3N, N-Ethylpiperidine all suitable bases.
- DBU and tetramethylguanidine do not provide enolate.
- CH_2Cl_2 is the only suitable solvent for these enolizations.

N-Propionyloxazolidone (**1**)

Lewis Acid	% Enolization
$TiCl_4$	100
i-PrOTiCl$_3$	100
$TiCl_4$•2THF	80
(*i*-PrO)$_2$TiCl$_2$	70
(*i*-PrO)$_3$TiCl	~10

Ethylisopropylketone

Lewis Acid	% Enolization
$TiCl_4$	100
i-PrOTiCl$_3$	80
(*i*-PrO)$_2$TiCl$_2$	50



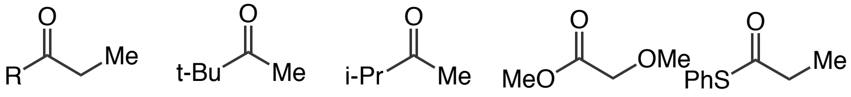
- Order of addition of reagents is important for $TiCl_4$.

$R_3N \quad + \quad TiCl_4 \longrightarrow \overset{+}{R_3N}\text{-}\overset{-}{TiCl_4}$ Irreversible Complexation

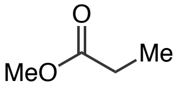
- Order of addition of reagents is not important for *i*-PrOTiCl$_3$ or (*i*-PrO)$_2$TiCl$_2$.

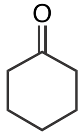
$R_3N \quad + \quad i\text{-PrOTiCl}_3 \rightleftharpoons \overset{+}{R_3N}\text{-}\overset{-}{TiCl_3}(O\mathit{i}Pr)$ Reversible Complexation

- Enolizable substrates:

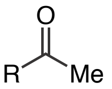


- Substrates Which present problems:





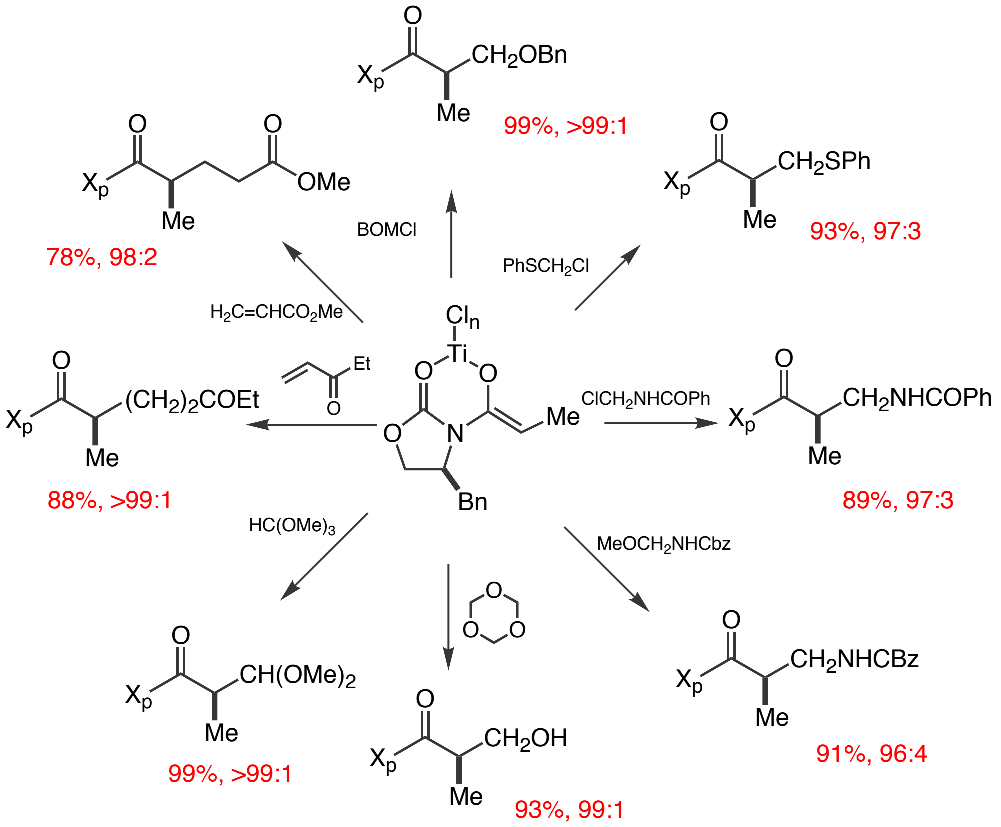
self condensation



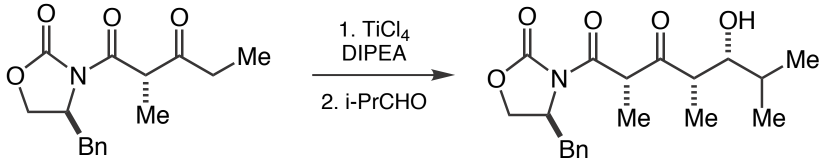
R=Ar, R<i-Pr

self condensation

Reactions with Representative Electrophiles



J. Am. Chem. Soc. **1990**, *112*, 8215-8216.; *J. Org. Chem.* **1991**, *56*, 5750-5752.



86% yield, >99:1

Evans, Clark, Metternich, Novack, Sheppard *J. Am. Chem. Soc.* **1990**, *112*, 866.

A Survey of 'Soft' Enolization Techniques: Boron Enolates-1

Dialkylboron Triflates

Di-n-butylboron triflate

Mukaiyama, Inoue *Chem. Lett.* **1976**, 559-562.
Bull. Chem. Soc. Jpn. **1980**, *53*, 174-178.

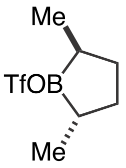
Enolizes ketones with 2,6-lutidine or DIPEA in ethereal solvents.

Diastereoselective Aldol Reactions of Boron Enolates.

Evans, Vogel, Nelson *J. Am. Chem. Soc.* **1979**, *101*, 6120.
Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
Evans, Bartroli, Shih *J. Am. Chem. Soc.* **1981**, *103*, 2127.
Masamune, S. et. al. *Tetrahedron Lett.* **1979**, 2225, 2229, 3937.
Masamune, S. et. al. *J. Am Chem. Soc.* **1981**, *103*, 1566-1568.

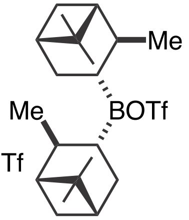
Chiral dialkylboron triflates

Masamune, Sato, Kim, Wollmann
J. Am. Chem. Soc. **1986**, *108*, 8279-8281.



Paterson, I. et. al.

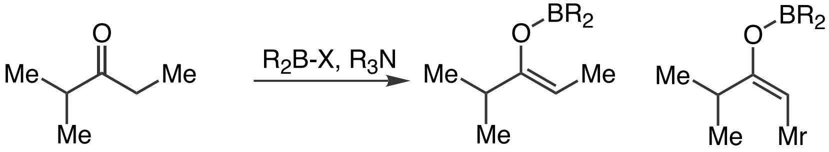
Tetrahedron **1990**, *46*, 4663-4684.
Tetrahedron Lett. **1989**, *30*, 997-1000.
Tetrahedron Lett. **1986**, *27*, 4787-4790.



(-)-(Ipc)$_2$BOTf

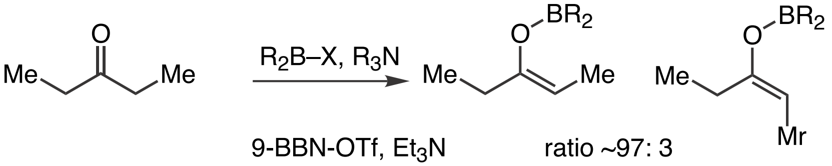
Enolate Stereochemistry

Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
Goodman, *Tetrahedron Lett.* **1992**, *33*, 7219.
Enolization Model: Paterson, *Tetrahedron Lett.* **1992**, *33*, 7223.



9-BBN-OTf, Et_3N	ratio ~ 88: 12
Cy_2B-Cl, Et_3N	ratio ~ 3: 97

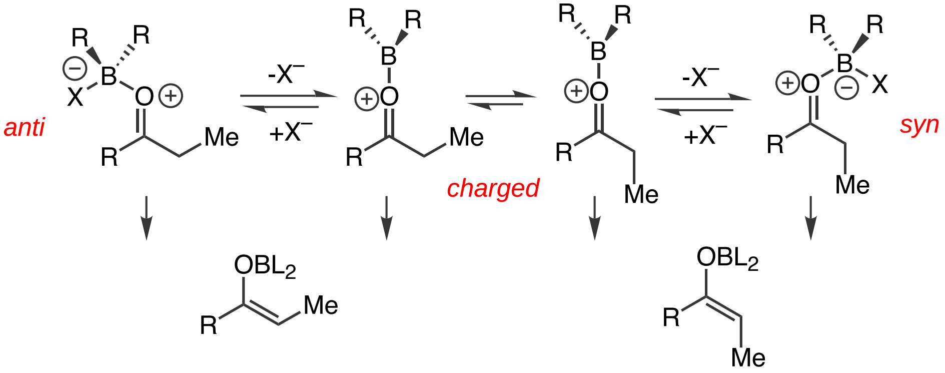
Brown, *J. Org. Chem.* **1993**, *58*, 147-153

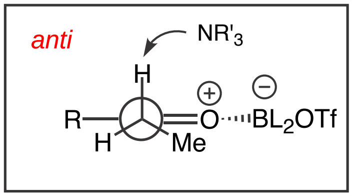


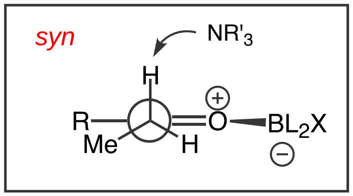
9-BBN-OTf, Et_3N	ratio ~97: 3
Cy_2B-Cl, Et_3N	ratio 21:79
Bu_2B-OTf, Et_3N	ratio ~97: 3

Borane and lutidine or DIPEA form 1:1 complex with L_2B-OTf. Complexation reversible as enolization will occur upon addition of ketone. Less hindered nitrogen bases - pyridine, Dabco, DBU, irreversibly complex with L_2B-OTf.

The Ketone-Boron Complexes as enolate precursors:







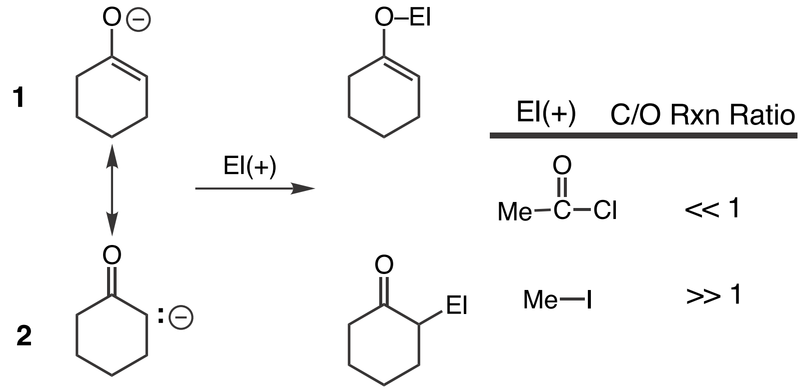
Cy_2BCl-ketone complex may deprotonate through syn complex

R_2BOTf-ketone complex may deprotonate through charged complex with (Z) preference

C versus O Enolate Reactivity & the Hammond Postulate

Question: Why do we generally show enolates reacting with electrophiles at carbon as opposed to oxygen ?? Let's begin the the discussion with an observation:

■ "As electrophile reactivity increases, the percentage of reaction at the enolate oxygen increases." For example, consider the reactions of cyclohexanone enolate with the two electrophiles, methyl iodide and the much more reactive acetyl chloride:



El(+)	C/O Rxn Ratio
$Me-C(=O)-Cl$	<< 1
Me—I	>> 1

■ The very reactive acid chloride gives almost exclusively the O-acylation product while the less reactive methyl iodide affords the alternate C-alkylation product.

These results may be understood in the context of qualitative statements made by Hammond (**The Hammond Postulate**) and Hine (**The Principle of Least Motion**)

The Principle of Least Motion:
"As reactions become more exothermic, the favored reaction becomes that path which results in the least structural (electronic) reorganization."

See Hine in Advances in Phys. Org. Chem. 1977, 15, 1-61

Since the X-ray data clearly support the picture that resonance structure **1** best represents the enolate structure, highly reactive electrophiles will favor O-attack according to Hine's generalization.

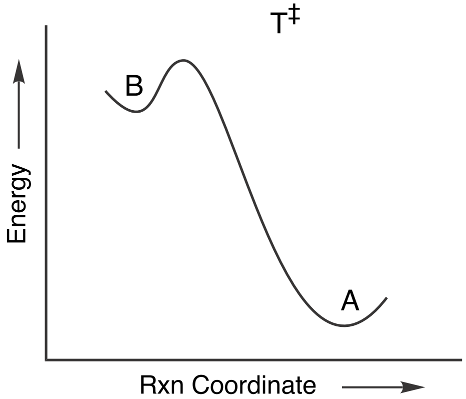
The Hammond Postulate is also relevant to this issue and is broadly used to make qualitative statements about transition state structure.

Hammond, *JACS* **1955**, *77*, 334 (handout)

■ In attempting to grasp the Hammond Postulate, let's consider two extreme reactions, one which is strongly endothermic and one which is strongly exothermic.

Strongly Exothermic Reactions
$\Delta H^\circ > 20$ kcal/mol

$B \longrightarrow A$

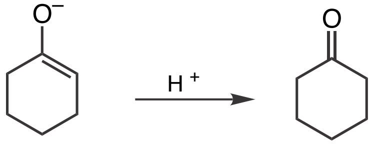


Hammond Postulate
"For strongly exothermic reactions, the transition state T‡ looks like reactant(s) e.g. B."

■ As applied to the enolate-electrophile reaction, for very exothermic reactions, e.g. the reaction with acetyl chloride, the transition state for the process will involve little enolate structural reorganization. Hence in this instance the electrophile heads for the site of highest electron density

Carey & Sundberg: **Part A**; Chapter 4, pp217-220
for discussion of Hammond's Postulate

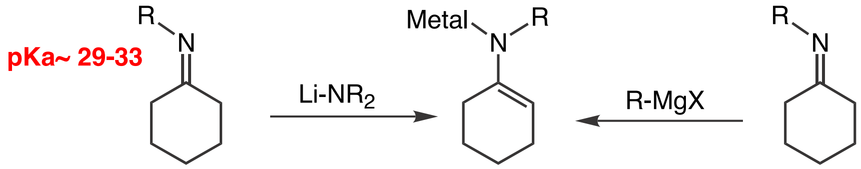
Based upon the above discussion draw a detailed mechanism for the protonation of cyclohexanone enolate.



Enols, Enolates, Enamines & Metalloenamines: Reactivity Hierarchy

■ Metalloenamines:

Imines may be transformed into their conjugate bases (enolate counterparts) with strong bases:

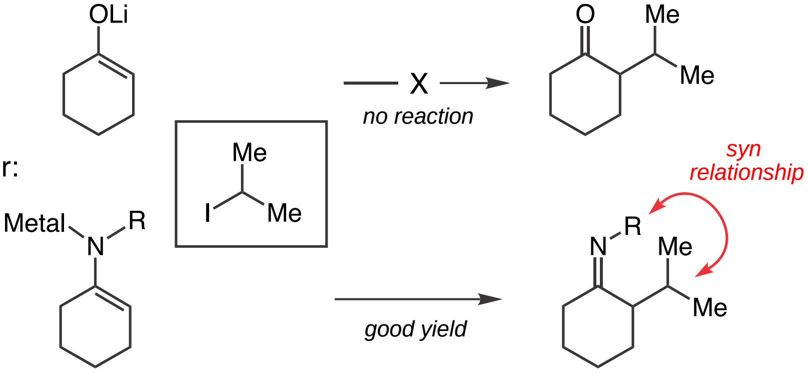


The usual bases employed are either lithium amides (LDA) or Grignard reagents. Note that Grignard reagents do not add to the C=N pi-bond due to the reduced dipole. With this functional group, deprotonation is observed to be the preferred reaction.

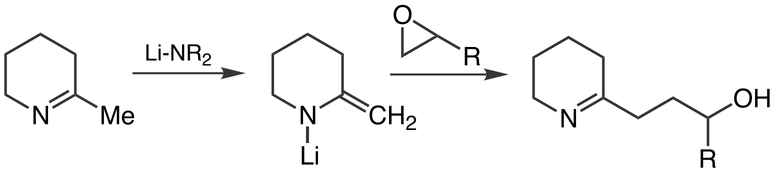
■ When to use a metalloenamine:

Metalloenamines are significantly more nucleophilic than ketone or aldehyde enolates. They are used when less reactive electrophiles are under consideration. For example:

However:

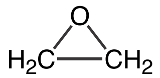


Metalloenamines are reactive enough to open epoxides in good yield. Ketone enolates are only marginally reactive enough for this family of electrophiles.



Decreasing Nucleophilicity - - - - - →

Decreasing Electrophilicity - - - - - →

Nucleophile / Electrophile	C=C–NR$^{\ominus}$	C=C–O$^{\ominus}$	C=C–NR$_2$	C=C–OMe
Br_2, O_3	+	+	+	+
H_3O^+	+	+	+	+
$R{-}\overset{O}{\overset{\|}{C}}{-}Cl$	+	+	+	■
$R{-}\overset{O}{\overset{\|}{C}}{-}H$	+	+	+	■
$R{-}\overset{O}{\overset{\|}{C}}{-}R$	+	+	▨	■
Me—I	+	+	▨	■
$R{-}\overset{O}{\overset{\|}{C}}{-}OR$	+	+	■	■
	+	▨	■	■
Me_2CH—I	+	▨	■	■
$R{-}\overset{O}{\overset{\|}{C}}{-}NR_2$	■	■	■	■

■ Nature uses enamines, "stabilized" enolates, and enol derivatives in C–C bond constructions extensively.

Quote for the Day

"640K ought to be enough for anybody." Bill Gates, 1981

Today's astrological forecast, Boston Globe, Monday, November 10, 2003

Capricorn (Dec 22–Jan 19th)

"Be prepared for someone to try to steal your ideas or take credit for your work. You're on to something tangible and you need to act fast."

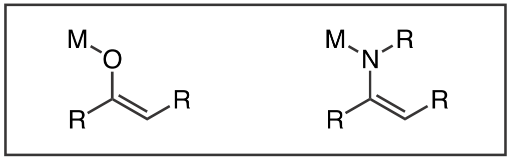
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 24

Enolates & Metalloenamines-2



- Introduction and General Trends
- Enolate Alkylation: Electronic & Steric Control Elements
- Enolate Alkylation: Unusual Cases
- Chiral Amide Enolates
- Chiral Ester Enolates
- Chiral Imide Enolates
- Chiral Metalloenamines

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Monday,
November 10, 2003

Assigned Journal Articles

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983). **(handout)**

"Stereoselective Alkylation Reactions of Chiral Metal Enolates".
D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984). **(handout)**

Other Useful References

"Advances in Asymmetric Enolate Methodology" Arya, Qin, *Tetrahedron* **2000**, *56*, 917-947 **(pdf)**

"Recent Advances in Dianion Chemistry". C. M. Thompson and D. L. C. Green *Tetrahedron*, **47**, 4223 (1991).

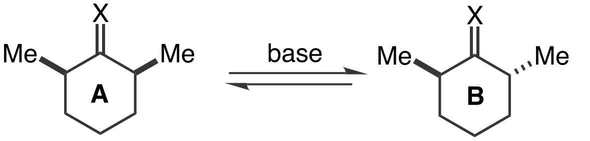
The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (1982).

"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res*. **21**, 121 (1988).

"Keto-Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution". Keeffe, Kresge, and Schepp *JACS*, 112, 4862 (1990).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (1984).

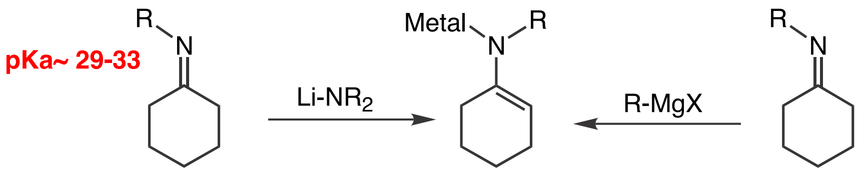
Explain why **A** is favored for X = O while **B** is favored for X = NNHR



Enols, Enolates, Enamines & Metalloenamines: Reactivity Hierarchy

■ Metalloenamines:

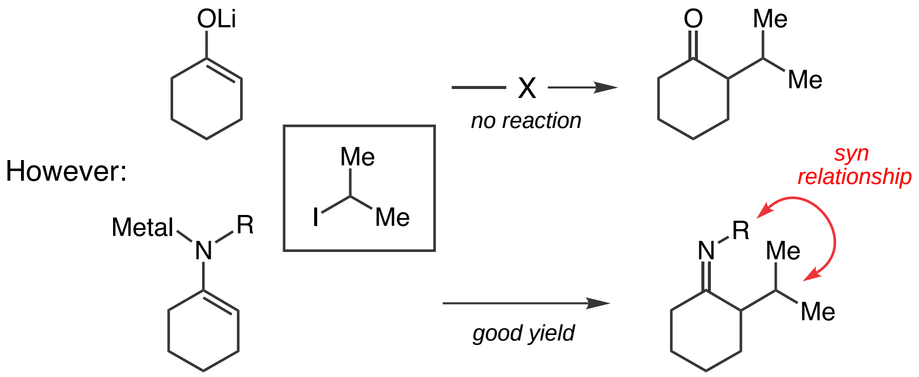
Imines may be transformed into their conjugate bases (enolate counterparts) with strong bases:



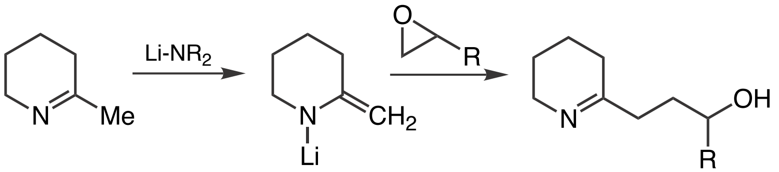
The usual bases employed are either lithium amides (LDA) or Grignard reagents. Note that Grignard reagents do not add to the C=N pi-bond due to the reduced dipole. With this functional group, deprotonation is observed to be the preferred reaction.

■ When to use a metalloenamine:

Metalloenamines are significantly more nucleophilic than ketone or aldehyde enolates. They are used when less reactive electrophiles are under consideration. For example:



Metalloenamines are reactive enough to open epoxides in good yield. Ketone enolates are only marginally reactive enough for this family of electrophiles.



Decreasing Nucleophilicity ⇢

Decreasing Electrophilicity ⇣

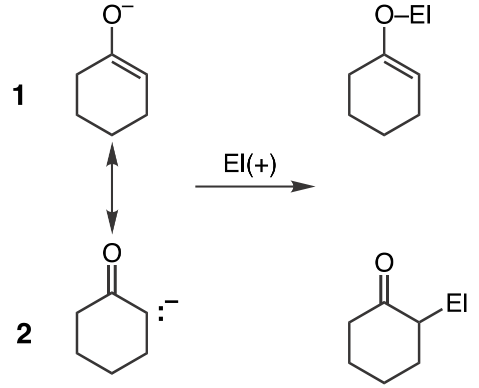
Nucleophile / Electrophile	$C{=}C{-}NR^{-}$	$C{=}C{-}O^{-}$	$C{=}C{-}NR_2$	$C{=}C{-}OMe$
Br_2, O_3	+	+	+	+
H_3O^+	+	+	+	+
$R{-}\overset{O}{\overset{\Vert}{C}}{-}Cl$	+	+	+	■
$R{-}\overset{O}{\overset{\Vert}{C}}{-}H$	+	+	+	■
$R{-}\overset{O}{\overset{\Vert}{C}}{-}R$	+	+	▒	■
Me—I	+	+	▒	■
$R{-}\overset{O}{\overset{\Vert}{C}}{-}OR$	+	+	■	■
O H_2C——CH_2	+	▒	■	■
Me_2CH—I	+	▒	■	■
$R{-}\overset{O}{\overset{\Vert}{C}}{-}NR_2$	■	■	■	■

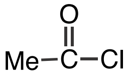
■ Nature uses enamines, "stabilized" enolates, and enol derivatives in C–C bond constructions extensively.

C versus O Enolate Reactivity: Hine "Least Motion Principle"

Question: Why do we generally show enolates reacting with electrophiles at carbon as opposed to oxygen ?? Let's begin the the discussion with an observation:

■ "As electrophile reactivity increases, the percentage of reaction at the enolate oxygen increases." For example, consider the reactions of cyclohexanone enolate with the two electrophiles, methyl iodide and the much more reactive acetyl chloride:



El(+)	C/O Rxn Ratio
 $\mathrm{Me{-}\overset{\overset{\large O}{\|}}{C}{-}Cl}$	<< 1
Me—I	>> 1

■ The very reactive acid chloride gives almost exclusively the O-acylation product while the less reactive methyl iodide affords the alternate C-alkylation product.

These results may be understood in the context of qualitative statements made by Hammond (**The Hammond Postulate**) and Hine (**The Principle of Least Motion**)

The Principle of Least Nuclear Motion:

"As reactions become more exothermic, the favored reaction becomes that path which results in the least structural (electronic) reorganization."

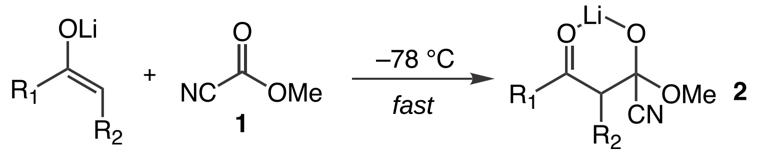
Hine in Advances in Phys. Org. Chem. 1977, 15, 1-61 (handout)

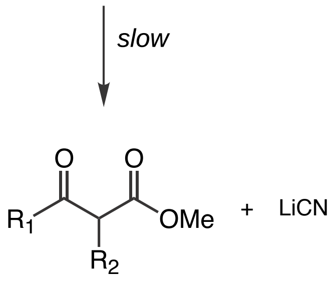
Since the X-ray data clearly support the picture that resonance structure **1** best represents the enolate structure, highly reactive electrophiles will favor O-attack according to Hine's generalization.

See reinforcing examples on the accompanying page.

C versus O Enolate Reactivity: Enolate Acylation

■ **Kinetic C–Acylation of ketone enolates can be carried out:**





Enolate acylation with **1** is fast

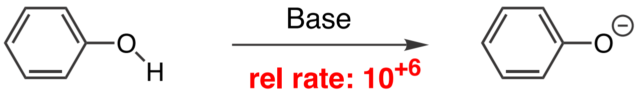
Intermediate **2** breaks down to product more slowly than the acylation step

Under these conditions, proton transfer from product to enolate does not occur.

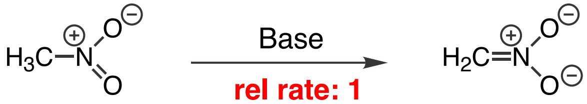
See accompanying "Acylation Handout"

■ **Kinetic Acidities nicely illustrate LNM Principle: *Lecture 18"**

pKa(H_2O)
~10

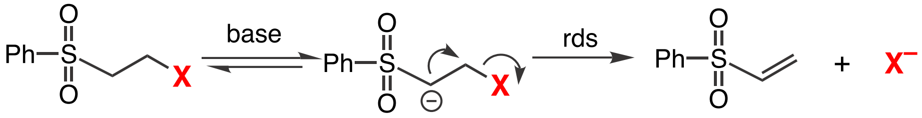


pKa(H_2O)
~10

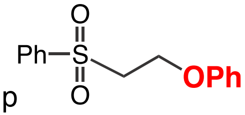


Proton kinetically controlled transfers from C-H Bonds are slow due to the extensive reorganization required in conjugate base.

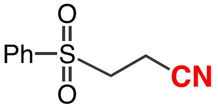
■ **Leaving Group Ability:** Stirling, *Chem. Commun.* **1975**, 940



The greater the structural reorganization of the leaving group during E1cb elimination, the slower the rate of elimination.



krel = 1
pKa = 10



krel = <10^{-8}
pKa = 9.5

C versus O Enolate Reactivity: "The Hammond Postulate"

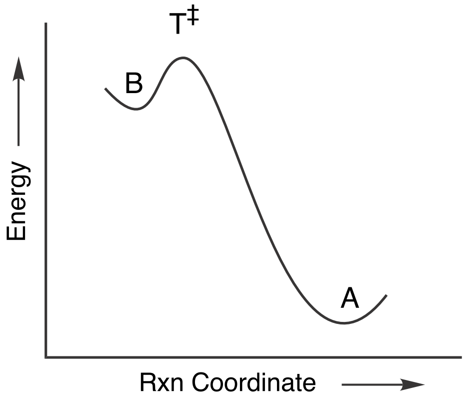
The Hammond Postulate is also relevant to this issue and is broadly used to make qualitative statements about transition state structure.

Hammond, *JACS* **1955**, *77*, 334

■ In attempting to grasp the Hammond Postulate, let's consider two extreme reactions, one which is strongly endothermic and one which is strongly exothermic.

Strongly Exothermic Reactions
ΔH° > –20 kcal/mol

$B \longrightarrow A$

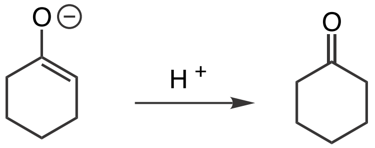


Hammond Postulate
"For strongly exothermic reactions, the transition state T‡ looks like reactant(s) e.g. B."

■ As applied to the enolate-electrophile reaction, for very exothermic reactions, e.g. the reaction with acetyl chloride, the transition state for the process will involve little enolate structural reorganization. Hence in this instance the electrophile heads for the site of highest electron density

Carey & Sundberg: **Part A**; Chapter 4, pp217-220
for discussion of Hammond's Postulate

Based upon the above discussion draw a detailed mechanism for the protonation of cyclohexanone enolate.

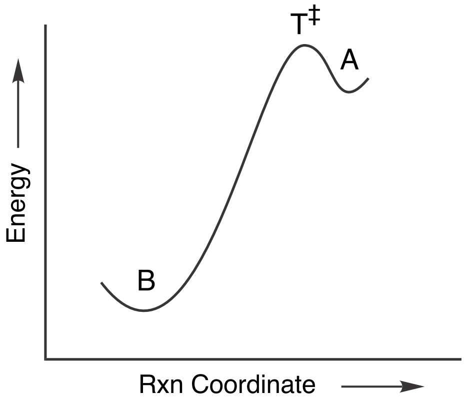


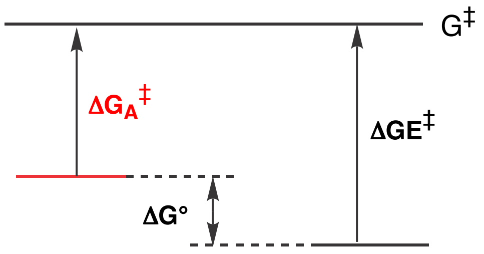
Strongly Endothermic Reactions
ΔH° > +20 kcal/mol

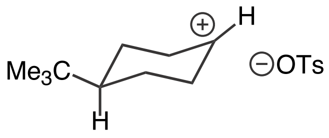
$B \longrightarrow A$

S_N1 reactions are typical examples of strongly endothermic processes

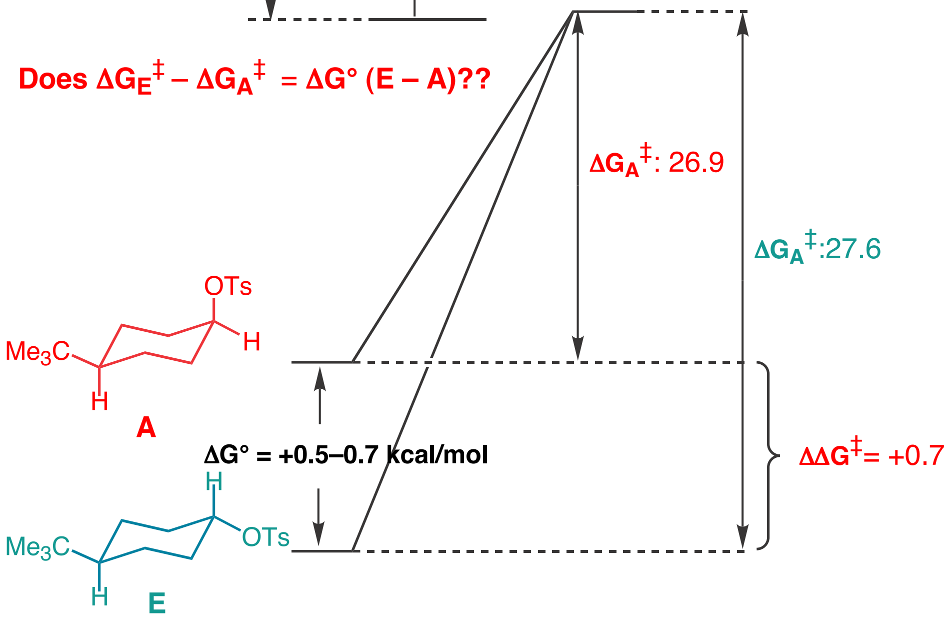
Hammond: "The transition state will look like products."







Does $\Delta G_E^‡ – \Delta G_A^‡ = \Delta G°$ (E – A)??

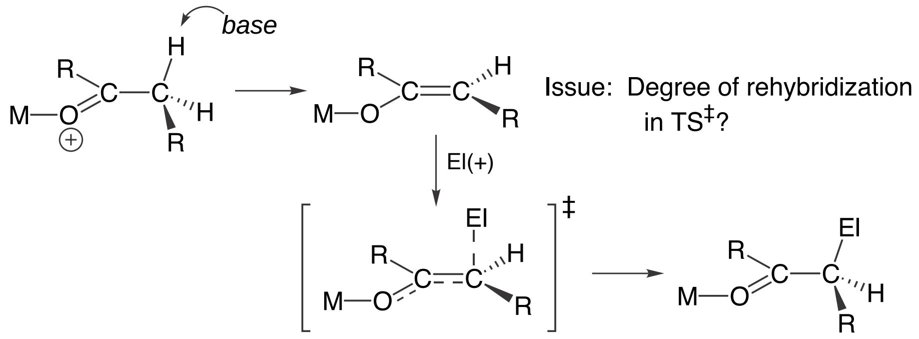


Wnstein & Holness, *JACS* **1955**, *55*, 5562

Review Evans, D. A. *Stereoselective Alkylation Reactions of Chiral Metal Enolates.*; Morrison, J. D., Ed.; AP: New York, 1984; Vol. 3, pp 1-110.

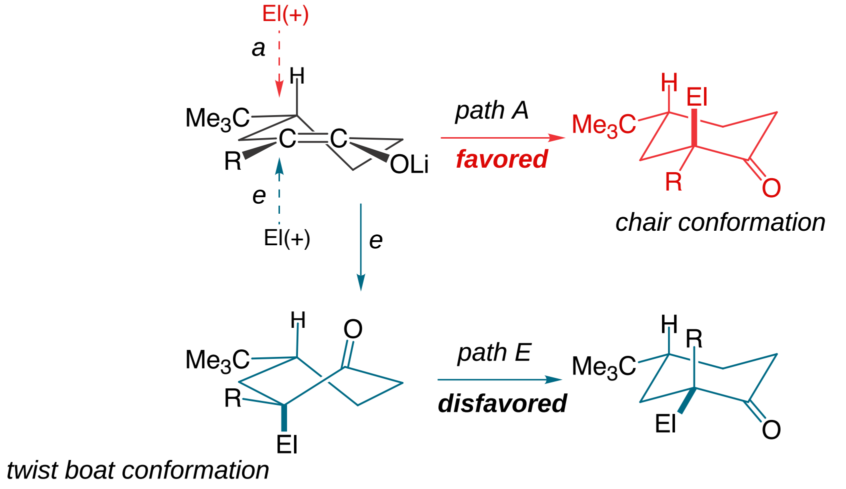
Stereoelectronic Issues

- Enolization: Breaking C–H bond must overlap with $\pi*$ C–O in TS‡
- Alkylation: Forming C–El bond must overlap with $\pi*$ C–O in TS‡



Issue: Degree of rehybridization in TS‡?

Cyclohexanone Enolate:



chair conformation

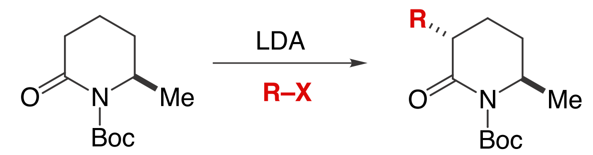
twist boat conformation

Metal	R-substituent	Electrophile	Ratio, a:e
Li	Me	CD_3I	70:30
Li	CO_2Me	Me-I	83:17

Chair vs boat geometries not stongly reflected in diastereomeric TS‡s. The transition states is early and enolate-like.

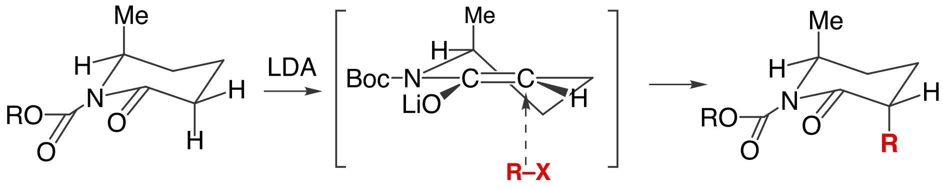
Examples where stereoelectronic factors are dominant

Pilli, *Tetrahedron*, **1999**, *55*, 13321

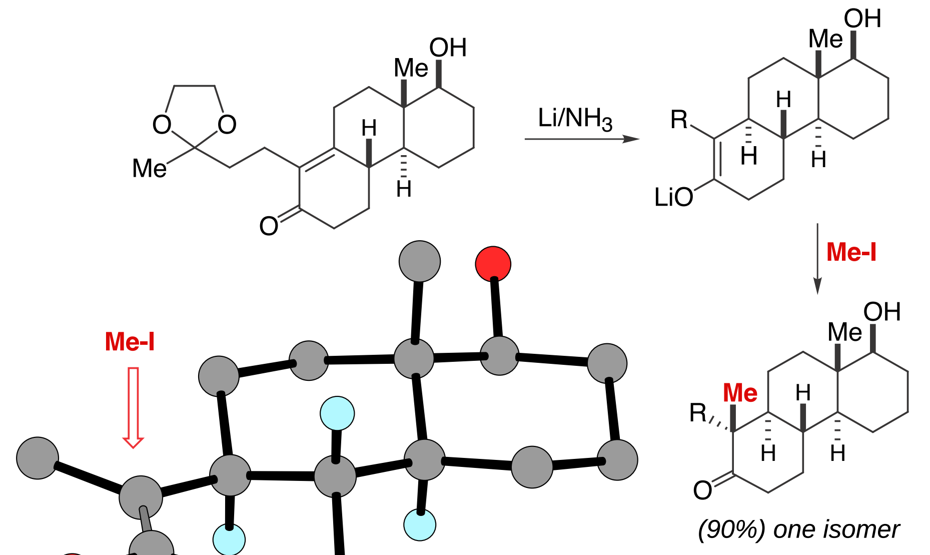


R–X	ratio
Bn–Br	>99:1
Allyl–Br	93:7

good illustration of the impact of allylic strain



The C_{19} Angular Methyl Group in the steroid nucleus



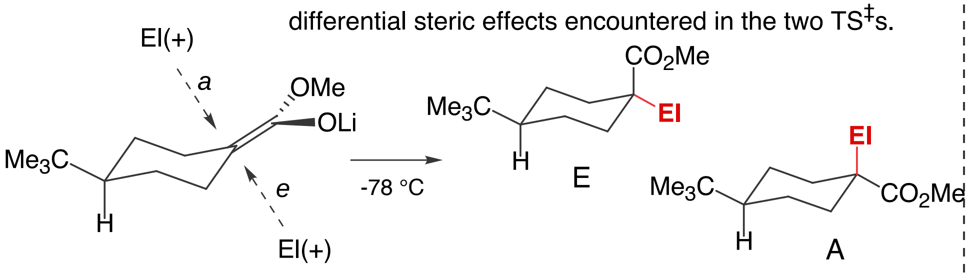
(90%) one isomer

The enolate (Chem 3D)

Enolate Alkylation: Steric Control Elements

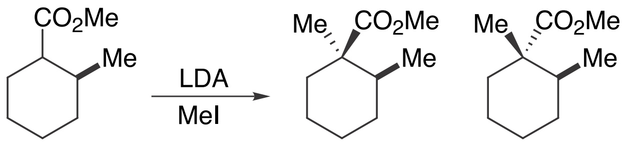
Steric Effects

In this case, both e and a paths are stereoelectronically equivalent. Diastereoselectivity is now determined by the differential steric effects encountered in the two TS‡s.

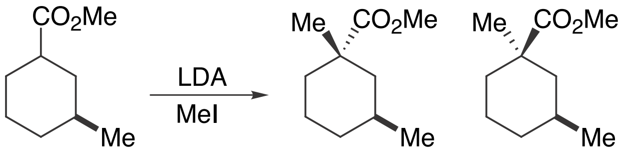


Electrophile	Ratio, E:A
Me-I	84:16
n-Bu-Br	87:13

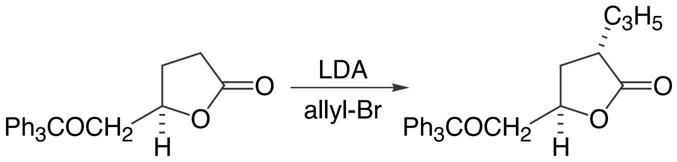
Representative cases



Ratio, 80 : 20

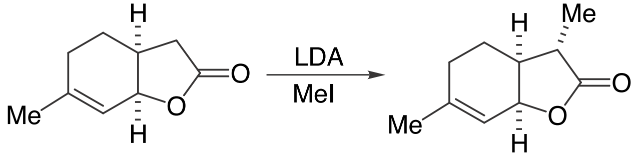


Ratio, 90 : 10



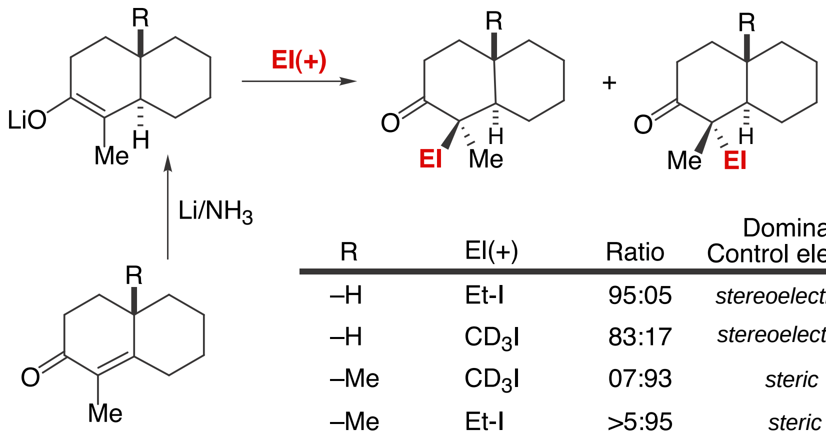
Ratio, >97 : 3

diastereoselectivity depends stongly on O-protecting group

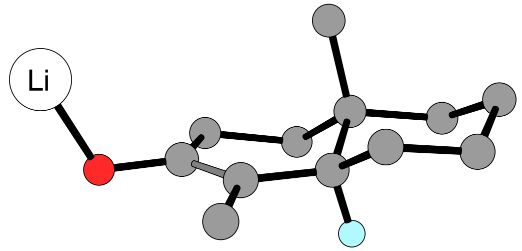


Ratio, >97 : 3

Cases with Opposed steric & electronic effects

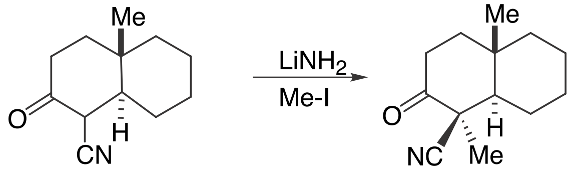


R	El(+)	Ratio	Dominant Control element
–H	Et-I	95:05	*stereoelectronic*
–H	CD_3I	83:17	*stereoelectronic*
–Me	CD_3I	07:93	*steric*
–Me	Et-I	>5:95	*steric*



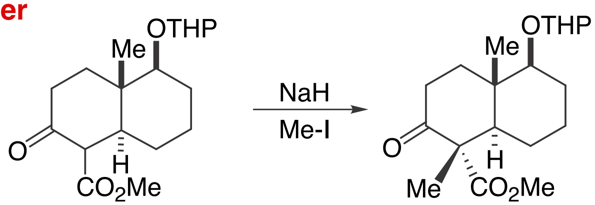
The enolate R = Me (Chem 3D)

Based on above data, this case is reasonable:



(58%) >90 : 10

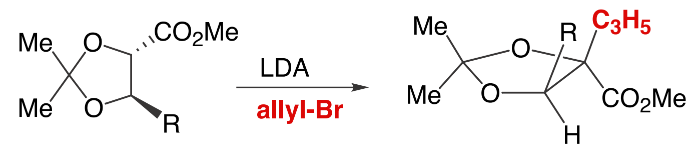
However



(67%) 93 : 7

Enolate Alkylation: Unusual Cases

Cases which do not appear to give the expected product based on the analysis of steric effects



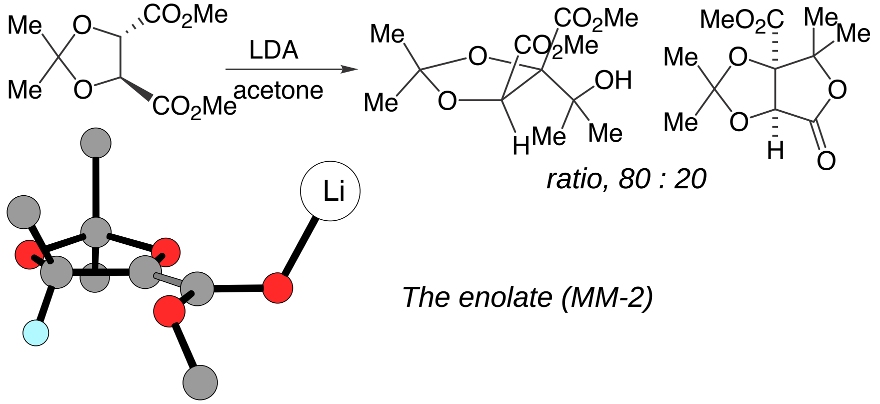
R = Me, Et, CO_2Me

≥ 88 : 12

Seebach, *Angew. Chem. Int. Ed* **1981**, *20*, 1030

Ladner, *Angew. Chem. Int. Ed* **1982**, *21*, 449

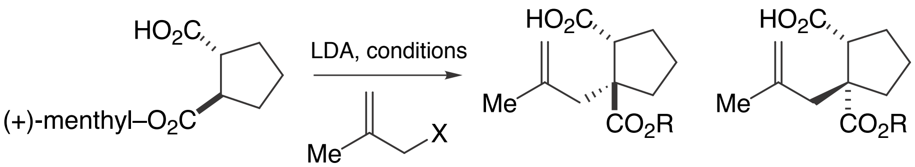
- **However:**

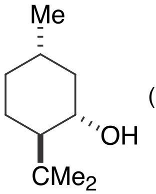


ratio, 80 : 20

The enolate (MM-2)

Here is another example of a contrasteric alkylation



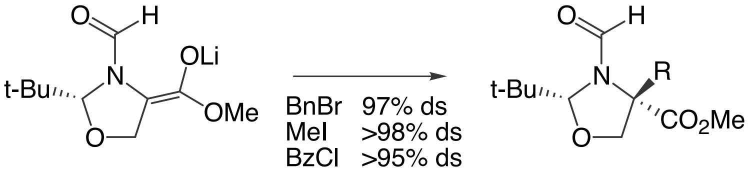


(+)-menthol

X	conditions	Ratio
R-Cl	THF, 23 °C	80:20
R-Br	THF-HMPA -78→-20 °C	02:98

K. Yamada, *Organic Synthesis Past Present, and Future*, p 525

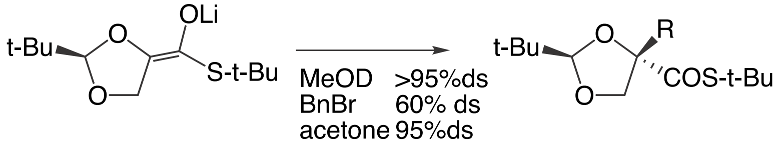
Sterically Expected Results:



BnBr 97% ds
MeI >98% ds
BzCl >95% ds

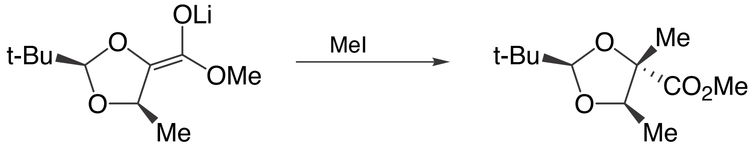
Seebach, *Helv. Chim. Acta* **1987**, *70*, 1194.

Contrasteric relatives:

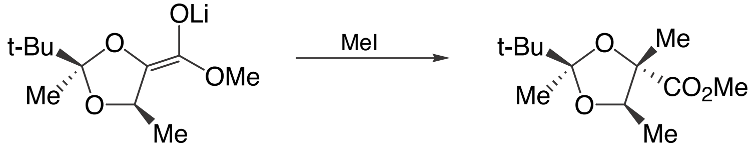


MeOD >95%ds
BnBr 60% ds
acetone 95%ds

Seebach, *Helv. Chim. Acta* **1987**, *70*, 1194.



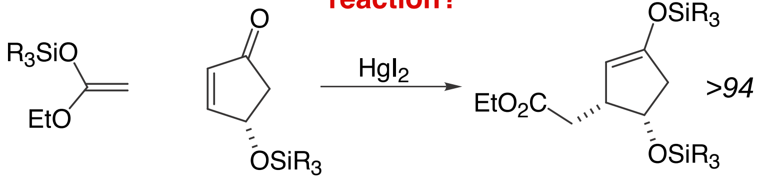
70 : 30



>95 : 5

Ladner, *Chem. Ber.* **1983**, *116*, 3413-3426.

Those factors defining olefin face selection are currently being defined: Would you have predicted the outcome of the following reaction?



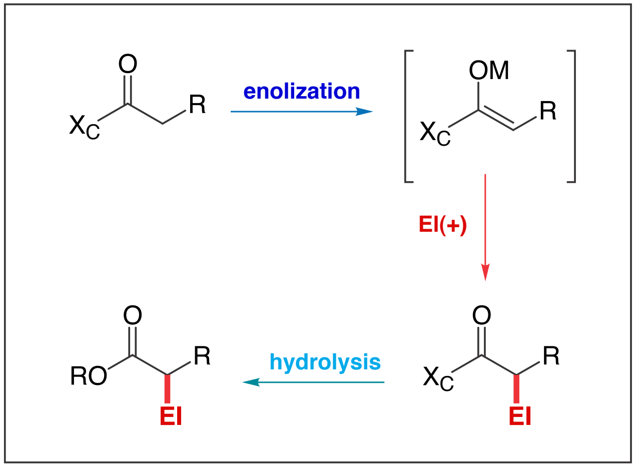
>94 : 6

Danishefsky *J. Org. Chem.* **1991**, *56*, 387

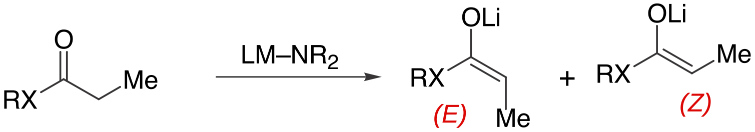
Chiral Enolate Design Requirements Circa 1978

Overall enantioselection will be the sum total of the defects introduced through:

- **Enolization selectivity**
- **Enolate-electrophile face selectivity**
- **Racemization attendant with X_c removal**

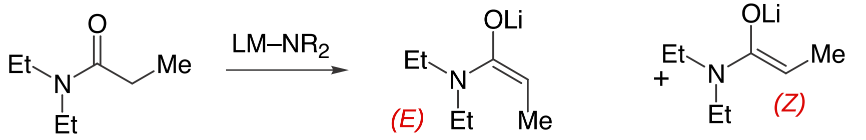


Enolization selectivity: Ester-based chiral controllers X_C limited by enolization selectivity (Lecture 23)

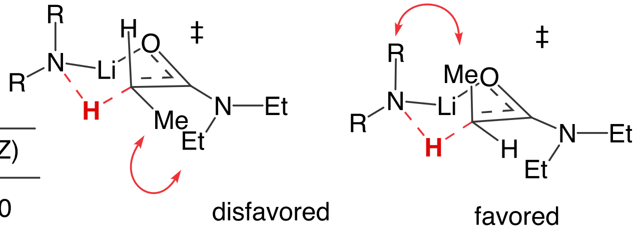


Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5

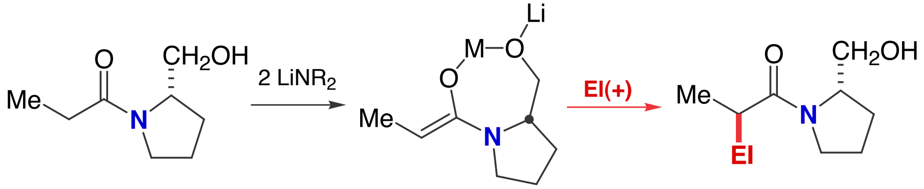
Enolization selectivity: Amide-based controllers X_C limited by enolization selectivity (Lecture 22)



Base	Ratio, (E):(Z)
LDA (THF)	0 : 100
s-BuLi (THF)	25 : 75



Amide Based Chiral Auxiliaries

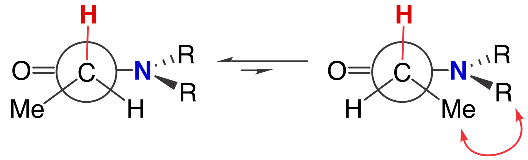


With Takacs, *Tetrahedron Lett.* **1980**, 4233

diastereoselection Ca 95 %

Allylic Strain controls Enolate Geometry:

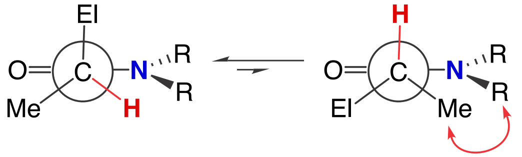
strongly favored



strongly disfavored

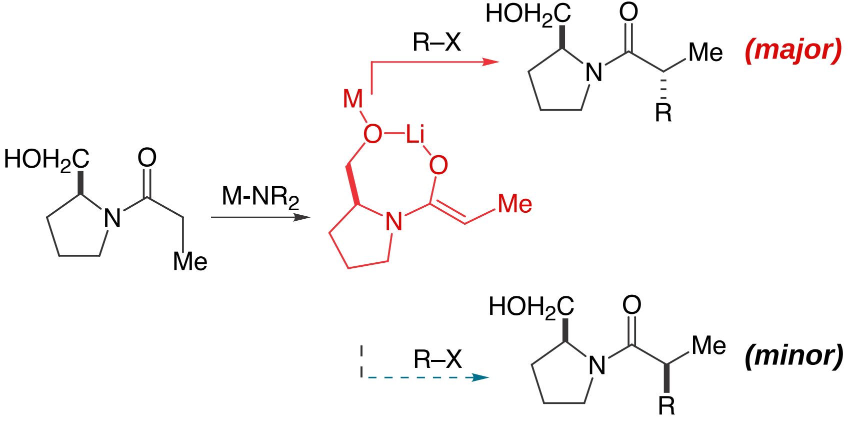
Allylic Strain Prevents Product Enolization:

strongly favored

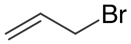


strongly disfavored

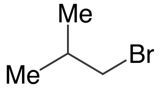
Chiral Amide Enolates



Evans, Takacs,
Tet. Lett. **1980**, *21*, 4233-4236

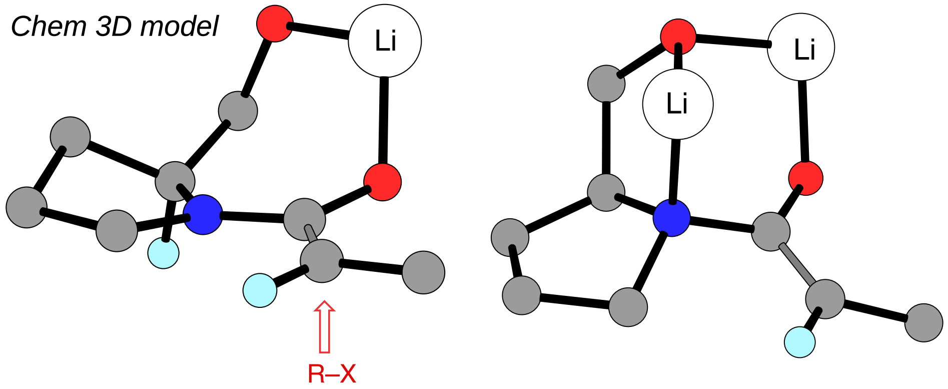


96:4 (98%)

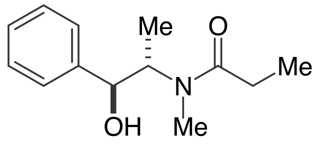


98:2 (84%)

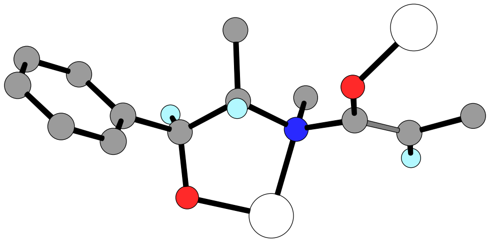
Chem 3D model



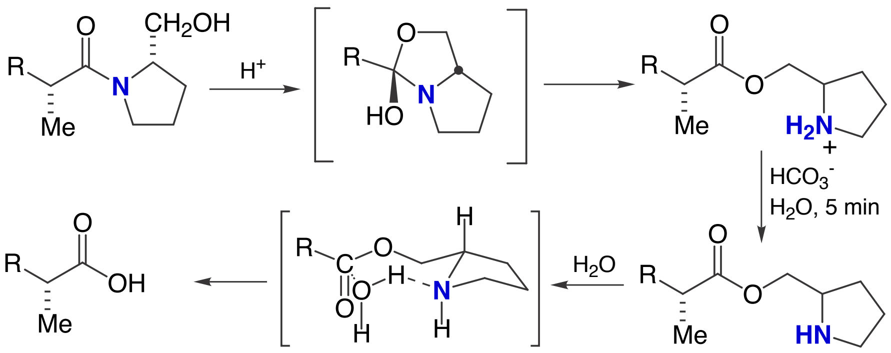
The nature of enolate chelation is ambiguous. Nitrogen chelation is a real possibility.



Myers, *JACS* **1997**, *119*, 6496



Amide Hydrolysis

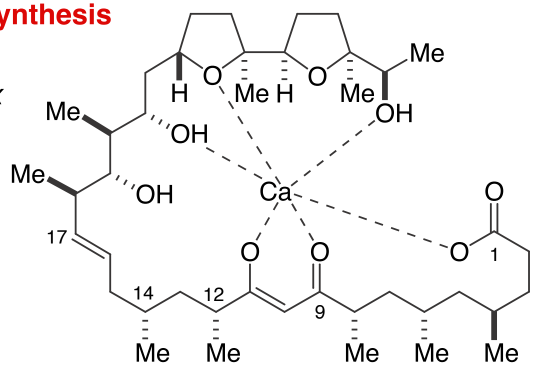


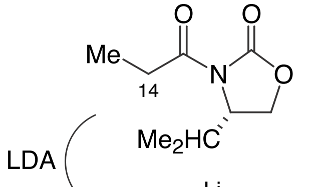
intramoleclar general base catalysis

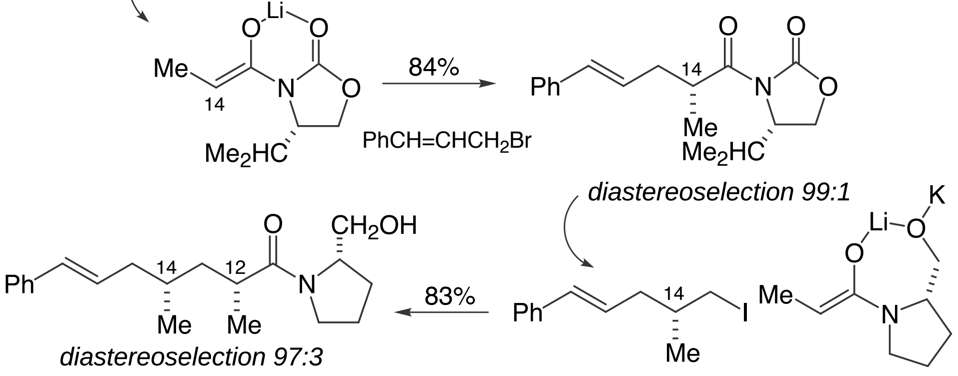
Applications in Ionomycin synthesis

Ionomycin Calcium Complex

JACS **1990,** *112*, 5290-5313





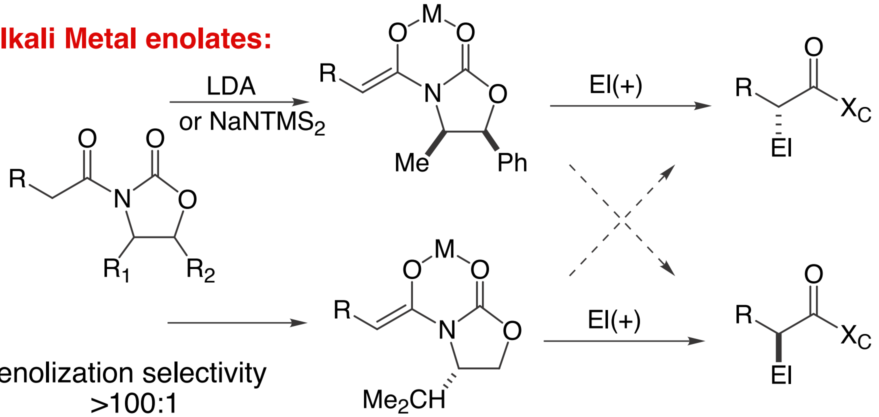


diastereoselection 99:1

diastereoselection 97:3

Enolate Alkylation: Chiral Imide Enolates

Alkali Metal enolates:



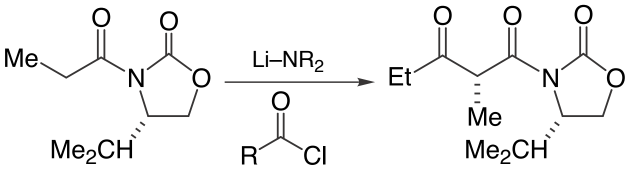
enolization selectivity
>100:1

M = Li, THF < 0 °C
M = Na, THF -78 to 0 °C

	Alkyl Halide	Ratio
	$ArCH_2Br$	50-120 : 1
	$CH_2C{=}CHCH_2Br$	50 : 1
	$ArCH_2OCH_2Br$	50 : 1
marginal reaction	CH_3CH_2I	25 : 1
	CH_3I	13 : 1

JACS. **1982**,*104*, 1737.

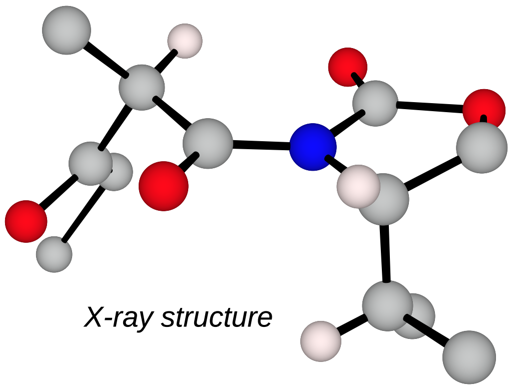
Enolate Acylation



JACS ***1984****, 106, 1154.*

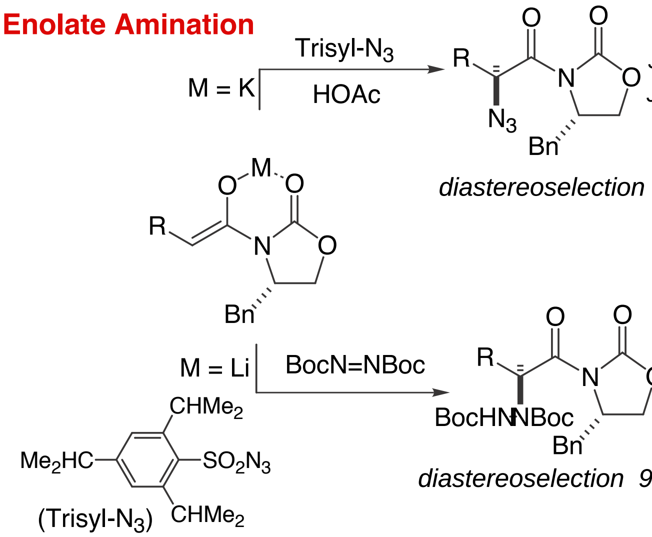
Diastereoselection ~ 97 : 3

New stereocenter not lost through enolization



X-ray structure

Enolate Amination



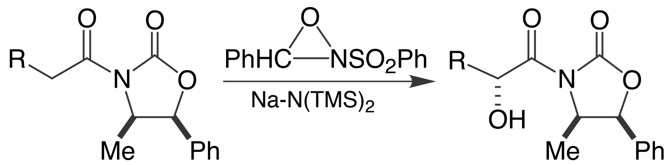
JACS **1987**,*109*, 6881.
JACS **1990**,*112*, 4012-4030

diastereoselection 91-99+ %

JACS **1986**,*108*, 3695.
Tet. **1988**, *44*, 5525-40

diastereoselection 97-99$^+$ %

Enolate Hydroxylation



Na enolate is required.
Why?

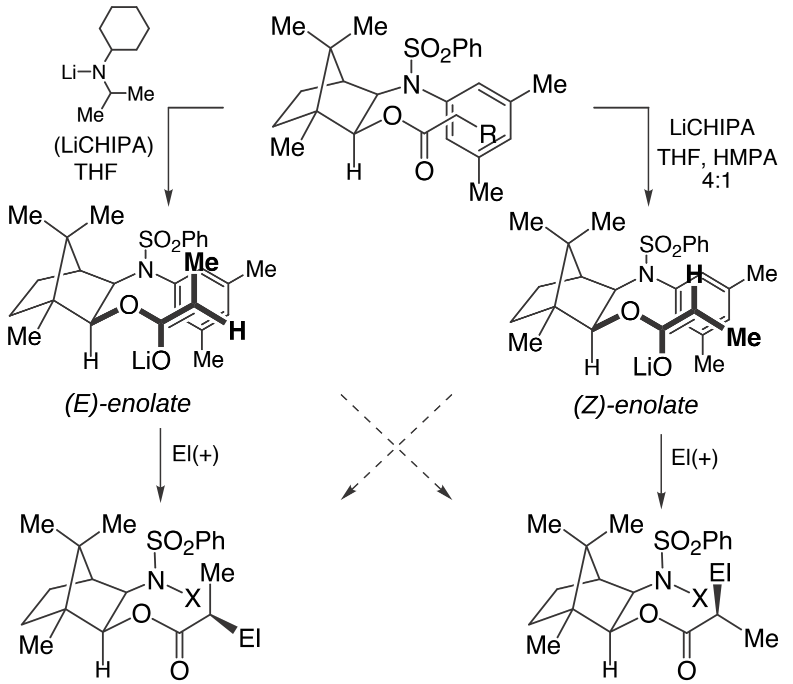
Imide (R)	Ratio	Yield *
$PhCH_2$-	94 : 6	86 %
$CH_2{=}CHCH_2$-	95 : 5	91 %
$MeO_2CCH_2CH_2CH_2$-	96 : 4	68 %
Ph-	90 : 10	77 %
Me_3C-	>99 : 1	94 %

JACS. **1985**,*107*, 4346.

For all indicated rxns, as the R on the enolate grp increases in size enolate-El face selectivity increases. Explain.

Chiral Ester Enolates

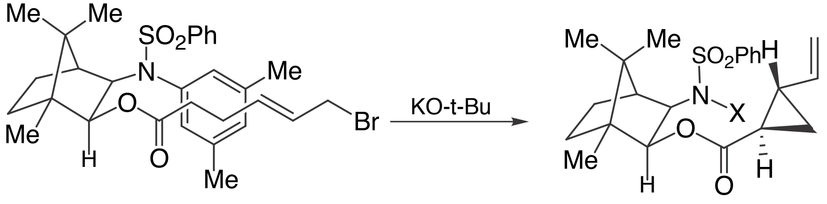
Helmchen, *Angew. Chem. Int.Ed.* **1981**, *20*, 207-208



enolate	El(+)	Ratio
(E)	n-$C_{14}H_{29}$–I	98.5:1.5
(Z)	n-$C_{14}H_{29}$–I	06:94

enolate contamination

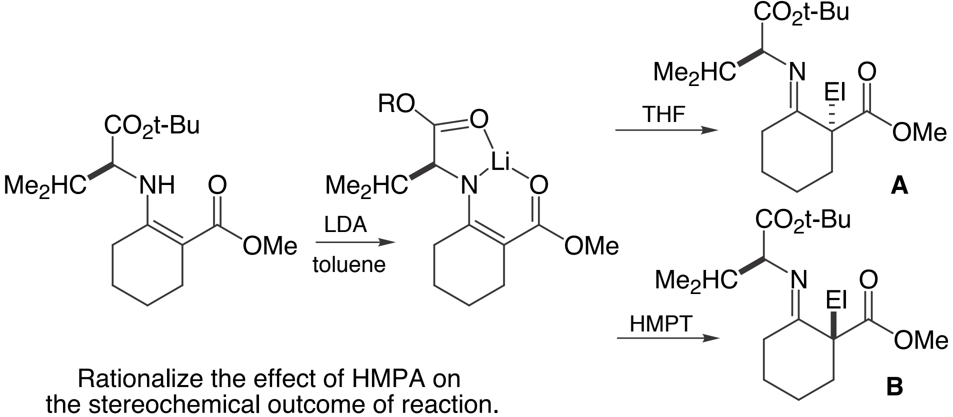
Helmchen, *Angew. Chem. Int.Ed.* **1984**, *23*, 60-61
Helmchen, *Tet. Lett.* **1983**, *24*, 1235-1238
Helmchen, *Tet. Lett.* **1983**, *24*, 3213-3216



Ratio, 93:7 (74%)

Helmchen, *Tet. Lett.* **1985**, *26*, 3319-3322

Chiral β-Keto Ester Enolates

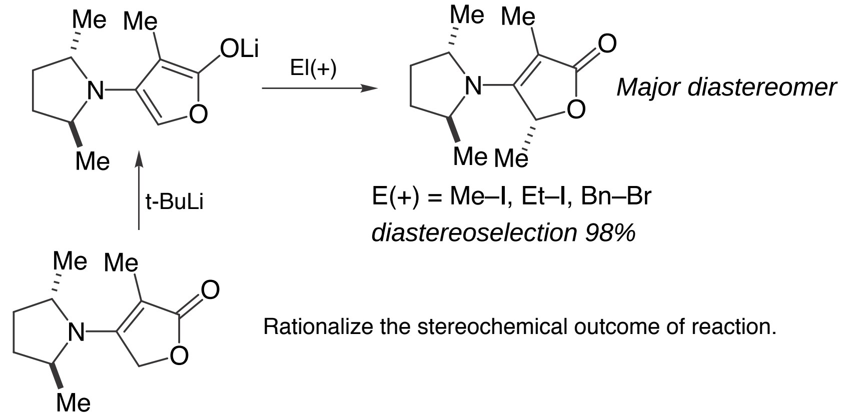


Rationalize the effect of HMPA on
the stereochemical outcome of reaction.

El(+)	addend	Yield	Ratio (A:B)
Me–I	THF	63%	96:04
Me–I	HMPT	57%	01:99
Bn-Br	THF	48%	99:01
Bn-Br	HMPT	77%	15:85

Koga, *JACS* **1984**, *106*, 2718-2719

Chiral β-Keto Ester Dienolates



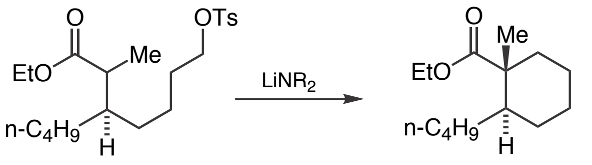
Major diastereomer

E(+) = Me–I, Et–I, Bn–Br
diastereoselection 98%

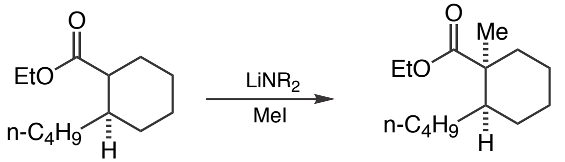
Rationalize the stereochemical outcome of reaction.

Schlessinger, *Tet. Lett.* **1988**, *29*, 1489-1492

Allylic Strain & Enolate Diastereoface Selection

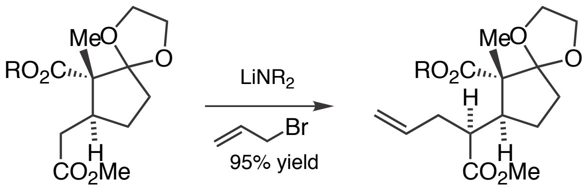


diastereoselection 98:2



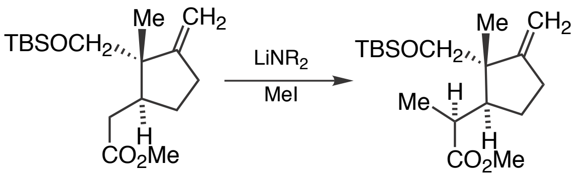
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.



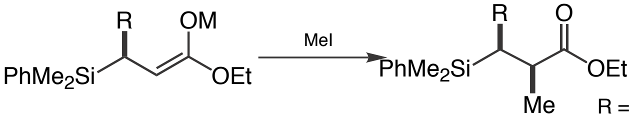
"one isomer"

G. Stork & Co-workers, *Tetrahedron Lett*. **1987**, *28*, 2088.



"one isomer"

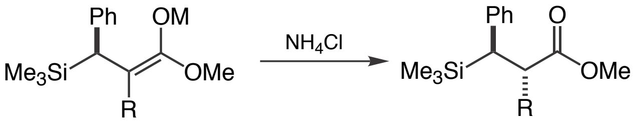
T. Money & Co-workers, *Chem. Commun*. **1986**, 288.



R = Me: *diastereoselection 99:1*

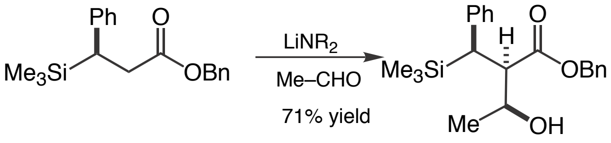
R = Ph: *diastereoselection 97:3*

I. Fleming & Co-workers, *Chem. Commun*. **1984**, 28.



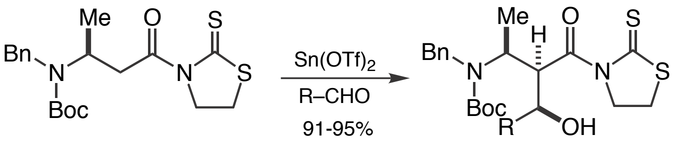
R-substituent	*diastereoselection*
R = Me	87:13
R = Et	80:20
R = $CHMe_2$	40:60 major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun*. **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun*. **1984**, 904.



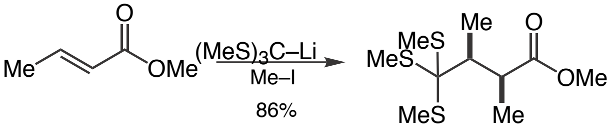
diastereoselection 90:10 at C_3
one isomer at C_2

I. Fleming & Co-workers, *Chem. Commun*. **1986**, 1198.



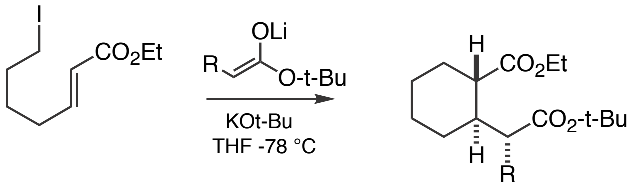
diastereoselection >95%

T. Mukaiyama & Co-workers, *Chem. Letters* **1986**, 637



diastereoselection 99:1

K. Koga & Co-workers, *Tetrahedron Letters* **1985**, *26*, 3031.



R = H: one isomer
R = Me: > 15 :1

Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, *26*,1723.

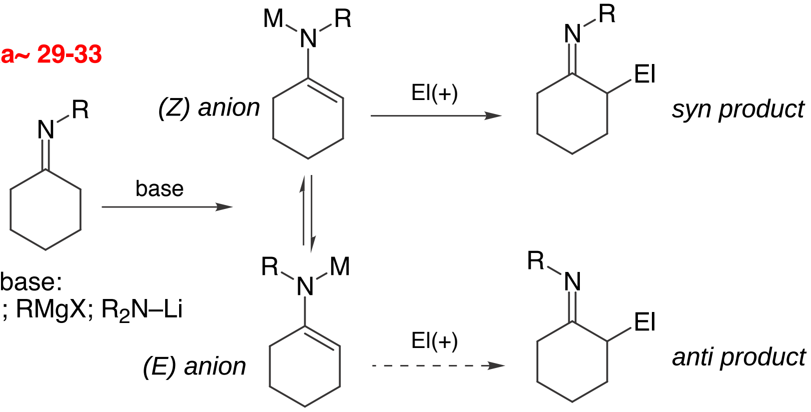
Seminal Paper: Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

Reviews:

Martin in *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.16, pp 475-502
Whitesell *Synthesis*, **1983**, 517-535
Bregbreiter in *Asymmetric Synthesis*, **1983**; Vol 2, Chapter 9, pp 243-273
Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

Generation & Structure:

pKa~ 29-33



The base:
R–Li; RMgX; R_2N–Li

Acidity Measurements: (Streitwiser, *JOC* **1991**, *56*, 1989; Fraser, *ibid*. **1985**, *50*, 3234):

Kinetic product geometry strongly favors the *syn* isomer (>99%) (Fraser)

Fraser, *JACS* ***1978***, *100*, 7999
Fraser, *Chem. Commun.* ***1979***, 47

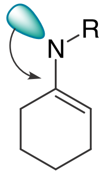
Solid State & Solution Structure:

X-ray structure reveals the following:

❒ Anion geometry is (Z)
❒ For M = Li, anion is delocalized rather than localized as pictured

Collum, *JACS* ***1984***, *106*, 4865-4869
Collum, *JACS* ***1985***, *107*, 2078-2082
Collum, *JACS* ***1986***, *108*, 3415-3422
Collum, *JACS* ***1993***, *115*, 789-790

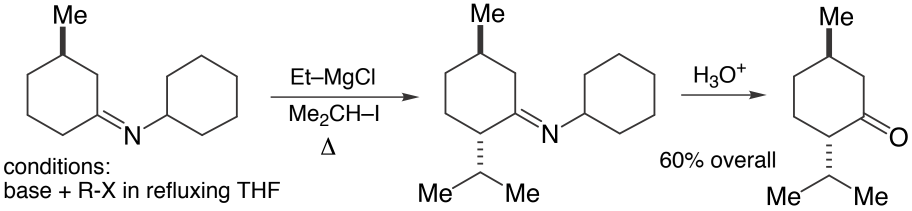
Geometry Rationalization:



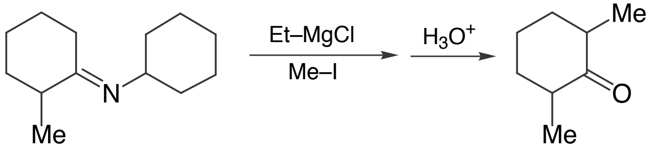
nonbonding N-lone pair may be stabilized by delocalizatin into antibonding orbital of C=C.

Remember, (Z) geometry also favored for enol ethers

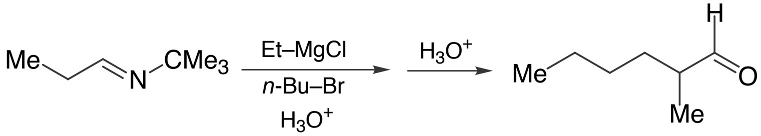
Representative Reactions:



conditions:
base + R-X in refluxing THF



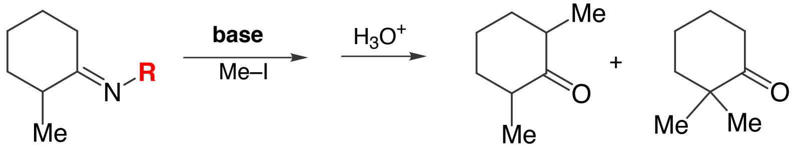
83% overall



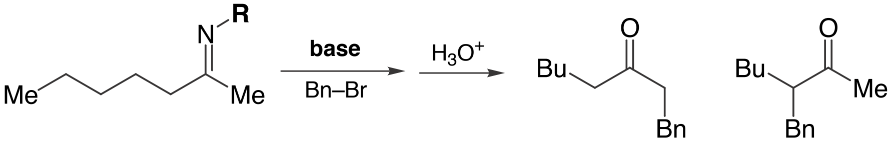
60% overall

Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

Nature of N-substituent, base, and solvent additive can play a role in deprotonation regioselectivity: Hosomi, JACS, 1982, 104, 2081-2082

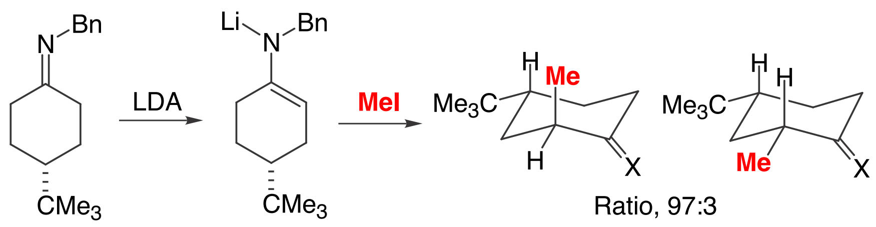


R	base	ratio
–cyclohexyl	*s*-BuLi	10:90
$-NMe_2$	*s*-BuLi	100:0



	R	base	ratio
	–cyclohexyl	*s*-BuLi	74:26
+ 1 equiv HMPA	–cyclohexyl	*s*-BuLi	100:0

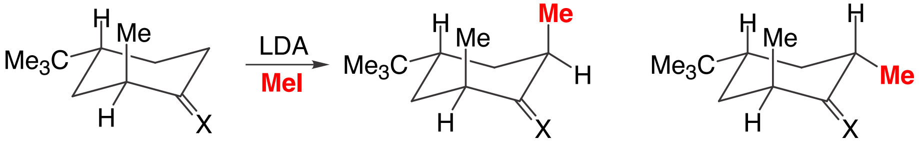
Stereoelectronic Issues:



Ratio, 97:3

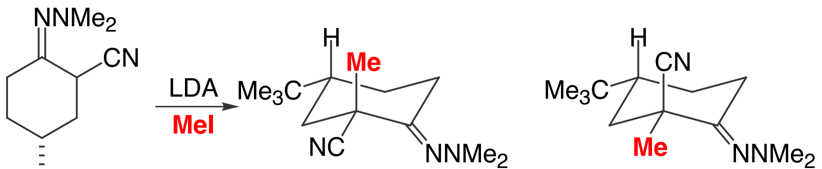
Fraser, *JACS* ***1978***, *100*, 7999 **(handout)**

Tendency for axial-chair alkylation is significantly greater that for ketones

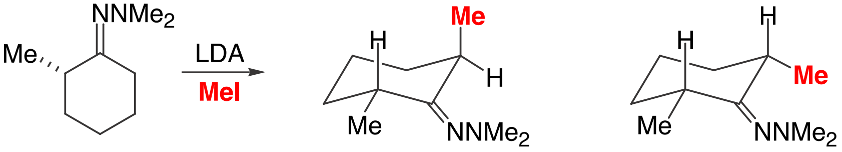


Fraser, *JACS* ***1978***, *100*, 7999 **(handout)**

X	Ratio
X = N-Bn	94:06
X = O	60:40



Ratio, 96:04



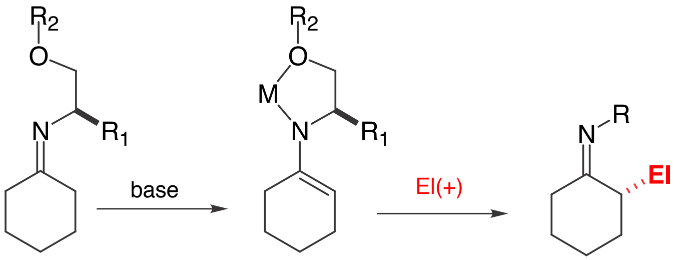
Ratio, 90:10

Collum, *JACS* ***1984***, *106*, 4865-4869 **(handout)**

Chiral Metalloenamines:

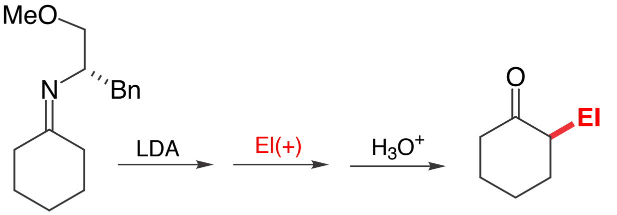
early papers:
- Meyers, *J. Am. Chem. Soc* ***1976***, *98*, 3032
- Whitesell, *J. Org. Chem.* ***1978***, *42*, 377-378

full papers:
- Meyers, *J. Org. Chem* ***1978***, *43*, 892
- Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3081
- Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3088



Major Product

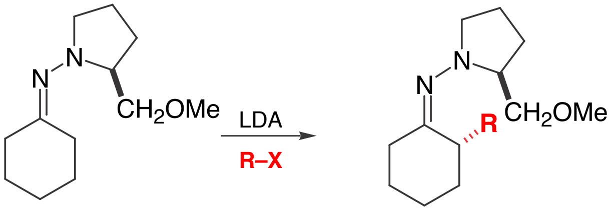
The base:
$R–Li$; $RMgX$; $R_2N–Li$



Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3081

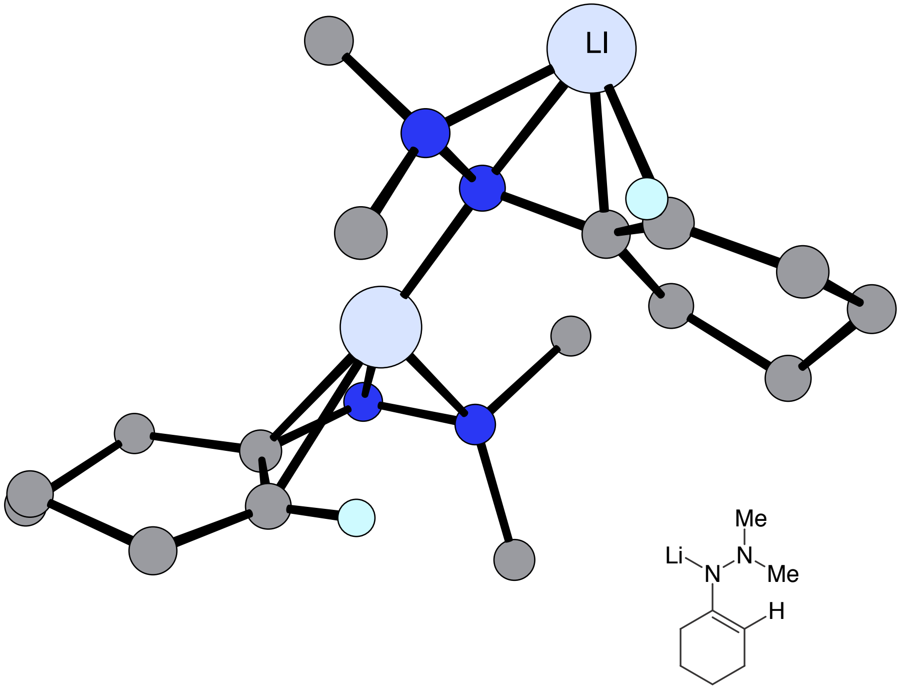
R–X	ee
Me–I	87
Et–I	94
n-Pr–I	99

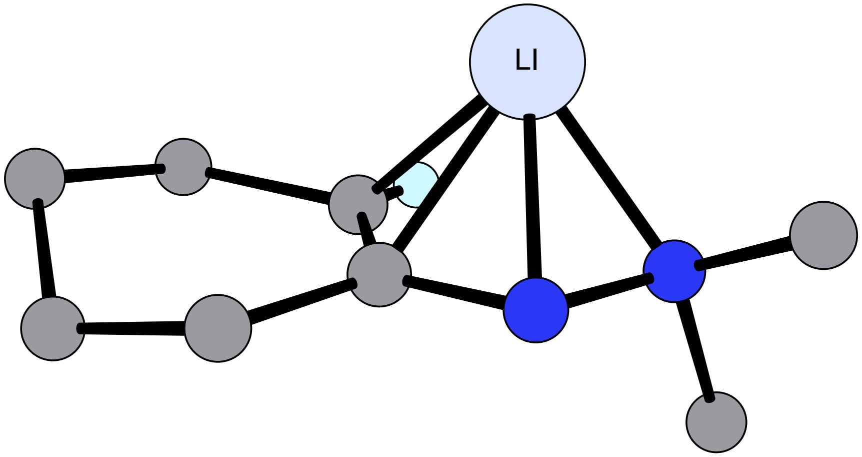
Chiral Metallated Hydrazones



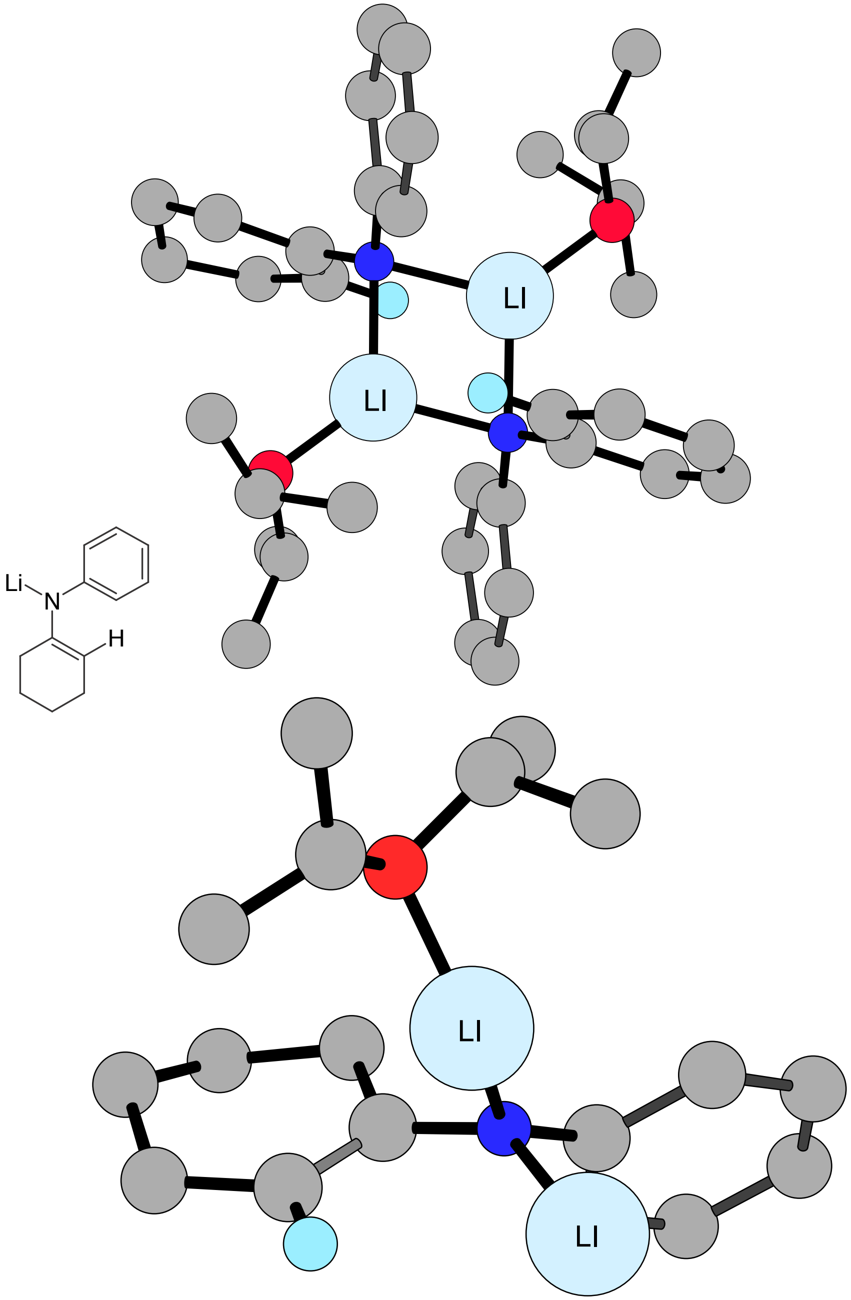
Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

Metalloenamine X-ray Structures



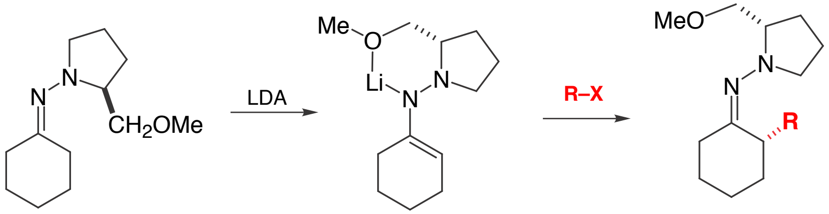


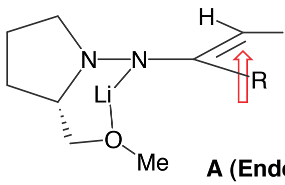
Collum & Clardy, *JACS* **1984**, *106*, 4865



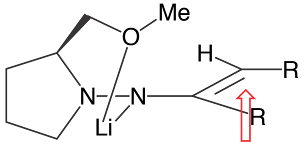
SAMP-Metalloenamine X-ray Structure

Chiral Metallated Hydrazones





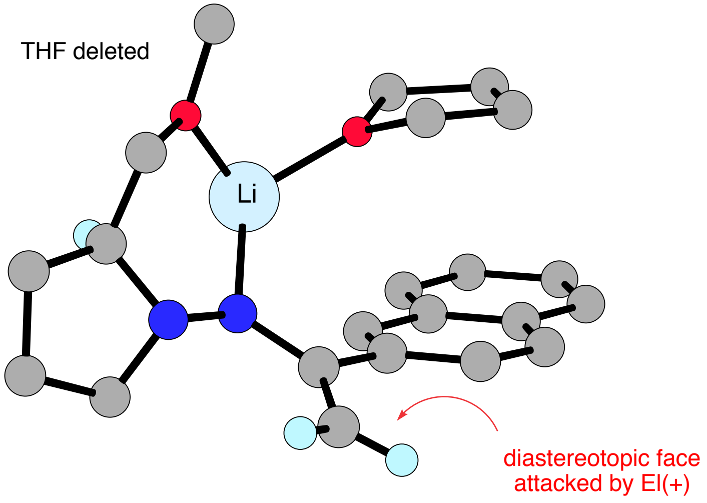
A (Enders)

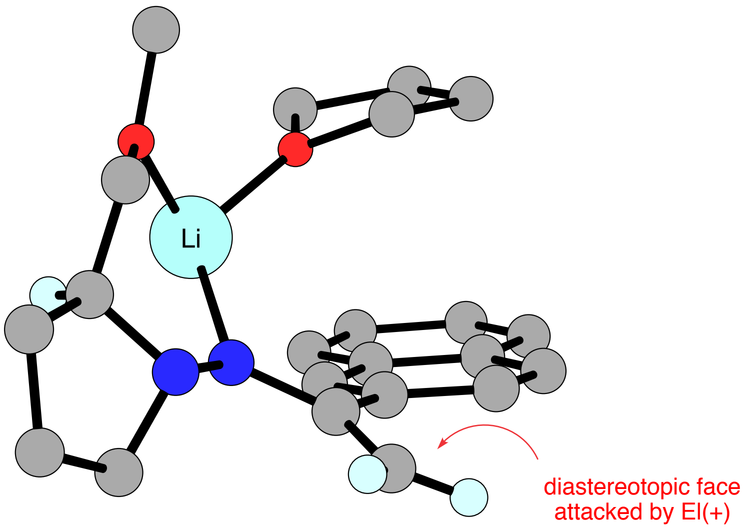


B

Which of the reactive chelate conformations are we to begin our analysis from?

For a review of this methodology see Enders, D. in *Asymmetric Synthesis*.; Morrison, J. D., Ed.; AP: New York, **1984**; Vol. **3**, p 275-339.





Chemistry 206

Advanced Organic Chemistry

Handout–24A

Enolate Acylation

D. A. Evans

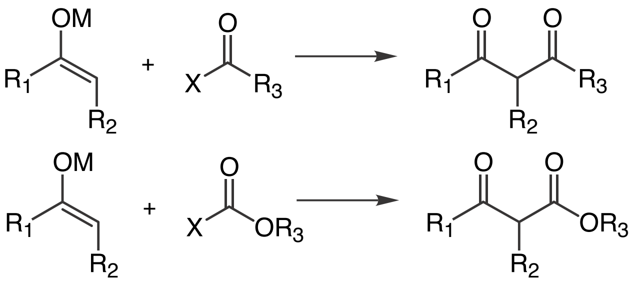
Monday ,
November 10, 2003

Enolate Acylation Acylation & Carboxylation

The Reaction:

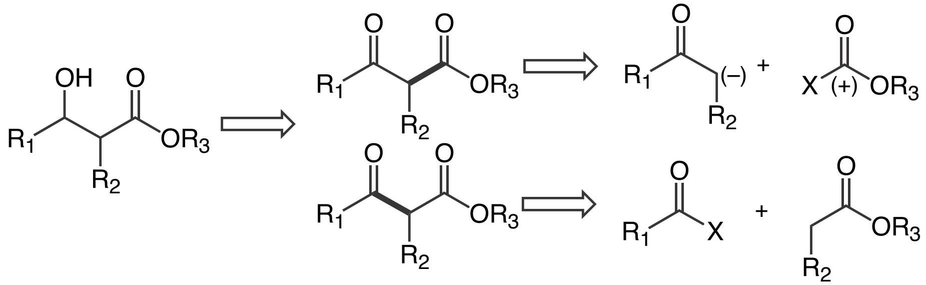
Acylation

Carboalkoxylation

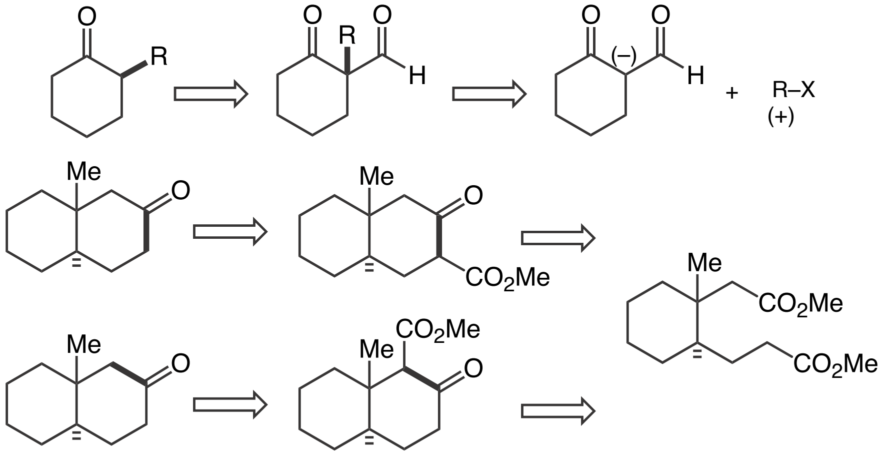


Situations where the reaction is employed:

■ Acyl moiety is a constituent of the target structure:

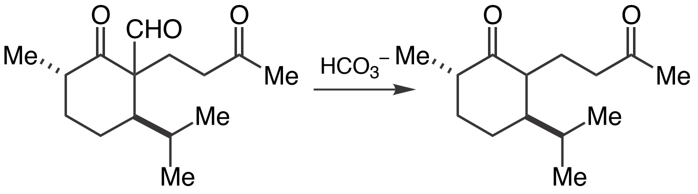


■ Acyl moiety employed in assisting bond construction but not part of the target structure:



Deacylation: When an acyl residue is employed in the one of the illustrated bond constructions, it may then be removed by nucleophilic deacylation: Several examples are provided.

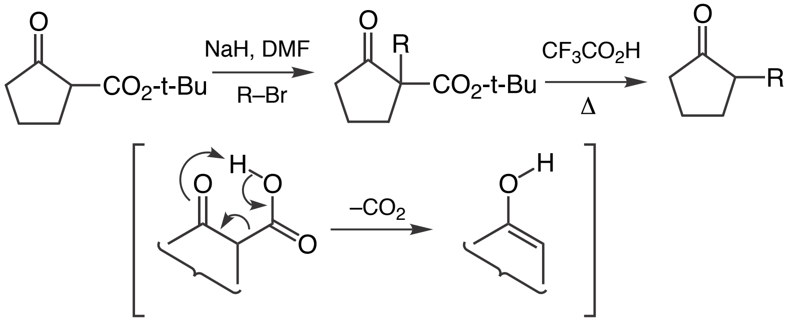
Deformylation:



competitive ring cleavage not a problem due to more electrophilic formyl C=O

Decarboxylation:

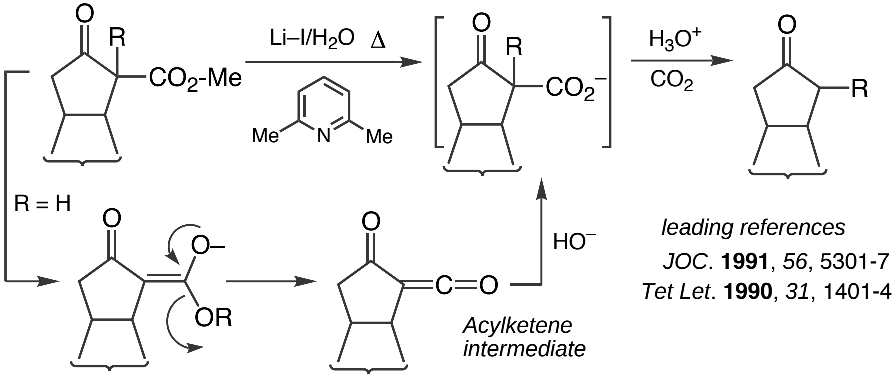
■ Alkyl-Oxygen Cleavage: *tert*-butyl esters



Decarboxylation in this system is a sigmatropic rearrangement involving C=O participation

representative procedure: Henderson, *Synthesis* **1983**, 996

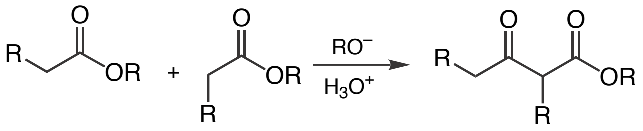
■ Alkyl-Oxygen Cleavage: Methyl esters



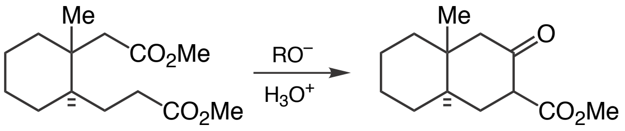
leading references
JOC. **1991**, *56*, 5301-7
Tet Let. **1990**, *31*, 1401-4

Claisen Condensation & Related Processes

Claisen Condensation: Condensation of 2 esters

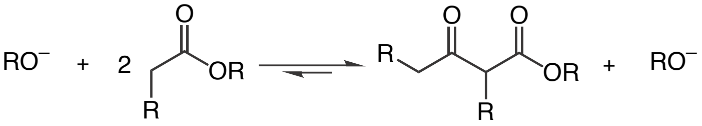


Intramolecular Variant: Dieckmann Condensation

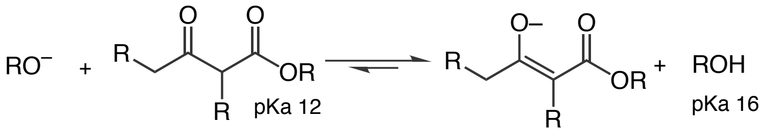


Strictly speaking, the Claisen and Dieckmann condensations are defined as condensations between ester enolates & ester electrophiles.
In this discussion, we choose to liberalize the classifcation to include ketone enolates as well.

Reaction Thermodynamics: Overall Keq ~ 1

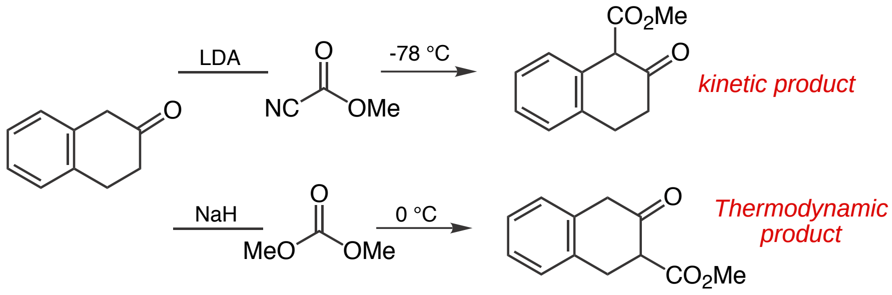


Final enolization Step: Keq ~ 10^{+4}



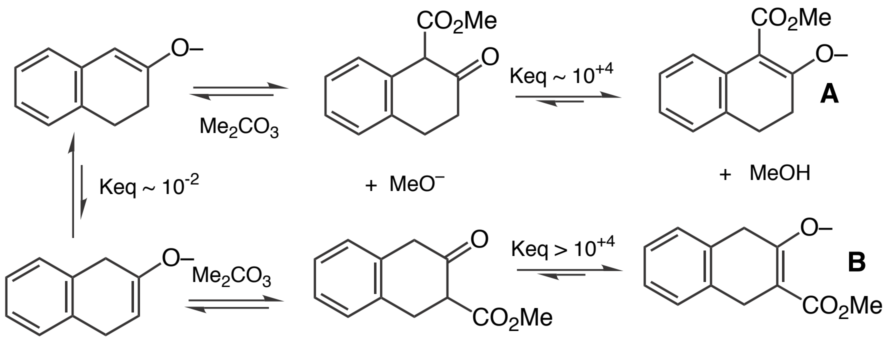
Contrary to popular belief, final enolization step does not render the process irreversible

Reaction Control Elements: These reactions can be manipulated to give either kinetic or thermodynamic control:

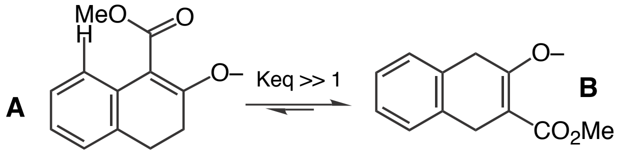


Analysis of the two processes:

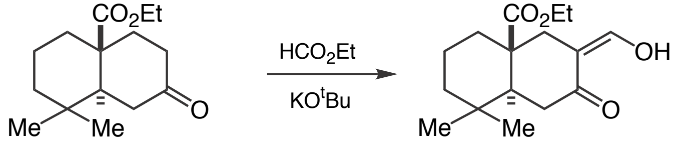
Conventional Carbomethoxylation: Equilibrium achieved between all species



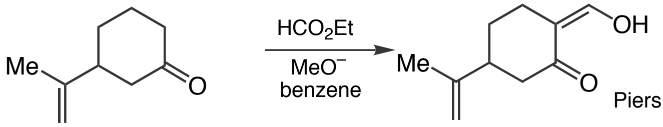
Critical issue: Product enolate **A** is significantly destabilized by peri-interaction with aromatic ring disrupting the required planarity of the delocalized enolate. Hence, the greater stability of **B** dictates the product.



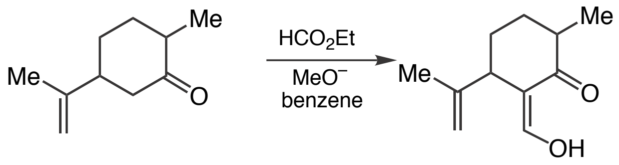
This type of control is general:



Meyers, *JOC* **1976**, *41*, 1976

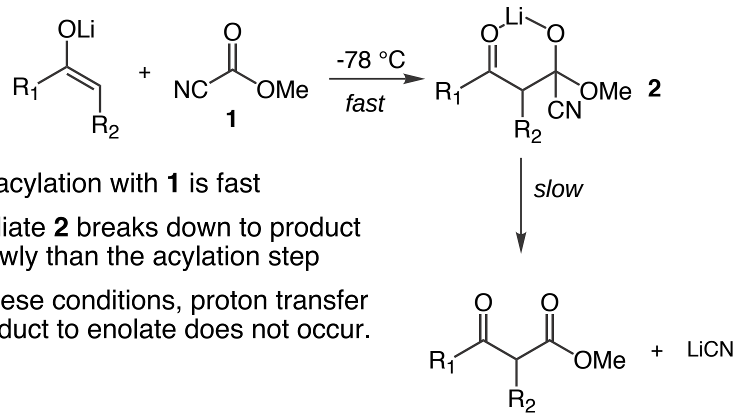


Piers, *Tet. Let* **1968**, 583



JACS **1965**, 87, 5728

Kinetic Acylation: Methyl Cyanoformate (1):

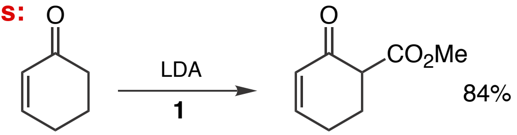


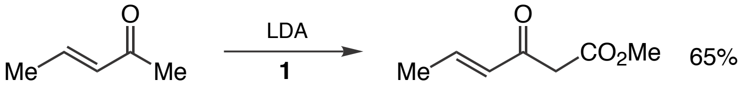
Enolate acylation with **1** is fast

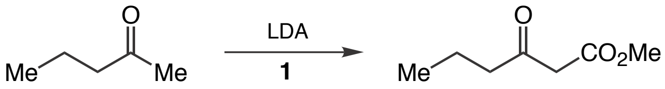
Intermediate **2** breaks down to product more slowly than the acylation step

Under these conditions, proton transfer from product to enolate does not occur.

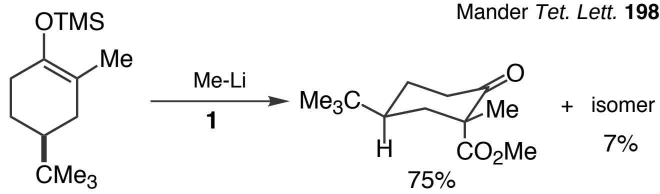
Examples:



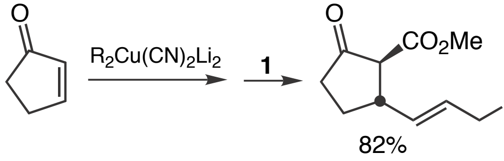




Mander *Tet. Lett.* **1983**, *24*, 5425

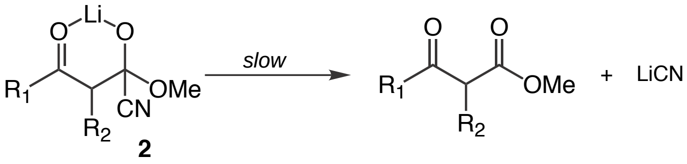


Mander, *SynLett.* **1990**, 169



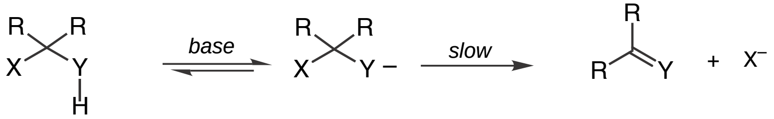
Hashimoto, *Chem. Lett.* **1989**, 1063

The Tetrahedral Intermediate 2; Why is it so stable?



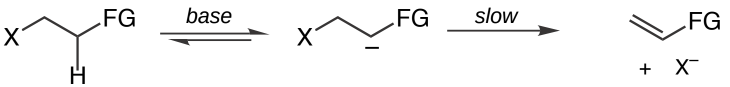
Consider this process in the broader context of elimination reactions of the E1cb classification where:

Y might be either C or some heteroatom
X might be various leaving groups such as CN, OR etc.



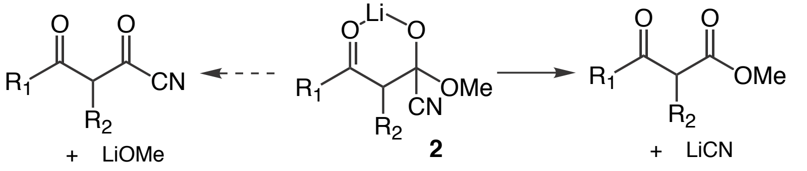
Data is available for the case where X = CN, OR & Y = carbanion:

Stirling, *Chem. Commun*. **1975**, 940-941



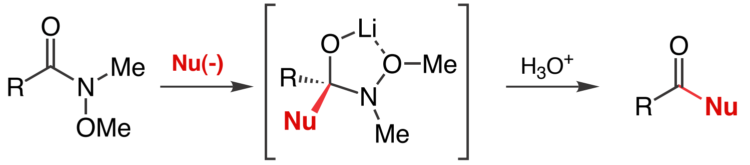
leaving grp (X)	pKa H–X	$\log\left[\frac{k_X}{k_{OPh}}\right]$
–OPh	10	1
–CN	9.5	<-7
$-C(Me)_2-NO_2$	~10	<-9
–OMe	16	-3.9

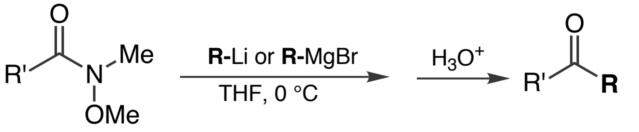
Above data makes the point that CN is a poor LG but it also leads one to the faulty conclusion that **2** should partition to acyl cyanide rather than methyl ester!



Carbon Acylation with *N*-Methoxy-*N*-methylamides

Acylating agents can be desiged where the tetrahedral intermediate exhibits exceptional stability:

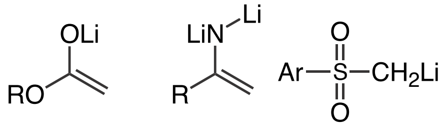
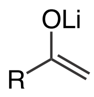




R = Me, n-Bu, or Ph; yields > 90%

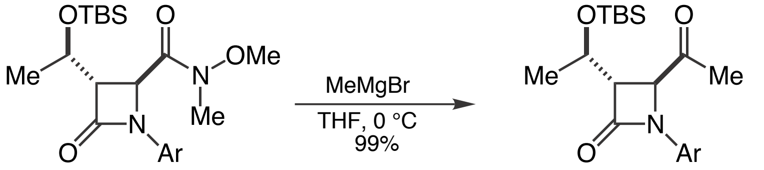
Weinreb *Tet. Lett.* **1981**, *22*, 3815.

Nucleophiles:

Acceptable	Unacceptable
R–Li, R–MgX R–C≡C–Li(MgX)	R–ZnX & other colalent metal alkyls
	 other colalent metal enolates
DIBAL $LiAlH_4$ $LiB(R)_3H$	Weak hydride reagents: $NaBH_4$

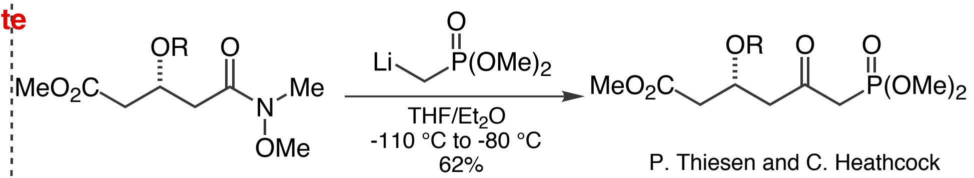
An excellent review on all aspects of Weinreb amide chemistry:
M. Sibi, *Organic Preparations and Procedures Int.*, **1993**, *25 (1)*, 15-40.

Representative Organometals:

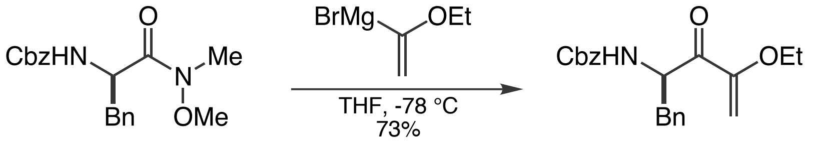


Several other examples reported.

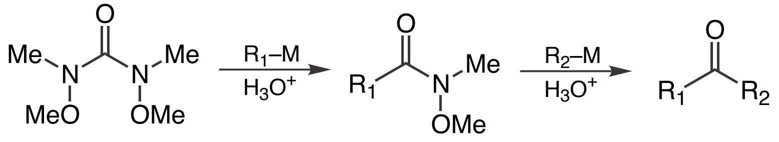
J. Prasad and L. Liebeskind
Tetrahedron Lett. **1987**, *28*, 1857.



P. Thiesen and C. Heathcock
J. Org. Chem. **1988**, *53*, 2374.

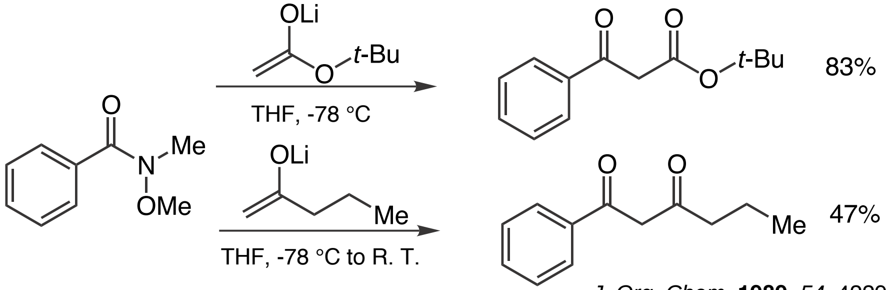


M. Angelastro, N. Peet and P. Bey
J. Org. Chem. **1989**, *54*, 3913.



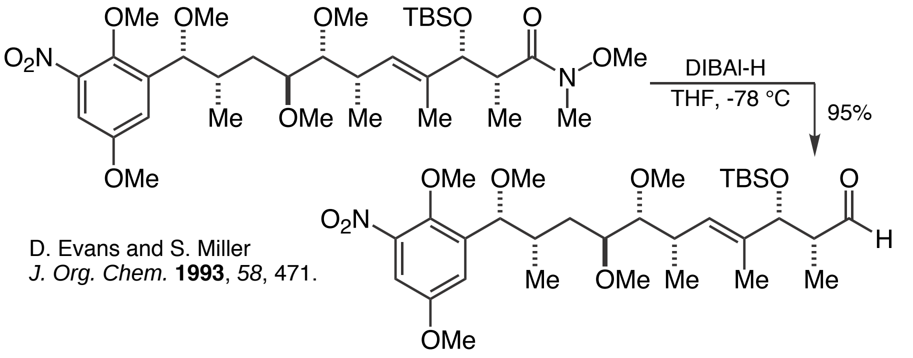
W. Wipple, H. Reich
J. Org. Chem. **1991**, *56*, 2911-2.

Enolates and Metalloenamines:



J. Org. Chem. **1989**, *54*, 4229.

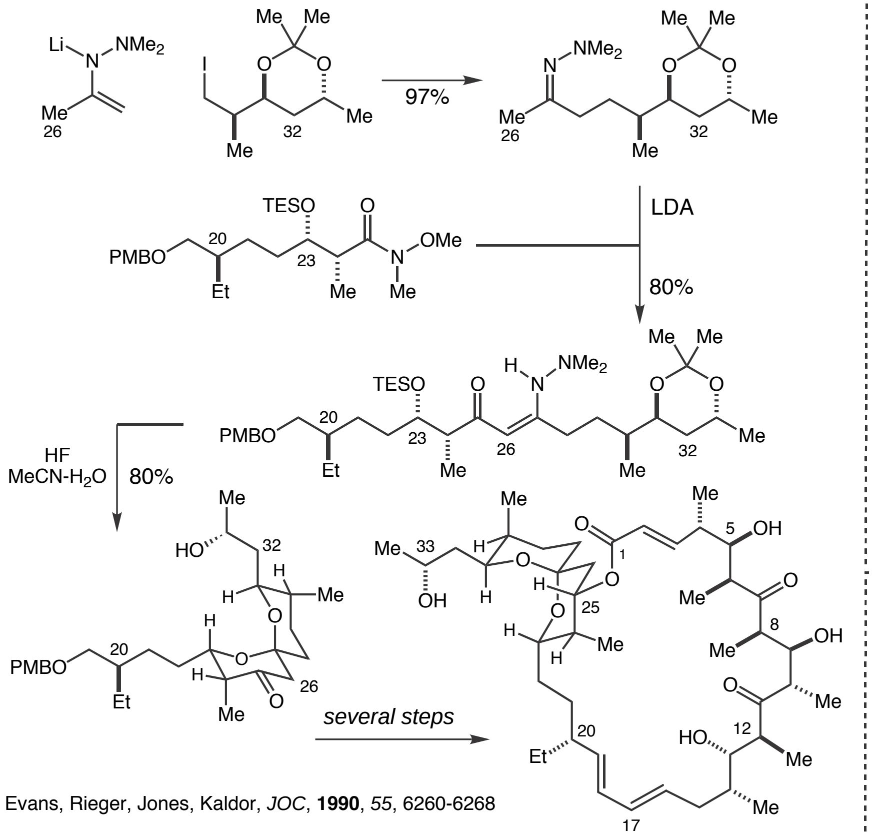
Hydride Reductions:



D. Evans and S. Miller
J. Org. Chem. **1993**, *58*, 471.

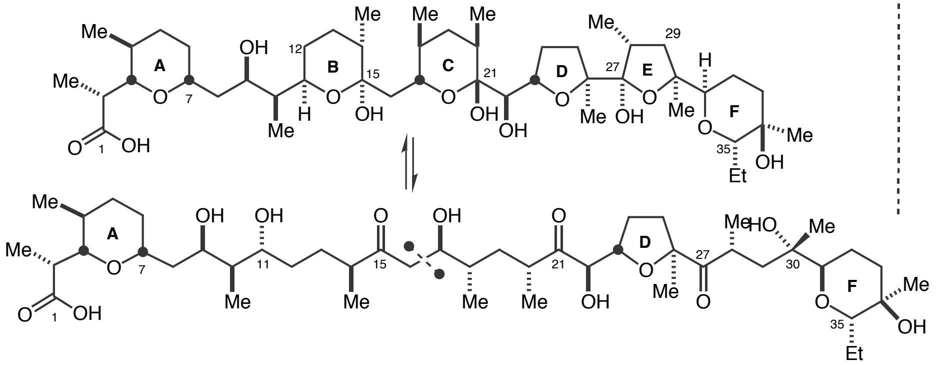
Carbon Acylation with *N*-Methoxy-*N*-methylamides-2

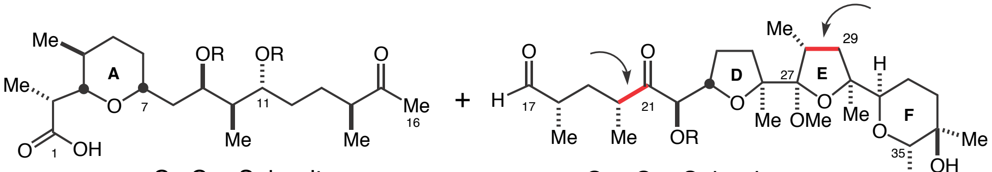
The Rutamycin B Synthesis, *H. Ng, Ph. D. Thesis, Harvard University, 1993*



Evans, Rieger, Jones, Kaldor, *JOC*, **1990**, *55*, 6260-6268

The X-206 Synthesis, *S. L. Bender, Ph. D. Thesis, Harvard University, 1986*

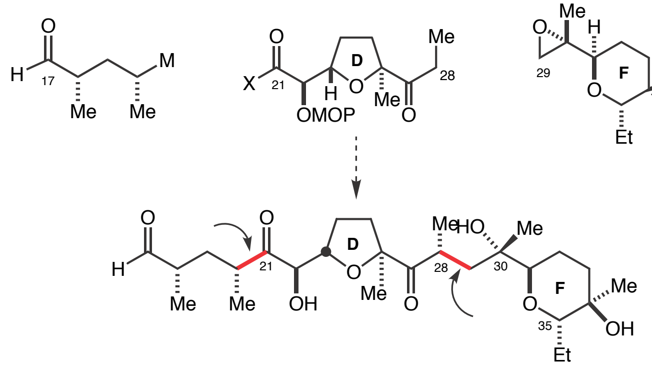




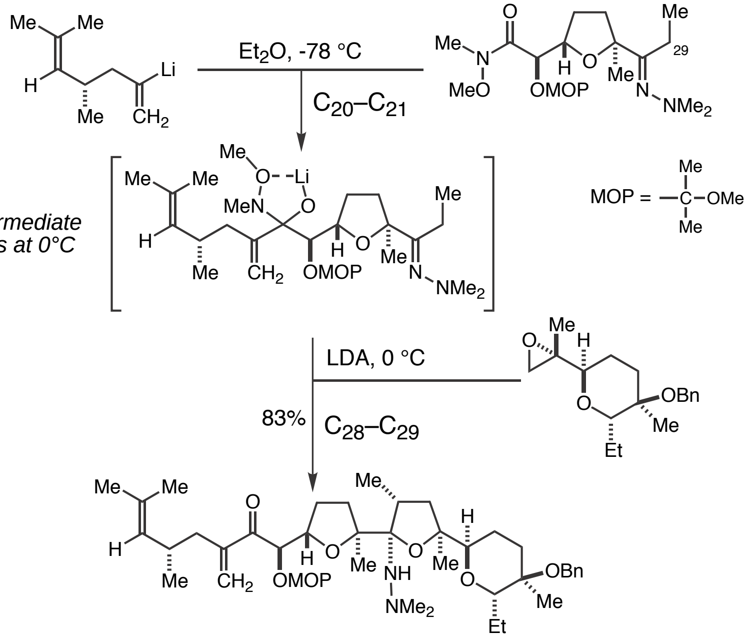
C_1-C_{16} Subunit

C_{17}-C_{37} Subunit

Problem is to control C=O reactivity on central D-fragment



The Solution:



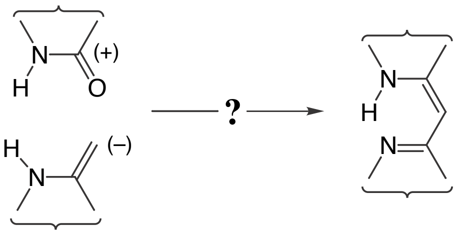
tetrahedral intermediate stable for hours at 0°C

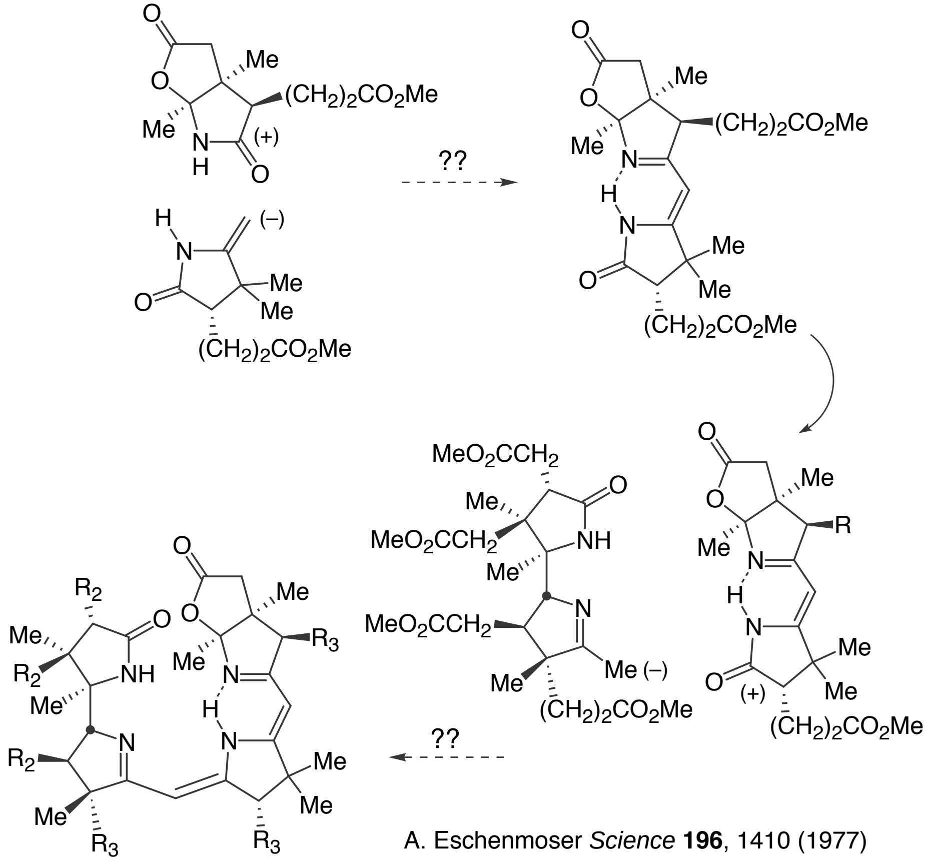
Evans, Bender, Morris J. Am. Chem. Soc. **1988**, *110*, 2506.

The Eschenmoser Coupling Reaction

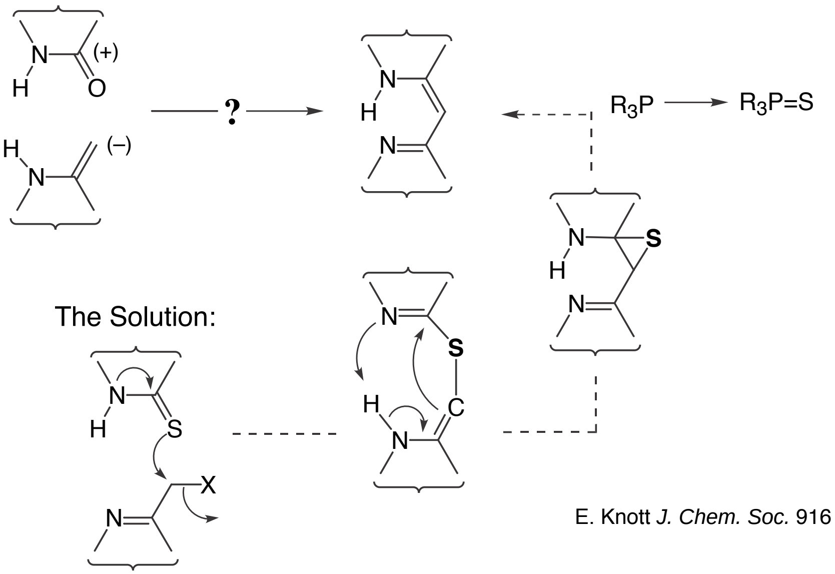
Key Bond Construction Needed for the B12 Synthesis:

The Problem:





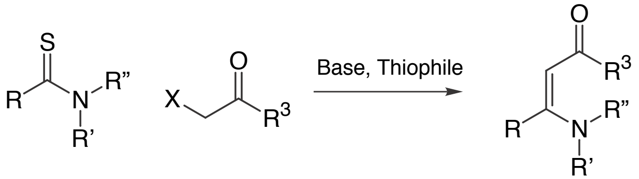
A. Eschenmoser *Science* **196**, 1410 (1977)



The Solution:

E. Knott *J. Chem. Soc.* 916 (1955)

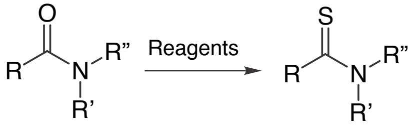
The General Reaction: Acylation of an Amide C=O

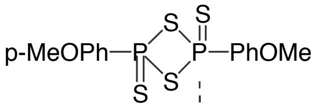


Key papers:

A. Eschenmoser *Helv. Chim. Acta.* **54**, 710 (1971)
A. Eschenmoser *Angew. Chem., Int. Ed. Engl.* **6**, 866 (1967)
A. Eschenmoser *Angew. Chem., Int. Ed. Engl.* **8**, 343 (1969)
Review: Trost *Comp. Org. Synth.* Vol. 2, Ch. 3.7 (1991)

The Thioamide component:





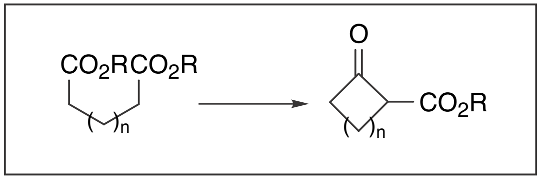
Lawesson's Reagent

P_4S_{10} JOC 46, 3558 (1981), Synthesis 149 (1973)
Lawesson's Reagent Bull. Chim. Soc. Belg. 87, 229 & 293 (1978)
P_4S_{10}, Et_3N or $NaHCO_3$ Indian J. Chem., Sect. B 14, 999, (1976)
JACS 102, 2392 (1980)
$RCS_2R' + R_2NH \longrightarrow$ Thioamide Chem. Ind. (London) 803 (1974)
Imidate $+H_2S \longrightarrow$ Thioamide Angew. Chem. 79, 865 (1967)

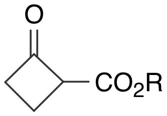
Intramolecular Enolate Acylation–Dieckmann Condensation

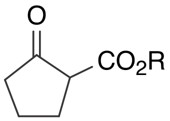
The Dieckmann Condensation

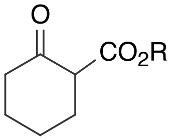
Reviews: Schaefer, Bloomfield, *Organic Reactions* **1967**, *15*, 1.
Davis & Garratt, *Comprehensive Organic Synthesis* **1991**, *2*, 806-829

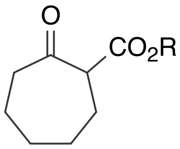


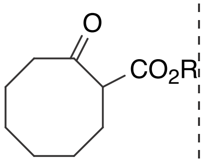
Accesible Ring Sizes


not viable


excellent

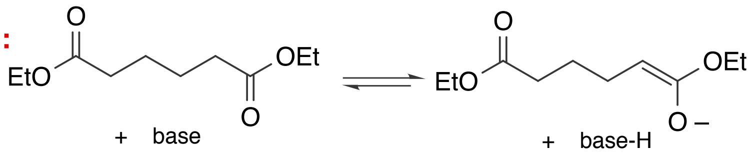

excellent


acceptable


situation dependent
high dilution required

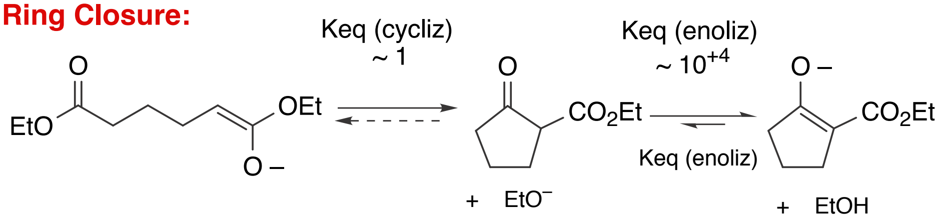
The individual steps:

Enolization:



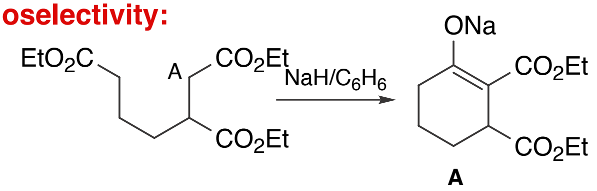
A variety of bases may be considered for the enolization step.
Either alkoxide or a non-nucleophilic base such as NaH are commonly used.
Choice of base can be important (Vide infra).

Ring Closure:

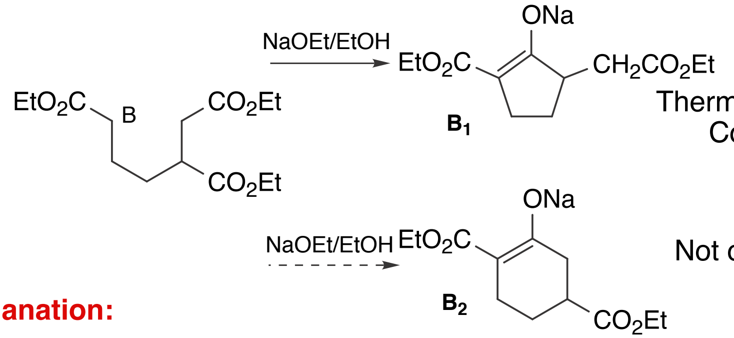


Statements claiming that the final enolization step renders the process irreversible are simply incorrect.

Regioselectivity:



Kinetic Control?



Thermodynamic
Control?

Not observed

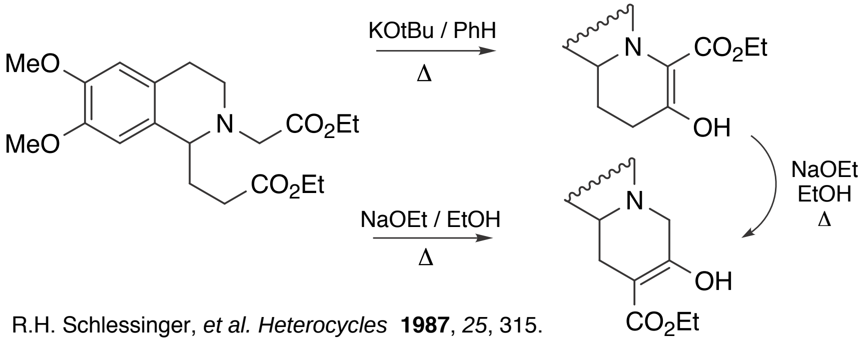
Explanation:

Enolization at (A) preferred on basis of inductive effects. Hence, Path A preferred in kinetically controlled situation

Enolates (B1) and (B2) both more stable than enolate (A)

Under equilibrating conditions (B1) appears to be preferred over (B2)

The effect of beta heteroatoms: classical kinetic vs. thermodynamic control



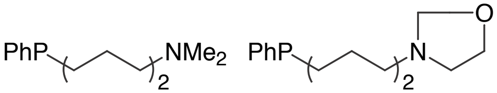
R.H. Schlessinger, *et al. Heterocycles* **1987**, *25*, 315.

Reagents for the Reaction:

Bases:
Inorganic: $MHCO_3$, MOH, MH, MOR
Organic: R_3N, N-methylmorpholine, buffered solutions

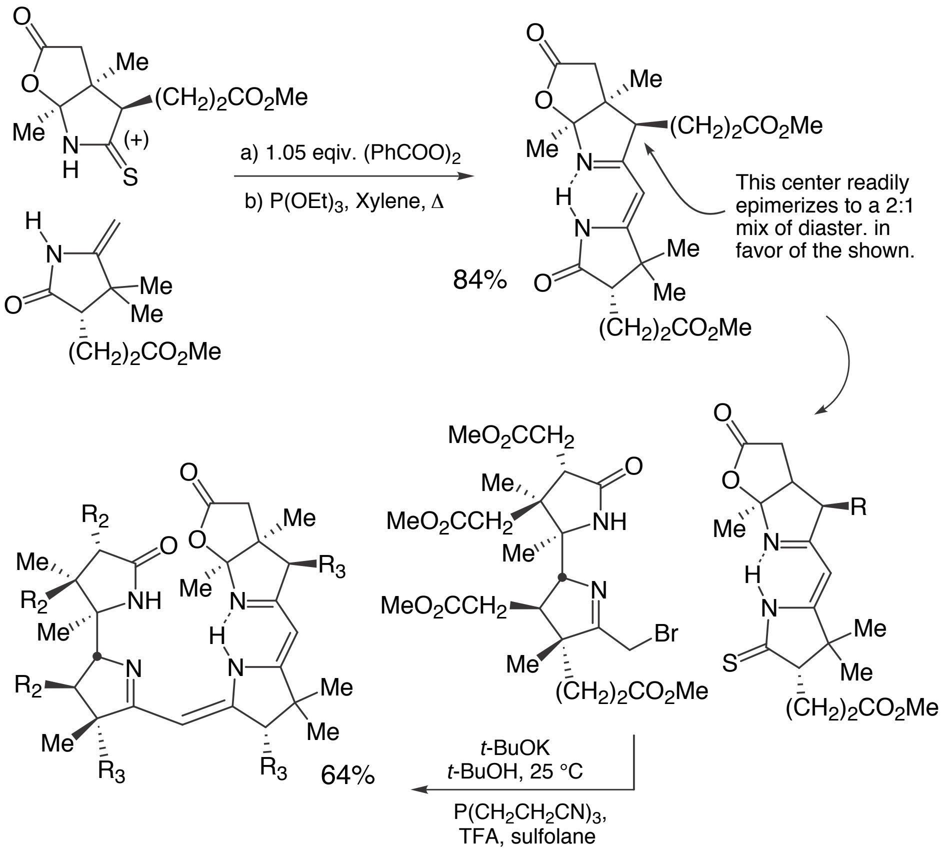
Thiophiles: Ar_3P, R_3P, $(RO)_3P$

Combination:

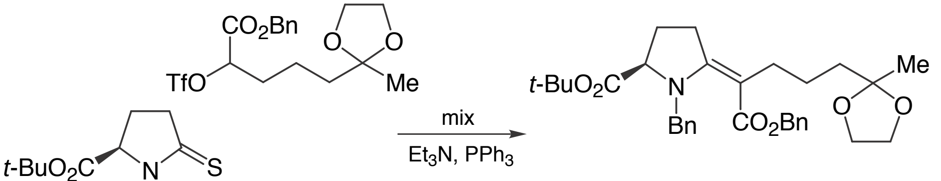


H. Rapoport *J. Org. Chem.* **46**, 3230 (1981)
A. Eschenmoser *Helv. Chim. Acta.* **54**, 710 (1971)

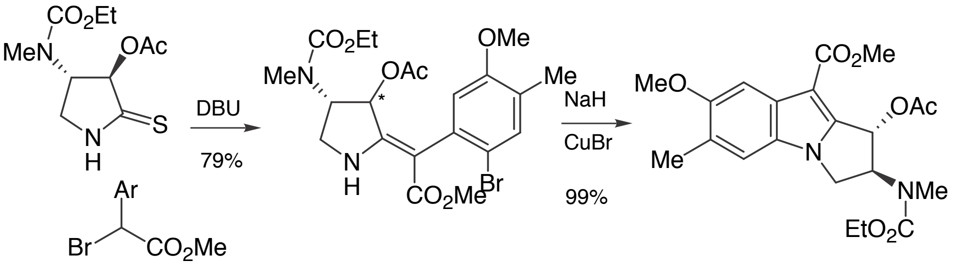
A. Eschenmoser *Science* **196**, 1410 (1977)



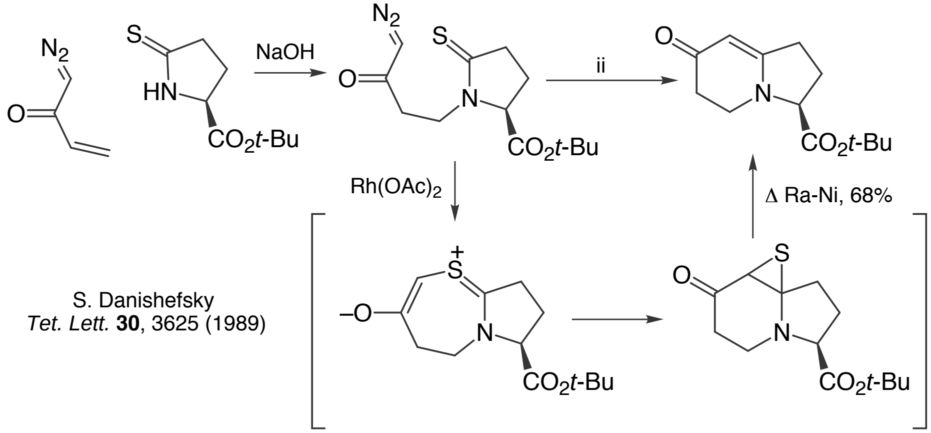
This center readily epimerizes to a 2:1 mix of diaster. in favor of the shown.



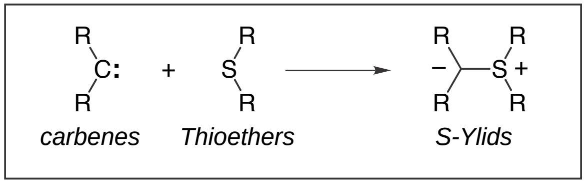
H. Rapoport *J. Org. Chem.* **46**, 3230 (1981)



T. Kametani *J. Chem. Soc., Perkin Trans. I* 1607 (1980)

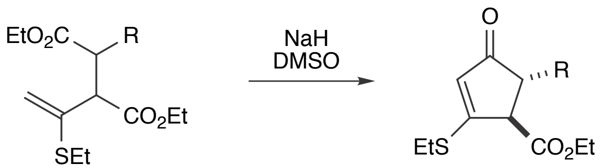


S. Danishefsky
Tet. Lett. **30**, 3625 (1989)

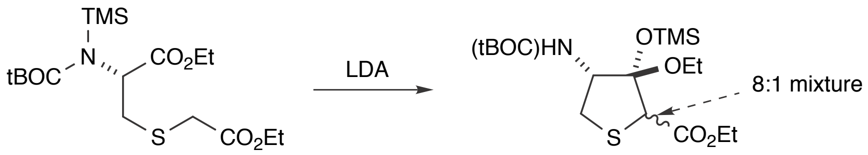


Intramolecular Enolate Acylation–Dieckmann Condensation

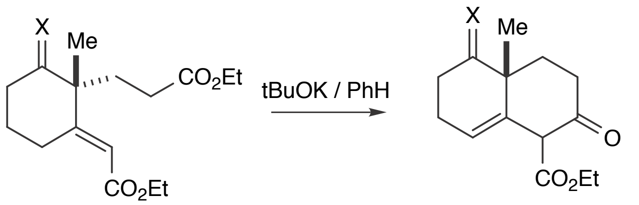
Miscellaneous Dieckmann Reactions of Potential Interest



R.Danieli, *J.Org.Chem.* **1983**, *48*, 123.

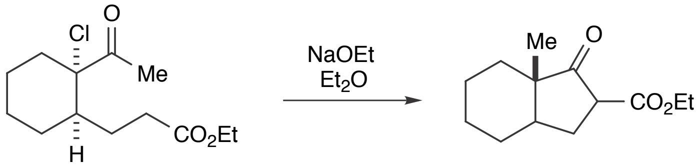


J.L. Adams, *J.Org.Chem.* **1985**, *50*, 2730.



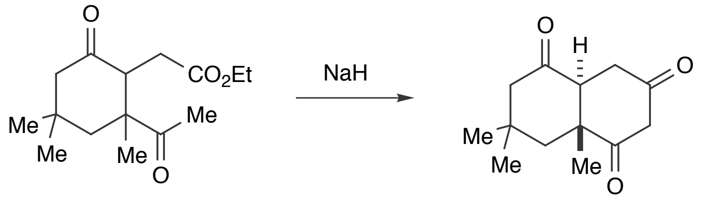
Peterset, *Recl.Trav.Chim.Pays-Bas* **1977**, *96*, 219.

Deduce the mechanism of this multistep process.

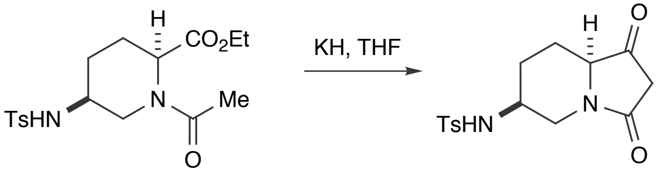


G.Stork and Co-workers, *J.Am.Chem.Soc.* **1960**, *82*, 4315.

Intramolecular Ketone Acylation

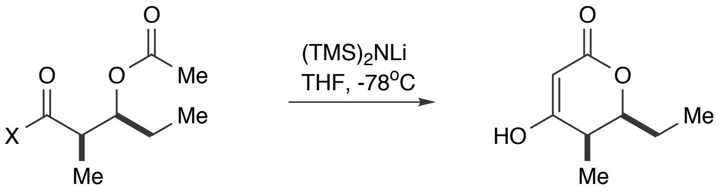


H.-J. Liu and Co-workers, *Tet.Lett.* **1982**, *23*, 295.



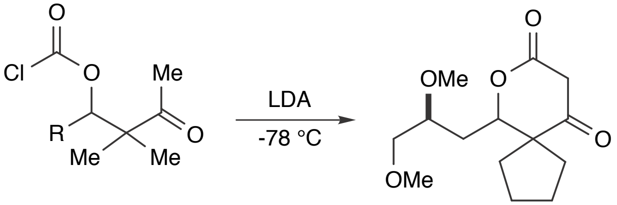
no loss of stereochemical integrity

T.M. Harris and Co-workers, *J.Org.Chem.* **1984**, *49*, 3681.



When X = NR_2, this is a good reaction, but when X = OR, it is a poor reaction.

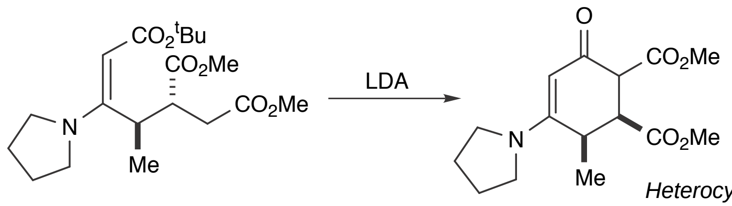
S.Brandawge and Co-workers, *Tet.Lett.* **1992**, *33*, 3025.



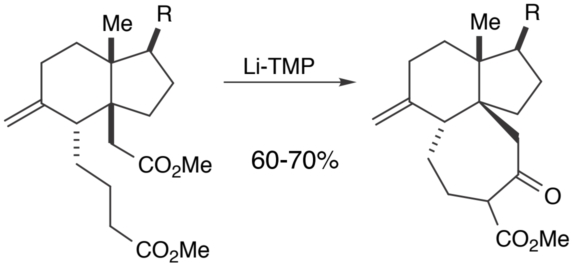
Kocienski and Co-workers, *Tet.* **1990**, *46*, 1716

Intramolecular Enolate Acylation–Dieckmann Condensation

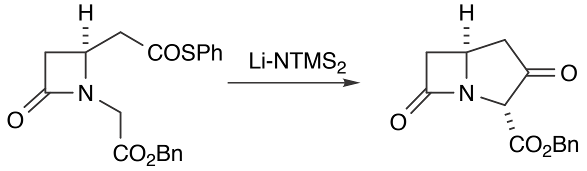
Kinetically controlled Cyclizations



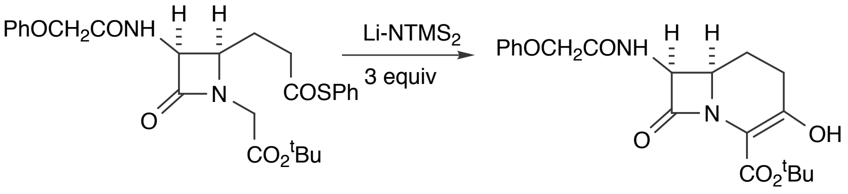
Heterocycles, **1987**, *25*, 315



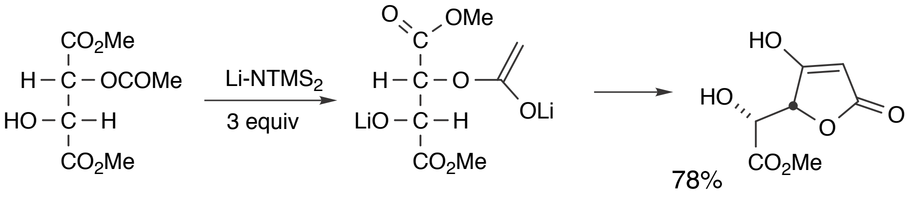
JACS, **1979**, *101*, 5060



Tet. Let, **1981**, *22*, 3883

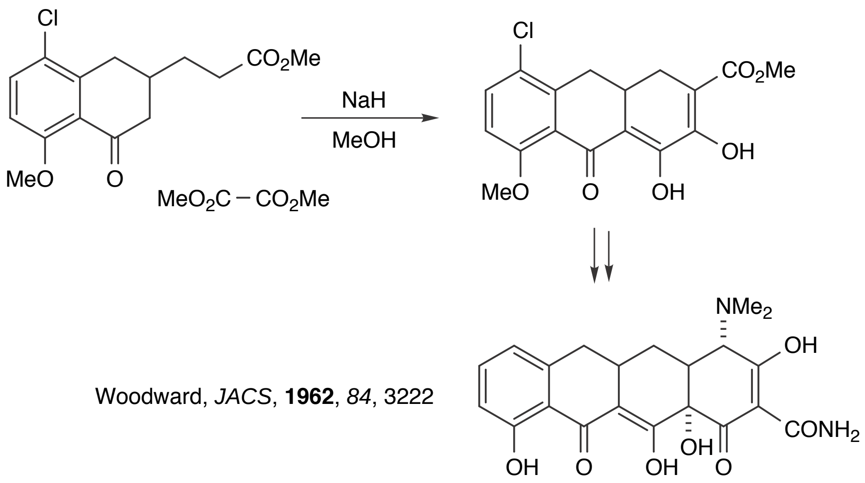


Hatanaka, *Tet. Let*, **1983**, *24*, 4837



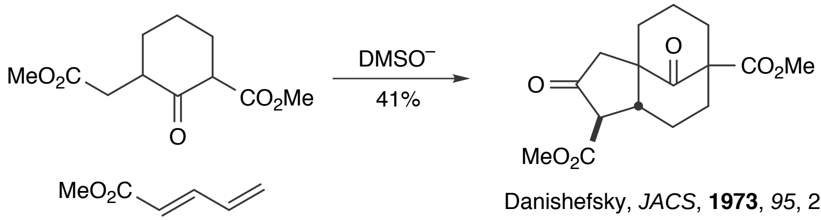
Brandange, *JOC*, **1984**, *49*, 927

Multistep Condensations

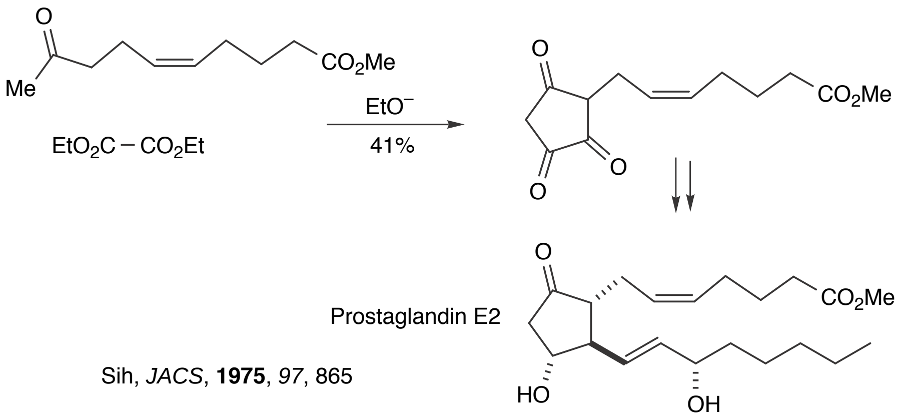


Woodward, *JACS*, **1962**, *84*, 3222

6-demethyl-6-deoxy-tetracycline



Danishefsky, *JACS*, **1973**, *95*, 2410

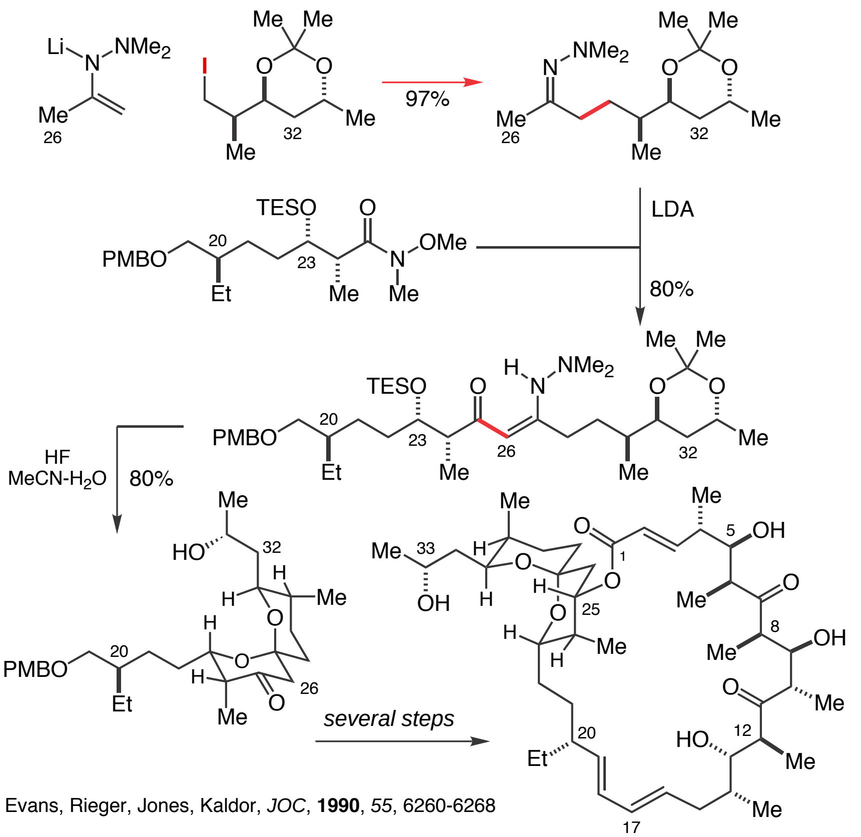


Prostaglandin E2

Sih, *JACS*, **1975**, *97*, 865

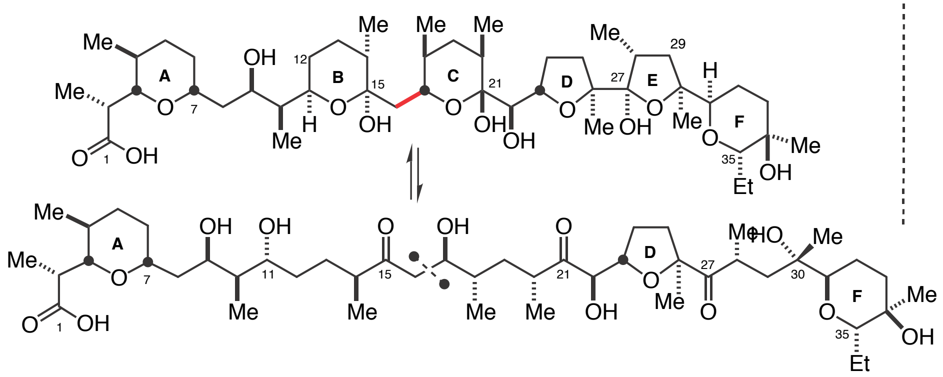
Synthetic Applications of Metalloenamine Nucleophiles

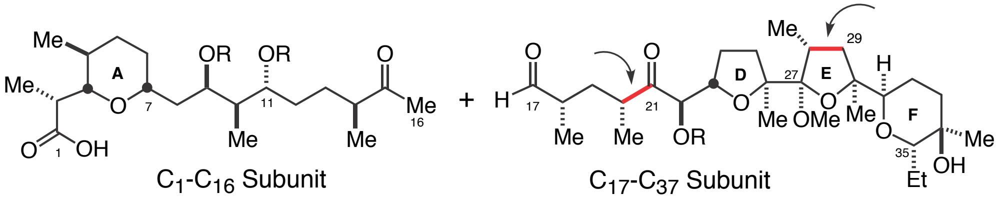
The Rutamycin B Synthesis, *H. Ng, Ph. D. Thesis, Harvard University, 1993 JACS 1993, 115, 11446-11459.*



Evans, Rieger, Jones, Kaldor, *JOC*, **1990**, *55*, 6260-6268

The X-206 Synthesis, *S. L. Bender, Ph. D. Thesis, Harvard University, 1986*

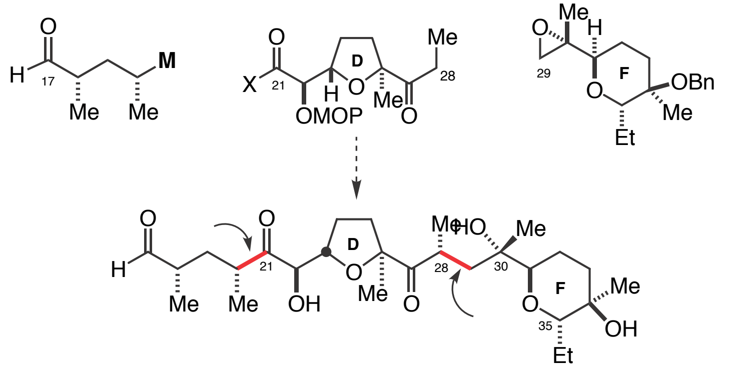




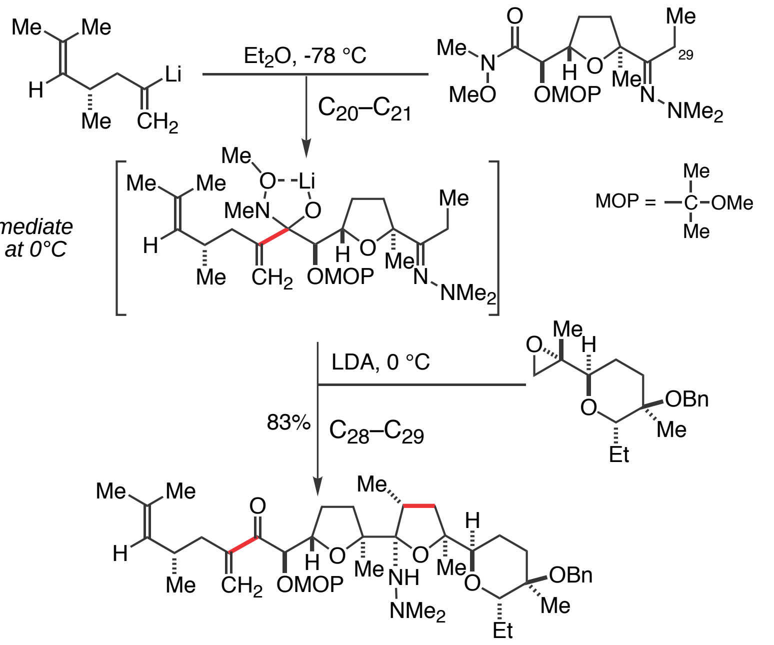
C_1-C_{16} Subunit

C_{17}-C_{37} Subunit

Problem is to control C=O reactivity on central D-fragment



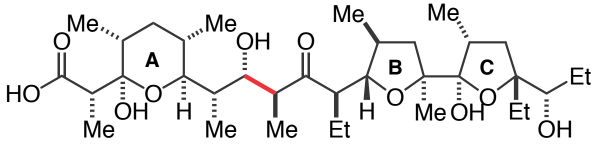
The Solution:



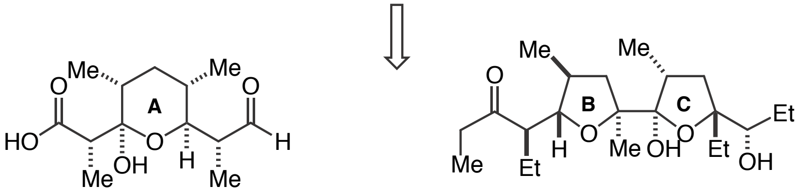
Evans, Bender, Morris J. Am. Chem. Soc. **1988**, *110*, 2506.

Synthetic Applications of Metalloenamine Nucleophiles

■ The Ferensimycin B Synthesis, *JACS* **1991**, *113, 7613-7630*

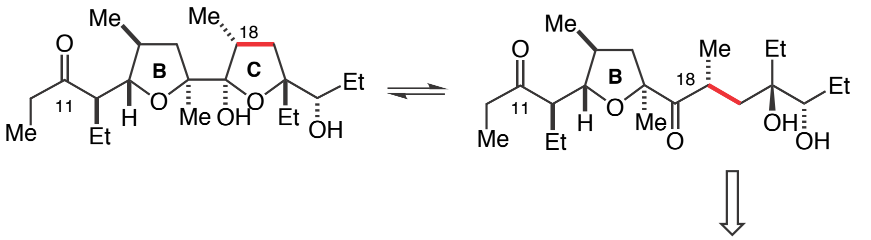


Ferensimycin B

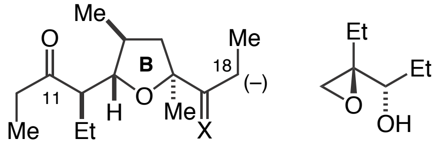


C_{10}-C_{23} Synthon

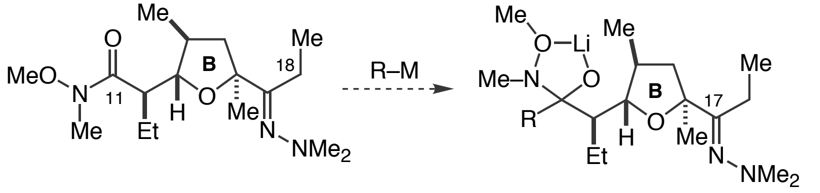
■ The B–C Fragment (*C_{10}-C_{23} Synthon*)



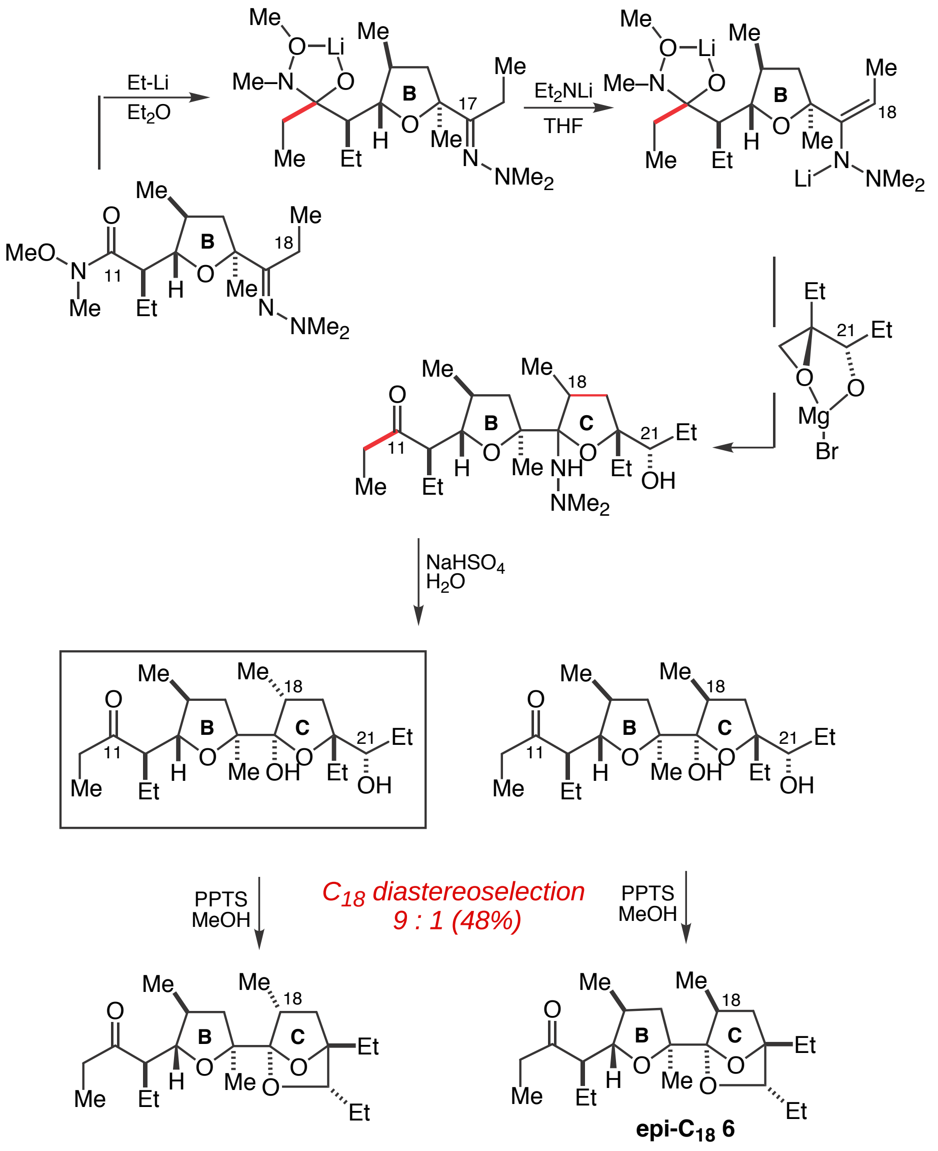
The C-11 ketone must be protected during the C-18C-19 bond construction



■ The In situ protection of the C–11 Carbonyl



carbonyl-protected intermediate



C_{18} diastereoselection
9 : 1 (48%)

epi-C_{18} 6

Quote for the Day

Quote and limrick by J. W. Cornforth

"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations."

"That Outpost of Empire, Australia
Produces some Curious Mammalia
The Kangaroo Rat
The Blood-sucking Bat
and Aurthur J. Birch, inter alia."

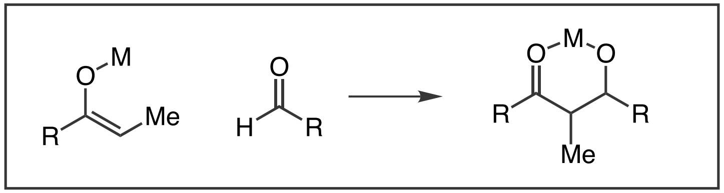
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 25

The Aldol Reaction–1



- Polyketide Biosynthesis
- Historical Perspective on the Aldol Reaction
- Aldol Diastereoselectivity
- Enolate Diastereoface Selectivity
- Absolute Control in the Aldol Process

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Wednesday,
November 12, 2003

Suggested Reading

Stereoselective Aldol Reactionsw in the Synthesis of Polyketide natural Products, I. Paterson et al. in Modern Carbonyl Chemistry, pp 249-297, J. Otera, Ed. Wiley VCH, **2000** **(handout)**

Ager, D. J., I. Prakash, et al. (**1997**). "Chiral oxazolidinones in asymmetric synthesis." Aldrichimica Acta 30(1): 3-12

Other Useful References

Evans, D. A., J. V. Nelson, et al. (**1982**). "Stereoselective Aldol Condensations." Top. Stereochem. 13: 1.

Heathcock, C. H. (**1984**). The Aldol Addition Reaction. Asymmetric Synthesis. Stereodifferentiating Reactions, Part B. J. D. Morrison. New York, AP. 3: 111.

Oppolzer, W. (**1987**). "Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis." Tetrahedron **43**: 1969.

Heathcock, C. H. (**1991**). The Aldol Reaction: Acid and General Base Catalysis. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 133.

Heathcock, C. H. (**1991**). The Aldol Reaction: Group I and Group II Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 181.

Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

Franklin, A. S. and I. Paterson (**1994**). "Recent Developments in Asymmetric Aldol Methodology." Contemporary Organic Synthesis 1: 317-338.

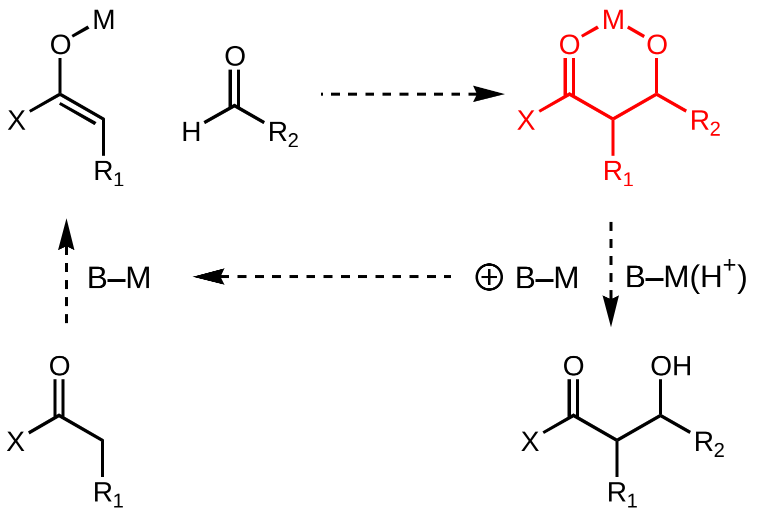
Cowden, C. J. and I. Paterson (**1997**). "Asymmetric aldol reactions using boron enolates." Org. React. (N.Y.) 51: 1-200.

Nelson, S. G. (**1998**). "Catalyzed enantioselective aldol additions of latent enolate equivalents." Tetrahedron: Asymmetry 9(3): 357-389.

Mahrwald, R. (**1999**). "Diastereoselection in Lewis-acid-mediated aldol additions." Chem. Rev. 99(5): 1095-1120.

Aldol Reaction Variants: Each has its Merits & Liabilities

Metal Aldol Process

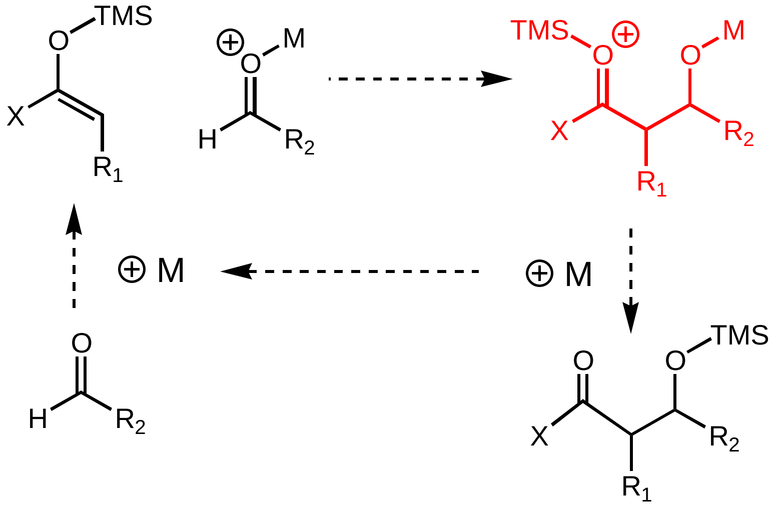


Generally stoichiometric in Metal
Good diastereomer control now possible

Teruaki Mukaiyama

Chem Lett. **1973,** 1011

Mukaiyama Aldol Process



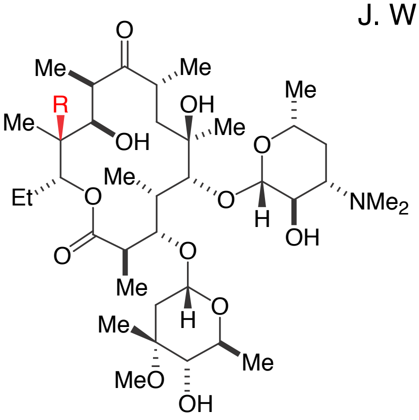
Generally catalytic in Metal
Diastereomer control not highly regulated

Clayton Heathcock

Satoru Masamune

The Aldol Reaction: Polypropionate Biosynthesis

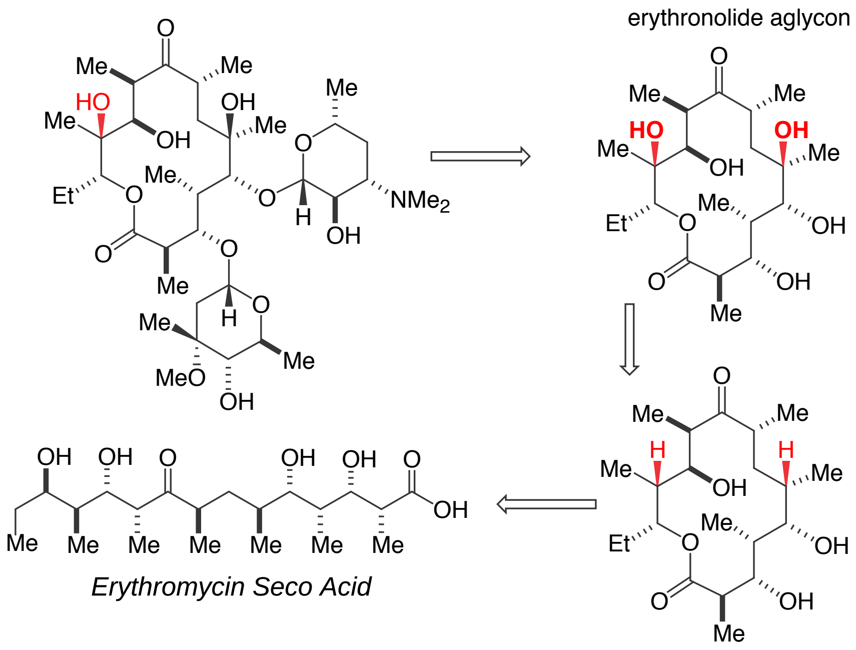
> *"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations."*
> J. W. Cornforth



J. W. Cornforth
Nobel Prize, 1975

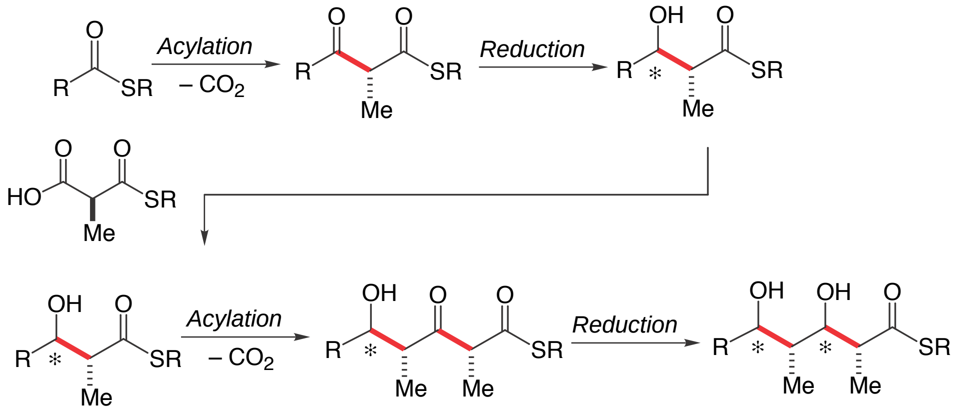
Erythromycin A, R = OH
Erythromycin B, R = H

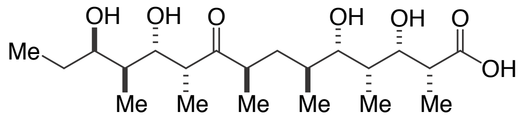
Retro-biosynthesis: Erythromycin A



Recent overview: Staunton, "Polyketide biosynthesis: a millennium review." *Nat. Prod. Rep.* **2001**, *18*, 380-416.

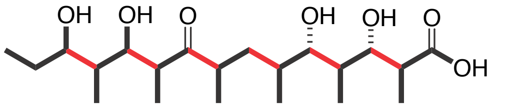
Polypropionate Biosynthesis: The Elementary Steps





Erythromycin Seco Acid

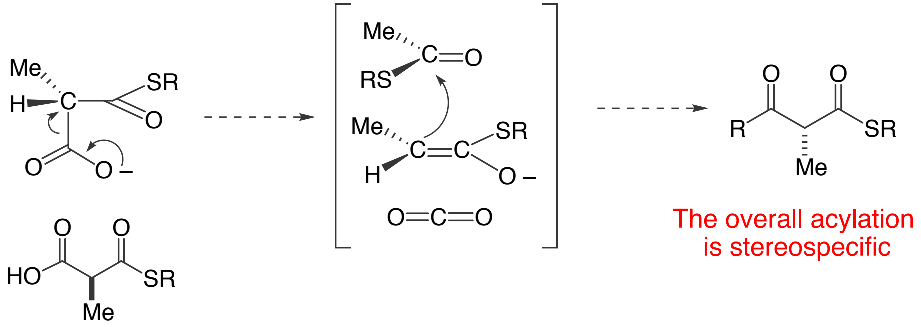
The 7 Propionate Subunits



The Acylation Event

Decarboxylation-Acylation could either be stepwise (Option A) or concerted (Option B).

The stepwise Option

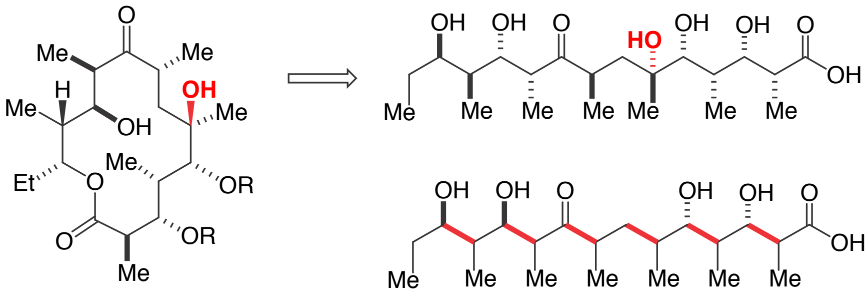


The overall acylation is stereospecific

See Lecture 24; page 24-08 for first laboratory example

Polypropionate Biosynthesis: A Laboratory Simulation

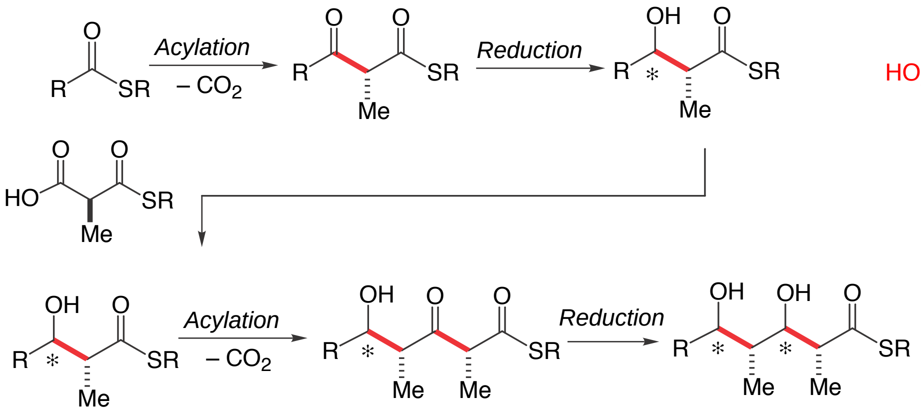
Polypropionate & Polyacetate Biosynthesis: Develop a Laboratory Simulation



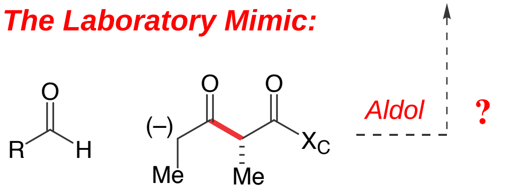
Erythrolide B

The 7 Propionate Subunits

Polypropionate Biosynthesis: The Elementary Steps

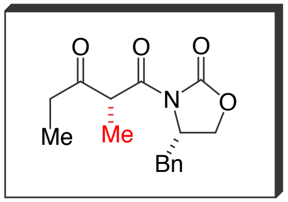


The Laboratory Mimic:

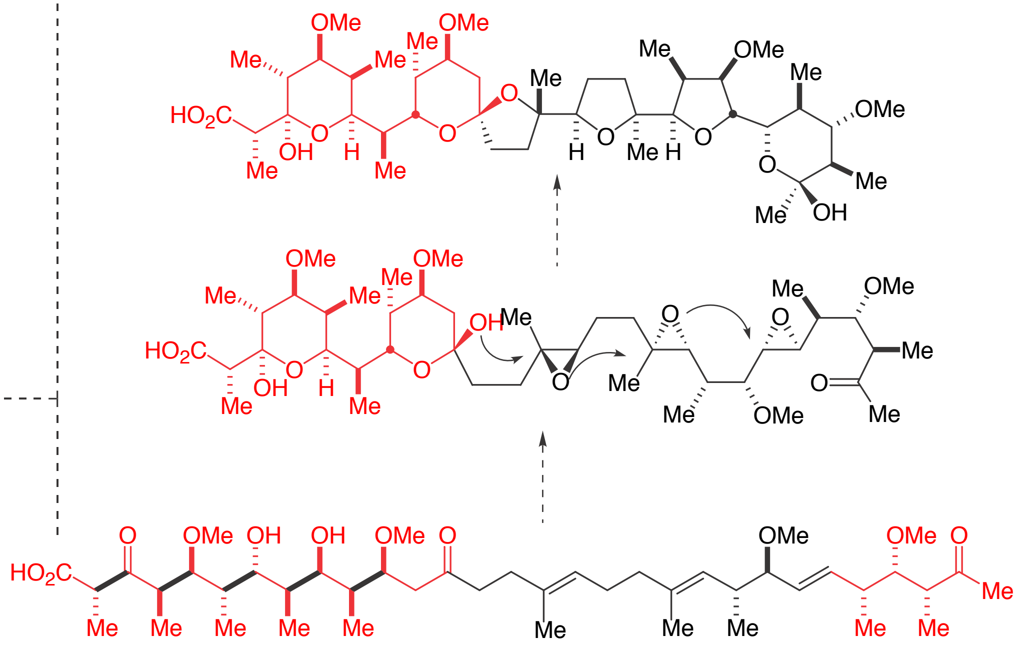


See Lecture 23; page 23-08:
with M. Ennis JACS ***1984****, 106, 1154.*

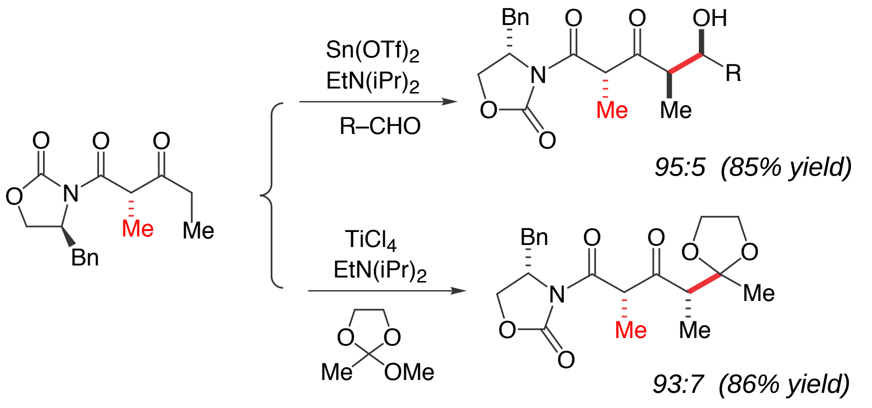
Dipropionyl Synthon



Latter Stages of Lonomycin Biosynthesis



Cane, Celmer, Westley *JACS* **1983**, *105*, 3594



with Ratz, Huff, & Sheppard, *JACS* **1995**, *117*, 3448

The Aldol Reaction: Early Contributions

General Reviews of the Aldol Literature:

Mukaiyama in *Organic Reactions*, **1982**; Vol 28, pp 203-331
Evans in *Topics in Stereochemistry*, **1982**; Vol 13, pp 1-115
Heathcock in *Asymmetric Synthesis*, **1984**; Vol 3, pp 111-212

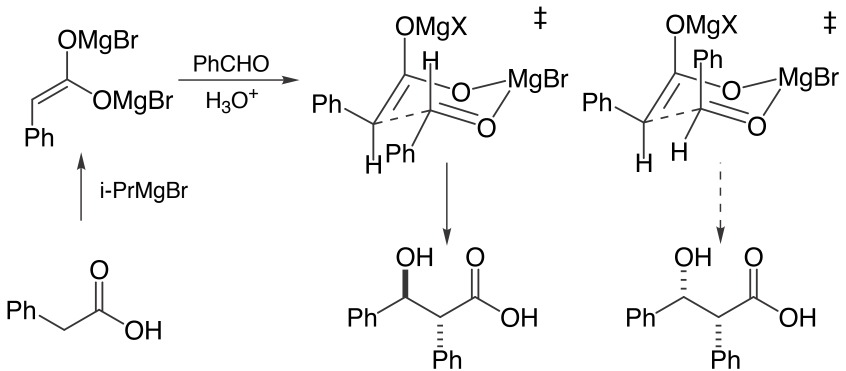
Comprehensive Organic Synthesis, **1991**; Vol 2

Group I & II metal enolates: Heathcock; Chapter 1.6, pp 181
Group III metal enolates: Masamune; Chapter 1.7, pp 239
Transition metal enolates: Paterson; Chapter 1.9, pp 301

Control relative stereochemical relationships

Zimmerman 1957:

Proposed chair-like geometry for the Ivanov Reaction



ratio, 75:25

Zimmerman recognized that diastereoselection should be a function of the relative sizes of the substituents on the carbonyl component.

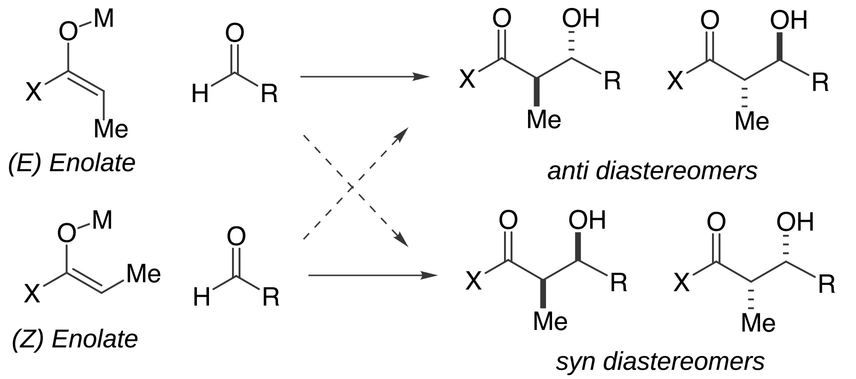
He also speculated on the role that the metal center might play in controlling the process.

The only flaw in the study was that he failed to determine whether the aldol adducts were stable to the reaction conditions.

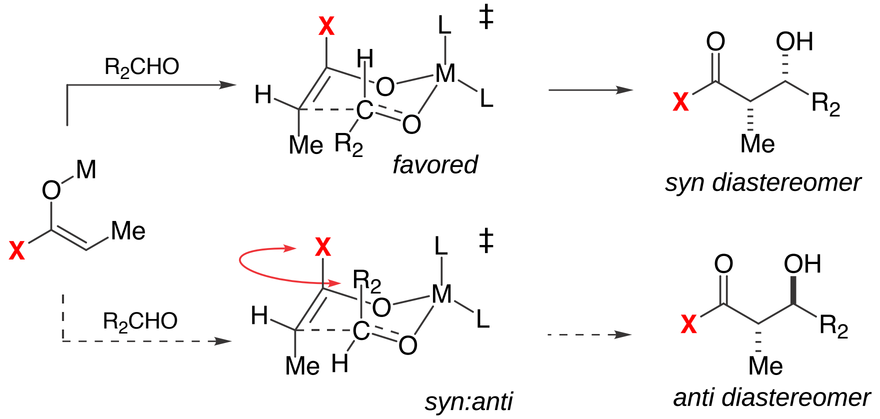
Zimmerman, *J. Am. Chem. Soc* ***1956***, *79*, 1920 **(handout)**

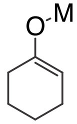
DuBois 1965-67:

Rough correlation between enolate stucture & product stereochemistry for alkali and alkaline earth enolates



Zimmerman-Traxler Model for *(Z)* Enolates



X = CMe_3	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972
X = C_6H_5	M = Li	80 : 20	
	M = Li	48 : 52	
	M = $AlEt_2$	50 : 50	House 1971

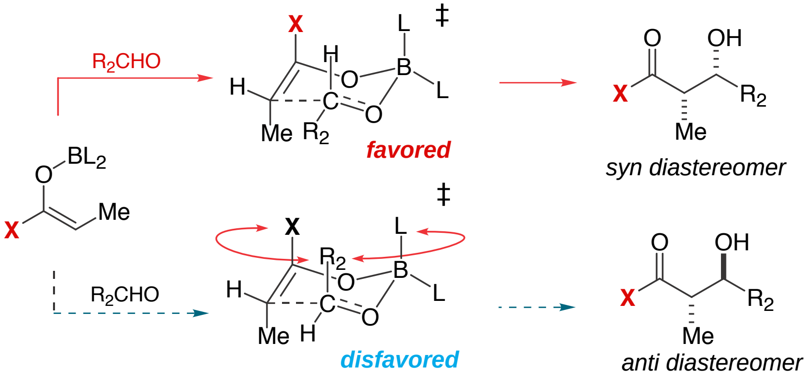
Stereocontrol optimal for "large" X; the reaction is not general.

The Aldol Reaction: Boron Enolates

Why Boron?

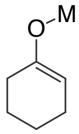
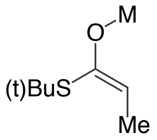
To tighten up the transition state.
Design TS where control can come exclusively from metal center

M–O → B–O		M–C → B–C	
1.9-2.2 Å	1.4-1.5 Å	2.0-2.2 Å	1.5-1.6 Å



syn diastereomer

anti diastereomer

		syn:anti	
X = CMe$_3$	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972
	M = BBu_2	> 97 : 3	DuBois 1972
X = C$_6$H$_5$	M = Li	80 : 20	Evans, Masamune 1979-81
	M = BBu_2	> 97 : 3	
X = Et	M = Li	80 : 20	
	M = BBu_2	> 97 : 3	
	M = Li	48 : 52	House 1971
	M = $AlEt_2$	50 : 50	Yamamoto 1977
	M = BBu_2	33 : 67 (ether)	
	M = BBu_2	17 : 83 (pentane)	Evans, Masamune 1979-81
	M = BCy(thex)	6 : 94 (CH_2Cl_2)	
	M = $B(Cyp)_2$	<5 : 95 (pentane)	

Evans et al. *JACS* ***1979***, *101*, 6120-6123; *JACS* ***1981***, *103*, 3099-3111

Masamune, *Tet. Lett* ***1979***, 1665, 2225, 2229, 3937

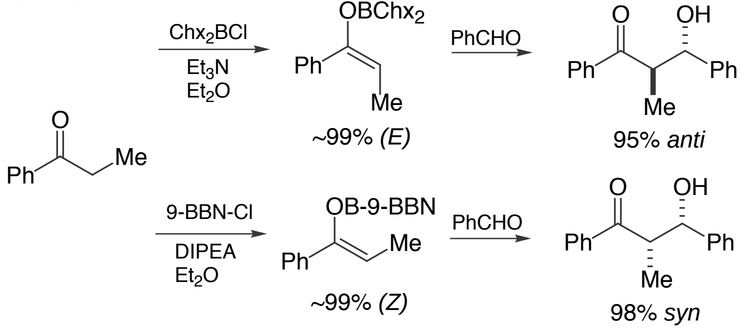
Are (E) enolates intrinsically less diastereoselective?

Now that there are good methods for preparing (E) enolates, it appears that both enolate geometries are nearly equivalent.

Dialkylboron chlorides (Brown)

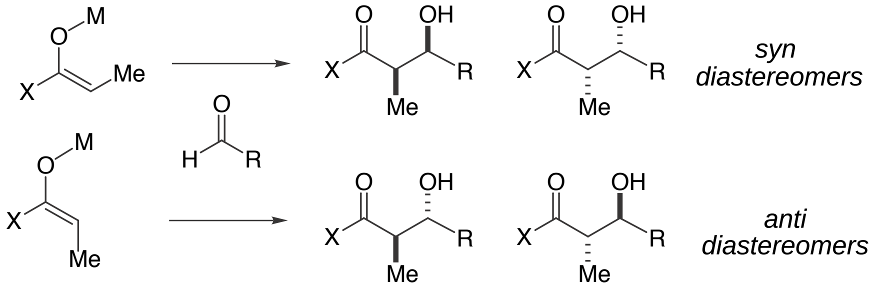
JACS. **1989**, *111*, 3441-3442.
J. Org. Chem. **1992**, *57*, 499-504.
J. Org. Chem. **1992**, *57*, 2716-2721.
J. Org. Chem. **1992**, *57*, 3767-3772.
J. Org. Chem. **1993**, *58*, 147-153.

JACS. **1989**, *111*, 3441-3442.

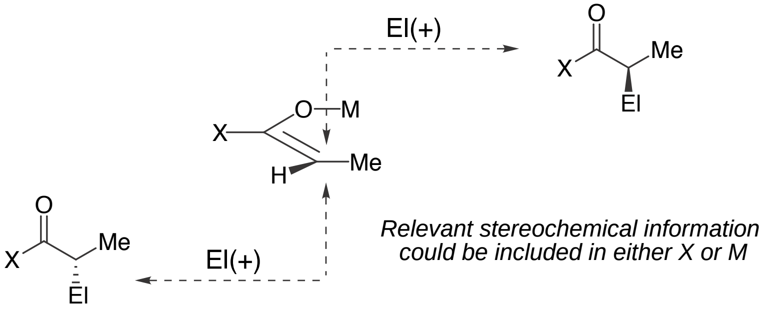


It appears that there is not a great difference in aldol diastereoselectivity

Dissection of the Aldol Problem: Select for one product diastereomer



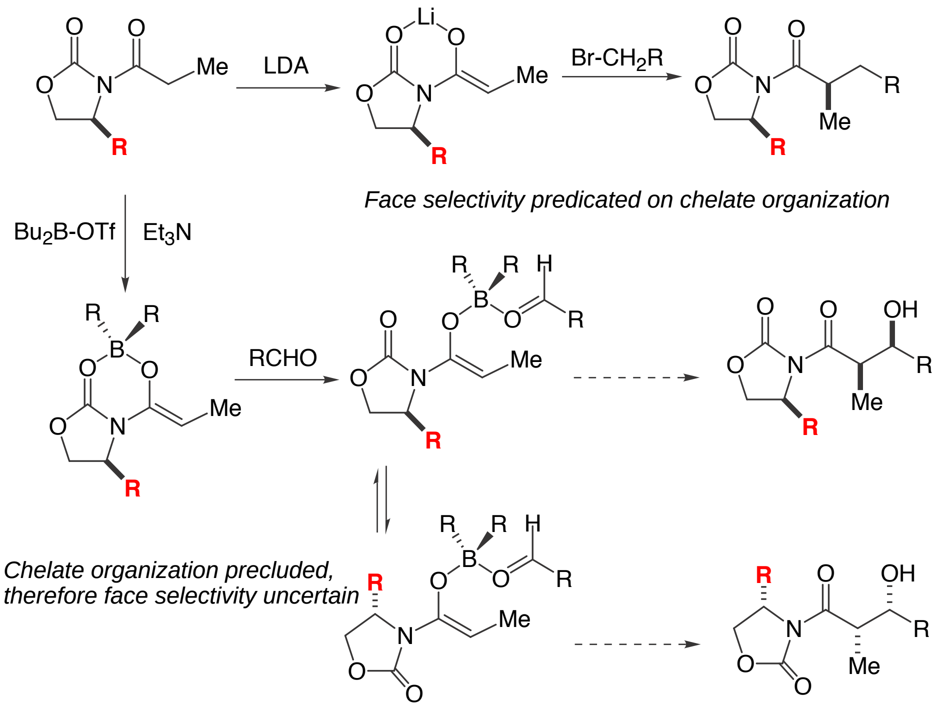
Control attack on the two enolate enantiofaces



Relevant stereochemical information could be included in either X or M

The Aldol Reaction: Boron Imide Enolates

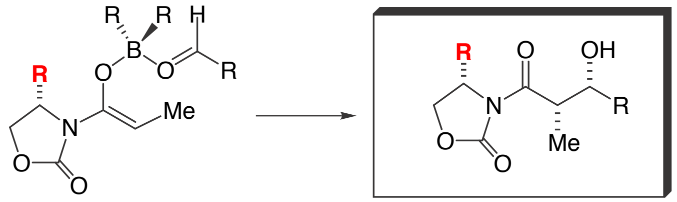
Imide Enolates: The problem of enolate face selectivity



Face selectivity predicated on chelate organization

Chelate organization precluded, therefore face selectivity uncertain

The aldol reaction selects for the opposite enolate diastereoface

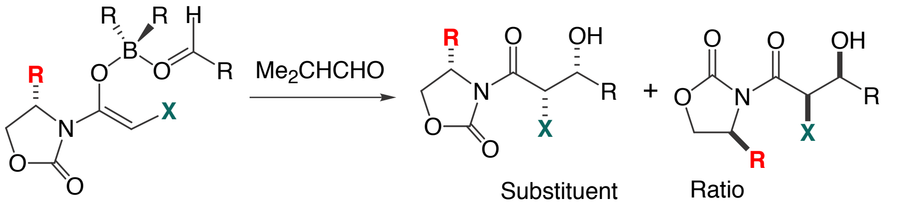


Result discovered but not predicted

diastereoselection > 98%

J. Am. Chem. Soc ***1981****, 103,* 2127-2129 **(Handout)**

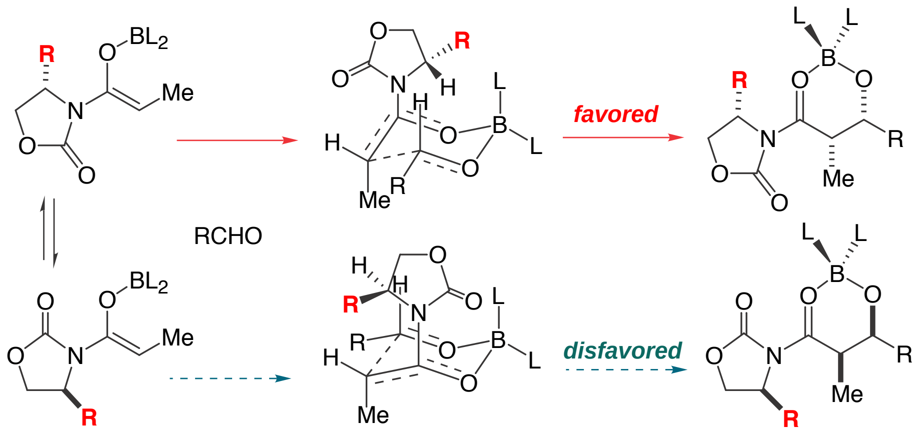
The Alpha substituent, X, plays pivotal role in aldol diastereoselection



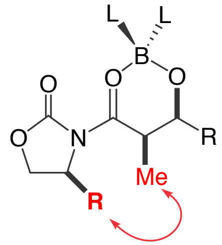
How can we rationalize these data ?

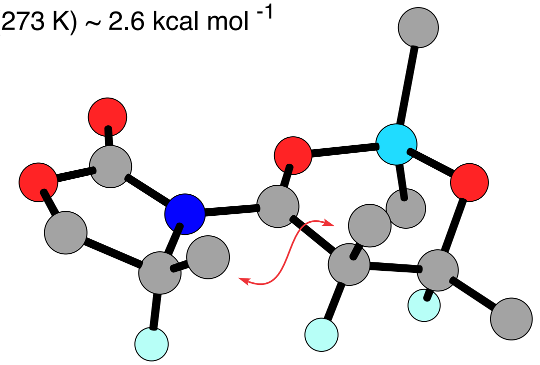
Substituent	Ratio
X = Me	> 300 : 1
X = SMe	60 : 1
X = H	1 : 1

Model for Asymmetric Induction (unpublished)



$\Delta\Delta G^{\ddagger}$ (273 K) ~ 2.6 kcal mol $^{-1}$

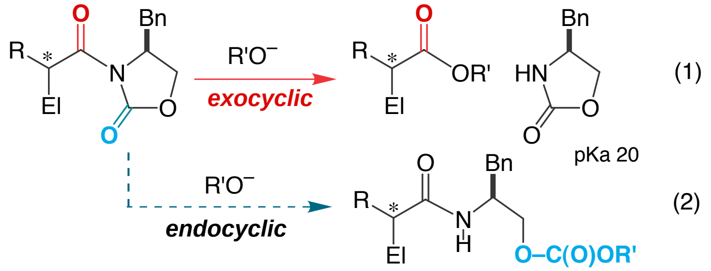




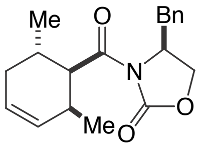
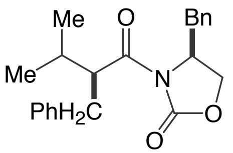
disfavored product diastereomer: The destabilizing interaction?

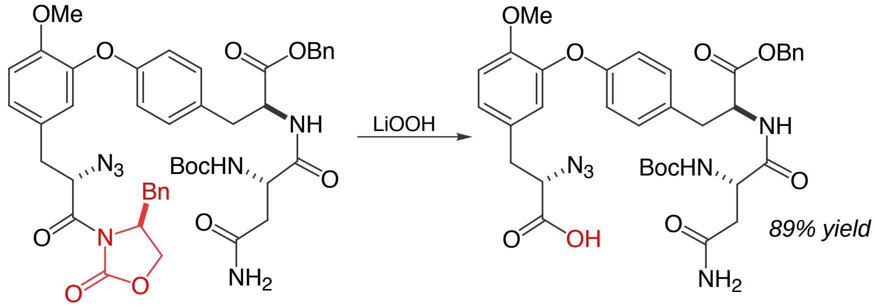
Imide Hydrolysis

Imides may suffer attack at either of the two C=O functions (eq 1, eq 2)

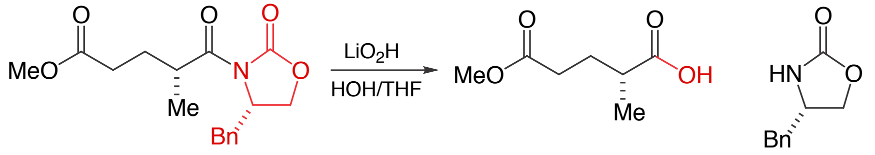


Product distribution a function of attacking nucleophile (*Tet. Lett.* ***1987***, *28*, 6141)

Substrate	Reagent	Exo:Endo Ratio	Substrate	Reagent	Exo:Endo Ratio
	LiOH	0 : 100		LiOH	06 : 89
	LiOOH	76 : 16		LiOOH	96 : 04



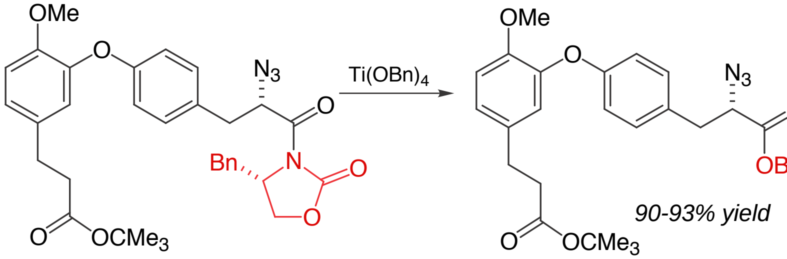
(OF-4949 Synthesis) JACS ***1989***, *111*, 1063



M. Bilodeau, unpublished results

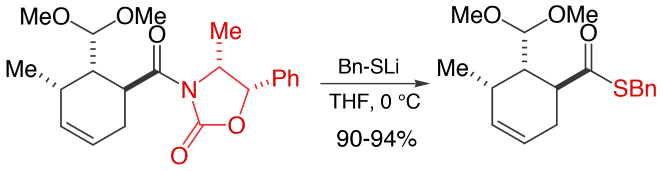
complete hydroytic selectivity possible

Trans-esterification

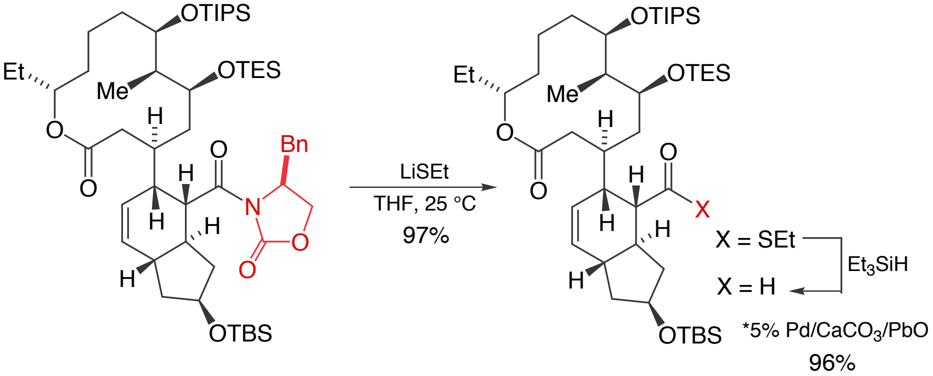


*(OF-4949 Synthesis) JACS****1989***, *111*, 1063

Trans-thioesterification:



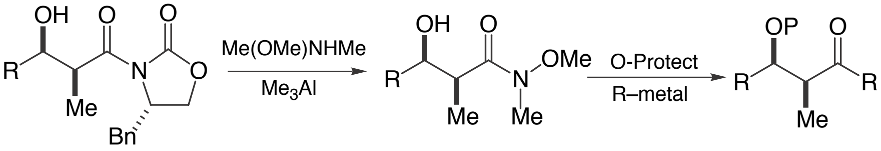
Damon, *Tet. Lett.* ***1990***, *31*, 2849-2852



(Lepicidin Synthesis) J. Am. Chem. Soc ***1993***, *115*, 4497-4513

$RCOSR \longrightarrow RCHO$ Fukuyama, *J. Am. Chem. Soc* ***1990***, *112*, 7050-7051

Transamination to Weinreb Amides (see Handout 24A)

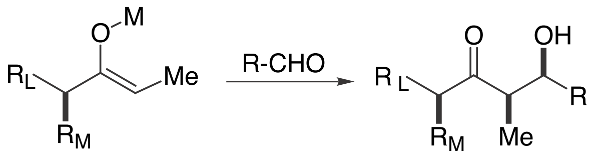


for recent examples see, *J. Am. Chem. Soc* ***1992***, *114*, 9434-9453

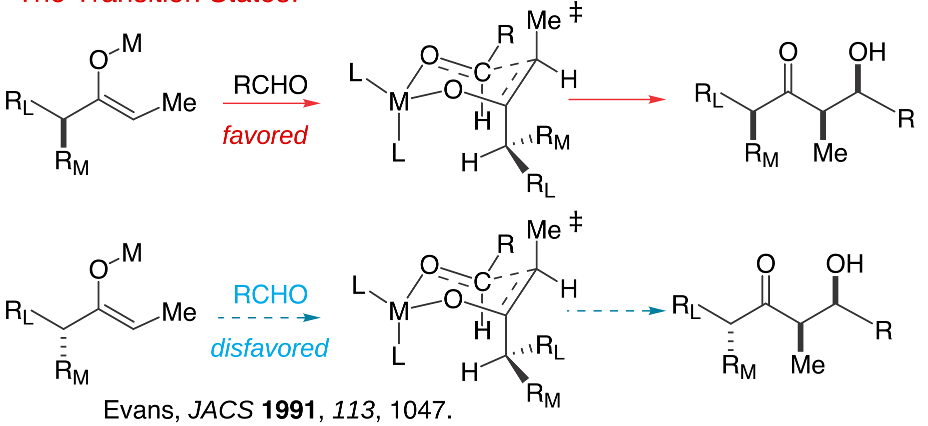
The Aldol Reaction: Syn Aldol Rxns of Chiral Ethyl Ketones

General Reaction for Syn Aldols: M = B, Ti

M = B, Ti

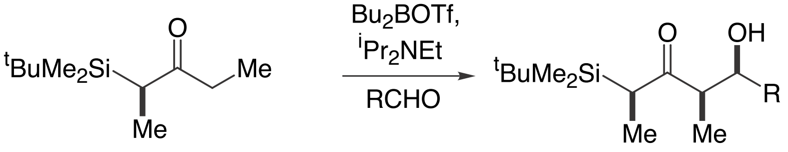


The Transition States:



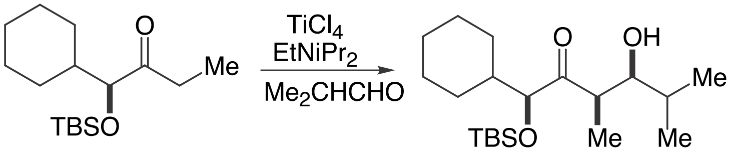
Evans, *JACS* **1991**, *113*, 1047.

Examples:



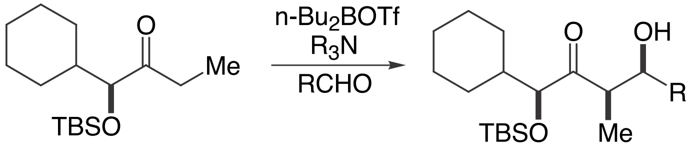
Enders *ACIEE* **1988**, *27*, 581.

Diastereoselection = 96-98%



Evans, *JACS* **1991**, *113*, 1047.

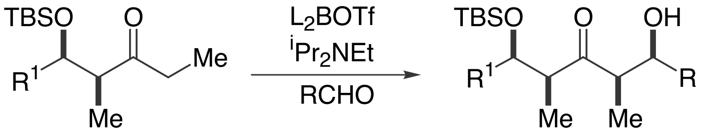
Diastereoselection: 99:1 (81%)



TBS = SiMe$_2{}^t$Bu

Masamune, *JACS* **1981**, *103*, 1566.

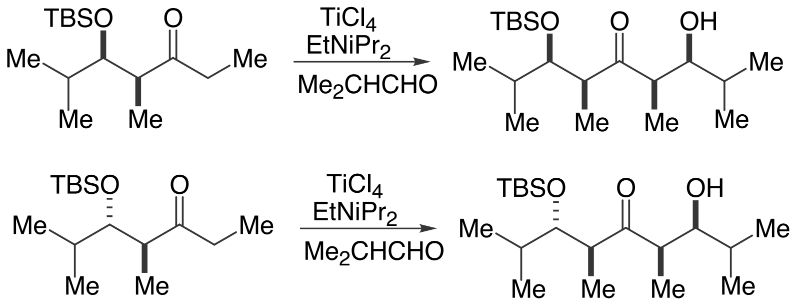
R	Diastereoselection
Ph	97:3
Et	98:2
BnOCH$_2$CH$_2$	96:4
Me$_2$CH	>99:<1



This system does not give a completely clean (Z) enolate

L	Diastereoselection
Bu	63:37 - 84:16
9-BBN	83:17 - 85:15
(-)-Ipc	72:28
(+)-Ipc	91:9 - 94:6

Paterson, McClure, *Tet.Lett.* **1987**, *28*, 1229.

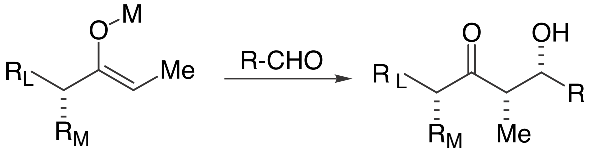


Evans, *JACS* **1991**, *113*, 1047.

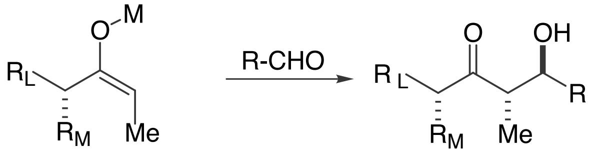
Diastereoselection: 95:5 (80-90%)

The Aldol Reaction: Anti Aldol Rxns of Chiral Ethyl Ketones

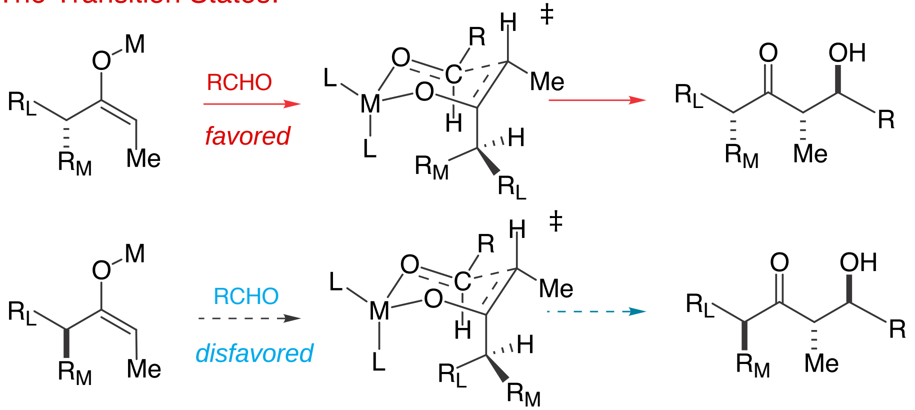
General Reaction for Syn Aldols:



General Reaction for Anti Aldols:

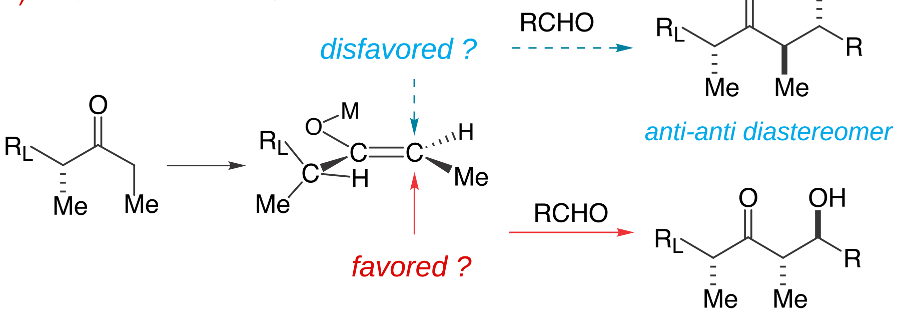


The Transition States:

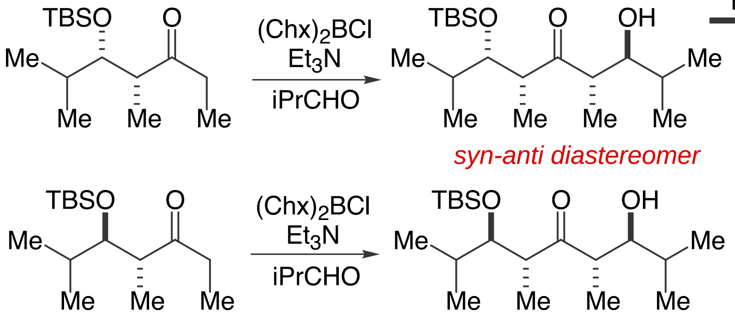


Evans, *JACS* **1991**, *113*, 1047.

(E) Enolate Facial Bias

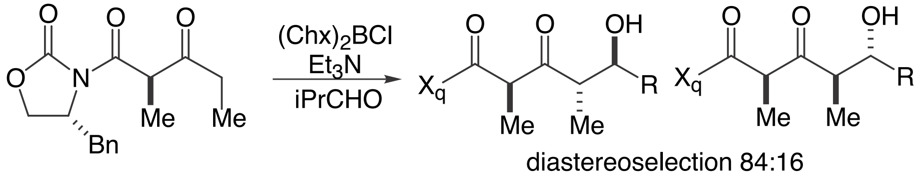


Examples:



Diastereoselection major : Σ others
94:6 (90%)
96:4 (75%)

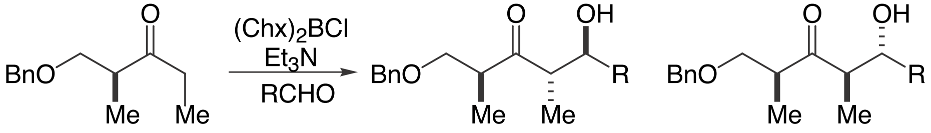
However, the preceding precedent does not extend to these systems:



diastereoselection 84:16

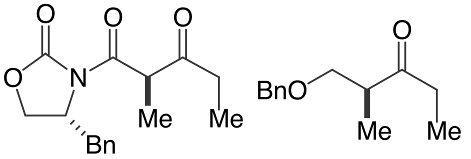
D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger *Tetrahedron*, **1992**, *48*, 2127-2

An analogous case:



diastereoselection 95:5

I. Patterson, J. M. Goodman, M. Isaka *Tetrahedron Lett.* **1989**, *30*, 7121-7

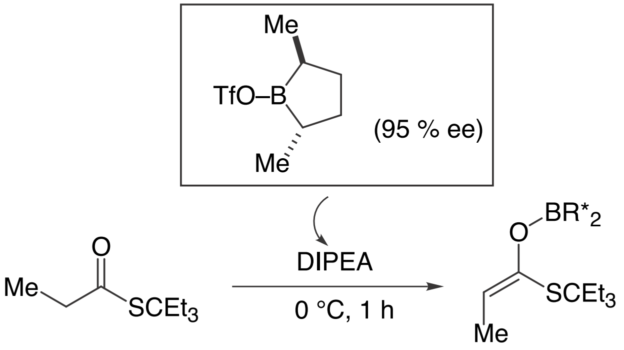


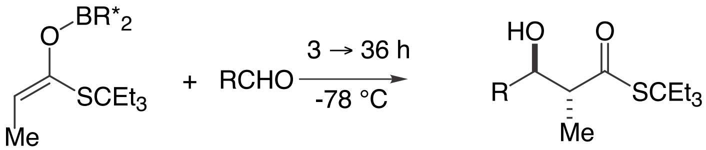
These enolates do not comply with steric analysis: → electronic effects?

Tetrahedron, **1992**, *48*, 2127-2142.

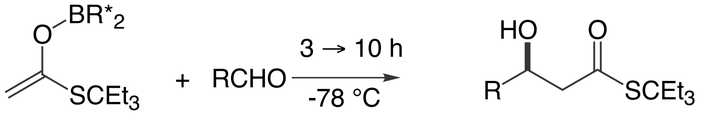
The Aldol Reaction: Metal-Centered Chirality

Masamune, Sato, Kim, Wollmann *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281.

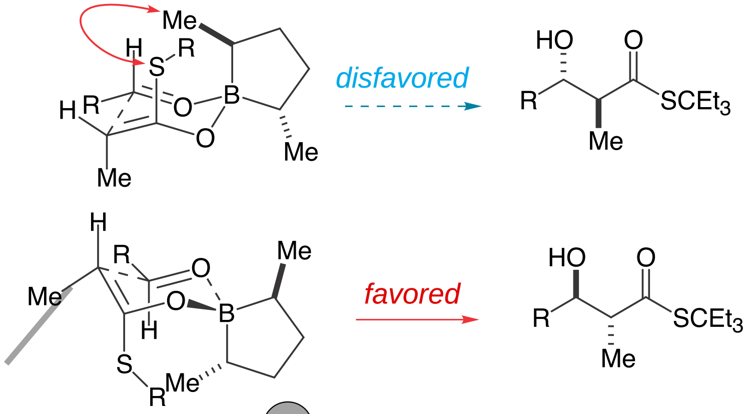


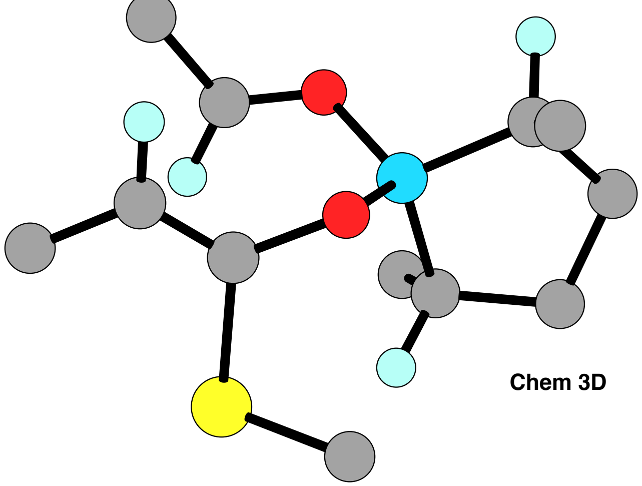


RCHO	Yield, %	anti/syn	ee % (corrected)
n-PrCHO	91	33:1	93 (98)
i-PrCHO	85	30:1	95 (99)
t-BuCHO	95	30:1	96 (99.9)
c-C_6H_{11}CHO	82	32:1	93 (98)
PhCHO	(71)	33:1	96 (99.8)



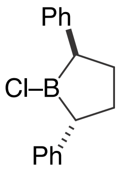
RCHO	Yield, %	ee % (corrected)
n-PrCHO	82	87 (91)
i-PrCHO	81	87 (92)
t-BuCHO	71	94 (98)
c-C_6H_{11}CHO	95	86 (90)
PhCHO	78	88 (92)





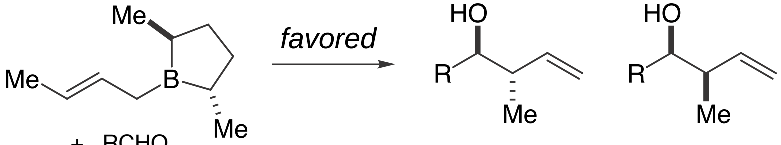
See analogous study by Reetz

Reetz *Tetrahedron Lett.* **1986**, 4721



Analogous Carbonyl Allylation

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831

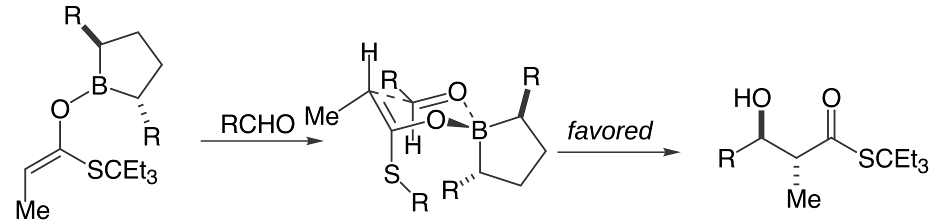


syn:anti, 96:4

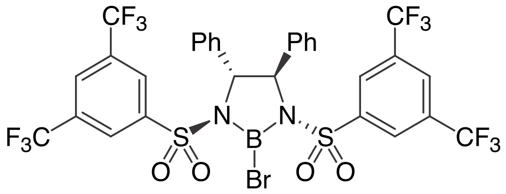
enantioselection: 95-97%

The Aldol Reaction: Metal-Centered Chirality

Masamune-Reetz Analogy:



Metal-Based Chiral Auxilliary:



1

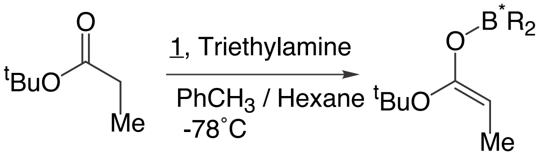
References:

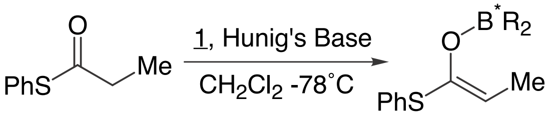
(Corey) *JACS*. **1989**,*111*, 5494
(Corey) *JACS*. **1990**,*112*, 4977
(Corey) *TL*. **1991**,*32*, 2857
(Corey) *TL*. **1993**,*34*, 1737.

Does this reagent perform in accord with the Masamune-Reetz analogy?
Note: The sulfonamide nitrogens are pseudo-tetrahedral

Enolization:

Either enolate geometry possible with proper choice of base, solvent, and substrate.

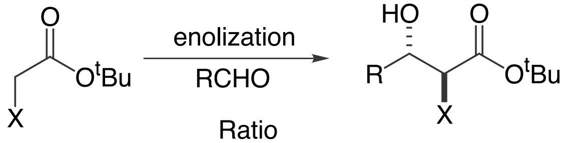




A mechanistic proposal for enolization control is presented in paper

(Corey) *JACS*. **1989**,*111*, 5494

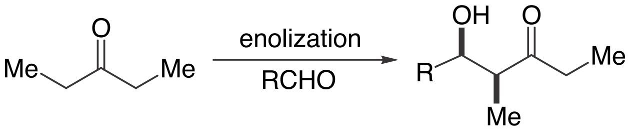
Chiral Anti Aldol Reaction: *JACS* **1990**,*112*, 4977; *TL* **1991**,*32*, 2857.



(R)	(X)	Ratio syn:anti	% ee	Yield
Ph-	Me	2 : 98	94	93 %
chex-	Me	6 : 94	75	82 %

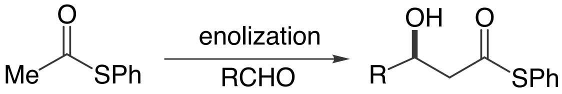
(R)	(X)	Ratio syn:anti	% ee	Yield
Ph-	Br	2 : 98	96	86 %
chex-	Br	2 : 98	91	65 %

Chiral Syn Aldol Reaction *JACS* **1989**,*111*, 5494.



(R)	Ratio syn:anti	% ee	Yield
Ph-	94 : 6	97	86 %
Me$_2$CH-	98 : 2	95	91 %
MeCH$_2$-	>98 : 2	>98	68 %

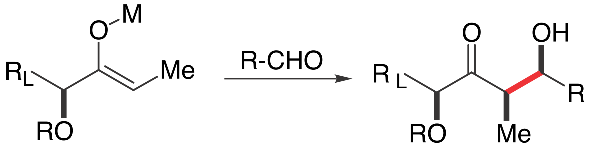
Chiral Acetate Aldol Reaction *JACS* **1989**,*111*, 5494.



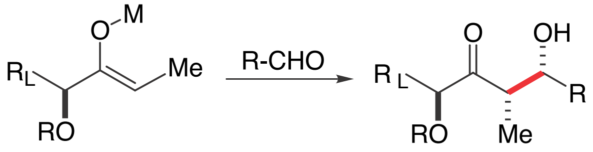
(R)	% ee	Yield
Ph-	91	84 %
Me$_2$CH-	83	82 %

The Aldol Reaction: Chelate vs Steric Control

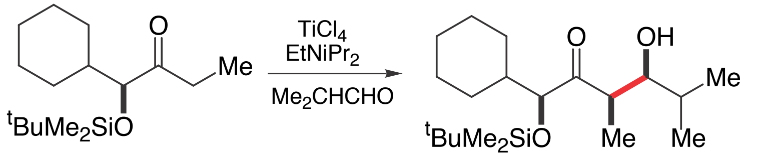
Reference Rxn



Chelate-Organized Variant

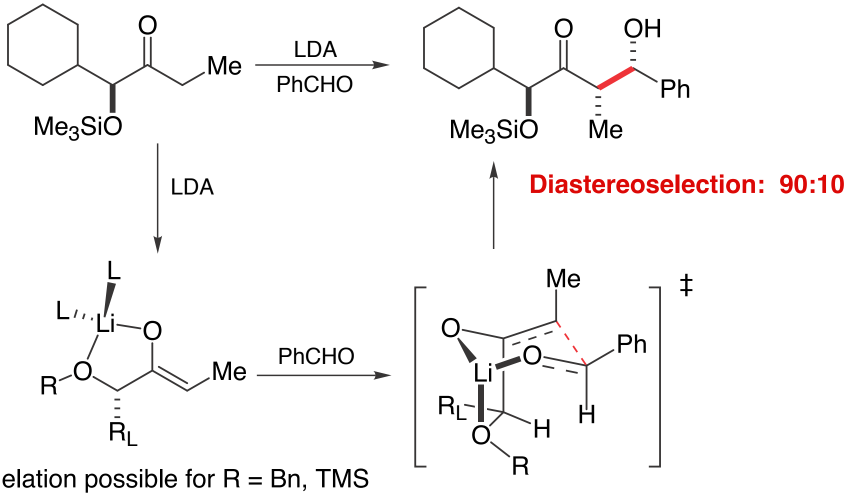


Nonchelate Reaction



Masamune, *JACS* **1981**, *103*, 1566 (boron enolate)
Evans, *JACS* **1991**, *113*, 1047 (titanium enolate)

Diastereoselection: 99:1

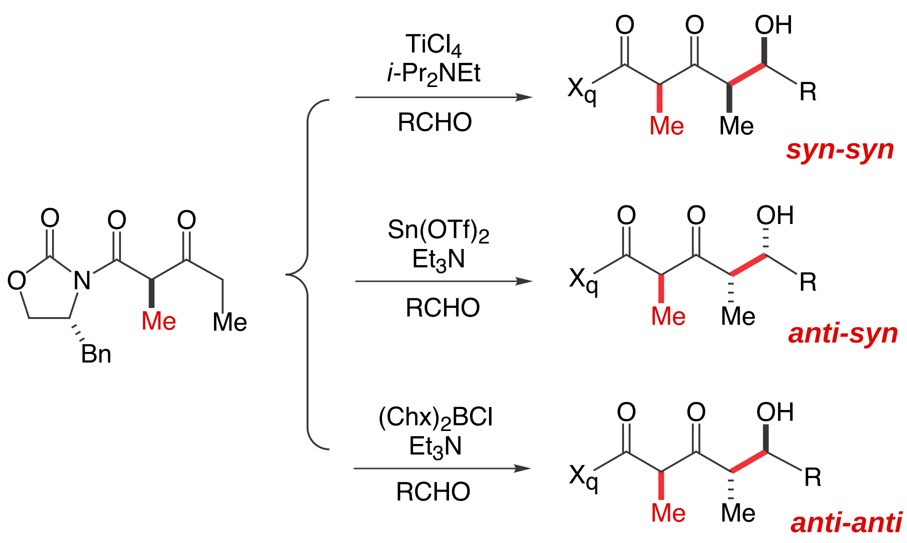


Diastereoselection: 90:10

Chelation possible for R = Bn, TMS
but marginal for TBS

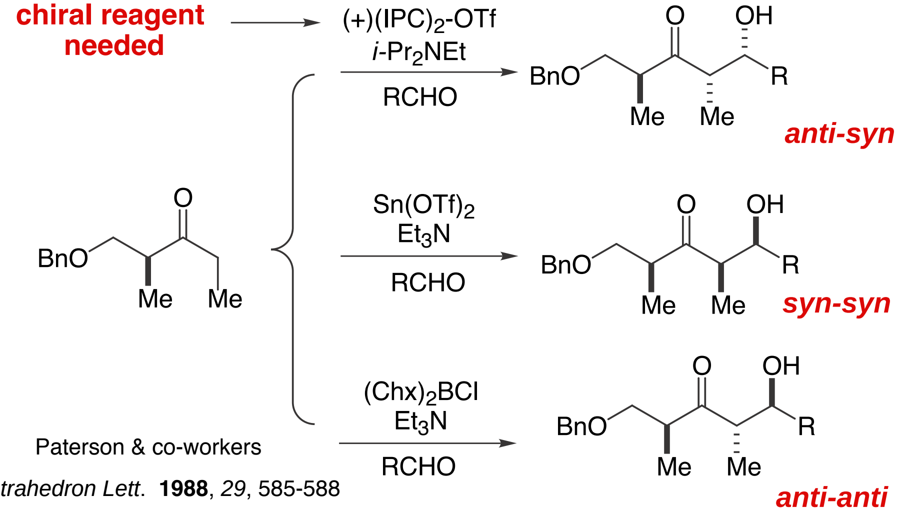
Thorton, *Tet. Let.* **1990**, *31*, 6001

Complimentary aldol reactions may be obtained by changing metal as well as enolate geometry



JACS, **1990**, *112*, 866; *Tetrahedron*, **1992**, *48*, 2127-2142.

chiral reagent needed



Paterson & co-workers

Tetrahedron Lett. **1988**, *29*, 585-588
Tetrahedron Lett. **1989**, *30*, 7121-7124
Tetrahedron Lett. **1992**, *33*, 4233-4236

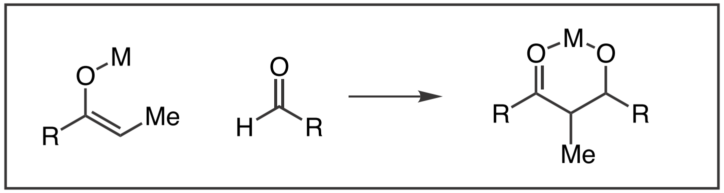
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 26

The Aldol Reaction–2



- (E) & (Z) Enolates: Felkin Selectivity
- Double Stereodifferentiating Aldol Reactions
- The Mukaiyama Aldol Reaction Variant
- Allylmetal Nucleophiles as Enolate Synthons

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Monday,
November 17, 2002

Assigned Reading

Lithium Diisopropylamide-Mediated Lithiations of Imines: Insights into highly Structure -Dependent Rates and Selectivities. D. Colum, *JACS* **2003**, *125*, ASAP **(handout)**

W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157. **(handout)**

Other Useful References

Evans, D. A., J. V. Nelson, et al. (**1982**). "Stereoselective Aldol Condensations." Top. Stereochem. 13: 1.

Heathcock, C. H. (**1984**). The Aldol Addition Reaction. Asymmetric Synthesis. Stereodifferentiating Reactions, Part B. J. D. Morrison. New York, AP. 3: 111.

Oppolzer, W. (**1987**). "Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis." Tetrahedron **43**: 1969.

Heathcock, C. H. (**1991**). The Aldol Reaction: Acid and General Base Catalysis. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 133.

Heathcock, C. H. (**1991**). The Aldol Reaction: Group I and Group II Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 181.

Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

Franklin, A. S. and I. Paterson (**1994**). "Recent Developments in Asymmetric Aldol Methodology." Contemporary Organic Synthesis 1: 317-338.

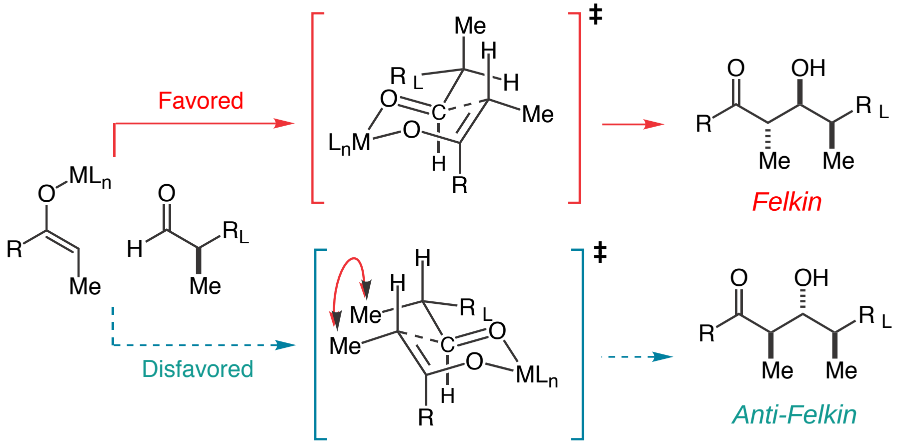
Cowden, C. J. and I. Paterson (**1997**). "Asymmetric aldol reactions using boron enolates." Org. React. (N.Y.) 51: 1-200.

Nelson, S. G. (**1998**). "Catalyzed enantioselective aldol additions of latent enolate equivalents." Tetrahedron: Asymmetry 9(3): 357-389.

Mahrwald, R. (**1999**). "Diastereoselection in Lewis-acid-mediated aldol additions." Chem. Rev. 99(5): 1095-1120.

Carbonyl Addition Reactions: (E)-Enolate Nucleophiles

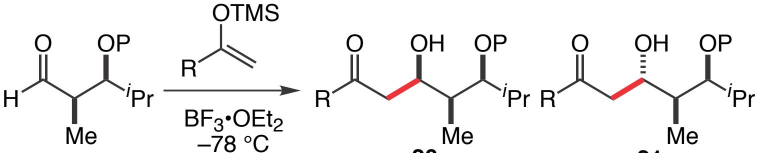
(E) Enolates Exhibit Felkin Aldehyde Diastereoface Selection



- ■ The illustrated syn-pentane interaction disfavors the anti-Felkin pathway.

Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157.

The Non-Reinforcing syn- RCHO is the most Interesting Dependence of the Selectivity of Felkin-controlled Reactions on Nu Size



19 P = PMB
6 P = TBS

20
Felkin/1,3-*syn*

21
anti-Felkin/1,3-*anti*

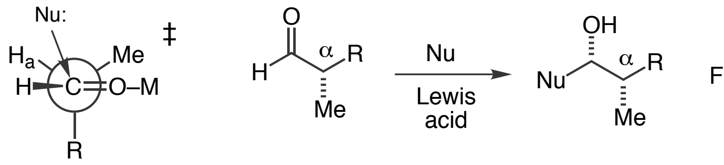
α-substituent dominates for Large Nu

β-substituent dominates for small Nu

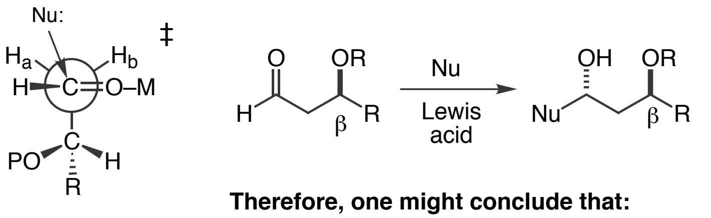
	P = PMB	P = TBS
R	**20** : **21**	**20** : **21**
t-Bu	96 : 04	94 : 06
i-Pr	56 : 44	75 : 25
Me	17 : 83	40 : 60

Background Information: The influence of β-OR substituents on RCHO

Evans, *JACS* **1996**, *118*, 4322-4343

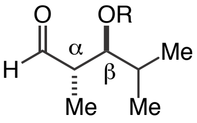


Felkin Selecton

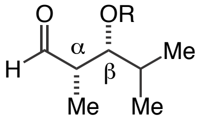


1,3-selection

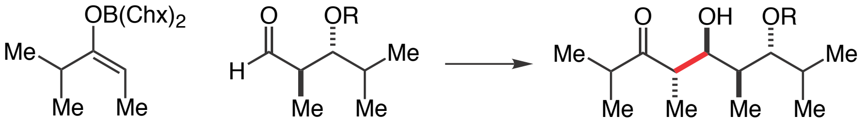
Therefore, one might conclude that:



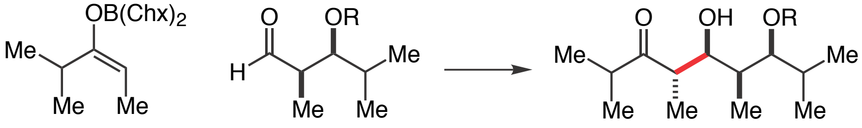
stereocenters reinforcing



stereocenters non-reinforcing



both centers reinforcing	major : Σ minors	
R = TBS	99 : 1	(77% yield)
R = PMB	93 : 7	(84% yield)



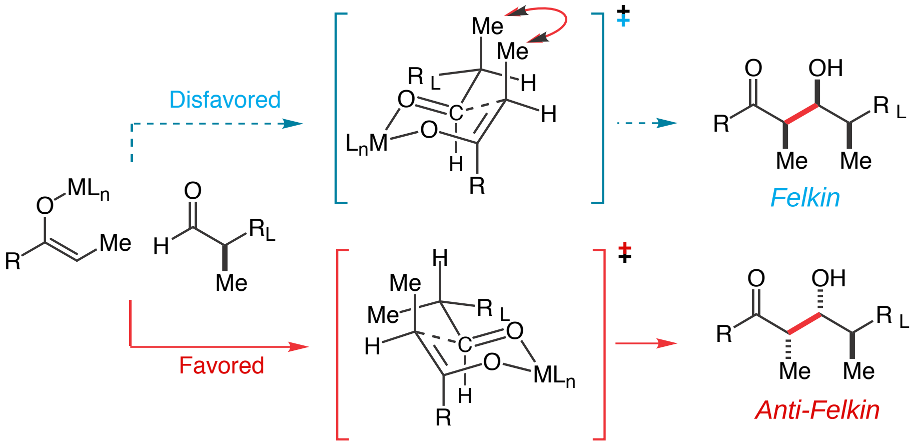
centers non-reinforcing	major : Σ minors	
R = TBS	94 : 6	(79% yield)
R = PMB	74 : 26	(82% yield)

Achiral (*E*) enolates preferentially add to the Felkin diastereoface
High *anti*:*syn* diastereoselectivity (≥ 97 : 3) is observed in all cases

Evans etal. *JACS* ***1995***, *117*, 9073

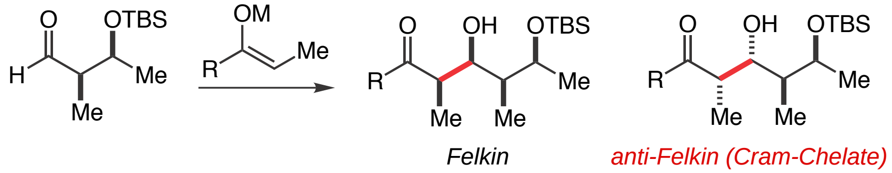
Carbonyl Addition Reactions: (Z)-Enolate Nucleophiles

(Z) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection

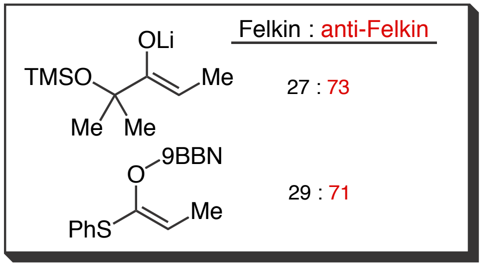


The illustrated syn-pentane interaction disfavors the Felkin pathway.

Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157.

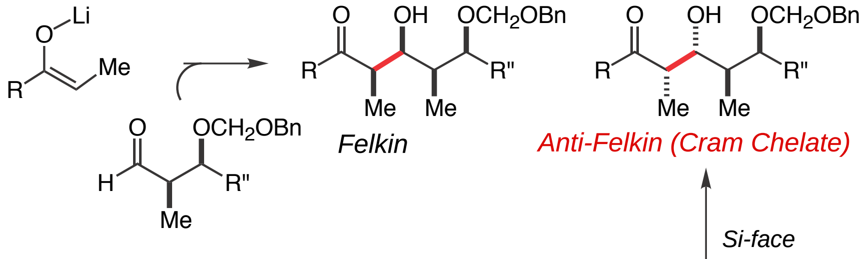


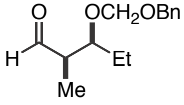
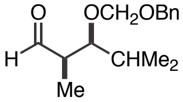
D. W. Brooks & Co-workers
Tetrahedron Lett. **1982**, *23*, 4991-4994.

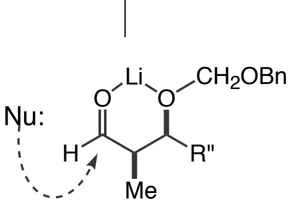


- The bulky OTBS group disfavors chelation. (see Keck, *JACS* **1986**, *108*, 3847.)
- The boron and lithium enolates display nearly equal levels of anti-Felkin selectivity.

An Early study rationalized results through chelated transition states:

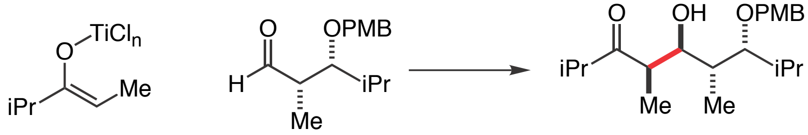


(R)	(R")	Felkin : Anti-Felkin
Et		17 : 83
C_6H_{11}		10 : 90
Et		13 : 87
C_6H_{11}		8 : 92

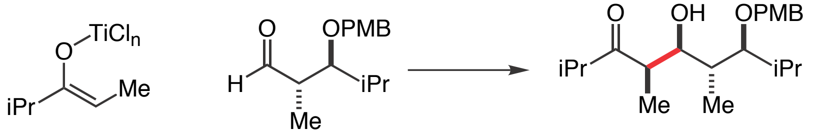


Masamune
JACS ***1982****, 104,* 5526

Titanium enolates exhibit the same trend



anti-Felkin : Felkin 77 : 23 (78%)

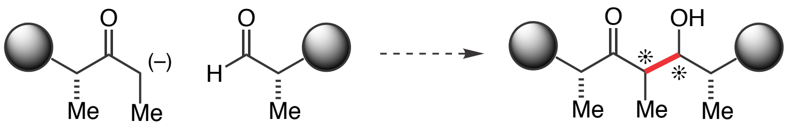


anti-Felkin : Felkin 56 : 44 (84%)

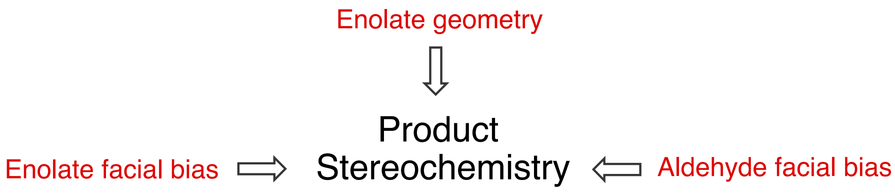
Evans etal. *JACS* ***1995****, 117,* 9073

Double Stereodifferentiating Bond Constructions-1

Double Stereodifferentiating Aldol Bond Constructions



Stereochemical Control Elements


Enolate geometry

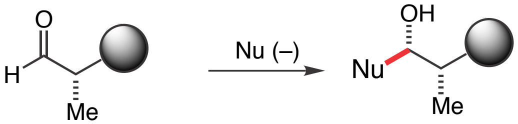
Product Stereochemistry

Enolate facial bias

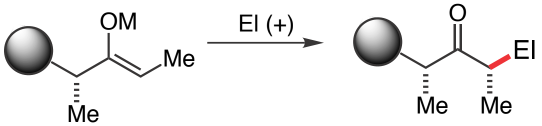
Aldehyde facial bias

The Issue: Can one reliably take the diastereoselectivites of the individual reaction partners and use this information in the illustrated extrapolation:

The model reactions:

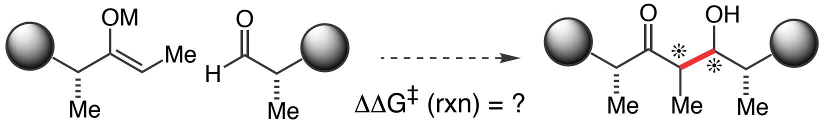


$\Delta\Delta G^{\ddagger}$ (aldehyde)



$\Delta\Delta G^{\ddagger}$ (enolate)

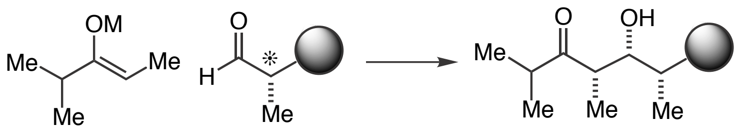
The extrapolation:



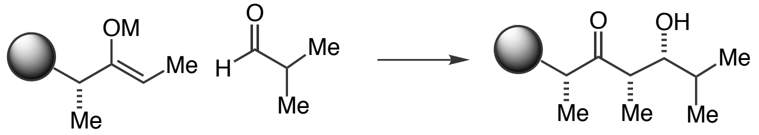
Masamune, *Angew. Chem. Int. Ed.* **1985**, *24*, 1-76

Matched reactant pair: Stereo-induction from both partners reinforcing

The reference reactions:

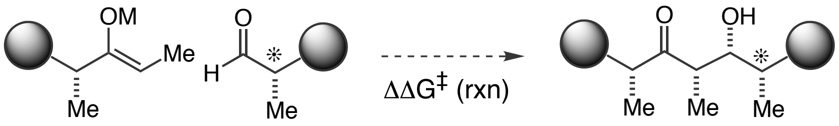


[aldehyde prod ratio] = 10/1



[enolate prod ratio] = 10/1

- The double stereodifferentiating situation: Stereoselectivity?



- The assumption: (Masamune, Heathcock)

It is presumed that useful information can be obtained from related achiral enolate & RCHO addition reactions and that the free energy contributions will be additive:

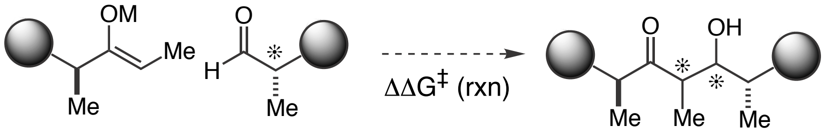
$$\Delta\Delta G^{\ddagger}\text{ (Rxn)} \sim \Delta\Delta G^{\ddagger}\text{ (enolate)} + \Delta\Delta G^{\ddagger}\text{ (RCHO)}$$

$$\log\text{ [Product ratio]} \sim \log\text{ [enolate ratio]} + \log\text{ [aldehyde ratio]}$$

$$\text{[Product ratio]} \sim \text{[enolate prod ratio]} \times \text{[aldehyde prod ratio]}$$

- Hence, for the case at hand: [Product ratio] ~ [10] x [10] ~ 100

Mismatched reactant pair: Stereo-induction from partners nonreinforcing

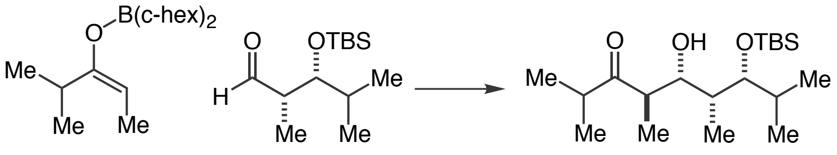


$$\Delta\Delta G^{\ddagger}\text{ (Rxn)} \sim \Delta\Delta G^{\ddagger}\text{ (enolate)} - \Delta\Delta G^{\ddagger}\text{ (RCHO)}$$

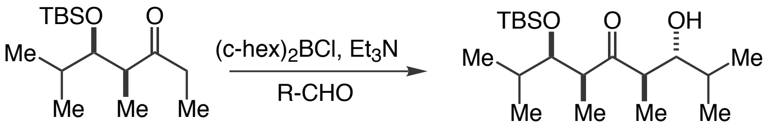
Double Stereodifferentiating Bond Constructions-2

The Masamune-Heathcock generalizations hold to a point:

(E)-Boron Enolates: The reference reactions

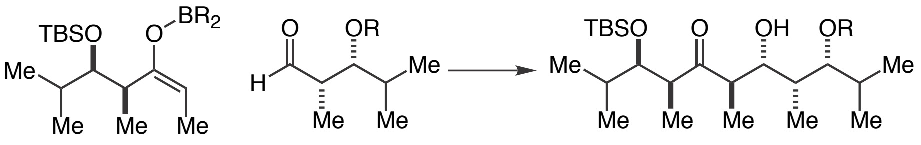


diastereoselection 94 : 6



diastereoselection 96 : 4

(E)-Boron Enolates: The matched cases

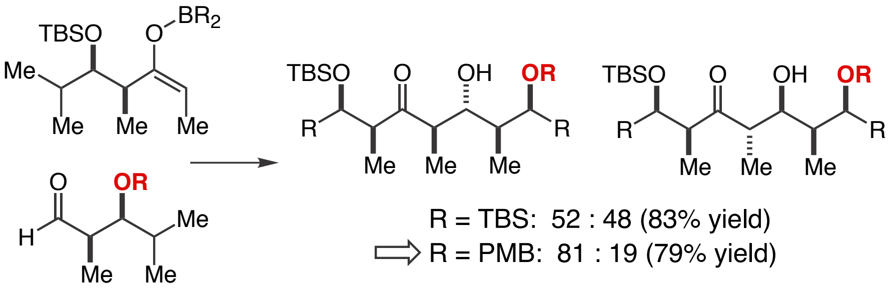


diastereoselection: anti : Σ others

R = TBS: >99 : 1 (85% yield)

R = PMB: >99 : 1 (84% yield)

(E)-Boron Enolates: The mismatched cases

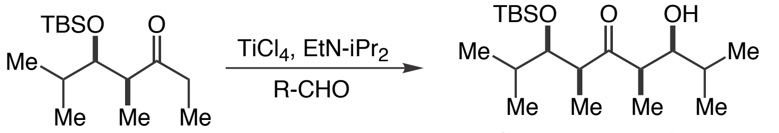


R = TBS: 52 : 48 (83% yield)

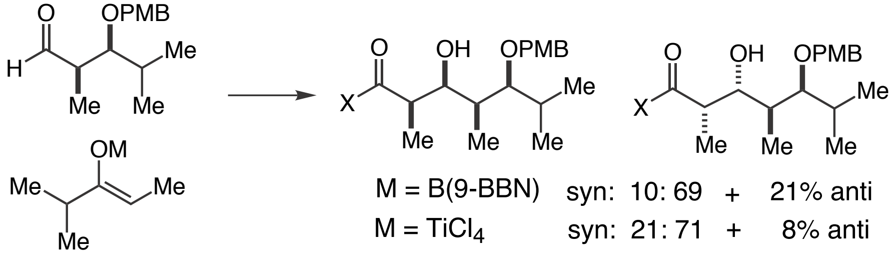
⇨ R = PMB: 81 : 19 (79% yield)

β-center on RCHO can play a significant role in this marginal situation

(Z)-Titanium Enolates: The reference reactions



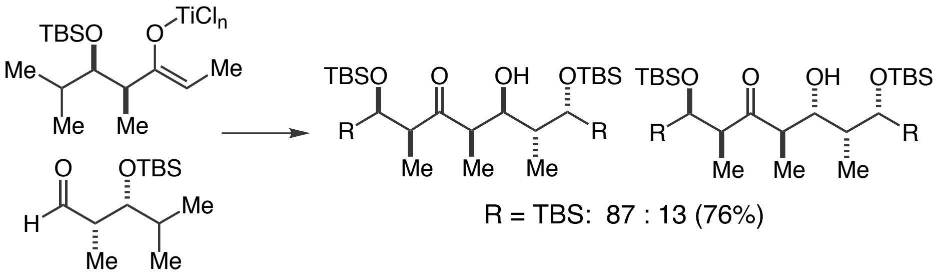
diastereoselection 96 : 4



M = B(9-BBN) syn: 10: 69 + 21% anti

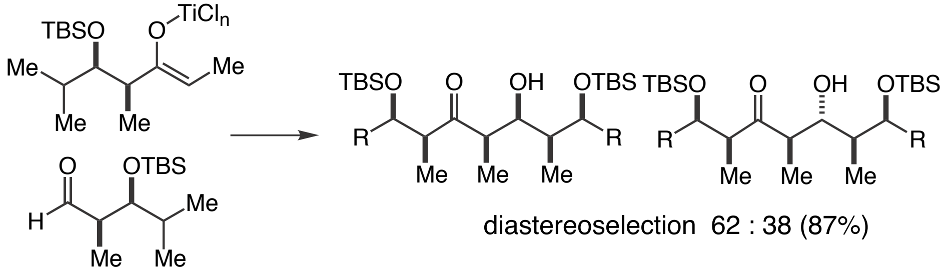
M = $TiCl_4$ syn: 21: 71 + 8% anti

(Z)-Titanium Enolates: The matched cases



R = TBS: 87 : 13 (76%)

(Z)-Titanium Enolates: The mismatched cases

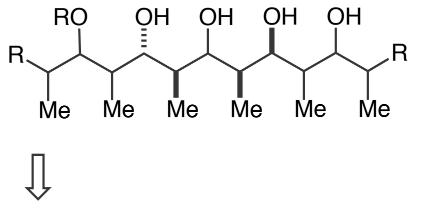


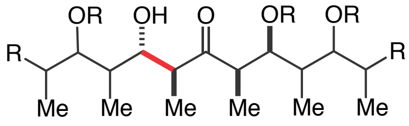
diastereoselection 62 : 38 (87%)

"Double Stereodifferentiating Aldol Reactions. The Documentation of "Partially Matched" Aldol Bond Constructions". Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *JACS* **1995**, *117*, 9073-9074.

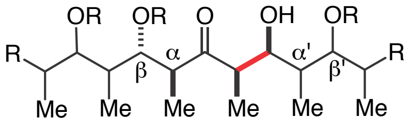
Synthesis of Polyketide chains

Given a polyprpionate chain of alternating Me & OH substitutents, select a disconnection point sectioning the fragments into subunits of comparable complexity by adding C=O as illustrated.





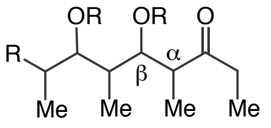
$T1_A$



$T1_B$

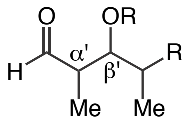
aldol

Focusing on the =O FG, there are 2 1st-order aldol disconnections highlighted. Let's proceed forward with **$T1_B$**. Carry out the dissconnection to subunits **2_K** and **2_A**.



2_K

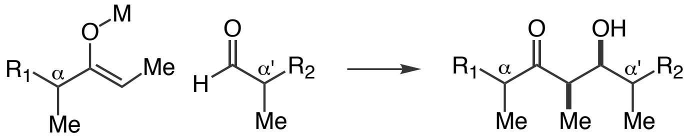
α center important
β center ignore



2_A

Both centers important

For substituted enolate and enolsilane-based processes, there are at least three identifiable **stereochemical determinants** that influence reaction diastereoselectivity (eq 1). Two of these determinants are associated with the local chirality of the individual reaction partners. For example, enolate (enolsilane) chirality influences the absolute stereochemistry of the forming methyl-bearing stereocenter, and in a similar fashion, aldehyde chirality controls the absolute stereochemical outcome of the incipient hydroxyl-bearing stereocenter. The third determinant, the pericyclic transition state, imposes a relative stereochemical relationship between the developing stereocenters. This important control element is present in the aldol reactions of metal enolates (M = BR_2, TiX_3, Li, etc.), but is absent in the Lewis acid catalyzed (Mukaiyama) enolsilanes aldol variants that proceed via open transition states.

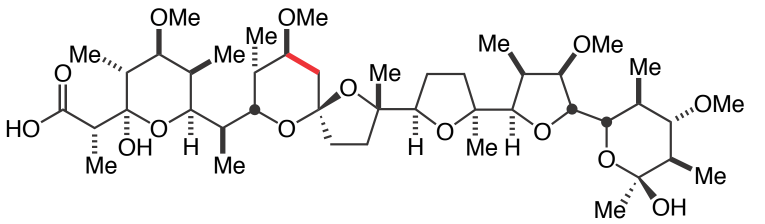


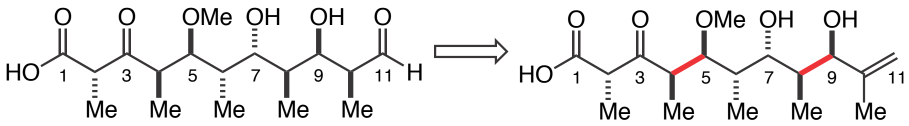
(1)

Stereochemical Determinants	M = BR_2	M = SiR_3
enolate facial bias	✔	✔
aldehyde facial bias	✔	✔
pericyclic transition state	✔	✘

The Lonomycin Synthesis: An example of polypropionate assembage

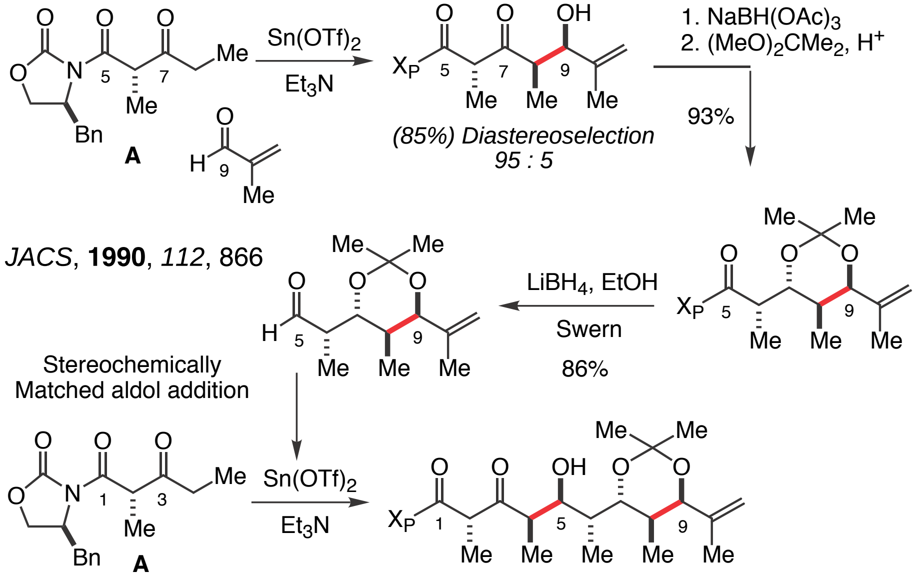
Evans, Ratz, Huff, Sheppard *JACS* **1995**, *117*, 3448





BH_3 Transform: See Lecture No. 8

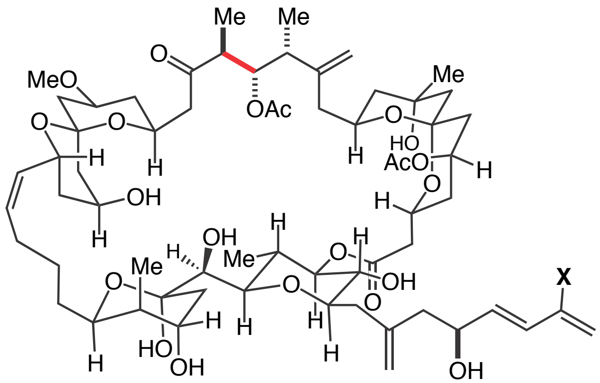
C_1–C_{11} Assemblage



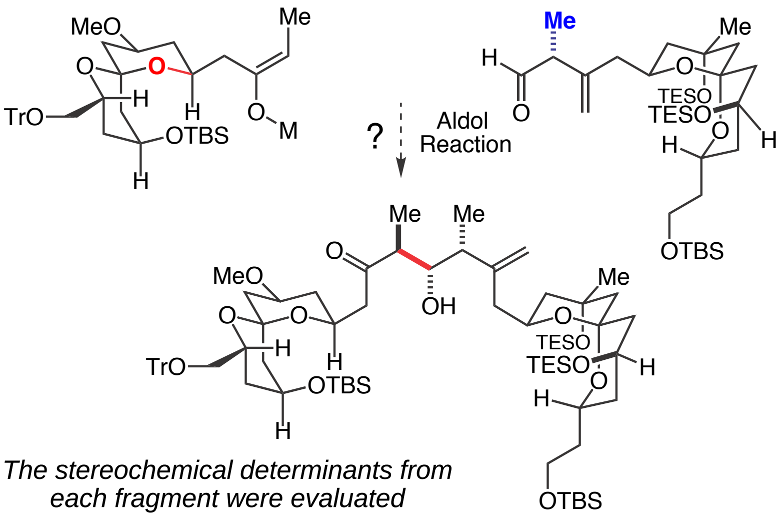
Anti-Felkin Adduct Diastereoselection >95 : 5 (86%)

The $Sn(OTf)_2$ aldol reaction of A: seethis lecture + *JACS*, **1990**, *112*, 866

The Altohyrtin Synthesis: An example of polypropionate assembage

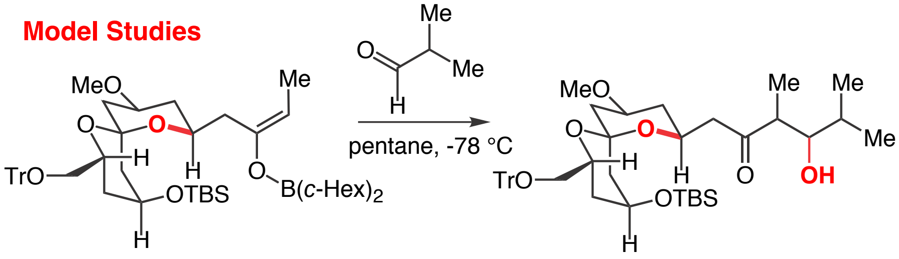


Evans, Trotter, Coleman, Cote, Dias, Rajapakse, *Tetrahedron* **1999**, *55*, 8671-8726.



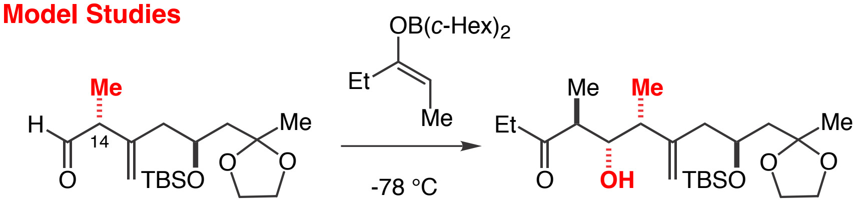
The stereochemical determinants from each fragment were evaluated

Model Studies



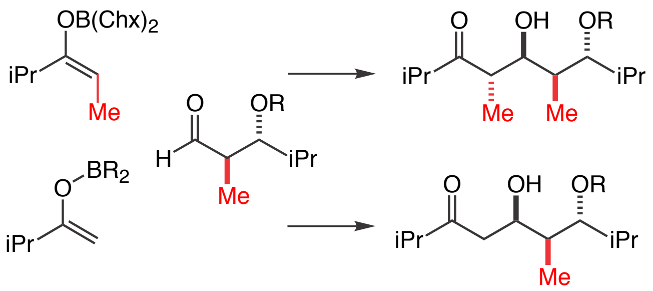
2:1 mixture of diastereomers

Model Studies



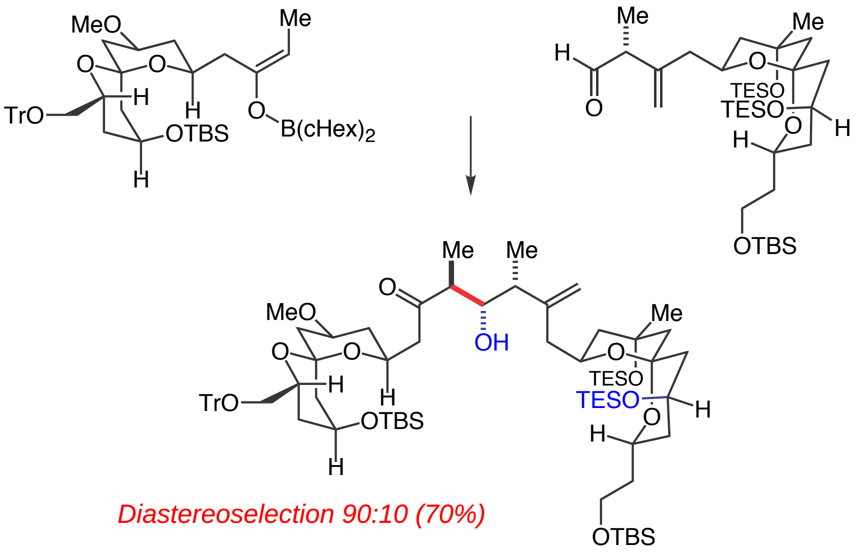
Diastereoselection 97:3

Background



	major : Σ others
R = TBS	99 : 1
R = PMB	93 : 7
R = PMB	69:31

The Aldol Fragment Coupling

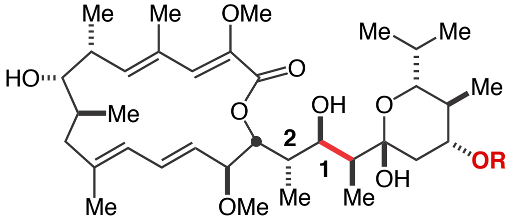


Diastereoselection 90:10 (70%)

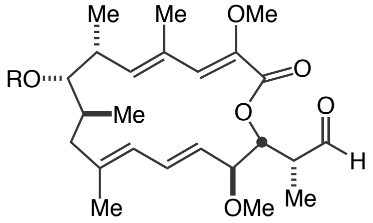
Bafilomycin A_1 Synthesis: An example of polypropionate assembage

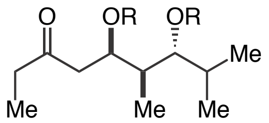
Evans, Calter, *Tetrahedron Lett.* **1993**, 34, 6871

Bafilomycin A_1



Critical Aldol Disconnection





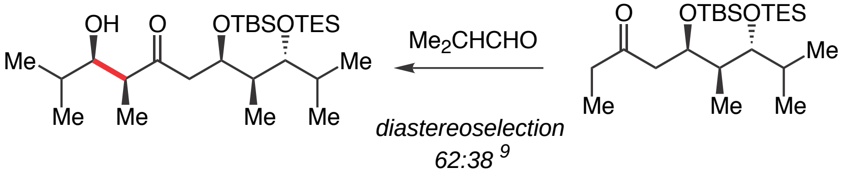
Required: Syn aldol addition

Aldehyde Fragment: Target contains syn aldol retron wilth anti-Felkin relationship at 1 & 2

Enolate Fragment: Can the needed enolate facial bias be built into the reaction??

Aldol Model Studies

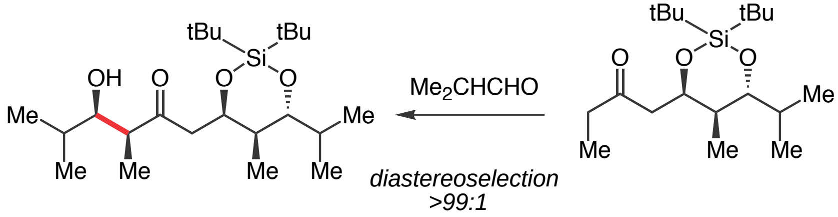
Enolization Conditions: $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78°C.



Me_2CHCHO

diastereoselection
62:38 [9]

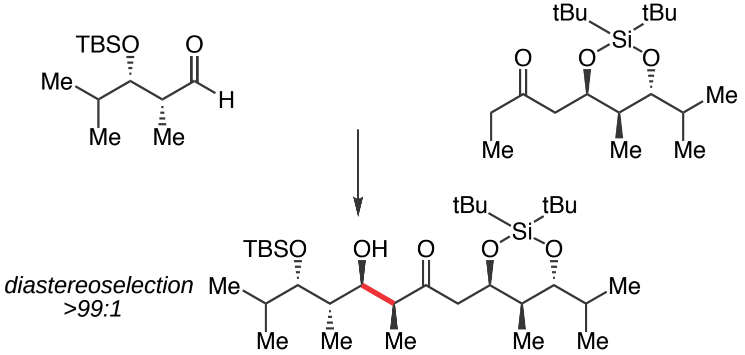
The Critical Observation



Me_2CHCHO

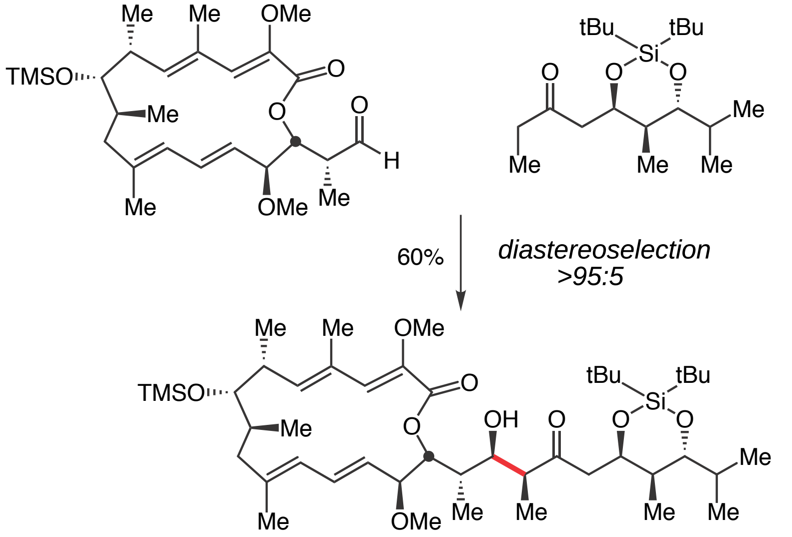
diastereoselection
>99:1

Enolization Conditions: $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78°C.

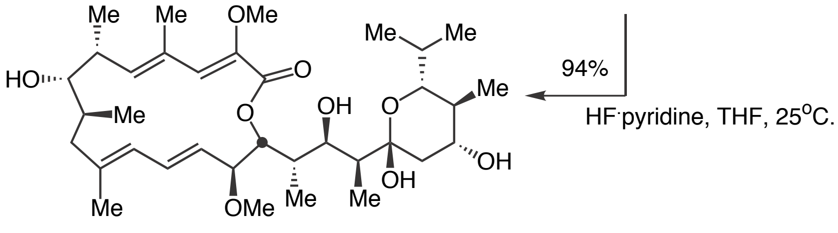


diastereoselection
>99:1

Critical Aldol Disconnection



diastereoselection
>95:5

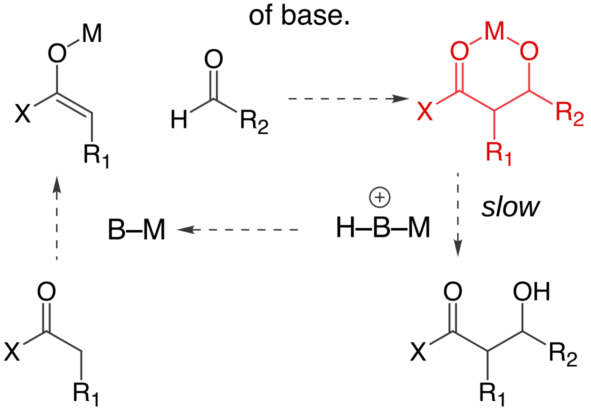


HF·pyridine, THF, 25°C.

Bafilomycin A_1

Type I Aldol Reaction: Metal Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of base.

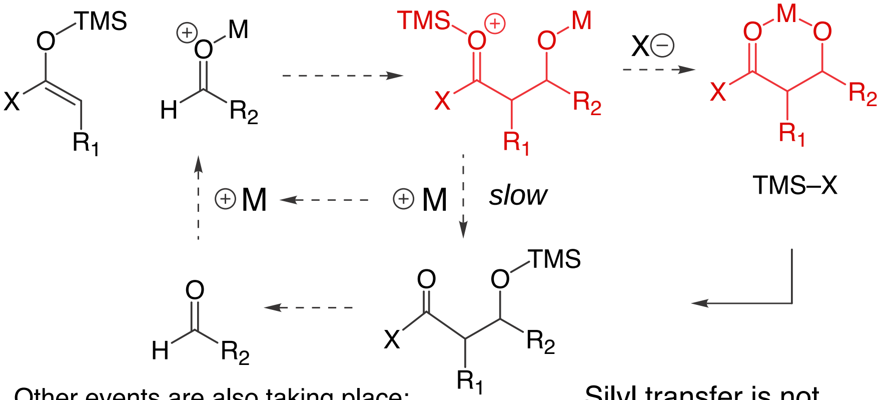


Catalytic Version: Slow step in the catalytic variant is protonation of the intermediate metal aldolate

Type II Aldol Reaction: Mukaiyama Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of Lewis acid.

The minimalist mechanism: MX = Lewis acid



Other events are also taking place:
Carreira *Tet. Lett* **1994**, *35*, 4323

Silyl transfer is not necessarily intramolecular

Recent Reviews

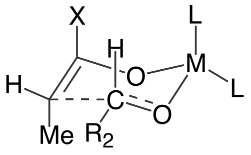
R. Mahrwald, *Diatereoselection in Lewis Acid Mediated Aldol Additions*, *Chem. Rev.* **1999**, *99*, 1095-1120

S. G. Nelson, *Catalyzed enantioselective aldol additions of latent enolate equivalents Tetrahedron: Asymmetry* **1998**, *9*, 357-389.

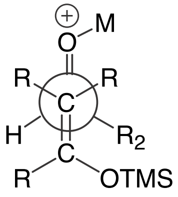
Mukaiyama Aldol Reaction, E. Carreira In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 998-1059.

Reaction Mechanism: "Closed" versus "Open" Transition States

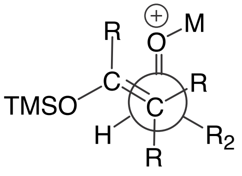
The Mukaiyama aldol reaction proceeds through an "open" transition state. The two illustrated competing TS orientations do not differ significantly in energy. For most reactions in this family there is not a good understanding of reactans-pair orientation. There is a prevalent view that the anti-periplanar TS is favored on the basis of electrostatic effects.



Metal aldolate TS
"Closed"

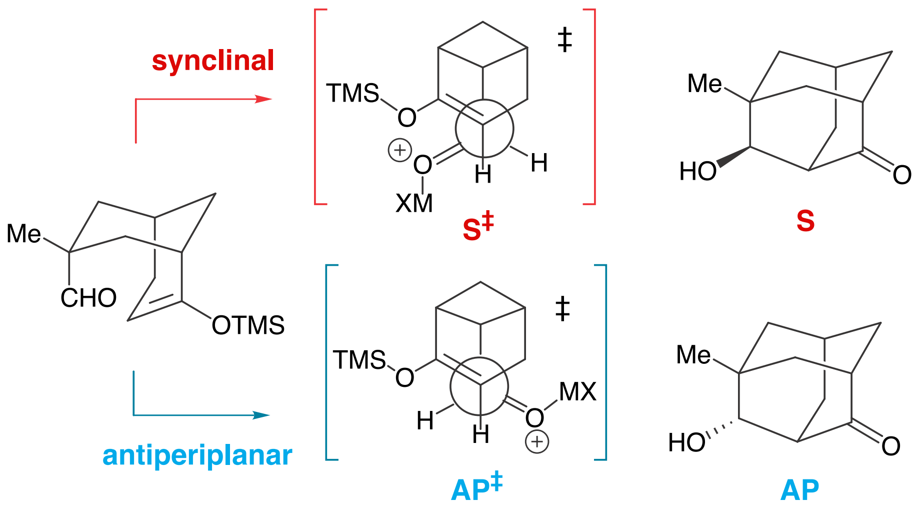


anti-periplanar TS
"Open"



synclinal TS
"Open"

Denmark has designed a nice substrate to distinguish between synclinal and anntiperiplanat transition states:
Denmark, *J. Org. Chem.* **1994**, *59*, 707-709

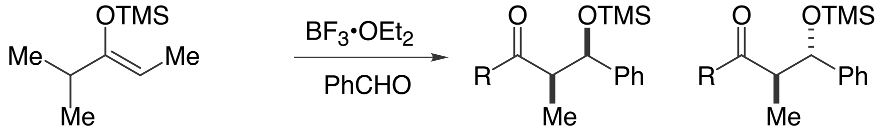


Lewis Acid	**syn**:**anti**
$TiCl_4$	21:79
$SnCl_4$	18:82
$BF_3{\cdot}OEt_2$	29:71
$TrClO_4$	27:73
$SnCl_2$	78:22

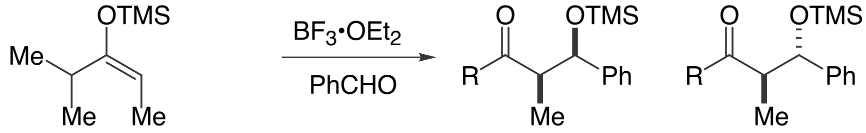
conclusion: there is a modestpreference for the antiperiplanar TS

Syn-Anti Aldol Diastereoselection

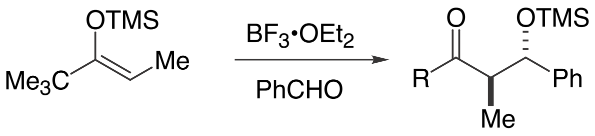
Heathcock: *J. Org. Chem* **1986**, *51*, 3027



56:44



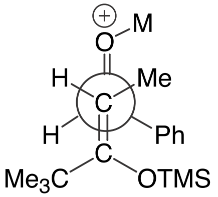
56:44



The effectice size of the enol substituents are probably dominant.

>95:5

The transition state?

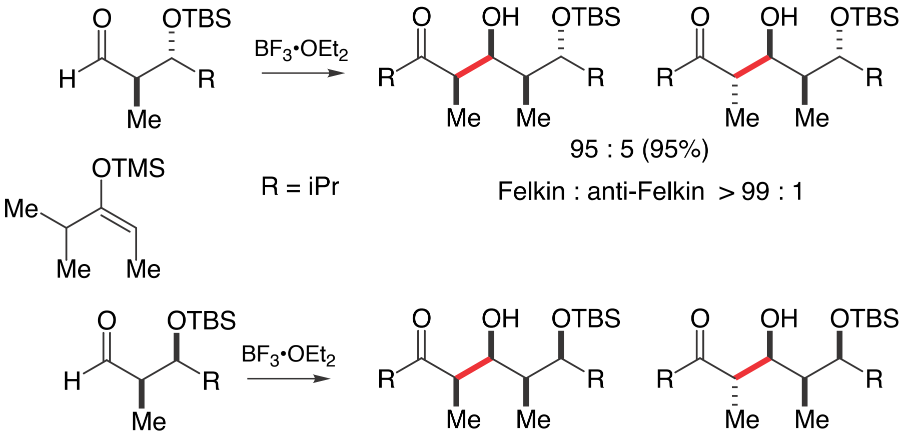


These reactions "exhibit little simple diastereoselection except in special cases."....Heathcock

The Mukayama Aldol Reaction-3

Merged Syn-Anti & Felkin Diastereoselection

Evans: *JACS* **1995**, *117*, 9598



R = iPr

95 : 5 (95%)

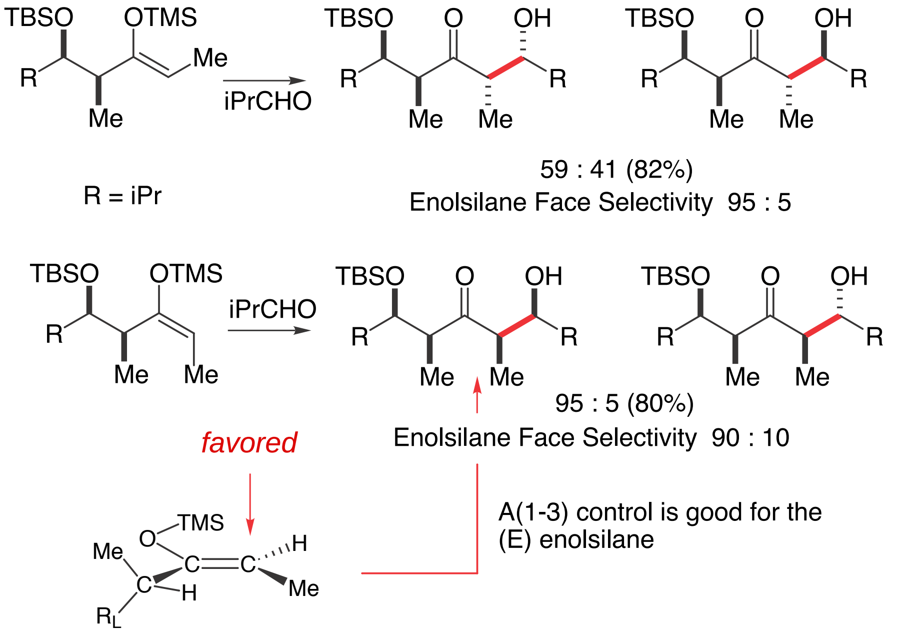
Felkin : anti-Felkin > 99 : 1

70 : 30 (89%)

Felkin : anti-Felkin 99 : 1

Conclusions:
Moderate to Good syn diastereoselectlion
Excellent Felkin diastereoselectlion

Enolslane Face Selection



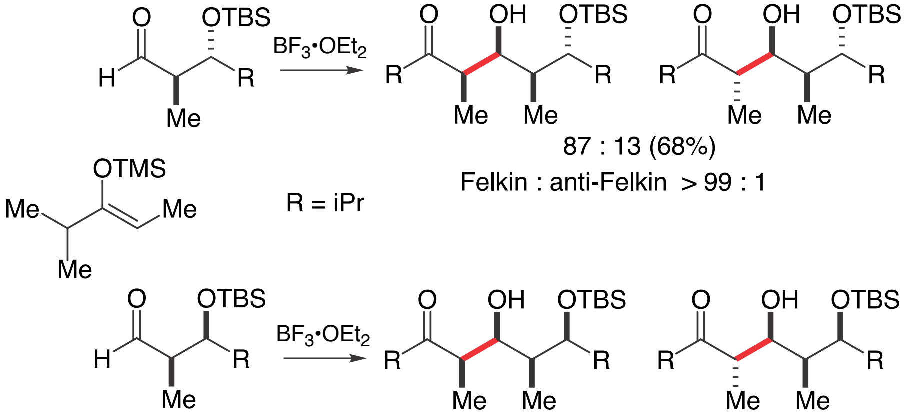
R = iPr

59 : 41 (82%)
Enolsilane Face Selectivity 95 : 5

95 : 5 (80%)
Enolsilane Face Selectivity 90 : 10

favored

A(1-3) control is good for the
(E) enolsilane



87 : 13 (68%)

Felkin : anti-Felkin > 99 : 1

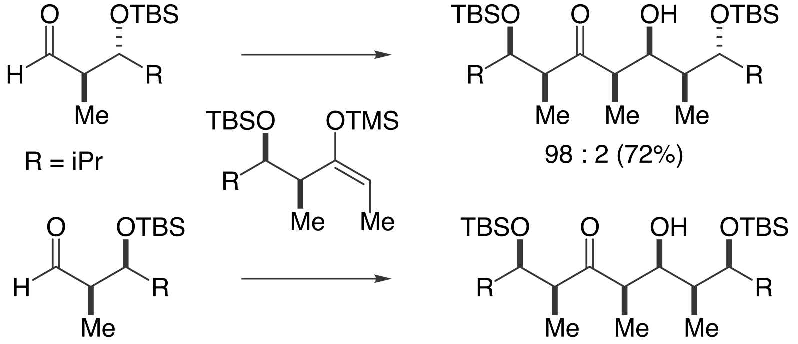
R = iPr

91 : 9 (75%)

Felkin : anti-Felkin 87 : 13

Conclusions:
Moderate to Good syn diastereoselectlion
Excellent Felkin diastereoselectlion

Double Stereodifferentiating *Syn* Aldol Rxns with Enolsilanes



R = iPr

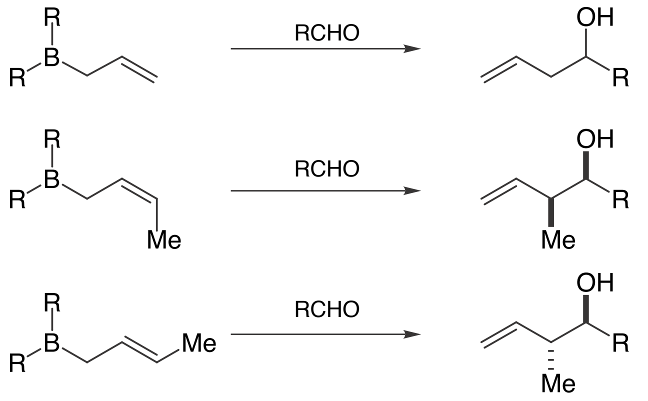
98 : 2 (72%)

98 : 2 (83%)

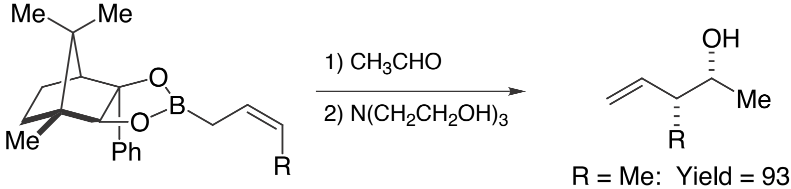
Allyl and Crotylmetal Species–1 : Boron

■ General Reviews of Allyl Metal Reagents:
Comprehensive Organic Synthesis, **1991**;Vol. 2.

■ The General Reactions



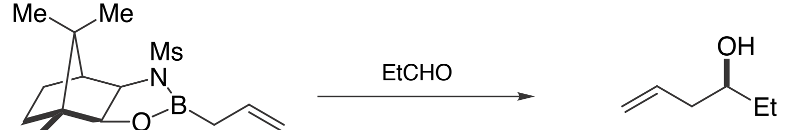
■ The Hoffman Chiral Allylboronic Esters



R = Me: Yield = 93%
ee = 60-70%

R = H: Yield = 92%
ee = 65%

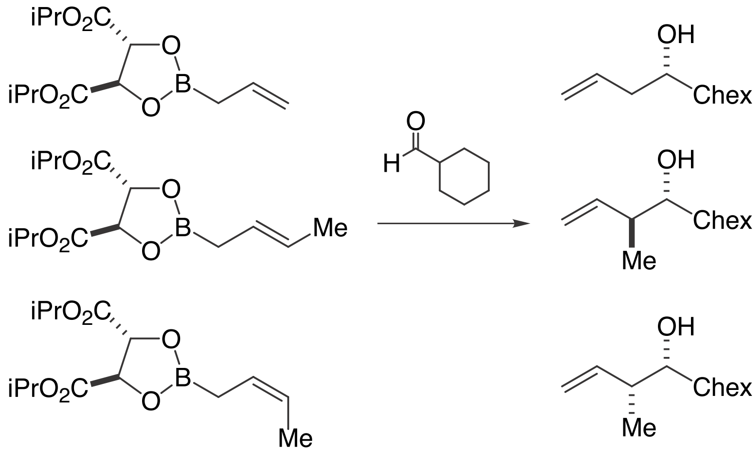
R. Hoffman *Tetrahedron Lett*. **1979**, 4653-4656.
ACIEE, **1978**, *17*, 768-769.



Yield = 92%
ee = 92%

M. Reetz *Chem. Ind. (London)* **1988**, 663-664.

■ The Tartrate-derived Allylboronic Esters

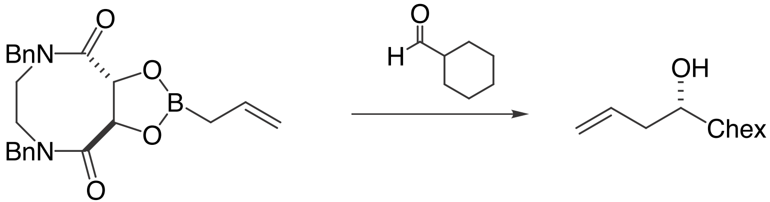


Yield = 72%
ee = 87%

Yield = 100%
ee = 91%

Yield = 90%
ee = 83%

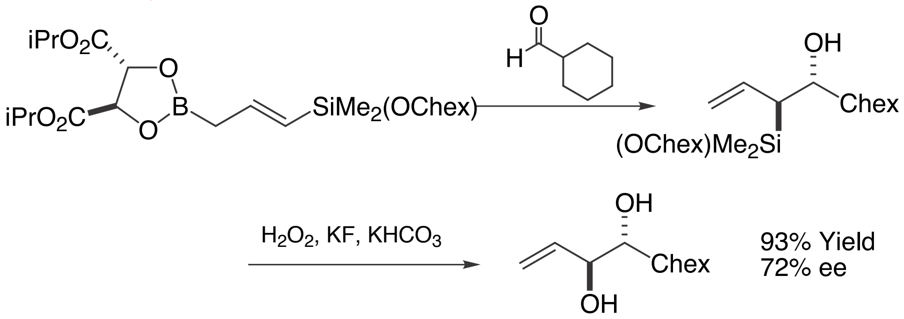
W. Roush, *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.
Tetrahedron Lett. **1988**, *29*, 5579-5582.



Yield = 40%
ee = 97%

W. Roush, *J. Am. Chem. Soc.* **1988**, *110*, 3979-3982.

■ A Reagent for the Generation of Anti-1,2-Diols

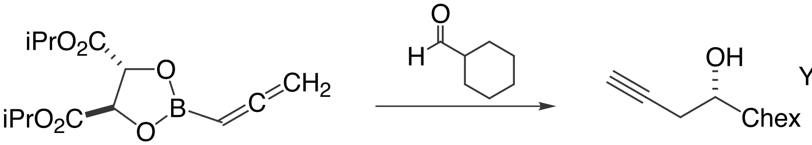


93% Yield
72% ee

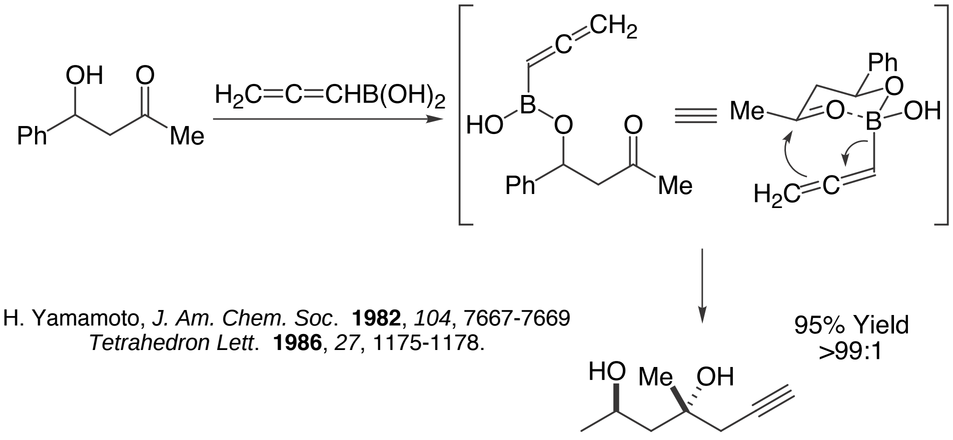
W. Roush, *Tetrahedron Lett*. **1990**, *31*, 7563-7566.

Allyl and Crotylmetal Species–2 : Boron

■ Allenylboronic Esters: Tartrate-derived Controllers and Internal Delivery



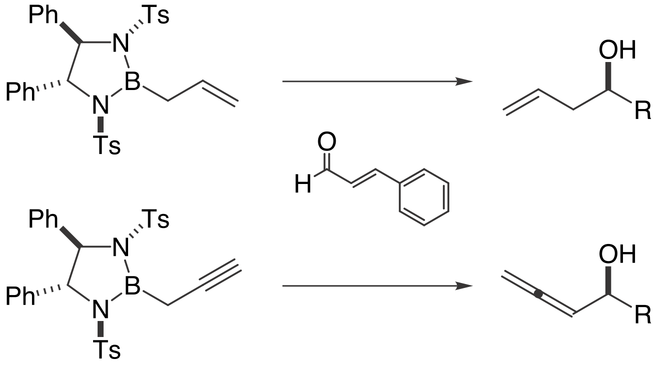
Yield = 56%
ee = 92%



95% Yield
>99:1

H. Yamamoto, *J. Am. Chem. Soc*. **1982**, *104*, 7667-7669
Tetrahedron Lett. **1986**, *27*, 1175-1178.

■ The Corey Stein Controller

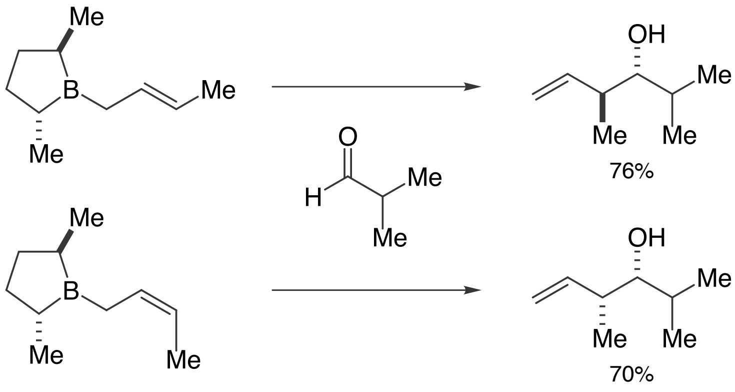


98% ee

98% ee

E. J. Corey, *J. Am. Chem. Soc*. **1989**, *111*, 5495-5496.
J. Am. Chem. Soc. **1990**, *112*, 878-879.

■ The Masamune Borolane

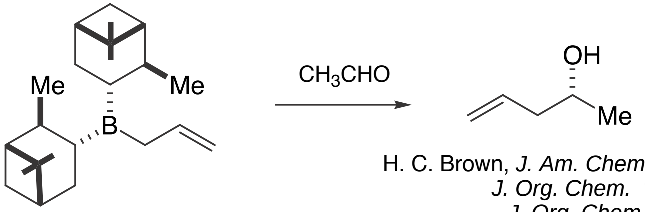


96:4
97% ee

96:4
93% ee

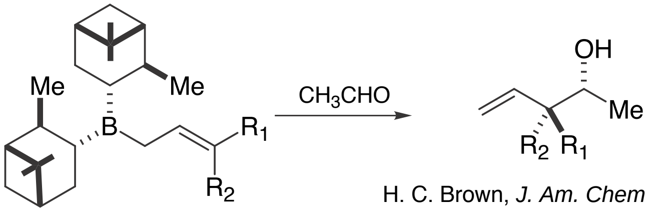
S. Masamune, *J. Org. Chem.* **1987**, *52*, 4831-4832.

■ The Brown IPC Controller



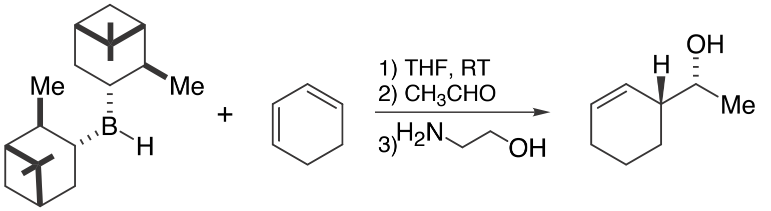
> 99% ee

H. C. Brown, *J. Am. Chem. Soc*. **1983**, *105*, 2092-2093.
J. Org. Chem. **1991**, *56*, 401-404.
J. Org. Chem. **1992**, *57*, 6614.



R_1 = Me, R_2 = H: ee = 90%
R_1 = H, R_2 = Me: ee = 90%
R_1 = H, R_2 = OMe: ee = 90%

H. C. Brown, *J. Am. Chem. Soc*. **1988**, *110*, 1535-1538.
See also: *Tetrahedron Lett*. **1990**, *31*, 455-458.

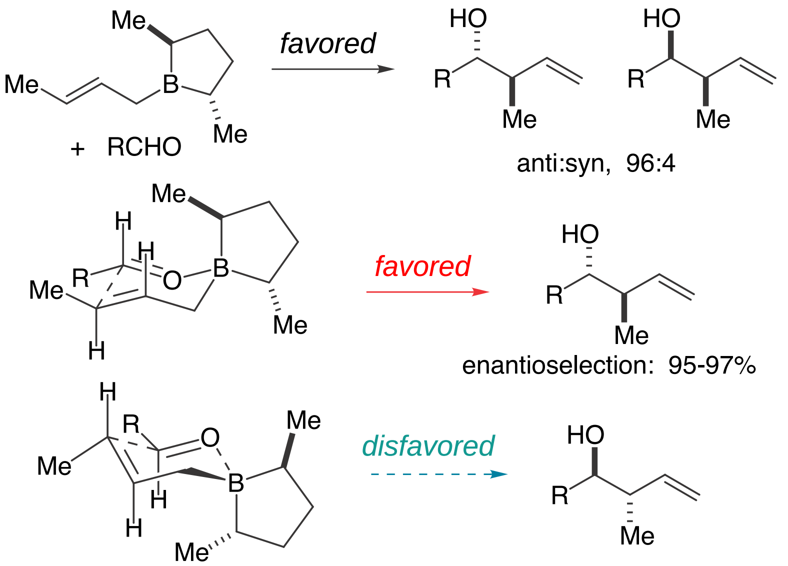


ee = 94%

H. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2633.

The Allylboron Reagents Add to Carbonyl Compounds via a Zimmerman-Traxler Transition State

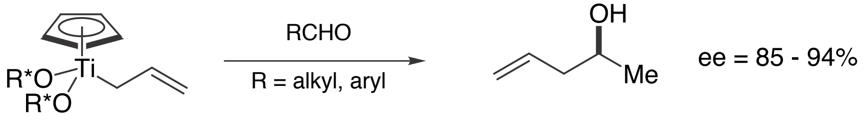
Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831



anti:syn, 96:4

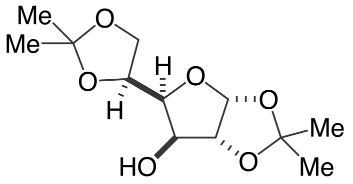
enantioselection: 95-97%

An Enantioselective Allyltitanium Reagent



ee = 85 - 94%

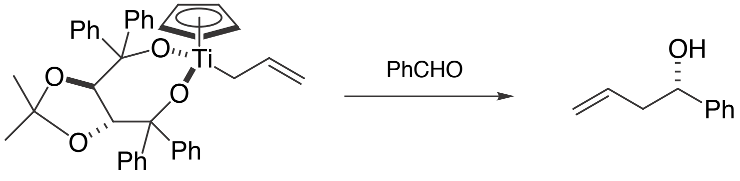
R*OH =



M. Riediker, R. Duthaler, *ACIEE*, **1989**, *28*, 494-495.
In *Organic Synthesis via Organometallics*, **1991**, 285-309.
J. Am. Chem. Soc. **1992**, *114*, 2321-2336.

Duthaler *Chem. Rev.* **1992**, *92*, 807

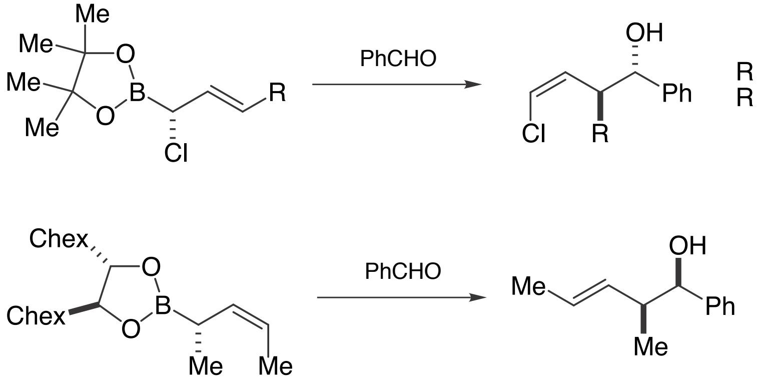
Another Enantioselective Allyltitanium Reagent



95% ee

R. Duthaler, *J. Am. Chem. Soc*. **1992**, *114*, 2321-2336.

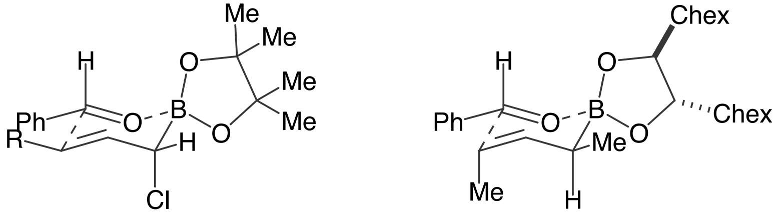
Chiral α-Substituted Allyl Metal Reagents: Boron



R = H: 92% ee
R = Me: 98% ee

68% Yield
99% ee

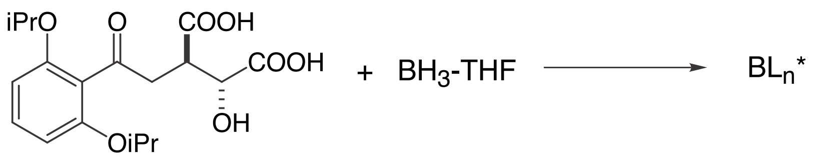
R. Hoffman, *Chem. Ber*. **1986**, *119*, 2013-2024.
Chem. Ber. **1988**, *121*, 1501-1507.
ACIEE, **1986**, *25*, 1028-1030.

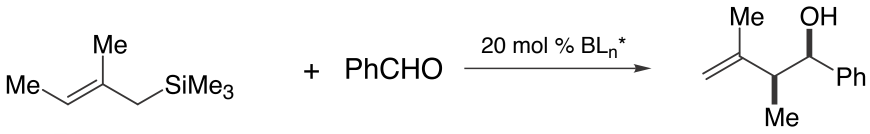


The favored transition states

Allyl and Crotylmetal Species–4: Catalytic Systems

■ Three Catalytic Asymmetric Allylations of Aldehydes are Known

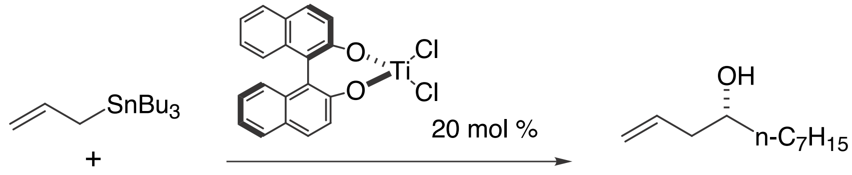




E/Z = 61/39

63% yield
90% ee

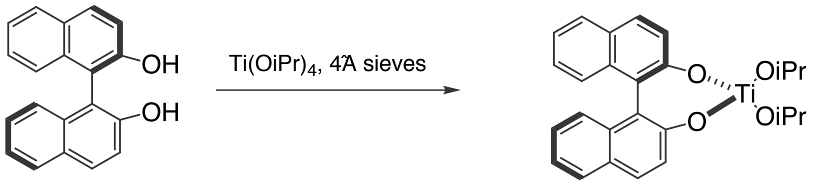
H. Yamamoto, *Synlett* **1991**, 561-562.



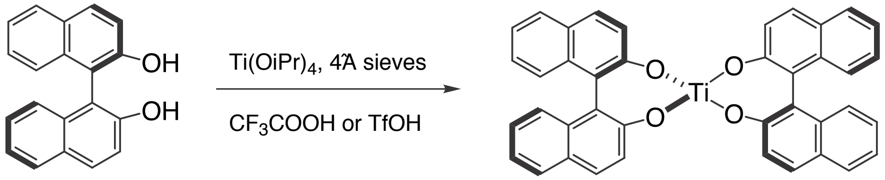
n-C_7H_{15}CHO

81% yield
97.4% ee

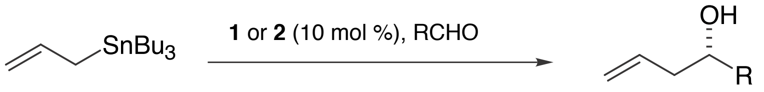
E. Tagliavini, A. Umani-Ronchi *J. Am. Chem. Soc.* **1993**, *115*, 7001-7002.

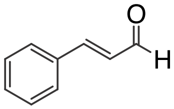


1



2



R	Catalyst	Yield (%)	ee (%)
Ph	**1**	88	95
	2	98	92
Chex	**1**	66	94
	2	95	92
	**1**	42	89
	2	78	77

G. Keck *J. Am. Chem. Soc.* **1993**, *115*, 8467-8468.

■ Many Other Metals Have Been Employed in the Allylation Reaction ...

Pb: S. Torii, *Chem. Lett.* **1986**, 1461-1462.
Mo: J. Faller, *Tetrahedron Lett.* **1991**, *32*, 1271-1274.
Cr: Y. Kishi, *Tetrahedron Lett.* **1982**, *23*, 2343-2346.
P. Knochel, *J. Org. Chem.* **1992**, *57*, 6384-6386.
Sb: Y. Butsugan, *Tetrahedron Lett.* **1987**, *28*, 3707-3708.
Mn: T. Hiyama, *Organometallics*, **1982**, *1*, 1249-1251.
Zn: T. Shono, *Chem. Lett.* **1990**, 449-452.
Ba: H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 8955-8956.

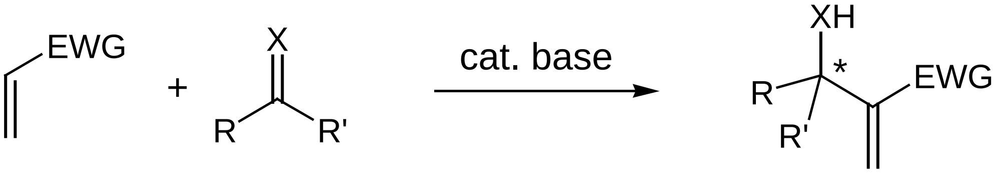
Chemistry 206

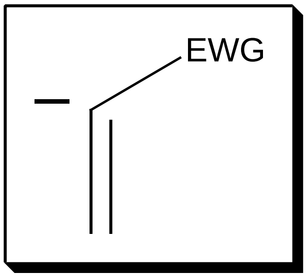
Advanced Organic Chemistry

Handout 26A

The Asymmetric Baylis-Hillman Reaction

An Evans Group Afternoon Seminar
Jake Janey
March 29th, 2001





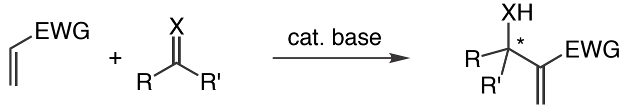
J. Janey

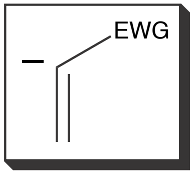
Monday,
November 17, 2003

An Evans Group Afternoon Seminar

Jake Janey

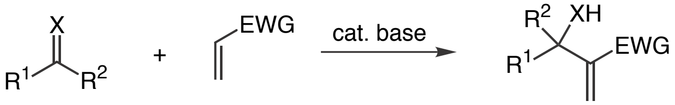
March 29th, 2001





Leading References:
Langer, P. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3049-3052.
Ciganek, E. *Org. React.* **1997**, *51*, 201-350.
Basavaiah, D.; *et. al. Tetrahedron*, **1996**, *52*, 8001-8062.
Drewes, S. E.; Roos, G. H. P. *Tetrahedron*, **1988**, *44*, 4653-4670.

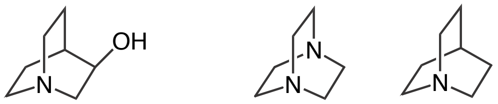
Baylis-Hillman Reaction Scope



X = O, NTs, NCO_2R, $NPPh_2$, NSO_2Ph
R^1 = alkyl, aryl
R^2 = H, alkyl, EWG

EWG = CO_2R, CN, $POEt_2$, CHO, COR, SO_2Ph, SO_3Ph

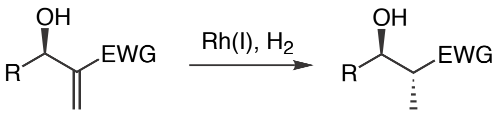
cat. bases:



n-Bu_3P:

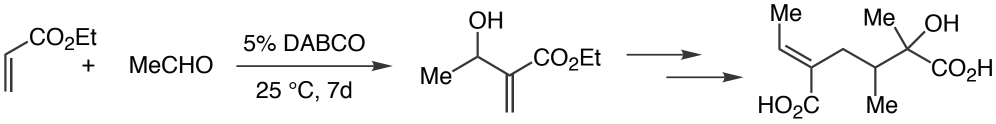
3-hydroxyquinuclidine (3-QDL) DABCO quinuclidine

An anti propionate aldol equivalent...



Early Synthetic Examples

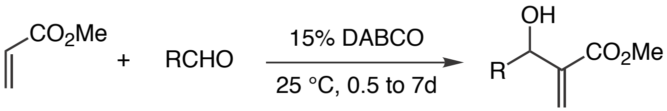
10 years after the Baylis-Hillman German patent...used in a C_{10} integerrinecic acid synthesis:



94% yield

Drewes, S. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079-2083.

Shortly thereafter, a more extensive, published study:



R = alkyl or aromatic

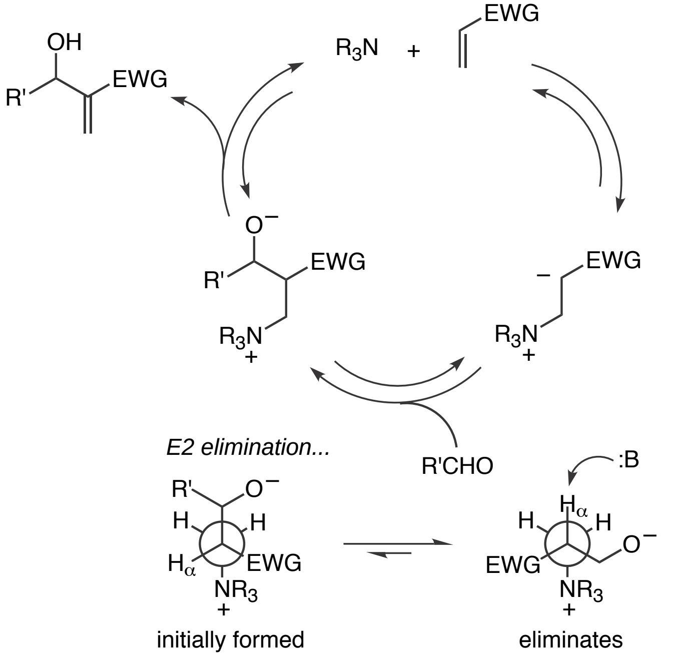
94% yield

- All reactions run neat in a sealed tube with 1.5-2 equivalents of acrylate.

Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795-797.

The Asymmetric Baylis-Hillman Reaction

Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, *3*, 285-288.
Kaye, P. T.; Bode, M. L. *Tetrahedron Lett.* **1991**, *32*, 5611-5614.

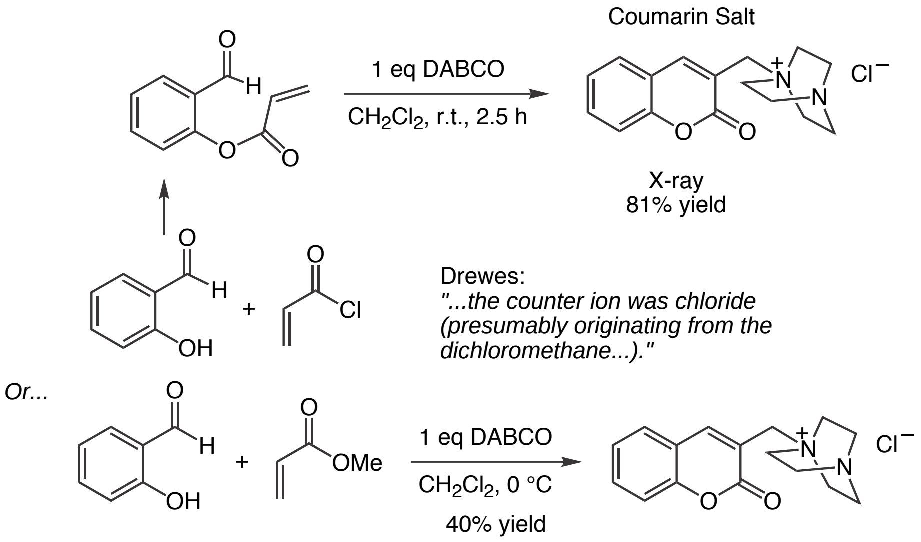


E1cB is also possible

- rate = K_{obs}[aldehyde][alkene][amine]
- pseudo-second order if [amine]≈constant
- addition to aldehyde is r.d.s. because the dipole is increased by further charge seperation
- acrylonitrile and methyl acrylate studied
- enolate geometry not considered
- ethereal solvent inhibits reaction whereas alcohols (especially diols) accelerate reaction
- huge volume of activation: $\Delta V^{\ddagger}$ of -79 $cm^3\ mol^{-1}$ (the Diels-Alder is -35 $cm^3\ mol^{-1}$) found by plotting $\ln k_{obs}$ vs. P. 5000 bar increases rate by 1.1 x 10^6
- Reaction is reversible (i.e. a Grob type fragmentation), thus mechanism could be ternary, with no discrete enolate intermediate (supported by $\Delta V^{\ddagger}$ and temperature effects).

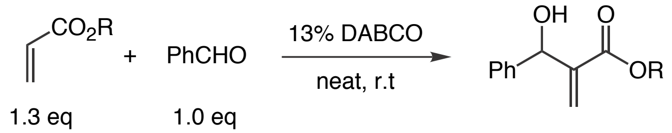
Evidence for an Intermediate

Drewes, S. E.; *et. al. Syn. Comm.* **1993**, *23*, 2807-2815.



Drewes:
"...the counter ion was chloride (presumably originating from the dichloromethane...)."

Effects of Acrylate Ester Substituent



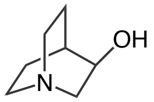
R	time (days)	yield (%)
Me	6	89
Et	7	79
Bn	2	88
n-$C_{10}H_{21}$	14	75
t-Bu	65	65
2-adamantyl	62	40
CH_2CH_2F	3	81
CH_2CH_2Br	2	NR
CH_2CF_3	**15 h**	**58**
CH_2CH_2OMe	4	89
$CH_2CH_2NMe_2$	8	82
$(CH_2)_6Cl$	15	NR

- For aryl substituted benzyl ethers, no clear relation between σ values and reactivity was observed.
- Trends hold for furfural.
- The products undergo retro Baylis-Hillman, i.e. the reaction is reversible.

Caubere, P.; *et. al. Tetrahedron* **1992**, *48*, 6371-6384.

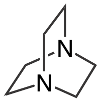
Bases for Catalysis

pK_a H_2O (DMSO)



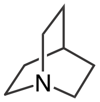
3-Hydroxyquinuclidine (3-QDL)
9.5 (~8.5)

>



DABCO
2.97, 8.82 (2.97, 8.93)

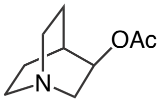
>



Quinuclidine
10.9 (9.80)

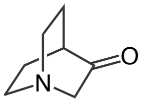
>>

>>

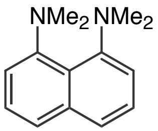


3-Acetoxyquinuclidine

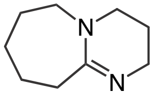
or



3-Quinuclidone
6.9



Proton sponge
12.0 (7.50)



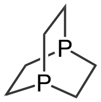
DBU
(~12)

Sterics also important:

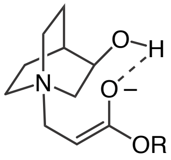
$Me_2NH > Me_2NEt > MeNEt_2 > NEt_3$ 10.75 (9.00)

Many, many phosphines screened...the winner: *n*-Bu_3P ~9

- *n*-Bu_3P is only a slightly better catalyst than DABCO.

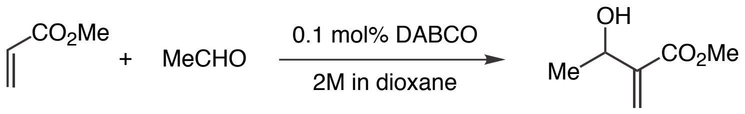


unreactive



...or could accelerate protonation of intermediate, as any alcohol additive will accelerate reaction

Temperature Effects



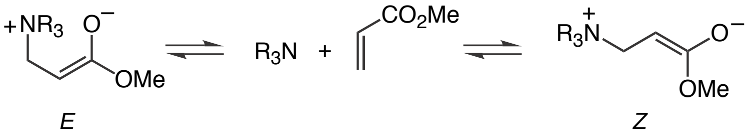
0.1 mol% DABCO

2M in dioxane

74% yield

25 °C 1 week
0 °C 8 hours!

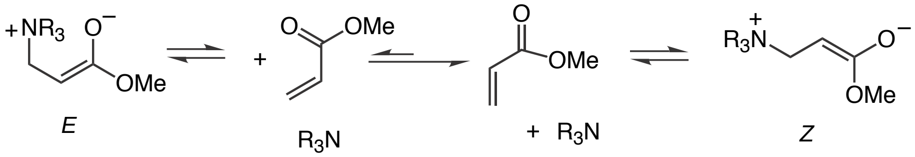
- Reaction is accelerated for a wide variety of aldehydes when conducted at 0 °C
- Temperature effect not seen with acrylonitrile (cannot form enolate)
- Author concludes that one enolate must react faster than another (i.e. a kinetic versus a thermodynamic enolate).



Which enolate is more stable and which is more reactive?

Leahy, J. W.; Rafel, S. *J. Org. Chem.* **1997**, *62*, 1521-1522.

Enolate Geometry

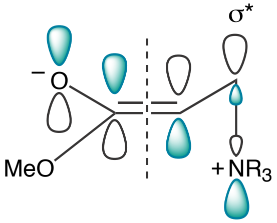


Thermodynamic

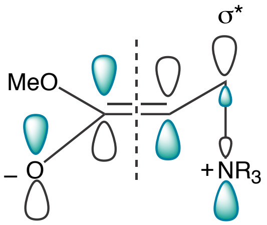
- less charge seperation
- less reactive

Kinetic

- more charge separation
- less stable
- enolate twists out of plane by PM3



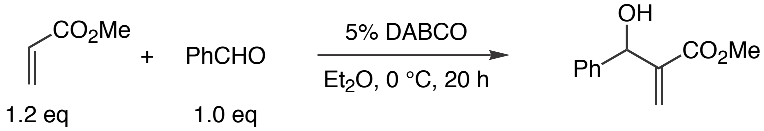
4π e^-
HOMO



better conjugation into σ*

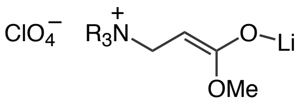
The Asymmetric Baylis-Hillman Reaction

Salt Additive



$LiClO_4$ (mol%)	yield (%)
0	trace
5	12
10	40
50	63
70	72 (81)[a]
100	25
200	12
500	trace

[a] 15 mol% DABCO was used.

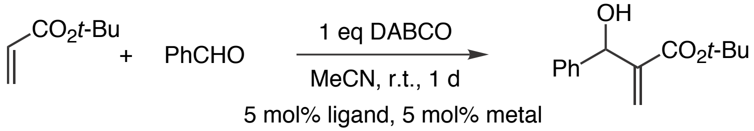


Stablize enolate?

- Ether was found to be optimal from solvent screening.
- General for a variety of alkenes and aldehydes.

Kobayashi, S.; Kawamura, M. *Tetrahedron Lett.* **1999**, *40*, 1539-1542.

Lewis Acid Catalysis



Relative Reaction Rates

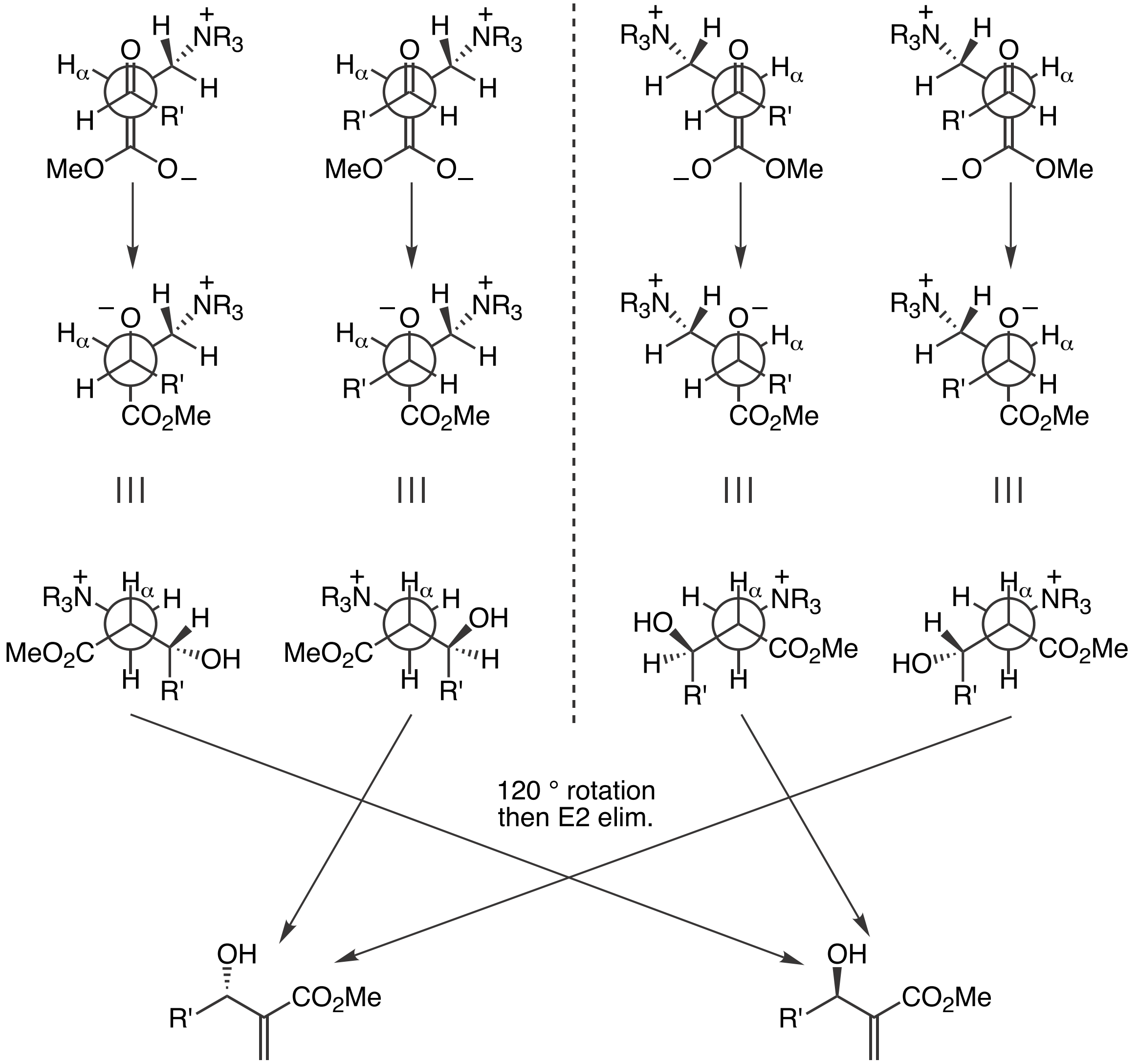
ligand	$Sc(OTf)_3$	$Yb(OTf)_3$	$Eu(OTf)_3$	$La(OTf)_3$
none	3.3	3.6	3.5	4.7
(+)BINOL	9.4	14.4	12.8	**14.6**
(+)diethyl tartrate	5.2	9.7	5.5	7.3
(+)diisopropyl tartrate	3.5	9.5	4.6	8.1
(+)TMTDA	4.1	8.0	3.6	4.0
(+)hydrobenzoin	3.5	**16.2**	5.8	5.3
(+)triphenylethanediol	3.2	5.2	2.2	5.9
(+)TADDOL	2.9	4.5	3.8	4.7
ethylene glycol	3.3			
triethanolamine	4.65			**10.8**
salen	2.31	6.3	5.2	4.0
box	3.6			
N-methylephedrine	2.87	5.8	3.2	4.4

- no enantioselectivity observed
- DABCO loading dropped to <10 mol% with (+)-BINOL
- *rac* -BINOL showed no rate acceleration

Aggarwal, V. K.; *et. al. Chem. Commun.* **1996**, 2713-2714.
Aggarwal, V. K.; *et. al. J. Org. Chem.* **1998**, *63*, 7183-7189.

The Asymmetric Baylis-Hillman Reaction

Possible Stereoisomers

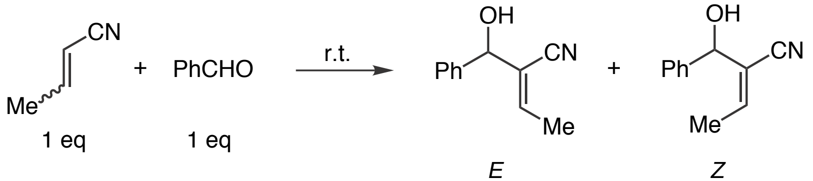


Assumptions:

- *E* enolate formed
- E2 favored over E1 pathway
- $-NR_3^+$ is orthogonal to π face (stereoelectronics)

The Asymmetric Baylis-Hillman Reaction

E/Z Selectivity with Crotononitrile



Solvent	*E/Z* ratio
neat	1.2 : 1
THF	1.4 : 1
$CHCl_3$	1.5 : 1
CH_3CN	3.1 : 1
MeOH	4 : 1

5 mol% DABCO, 8 kbar,
17 h, solvent 50 vol%

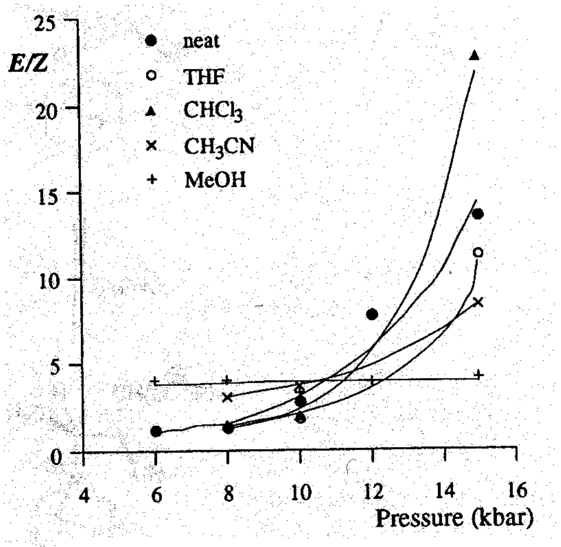
Base	*E/Z* ratio
DABCO	1 : 1
3-QDL	2 : 1
NEt_3	4 : 1

10 mol% base, 8 kbar,
17 h, $CHCl_3$ 50 vol%

- *E* and *Z* crotononitrile is easily isomerized under the reaction conditions.

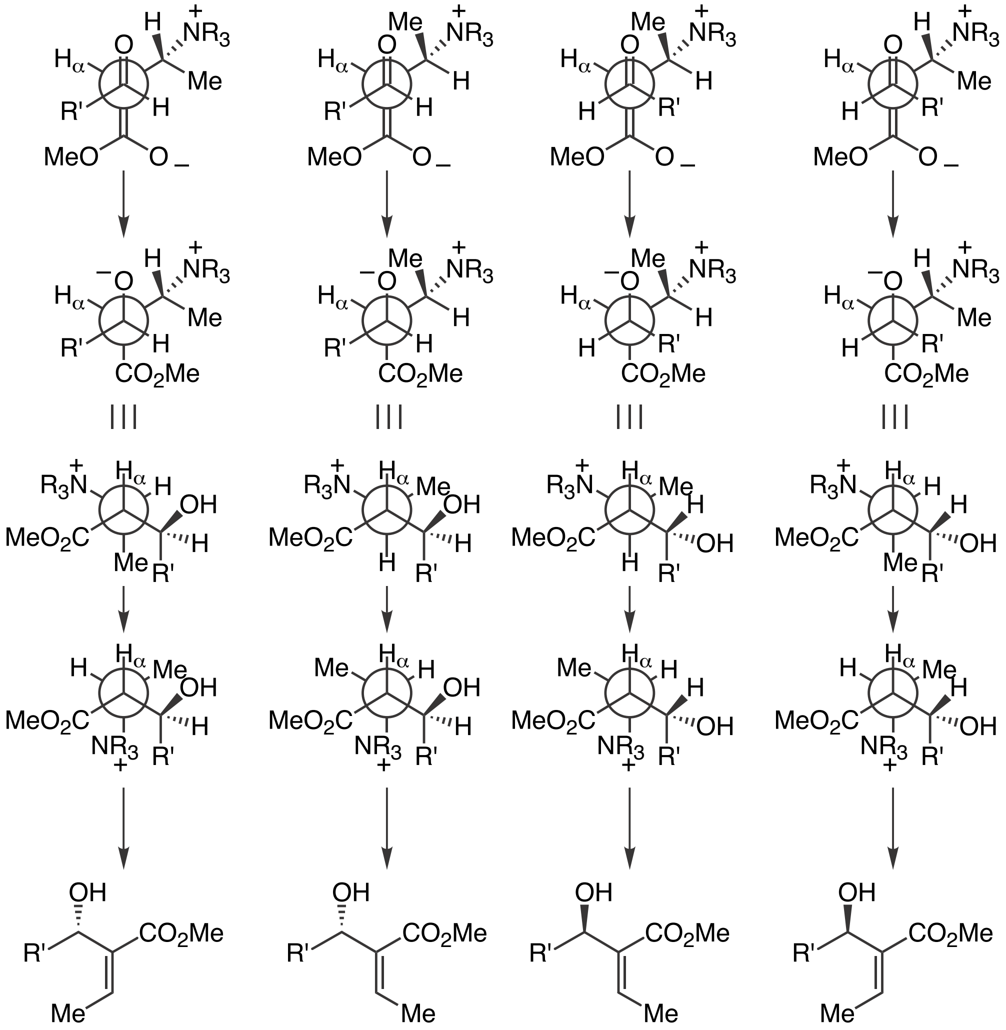
- Products did not undergo retro-Baylis-Hillman.

Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 6931-6936.



5 mol% DABCO,17 h, solvent 50 vol%

Possible Stereoisomers for Methylcrotonate

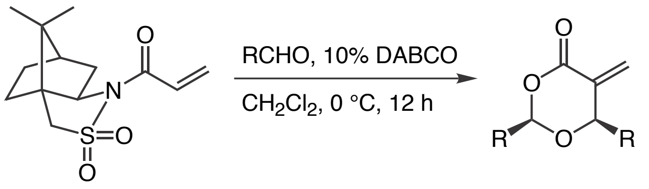


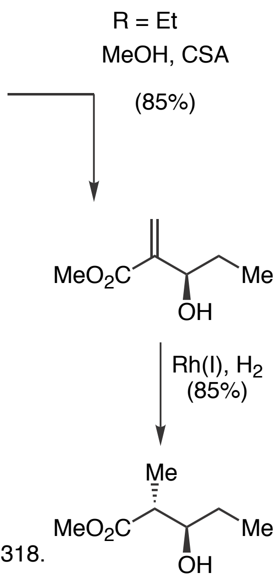
Assumptions:

- *E* enolate formed
- E2 favored over E1 pathway, only after rotation of ammonium to *anti* conformation
- $-NR_3^+$ is orthogonal to π face (stereoelectronics)
- only **one** π face of enolate considered, thus there are an **additional 4 stereoisomers** possible
- starting geometry of methylcrotonate and *in situ* isomerization not considered
- retro-Baylis-Hillman not considered

The Asymmetric Baylis-Hillman Reaction

Camphorsultam Acrylate Baylis-Hillman



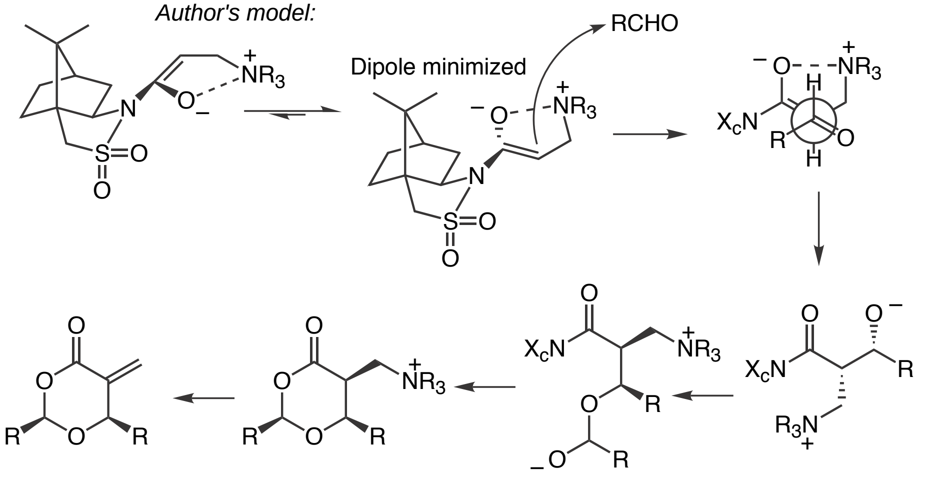


R	yield (%)	*ee* (%)
Me	85	>99
Et	98	>99
n-Pr	70	>99
i-Pr	33	>99
$PhCH_2CH_2$	68	>99
$AcOCH_2$	68	>99
$(CH_3)_2CHCH_2$	67	>99
Ph	0	

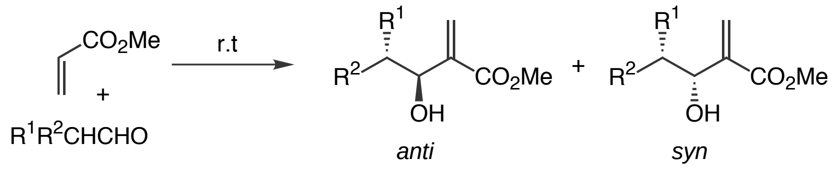
Leahy, J. W.; *et. al. J. Am. Chem Soc.* **1997**, *119*, 4317-4318.

Camphorsultam Acrylate Mechanism

Author's model:



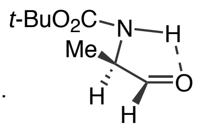
α-Branched Aldehydes: Modest Felkin-Anh Selection



R^1	R^2	Conditions	yield (%)	*anti:syn*
$MeOCH_2O$	Me	DABCO, 4 d	55	70:30
$MeOCH_2O$	Me	3-QDL, 1.5 d	60	72:28
$BnOCH_2O$	Me	DABCO, 6 d	42	70:30
$MeOCH_2O$	Ph	DABCO, 10 d	42	37:63
Me	*n*-Pr	3-QDL, 60 d	30	35:65
$-OC(Me)_2OCH_2-$		DABCO, 55 d	62	69:31
$NHCO_2$*t*-Bu	Me	DABCO, 7 d	80	26:74
N-Phthalimidyl	Me	DABCO, 3.5 d	28	46:54
$-N(CO_2$*t*-Bu$)C(Me)_2OCH_2-$		DABCO, 11 d	43	89:11

- Varying the amount of catalyst only affects the rate, not selectivity.
- *Anti* and *syn* drawn incorrectly in review, should be reversed.

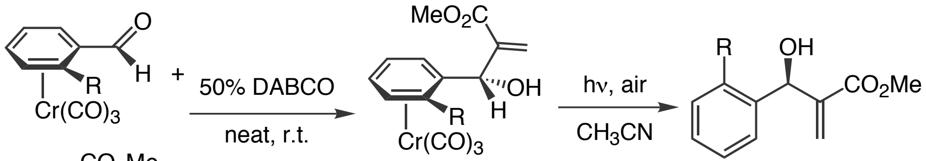
Ciganek, E. *Org. React.* **1997**, *51*, 217-218.

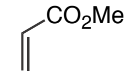


syn selective

The Asymmetric Baylis-Hillman Reaction

Chiral Aldehydes: Chromium Auxiliary





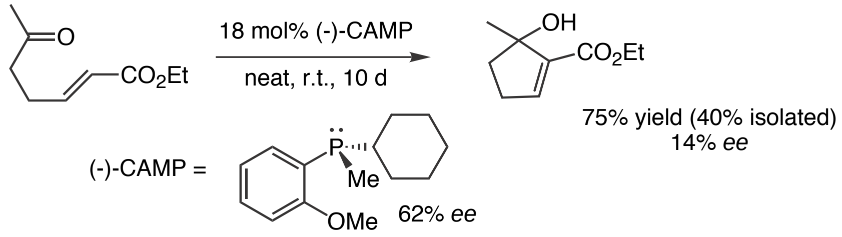
excess

aldehyde	R	time (h)	yield (%)	dr
rac	OMe	93	87	>98:2
rac	Cl	6	89	>98:2
rac	F	7	92	92:8
rac	Me	58	90	84:16
S-(+)	OMe	93	85	>98:2
S-(+)	Cl	8	97	>98:2

- dr determined by 200 MHz ^{1}H NMR
- *N*-Tosyl arylimine chromium complex also reacts

Kundig, P. E.; *et. al. Tetrahedron Lett.* **1993**, *34*, 7049-7052.

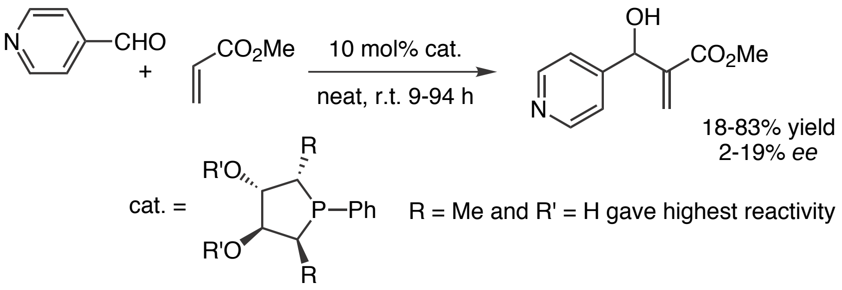
Chiral Phosphine Catalysts



75% yield (40% isolated)
14% *ee*

62% *ee*

Frater, G.; *et. al. Tetrahedron Lett.* **1992**, *33*, 1045-1048.

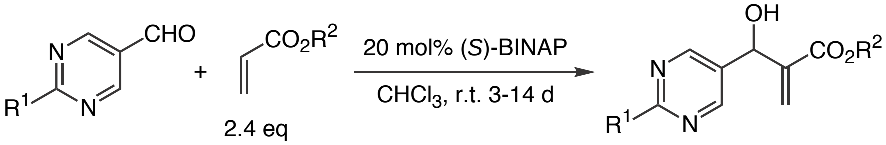


18-83% yield
2-19% *ee*

R = Me and R' = H gave highest reactivity

Zhang, X.; *et. al. J. Org. Chem.* **2000**, *65*, 3489-3496.

The High Point of Chiral Phosphine Catalysts



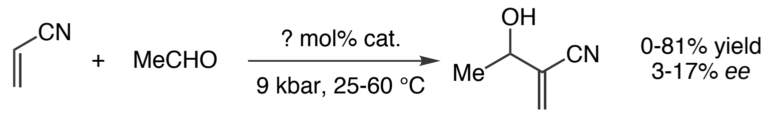
R^1	R^2	time (d)	yield (%)	*ee* (%)
H	*i*-Pr	4	8	9
H	Et	3	12	25
H	Me	4	24	44
Me	Me	14	18	37
Me	Me	3	26	30[a]

[a] Tol-BINAP was used

- other phosphines screened gave ~racemic products: DIOP, NORPHOS, BPPFOH, and MOP

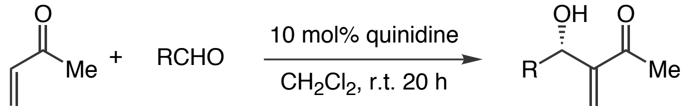
Soai, K.; *et. al. Chem. Commun.* **1998**, 1271-1272.

Naturally Occurring Alkaloids as Chiral Catalysts



- (-)-quinine, (1*R*,2*S*) *N*-methylephedrine, *S*-(-)-nicotine, *S*-(-)-*N*-methylprolinol screened
- (-)-menthyl acrylate ester gave 100% *de* with aromatic aldehydes and DABCO under high P

Isaacs, N. S.; *et. al. Tetrahedron: Asymm.* **1991**, *2*, 969-972.



40-50% yield

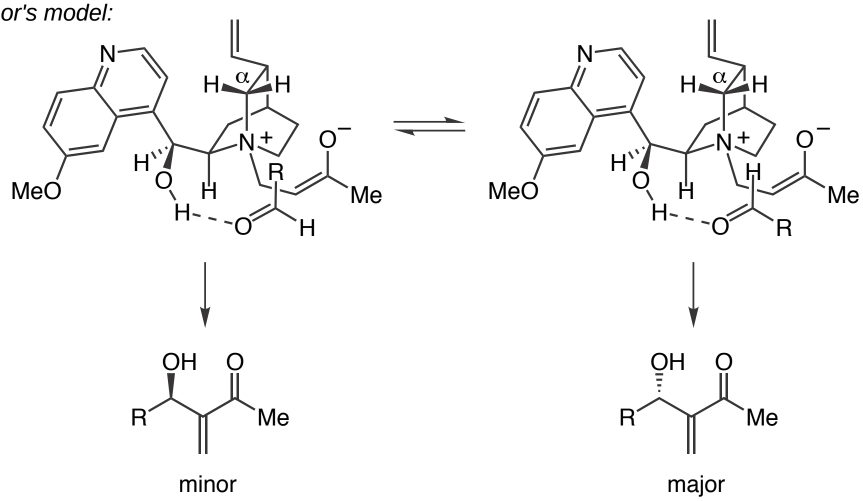
R	Pressure	*ee* (%)
n-Pr	3 kbar	18
n-C_9H_{19}	10 kbar	31
i-Pr	3 kbar	37
c-hex	3 kbar	45

- 3-QDL, quinine, cinchonine, cinchonidine, *O*-acetyl quinidine, *N*-methylprolinol, *N*-methylephedrine also screened
- *ee* is highly pressure dependent, optimized pressure is shown in table

Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015-1024.

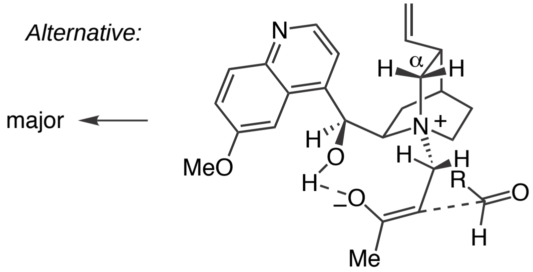
Model For Quinidine Catalyst

Author's model:



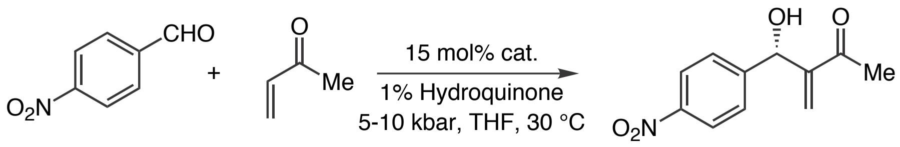
- C_α hydrogens control π face of the aldehyde
- bulky R should enhance selectivity, a trend that they say is "...clearly visible."
- H-bonding plays a "clear role" as *O*-acyl quinidine gives no enantioselectivity

Alternative:



Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015-1024.

C_2 Symmetric DABCO Catalyst



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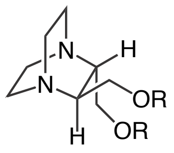
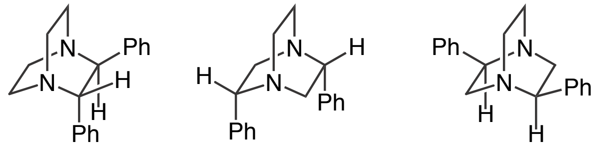


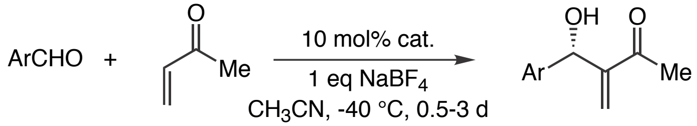
R	time (h)	yield (%)	*ee* (%)
Bn	12	45	47
TBDPS	12	23	34
TIPS	28	33	19
Ph	16	60	35
Mesityl	28	67	16
1-naphthyl	16	66	42
1-anthranyl	24	9	11
1-napththoyl	17	68	15
N-Cbz-Gly	24	63	21

- racemic alcohol product can be easily resolved by kinetic resolution with Sharpless asymmetric epoxidation
- other chiral DABCO's made, but not tested...



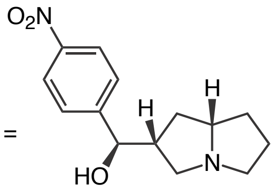
Hirama, M.; *et. al. Tetrahedron: Asymm.* **1995**, *6*, 1241-1244.

Chiral Pyrrolizidine Catalyst

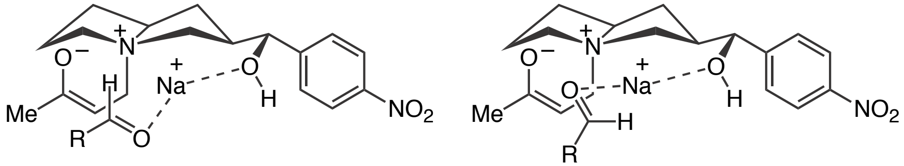


Ar	yield (%)	*ee* (%)
2-NO_2	71	67
2-F	31	63
2-Cl	58	72
2-Br	63	71
3-NO_2	51	37
2-pyridyl	83	21
3-pyridyl	93	49
4-quinolinyl	63	70
4-NO_2	17	39

cat. =



Author's model:



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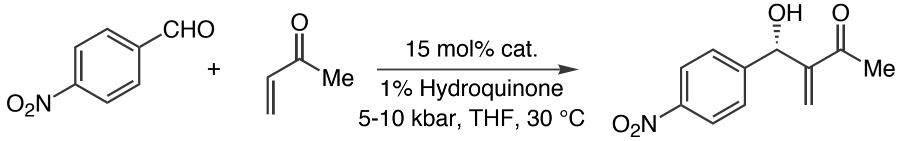
Barrett, A. G. M.; *et. al. Chem. Commun.* **1998**, 2533-2534.

C_2 Symmetric DABCO Catalyst



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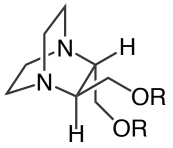
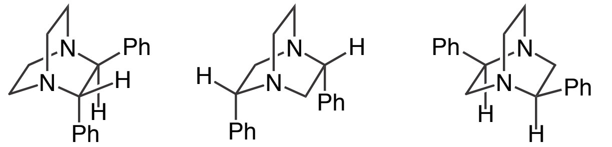


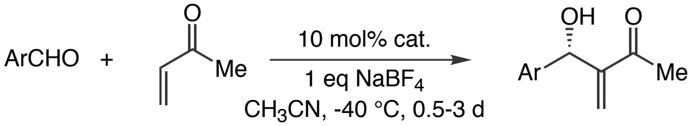
R	time (h)	yield (%)	*ee* (%)
Bn	12	45	47
TBDPS	12	23	34
TIPS	28	33	19
Ph	16	60	35
Mesityl	28	67	16
1-naphthyl	16	66	42
1-anthranyl	24	9	11
1-napththoyl	17	68	15
N-Cbz-Gly	24	63	21

- racemic alcohol product can be easily resolved by kinetic resolution with Sharpless asymmetric epoxidation
- other chiral DABCO's made, but not tested...



Hirama, M.; *et. al. Tetrahedron: Asymm.* **1995**, *6*, 1241-1244.

Chiral Pyrrolizidine Catalyst



Ar	yield (%)	*ee* (%)
2-NO_2	71	67
2-F	31	63
2-Cl	58	72
2-Br	63	71
3-NO_2	51	37
2-pyridyl	83	21
3-pyridyl	93	49
4-quinolinyl	63	70
4-NO_2	17	39

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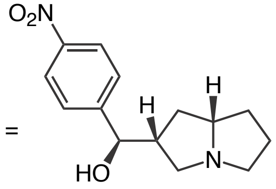
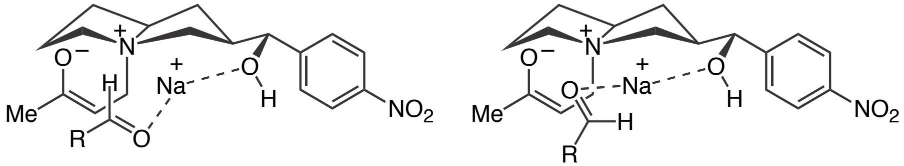


Author's model:



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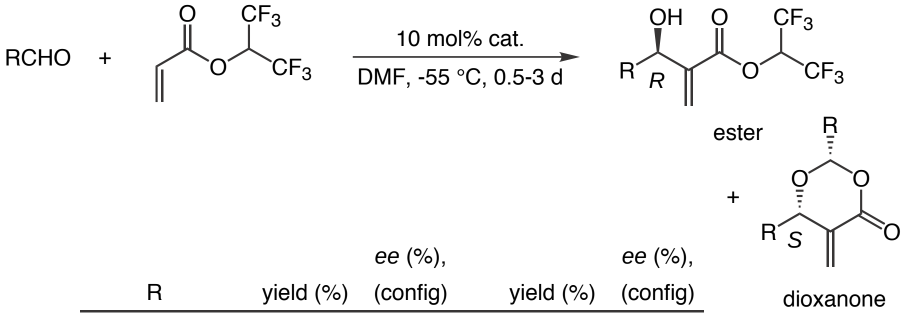
Barrett, A. G. M.; *et. al. Chem. Commun.* **1998**, 2533-2534.

Quinidine Ether Catalyst



R	yield (%)	ee (%), (config)	yield (%)	ee (%), (config)
p-NO_2	58	91 (*R*)	11	4 (*R*)
Ph	57	95 (*R*)	--	--
(*E*)-PhCH=CH	50	92 (*R*)	--	--
Et	40	97 (*R*)	22	27 (*S*)
i-Bu	51	99 (*R*)	18	18 (*S*)
i-Pr	36	99 (*R*)	25	25 (*S*)
c-Hex	31	99 (*R*)	23	23 (*S*)
t-Bu	--	--	--	--

- Quinidine and other acyclic derivatives showed no enantioselection and very low reactivity.
- Free hydroxyl on quinoline is essential for enantioselectivity.
- Reactions conducted at room temperature showed lower enantioselection.
- Racemic ester does not react to give dioxanone under the reaction conditions.

Hatakeyama, S.; *et. al J. Am. Chem. Soc.* **1999**, *121*, 10219-10220.

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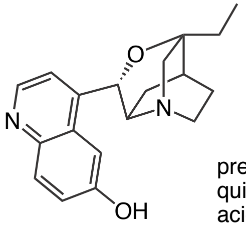
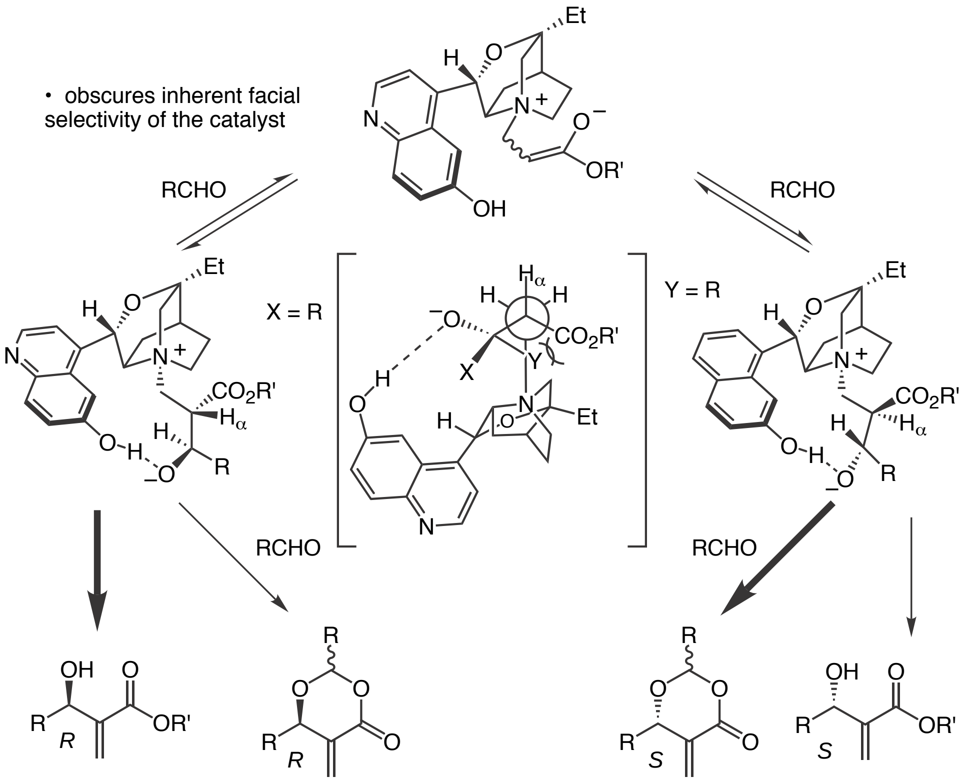


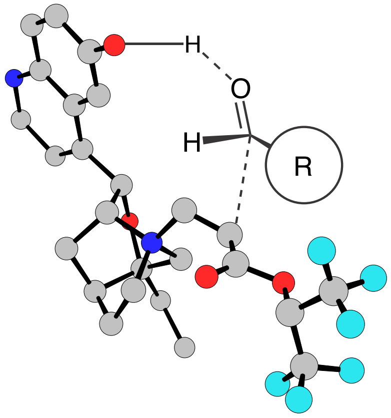
prepared in 65% yield from quinidine in 85% phosphoric acid and KBr (100 °C, 5 d).

Proposed Mechanism: Partial Kinetic Resolution

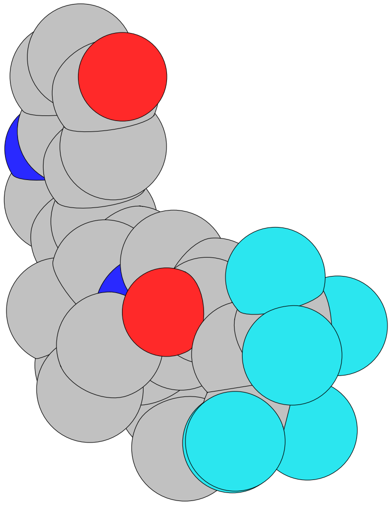
- obscures inherent facial selectivity of the catalyst



A Model for Facial Selectivity

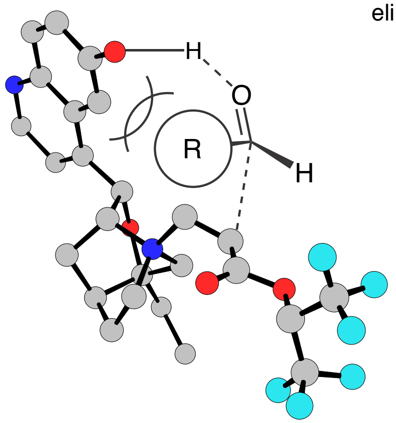


Favored



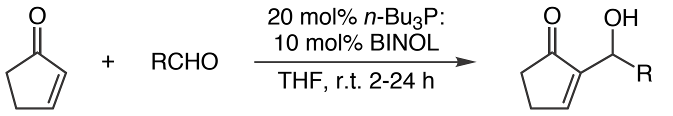
PM3 minimized: C-N bond to enolate constrained to 1.6 Å

- Catalyst orthogonal to opposite π face of the enolate leads to same major enantiomer after elimination.



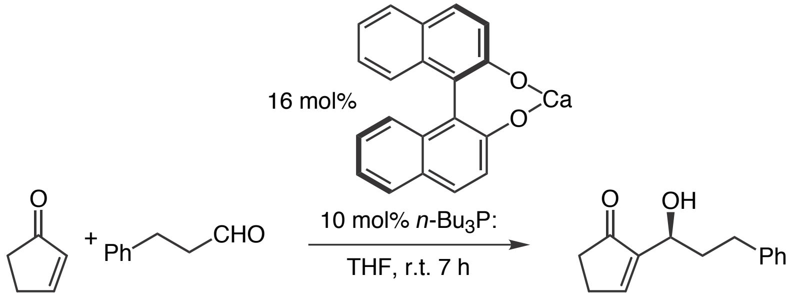
Disfavored

BINOL as an Additive or Ligand



R	yield (%)
n-C_7H_{15}	quant.
Ph	92
MEMO$(CH_2)_3$	98
Et	91
$PhCH_2CH_2$	quant.

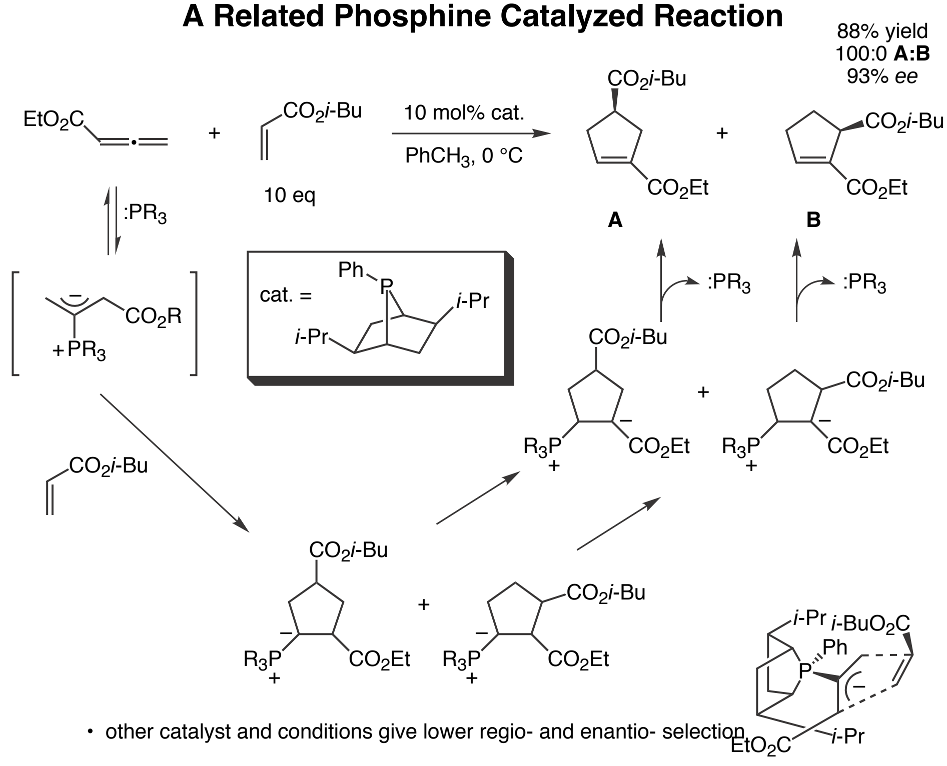
- *ee* were all <10%
- phenol also accelerates reaction
- other acrylates also tolerated



62% yield, 56% *ee*

Ikegami, S.; Yamada, Y. M. A. *Tetrahedron Lett.* **2000**, *41*, 2165-2169.

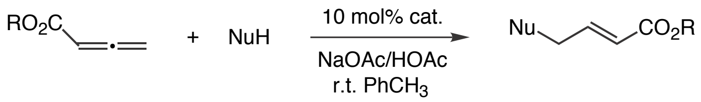
A Related Phosphine Catalyzed Reaction

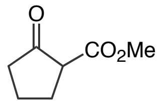
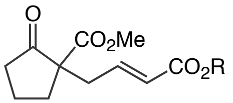
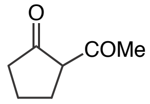
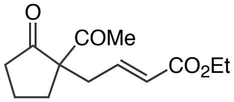
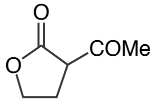
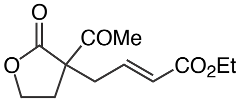
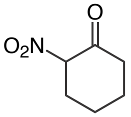
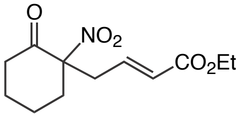
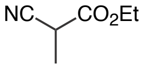
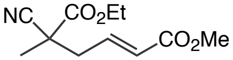


- other catalyst and conditions give lower regio- and enantio- selection

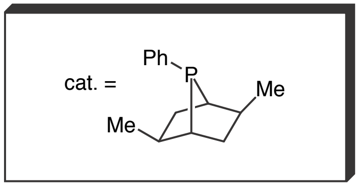
Zhang, X.; *et. al. J. Am. Chem. Soc.* **1997**, *119*, 3836-3837.
Lu, X.; *et. al. J. Org. Chem.* **1995**, *60*, 2906-2908.

Phosphine Catalyzed Addition



NuH	R	yield (%)	*ee* (%)	product
	Me	80	73	
	Et	76	74	
	t-Bu	74	75	
	Et	67	56	
	Et	83	48	
	Et	31	41	
	Me	47	45	

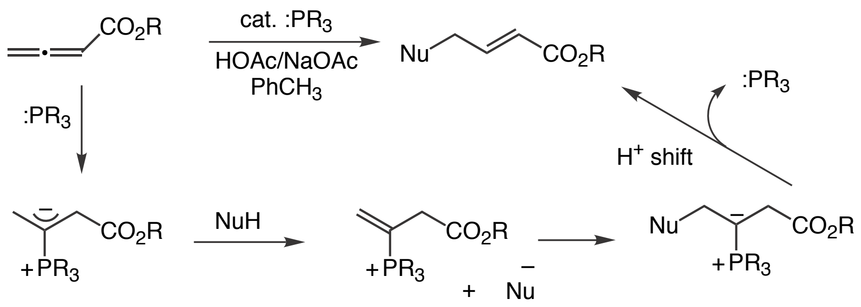
Zhang, X.; *et. al. J. Org. Chem.* **1998**, *63*, 5631-5635.



The Asymmetric Baylis-Hillman Reaction

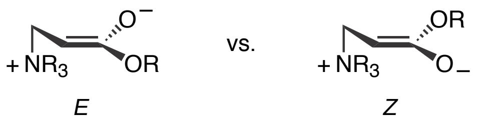
Addition Mechanism

Author's proposal:

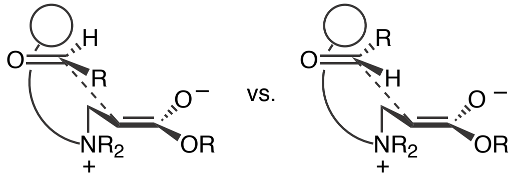


Recipe for a Good Catalyst?

Control enolate geometry...

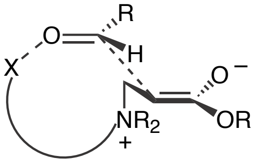


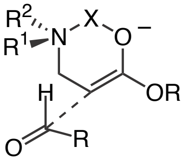
Control aldehyde π face...



- for substituted acrylates, must control enolate π facial selectivity
- chirality on catalyst may also gear ester substituent to influence aldehyde approach

or





Conclusions

- The Baylis-Hillman reaction provides convenient access to valuable allylic alcohol building blocks which may serve as synthetic equivalents to *anti*-propionate aldol addition products.
- The basics of the reaction mechanism are understood, but the mechanistic details still remain elusive at best.
- Few examples of a general, diastereoselective Baylis-Hillman have been reported and the successful ones are rather limited in scope.
- Only one synthetically useful enantioselective, base catalyzed Baylis-Hillman reaction exists. There is no rational design, nor models for asymmetric catalysis.
- The asymmetric, catalytic Baylis-Hillman reaction is very promising and attractive methodology, but remains an elusive goal of chiral Lewis base catalysis.

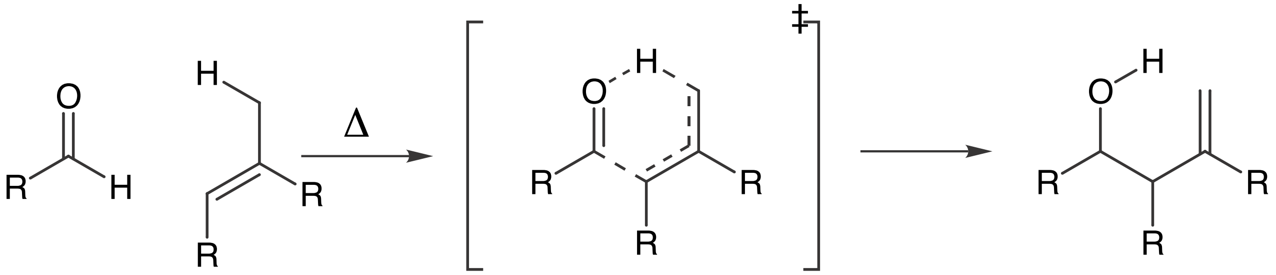
Chemistry 206

Advanced Organic Chemistry

Handout 26B

Asymmetric Carbonyl Ene Reactions

Evans Group Seminar
by
Steven Tregay, December 12, 1997



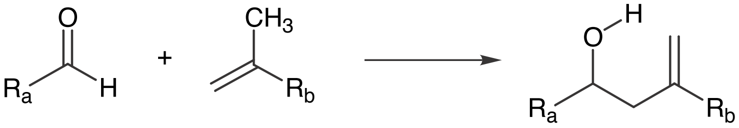
D. A. Evans

Monday,
November 17, 2003

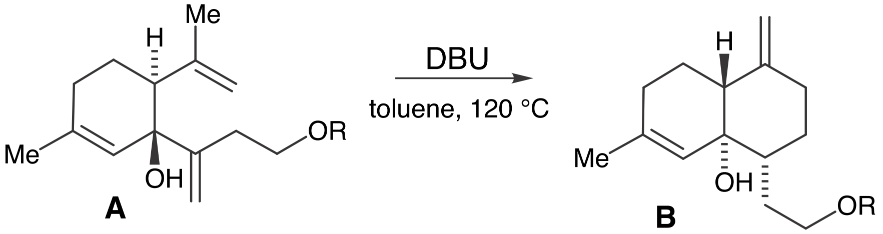
Chem 206 Problems Containing the Ene Reaction

The problems provided on this and the following page deal with the ene reaction either directly or indirectly. In the latter cases, this reaction is imbedded within a multistep rearrangement sequence. Answers to these questions may be obtained by entering the descriptors "Rearrangement" and "Ene" into the problems database: **http://evans.harvard.edu/problems/**

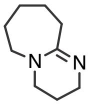
Problem 210. The carbonyl ene reaction is illustrated below. Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.



Problem 19. The following transformation was recently reported by Barriault and Deon in conjunction with their synthesis of arteanniun M (*Org. Lett.* **2001**, *3*, 1925-1927). Provide a mechanism for the illustrated thermal rearrangement(s) of **A** to **B**. Where stereochemical issues are at stake, provide clear three dimensional drawings to support your answer.

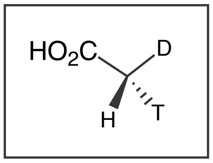


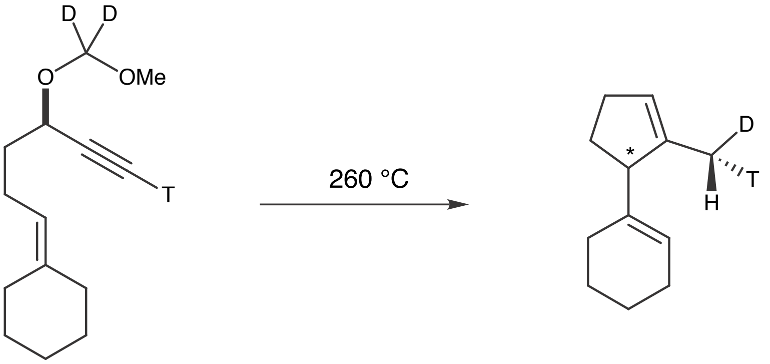
Single product diastereomer



DBU is a useful amidine base; pKa ~ 12

Problem 83. Chiral methyl groups are commonly used to probe the stereochemical outcome of biological reaction mechanisms. Many interesting strategies have been developed to synthesize chiral methyl groups in high enantiomeric excess. The first approach, designed by Arigoni (*Chem. Commun.* **1975**, 921), is illustrated below.

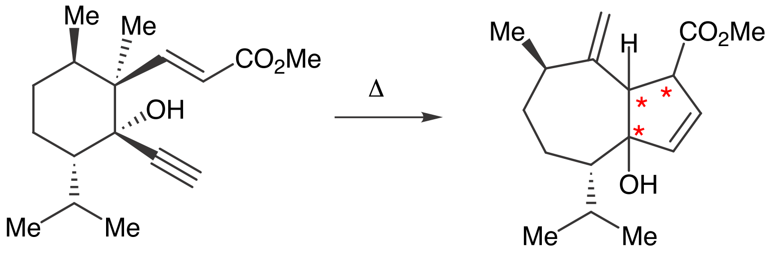




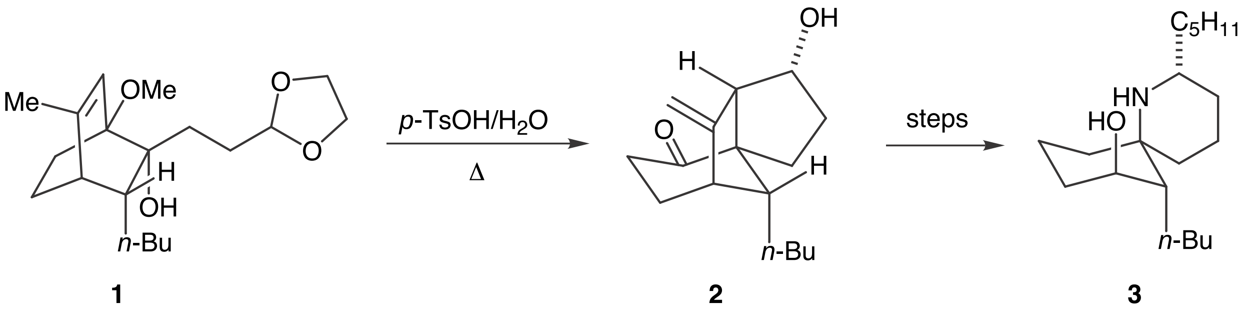
Provide a mechanism for the following transformation that accounts for the (H,D,T) stereochemistry of the chiral methyl group. You do not need to account for the stereochemistry at the starred carbon (it was not determined by the investigators).

Chem 206 Problems Containing the Ene Reaction

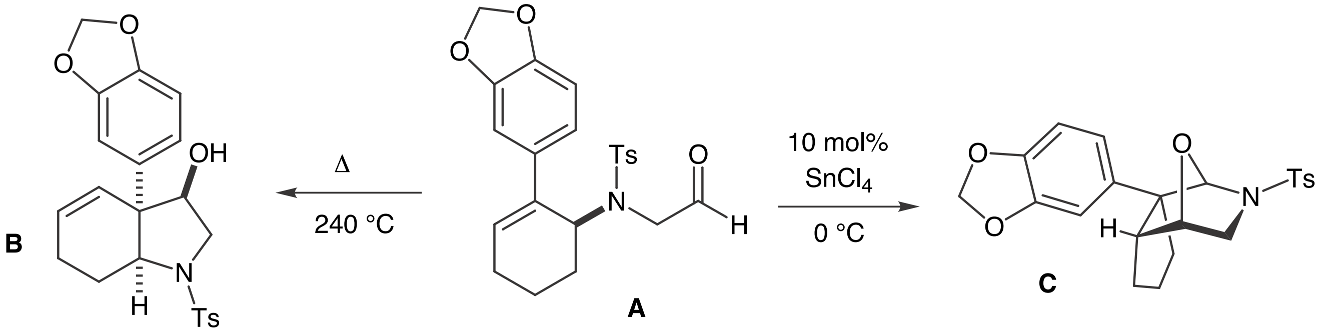
Problem 177. Provide a mechanism that predicts the observed stereochemistry at the starred (*) carbon atoms (Rajagopalan, *Tetrahedron Lett.* **1998**, *39*, 4133). Draw the starting material, each intermediate, and the product clearly in 3D.



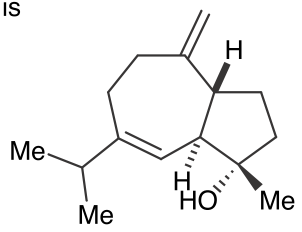
Problem 184. The key step in Kim's synthesis of perhydrohistrionicotoxin, **3**, was the conversion of intermediate **1** to ketone **2** in a single acid-catalyzed transformation (*Chem. Commun.*, **1997**, 2263). Provide a mechanism for the conversion of **1** to **2** that accounts for the observed stereochemistry.



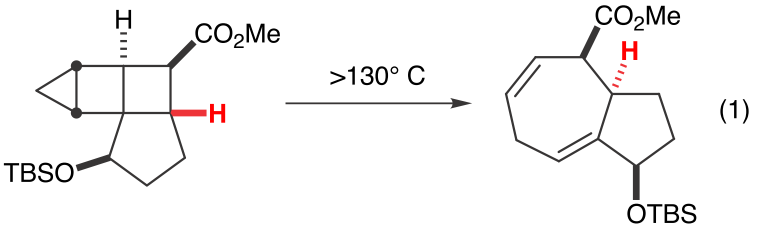
Problem 203. Provide mechanisms that account for the stereoselective formation of the products obtained by treatment of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions (*JOC*, **1998**, 7586).



Problem 233. Snapper and co-workers have reported an approach to the [5.3.0] ring system that is commmon to a number of sesquiterpenes(*JACS* **2001**, *123*, 5152). One cited example is alismol whose structure is provided for reference. Upon thermolysis, the illustrated tetracyclic ester is transformed into the illustrated bicyclic ring system in 64% yield (eq 1).

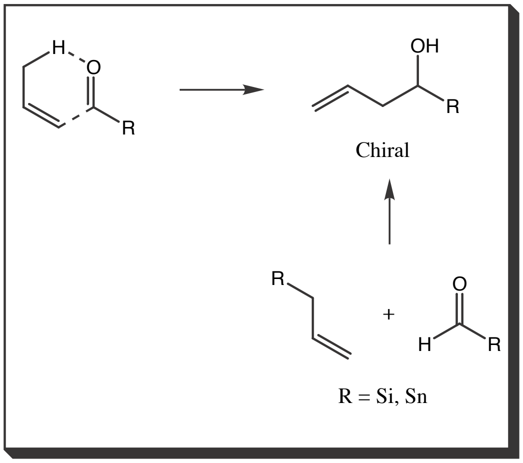


Alismol



Provide a plausible mechanism for this transformation. Your answer should include an explanatin of the somewhat unusual stereochemical inversion of the center carrying the flagged "red" hydrogen.

Seminar Topics



Covered in this Seminar:

Asymmetric Ene
(Metallo-Ene not covered)

Chiral Auxilaries

Catalytic/Promoted

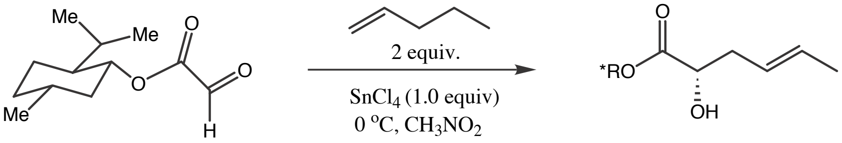
Reviews:

Snider in *Comprehensive Organic Chemistry,* **1991,** vol 2, 527.
Mikami, *Chem. Rev*. **1992**, *92*, 1021.
Mikami, *Advances* in Asymmetric Synthesis, **1995,** 1.
Bolm, ACIEE, **1995**, *34*, 1717.
Mikami, *Advances in Catalytic Processes*, **1995,** *1,* 123.
Mikami, *Pure & Applied Chem.,* **1996,** *68, 639*.

History:

Alder, *Ber*., **1943**, *76*, 27.
Alder, *Ann.,* **1962**, *651, 141*.

Early Work on Chiral Glyoxylates



2 equiv.

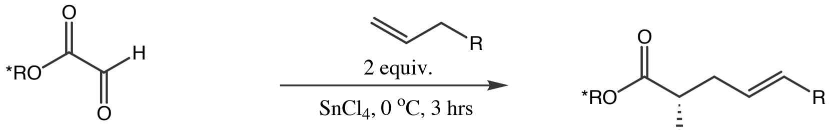
$SnCl_4$ (1.0 equiv)
0 °C, CH_3NO_2

31 % ee, 87 % yield

Thermal reaction (160 °C) gave no induction

Achmatzowicz, JOC, **1972**, *37*, 964.

Ene reactions of 8-Phenylmenthol Glyoxylate Ester

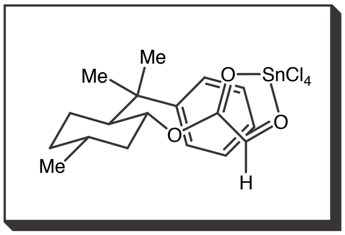


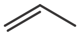
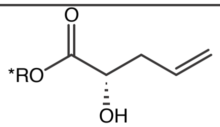
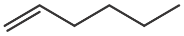
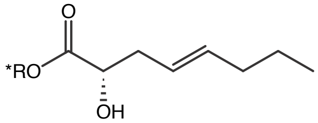
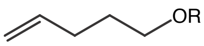
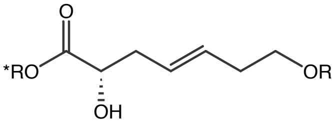
2 equiv.

$SnCl_4$, 0 °C, 3 hrs

*R = 8-Phenylmenthol

>97 % de
< 6 % *cis* olefin observed

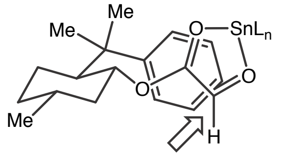


Alkene	Product	Yield
		99 %
		92 %
		R=H 100 % (2:1 *cis : trans)* R=OAc 59 % R=Bn 99 % R=TBS 89 %

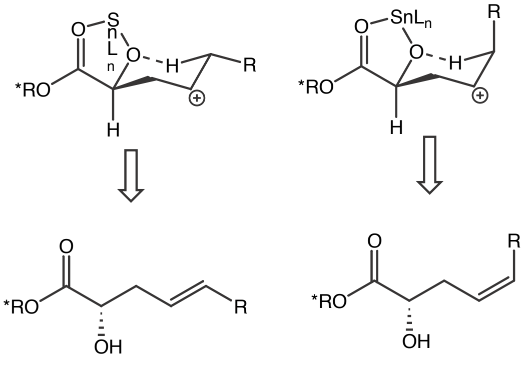
Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986,** *42,* 2993.

Mechanism for 1-Substituted Olefins

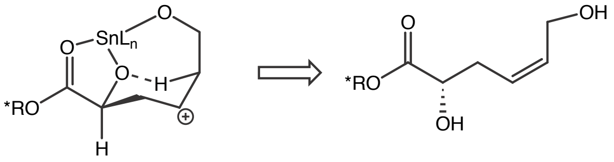
Absolute Configuration



Olefin Geometry

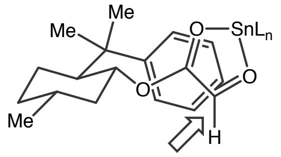


Competing Pathway for Free Hydroxyl

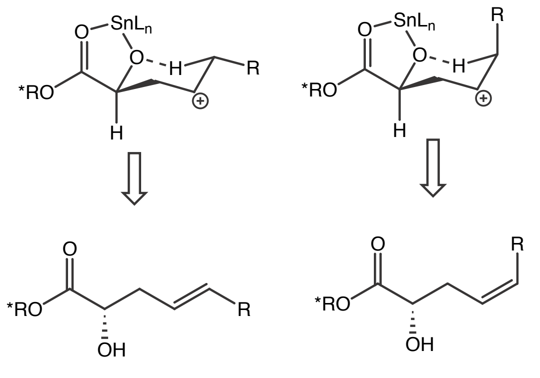


Mechanism for 1-Substituted Olefins

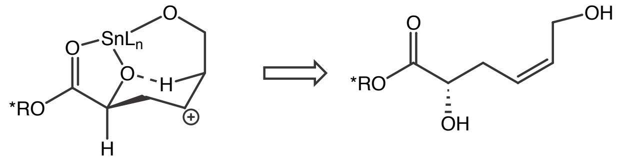
Absolute Configuration



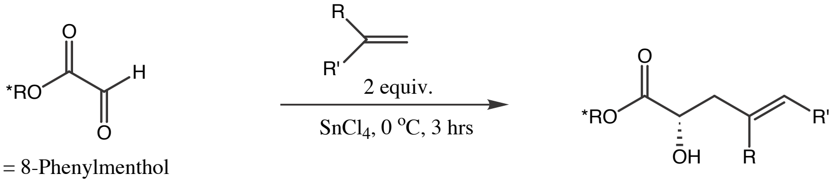
Olefin Geometry



Competing Pathway for Free Hydroxyl

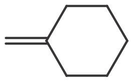
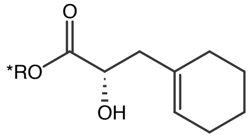
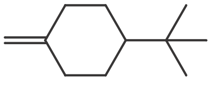
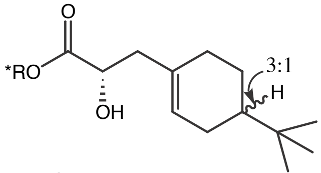
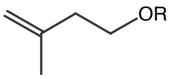
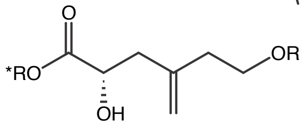


1,1 Disubstituted Olefins



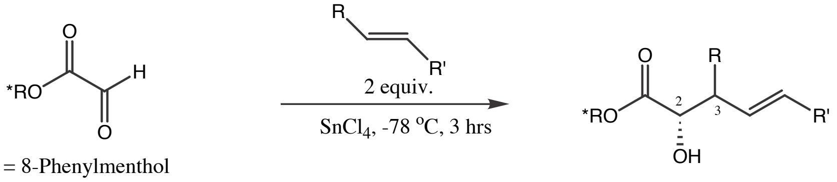
*R = 8-Phenylmenthol

>97 % de

Alkene	Product	Yield
		94 %
		84%
		R=H "Dominant product" R=OAc 42 % 24 % trans olefin 20 % cis olefin

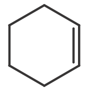
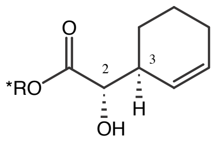
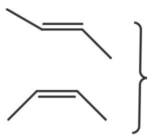
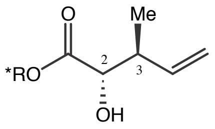
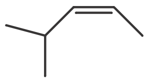
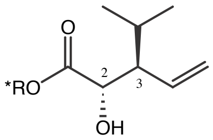
Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986,** *42*, 2993.

1,2 Disubstituted Olefins



*R = 8-Phenylmenthol

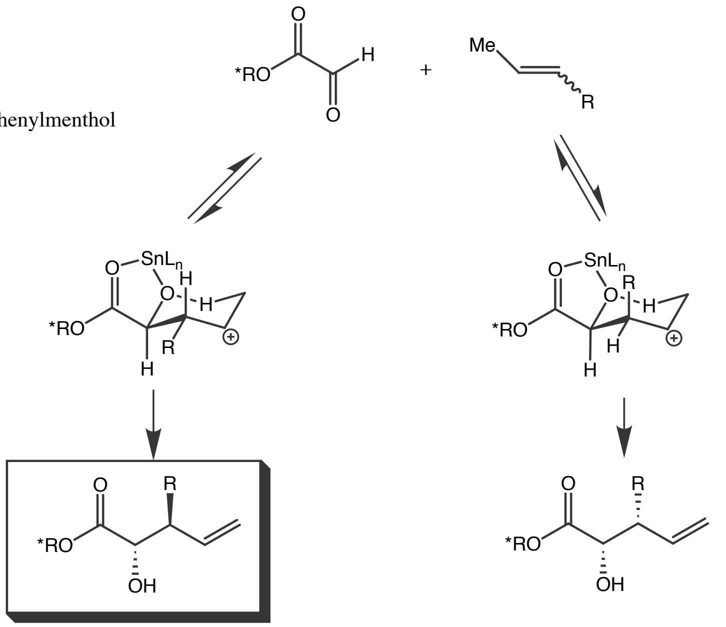
C-2 >97 % de

Alkene	Product	Yield
		C-3 92 % de "Exo TS" 90 % yield
		C-3 15 : 1 85 % yield C-3 8 : 1
		one compound 86 % yield

Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986,** *42,* 2993.

1,2 Disubstituted Olefin Mechanism

*R = 8-Phenylmenthol

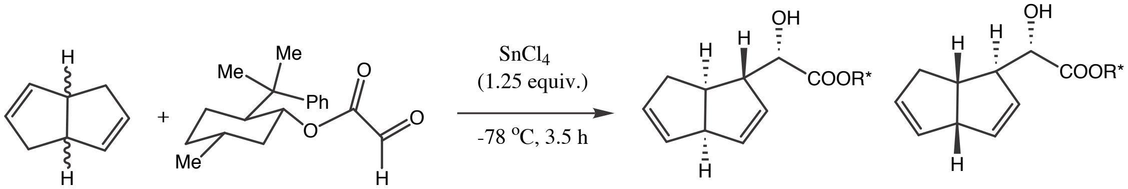


R = Me
trans-butene 15 : 1
cis-butene 8 : 1

R = i-Pr
4-methyl-*cis*-2-pentene one compound

Note: *cis*-butene does not isomerize in presence of SnCl$_4$ or SnCl$_4$ / isopropyl alcohol at -78 °C
Isomerization does occur in the presence of gyloxylate

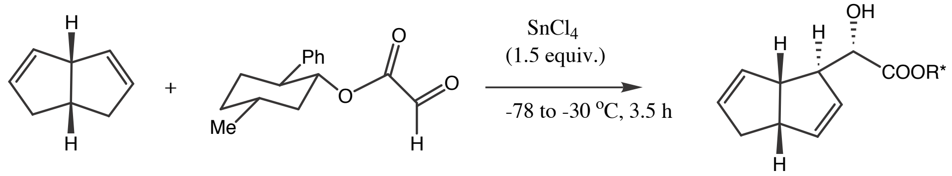
Asymmetric Desymmetrization using 8-Phenylmenthol Glyoxylate Ester



Excess

1

8 : 1 (72 % yield)



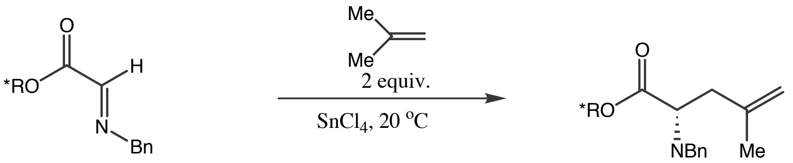
one diastereomer

(81 % yield)

Whitesell, JACS, **1988**, *110*, 3585.
Whitesell, JACS, **1986**, *108*, 6802.
Whitesell, JOC, **1985**, *50*, 3025.

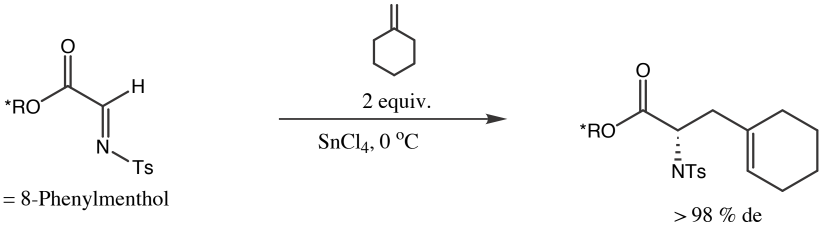
Note: 1 gives opposite bridgehead selectivity

Phenylmenthol Imine-Ene Reaction



*R = 8-Phenylmenthol

97 % de
76 % yield



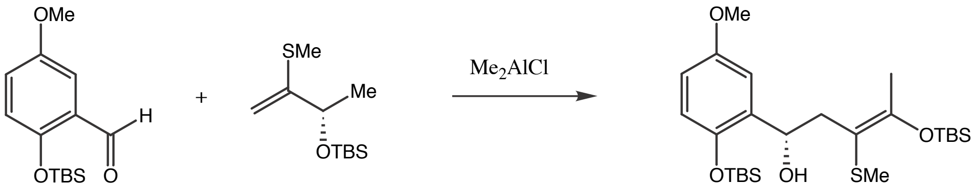
*R = 8-Phenylmenthol

> 98 % de
60 % yield

Use of Ts rather than Bn
was not discussed

Mikami, TL, **1993**, *34*, 4841.

Ene reaction of (S)-2-(Ethylthio)-3-siloxy-1-butene

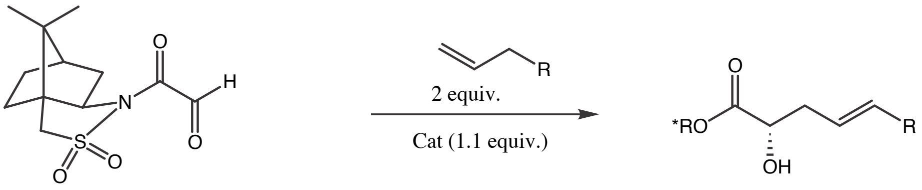


99 % ee
100 % yield

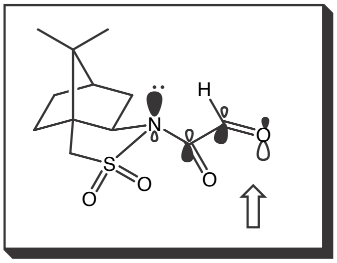
Referenced in Mikami, *Chem. Rev.*, **1992**, *92,* 1021

Kuwajima, Annual Meeting of the Chemical Society of Japan, 1991.

Ene Reactions of N-Glyoxyloyl -(2R)-bornane-10,2-Sultam



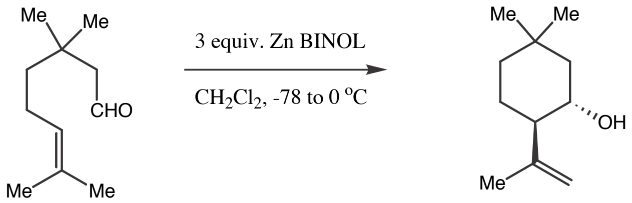
R =	Catalyst	Temp (°C)	% de	% Yield
Et	$SnCl_4$	-78	84 : 16	78
	$ZnBr_2$	5	90 : 10	50
n-Pr	$SnCl_4$	-78	75 : 25	93
	$ZnBr_2$	5	89 : 11	43



Most Reactive Conformation according to PM3 and *Ab initio* calculations
Chapuis, *Helv. Chim. Acta*, in preparation

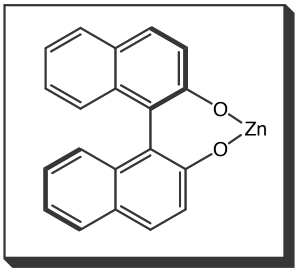
Jurczak, *Tet.: Asymm.*, **1997**, *8*, 1741.

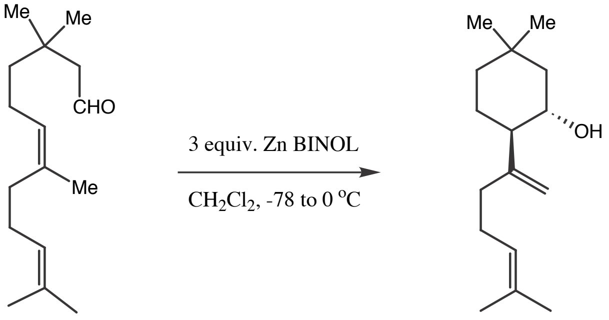
Zn BINOL Promoted Intramolecular Ene Cyclizations



88 % ee
86 % yield

Note: using 1.5 equiv.
reagent lowers % ee





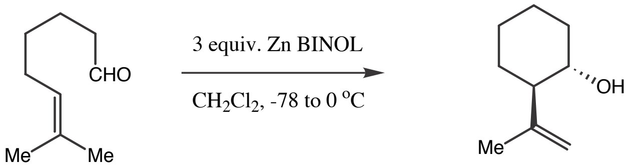
(*Z*)- methylfarnesal

88 % ee
89 % yield

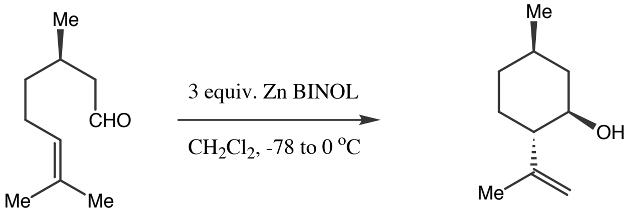
(E)-methylfarnesal afforded other
regiochemistry in 20 % ee

Yamamoto, *Tetrahedron*, **1986**, *42*, 2203.

Zn BINOL Promoted Intramolecular Ene Cyclizations



0 % ee
31 % yield

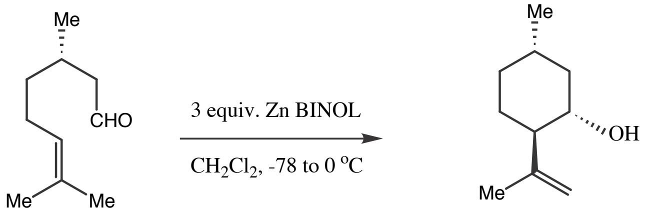


(*R*)- citronellal

(*R*)-isopulegol

one compound

Note : ZnBr$_2$ gives 95:5 ratio of products
of idenical configuration
See: Nakatani, *Syn. Comm.*, ***1978***, *147*.



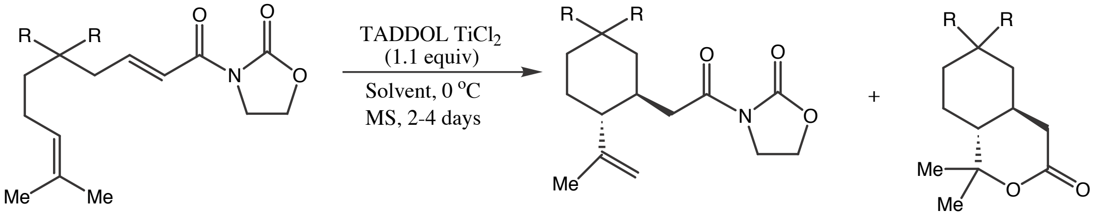
(*S*)- citronellal

(*S*)-isopulegol

one compound

Yamamoto, *Tetrahedron*, **1986**, *42*, 2203.

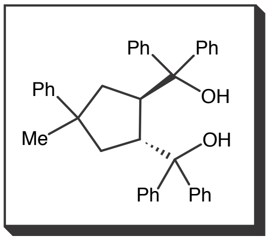
TADDOL Promoted Intramolecular Ene



1

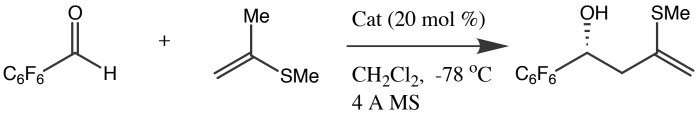
2

R =	Solvent	**1** % ee (% yield)		**2** % ee (% yield)	
H	Toluene (20 days)	ND	(17)	ND	(37)
Me	Toluene	82	(39)	92	(36)
	1,3,5 Trimethylbenzene	86	(32)	>98	(37)
	$CFCl_2CF_2Cl$/ CH_2Cl_2	97	(47)	ND	(16)
$-SCH_2CH_2S-$	$CFCl_2CF_2Cl$/ CH_2Cl_2	84	(ND)	>98	(ND)

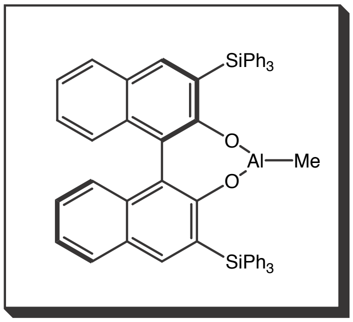


Narasaka, *Chem. Lett.*, **1988**, 1609.

3-3'-bis(triphenylsilyl)BINOL Aluminium Catalyst



88 % ee
88% yield



Note: Use of less reactive aldehydes (ie Chloral) afforded lower % ee and stoic. LA were required

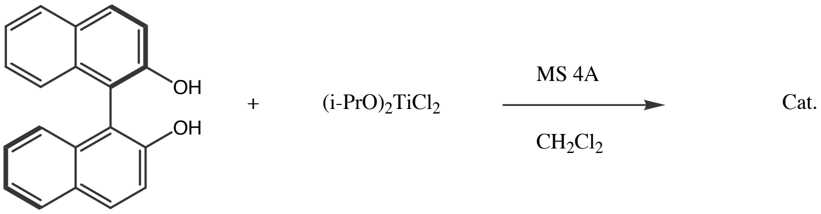
Use of MS is required for catalytic reaction

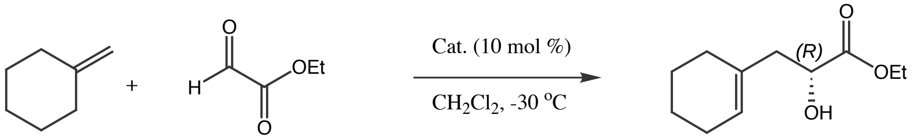
Use of 3-3'-diphenylbinaphthol complex gave 0 % ee

Yamamoto, TL, **1988**, *29*, 3967.

$(i\text{-}PrO)_2TiCl_2$ (*R*)-BINOL Catalyzed Ene Reaction

Preliminary Result:

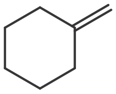
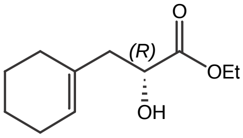
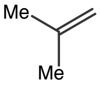
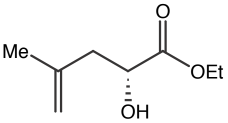
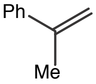
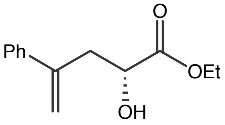
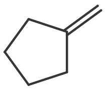
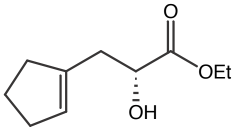




86 % ee
82 % yield

Nakai, JACS, **1989**, *111*, 1940.
Nakai; Mikami, JACS, **1990**, *112*, 3949.

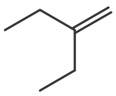
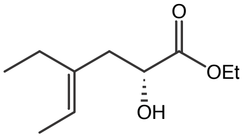
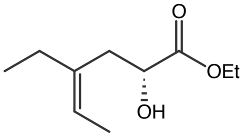
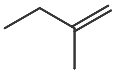
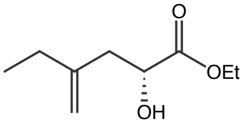
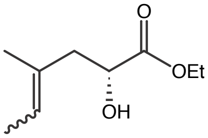
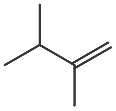
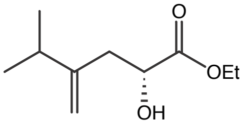
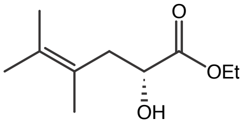
$(i\text{-}PrO)_2TiBr_2$ (*R*)-BINOL Catalyzed Ene Reaction : 1,1 Disubstituted

Olefin	Product	Cat. Mol %	% yield	% ee
		5	73	98
		10	87	94
		1.0	98	94
		5	92	89

Reaction conditions: Ethyl glyoxylate, -30 °C, 3 hr, MS, CH_2Cl_2

Nakai, JACS, **1989**, *111*, 1940.
Nakai; Mikami, JACS, **1990**, *112*, 3949.
Nakai, *Org*. *Syn*., **1993**, 14.

$(i\text{-}PrO)_2TiBr_2$ (*R*)-BINOL Catalyzed Ene Reaction : More 1,1 Disubstituted

Olefin	Products				
		*E* 91 % yeild 98 % ee		*Z* 9 % yeild >90 % ee	
		39 % yeild 91% ee		*E* 57% yeild >98 % ee	*Z* 4% yeild >90 % ee
		83 % yeild 92% ee		17% yeild >98 % ee	

Reaction conditions: Ethyl glyoxylate, 5 -10 mol % cat., -30 °C, 3 hr, MS, CH_2Cl_2

Nakai, JACS, **1989**, *111*, 1940.
Nakai; Mikami, JACS, **1990**, *112*, 3949.

Importance of Molecular Sieves

$$\text{BINOL-(OH)}_2 + (i\text{-PrO})_2TiCl_2 \xrightarrow[CH_2Cl_2]{\text{Additive}} \text{Method } \mathbf{A}$$

$$\text{BINOL-(OLi)}_2 + TiCl_4 \xrightarrow[CH_2Cl_2]{\text{Additive}} \text{Method } \mathbf{B}$$

ref: Reetz, *Chem. Ind. (London),* **1986**, 824.

For reaction of α-methyl Styrene and ethyl gloxylate (CH_2Cl_2, -30 °C)

	Additive 4 A MS (g/mmol)	Yield	% ee
Method **A**	5	100	97
	0	81	10
	5 then filter	96	97

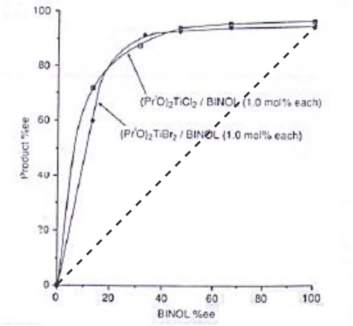
Note : By ^{13}C NMR no Ti BINOL complexation occurs until MS are added.
$(i\text{-}PrO)_2TiCl_2$ is a viable catalyst for the reaction.

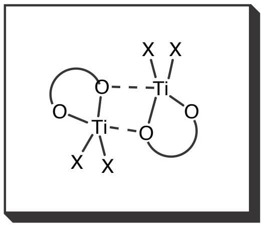
	Additive i-PrOH	Additive 4 A MS (g/mmol)	Yield	% ee
Method **B**	0	0	95	93
	10 mol %	0	90	95
	0	5	100	95
	10 mol %	5	98	96

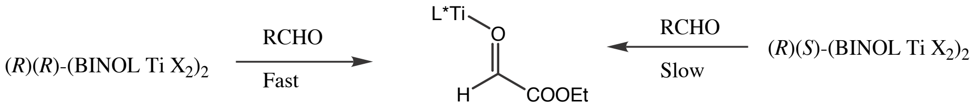
Note : MeOH, t-BuOH give similar results

Nakai; Mikami, JACS, **1990**, *112*, 3949.

NonLinear Effect in the(i-PrO)$_2$TiX$_2$ BINOL Catalyzed Ene Reaction







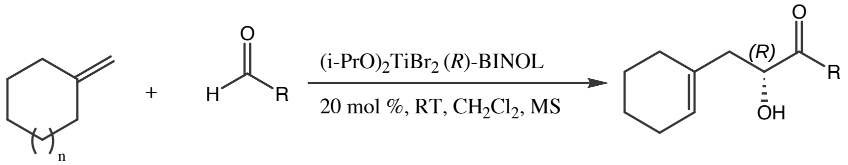
For chiral poisoning of racemic BINOL Complxes see:

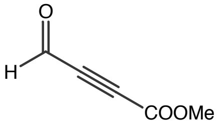
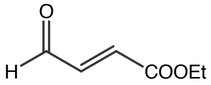
Faller, TL, **1996**, *37*, 3449.
Mikami, *Nature,* **1997,** *385*, 613.

Note : For X-ray crystal structure of dimeric ((PhO)$_2$TiCl$_2$)$_2$
See: Watenpaugh, *Inorg. Chem.* **1966**, *5*, 1782.

Mikami, *Tetrahedron*, **1992**, *48*, 5671.
Mikami, JACS, **1994**, *116,* 2812.

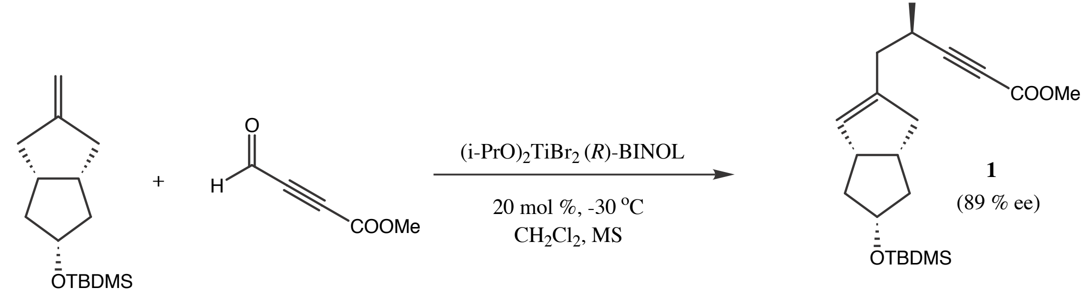
(i-PrO)$_2$TiBr$_2$ (*R*)-BINOL Catalyzed Ene Reaction : Other Enophiles



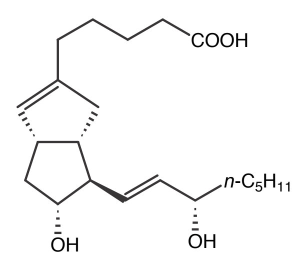
Enophile	n=	% Yield	% ee
	0	85	87
	1	70	94
	0	80	72
	1	60	86

Mikami, TL, **1996**, *47*, 8515.

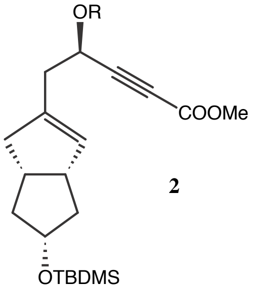
Asymmetric Desymmetrization using (i-PrO)$_2$TiBr$_2$ (*R*)-BINOL



1
(89 % ee)



isocarbacyclin

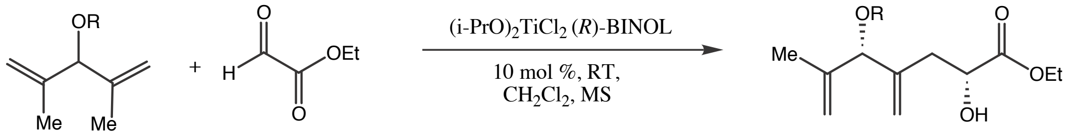


2

1 : 2 ratio 92 : 8

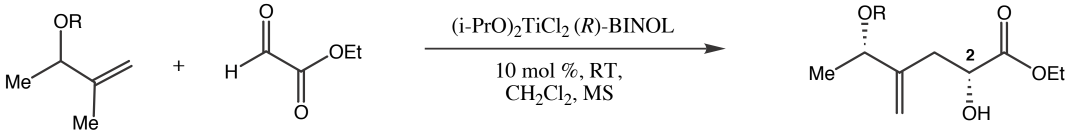
Mikami, TL, **1996**, *47*, 8515.
Mikami, Synlett, **1995**, 29.

Asymmetric Desymmetrization / Resolution using (i-PrO)$_2$TiCl$_2$ (*R*)-BINOL



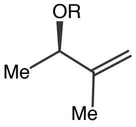
R = Dimethylthexylsilyl

> 99 % *syn*
(97 % ee)



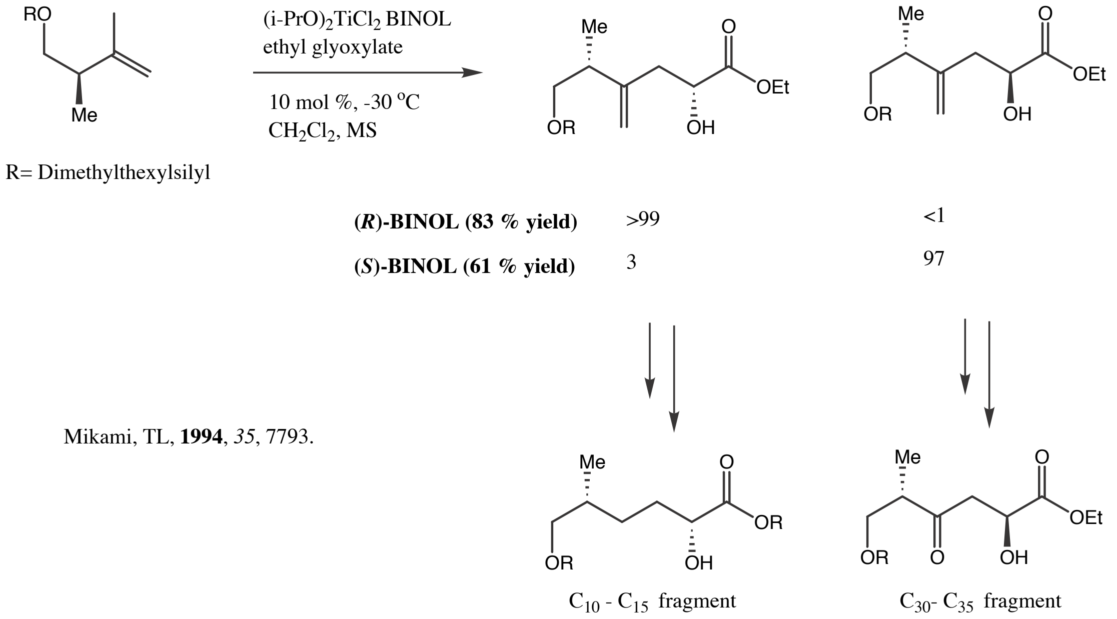
1

> 97% *syn*
(>95 % ee)

	Catalyst	Product
	(i-PrO)$_2$TiCl$_2$ (*S*)-BINOL	*ent*-**1** (>99 % *syn*, 71 % yield)
	(i-PrO)$_2$TiCl$_2$ (*R*)-BINOL	*ent*-**1** (50 : 50 at C-2, 31 % yield)

Mikami, Annual Meeting of the Chemical Scoiety of Japan, **1990** and **1991.**
See : Mikami, *Synlett*, **1992,** 255.

Synthesis of C_{10} - C_{15} and C_{30}- C_{35} fragments of Rapamycin



R= Dimethylthexylsilyl

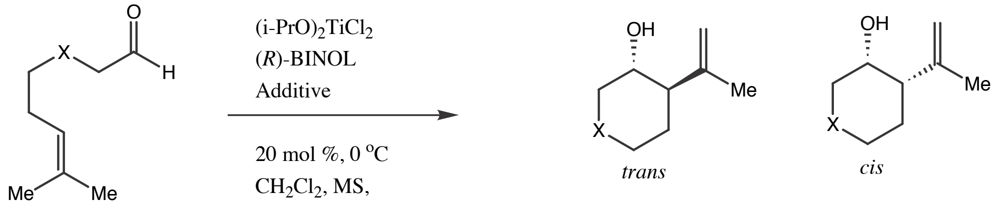
(*R*)-BINOL (83 % yield)	>99	<1
(*S*)-BINOL (61 % yield)	3	97

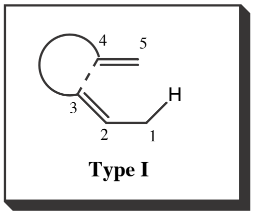
C_{10} - C_{15} fragment

C_{30}- C_{35} fragment

Mikami, TL, **1994**, *35*, 7793.

$(i\text{-}PrO)_2Ti(ClO_4)_2$ (*R*)-BINOL Catalyzed
{3, 4} *exo, exo* Intramolecular Ene Reaction

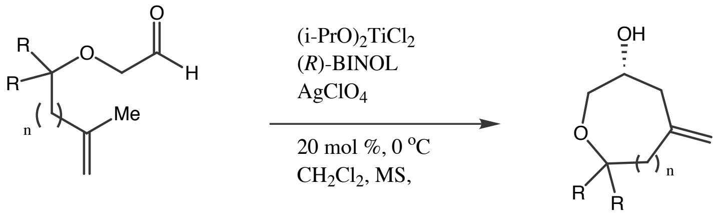




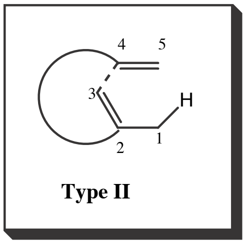
X =	Additive	time	% Yield	Ratio *trans : cis*	*trans* % ee
O	none	24 h	73	47 : 53	70
O	$AgClO_4$	24 h	50	80 : 20	84
$-CH_2-$	$AgClO_4$	48 h	66	69 : 31	55

Mikami, TL, **1991**, *32*, 6571.
Mikami, *Tet. :Asymm.*, **1991,** *2*, 1403.

$(i\text{-PrO})_2Ti(ClO_4)_2$ (*R*)-BINOL Catalyzed
{2, 4} *exo, exo* Intramolecular Ene Reaction



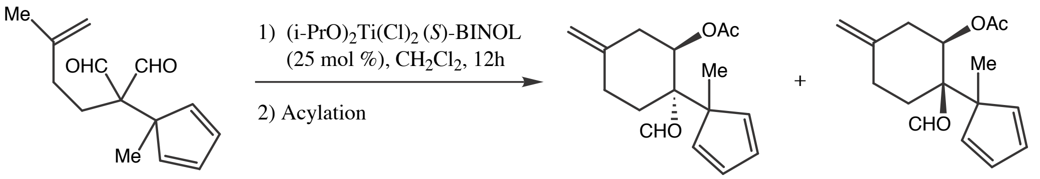
n=	R=	% yield	% ee
0	H or Me	NR	--
1	H	43	91
1	Me	40	82



Type II

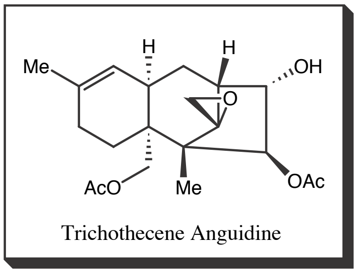
Mikami, TL, **1991**, *32*, 6571.
Mikami, *Tet. :Asymm.*, **1991,** *2*, 1403.

$(i\text{-PrO})_2Ti(Cl)_2$ (*S*)-BINOL Catalyzed
{2, 4} *exo, exo* Intramolecular Ene Reaction

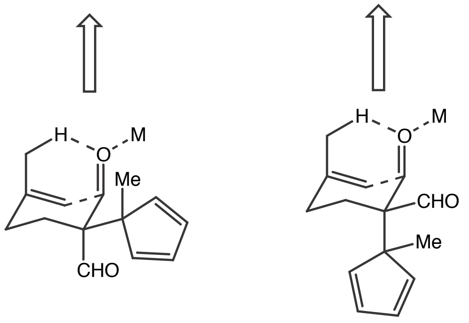


Me
OHC
CHO
Me
1) $(i\text{-PrO})_2Ti(Cl)_2$ (*S*)-BINOL
(25 mol %), CH_2Cl_2, 12h
2) Acylation
OAc
Me
CHO
+
OAc
Me
CHO

4.5 (38 % ee) : 1

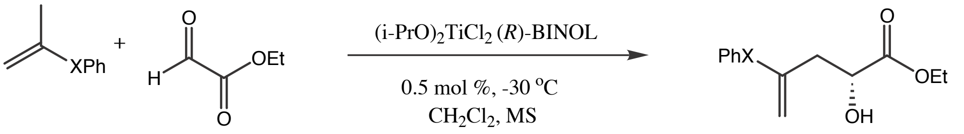


Trichothecene Anguidine

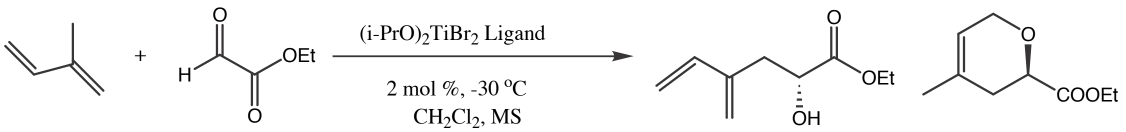


Ziegler, JACS, **1990**, *112*, 2749.

Approaches toward Ipsdienol

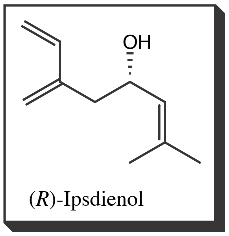


X= S	X= Se
94 % yield >99 % ee	95 % yield >99 % ee

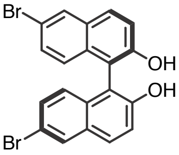


Ene

Hetero D.A.



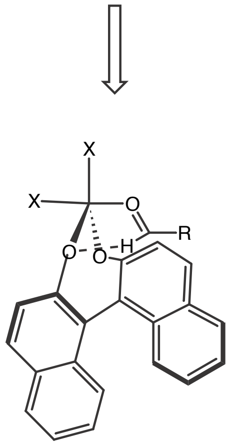
(*R*)-Ipsdienol

Ligand	Yield	Product Ratio Ene	Hetero D. A.
BINOL	94	79 (97 % ee)	21
 Br OH OH Br	84	92 (>99 % ee)	8

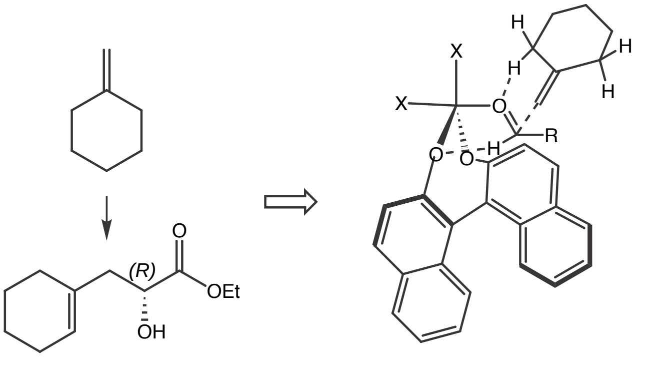
Mikami, JCS CC, **1995**, 2391.
Mikami, JCS CC, **1993**, 327.

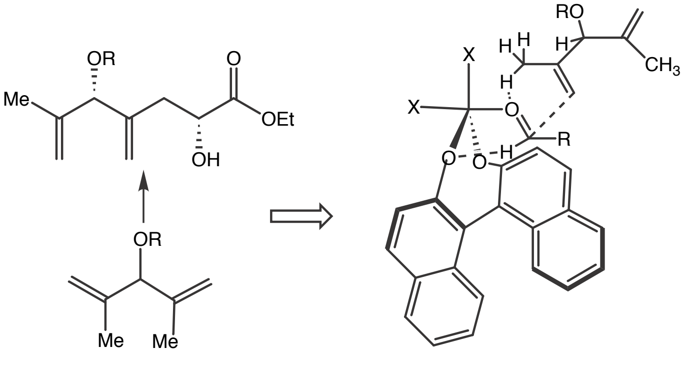
Corey's Model for Ti BINOL Ene Reactions

BINOL Ti X$_2$
Aldehyde Complex



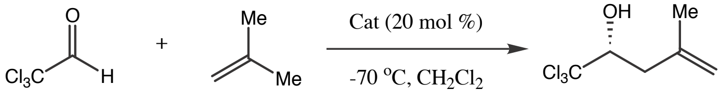
Corey, TL, **1997**, *38*, 6513.





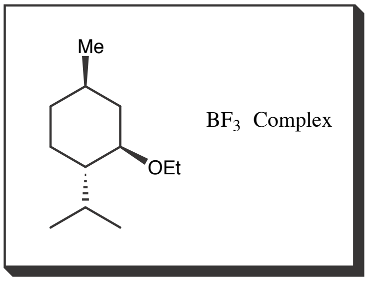
R= Dimethylthexylsilyl

BF_3 Menthylethyl Etherate catalyzed Ene reaction



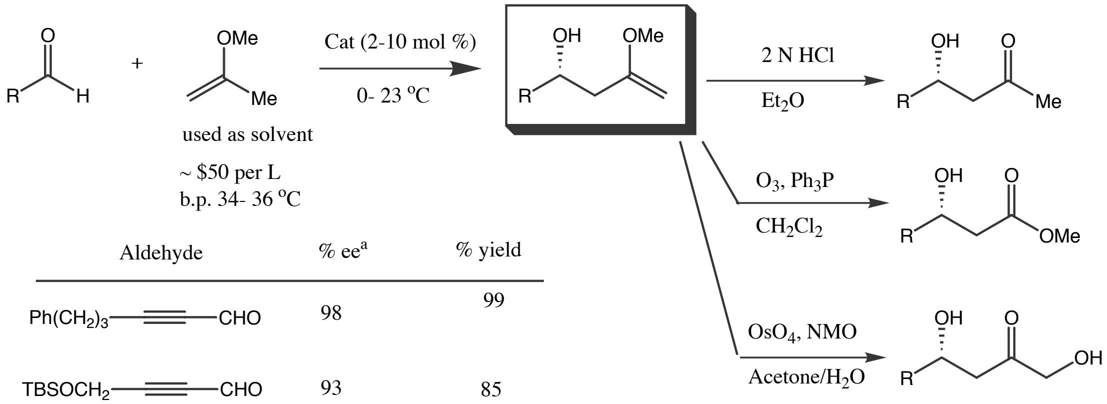
2 equiv.

22 % ee
55 % yield



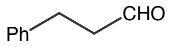
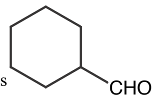
Demir, *Syn. Comm.* **1994**, *24*, 137.

Carreira's Catalytic Ene

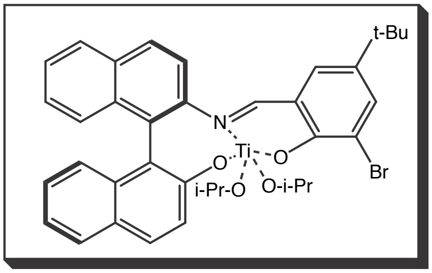


used as solvent

~ $50 per L
b.p. 34- 36 °C

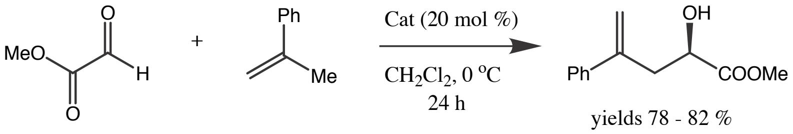
Aldehyde	% ee[a]	% yield
$Ph(CH_2)_3-C\equiv C-CHO$	98	99
$TBSOCH_2-C\equiv C-CHO$	93	85
$Ph-C\equiv C-CHO$	91	99
	90	98
PhCHO	66	83
Only α-branched aldehyde which reacts 	75	79

[a] % ee detrmind by NMR analysis of (*S*)-MPTA ester of methyl ketone

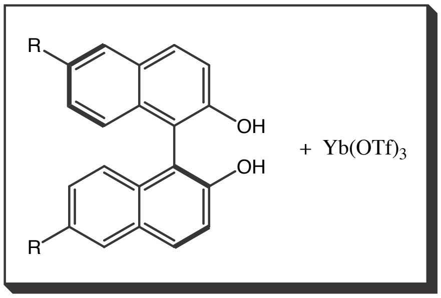


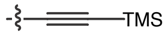
Carreira, JACS, **1995**, *117*, 3649.

Yb(OTf)$_3$ BINOL Catalyzed Ene Reaction



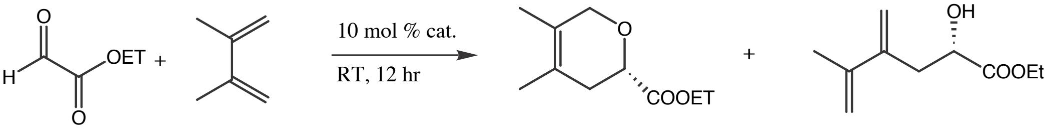
yields 78 - 82 %

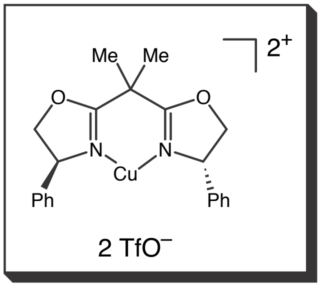


Ligand R=	% ee
H	12
Br	38
Ph	25
	29

Qain, TL, **1997**, *38*, 6721.

Jorgensen's Ene byproducts





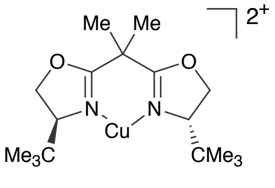
Solvent	Diels-Alder % ee	Ene Product % ee	DA :Ene Ratio
CH_2Cl_2	85	83	1 : 1.8
CH_3NO_2	90	78	1 : 0.8

Jorgensen, *Tetrahedron*, **1996**, *52*, 7321.

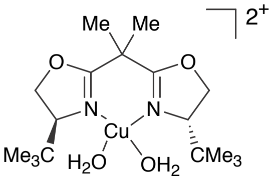
For optimization of hetero Diels-Alder reaction products
See: Jorgensen, JCS PT 2, **1997**, 1183.

Work from the Evans Groups

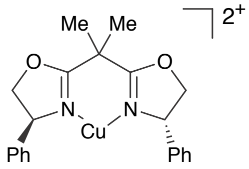
"C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Carbonyl-Ene Reactions with Glyoxylate and Pyruvate Esters". Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936-7943.



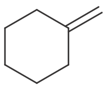
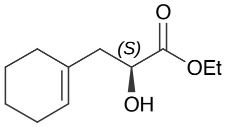
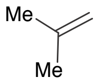
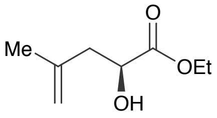
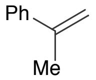
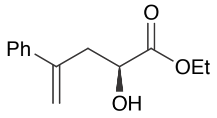
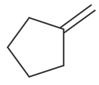
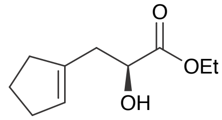
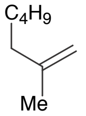
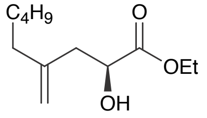
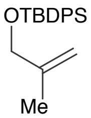
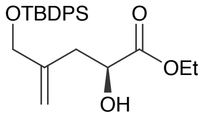
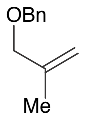
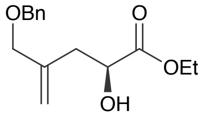
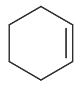
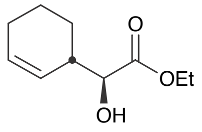
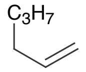
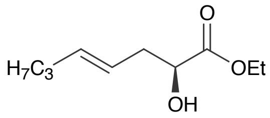
2 SbF_6^-



2 SbF_6^-

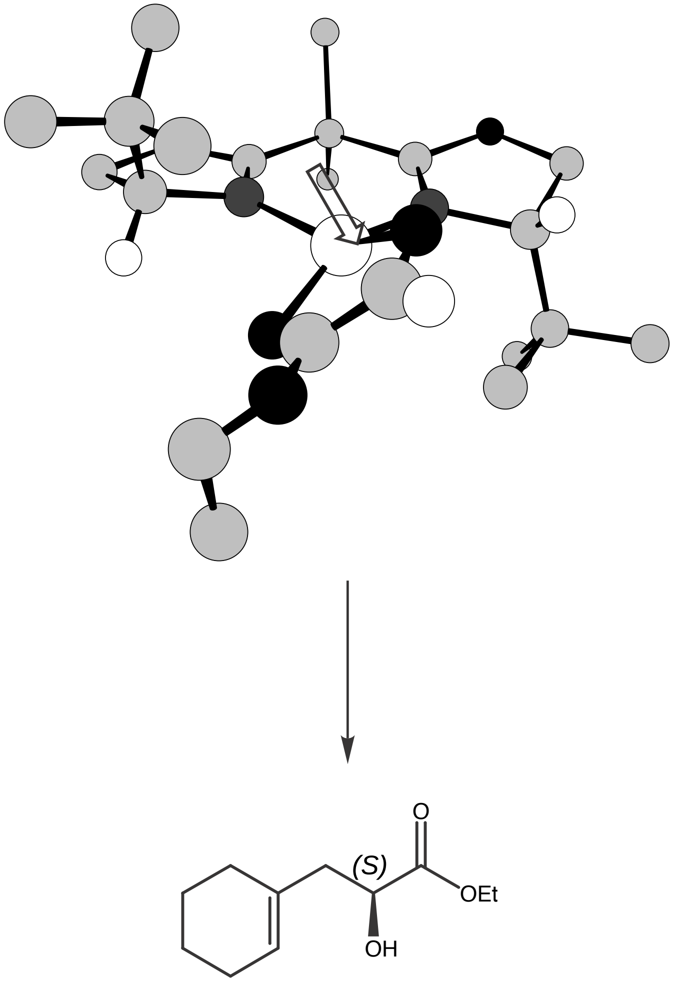


2 TfO^-

olefin	product[a]	catalyst	mol%	% yield	% ee	
		**2** **3**	1 10	90 99	97 (*S*) 87 (*R*)	
		**2** **3**	1 10	83 92	96 (*S*) 92 (*R*)	
		**2** **3**	1 10	97 99	93 (*S*) 89 (*R*)	
		**2** **3**	1 10	95 97	96 (*S*) 76 (*R*)	
		**2** **3**	1 10	89 81	96 (*S*) 92 (*R*)	Regiochemistry 75 : 25 90 : 10
		**2** **3**	1 10	72 85	96 (*S*) 91 (*R*)	one regioisomer
		**2** **3**	10 2	62 88	98 (*S*) 92 (*R*)	one regioisomer
		**1** **3**	10 10	95 70	98 (*S*) 94 (*R*)	*exo:endo* 86:14 95:5
		**1**	10	96	98 (*S*)	*E: Z* 96 : 4

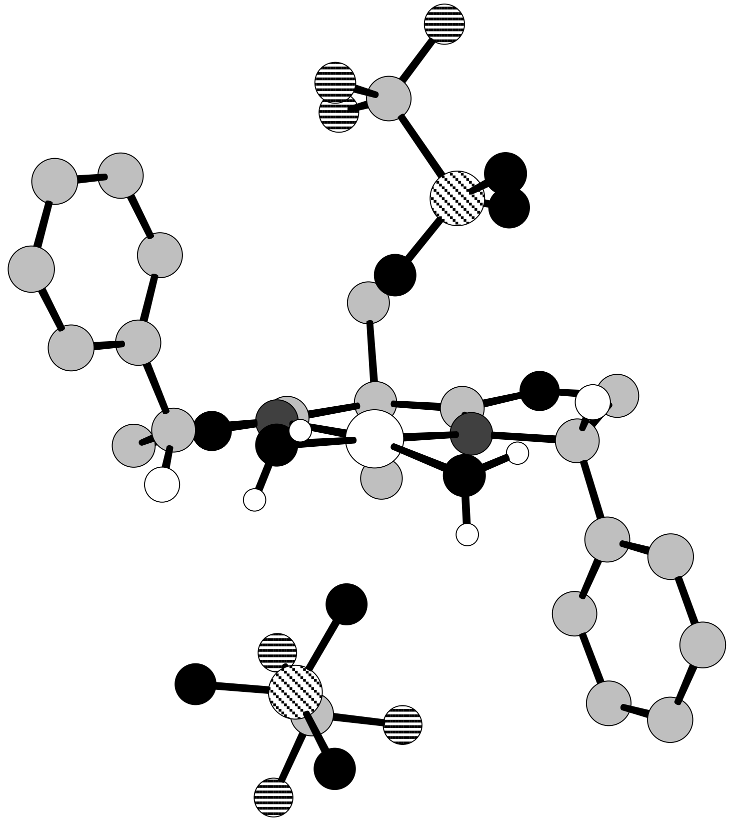
Origins of Enantioselectivity in Cu Box Ene Reactions

(*S*,*S*)-t-Bu Box Cu Glyoxylate (PM3^{tm})



However, (*S*,*S*)-Ph-Box Cu (OTf)$_2$ gives (R) configured alcohols:

Tetrahedral Cu center??
Jorgensen, JOC, 1995, *60*, 5757.



(*S*,*S*)-Ph Box Cu (OTf)$_2$(H$_2$O)$_2$ X-ray

Quotes for the Day

"In the last third of his life, there came over Laslo Jamf-so it seemed to those who from out of the wood lecture halls watched his eyelids slowly granulate, spots and wrinkles grow across his image, disintegrating it towards old-age hostility, a strangely personal hatred, for the covalent bond."

Thomas Pynchon, "Gravity's Rainbow"

"Faced with the choice between changing one's mind
and proving that there is no need to do so, almost everyone gets busy with the proof. "

John Kenneth Galbraith

Chemistry 206

Advanced Organic Chemistry

Handout–27A

An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships

D. A. Evans

Wednesday ,
November 19, 2003

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 27

Functional Group Classification Scheme for Polar Bond Constructions

- Historical Perspective
- Charge Affinity Patterns
- Functional Group Classification Scheme
- The Chemistry of the –NO_2 Group
- The Chemistry of the –N_2 Group

Reading Assignment for this Week:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."
D. A. Evans *Unpublished manuscript.* ***(Handout)***

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239. ***(Handout)***

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis"' Seebach, D. et. al, *Chimia*, **1979**, *33*, 1-18. ***(Handout)***

D. A. Evans

Wednesday,
November 19, 2003

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."
M. Saltzman *J. Chem. Ed.* **1972**, *49*, 750. ***(Handout)***

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."
A. Lapworth *J. Chem. Soc.* **1922**, *121*, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, *44*, 1293.

Monographs:

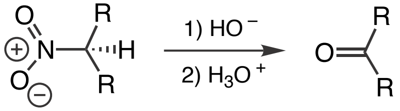
Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis".; John Wiley & Sons, Inc.: New York, 1987.

Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: NY, 1991.

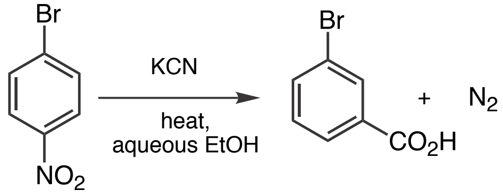
Ono, N., "The Nitro Group in Organic Synthesis", Wiley-VCH, 2001

Several Interesting Problems

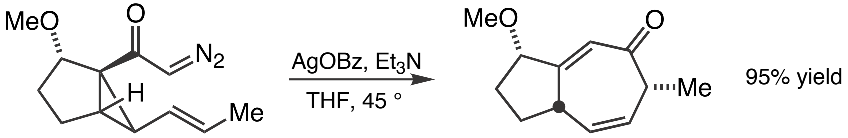
Provide a mechanism for the Nef reaction



The **von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If ^{15}N-labeled KCN is used, the N_2 formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.



Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, *125*, 13624). Please provide a mechanism for the illustrated transformation. Your answer should include clear 3-D drawings where relevant. the answer may be found in the database.



Ambiphilic Functional Groups

Required Reading:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."
D. A. Evans *Unpublished manuscript.*

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis'"
Seebach, D. et. al, *Chimia*, **1979**, *33*, 1-18.

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."
M. Saltzman *J. Chem. Ed.* **1972**, *49*, 750.

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."
A. Lapworth *J. Chem. Soc.* **1922**, *121*, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, *44*, 1293.

"Displacement of Aliphatic Nitro Groups by Carbon & Heteroatom Nucleophiles." R. Tamura, A. Kamimura, N. Ono *Synthesis* **1991**, 423.

"Functionalized Nitroalkanes as Useful Reagents for Alkyl Anion Synthons." G. Rosini, R. Ballini *Synthesis* **1988**, 833.

"Conjugated Nitroalkenes: Versatile Intermediates in Organic Synthesis."
A. G. M. Barrett, G. G. Graboski *Chem. Rev.* **1986**, *86*, 751.

Monographs:

Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis".; John Wiley & Sons, Inc.: New York, 1987.

Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: New York, 1991.

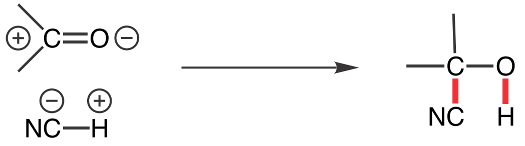
Arthur Lapworth (1872–1941)

Lapworth was among the first to understand and conceptualize the effect of heteroatomic substituents on the reactivity of individual carbon centers, and how this effect is propagated through the carbon framework of organic molecules.

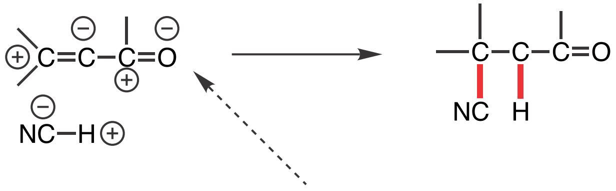
Lapworth's Theory of Alternating Polarities:

"Latent Polarities of Atoms and Mechanism of Reaction, with Special Reference to Carbonyl Compounds."
A. Lapworth *Mem. Manchester. Lit. Phil. Soc.* **1920**, *64 (3)*, 1.

"The addition of electrolytes to the carbonyl compound invariably proceeded as if the carbon were more positive than the oxygen atom, and invariably selected the negative ion; for example:"



"The extension of the influence of the directing, or "key atom," over a long range seems to require for its fullest display the presence of double bonds, and usually in conjugated positions...."



The "key atom" is the one with the most electronegative character, in this case the carbonyl oxygen.

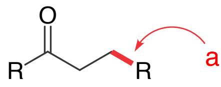
anionoid/cationoid - - - - - - - - → nucleophilic/electrophilic

The Lapworth polarity designations can be used to form the basis of a functional group classification scheme.

Reactivity Patterns of Functional Groups: Charge Affinity Patterns

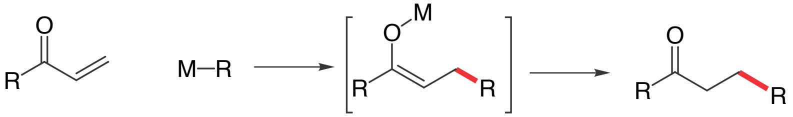
- Polar rxns form the basis set of bond constructions in synthesis
- Generalizations on conferred site reactivity will therefore be important

Given this target

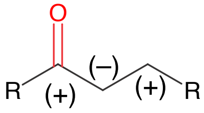


and the desire to form this bond

The functional group =O "dictates" the following bond construction



- Conferred site reactivity of =O



Charge Affinity Patterns

- Use the descriptors (+) and (–) to denote the polar disconnections shown.

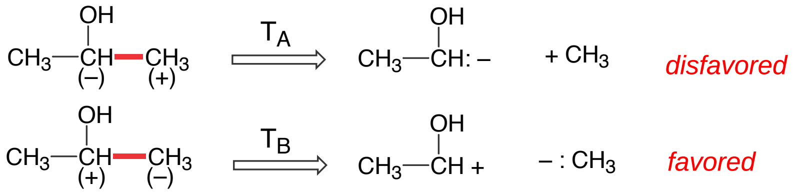
$$\overset{(-)}{A}-\overset{(+)}{B} \Longrightarrow A:^{-} \qquad B^{+}$$

$$\overset{(+)}{A}-\overset{(-)}{B} \Longrightarrow A:^{+} \qquad B:^{-}$$

- In the transforms illustrated above, symbols (+) & (–) are used to denote the particular polar transform illustrated.

In the present case there is NO INTRINSIC BIAS in favoring one transform over the other.

Let's now add an OH functional group (FG) to propane at C-2 and see whether one creates a bias in the favoring of one or the other transforms:



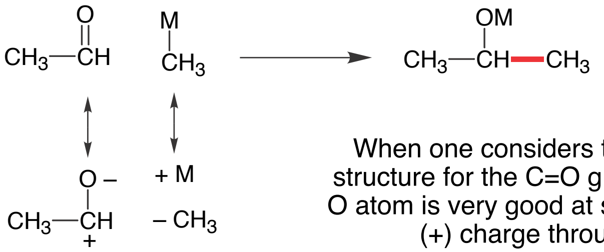
$$CH_3-\underset{(-)}{\overset{OH}{CH}}-\underset{(+)}{CH_3} \overset{T_A}{\Longrightarrow} CH_3-\overset{OH}{CH}:^{-} \qquad +\ CH_3$$

disfavored

$$CH_3-\underset{(+)}{\overset{OH}{CH}}-\underset{(-)}{CH_3} \overset{T_B}{\Longrightarrow} CH_3-\overset{OH}{CH}^{+} \qquad -:CH_3$$

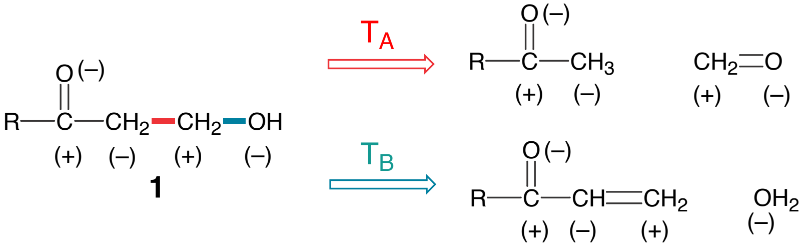
favored

- The actual reaction associated with this transform is the addition of organometals to carbonyl substrates.



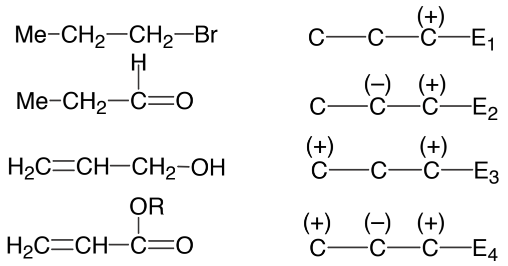
When one considers the polar resonance structure for the C=O group it is clear that an O atom is very good at stabilizing an adjacent (+) charge through resonance.

- Consider polar disconnections of the illustrated β-hydroxy ketone **1**:



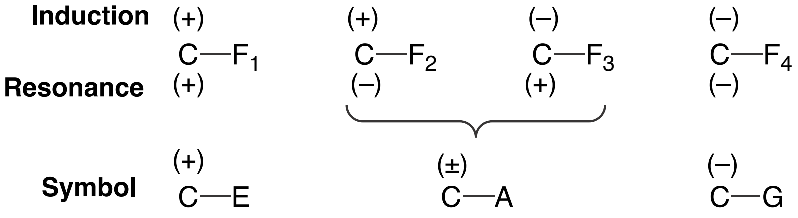
It is evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

Charge Affinity Patterns of Common Functional Groups



Classification of Functional Groups

Functional groups activate the carbon skeleton at the point of attachment by either induction & resonance.



$\underset{(+)}{\overset{(+)}{C}}-F_1 \qquad \underbrace{\underset{(-)}{\overset{(+)}{C}}-F_2 \qquad \underset{(+)}{\overset{(-)}{C}}-F_3}_{\overset{(\pm)}{C}-A} \qquad \underset{(-)}{\overset{(-)}{C}}-F_4$

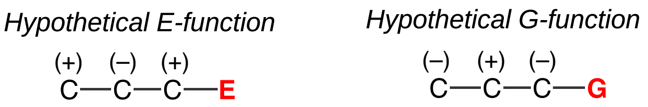
$\overset{(+)}{C}-E \qquad \overset{(\pm)}{C}-A \qquad \overset{(-)}{C}-G$

E = electrophilic at the point of attachment
A = ambiphilic at the pont of attachment
G = nucleophilic at the point of attachment

For simplicity, we will designate three FG classes according to the designations provided above.

E & G-Functions:

To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G, having the charge affinity patterns denoted below.

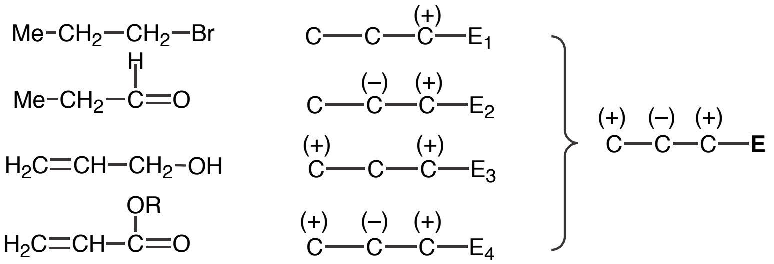


$\overset{(+)}{C}-\overset{(-)}{C}-\overset{(+)}{C}-E \qquad \overset{(-)}{C}-\overset{(+)}{C}-\overset{(-)}{C}-G$

Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated polar site reactivity patterns toward both electrophiles and nucleophiles.

Any FG that conforms either to the ideal charge affinity parrern or a sub-pattern thereof will thus be classified as either an E- or G-function.

Representative E-functions:



$Me-CH_2-CH_2-Br \qquad C-C-\overset{(+)}{C}-E_1$

$Me-CH_2-\overset{H}{C}=O \qquad C-\overset{(-)}{C}-\overset{(+)}{C}-E_2$

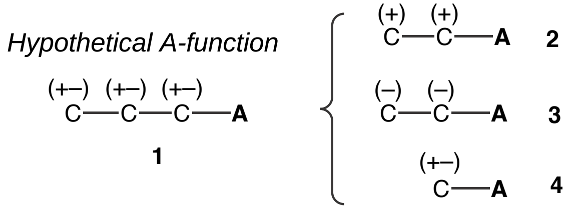
$H_2C=CH-CH_2-OH \qquad \overset{(+)}{C}-C-\overset{(+)}{C}-E_3$

$H_2C=CH-\overset{OR}{C}=O \qquad \overset{(+)}{C}-\overset{(-)}{C}-\overset{(+)}{C}-E_4$

$\overset{(+)}{C}-\overset{(-)}{C}-\overset{(+)}{C}-E$

A-Functions:

A 3rd hypothetical FG, designated as A, may be defined that has an unbiased charge affinity pattern as in **1**. Such an idealized FG's activates all sites to both nucleophilic and electrophilic reactions, and as such include those functions classifies as either E– or G–. The importance of introducing this third class designation is that it includes those functional groups having non-alternate charge affinity patterns such as **2–4**.



$\overset{(+-)}{C}-\overset{(+-)}{C}-\overset{(+-)}{C}-\mathbf{A}$ **1**

$\overset{(+)}{C}-\overset{(+)}{C}-\mathbf{A}$ **2**

$\overset{(-)}{C}-\overset{(-)}{C}-\mathbf{A}$ **3**

$\overset{(+-)}{C}-\mathbf{A}$ **4**

FG-Classification Rules

In the proposed classification scheme the following rules followed in the assignment of class designation of a given FG.

- Activating functions are to be considered as heteroatoms appended to or included within the carbon skeleton.
- Activating functions are inspected and classified according to their observed polar site reactivities.
- Since proton removal and addition processes are frequently an integral aspect of FG activation, the FG, its conjugate acid or base, and its proton tautomers are considered together in determining its class designation.
- The oxidation state of the FG is deemphasized since this is a subordinate strategic consideration.

Common E-Functions: Symbol: $(+)C-E$

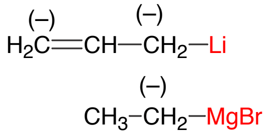
—OR ═O
—NR$_2$ ═NR
—X, X = halogen

exception: ≡O
exception: ≡N

Also consider all combinations of of above FGs; e.g =O + OR

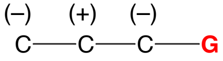
Common G-Functions: Symbol: (–)C—G

Typical G-class functions are the Group I-IV metals whose reactivity patterns, falls into a subset of the idealized G-FG **5**.



$\overset{(-)}{H_2C}{=}CH{-}\overset{(-)}{CH_2}{-}Li$

$CH_3{-}\overset{(-)}{CH_2}{-}MgBr$



$\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}G$

5

Common A-Functions: Symbol: (±)C—A

A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se).

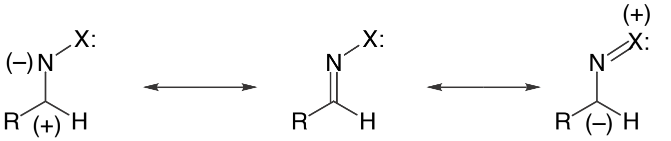
Typical A-functions, classified by inspection, are provided below

$-NO_2$ $=NOR$ $=NNR_2$ $=\underset{+}{N}(O)R$ $=N_2$ $\equiv N$

$-SR$ $-S(O)R$ $-SO_2R$ $-\underset{+}{S}R_2$

$-PR_2$ $-P(O)R_2$ $-\underset{+}{P}R_3$

■ These FG's are capable of conferring both (+) and (–) at point of attachment.



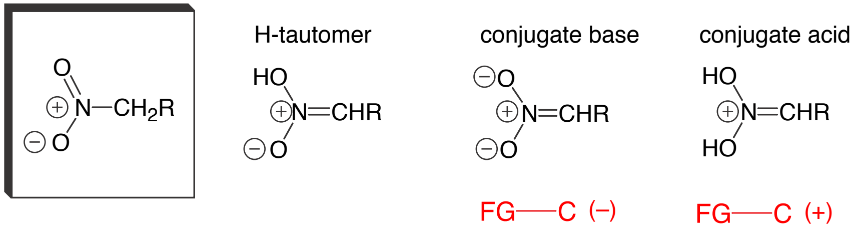
X = OR, NR_2

Remarkably, the dual electronic properties of oximes were first discussed by Lapworth in 1924 before the modern concepts of valence bond resonance were developed.

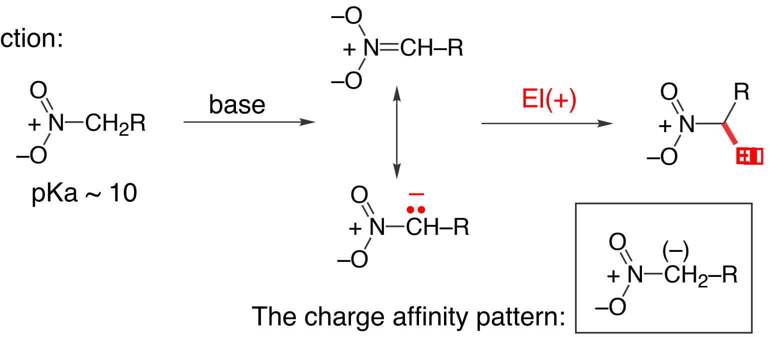
Lapworth, A. *Chemistry and Industry* **1924**, *43*, 1294-1295.

The Nitro Functional Group

As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base.



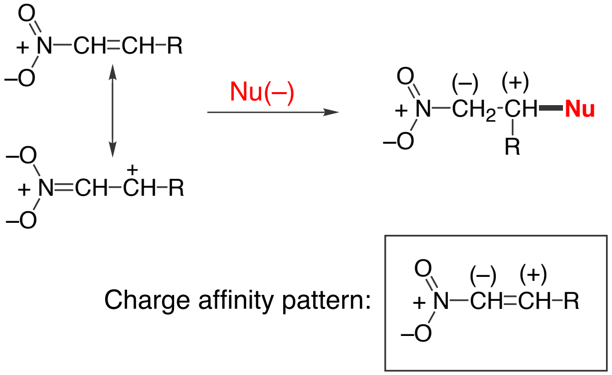
The Reaction:



The charge affinity pattern:

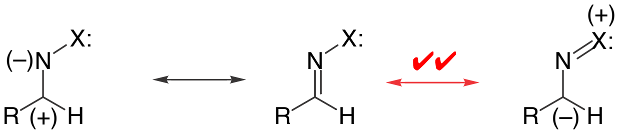
■ **This reactivity pattern may be extended via conjugation:**

The Reaction:



Charge affinity pattern:

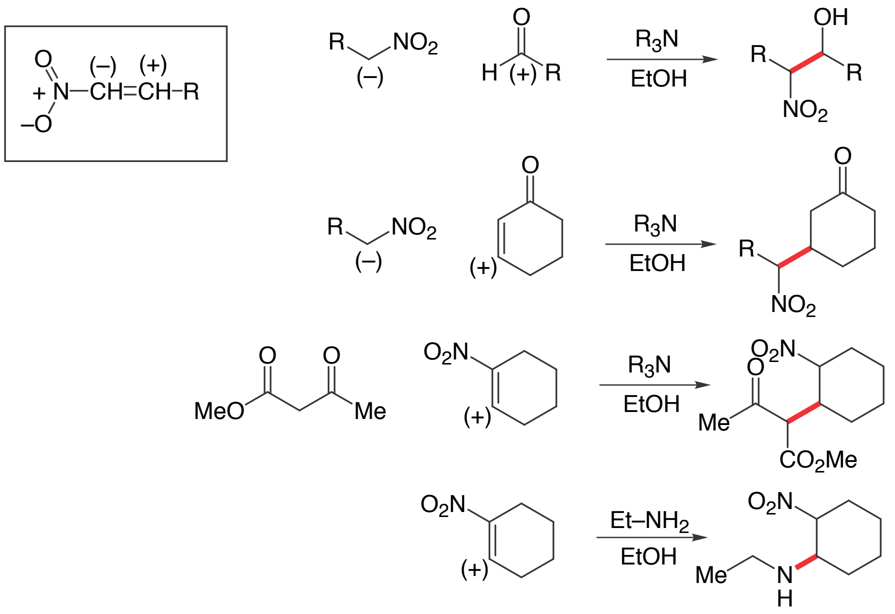
■ **The resonance feature which has been exploited:**



X = OR, NR_2

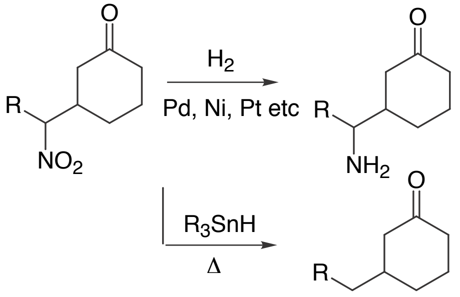
Charge Affinity Patterns & the Nitro Functional Group

Some Reactions of the Nitro Functional Group



Important Transformations of the $–NO_2$ Functional Group

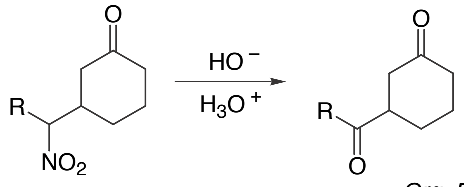
Reduction:



rxn is quite facile

Ono, N.; Kaji, A. *Synthesis* **1986**, 693.

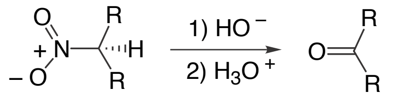
Nef Reaction:



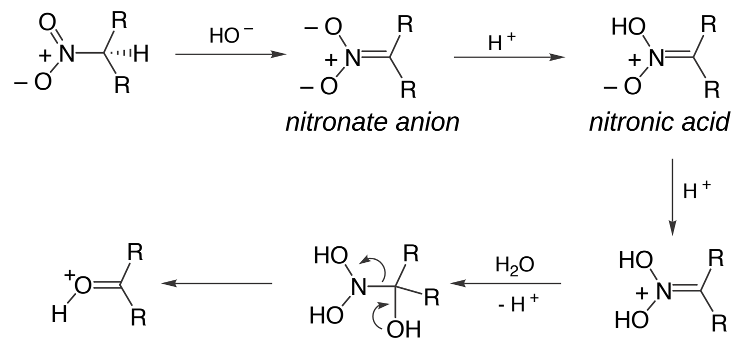
Pinnick, *Org. Reactions* **1990**, *38*, 655

The Nef Reaction

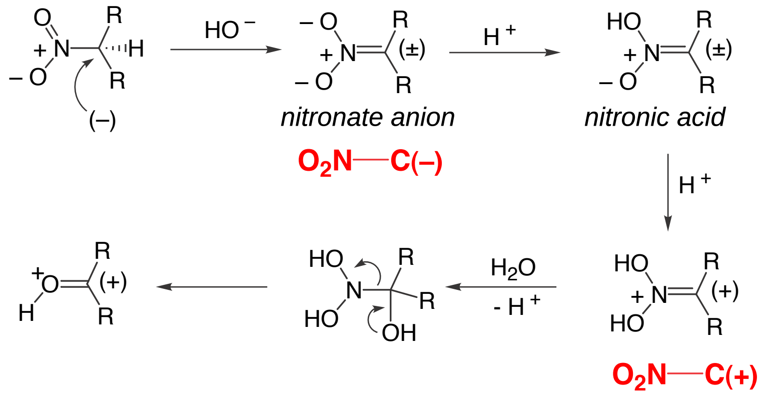
Overall Transformation:



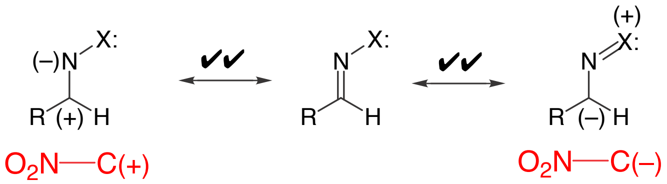
Mechanism



The charge affinity patterns represented

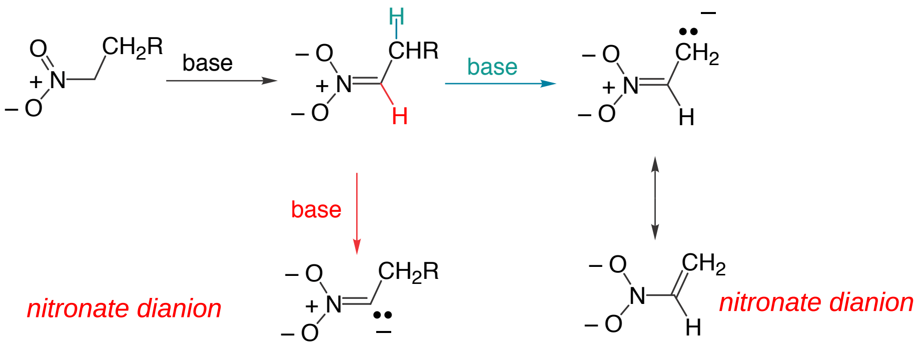


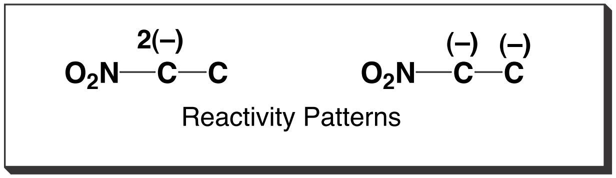
The resonance features which have been exploited:



X = OR, NR_2

Other Nonalternate Behavior of –NO_2 FG



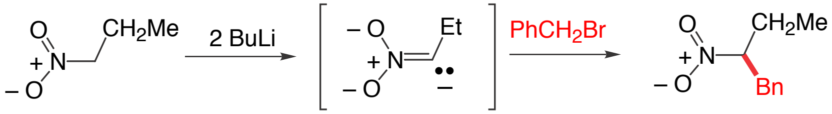


$$\mathrm{O_2N{-}\overset{2(-)}{C}{-}C} \qquad \mathrm{O_2N{-}\overset{(-)}{C}{-}\overset{(-)}{C}}$$

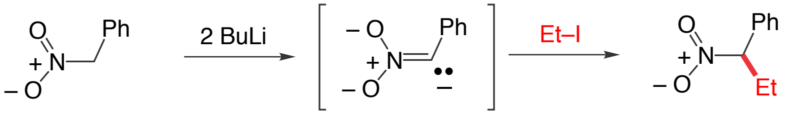
Reactivity Patterns

Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164

Representative examples: $\mathrm{O_2N{-}\overset{2(-)}{C}{-}C}$

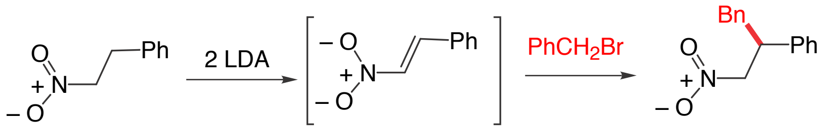


51% yield

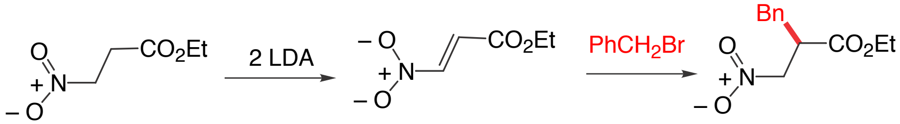


80% yield

Representative examples: $\mathrm{O_2N{-}\overset{(-)}{C}{-}\overset{(-)}{C}}$



40% yield



Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164

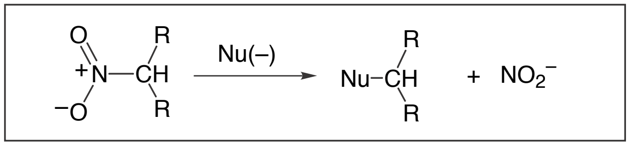
80% yield

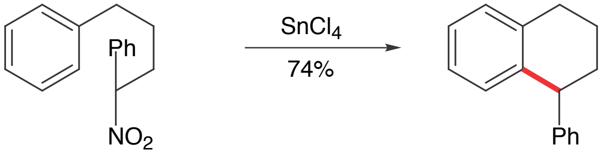
–NO_2 As a Leaving Group

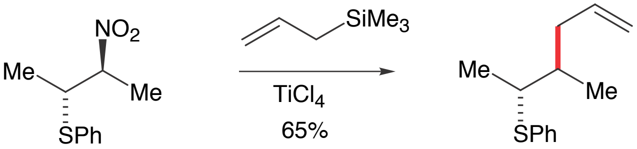
Review: Tamura et. al. *Synthesis* **1991**, 423-434.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis"'
Seebach, D. etal, *Chimia*, **1979**, *33*, 1-18

Representative examples: $\mathrm{O_2N{-}C(+)}$

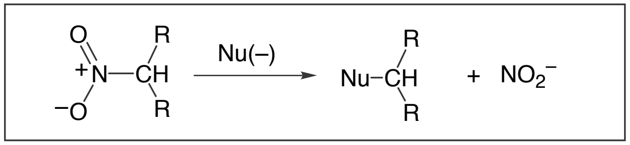


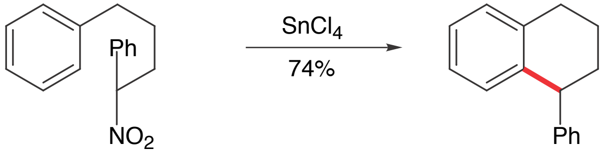


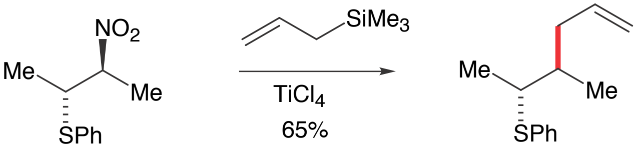


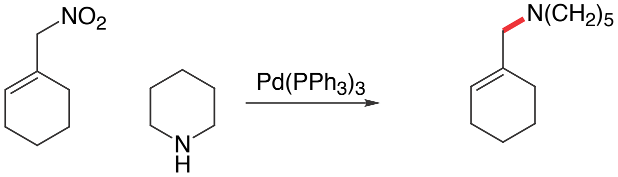
–NO_2 As a Leaving Group

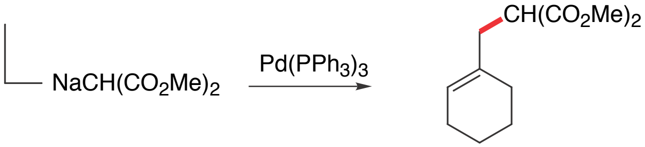
Representative examples: **O_2N—C (+)**

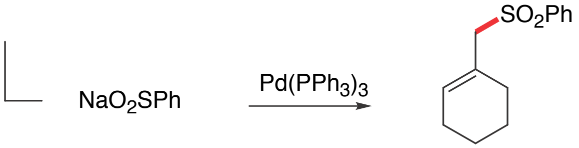


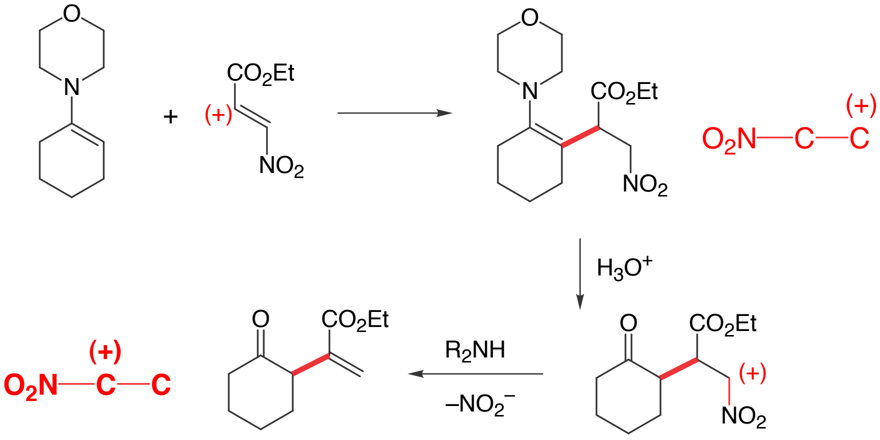




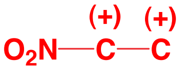




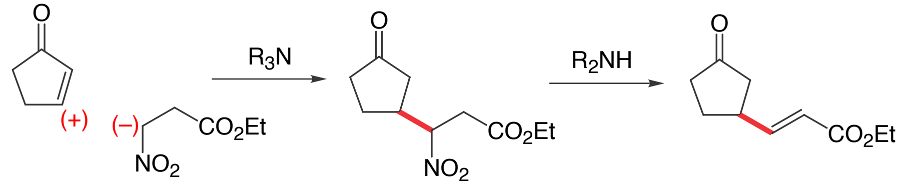




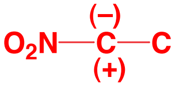
McMurry etal. *Chem Comm*. **1971** 488-489.



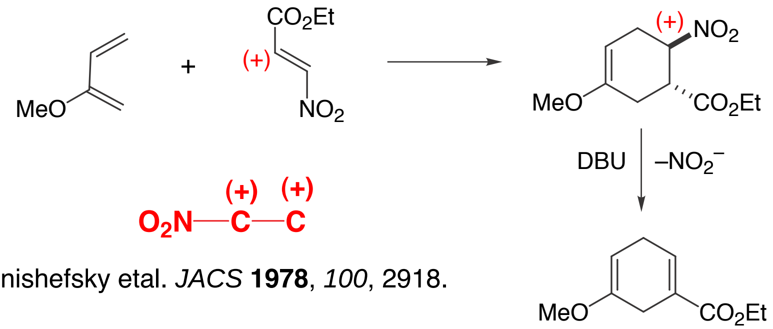
$$\overset{(+)}{\mathbf{C}}\;\overset{(+)}{\mathbf{C}}: \quad \mathbf{O_2N—\overset{(+)}{C}—\overset{(+)}{C}}$$



Bakuzis etal. *Tetrahedron Lett.* **1978** 2371.



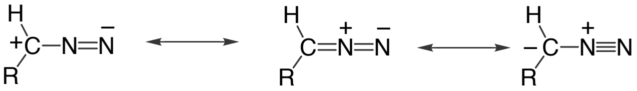
$$\mathbf{O_2N—\overset{(–)}{\underset{(+)}{C}}—C}$$



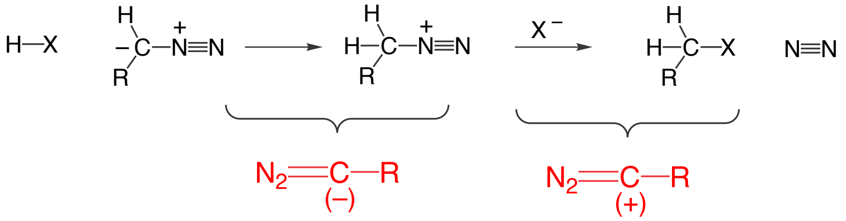
Danishefsky etal. *JACS* **1978**, *100*, 2918.

Nonalternate Reactivity Patterns of Diazo Functional Groups

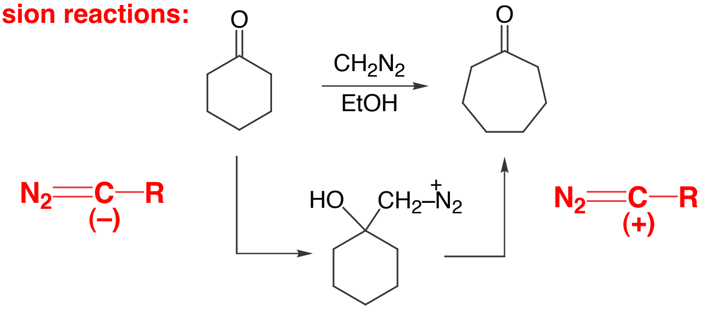
The Diazo Functional Group



- Both (+) and (–) reactivity patterns suggested by resonance structures
- Rxns with acids:

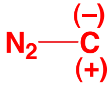


- **Initiating reactivity is (–); subsequent reactivity is (+)**
- **Ring expansion reactions:**

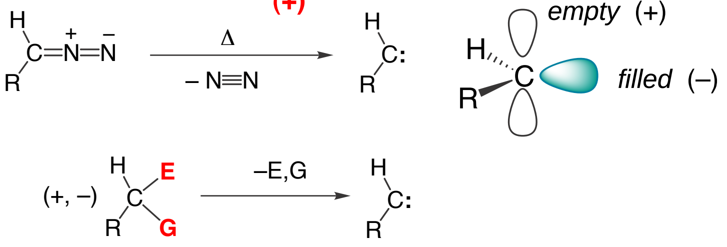


Restriction: Starting ketone must be more reactive than product ketone

- **Precursors to Carbenes:**

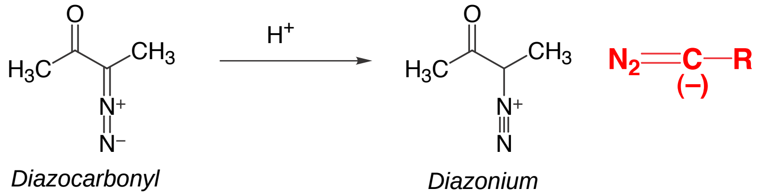


$$N_2\!-\!\overset{(-)}{\underset{(+)}{C}}$$



Acid Catalyzed Reactions of Diazo Compounds

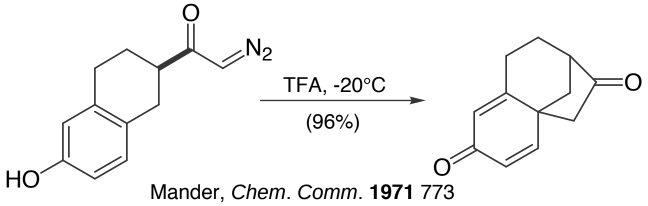
Review: Smith, Tet. 1981 2407



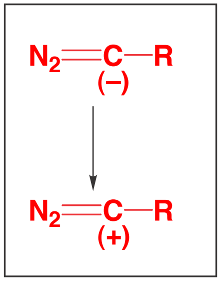
Common acids include BF_3•OEt_2, HBF_4, TFA, etc.

Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

Acid-Catalyzed Reactions

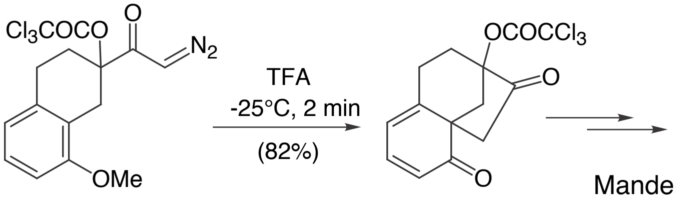


Mander, *Chem. Comm.* **1971** 773
Tet., **1991** 134



"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantites of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

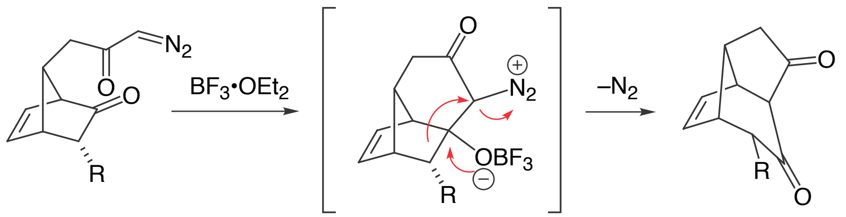
Lewis Mander



Mander, *JACS* **1980** 6626

Nonalternate Reactivity Patterns of Diazo Functional Groups

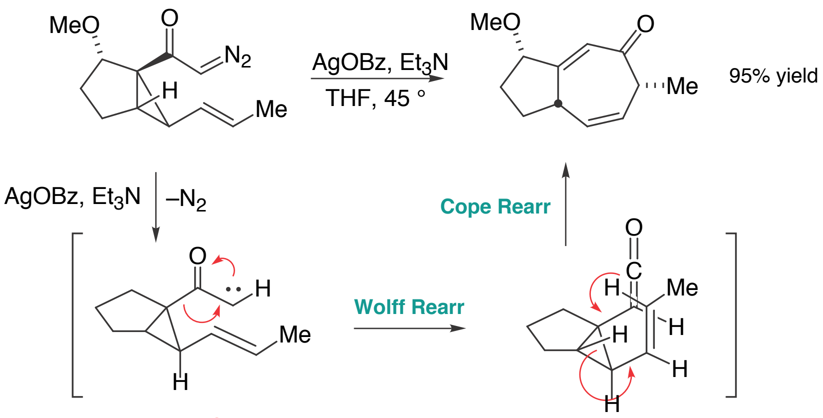
Diazo–Carbonyl Insertions:



Mander, *Aust. J. Chem.* **1979** 1975

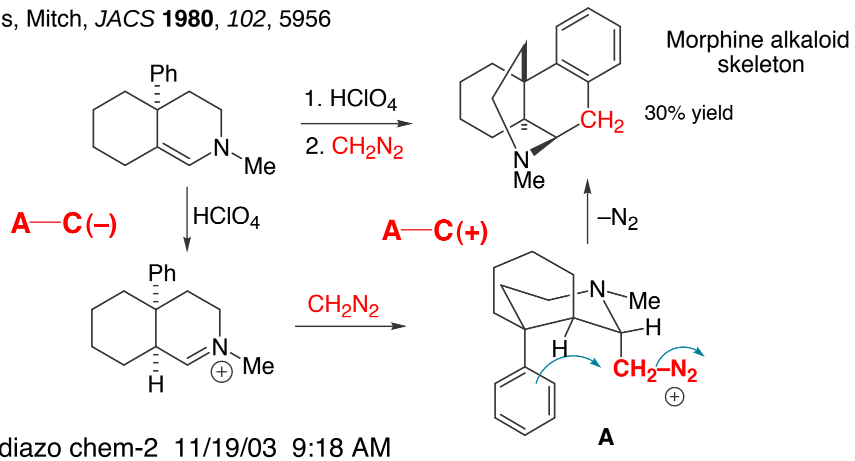
Wolff Rearrangements

Web Problem 332. Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, *125*, 13624).

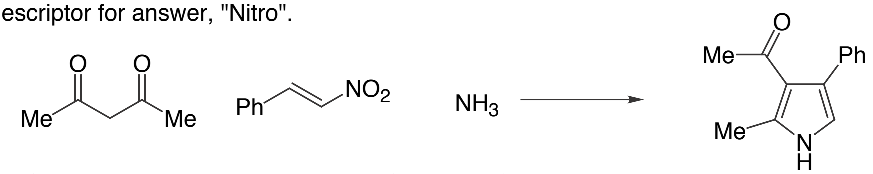


Diazo-mediated Ring Construction:

Evans, Mitch, *JACS* **1980**, *102*, 5956

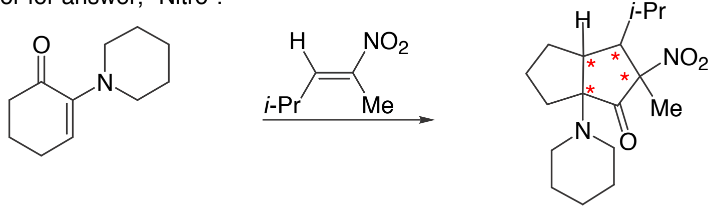


Web Problem 109. The following is a general reaction for the formation of pyrroles. In this condensation, any of the three reaction constituents may be widely varied. (Ono, "The Nitro Group in Organic Synthesis" Wiley-VCH, **2001**. Chapter 10, pp 326-328). Siince it is not clear what the "inorganic" reaction product is, provide us with anything that is mechanistically sound using the reagents illustrated. Key descriptor for answer, "Nitro".

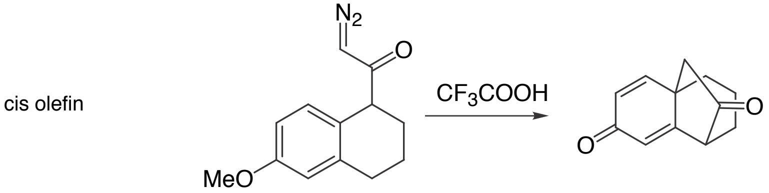


In the space below provide a plausible mechanism for this transformation.

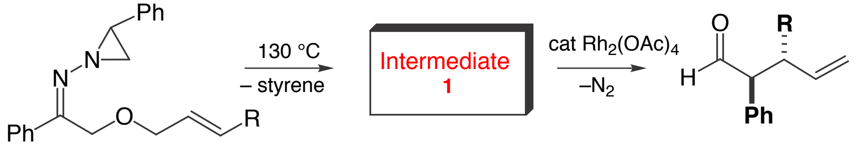
Web Problem 188. Provide a mechanism for the following reaction that predicts the stereochemistry at the starred (*) carbon atoms (Valentin, *TL*, **1983**, 1621). Key descriptor for answer, "Nitro".



Web Problem 150. Provide a concise mechanism for the indicated reaction in the space below. Key descriptor for answer, "Carbene".



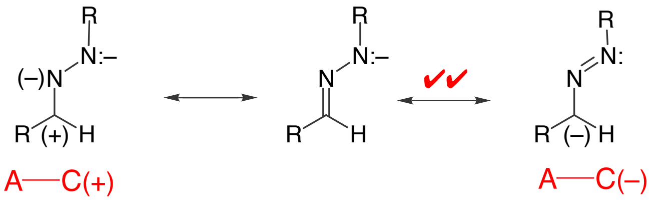
Web Problem 13. The following transformation was recently reported by Stoltz (*J. Am. Chem. Soc* **2002**, *124*, 12426). In addition to the illustrated product, styrene and dinitrogen are produced as by-products in this transformation. Key descriptor for answer, "Carbene".

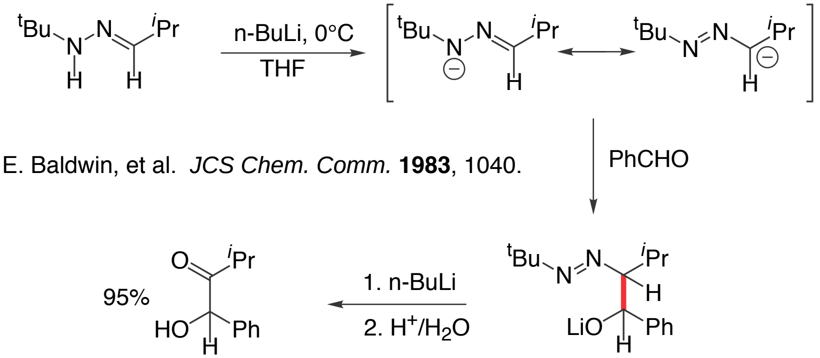


anti diastereoselection > 20:1, 80% yield

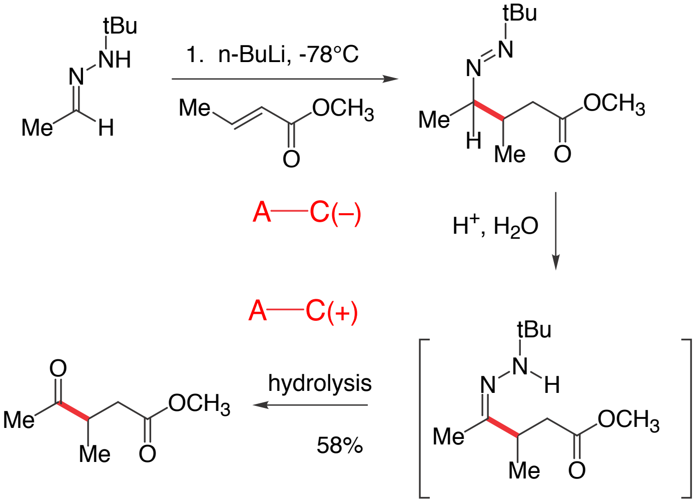
Provide a plausible mechanism for this transformation and identify intermediate **1**. Your mechanism should provide a rationalization for the product stereochemical relationship.

Hydrazone Anions: A useful Reversed Polarity Equivalent

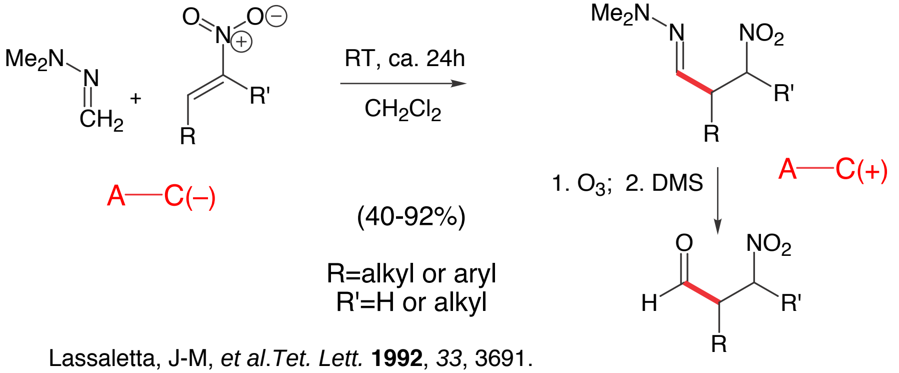




J. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.

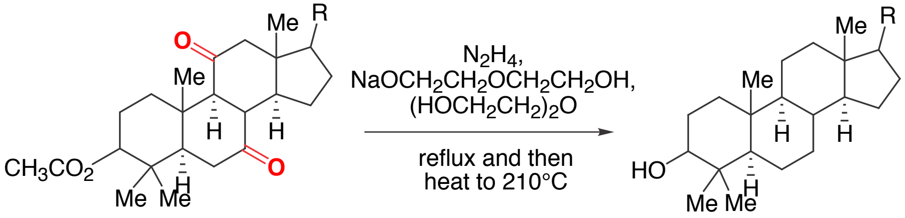


J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.



Lassaletta, J-M, *et al.Tet. Lett.* **1992**, *33*, 3691.

Wolff-Kishner Reduction Procedures

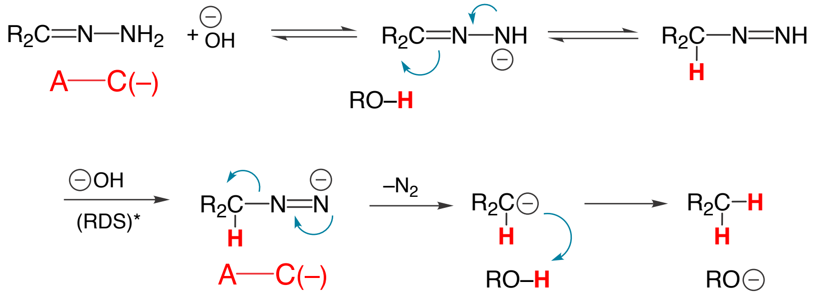


Barton, D. H. R., Ives, D. A. J., and Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.

For particulary hindered ketones: anhydrous hydrazine or formation of hydrazone under acid catalysis (hydrazine/hydrazine dihydrochloride), then basify.

Under these forcing conditions, saponification, epimerization, and methyl ether cleavage can occur.

Mechanism



Chemistry 206

Advanced Organic Chemistry

Handout–27A

An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships

D. A. Evans

Wednesday ,
November 19, 2003

An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships

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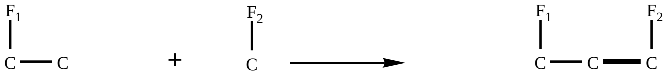
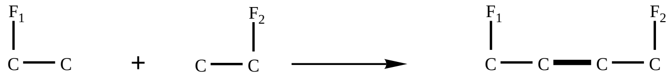
Introduction

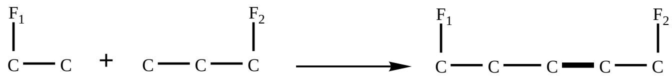
Among the subdisciplines of chemistry the area of organic synthesis is probably the least organized in terms of unifying concepts and general methodology. This conclusion has been made quite obvious by the relative scarcity of critical monographs covering this important topic.[1] The wide structural diversity of organic molecules, the vast abundance of organic reactions, and the restrictions imposed upon these reactions when applied to the synthesis of a complex structure all contribute to the magnitude of the problem of making generalizations in this area.

However difficult the overall task of explicitly defining *a priori* a total synthesis of an organic structure may be, there are certain simplifying features which can be developed to generate logical sets of potential synthetic pathways to a given molecular target . Some of the general guidelines which help to define this task have been outlined.[2] Recently, some of the problems associated with reducing synthetic design to a mathematical basis and the application of machine computation to synthetic analysis have been reported.[3,4]

Difunctional Relationships. One aspect of the synthesis of any polyfunctional target structure deals with strategies associated with the construction of arrays of relationships between heteroatom functional groups which may be denoted as F_1, F_2, etc. The general reactions illustrated below simply represent the union of two monofunctional organic fragments where the functional groups F_1, F_2 provide the necessary activation for the coupling process. In these reactions, the oxidation states of the associated carbon fragments are purposely left undefined. In relating the generalized notation below to a real situation, if F_1-C-C were an enolate, Equation 1 might be used to represent a generalized aldol or Mannich reaction while equation 3 might represent a Michael reaction.


(1)


(2)


(3)

Henrickson has provided some useful generalizations on the construction of difunctional relationships which are worth summarizing. For example, he defines the **construction span** as the number of carbons linking F_1 and F_2. In the cases illustrated above, the product of the reaction illustrated in Equation 1 has a construction span of three. The **construction fragments** are then defined as the monofunctional reactants, such as F_1-C-C and F_1-C. *In general, construction spans are limited to six or less.* This is a consequence of the fact that the operational utility of a given functional group diminishes as it is removed from the C-C bond being formed. The problem of site or ambident reactivity in systems possessing extended conjugation is the principal liability in the extension of the construction span. This point is illustrated below for both conjugate addition and enolate alkylation (Scheme I).

---

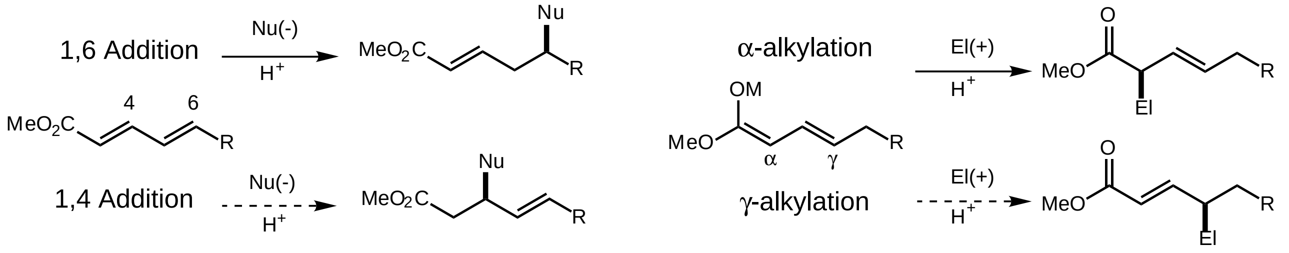
[1] (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley, New York, 1979. (b) Fuhrhop, J.; Penzlin, G. *Organic Synthesis: Concepts, Methods, Startimg Materials*; Verlag Chemie, Weinheim, 1983. (c) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3nd ed.; Cambridge Univ. Press, Cambridge, 1987. (d) *Organic Synthesis, The Disconnection Approach*; Wiley, New York, 1982. (e) Payne, C. A.; Payne, L.B. *How To Do An Organic Synthesis*; Allyn and Bacon., Boston, 1969. (f) Ireland, R. E. *Organic Synthesis*, Prentice-Hall, Inc., Englewood Cliffs, 1969.

[2] (a) Corey, E. J. *Pure Appl. Chem.* **1967**, *14*, 19. (b) Corey, E. J. *Quart. Rev.* **1971**, *25*, 455.

[3] (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 6487. (b) Ugi, I; Gillespie, P. *Angew. Chem. Int. Ed.* **1971**, *10*, 914. (c) Corey, E. J.; Wipke, W. T.; Cramer, III, R. D.; Howe, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 421. (d) Corey, E. J.; Cramer, III, R. D.; Howe, W. J. *ibid*. **1972**, *94*, 440, and earlier references cited therein. (e) Corey, E. J.; Howe, W. J.; Pensak, D. A. *ibid.* **1974**, *96*, 7724. (f) Blair, J.; Gasteiger, J.; Gillespie, C.; Gillespie, P. D.; Ugi, I. *Tetrahedron* **1974**, *30*, 1845. (g) Bersohn, M. *J. Chem. Soc., Perkin I* **1973**, 1239.

[4] (a) Thakkar, A. J. *Fortschritte Chem. Forschung* **1973**, *39*, 3. (b) Dungundji, J.; Ugi, I. *ibid.* **1973**, *39*, 19. (c) Gelernter, H.; Sridharan, N. S.; Hart, A. J.; Yen, S. C.; Fowler, F. W.; Shue, J.-J. *ibid.* **1973**, *41*, 113.

Scheme I The Problem of Ambident Reactivity



The objectives of the present discourse are to present an organizational format which can serve to correlate strategies for the construction simple pairwise functional group relationships. As a result of the overwhelming predisposition of nature to employ **polar** rather than **free radical** processes in the biosynthesis of organic compounds the chosen organizational format reflects this bias in reaction type. The designation of reactions as polar is recognized to be rather arbitrary since known reactions vary widely in their polar character, ranging from essentially nonpolar radical reactions and weakly polar electrocyclic reactions to strongly polar ionic processes. *Of primary concern in this discussion will be those reactions that involve charged species at some point along the reaction coordinate.*

Charge Affinity Patterns.

In order to describe an organizational model for the classification and synthesis of heteroatom-heteroatom (difunctional) relationships in organic molecules, two familiar ideas will be employed. The first is that in a given target molecule the various bonds can be ionically "disconnected" (eq 4, 5). That is, if the A-B bond could be cleaved heterolytically, the indicated set of polar fragments would result.

$$\mathrm{A{-}B} \Longrightarrow \mathrm{A{:}\,-} \qquad \mathrm{B+} \qquad (4)$$

$$\mathrm{A{-}B} \Longrightarrow \mathrm{A{:}\,+} \qquad \mathrm{B{:}-} \qquad (5)$$

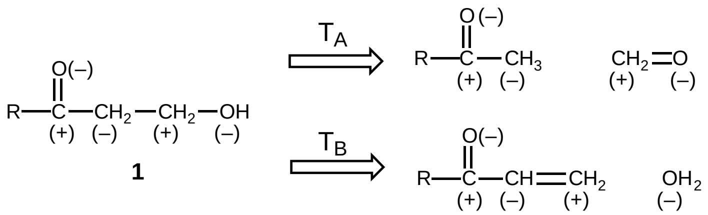
This antithetic process suggests ionic precursors suitable for the construction of the target molecule *via* polar coupling processes. *The second well accepted idea is that functional groups determine site reactivities on a carbon skeleton based upon known reactions.* That is, the oxygen atom in both acetone and anisole dictates the site reactivities that are displayed for each molecule with nucleophilic and electrophilic reagents. Thus, if the molecule A-B contained one or more functional groups proximal to the bond to be disconnected, one pair of ionic precursors, eq 6 or 7, would be strongly favored as plausible precursors. In such a case the favored ionic precursors to A-B could be symbolized with either (+) or (-) in the target molecule, e.g.[5]

$$\overset{(-)}{\mathrm{A}}{-}\overset{(+)}{\mathrm{B}} \Longrightarrow \mathrm{A{:}\,-} \qquad \mathrm{B+} \qquad (6)$$

$$\overset{(+)}{\mathrm{A}}{-}\overset{(-)}{\mathrm{B}} \Longrightarrow \mathrm{A{:}\,+} \qquad \mathrm{B{:}-} \qquad (7)$$

As an example, two possible polar disconnections for ketone **1** are illustrated below. The parity labels in the target structure suggest plausible monofunctional precursors from which the target structure can be assembled by polar processes. It is also evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

cheme II Polar Disconnections and Charge Affinity Pattterns



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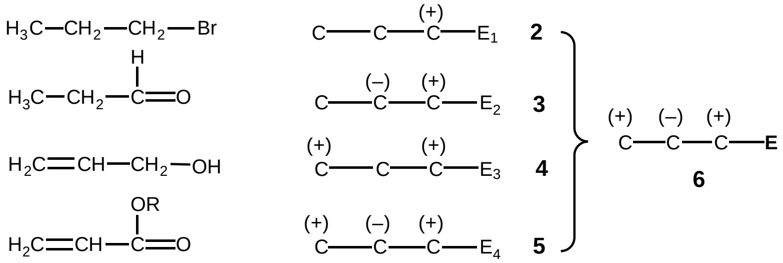
[5] The use of the symbols, (+) and (-), in no way represents formal positive or negative charges and will always be bracketed to denote this distinction. Other forms of notation have been considered such as (0) and (1) to denote a potential site of electrophilicity or nucleophilicity; however, the chosen symbols convey more direct information to the organic chemist.

For any given atom or heteroatom assemblage which is defined as a functional group linked to a carbon skeleton, the parity labels, (+) and (-), may be employed to denote the positional polar site reactivity, or ***charge affinity pattern*** *which the functional group confers upon the carbon framework.* For the simple molecules shown below (Scheme III) containing a homogeneous set of activating functions, E, there are associated charge affinity patterns **2 - 5** of which each is a sub-pattern of the generalized structure **6**. Note that the carbonyl function is defined as =O rather that C=O in this discussion. You might contemplate why this functional group is defined in this fashion.

Scheme III Charge Affinity Patterns of Common Functional Groups

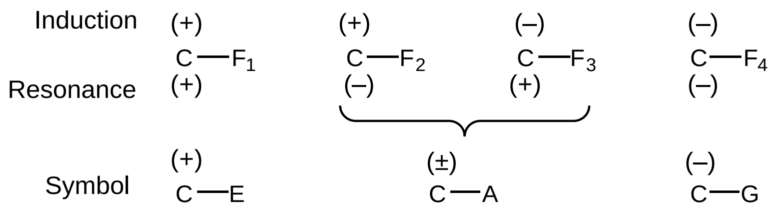


The notion that an organic structure can be viewed as an "ion assemblage" has an interesting history originating with the work of Lapworth and others.[6,7] Although the ion assemblage viewpoint was developed historically to predict site reactivity in both aliphatic and aromatic systems, this description of an organic structure is equally instructive in defining rational sets of synthetic pathways for a given target structure employing heterolytic processes as the primary set of coupling reactions. Indeed, the thought processes associated with the construction of organic molecules operate intuitively to recognize many subunits of a given structure in terms of polar fragments. The present use of parity labels to denote viable polar fragments simply formalizes this intuition.

Classification of Functional Groups (FG).

In order to organize general strategies that have been developed to construct heteroatom-heteroatom relationships from monofunctional precursors it is useful to develop a self-consistent classification scheme for single functional groups (FG) based on the concepts of polar disconnection and conferred site reactivity towards nucleophiles and electrophiles. The proposed scheme recognizes the dominate inductive and resonance components of various substituents and establishes[8] broad categories for activating functions which correlate similar conferred chemical properties to carbon.[9] Four possible functional group categories (F_1-F_4) are shown below. Those FGs which are *more electronegative than carbon* provide inductive activation defining the electrophilic potential at the point of attachment denoted as (+). In a complementary fashion, FGs which are *less electronegative than carbon* provide inductive activation creating nucleophilic potential at the point of attachment denoted as (–). Since FG activation through induction and resonance are independent variables which contribute to the overall FG reactivity pattern, four possible classes of functional groups can be defined (Scheme IV). This discussion is reminiscent of the classification of FGs according to their impact on electrophilic aromatic substitution.[10]

Scheme IV Classification of Functional Groups



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6) (a) Lapworth, A. *Mem. Proc. Manchester Lit. Phil. Soc.* **1920**, *64*, 1. (b) Lapworth, A. *J. Chem. Soc.* **1922**, *121*, 416. (c) Lapworth, A. *Chem. Ind.* **1924**, *43*, 1294. (d) Lapworth, A. *ibid.* **1925**, *44*, 397. For an excellent review of Arthur Lapworth's contributions to chemistry see: Saltzman, M. *J. Chem. Ed.* **1972**, *49*, 750-753.

7) (a) Vorländer, D. *Chem. Ber.* **1919**, *52B*, 263. (b) Stieglitz, J. *J. Am. Chem. Soc.* **1922**, *44*, 1293.

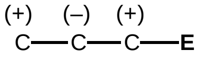
8) See reference 3c for an alternate classification scheme for functional groups.

9) For an analysis of the relative importance of field and resonance components of substitutent effects see: Swain, C. G.; Lupton, Jr., E. C. *J. Am. Chem. Soc.* **1968**, *90*, 4328.

10) March, J. *Advanced Organic Chemistry,* 4th ed.; Wiley-Interscience: New York, 1992; pp 507-512.

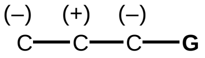
E & G-Functions. From the preceding discussion, one might opt for the creation of four classes of functional groups; however, for the sake of simplicity, three FG class designations will be chosen. To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G,[11] having the charge affinity patterns denoted in **6** and **7** respectively. Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated potential site reactivity patterns towards both electrophilic and nucleophilic reagents. *Any functional groups whose reactivity pattern conforms to the ideal pattern or to a sub-pattern of these hypothetical functions will be thus classified as an E- or G-function respectively.* For example, the halogen and oxygen-based functional groups in four molecules illustrated in Scheme III may be classified as E-functions since their respective charge affinity patterns conform to a subset of the charge affinity pattern of the hypothetical E-function.

ypothetical E-function



6

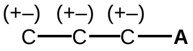
ypothetical G-function



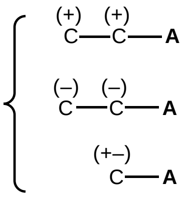
7

A-Functions. A third hypothetical function, A, (A for amphoteric!) can be defined which has an unbiased charge affinity pattern as in **8**. Such an idealized functional group activates all sites to both nucleophilic and electrophilic reactions and, as such, include those functions classified as either E or G. The importance of introducing this third class designation is that it includes those functional groups having non-alternate charge affinity patterns as in **9**, **10** and **11**.

ypothetical A-function



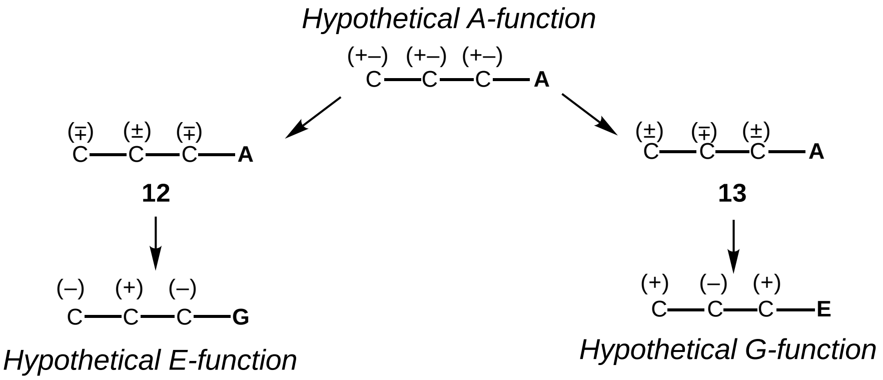
8



9 **10** **11**

The differentiation of polar reactivity patterns can be described in an alternative manner. Starting with an ideal A-function, one could imagine a process in which the reactivity pattern is gradually polarized towards E- or G-behavior (Scheme V). Since site reactivity is not an on-off property but varies continuously over a wide range, one could further subdivide A-class functions into those functions with a bias towards E-class or G-class properties. Such a bias could be denoted by the dominant subordinate charge affinity notation in **12** and **13**; however, for the concepts to be presented in this discourse, such A-function subclasses are nonessential. It should be emphasized that the purpose of the E- and G-classification is not to rigidly pigeon-hole functional groups based on site reactivity, but only to separate those which are strongly polarized toward E or G behavior. The decision has been made to avoid the pursuit of an overly detailed FG classification scheme since such attempts will dangerously oversimplify problems since an essentially contiguous function cannot be segmented in to discrete parts.

Scheme V Alternate vs Nonalternate Reactivity Patterns



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[11] The symbol E was selected to denote *electrophilic* at the point of attachment to the carbon skeleton Unfortunately, the symbol N cannot be used to represent those FGs which are *nucleophilic* at the point of attachment since this is also the symbol for nitrogen. To avoid this conflict, the symbol G was chosen for this FG class designation.

FG Classification Rules. In the proposed classification scheme the following rules are followed in the assignment of class designations to functional groups.

- Activating functions are to be considered as heteroatoms appended to or included within the carbon skeleton.
- Activating functions are inspected and classified according to their observed polar site reactivities.
- Since both proton removals and addition processes are frequently an integral component in functional group activation, the function, its conjugate acid or base, and its possible proton tautomers are considered together in determining its class designation.
- The oxidation state of the FG is de-emphasized since this is a subordinate strategic consideration.

E-Functions. For example, carbonyls and carbonyl derivatives will be represented as =X where X may be either oxygen or substituted nitrogen. Well recognized exceptions to the polar class designations illustrated in Scheme I may be found in the chemistry of CO and HCN. In these instances the carbon bearing the heteroatom exhibits well-defined nucleophilic properties. Accordingly these two functional groups will be classified as A-functions by inspection (*vide infra*).

Table I. Common E-Functions: Symbol $^{(+)}\mathrm{C}-\mathrm{E}$

$-\mathrm{OR}$ $\quad =\mathrm{O}$

$-\mathrm{NR_2}$ $\quad =\mathrm{NR}$

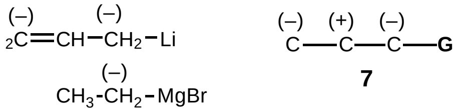
$-\mathrm{X}$, X = halogen

exception: $\equiv\mathrm{O}$

exception: $\equiv\mathrm{N}$

Also consider all combinations of of above FGs; e.g =O + OR

G-Functions. Typical G-class functions are the Group I-IV metals whose reactivity pattern, falls into a subset of **7**.



7

A-Functions. A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se). Typical A-functions, classified by inspection, are provided in Table II.

Table II. Common A-Functions: Symbol $^{(\pm)}\mathrm{C}-\mathrm{A}$

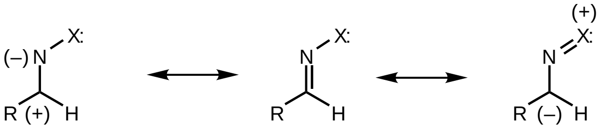
$-\mathrm{NO_2}$ $\quad =\mathrm{NOR}$ $\quad =\mathrm{NNR_2}$ $\quad =\underset{+}{\mathrm{N}}(\mathrm{O})\mathrm{R}$ $\quad =\mathrm{N_2}$ $\quad \equiv\mathrm{N}$

$-\mathrm{SR}$ $\quad -\mathrm{S(O)R}$ $\quad -\underset{+}{\mathrm{SO}}\mathrm{_2R}$ $\quad -\mathrm{SR_2}$

$-\mathrm{PR_2}$ $\quad -\mathrm{P(O)R_2}$ $\quad -\mathrm{PR_3}$

Functional groups possessing the following general structure, =N-X where X is a hetroatom bearing a nonbonding electron pair, have an expanded set of resonance options which create either an electrophilic or nucleophilic potential at the point of attachment. Remarkably, the dual electronic properties of oximes were first discussed by Lapworth[12] in 1924 before the modern concepts of valence bond resonance was developed.

■ These FG's are capable of conferring both (+) and (–) at the point of attachment.



X = OR, NR$_2$

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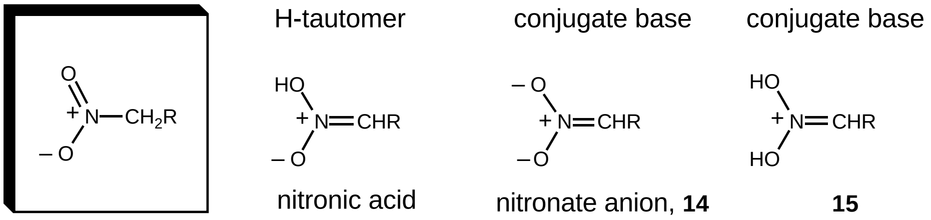
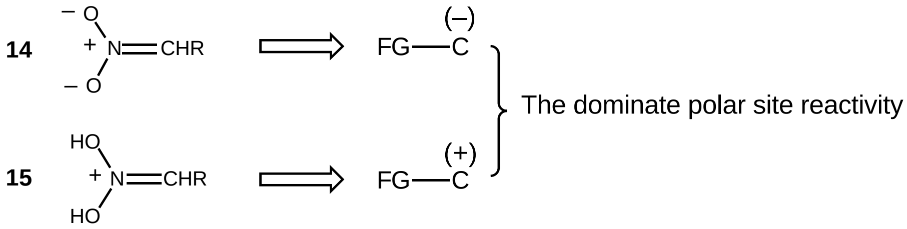
12) Lapworth, A. *Chemistry and Industry* **1924**, *43*, 1294-1295.

A Case Study: The Nitro Group. As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base **14** and **15**.

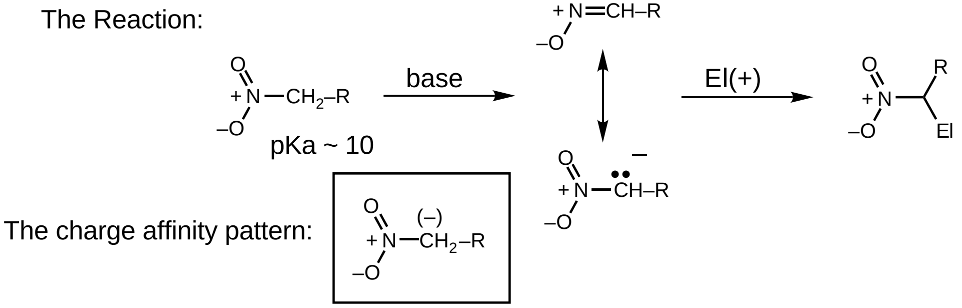


From the collection of transformations of the nitro group one finds that the dominate mode of reactivity of the nitronate anion **14** is that of a G-function while the protonated nitronic acid **15** mirrors the reactivity of an E-function.



The typical behavior of nitronate anions **14** is summarized in the representative transformations provided in Scheme VI. These moderately nucleophilic species, although they are not readily alkylated, readily undergo aldol and conjugate addition reactions.

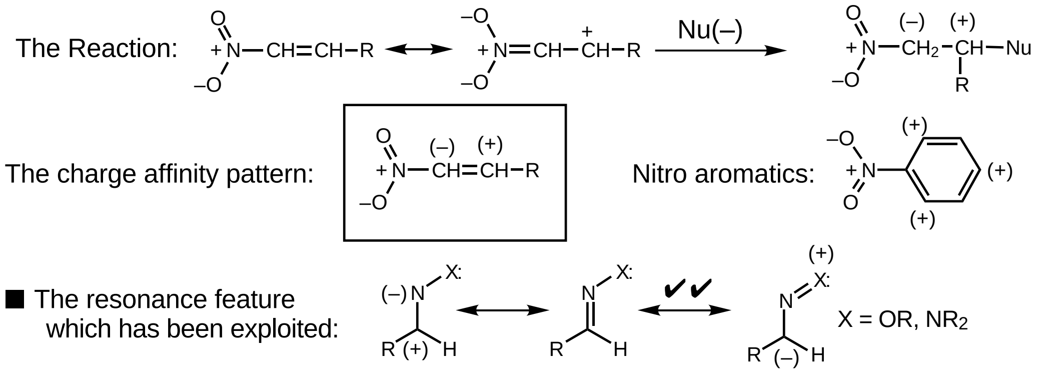
cheme VI Selected Reactions of the Nitronate Anion



■ This reactivity pattern may be extended via conjugation:

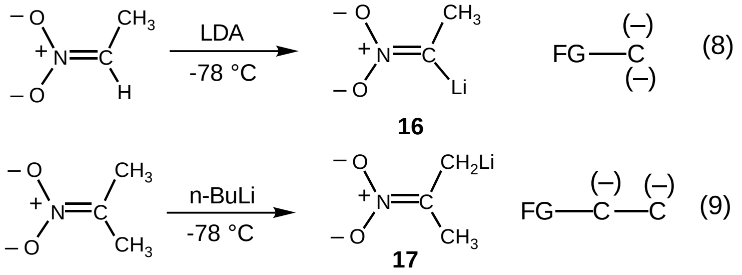
It is no surprise that the charge affinity pattern of this FG may be extended by conjugation, and α,β-unsaturated nitro compounds readily participate in conjugate addition reactions (Scheme VII).

Scheme VII Selected Reactions of the Nitronate Anion


The Reaction:
Nu(–)
The charge affinity pattern:
Nitro aromatics:
■ The resonance feature which has been exploited:
X = OR, NR2

The non-alternate behavior of the nitro functional group is dramatically illustrated in the transformations provided in Scheme VIII. In both instances the derived anions **16** and **17** are highly nucleophilic.[13] The non-alternate charge affinity patterns of these nucleophiles is provided.

Scheme VIII Deprotonated Nitronate Anions



The nitro group also exhibits the potential of undergoing direct displacement under specific conditions, a general transformation characteristic of E-functions. A recent review by Tamura provides numerous literature precedents for this general class of reactions.[14] while table III provides some of the cited reactions. Although the NO_2 group cannot be considered as a general leaving group, there are a number of conditions under which this moiety can be exploited, particularly when it is either allylic or tertiary.

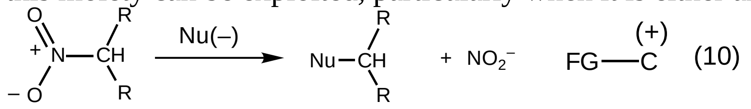
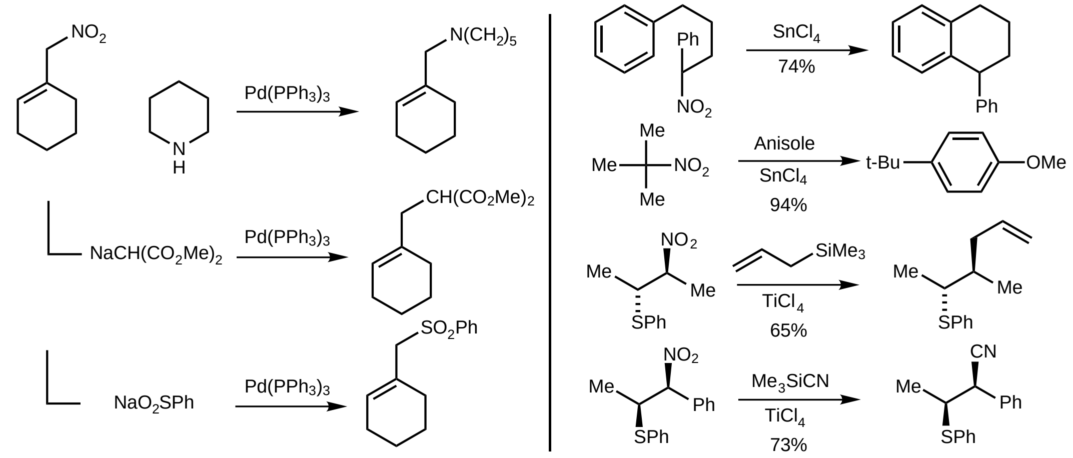


Table III. Representative Substitution Reactions of the Nitro Group (eq 10).



A particularly useful transformation of the nitro group is the Nef Reaction, a process which transforms NO_2 into =O (Scheme IX). A recent comprehensive review of this transformation provides a detailed discussion of this process.[15] In addition to the Pinnick review, Seebach has also written a comprehensive review of the diverse chemistry of the nitro functional group.[16]

---

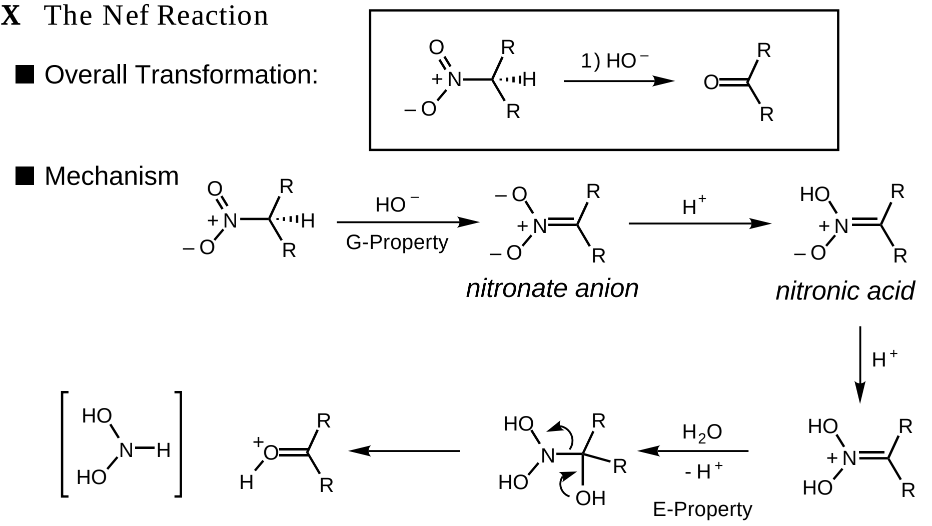
13) (a) Henning, R.; Lehr, F.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2213-2217; (b) Seebach, D.; Henning, R.; Lehr, F.; Gonnermann J. *Tetrahedron Lett.* **1977**, 1161-1164.

14) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434.

15) Pinnick, H. W.; *Org. Reactions* **1990**, *38*, 655-792.

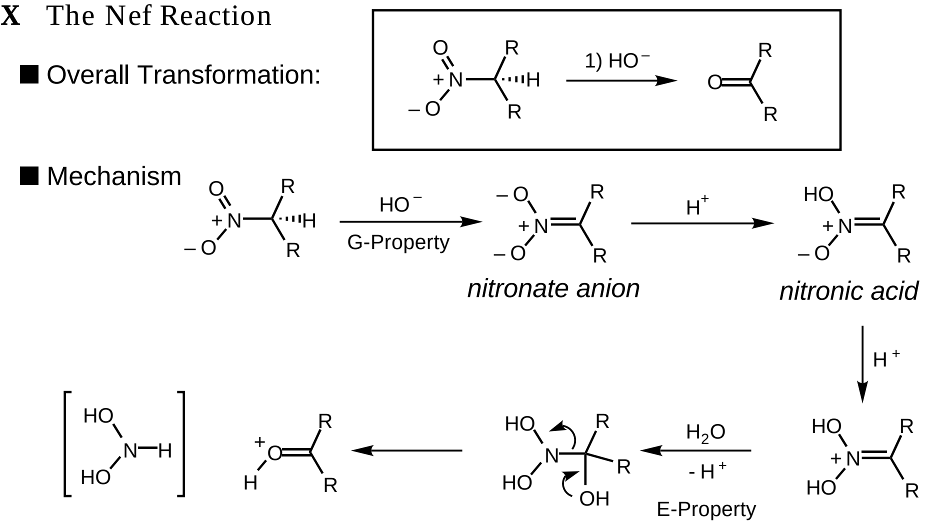
16) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T.; *Chimia* **1979**, *33*, 1-18.

Scheme IX The Nef Reaction



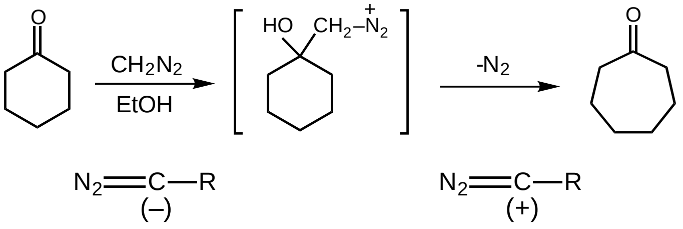
The Diazo Functional Group. This functional group provides one of the best illustrations of an A-function. As illustrated in Scheme X, both (–) and (+) polar site reactivity is observed in is reactions with carboxylic acids.

Scheme IX The Nef Reaction



The same overall reactivity pattern is expressed by the diazo functional group in the Tiffeneau-Demjanov ring expansion reaction[17] wherein diazomethane functions as the nucleophilic agent in the first step and the functional group is lost as a leaving group in the subsequent step (Scheme XI).

Scheme XI The Tiffeneau-Demyanov Ring Expansion



Restriction: Starting ketone must be more reactive than product ketone

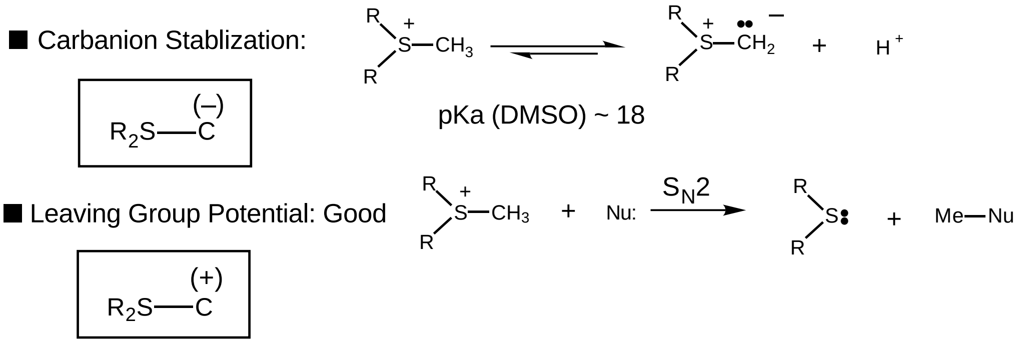
---

[17] For a monograph on ring expansion reactions see: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991.

Sulfur-Based Functional Groups

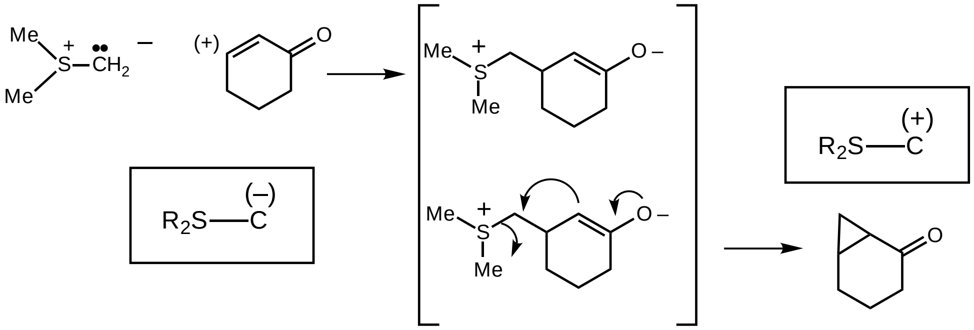
Sulfonium Salts. The dual electronic behavior of sulfur functions may be illustrated in the reactions of sulfur ylids which are excellent examples of A-functions. As illustrated in Scheme XII, sulfonium salts are effective in carbanion stabilization, a characteristic of G-functions, and sulfonium salts are effective leaving groups, a characteristic of E-functions.

Scheme XII. Sulfonium Salts: Modes of Reactivity



The non-alternate reactivity pattern of trimethylsulfonium ylids is revealed in the cyclopropanation of unsaturated ketones as illustrated in the case below (Scheme XIII).[18]

Scheme XIII. Reactions of Sulfonium Ylids: Conjugate Addition

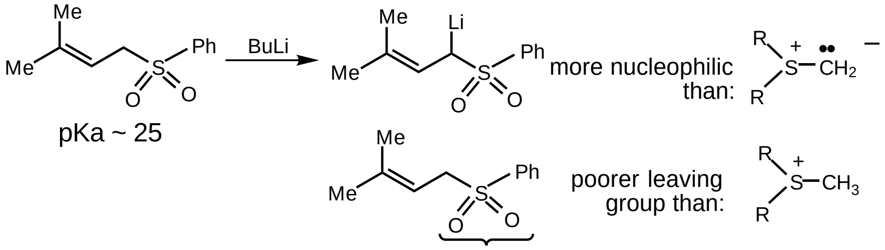


■ Nonalternate reactivity pattern revealed in consecutive reactions

Sulfones. Other types of sulfur-derived functional groups exhibit reactivity profiles similar to that exhibited by sulfonium salts. A number of excellent applications of the arylsulfonyl functional group illustrate this point. Two applications utilizing the sulfone functional groups are presented below.

The phenylsufonyl moiety strongly stabilizes carbanions and may be equated with the –CN FG in its potential for hydrocarbon acidification.[19] In addition, this FG is a respectable leaving group in selected situations. In comparisons with sulfonium ions (Scheme XV), arylsulfonyl-stabilized carbanions are more nucleophilic than sulfonium ylids (G-property), while $ArSO_2$- is a poorer leaving group than Me_2S- (E-Property).

Scheme XV. Sulfones: Modes of Reactivity



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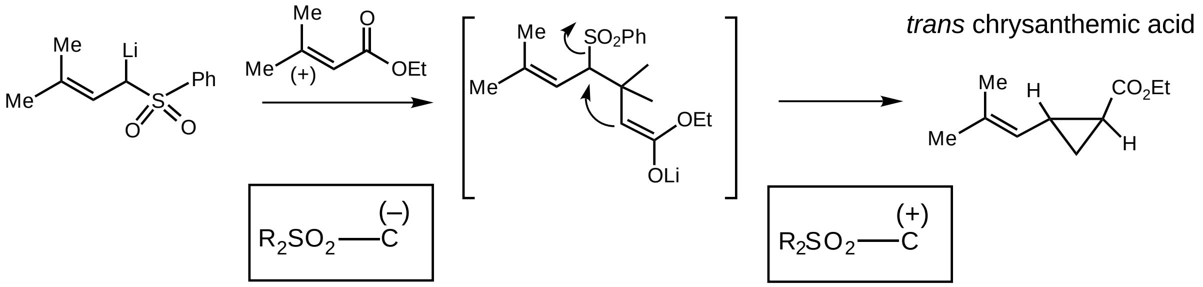
[18] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1352-1364.

[19] For an excellent compilation of pKa data for organic functional groups in DMSO see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

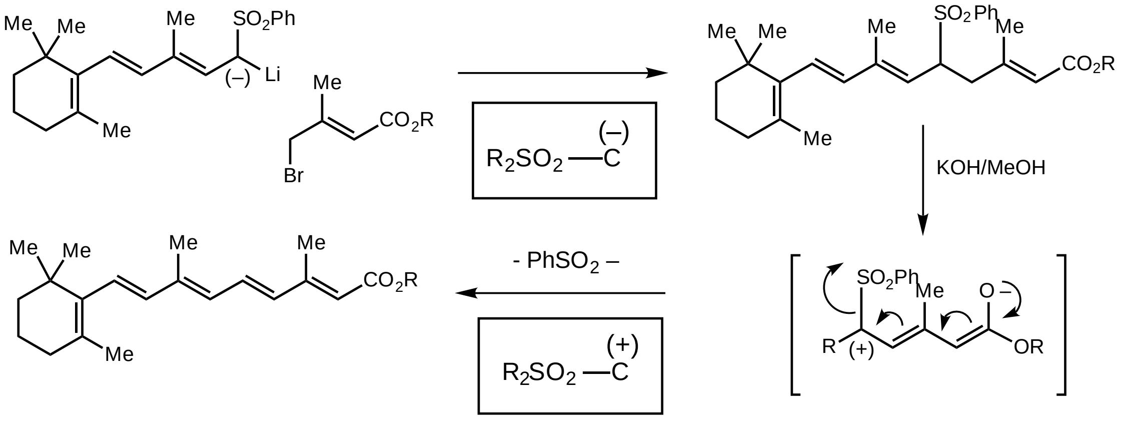
Julia's use of phenylsulfonyl carbanions in the synthesis of *trans*-chrysanthemic acid provides the justification for defining this functional group as an A-function (Scheme XVI).[20]

Scheme XVI. The Julia Chrysanthemic Acid Synthesis



The dual electronic properties of the sulfone functional group are illustrated in the Julia synthesis of vitamin A (Scheme XVII).[21] In this application, the E-property of the FG is exploited in the base-induced elimination reaction to generate the fully conjugated polyene.

Scheme XVII. The Julia Vitamin A Synthesis



Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130

For additional reading on the utility of the utility of sulfones in organic synthesis a monograph on this subject has recently appeared.[22] Several other reviews providing extensive literature coverage are worth reading.[23]

Organoboranes. The boron atom exhibits many of the common reactions normally attributed to metals, and when bound to carbon, serves as an excellent source of nucleophilic carbon.[24] The transformations provided in (Table IV) represent but a few cases which demonstrate the G-properties of this activating function.[25,26,27,28,29,30,31]

---

20) (a) Julia, M.; Guy-Rouault, *Bull. Soc. Chim. Fr.* **1967**, 1141. (b) Campbell, R. V. M.; Crombie, L.; Findley, D. A. R.; King, R. W.; Pattenden, G.; Whiting, J. *J. Chem. Soc., Perkin Trans. I* **1975**, 897.

21) Arnould, D.; Chabardes, P. Farge, G.; Julia, M. *Bull. Soc. Chim. Fr.* **1985**, 130.

22) Simpkins, N. S. *Sulfones in Organic Synthesis*, Pergamon Press, New York 1993.

23) (a) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107-124. (b) Magnus, P. D. *Tetrahedron*, **1977**, *33*, 2019-2045.

24) (a) Brown, H. C. *Boranes in Organic Chemistry*, Cornell University Press, New York 1973. (b) Cragg, G. M. L. *Organoboranes in Organic Synthesis*, Marcel Dekker, New York, 1973

25) (a) Kow, R.; Rathke, M. *J. Am. Chem. Soc.* **1973**, *95*, 2715. (b) Zweifel, G.; Fisher, R. P.; Horng, A. *Synthesis* **1973**, *37*. (c) Matteson, D. S. *ibid.* **1975**, 147.

26) Negishi, E.; Abramovitch, A.; Merrill, R. E. *J. Chem. Soc., Chem. Commun.* **1975**, 138.

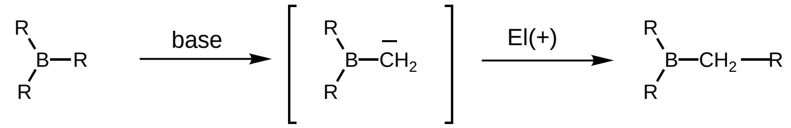
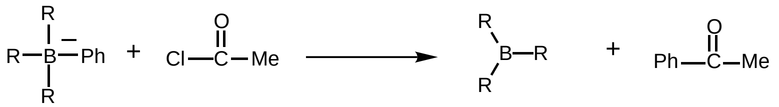
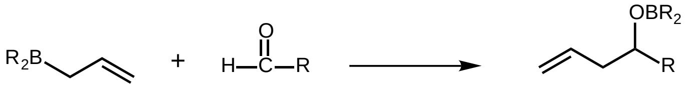
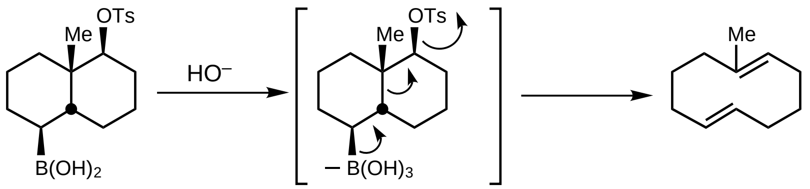
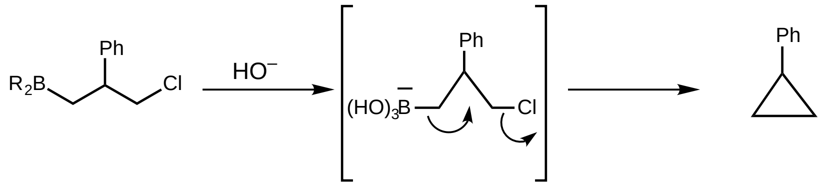
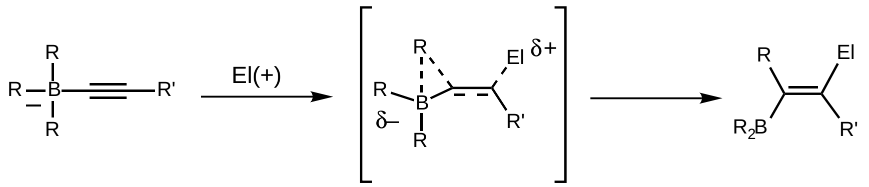
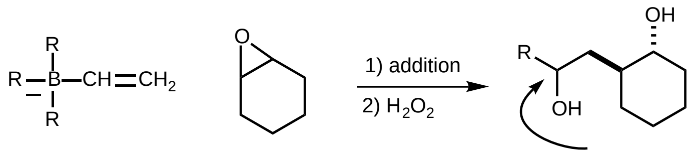
27 For a recent citation on allylboron-based nucleophiles see: Wang, Z.; meng, X. J.; Kablaka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677-5680 and references cited therein.

28) Marshall, J. A. *Synthesis* **1971**, 229.

29) (a) Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *2149*, 2149. (b) Hawthorne, M. F.; Dupont, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 5830.

30) (a) Pelter, A.; Subrahmanyan, C.; Laub, R. J.; Gould, K. J.; Harrison, C. R. *Tetrahedron Lett.* **1975**, 1633. (b) Pelter, A.; Harrison, C. R.; Kirkpatrick, D. *ibid.* **1973**, 4491. (c) Pelter, A.; Harrison, C. R. *J. Chem. Soc., Chem. Comm.* **1974**, 828. (d) Naruse, M.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1974**, *30*, 3037.

Table IV. Reactivity Patterns for Organoboranes

Entry	Reaction	Charge Affinity Pattern
A[25]		$\overset{(-)}{C}-\mathbf{A}$
B[26]		$\overset{(-)}{C}-\mathbf{A}$
C[27]		$\overset{(-)}{C}-C-\overset{(-)}{C}-\mathbf{A}$
D[28]		$\overset{(-)}{C}-\mathbf{A}$
E[29]		$\overset{(-)}{C}-\mathbf{A}$
F[30]	 El(+) = n-$C_6H_{13}I$, C_3H_5Br, ethylene oxide, CH_2I_2, $MeSO_3H$	$\overset{(-)}{C}-\overset{(+-)}{C}-\mathbf{A}$
G[31]	 *stereochemical aspects of this reaction not determined*	$\overset{(-)}{C}-\overset{(+-)}{C}-\mathbf{A}$

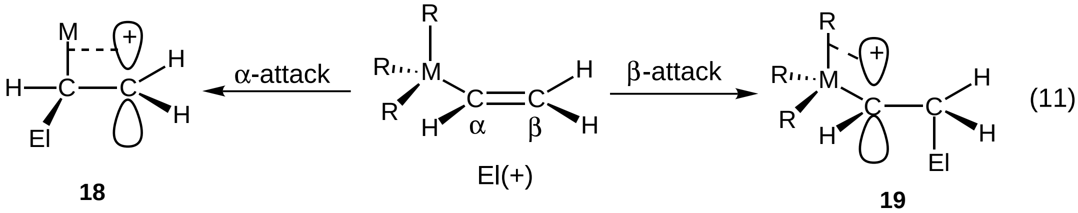
The potential for non-alternate charge affinity patterns for boron have been revealed in the reactions of acetylenic and vinylic boron ate complexes (Table IV, entries F, G).[30,31] *These compounds exhibit high nucleophilicity towards a variety of electrophiles β to the boron atom.* The origin of such β-nucleophilicity could be a consequence of σ–π conjugation[32] (e.g., **19**) not observed with the heavier metallic elements which are attacked by electrophiles α to the metal where the alternate mode of conjugation **18** is possible.[33] In principle, both types of conjugative stabilization are possible with a range of organometaloids; however, in practice this is not the case. It would be expected that the effects of σ–π conjugation, such as that illustrated in **24**, would be more important in those systems having shorter C-M bonds, a situation which may be unique to boron. It is noteworthy that the other group III and IV organometallic compounds, $R_3M—CH=CH_2$ (M = Al, Si, Ge, Sn) react with electrophilic reagents α to the metal. These elements all exhibit polar reactivity patterns common to G-class functions.

---

[31] (a) Utimoto, K.; Uchida, K.; Nozaki, H. *Tetrahedron* **1973**, *30*, 4527. (b) Utimoto, K.; Uchida, K.; Nozaki, H. *Chem Lett.* **1974**, 1493.

[32] (a) Harmon, G. D.; Traylor, T. G. *Tetrahedron Lett.* **1975**, 939, and reference cited therein. (b) for example of σ–π delocalization of type **25** involving R_3B— see Hanstein W.; Traylor, T. G. *ibid.* **1967**, 4451; (c) for the reaction of vinylsilanes electrophiles see Miller, R. B.; Reichenbach, T. *ibid.* **1974**, 543, and references cited therein.

[33] Kitching, W. in "Organometallic Reactions," Vol. 3, E. I. Becker and M. Tsutsui, Ed., Wiley-Interscience, New York 1972, pp. 319-398.



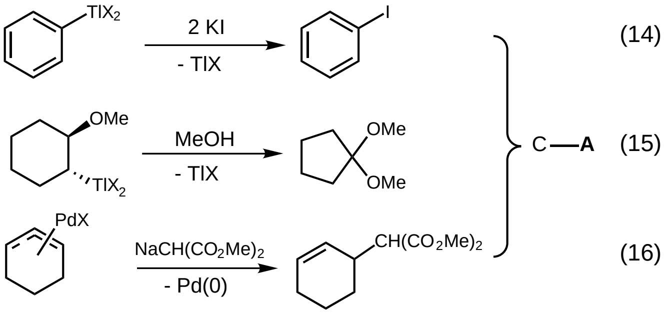
18

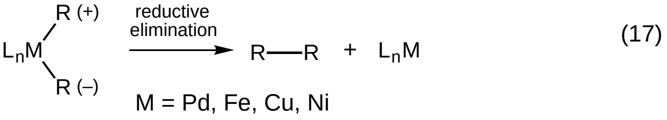
19

Metals. In deriving a class designation for metals, M, bound to carbon, two reaction types are considered. Metals undergoing *exclusive* substitution at the metal-carbon bond by electrophiles, El^+, are classified as G-functions (eq 12), while metals which are involved in redox processes (eq 13) are classified as A-functions since such organometallic compounds also exhibit G-type behavior.

$$\overset{(-)}{R}—\overset{(+)}{M} + El(+) \rightleftharpoons R—El + M(+) \qquad (12)$$

$$\overset{(+)}{R}—\overset{(-)}{M} + Nu(-) \rightleftharpoons R—Nu + M(-) \qquad (13)$$





The organic chemistry of Tl(III),[34] and Pd(II)[35] (eq 14-16) illustrate the role of metals as leaving groups (reductive elimination). Oxidative addition reactions of metal carbonyl anions and alkyl halides provide examples of the reverse process.[36] In general, transition metal-mediated cross-coupling reactions provide a useful illustration of the A-classification of redox metals (eq 17).[37] The assignment of charge affinity labels to R_1 and R_2 in this case is arbitrary.

Employing polar processes as the basis set of synthetic reactions, existing functional groups may be organized according to their known chemical properties. Any number of positions may be taken relative to the classification of atom reactivity. The goal of this section has been to define a general classification scheme which may be used to organize the multitude of different strategies which have been developed to construct pairwise functional group relationships in organic molecules.

---

[34]) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3,* 338.

[35]) Trost, B. M. *Acc. Chem. Res.* **1980**, *13,* 385-393.

[36]) Ellis, J. E. *J. Organomet. Chem.* **1975**, *86*, 1.

[37]) (a) Neuman, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (b) Normant, J. F. *Synthesis* **1972**, 63. (c) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. (d) Tamaki, A.; Magennis, S. A.; Kochi, J. K. *ibid*. **1973**, *95*, 6487.

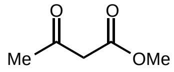
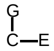
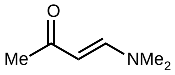
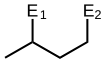
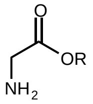
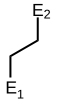
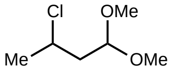
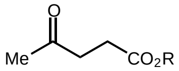
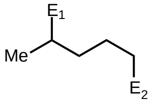
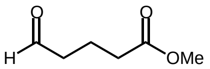
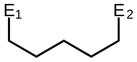
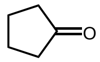
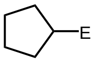
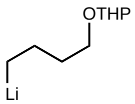
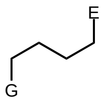
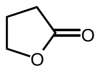
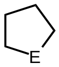
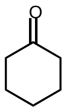
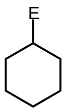
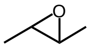
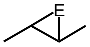
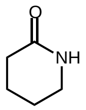
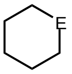
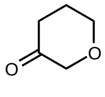
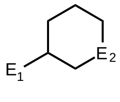
Classification of Difunctional Relationships.

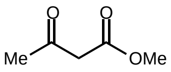
One of the basic assumptions employed in synthetic design involves the *maximum utilization of existing functionality at all intermediate points in the construction of a polyfunctional molecule*. Such guidelines aid in minimizing the number of side reactions and protection-deprotection steps during the assemblage operation. In the synthesis of even simple difunctional organic molecules, the relative positioning of the two activating functions on the carbon framework strongly influences the reaction types that will usually be employed to establish the difunctional relationship. Using the general notation developed in the previous section for activating functions, two distinct classes of difunctional relationships which may be defined between ideal E- and G-functions which may be defined are illustrated in Table V.

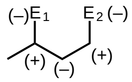
Paths. *Difunctional relationships between heteroatoms having "matched" charge affinity patterns will be defined as* ***consonant*** *while unmatched relationships will be labeled* ***dissonant****.*

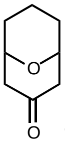
It should be pointed out that the charge affinity notation is unnecessary to define the appropriate relation; other parity labels could serve equally well. For example, the number of bonds between E- and G-functions could be used to define the appropriate relationship. Employing E-functions for the purpose of illustration, the two carbonyl groups in **20a** have a matched charge affinity pattern along the potential construction path. Since they are separated by three atoms they can be defined as 1,3-consonant (1,3-C). The symbol notation **20b** transmits information relative to the E—E' positioning along the construction path and since the E-symbol represents a homogeneous class of electronically equivalent functional groups, a common symbol is employed. In those cases where it is necessary to recognize oxidation states of carbon to derive a symbolic structural notation, one may easily do so.

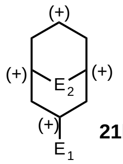
Table V. Consonant & Dissonant Difunctional Pairwise Functional Group Relationships

Consonant Relationships	Symbol	Notation	Dissonant Relationships	Symbol	Notation
			Li—CH$_2$—Cl		1,1–D
		1,3–C			1,2–D
					1,4–D
		1,5–C			D-cycles
		1,4–C			
		C-cycles			
					1,2–D, 1,4–D


20a

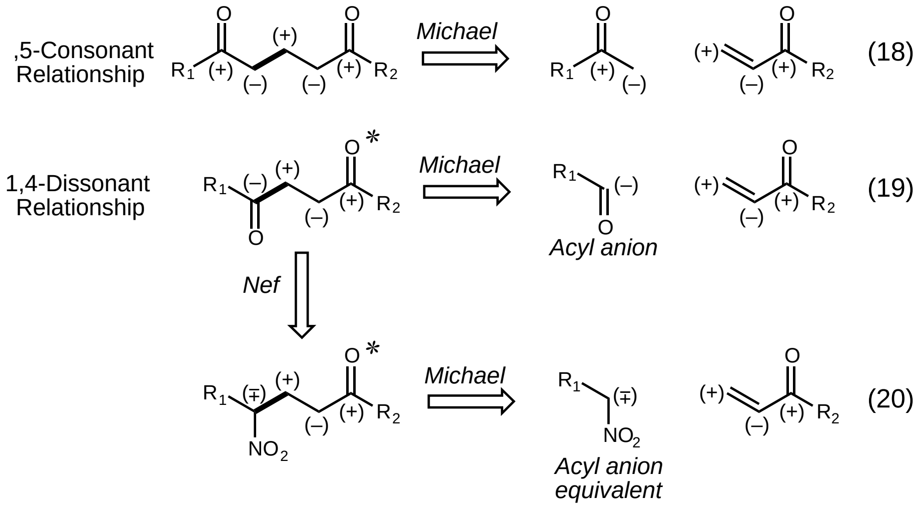

20b


21a


(-) symbol deleted for convenience
21b

Cycles. *In cyclic structures, a heteroatom attached to or contained within the cycle creates a relationship with itself. For non-arbitrary mathematical considerations it is convenient to define an even-membered ring with or without a single functional group as consonant and corresponding odd-membered rings as dissonant.* For the bicyclic ketone **21a**, both of the oxygen heteroatoms, denoted as E_1 and E_2, establish consonant relationships with each other via all bond paths and individually by virtue of their position either attached to or contained within an even-membered ring.

Consonant and Dissonant Bond Paths. In contrast to the uniformity with which consonant relationships may be established through common classes of polar processes, the synthetic methods and functional groups required for the construction of the bonds define a D-relationship are quite varied and involve either more steps, more functional groups or more reactive intermediates than reactions leading to C-paths. This statement will be reinforced in a series of case studies (*vide infra*); however a single case is presented to reinforce this assertion. Consider the Michael transform executed on the 1,5- and 1,4-diketones shown below (eq 18, 19). In the first instance, the transform may be executed using only the functional groups illustrated; however, this is not possible with the dissonant dicarbonyl relationship since one of the resulting polar fragments will be electronically mismatched with its associated FG. In the illustrated disconnection (eq 19), the electronically mismatched fragment is the carbonyl anion.

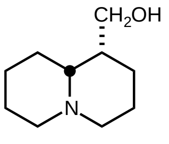


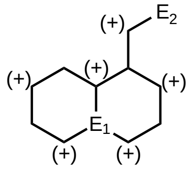
One possible solution to the construction of this dissonant relationship is through FG manipulation. In the present instance the application of the Nef transform (vide supra) provides the opportunity to match the charge affinity patterns so that the Michael transform may be properly executed. The use of A-functions in this fashion is just one of a number of strategies which may be employed to construct dissonant difunctional relationships.

In conclusion, dissonant pairwise relationships, either identified in simple acyclic molecules or within complex cyclic structures, generally pose a greater synthetic challenge and represent seams of lower flexibility within the carbon framework. At this point, it may be instructive to the reader to contemplate a synthesis strategy based on how and when D-relationships are incorporated into target structures. This point will be addressed later in the discussion.

Synthesis of Consonant Difunctional Relationships.

Every complex polyfunctional molecule may be analyzed structurally in terms of its individual consonant or dissonant construction paths or cycles. For example, in the alkaloid lupinine (**22**) all possible construction paths interconnecting E_1 and E_2 are consonant. On the other hand, mesembrine (**23**)[38] contains the potential dissonant paths and cycles illustrated in heavy lines. *Consonant paths within the polyatomic framework define seams in the structure that may be constructed using aldol and related condensation processes.*


22 ***(lupinine)***



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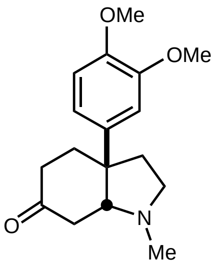
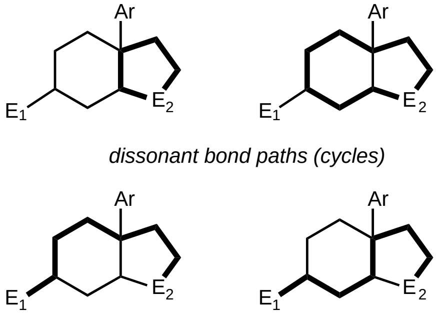
[38] (a) Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441. (b) Keely, S. L.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584. (c) Stevens, R. V.; Wentland, M. P. *ibid.* **1968**, *90*, 5580; (d) Shamma, M.; Rodrigues, H. R. *Tetrahedron* **1968**, *24*, 6583.

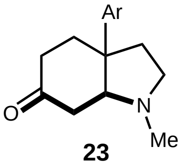
■ Regarding the number of different possibilities available for the synthesis of a consonant difunctional relationship interconnected by **n** bonds, there exists a set of **n** different connective operations that may be employed to establish any bond along the construction path from monofunctional or consonant polyfunctional precursors.[39]



23 *(lupinine)*



dissonant bond paths (cycles)

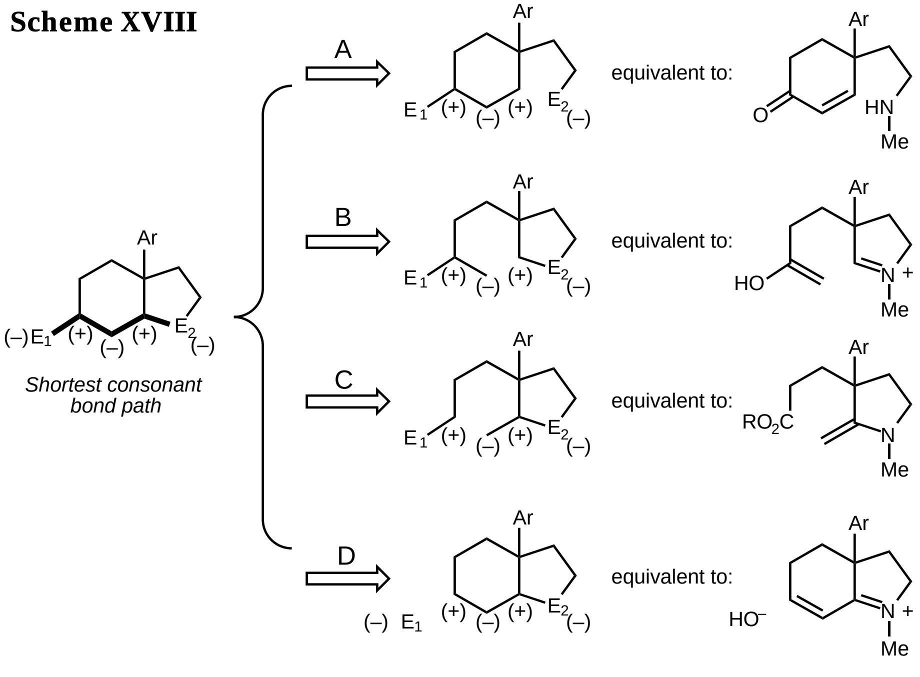


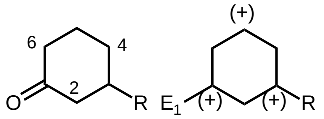
23

Shortest consonant bond path

In the analysis of potential routes to structures like lupinine, identify the shortest consonant bond path and then proceed to carry out all polar disconnections along that bond path (Scheme XVIII). Since there four bonds interconnecting =O and N (E$_1$ and E$_2$), there will be four associated transforms which one may execute using the illustrated functional groups. In each set of precursors the intrinsic polar reactivity patterns of the heteroatoms are accommodated in the coupling process. The resulting adducts containing the requisite nitrogen-oxygen relationship may then be ranked in order of desirability by considering criteria such as chemical feasibility of the coupling step, ease of subsequent transformation to the target structure, and availability of precursor fragments. In the present example, transforms A and B might be more highly ranked that transform C while transform D might be discarded since it does not lead to structural simplification.

Scheme XVIII





24

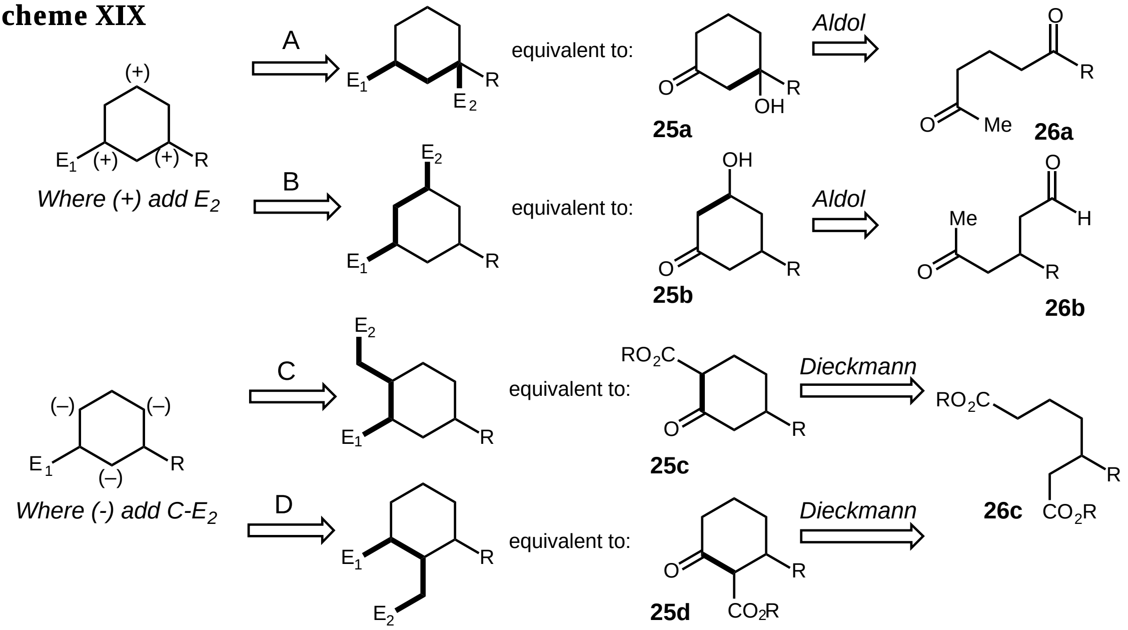
In those cases when a given consonant or dissonant relationship is separated by a significant number of bonds, it is strategically worthwhile to consider the option of incorporating additional functions to aid in the construction of the desired target molecule. The relative placement of such a functional group is of prime importance in dictating the subsequent polar disconnections that are perceived in generating a plausible synthetic tree. This point is illustrated when considering plausible precursors to ketone **24** (Scheme XIX). In this structure, the =O FG establishes a 1,5-relationship with itself on the six-membered ring. Through the addition of an appropriate second

---

39) The presence of a quaternary or bridgehead center along the construction path limits bond construction to those adjacent to the center.

activating function to the target molecule **24**, an expanded set of potential disconnections is created. In the placement of the second FG, the charge affinity pattern of the resident FG should be used. *For example, consider the installation of a second FG, E_2, at the (+) sites on the ring to set up aldol or Claisen transforms. In a complementary fashion the addition of C-E_2 fragments to the (–) sites will open up the execution of the two possible Dieckmann transforms.*[40] The preceding analysis leads to the three precursors **26a-26c**. Each of which contains a 1,5-consonant difunctional relationship between the carbonyl functions. These subgoals now become the focus of the next level of analysis wherein the preceding logic is again applied. It should be emphasized that the precursors illustrated in Scheme XIX are not inclusive but represent one set which leads to the generation of a synthetic tree based upon aldol and related reactions. *The point to be emphasized is that in the first stage of the analysis where functionality is being added to the target structure, consonant, rather than dissonant relationships should be created.*

Scheme XIX



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[40] To be completely rigorous with regard to this analysis, the addition of C-E_2 to the 4-position should also be considered; however, the E_1-E_2 construction span from such a precursor is sufficiently large as to render this precursor less attractive than the other precursors **25a-25d**.

Chemistry 206

Advanced Organic Chemistry

Handout 27B

Synthetic Applications of α-Diazocarbonyl Compounds

An Evans Group Afternoon Seminar

Krista B. Goodman

January 15, 1999

D. A. Evans

Monday,
November 17, 2003

Synthetic Applications of α-Diazocarbonyl Compounds

An Evans Group Afternoon Seminar

Krista Beaver

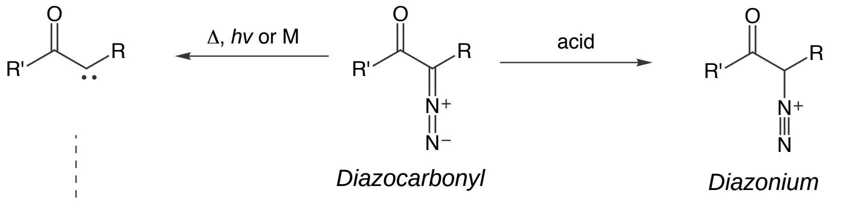
January 15, 1999

Leading References:

McKervey and Ye, *Chem. Rev.* **1994** 1091

Doyle, McKervey and Ye, Modern Methods for Organic Synthesis with Diazo Compounds, Wiley, 1998

Diazocarbonyl Compounds: Structure and Nomenclature

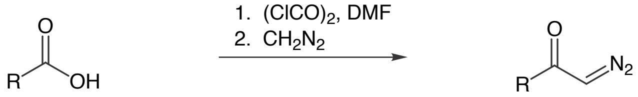


cyclopropanation
insertion
rearrangement
ylide formation

displacement
rearrangement
solvolysis

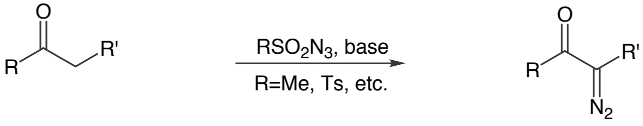
Synthesis of α-Diazocarbonyl Compounds

- First synthesized by Curtius in 1883 by diazotization of α-amino acids
- Arndt-Eistert synthesis (1927)



Arndt and Eistert, *Ber. Dtsch. Chem. Ges.* **1927** 60B 1122
Pettit, *JOC* **1986** 1282

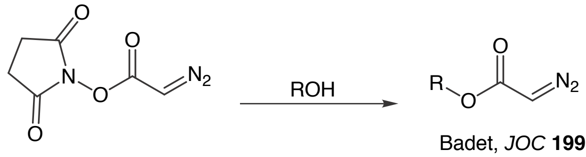
- Diazo Transfer



Regitz, *ACIEE* **1967** 733

For temporary activation of carbonyl compounds prior to diazo transfer, see Danheiser, *JOC* **1990** 1960

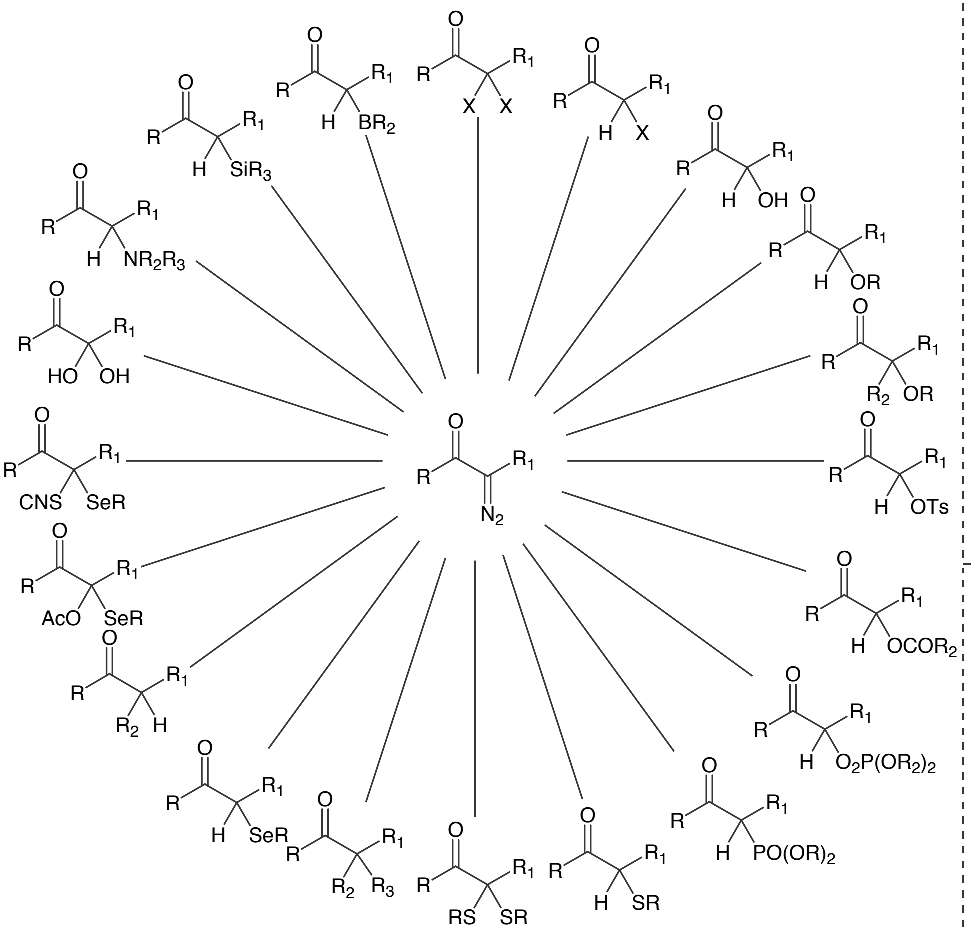
- Acyl Transfer



Badet, *JOC* **1993** 1641

Synthetic Applications of α-Diazocarbonyl Derivatives

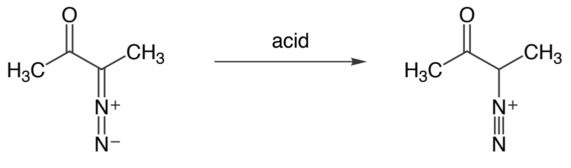
Some Reactions of α–Diazocarbonyl Compounds



Adapted from McKervey, *Chem. Rev.* **1994** 1090

Acid Catalyzed Reactions of Diazo Compounds

Review: Smith, Tet. 1981 2407



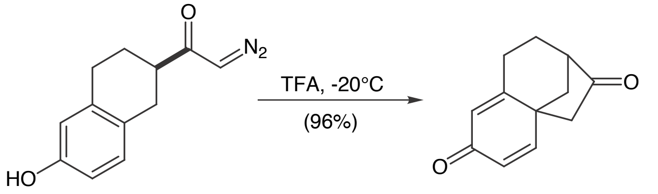
Diazocarbonyl

Diazonium

Common acids include BF_3•OEt_2, HBF_4, TFA, etc.

Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

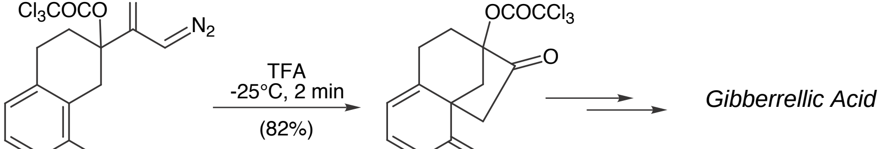
Acid-Catalyzed Reactions



Mander, *Chem. Comm.* **1971** 773
Tet., **1991** 134

"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantites of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

Lewis Mander

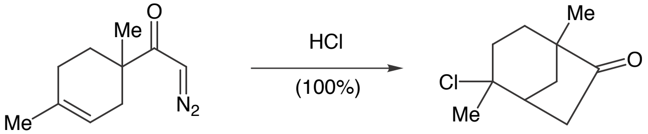


Mander, *JACS* **1980** 6626

Synthetic Applications of α-Diazocarbonyl Derivatives

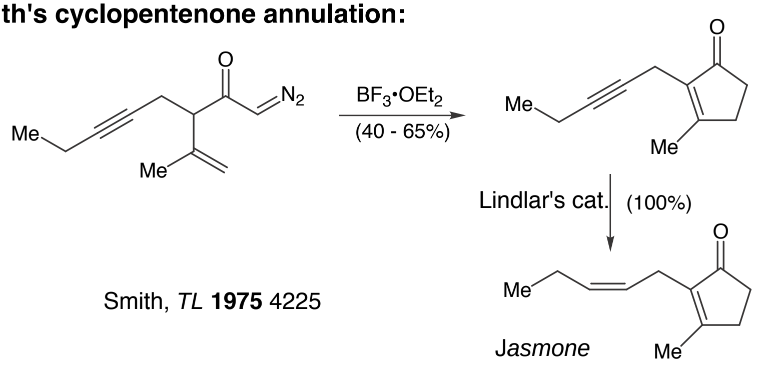
More Acid Catalysis

Olefins as nucleophiles:



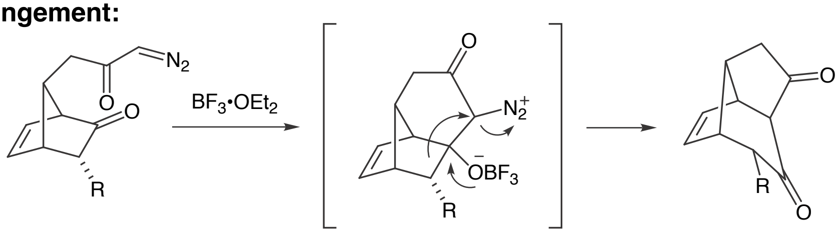
Mander

Smith's cyclopentenone annulation:



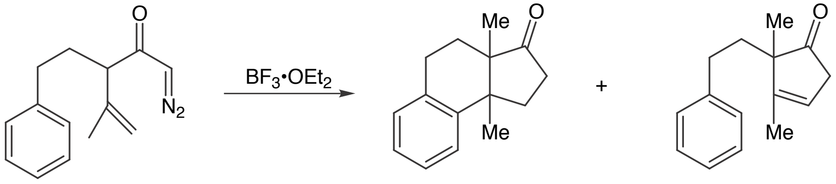
Smith, *TL* **1975** 4225

Rearrangement:



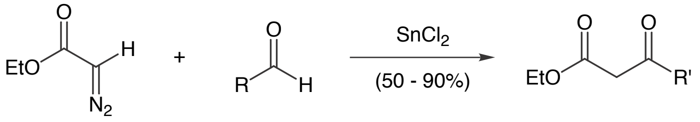
Mander, *Aust. J. Chem.* **1979** 1975

Polyene cyclizations:



Smith, *JACS* **1981** 2009

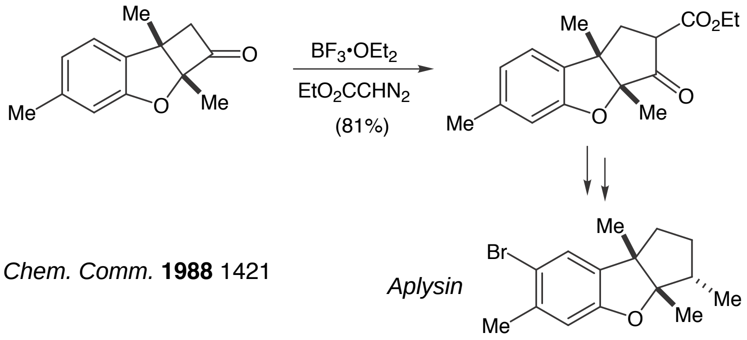
β-Ketoester synthesis:



Roskamp, *JOC* **1989** 3258

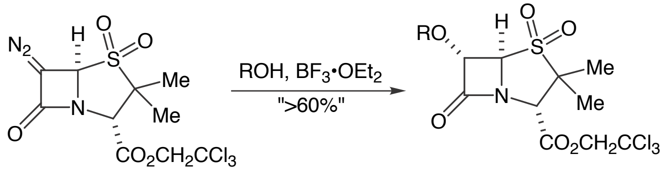
Yields are good when R is aliphatic; moderate when aromatic

Ring expansion:



Ghosh, Chem. Comm. **1988** 1421

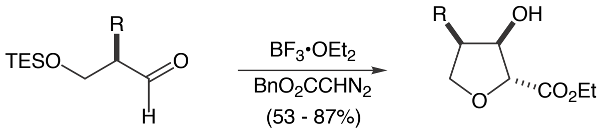
Substitution:



Thiols also work well

John and Thomas*TL* **1978** 995

Tetrahydrofuran Synthesis:



diastereoselection 3:1 - 20:1

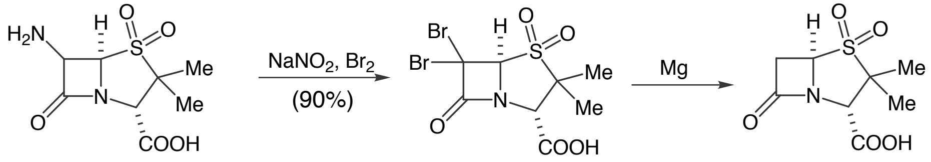
Diastereoselectivity increases with size of R; independent of Lewis acid or protecting group

Angle, *TL* **1998** 3119
TL **1998** 8195

Synthetic Applications of α-Diazocarbonyl Derivatives

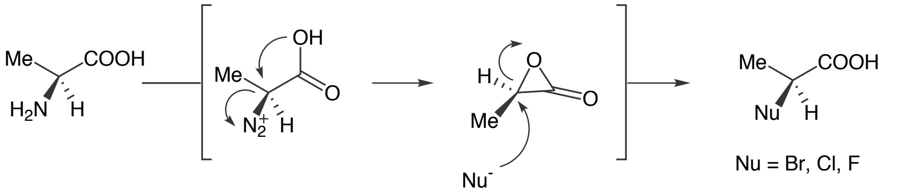
Substitution Reactions

Deamination:



Kapur and Fasel, *TL* **1985** 3875

Synthesis of α-substituted chiral acids:

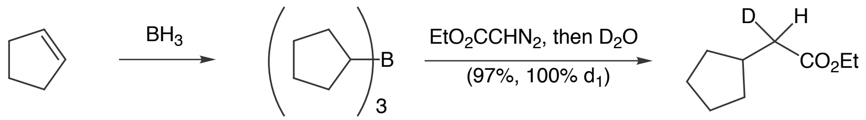


Displacement occurs with retention of stereochemistry

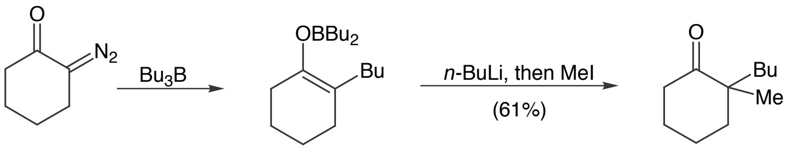
Ingold, *Nature* **1950** 179

For other examples, see McKervey, *Chem. Rev.* **1994** 1091

Reaction with Boranes



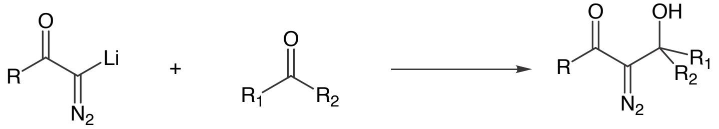
Hooz, *JACS* **1969** 6195



Wojtkowski, *JOC* **1971** 1790

Base-Induced Reactions

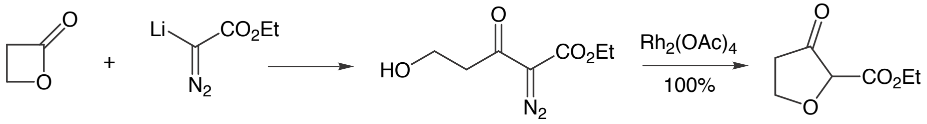
Aldol-type reactions:



LDA is the optimal base for lithiation

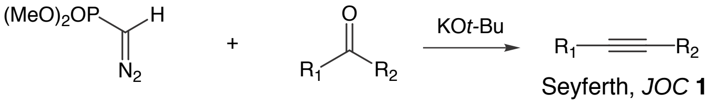
Pellicciari, *JCS Perkins I* **1985** 493

Ester alkylation:



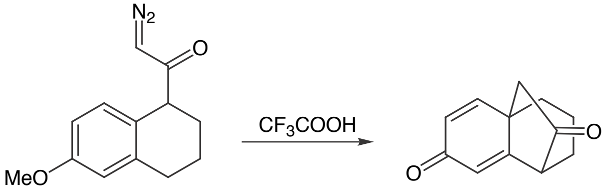
Rapoport, *JOC* **1985** 5223

Gilbert-Seyferth Reagent:



Seyferth, *JOC* **1971** 1379
Gilbert, *JOC* **1982** 1837

Mechanism?



Krista Beaver

Synthetic Applications of α-Diazocarbonyl Derivatives

Carbenoid Reactions: The Catalysts

Review: Padwa, *ACIEE* **1994** 1797

Decomposition can be catalyzed by:

Heat or light

Transition metals, including Cu^{II}, Rh^{II}, Mn^{II}, Fe^{II}, Co^{II}, Ni^{0}, Ni^{II}, Zn^{II}, Mo^{II}, Ru^{II}, Ru^{III}, Pd^{III}

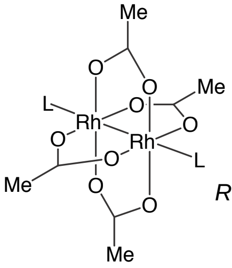
Most common catalysts:

Copper (I): CuOTf, $Cu(OTf)_2$, $CuSO_4$, CuX, $Cu(acac)_2$

Rhodium (II): Much milder catalyst than Cu (introduced in 1973 by Tessié)

Structures generally contain bridging ligands and contain a Rh-Rh single bond

Reaction pathways are highly sensitive to steric and electronic effects

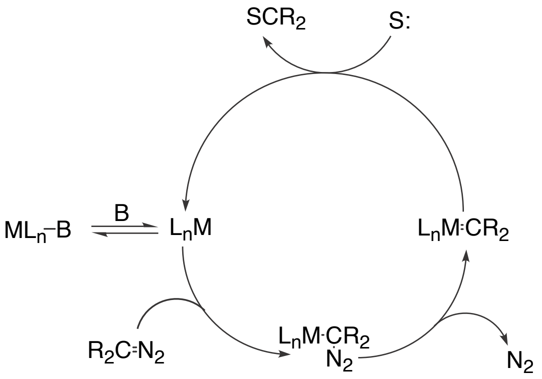


Rhodium Acetate

Rhodium Carboxylates: $Rh_2(OAc)_4$, $Rh_2(tfa)_4$, $Rh_2(oct)_4$, $Rh_2(tpa)_4$, $Rh_2(pfb)_4$

Rhodium Carboxamidates: $Rh_2(acm)_4$, $Rh_2(cap)_4$, $Rh_2(CF_3CF_2CF_2CONH)_4$

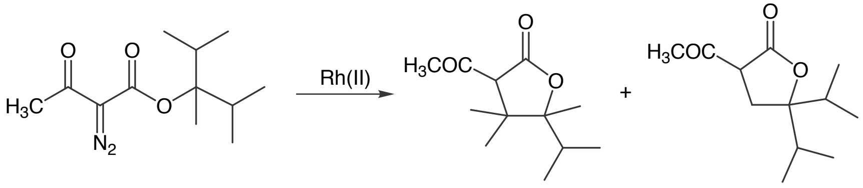
Transition Metal Catalyzed Diazo Decomposition



Doyle, *Chem. Rev.* **1986** 919

Ligand Effects: Selectivity

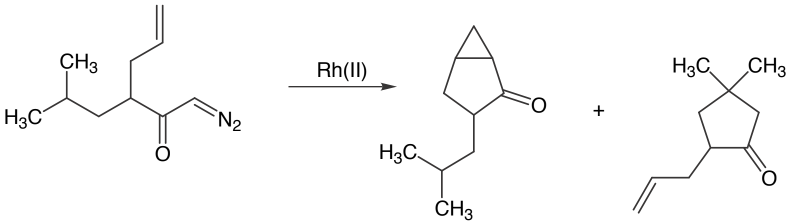
Methine versus methyl:



Doyle, *JACS* **1993** 958

$Rh_2(OAc)_4$	90:10
$Rh_2(pfb)_4$	38:61
$Rh_2(acam)_4$	100:0

Cyclopropanation versus C-H Insertion:

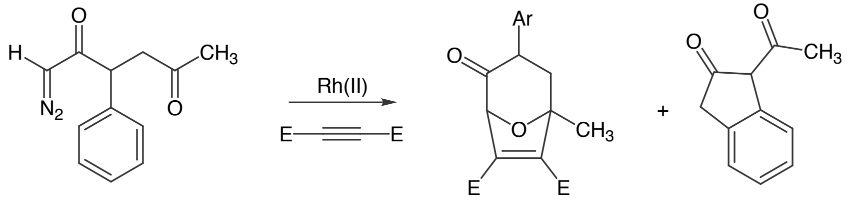


Padwa and Doyle, *JACS* **1993** 8669

$Rh_2(OAc)_4$	44:56
$Rh_2(pfb)_4$	0:100
$Rh_2(cap)_4$	100:0

More Competition Experiments

Dipolar Cycloaddition versus C-H insertion:



Padwa and Moody, *Tet.* **1993** 5109

$Rh_2(OAc)_4$	75:25
$Rh_2(pfb)_4$	0:100
$Rh_2(cap)_4$	100:0

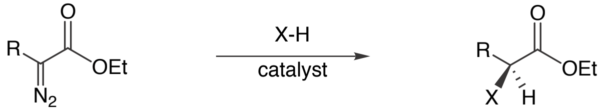
Conclusions:

These results imply that the metal is involved in the transition state

Reaction pathways can be controlled by tuning the ligands on the metal

Synthetic Applications of α-Diazocarbonyl Derivatives

Generalizations: Sigma Bond Insertion

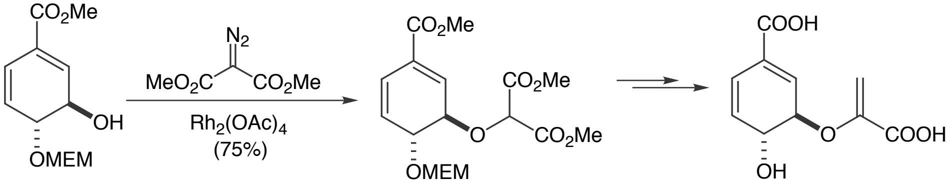


Reviews O-H Insertion: Moody *Tet.* **1995** 10811
C-H Insertion: Sulikowski *Tet. Asymm.* **1998** 3145

- When X is a heteroatom, insertion is facile
- When X is carbon:

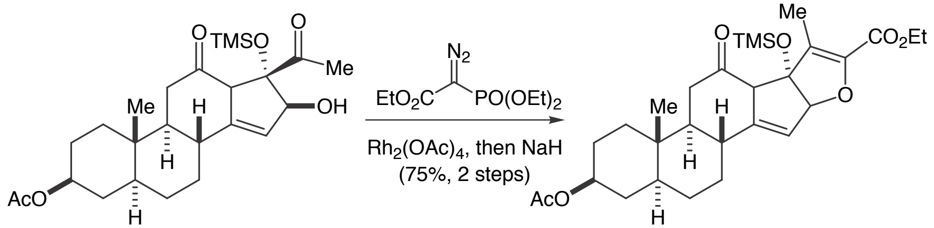
Only intramolecular processes are generally useful
5 - membered ring formation is favored in general
Order of selectivity: methine > methylene > methyl

O-H Insertion Reactions



Ganem, *JACS* **1982** 6787

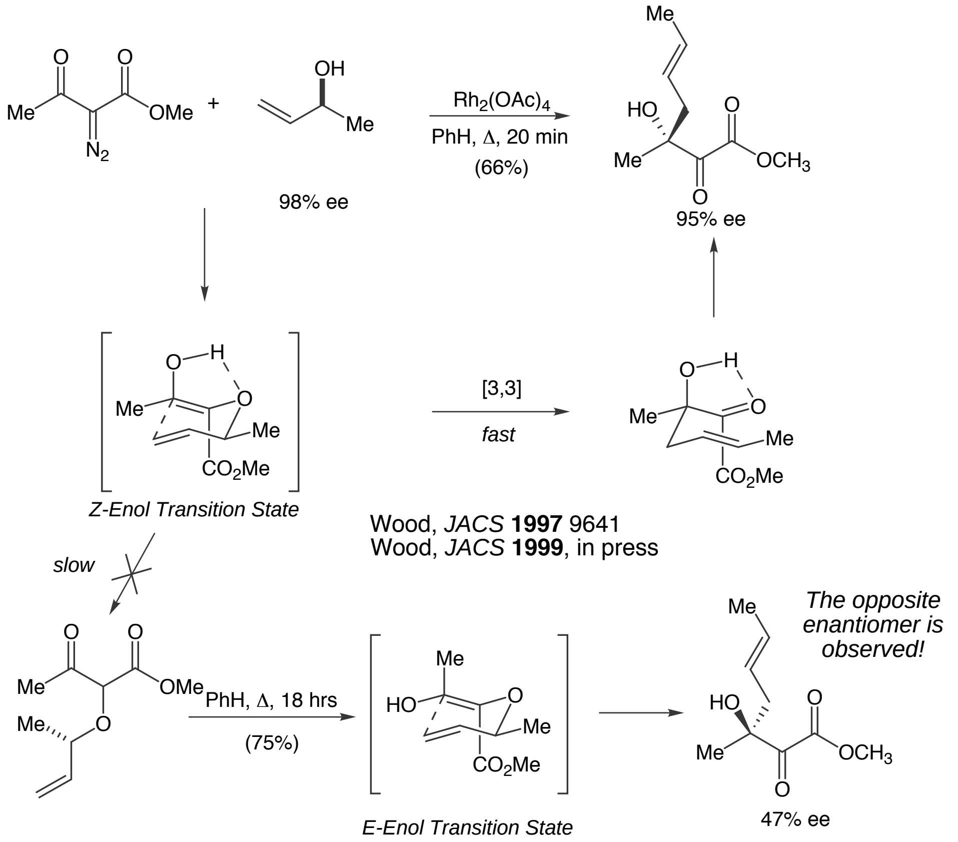
Chorismic Acid



"the most complex alkoxyphosphonate yet described"

Fuchs, *TL* **1994** 7163

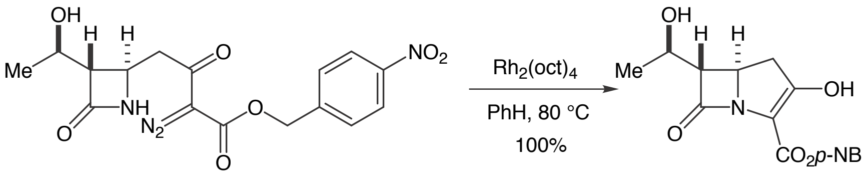
Tandem O-H Insertion/Claisen Rearrangement

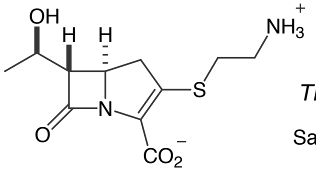


Wood, *JACS* **1997** 9641
Wood, *JACS* **1999**, in press

The opposite enantiomer is observed!

Merck Thienamycin Process

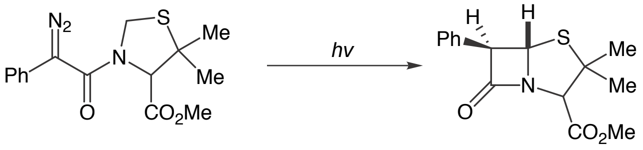




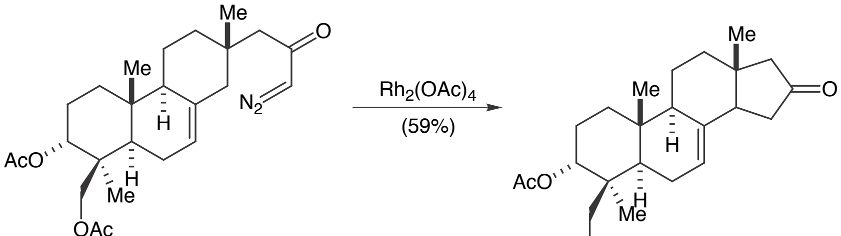
Thienamycin

Salzmann, *JACS* **1980** 6161

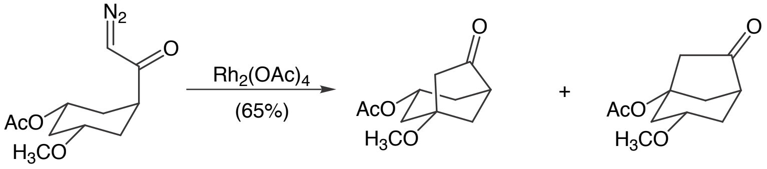
C-H Insertion: Reactions



Corey, *JACS* **1965** 2518

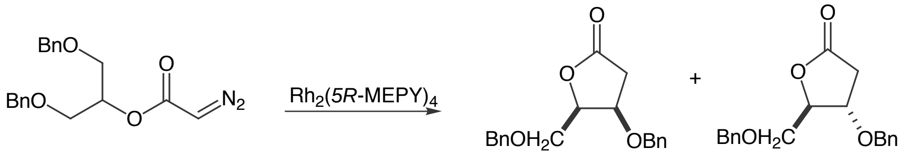


Wenkert, *JOC* **1982** 3243



Adams, *JACS* **1994** 3296

Diastereoselection > 99:1



97% ee

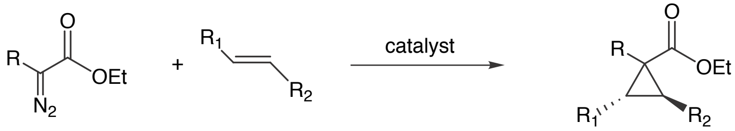
50% ee

Doyle, *JACS* **1994** 4507

Diastereoselection 93:7

For a review of catalytic enantioselective carbene reactions, see:
Doyle, *Chem. Rev.* **1998** 911

Generalizations: Cyclopropanation



Reviews: Davies, *Ald. Acta*. **1997** 107
Davies, *Tet*. **1993** 5203

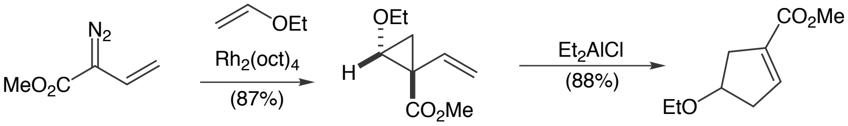
For subsequent reactions: Calter, Evening Seminar 1992

Electron rich olefins work best

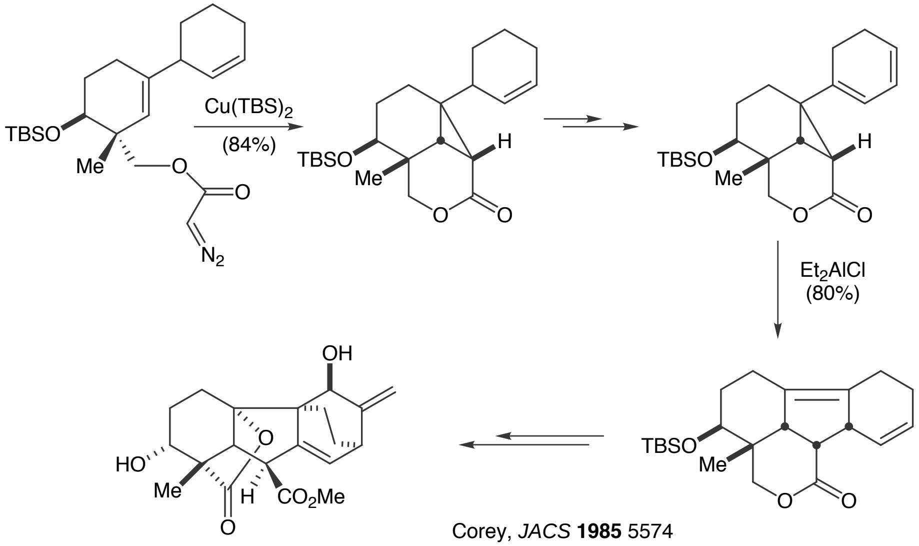
Both concerted asynchronous and stepwise mechanisms have been proposed

Cyclopropanes can participate in tandem reactions

Cyclopropanation Followed by Rearrangement



Davies, *JOC* **1992** 4309; *TL* **1992** 453

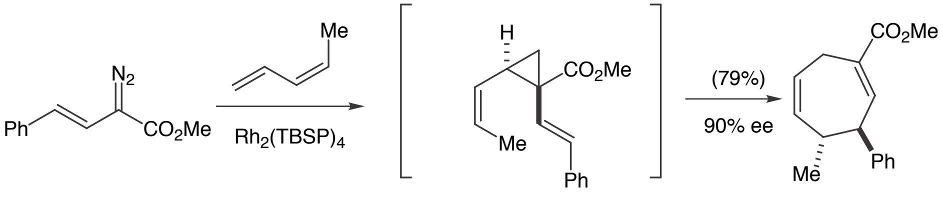


Antheridic Acid

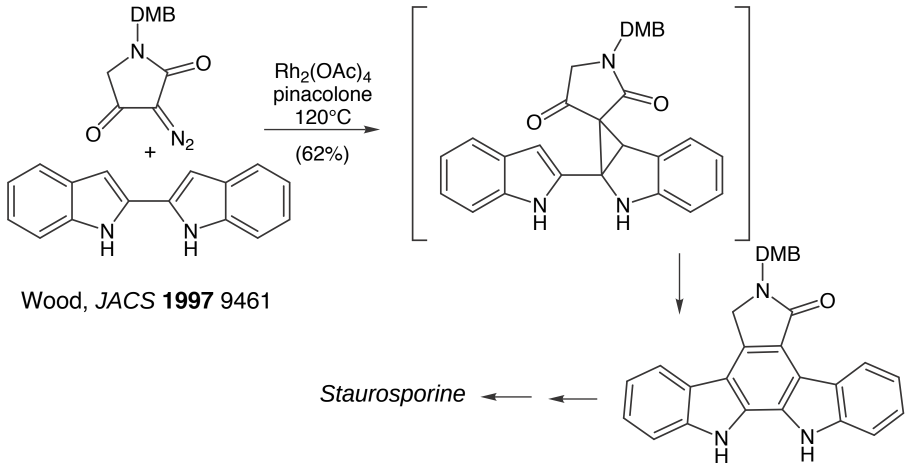
Corey, *JACS* **1985** 5574

Synthetic Applications of α-Diazocarbonyl Derivatives

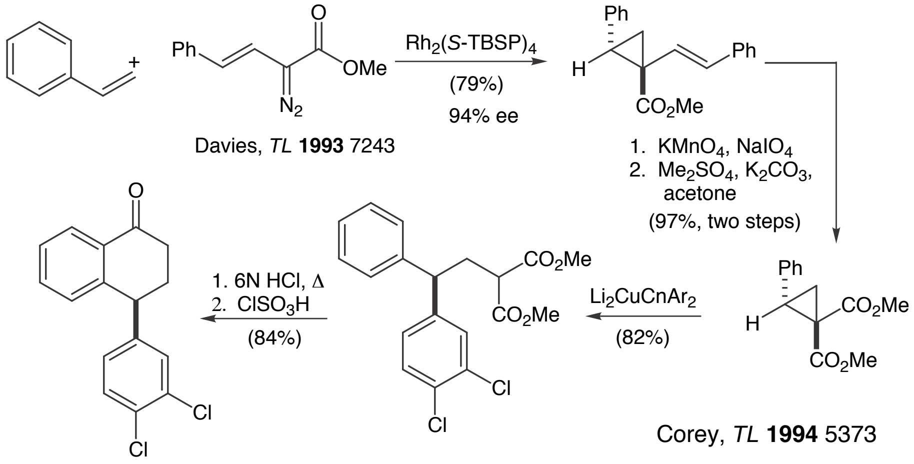
More Cyclopropanation



Davies, *TL* **1994** 8939



Wood, *JACS* **1997** 9461

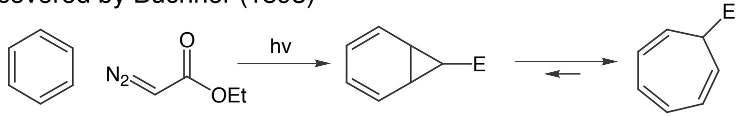


Davies, *TL* **1993** 7243

Corey, *TL* **1994** 5373

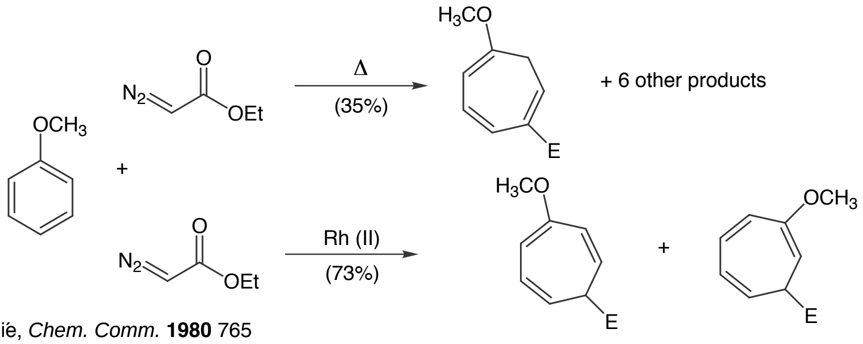
Reaction with Aromatic Rings

- Discovered by Bϋchner (1893)



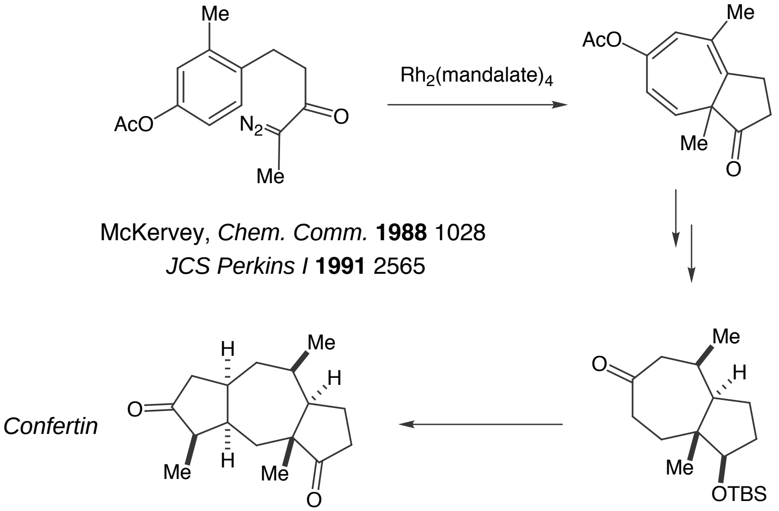
Bϋchner, *Liebigs Ann. Chem.* **1893** 214
Doering, *JACS* **1956** 5448

- Initial experiments gave poor selectivity, but transition metals help...



Tessiė, *Chem. Comm.* **1980** 765
JOC **1981** 873

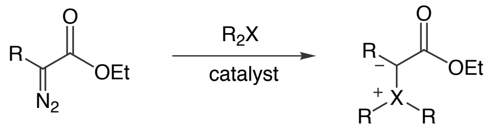
Bϋchner Reaction: Confertin Synthesis



McKervey, *Chem. Comm.* **1988** 1028
JCS Perkins I **1991** 2565

Synthetic Applications of α-Diazocarbonyl Derivatives

Ylide Formation

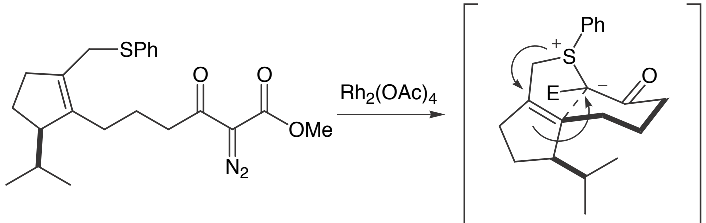


Reviews: Padwa, *Chem. Rev.* **1991** 263
Padwa, *Chem. Rev.* **1996** 223
Barnes, Evening Seminar, March 16, 1993

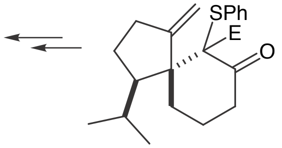
X is generally S, O or N and can be sp^2 or sp^3 hybridized

Ylides often undergo sigmatropic rearrangements or cycloadditions

[2,3]-Sigmatropic rearrangement:

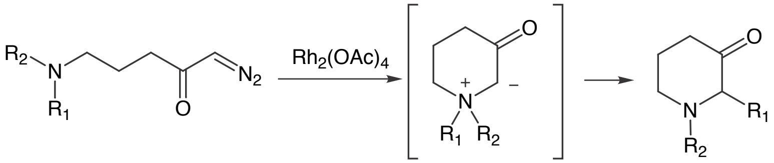


Kido and Kato, *JCS Perkins 1* **1992** 229



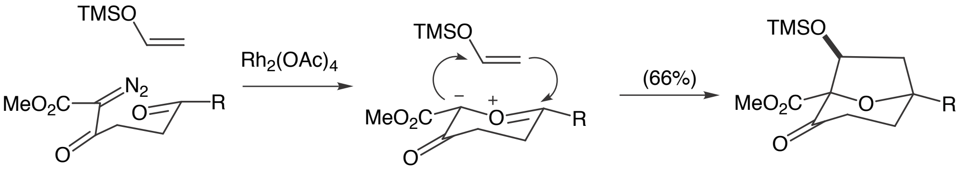
Acorenone B

Stevens Rearrangement ([1,2] alkyl shift):



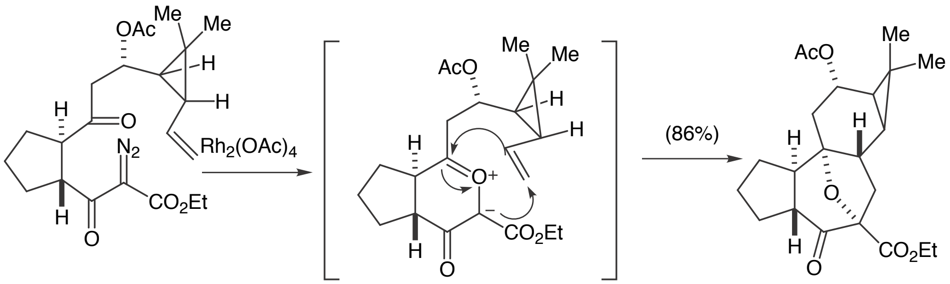
West, *JACS* **1993** 1177

Dipolar Cycloadditions: Carbonyl Ylides



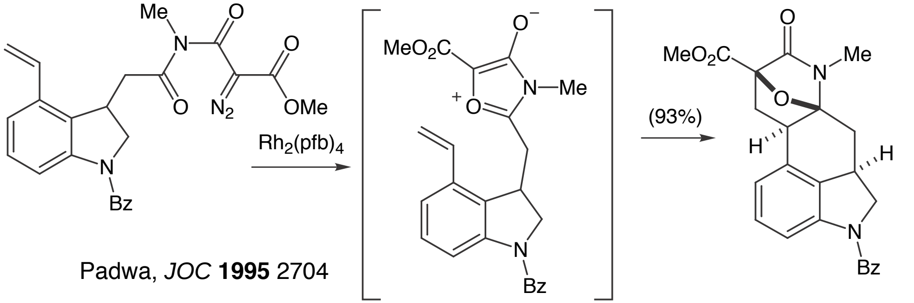
Merck, *TL* **1994** 9185

Zaragozic Acid Skeleton



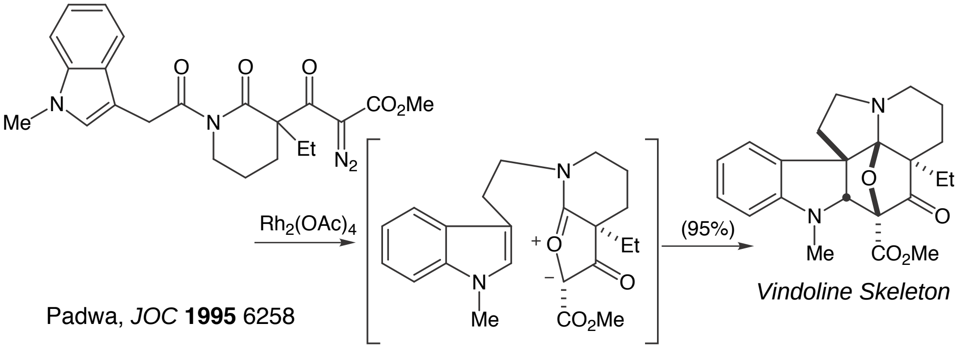
Dauben, *JOC* **1993** 7635

Tigilane Skeleton



Padwa, *JOC* **1995** 2704

Lysergic Acid Skeleton

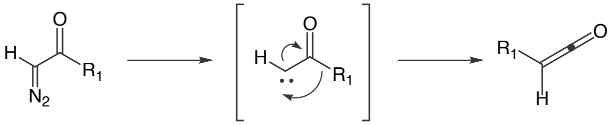


Padwa, *JOC* **1995** 6258

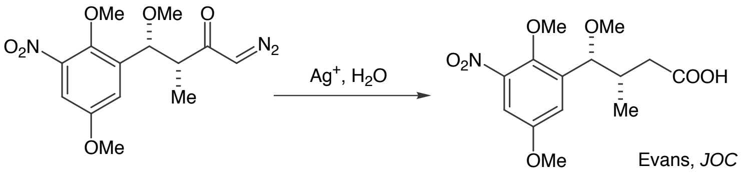
Vindoline Skeleton

Synthetic Applications of α-Diazocarbonyl Derivatives

Wolff Rearrangement

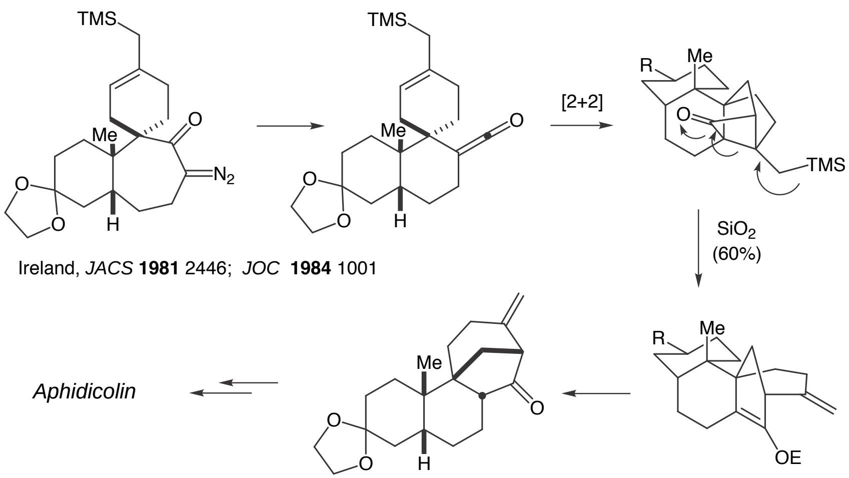


Arndt-Eistert Homologation:



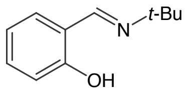
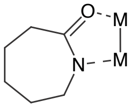
Evans, *JOC* **1993** 471

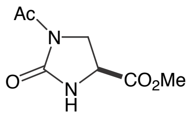
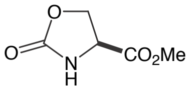
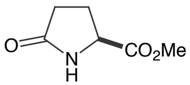
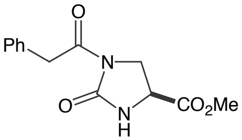
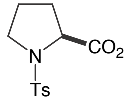
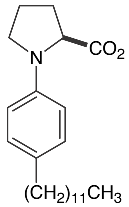
Wolff Rearrangement - [2+2] Cycloaddition

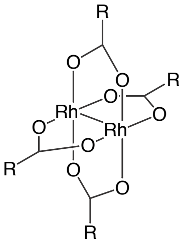


Ireland, *JACS* **1981** 2446; *JOC* **1984** 1001

Catalyst Glossary

$Cu(TBS)_2$	Copper *t*-Butylsalicylaldimine	
$Rh_2(OAc)_4$	Rhodium Acetate	CH_3CO_2
$Rh_2(acam)_4$ or $Rh_2(acm)_4$	Rhodium Acetamidate	CH_3CONH
$Rh_2(cap)_4$	Rhodium Caprolactamate	
$Rh_2(oct)_4$	Rhodium Octanoate	$CH_3(CH_2)_6CO_2$
$Rh_2(pfb)_4$	Rhodium Perfluorobutyrate	$CF_3CF_2CF_2CO_2$
$Rh_2(tfa)_4$	Rhodium Trifluoroacetate	CF_3CO_2
$Rh_2(tfm)_4$	Rhodium Trifluoroacetamidate	CF_3CONH
$Rh_2(tpa)_4$	Rhodium Triphenylacetate	Ph_3CCO_2

$Rh_2(MACIM)_4$	
$Rh_2(MEOX)_4$	
$Rh_2(MEPY)_4$	
$Rh_2(MPPIM)_4$	
$Rh_2(S\text{-}TBSP)_4$	
$Rh_2(S\text{-}DOSP)_4$	



All ligands on Rhodium are bridging through the carboxylate or the amide

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 28

Ambiphilic Functional Groups–2
Hydrazone-Based Transformations

- Wolff-Kischner Reduction
- Wharton Rearrangement
- Eschenmoser-Tanabe Fragmentation
- Reduction of Tosyl Hydrazones: "The Alkene Walk"
- Tosyl Hydrazone-Based Fragment Coupling
- The Shapiro Reaction
- Bamford-Stevens Reaction

Reading Assignment for this Week:

Shapiro Reaction: Chamberlin, and Bloom. “Lithioalkenes from arylsulphonyl-hydrazones.” *Org. Reactions* **1990**, 39: 1. **(handout)**

Wolff-Kishner & Related Reactions: Hutchins, (**1991**). "Reduction of C=X to CH_2 by Wolff-Kishner and Other Hydrazone Methods". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 8: 327. **(in library)**

D. A. Evans

Friday,
November 21, 2003

Relevant Background Reading

Hutchins, R. O. (**1991**). "Reduction of C=X to CH_2 by Wolff-Kishner and Other Hydrazone Methods". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 8: 327.

Shapiro, R. H. (**1976**). “Alkenes from Tosylhydrazones.” *Org. React.* (N.Y.) 23: 405.

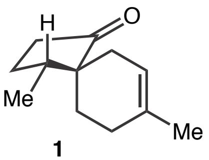
Addlington, R. M. and A. G. M. Barrett (**1983**). “Recent Applications of the Shapiro Reaction.” *Acc. Chem. Res*. 16: 55.

Chamberlin, and Bloom (**1990**). “Lithioalkenes from arylsulphonyl-hydrazones.” Org. React. (N.Y.) 39: 1.

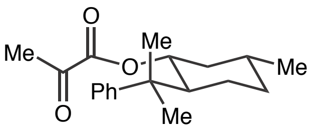
Bergbreiter, and Momongan (**1991**). "Hydrazone Anions". *Comprehensive Organic Synthesis.* Trost and Fleming. Oxford, Pergamon Press. 2: 503.

Cume Question, November, 2000

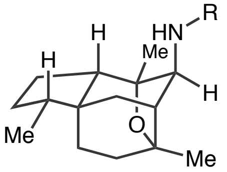
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS*. **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



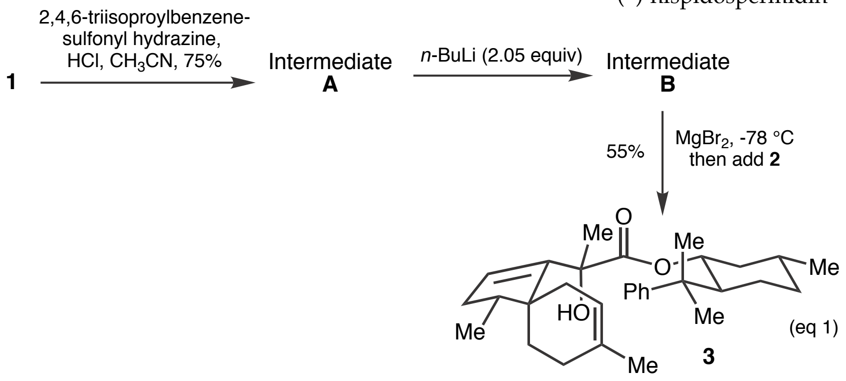
1



2

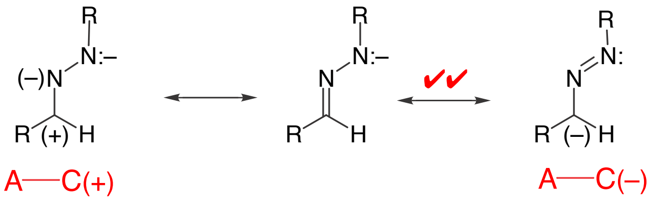


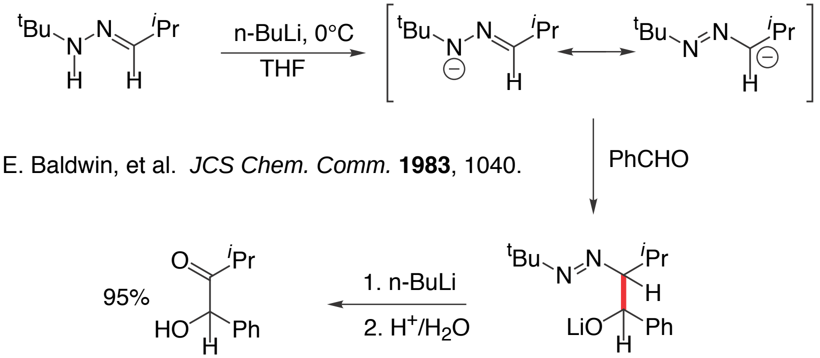
(–)-hispidospermidin



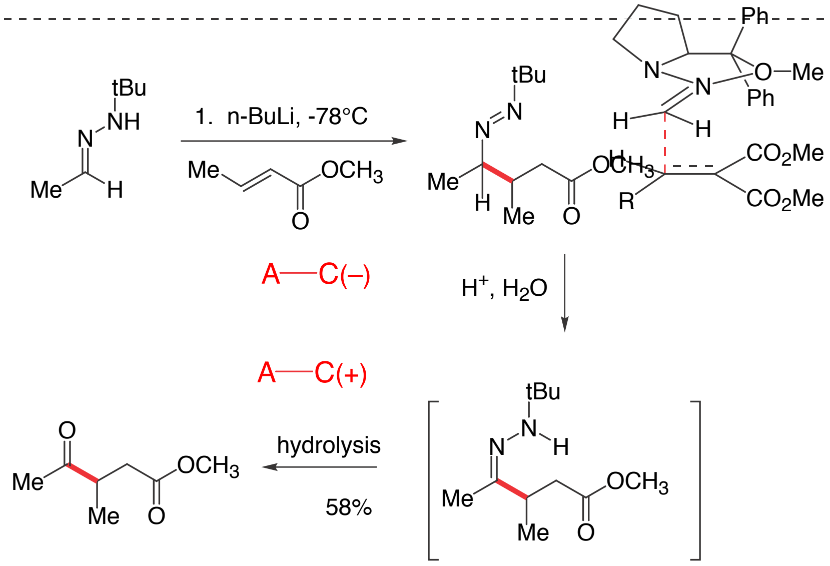
$$\mathbf{1}\xrightarrow[\text{HCl, } CH_3CN\text{, 75\%}]{\text{2,4,6-triisoproylbenzene-sulfonyl hydrazine,}}\text{Intermediate }\mathbf{A}\xrightarrow{n\text{-BuLi (2.05 equiv)}}\text{Intermediate }\mathbf{B}\xrightarrow[\text{55\%}]{MgBr_2\text{, -78 °C then add }\mathbf{2}}\mathbf{3}\quad\text{(eq 1)}$$

Hydrazone Anions: A useful Reversed Polarity Equivalent

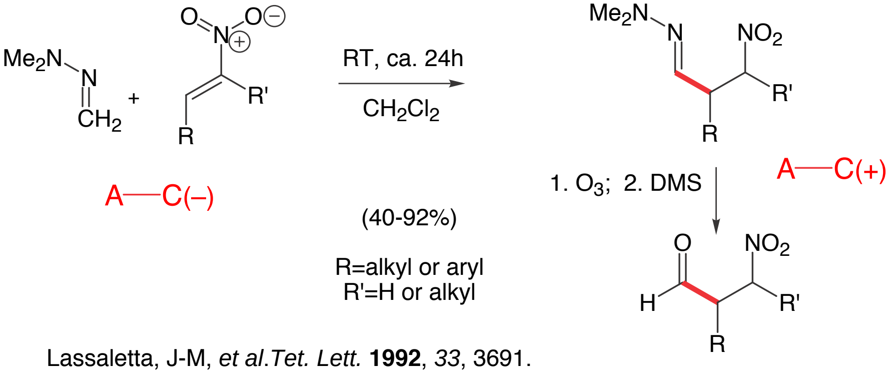




J. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.

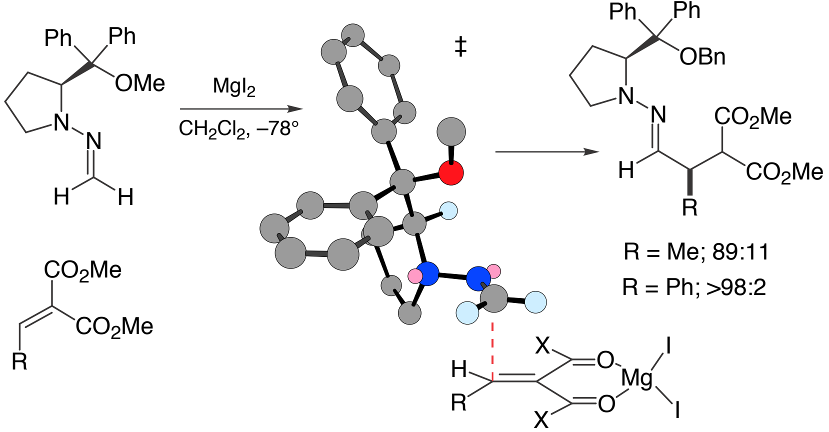


J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.

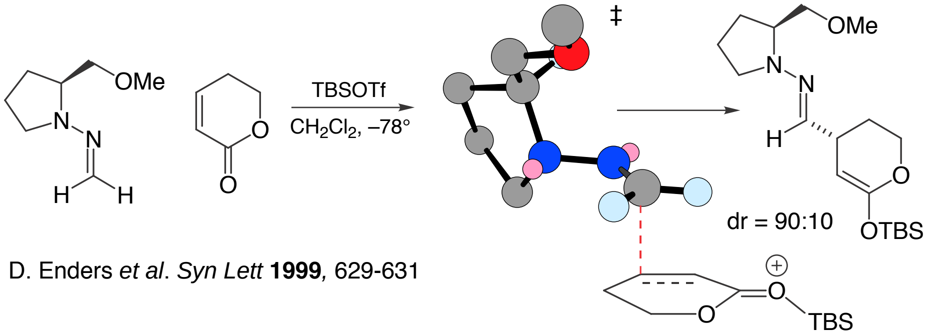


Lassaletta, J-M, *et al.Tet. Lett.* **1992**, *33*, 3691.

Chiral Hydrazones as Carbonyl Anion Equivalents

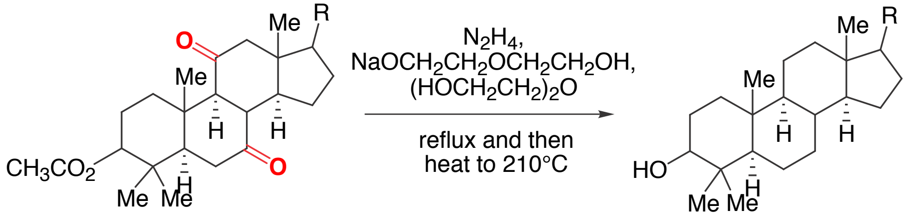


Lassaletta, J-M, *et al. Chem Commun* **2002**, 498-499



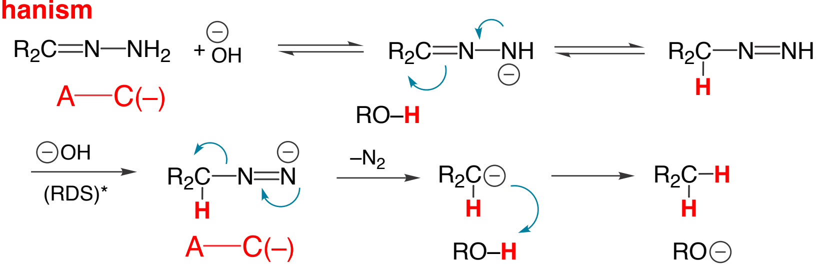
D. Enders *et al. Syn Lett* **1999**, 629-631

Wolff-Kishner Reduction

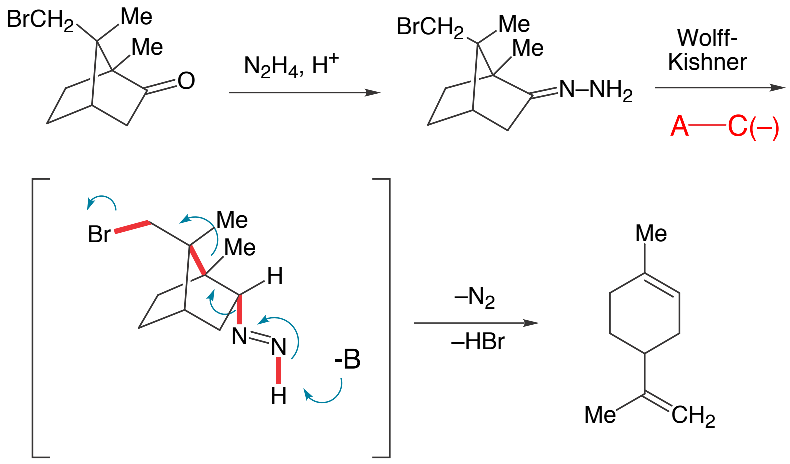


Barton, D. H. R., Ives, D. A. J., and Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.

Mechanism

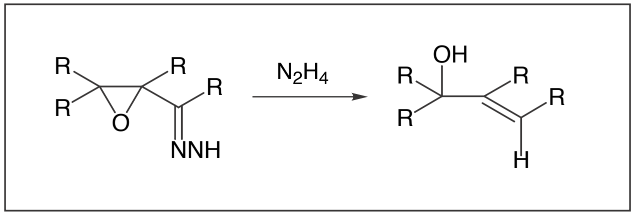


Elimination of α-Leaving Groups

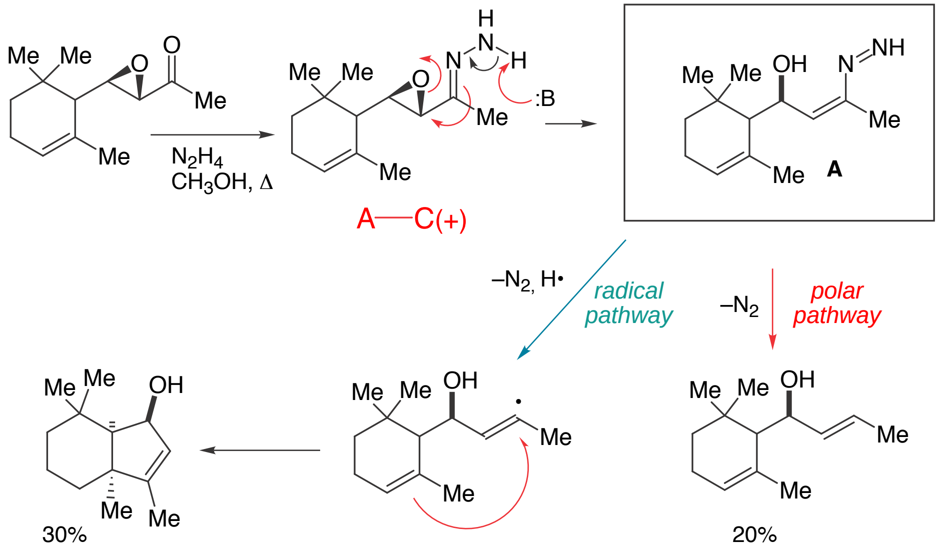


D. H. Gusyafson, W. F. Erman *J. Org. Chem.* **1965**, *30*, 1665.

The Wharton Rearrangement

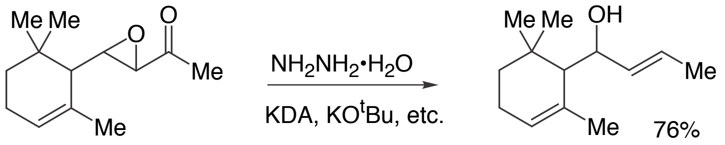


This example illustrates the 2 possible modes for the decomposition of **A**.



G. Stork et al. *JACS* **1977**, *99*, 7067.

Some procedural improvements:



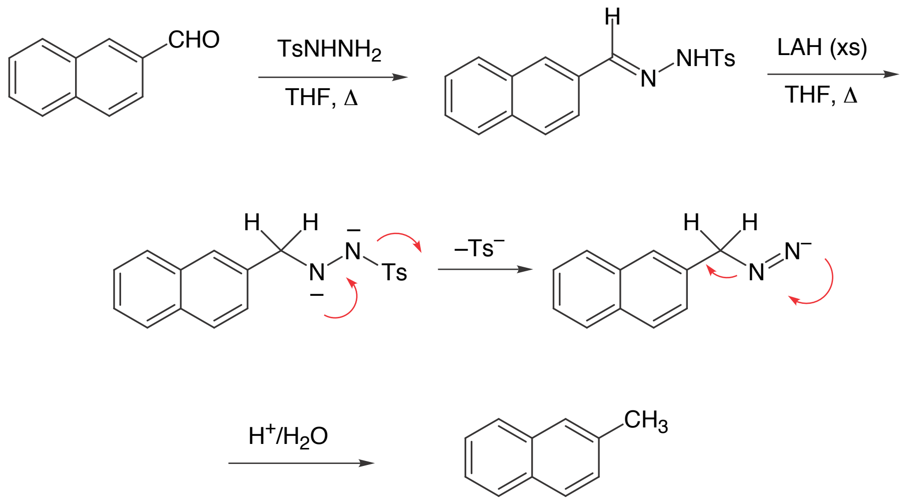
For stable hydrazones, strongly basic conditions favor the ionic pathway.

C. Dupuy, J. L. Luche *Tetrahedron Lett.* **1989**, *44*, 3437.

Tosylhydrazones – Better Than Hydrazones

Tosylhydrazones are isolable, stable, and easily prepared.

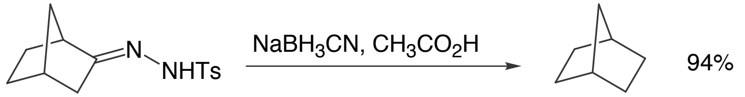
The presence of the tosyl leaving group strongly biases the system towards polar reaction pathways under hydridic reducing conditions.



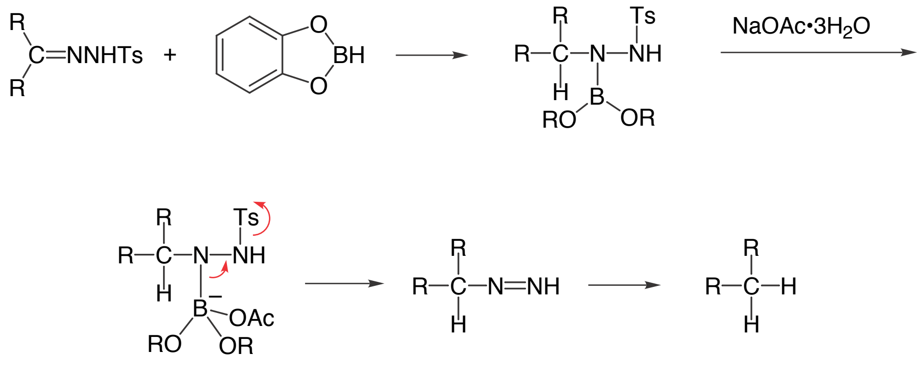
L. Caglioti, M. Magi *Tetrahedron* **1963**, *19*, 1127.

Further Refinements

Very mild reduction with $NaBH_3CN$ under slightly acidic conditions (pH 4-5).
No reduction in the absence of acid; carbonyl, nitro, nitrile FGs unaffected.
Aromatic, sterically hindered carbonyls very poor substrates.

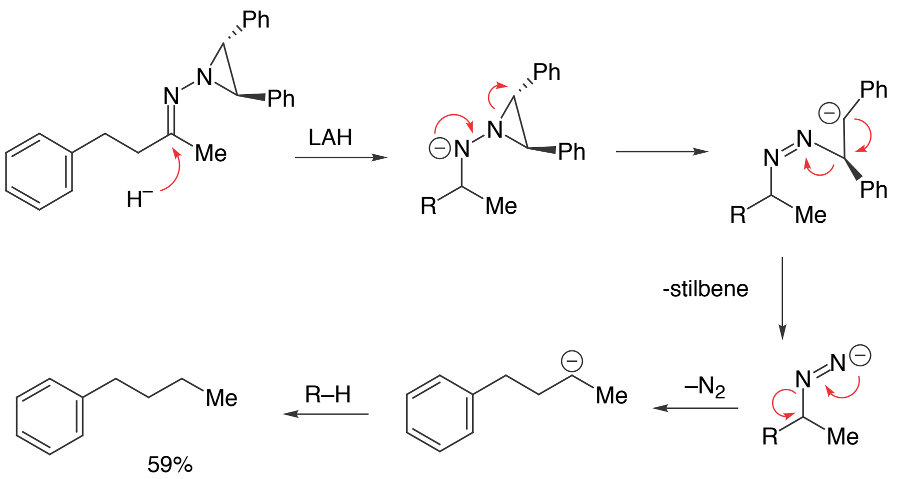


R. O. Hutchins, et al. *JACS* **1973**, *95,* 3662.



G. W. Kabalka, et al. *J. Org. Chem.* **1975**, *40,* 1834.

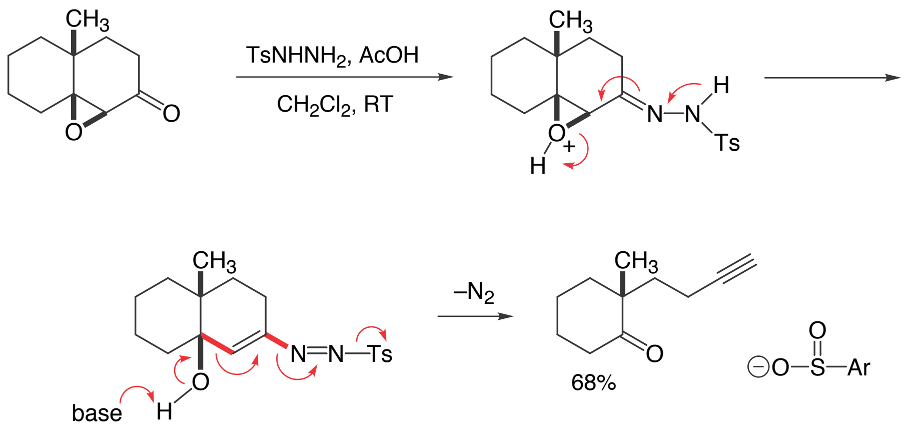
Another Interesting Leaving Group



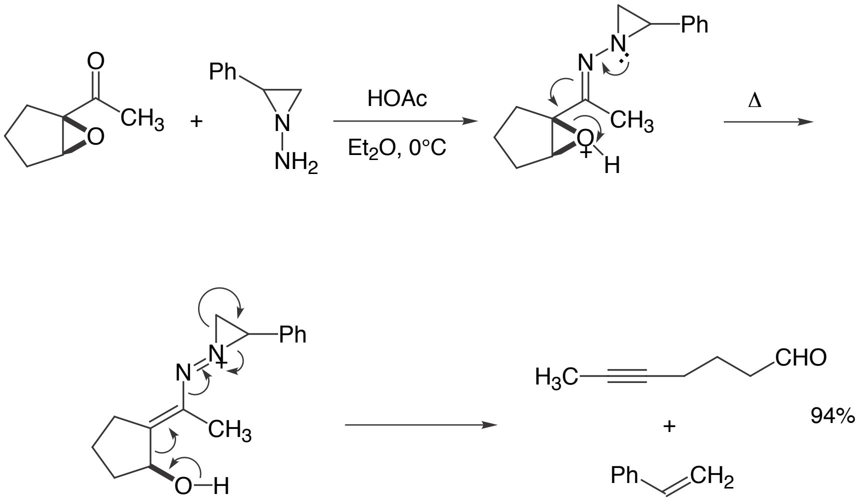
A. R. Chamberlin, et al. *Tetrahedron Lett.* **1991**, *32,* 1691.

Hydrazone Transformations-4

The Eschenmoser–Tanabe Fragmentation

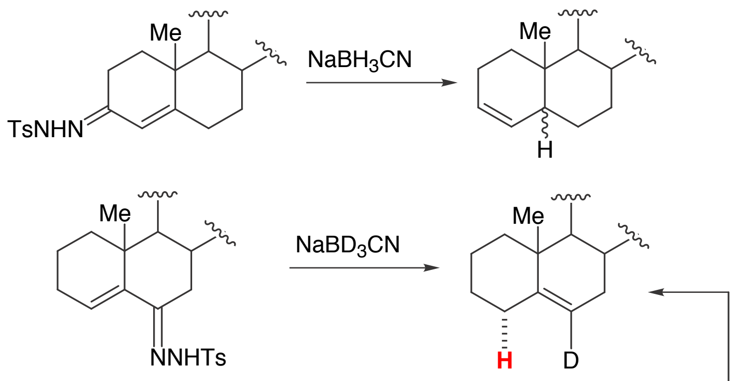


A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, *50,* 708.

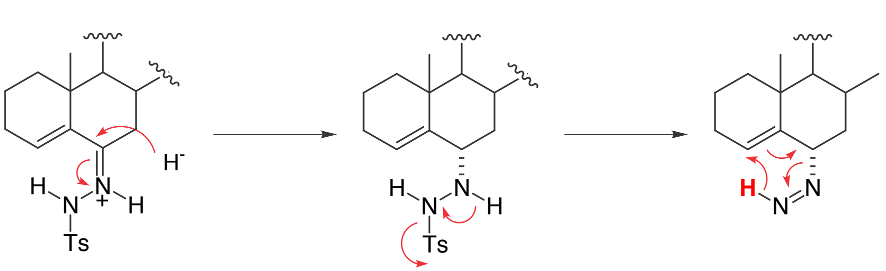


A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, *50,* 2108.

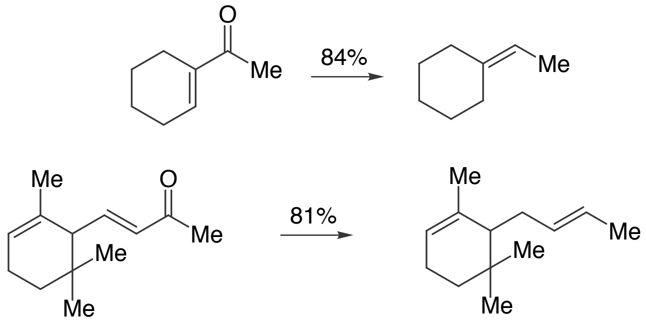
Tosylhydrazone Reductions: The Alkene Walk



C. Djerassi, et al. *JACS* **1976**, *98,* 2275.

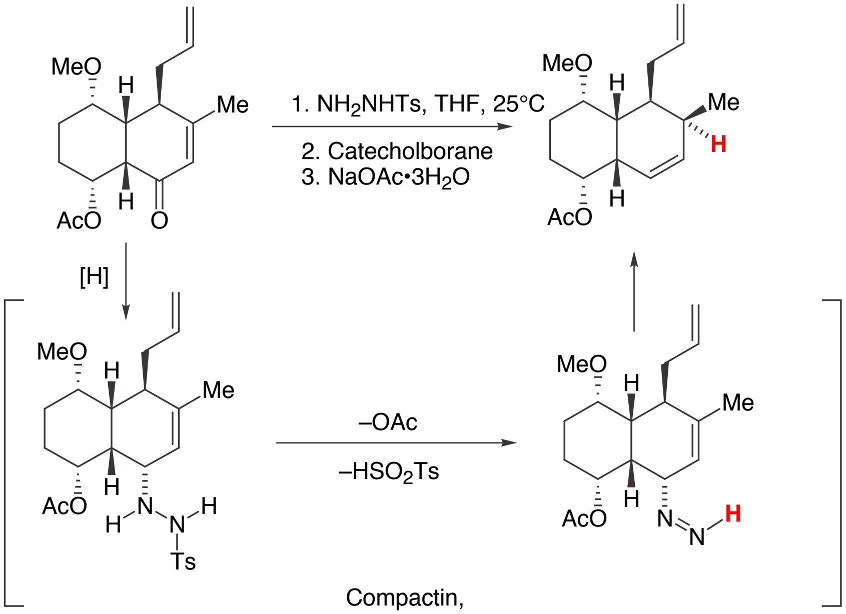


This has been developed into a reliable reduction



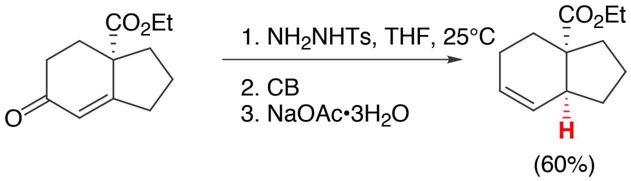
16 cases reported: Hutchins, et al. *JOC* **1975**, *40,* 923

Alkene Walk: Syntheses



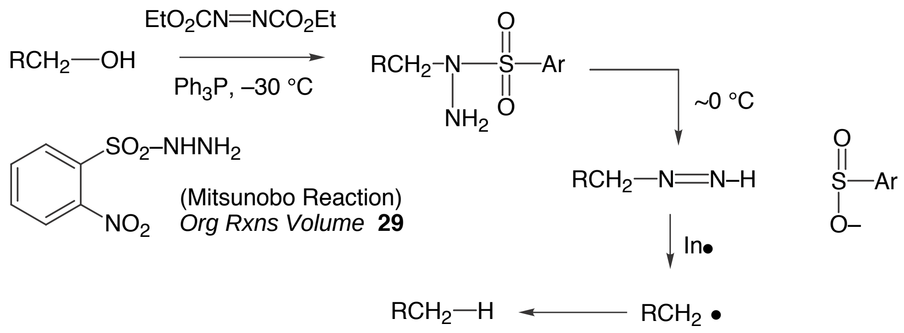
Compactin,
Wendler, N. L., *et al. Tet. Lett.* **1982**, *23,* 5501.

The stereochemical course of the hydrazone reduction may be stereospecifically transferred via the 1, 3-rearrangement

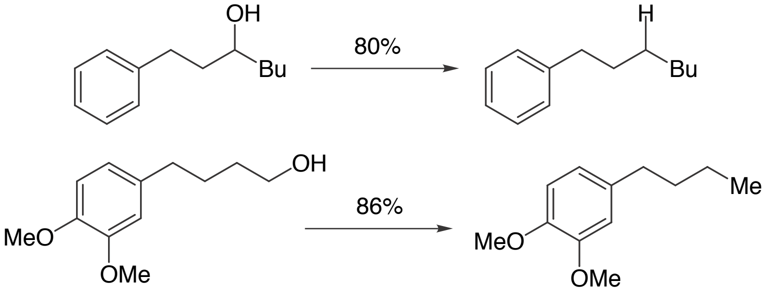


Topiramate,
Maryanoff, B. E., *et al. Tet. Lett.* **1992**, *33,* 5009.

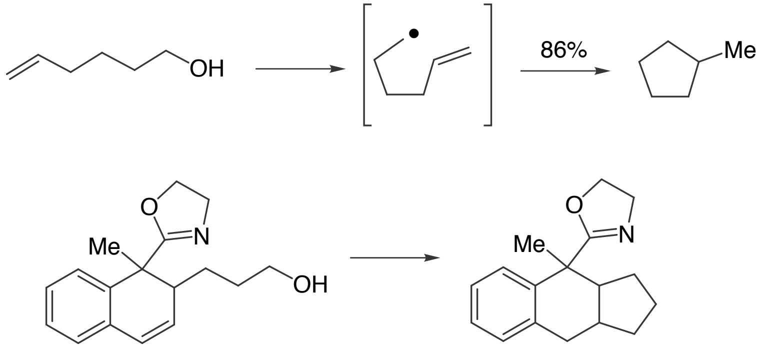
Sulfonylhydrazone Reductions: Alcohol Deoxygenation



(Mitsunobo Reaction)
Org Rxns Volume **29**

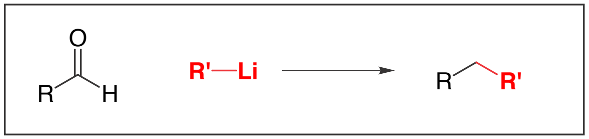


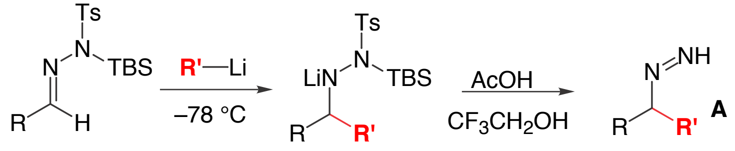
The intervention of radicals has been implicated (again):



10 cases reported: A. Myers, et al. *JACS* **1997**, *119,* 8572.

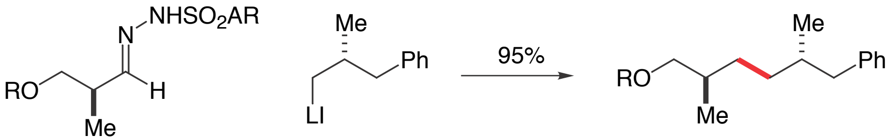
Tosylhydrazone-Based Fragment Coupling





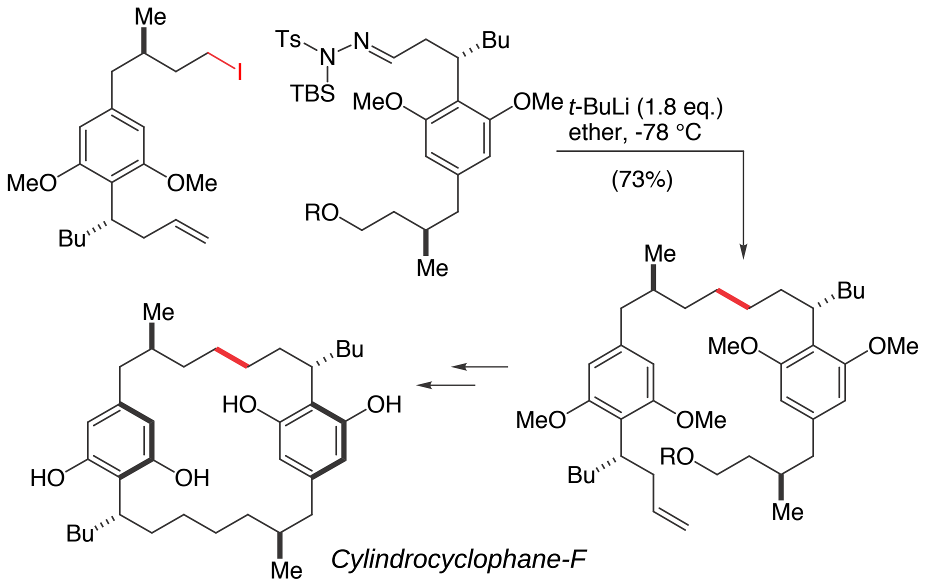
TBS = t-$BuMe_2Si$–

The monoalkyl azene **A** decomposes via a radical pathway



16 cases reported: A. G. Myers etal. *JACS*, **1998**, *120*, 8891.

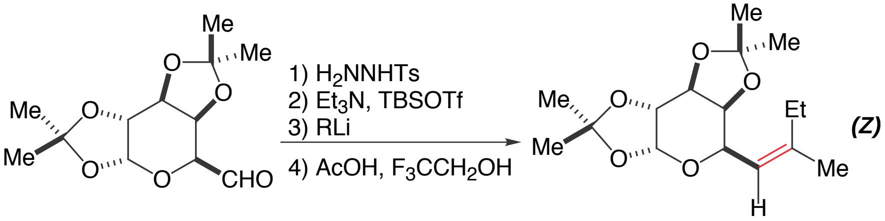
A Complex Application: A. Smith etal. *JACS* **1999**, *121*, 7423

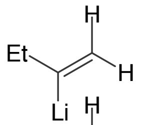
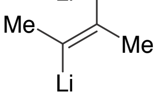


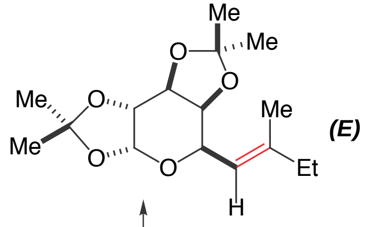
Cylindrocyclophane-F

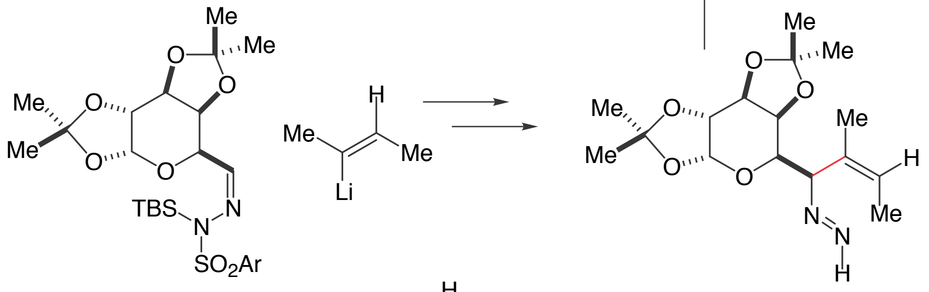
Stereoselective Construction of Trisubstituted Olefins

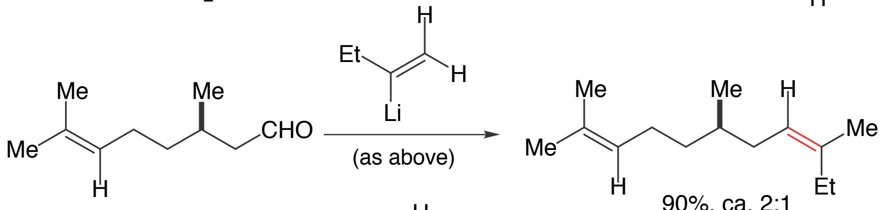
A. G. Myers, P. J. Kukkola *JACS*, **1990**, *112*, 8208.



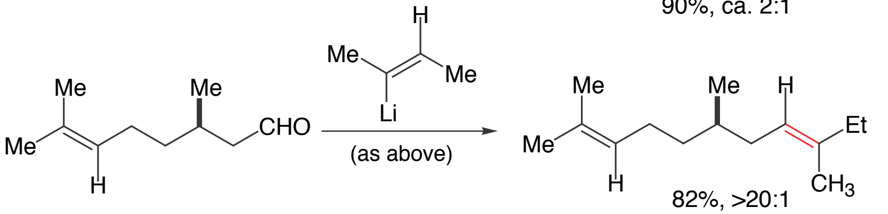
RLi	Ratio ***Z:E***	Yield
	50:50	79%
	<5:95	81%



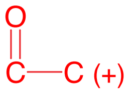




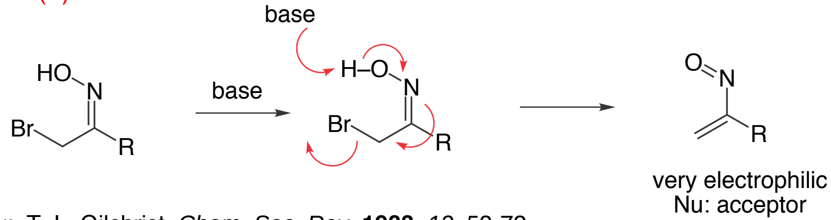
90%, ca. 2:1



82%, >20:1

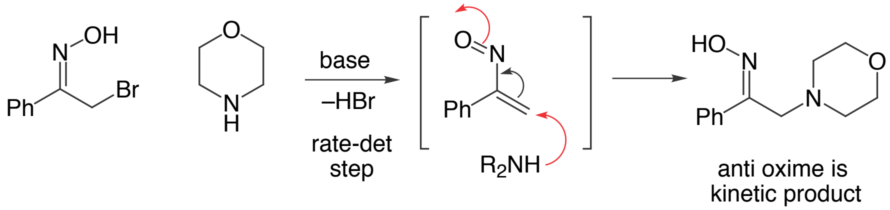


α-Keto Carbonium Ion Equivalents

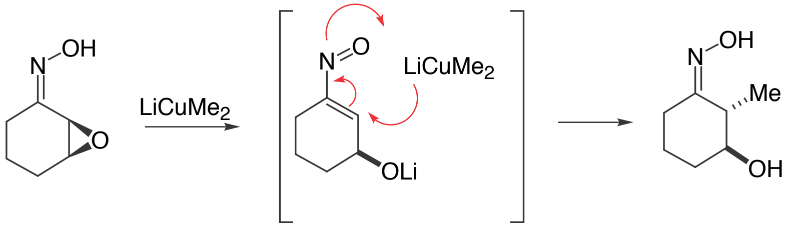


Review: T. L. Gilchrist, *Chem. Soc. Rev*. **1983**, *12*, 53-72

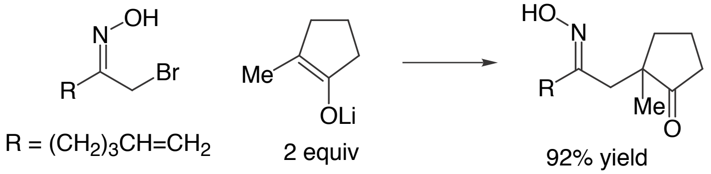
Reactions with Nucleophiles



T. Kaiser, *JACS*. **1972**, *94*, 9276-9277

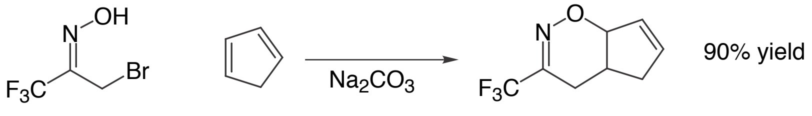


Corey, *Tetradedron Lett*. **1975**, 3117



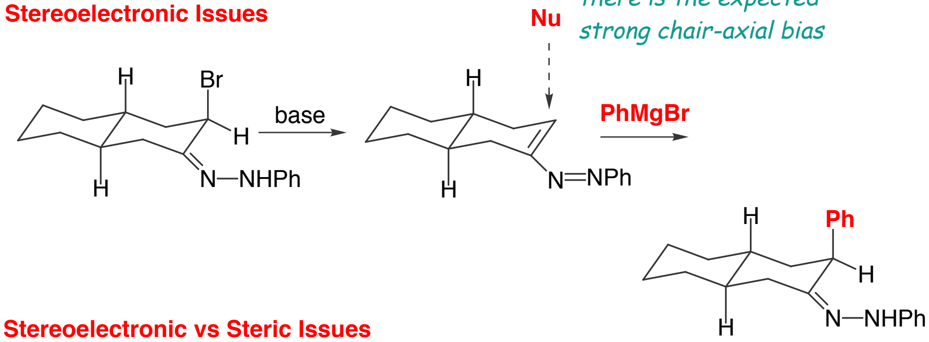
Corey, *Helv. Chem. Acta*. **1977**, *60*, 2964

Cycloadditions



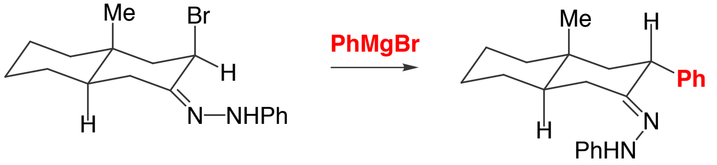
Ressig, *J. Org. Chem*. **1992**, *57*, 339

Stereoelectronic Issues

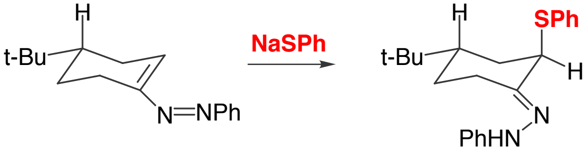


there is the expected strong chair-axial bias

Stereoelectronic vs Steric Issues

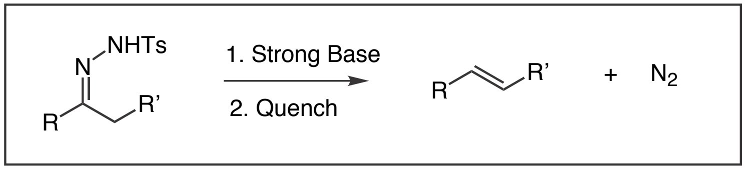


Bozzini, *Tetrahedron* **1982**, 38, 1459



there is the expected strong chair-axial bias

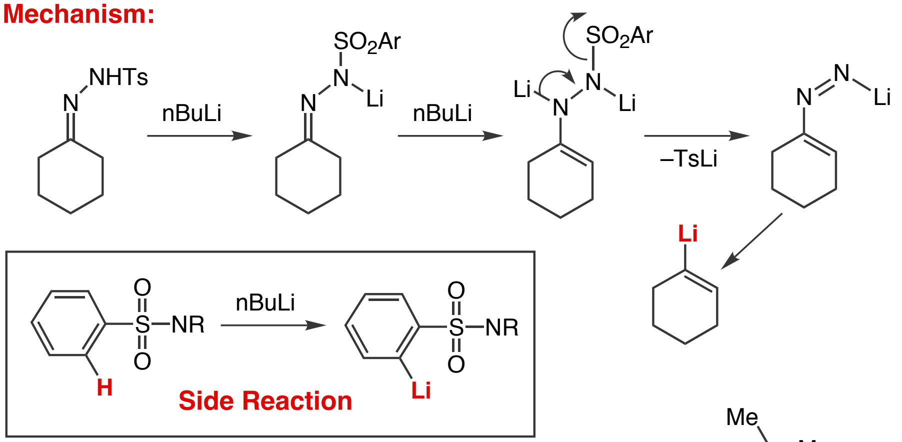
Bozzini, *Tetrahedron* **1982**, 39, 3413



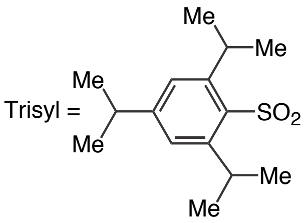
General Reviews:

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapters 4.3 .
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapters 4.6.
Shapiro, *Organic Reactions* **1976**, Vol 23, pp 405-507.

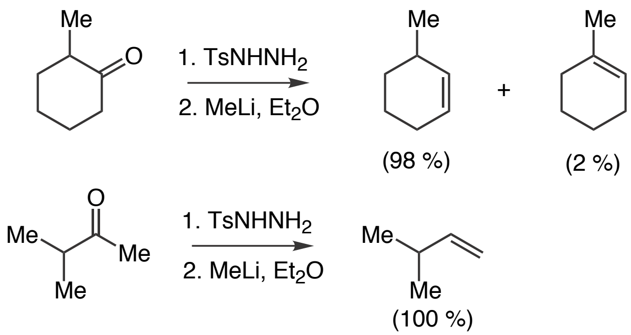
Mechanism:



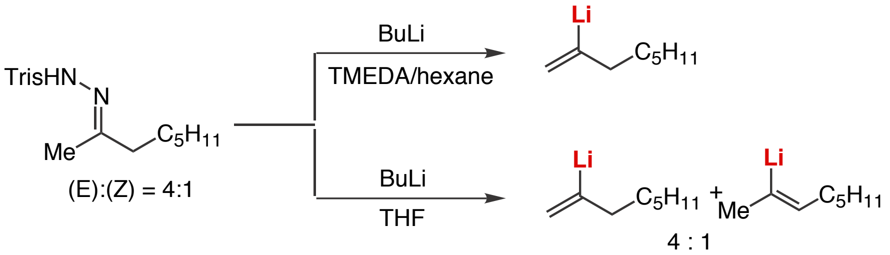
the Triisopropylsulfonyl (Trisyl) group is used (Roberts *Tet. Let.* **1981**, *22*, 4895).



Regiochemistry

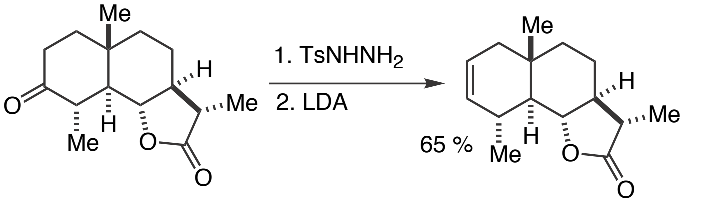


Deprotonation of the monoanion occurs predominantly at the kinetically more acidic site giving after elimination the less substituted alkene product.

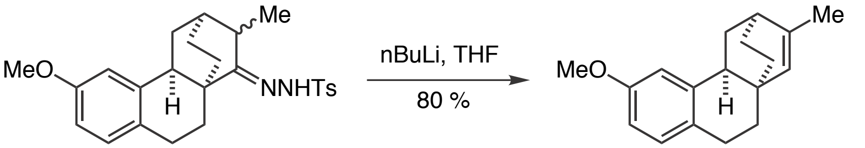


In THF solution regiochemical ratios generally reflect the starting hydrazone geometries

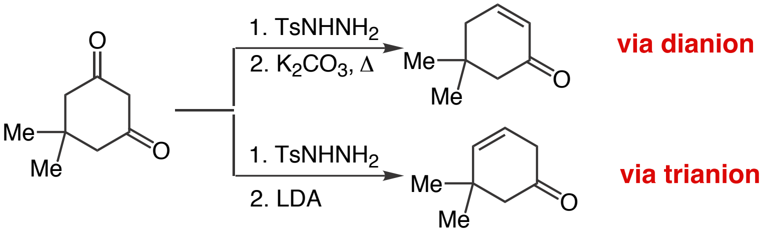
Bond *J. Org. Chem.* **1978**, *43,* 154.

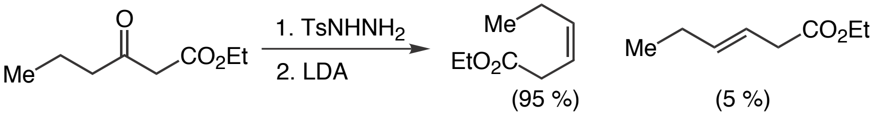


Grieco *J. Org. Chem.* **1977**, *42*, 1717.



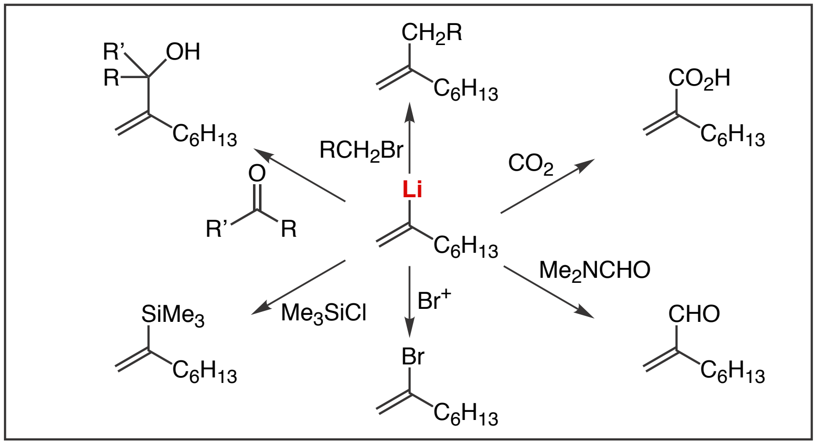
Nemoto *et. al. JCS, Perkin Trans. 1* **1985**, 927.

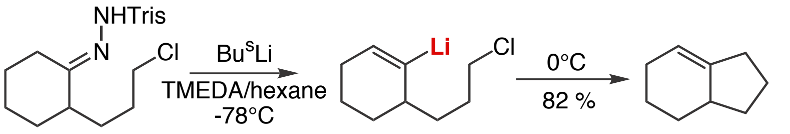




The Shapiro Reaction-2

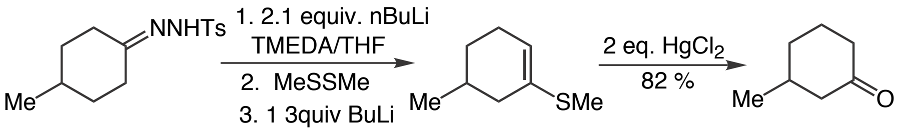
Trapping of the intermediate alkenyllithium





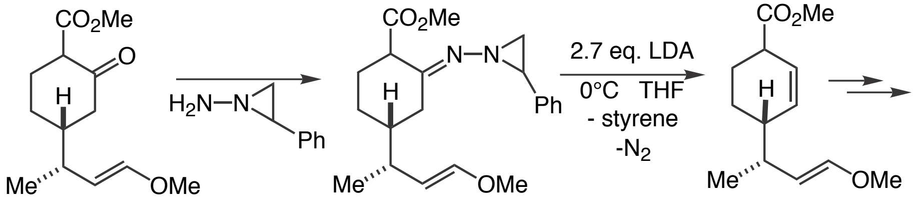
Bloom *Tet Lett.* ***1984***, *25*, 4901

Carbonyl Transposition

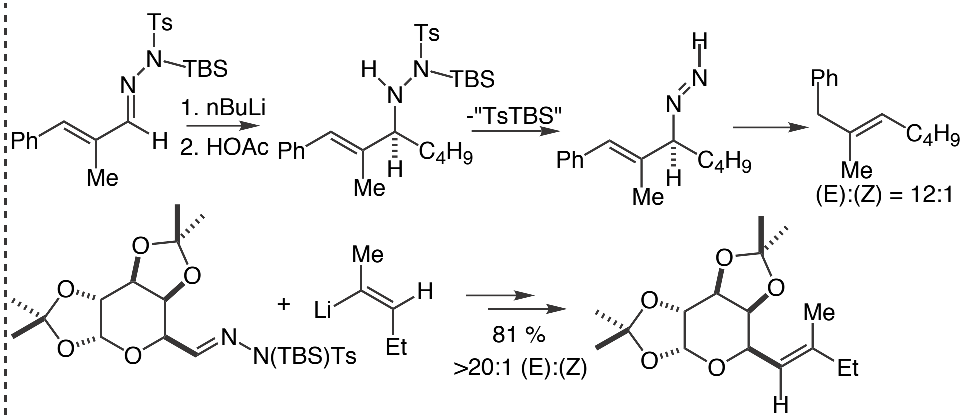


Nakai *Chem. Lett.* **1980**, 1099

Shapiro alternatives

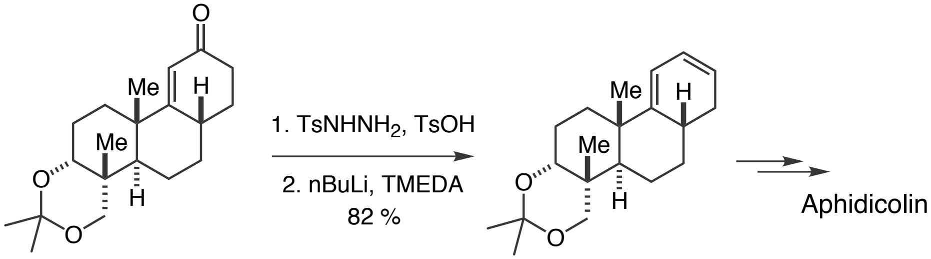


(Juvabione) Evans *J. Am. Chem. Soc.* **1980**, *102*, 774

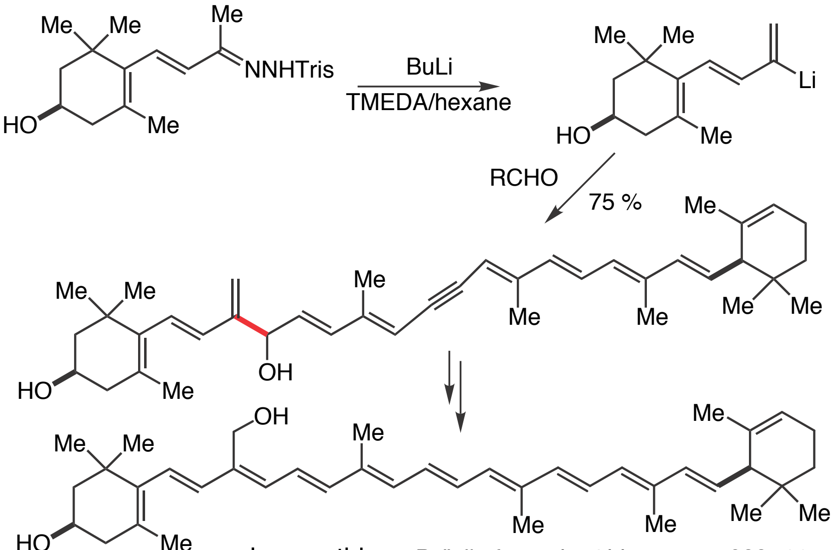


Myers, *J. Am. Chem. Soc.* **1990**, *112*, 8208

Applications



van Tamelen *J. Am. Chem. Soc.* **1983**, *105*, 142.

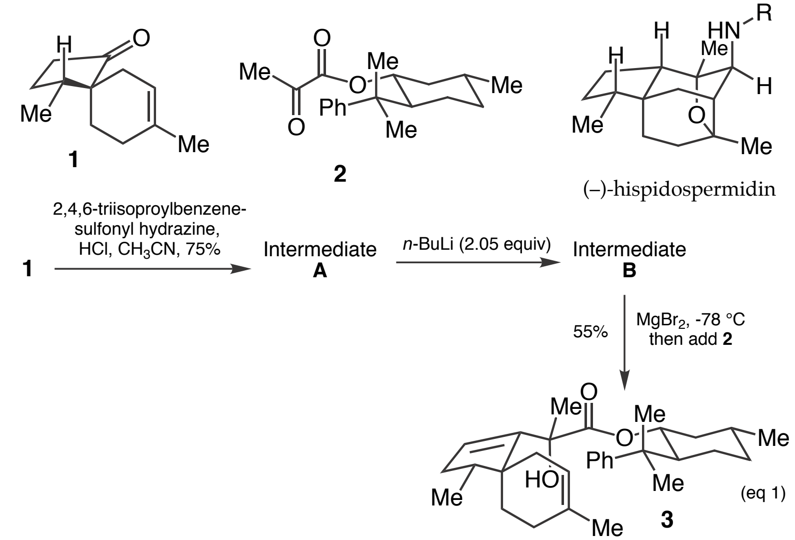


Ioroxanthin Baütikofer *Helv. Chim. Acta.* **1983**, *66*, 1148

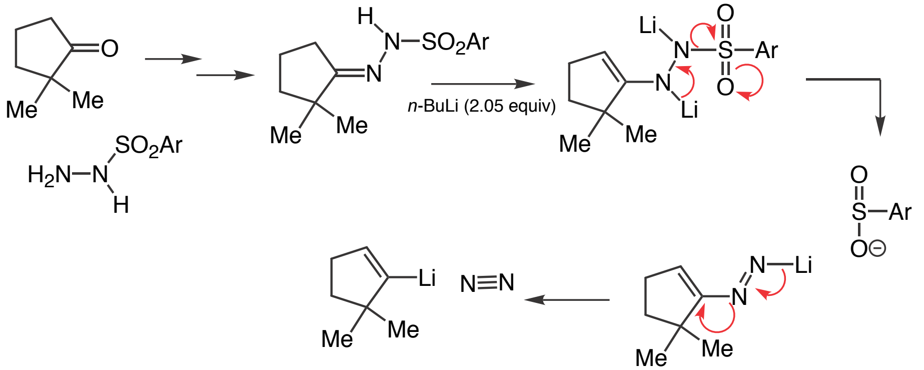
The Shapiro Reaction-Applications

A Recent Aplication of the Shapiro Reaction

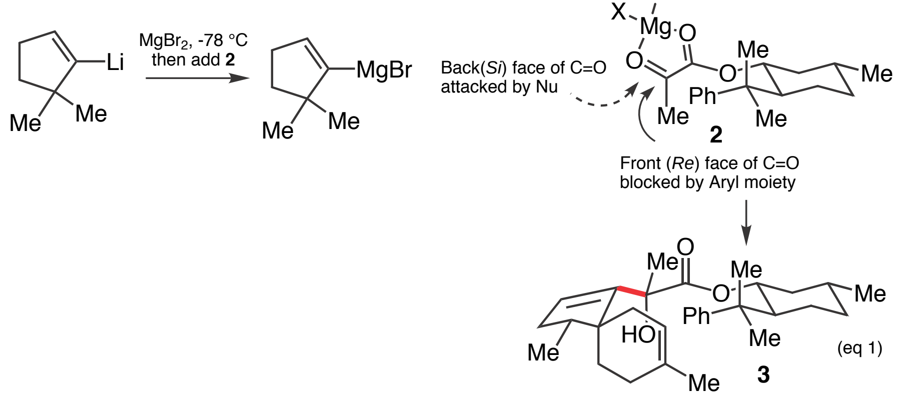
Web Problem 24. Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS.* **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



Part A (8 points). Provide a mechanism for the **Shapiro Reaction** of **1** to intermediate **B** in the space below. Feel free to use a simplified analog of **1** such as 2,2-dimethylcyclopentanone to answer this question.

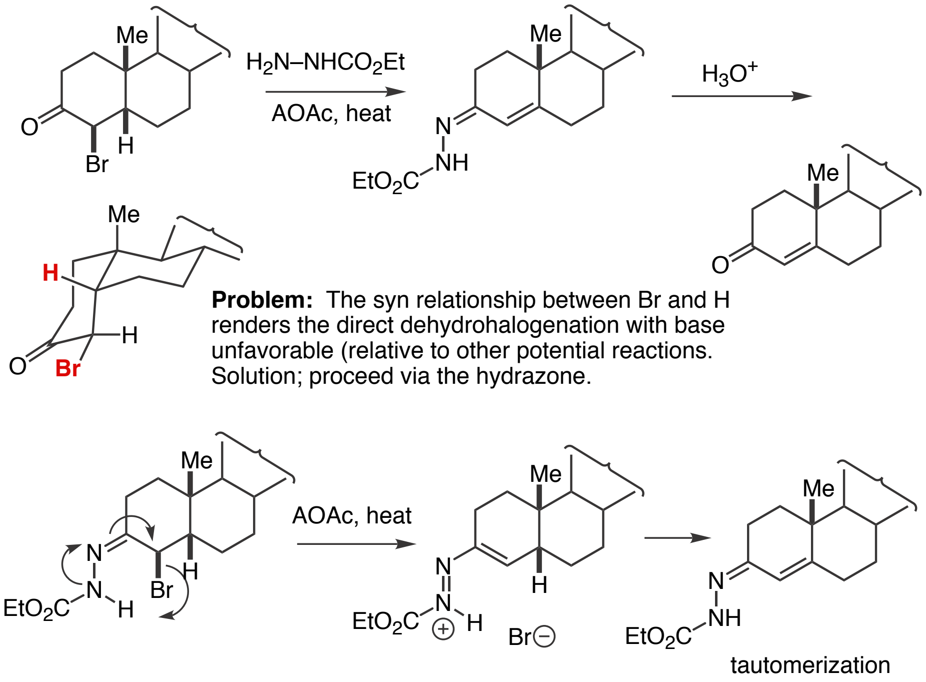


Part B (7 points). Provide a mechanism for the **transformation** of intermediate **B** to the illustrated product **3**. Use 3-dimensional representations to illustrate the stereochemical aspects of this individual step.



Li
Me
Me
$MgBr_2$, -78 °C then add 2
MgBr
Me
Me
Back(Si) face of C=O attacked by Nu
X
X
Mg
O
O
O
Me
Me
Ph
Me
Me
2
Front (Re) face of C=O blocked by Aryl moiety
Me
O
Me
O
Me
Ph
Me
Me
HO
Me
3
(eq 1)

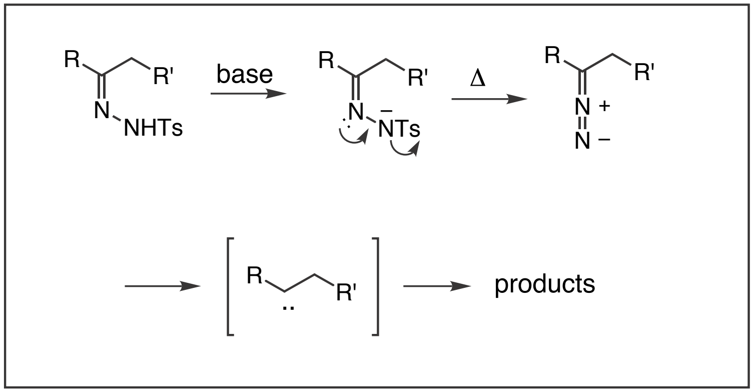
Mattox-Kendall Dehydrohalogenation (Paquette, *Reagents*, Vol 5, p 3509)



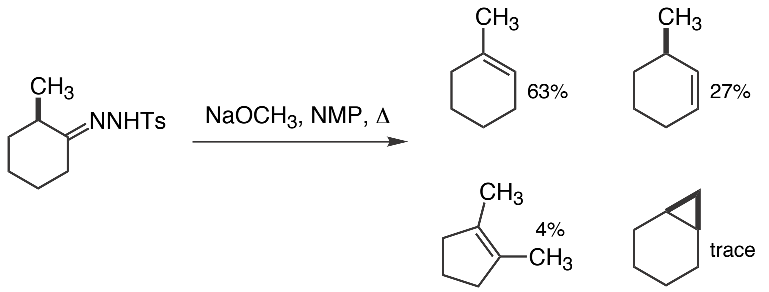
Problem: The syn relationship between Br and H renders the direct dehydrohalogenation with base unfavorable (relative to other potential reactions. Solution; proceed via the hydrazone.

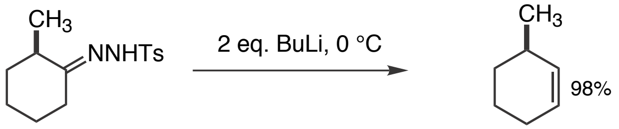
The Bamford-Stevens Reaction

An Alternate Decomposition Pathway for Tosyl Hydrazones

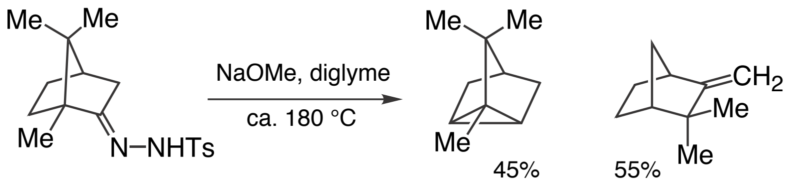


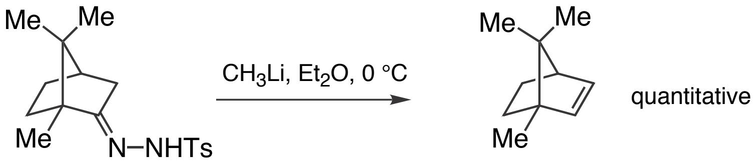
Bamford-Stevens vs. Shapiro



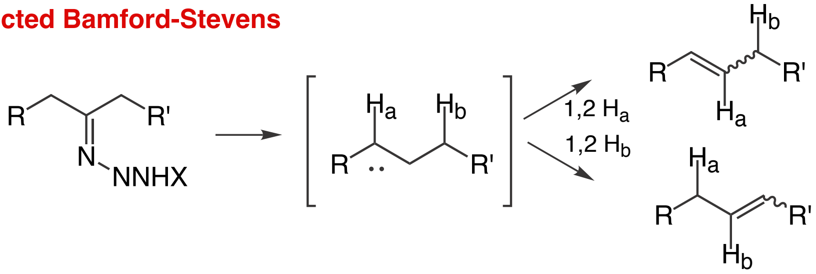


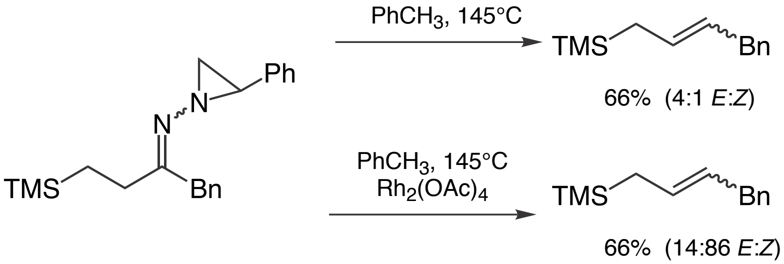
R. H. Shapiro *Org. React.* **1976**, *23*, 405.





Directed Bamford-Stevens





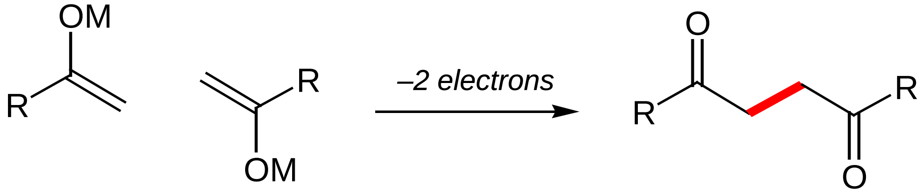
T. K. Sarkar, et al. *JCS Chem. Comm.* **1992**, 1184.

Chemistry 206

Advanced Organic Chemistry

Handout–28A

*O*xidative Coupling of Enolates & Enol Derivatives



Chuck Scales

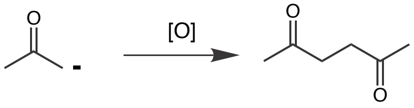
Evans Group Seminar, March, 1995

D. A. Evans

Friday ,
November 21, 2003

The Oxidative Coupling of Enolates and Enol Derivatives

Evans Research Seminars
March 14, 1995



An underappreciated umpolung of enolates

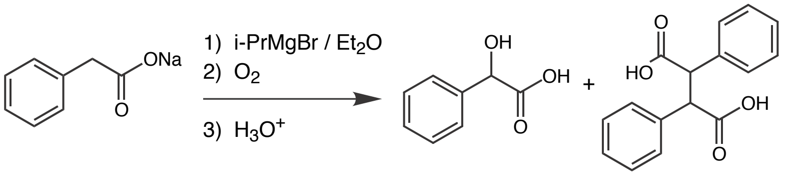
1. Ketone Enolates
2. Ester Enolates
3. Carboxylic Acid Dianions
4. Silyl Enolate Derivates
5. Applications to Organic Synthesis

Leading Papers:
Saegusa, T. *JACS*, **1977**, *99*, 1487
Fox, M.A. *JOC*, **1988**, *53*, 3745
Narasaka, K. *Chem. Letters*, **1992**, 2099

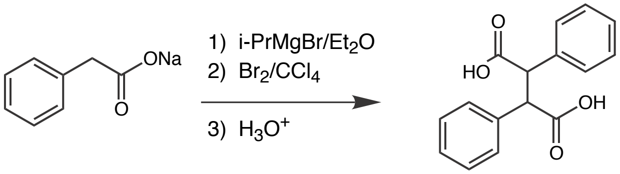
Chuck Scales

Reaction Background

Synthesis of 3,4-diphenyl succinic acid



38% 12%

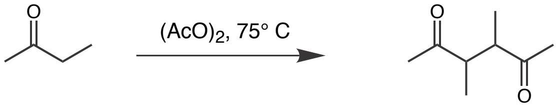


22%

- Also obtained a "high" yield of a-bromophenylacetic acid
- Proposed radical dimerization as mechanism for production of β-diphenylsuccinic acid.

Ivanoff, *Bull. Soc. Chem. Fr.*, **1935**, *2*, 76

Synthesis of 1,4 Diketones

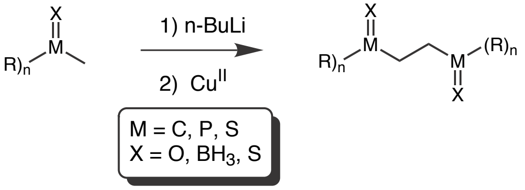


52%

Kharasch, M.S., McBay, H.C., and Urry, W.H., *JACS*, **1948**, *70*, 1269

Reaction Background

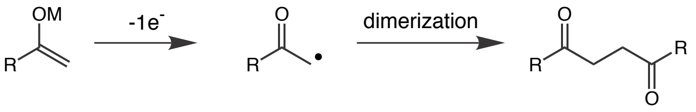
Coupling of Stabilized Anions



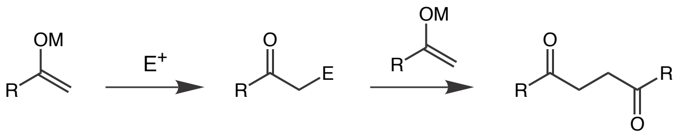
Mislow, K. *JACS*, **1973**, *95*, 5839
Tamaru, Y. *JACS*, **1978**, *100*, 1923
A. Muci and K. Campos, unpublished results

Anion Coupling Models

- Type 1 Oxidants

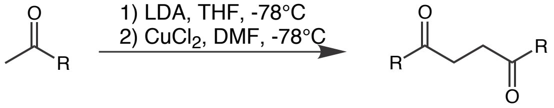


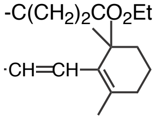
- Type 2 Oxidants



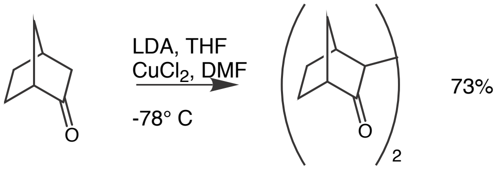
Synthesis of 1,4-Diketones

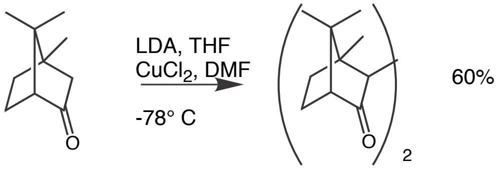
Methyl Ketone Dimerization



R	Yield
phenyl	95%
ferrocenyl	78%
furanyl	41%
cyclopropyl	46%
$-C(CH_2)_2CO_2Et$	64%
	82%

α-Substituted Ketone Dimerization



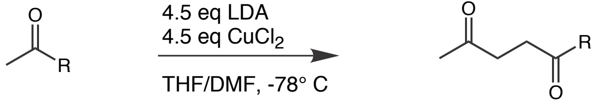


- Product mixture of exo-exo, exo-endo, and endo-endo isomers

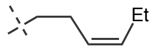
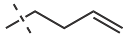
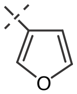
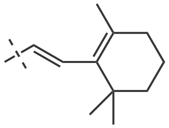
Saegusa, *JACS* **1977**, *99*, 1487

Synthesis of 1,4-Diketones

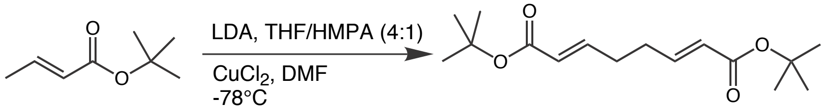
Cross-Coupling of Methyl Ketones



3 eq acetone
4.5 eq LDA
4.5 eq $CuCl_2$
THF/DMF, -78° C

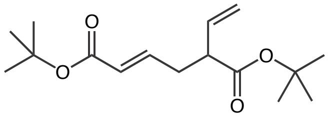
	Yield	
R	Cross-couple	Dimer
	68%	1%
	53%	1%
	59%	4%
	65%	2%

γ Coupling of α,β-unsaturated ketones



LDA, THF/HMPA (4:1)
$CuCl_2$, DMF
-78°C

33% γ,γ coupling product



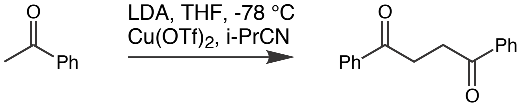
32% α,γ coupling product

- No α,α coupling product seen
- γ,γ couple not produced from thermal rearrangment of α,α product

Saegusa, T. et al. *JACS* **1977**, *99*, 1487

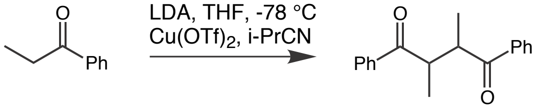
1,4-Diketones with Copper (II) Triflate

From enolates



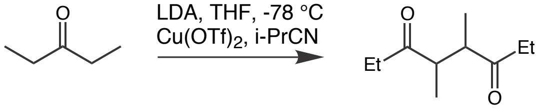
LDA, THF, -78 °C
Cu(OTf)$_2$, i-PrCN

83%



LDA, THF, -78 °C
Cu(OTf)$_2$, i-PrCN

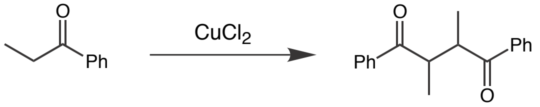
80%



LDA, THF, -78 °C
Cu(OTf)$_2$, i-PrCN

63%

Anions Make a Difference



$CuCl_2$

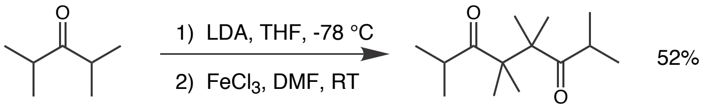
28%

- Yield difference may be due to lability of triflate versus chloride ions

Kobayashi, et al. *TL*, **18**, 3741 (1977)
Kobayashi, et al. *Chem. Pharm. Bull.*, **28**, 262 (1980)

Coupling of Ketone Enolates

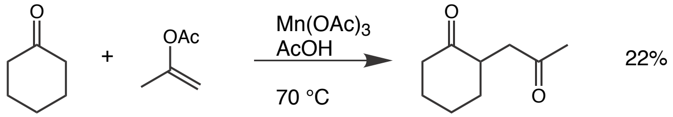
Oxidative Coupling with Ferric Chloride



- Dimers obtained from hindered enolates in moderate yields (40-60%)
- Prepared from kinetic and thermodynamic enolates

Frazier, R.H. et al. *JOC*, **1980**, *45*, 5408

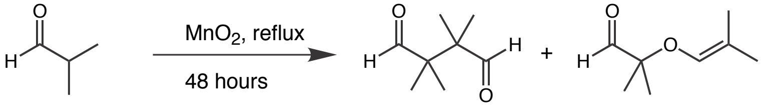
Oxidation with Manganic Acetate



- Proposed radical coupling mechanism for transformation

Dessau, R.M. et al. *JOC*, **1974**, *39*, 3457

Oxidative Dimerization of Aldehydes

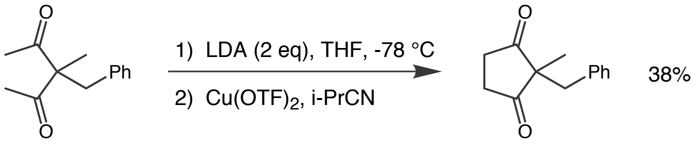


- All examples produced ca 80% yield of dimer in 45:55 ratio (C-C:C-O).

Leffingwell, J.C. *JCS Chem. Comm.*, **1970**, 357

Intramolecular Coupling

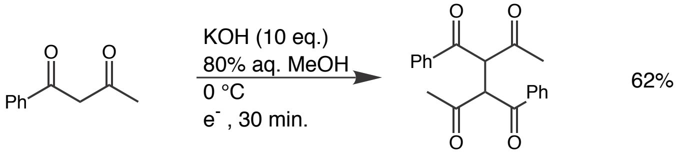
Ketone cyclization



- Generally poor yields; spirocyclic examples included.

Kobayashi, et al. *TL*, **1978**, *19*, 3555

Tetraketone Synthesis



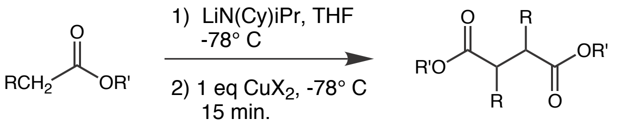
- Synthesized various aryl substituted 3,4-aroyl-2,5-hexanediones
- Observed that EDG favor oxidation and EWG disfavor oxidation (correlated to Hammett plot)

Hammett Plot Here

Lacan, M. et al. *Croat. Chem. Acta*, **1973**, *45*, 465

Ester Enolate Coupling

Synthesis of Succinate Esters



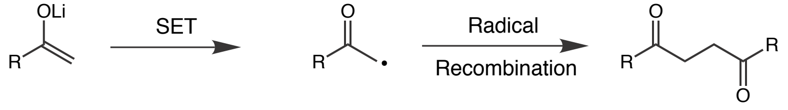
		Yield	
R	R'	$CuBr_2$	$Cu(O_2C_5H_9)_2$
-H	-t-Bu	85	95
-Me	-Et	81	50
-n-Bu	-Et	63	----
$-Me_2$	-Et	25	20
-i-Pr	-Et	20	20
-Ph	-Et	75	60

- Increasing alkyl substitution decreases yield of dimer
- Yield of a-bromoester increased with increasing alkyl substitution when copper (II) bromide used as oxidizing agent
- Yield of dimer not increased with copper (II) valerate
- Product obtained as an unspecified mixture of stereoisomers

Rathke, *J. Am. Chem. Soc.* **1971**, *93*, 4605

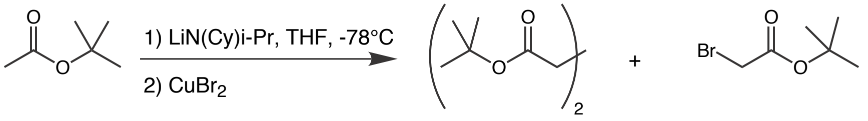
Oxidative Coupling Mechanism

Proposed Mechanism



- Radical may be associated with oxidizing agent

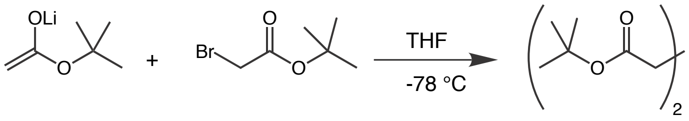
Evidence for Radical Mechanism



85%

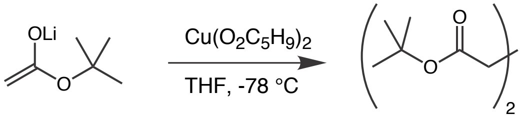
"minor side product"

- Investigation of possible S_N2 mechanism



10%

- Exclusion of bromide source also leads to product

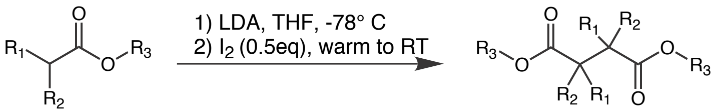


95%

Rathke, *J. Am. Chem. Soc.* **1971**, *93*, 4605

Succinate Esters with Other Oxidants

Oxidation with Iodine

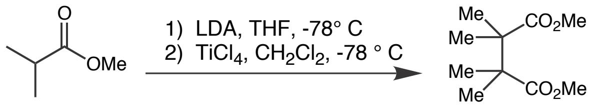


R_1	R_2	R_3	Yield
H	H	t-Bu	97%
Me	H	t-Bu	80%
Me	Me	Me	90%
Me	Me	Et	85%

- Authors propose an S_N2 mechanism for this transformation

Brocksom, T.J., et al. *Synthesis* **1987**, 396

Oxidation with $TiCl_4$



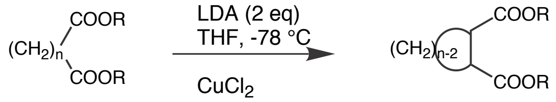
80 %

- Excellent yields with α-substituted esters (i-Pr, BnO)
- Other Lewis acids ($BF_3{\cdot}OEt_2$, $SnCl_4$) do not promote oxidation
- $ZrCl_4$ resulted in Claisen condensation products
- Not applicable for ketones or amides

Ojima, et al. *Chem. Letters* **1992**, 1591

Intramolecular Coupling

Ester cyclization

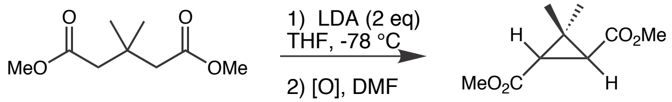


n	R	Yield
3	Me	88% (3:1 cis:trans)[a]
4	t-Bu	20% (undetermined mixture of stereoisomers)[b]
5	t-Bu	>50% (undetermined mixture of stereoisomers)[b]
6	Me	93% (0.6:1 cis:trans)[a]

- Equilibration between cis and trans isomers noted for all reactions.
- Dimethyl adipate and dimethyl pimelate gave exclusively Dieckmann cyclization under the reaction conditions.

[a] Chung, S.K. et al. *JOC*, **1983**, *48*, 1125
[b] Babler, J.H. et al. *JOC*, **1987**, *52*, 3462

Oxidation of dimethyl β,β-dimethylglutarate



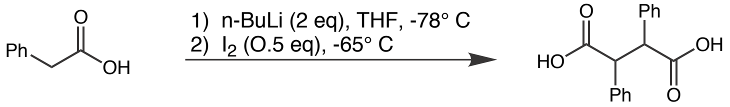
Oxidant	Temp.	Yield	cis:trans
$CuCl_2$	-78	71%	57:43
$CuCl_2$	0	83%	68:32
I_2	-78	76%	19:81
AgCl	-78	81%	80:20

- No attempt to rationalize stereochemical outcome of reaction

Babler, J.H. et al. *Synth. Comm.*, **1983**, *13*, 905

Carboxylic Acid Dianion Coupling

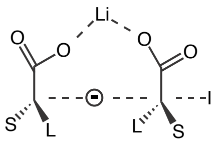
Coupling of Acid Dianions



90%, 11:1 dl:meso

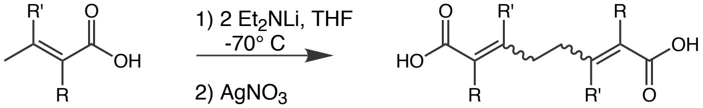
- Yields increased with dianion salt isolation

Stereochemical Model

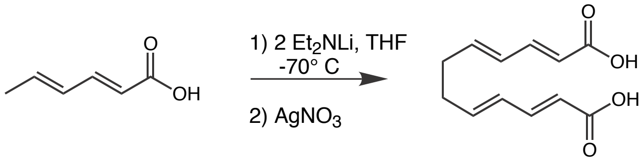


Belletire, J.L. et al. *TL*, **1984**, ***25***, 5969

γ Coupling of α,β-Unsaturated Carboxylic Acids



R	R'	Yield	E,E:E,Z:Z,Z
H	H	49	1:0:0
Me	H	63%	1:0:0
H	Me	38%	1:1:1
Me	Me	61%	7:3:0



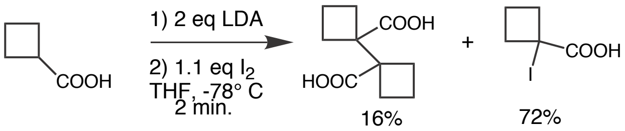
31%, E,E only

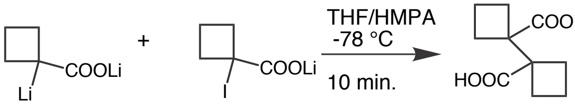
- No rational for observed stereochemistry
- Also observed unspecified yields of γ,α coupled product

Mestres, R. *TL*, **1988**, *29*, 6181

Iodine Oxidation Mechanism

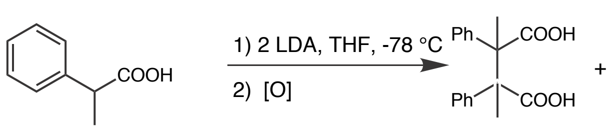
Mechanistic Investigations



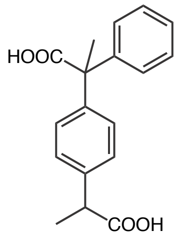


<10%

- "Dimerization reaction is much faster than nucleophilic substitution under the reaction conditions."



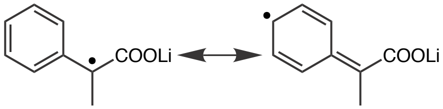
1



2

[O]	1	2
e^-	16	40
I_2	23	38

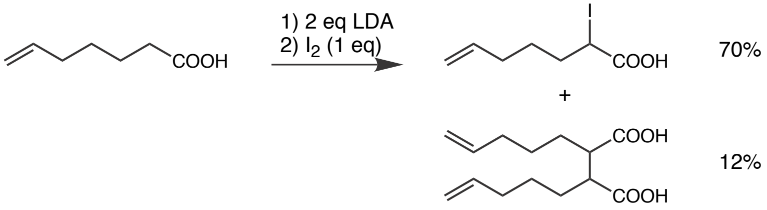
- Formation of α,para coupling product **2** supports radical anion intermediate

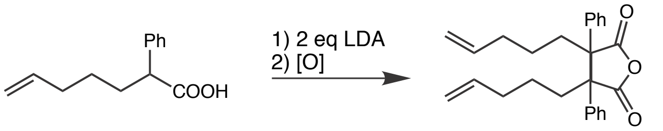


Fox, M.A. et al. *JACS* **1988**, *53*, 3745

Iodine Oxidation Mechanism

5-Hexenyl Radical Trap

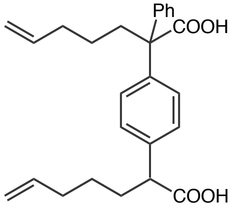




1

+

[O]	1	2
I_2	26%	32%
e^-	8%	36%

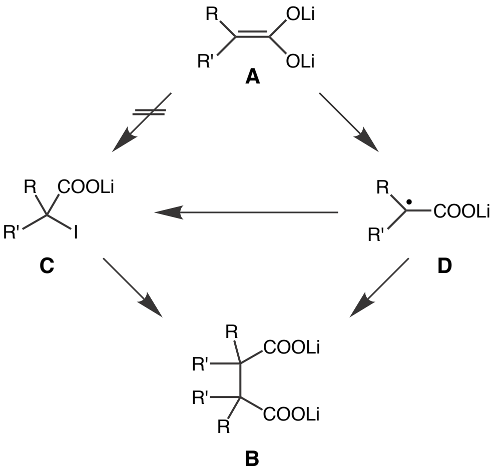


2

No cyclopentylmethyl products seen!

Fox, M.A. et al. *JACS* **1988**, *53*, 3745

Mechanism for Iodine Promoted Coupling

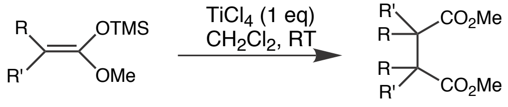


- Proposed initial step is SET to form radical anion (**D**).
- Radical anion (**D**) may iodinate, then form dimer (**B**) via S_N2 reaction
- Radical anion may form dimer directly, especially if R and R' are large (>H)
- Direct iodination of dianion neither supported or excluded by experiments

Fox, M.A. et al. *JACS* **1988**, *53*, 3745

Silyl Ketene Acetal Dimerization

Silyl Ketene Acetals

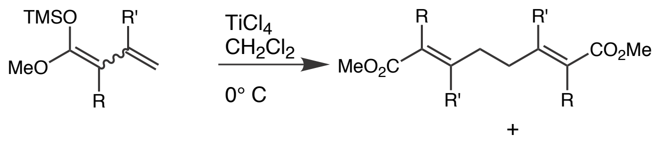


R	R'	Yield
H	Me	79%[a]
H	i-Pr	62%[b]
H	t-Bu	72%[b]
H	Cy	57%[b]
H	Ph	73%[a]
Me	Me	80%[a], 93%[b]
Et	Et	67%[b]

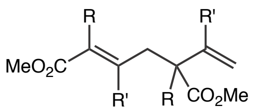
- No Claisen type products observed
- SET (Ti^{IV} --> Ti^{III}) followed by radical coupling mechanism proposed by both authors
- Other reagents (Cu^{II} salts, $FeCl_3$) ineffective for coupling reaction.

[a] Ojima, I. et al. *TL* **1977**, *18*, 2009
[b] Rhodes, Y.E. et al. *Synth. Comm.* **1985**, *15*, 301

Vinyl Ketene Silyl Acetal Coupling



γ,γ coupling



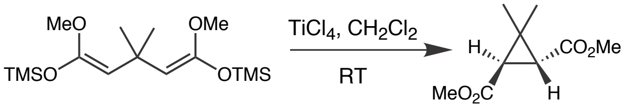
γ,α coupling

R	R'	Yield	γ,γ : γ,α
H	H	98%	83:17
H	Me	76%	64:36
Me	H	98%	96:4

Ojima, I. et al. *TL* **1983**, *24*, 785

Silyl Ketene Acetal Coupling

Carbocycle Synthesis

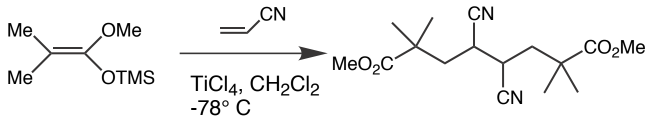


69% Yield
100% trans

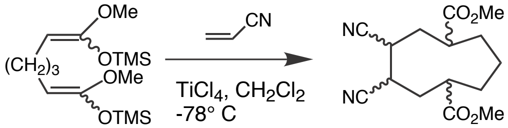
- Stereochemical course under thermodynamic control
- No coupling from ketone-derived enol silyl ethers
- Generally poor yields; exclusively 1,3-trans product.

Chan, T.H. *Tetrahedron,* **1983**, *39*, 847

Acrylonitrile Trapping



63% Yield
1:1 diast. ratio



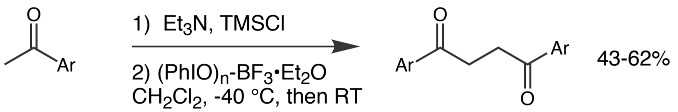
52% Yield
Mixture of all diastereomers

- Authors propose enoxyradical trapping by acrylonitrile, followed by dimerization
- Reactions with methacrylonitrile gave poor yields.
- Attempts to trap putative radical intermediate with $FeCl_3$, CCl_4, CBr_4, and tributyltin hydride failed.

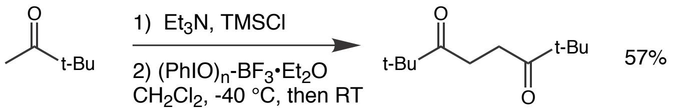
Rousseau, G. *Tetrahedron*, **1990**, *46*, 7011

Silyl Enol Ether Dimerization

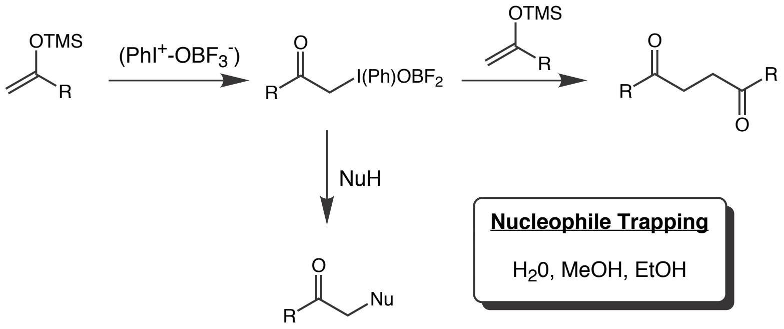
Hypervalent Iodine Oxidants



Ar = Ph, p-HOC_6H_4, p-$MeOC_6H_4$, p-ClC_6H_4, p-MeC_6H_4



Proposed Mechanism



Nucleophile Trapping

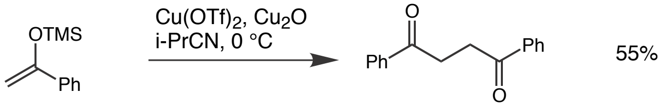
H_20, MeOH, EtOH

- Nucleophile trapping accomplished in "good yields."

Moriarty, R., et al. *JCS Chem. Comm.*, 420 (1985)
Moriarty, R., et al. *J. Chem. Soc. Perk. Trans. I*, 559 (1987)
Caple, R., et al. *JOC*, **54**, 2609 (1989)

Silyl Enol Ether Dimerization

Metal Oxidants

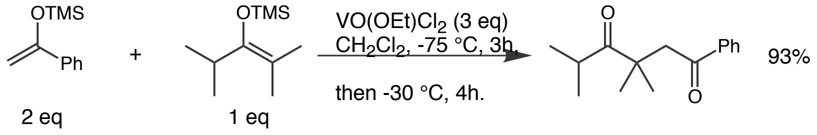


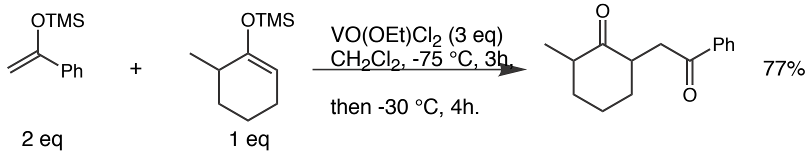
Oxidant	# eq	Solvent	Temp.(°C)	Time (hr)	Yield	Ref.
$Cu(OTf)_2/Cu_2O$	1,4	i-PrCN	0	2	55%	a
Ag_2O	1	DMSO	65	2	73%	b
$Pb(OAc)_4$	0.5	2:1 CH_2Cl_2:THF	-78, then 23	1.5;1	45%	c
$VO(OEt)Cl_2$	2	CH_2Cl_2	-75, then -40	3;4	30%	d

- All authors also reported yields for non-styrenyl silyl enol ethers.
- Yields are extremely substrate dependent.
- Generally, increasing steric hindrance decreases yields.
- All authors propose oxidation to cation radical, followed by loss of trimethylsilyl cation and radical coupling.

[a] Kobayashi, Y. et al. *Chem. Pharm. Bull.*, **1980**, *28*, 262
[b] Saegusa, T. et al. *JACS* **1975**, *97*, 649
[c] Moriarty, R.M. et al. *TL* **1987**, *28*, 873
[d] Ohshiro, Y. et al. *TL* **1992**, *33*, 5823

Cross Coupling Experiments



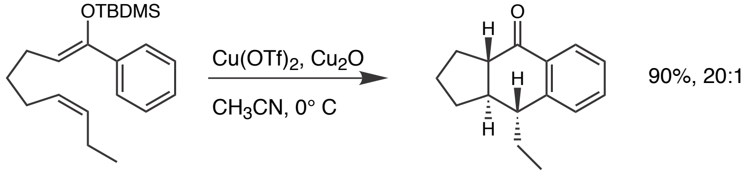


- Less reactive substrate added first, followed by more reactive substrate.
- In all cases, trace amounts of dimers isolated.

Ohshiro, Y. et al. ibid.

Silyl Enol Ether Coupling

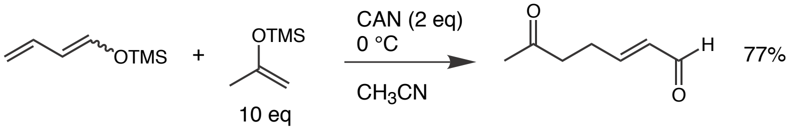
Alkene Trapping



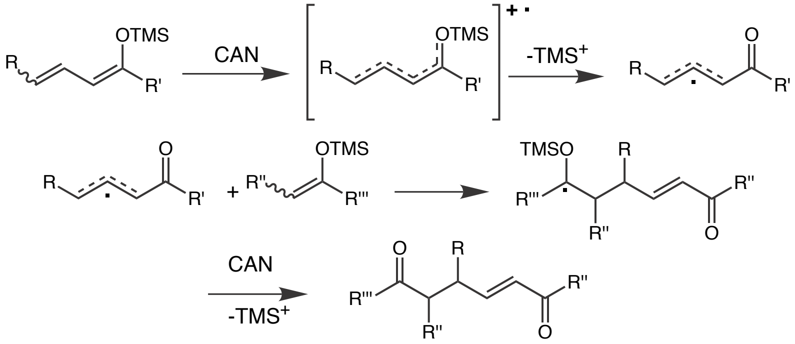
- Also observed for δ,ε olefins.
- Kinetic product can be isomerized in KOH/MeOH.

Snider, et al. *JOC*, **1990**, *55*, 4786

6-Oxo-α,β-Unsaturated Carbonyl Compounds



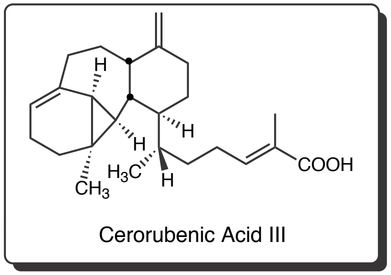
Proposed Mechanism



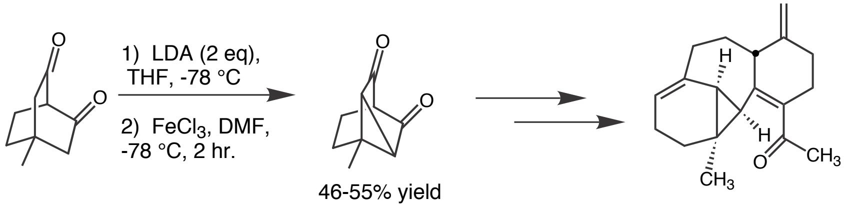
Ruzziconi, R. et al. *TL* **1993**, *34*, 721

Application: Ketone Enolates

Cerorubenic Acid III: Construction of the Tetracyclic Core



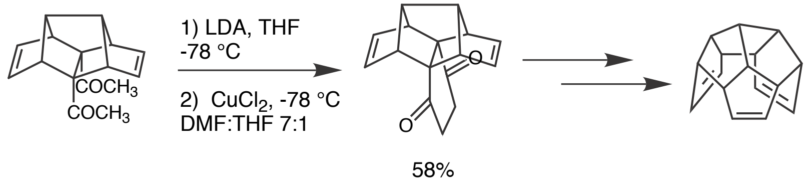
Cerorubenic Acid III



- Other oxidants ($CuCl_2$, $Cu(OTf)_2$) coupled with poor yields

Paquette, L.A. *JOC*, **1993**, *58*, 4245

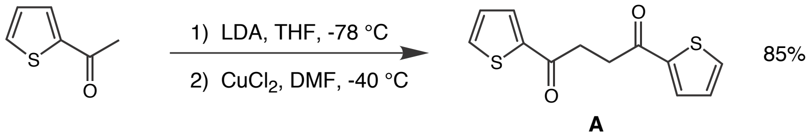
C_{16} Hexaquinacene

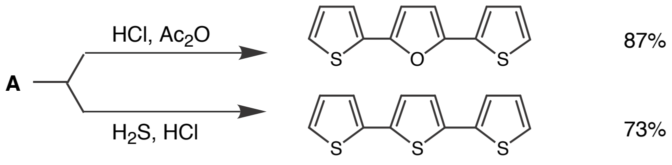


Paquette, L.A. et al. *JACS*, **1978**, *100*, 1600

Ketone Enolate Applications II

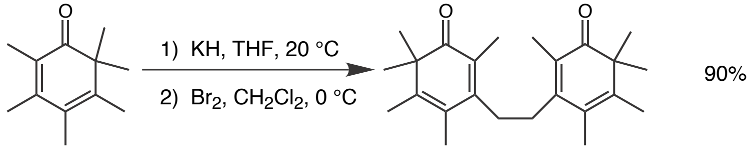
Coupling of 2-acetylthiophene

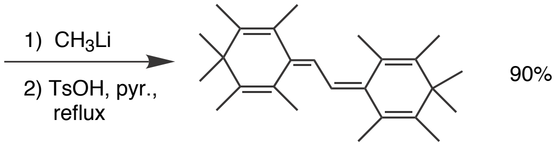




Kagan, J. et al *Heterocycles*, **1983**, *20*, 1941

γ-Coupling of Ketone Enolates

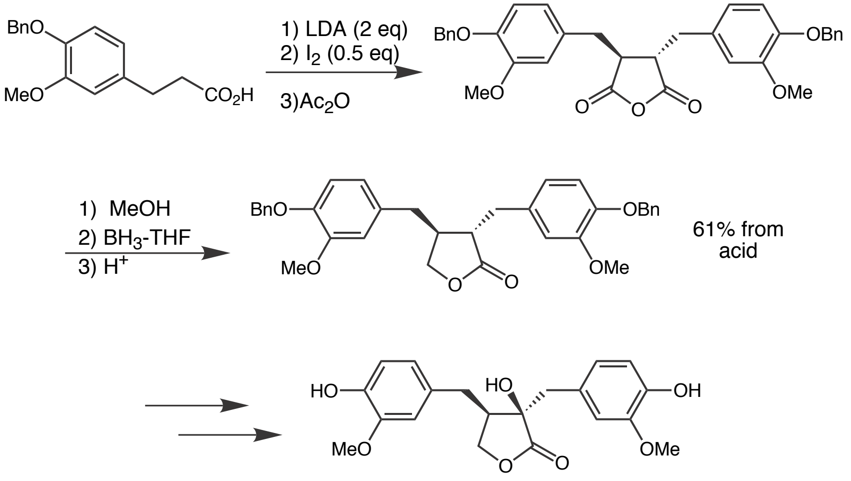




Hart, H. et al. *TL*, **1977**, *18*, 2307

Application: Carboxylic Acid Dianions

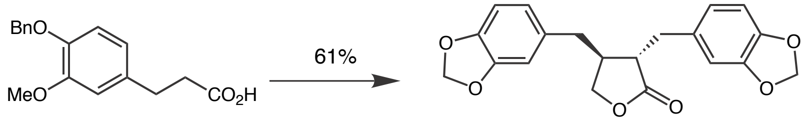
Total Synthesis of Racemic Wikstromol



Belletire, J.L. et al, *JOC*, **1988**, *53*, 4724

- Anhydride "obtained as a single diastereomer by NMR analysis."

Total Synthesis of Racemic Hinokinin

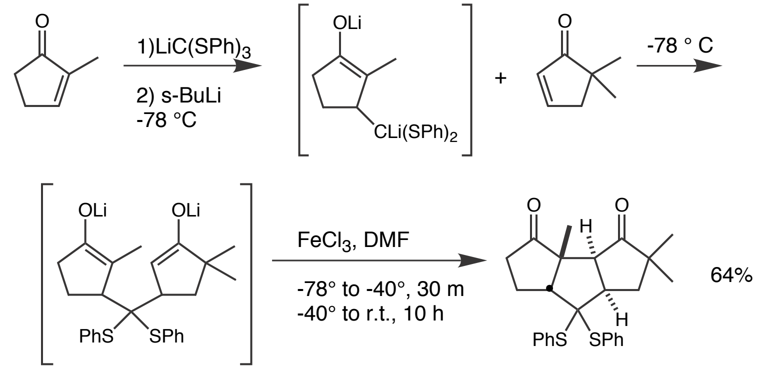


- Mixture of erythro and threo acids; anhydride exclusively threo.

Belletire, J.L. et al, *JOC*, **1987**, *52*, 2549

Applications: Ketone Enolates and Silyl Enol Ethers

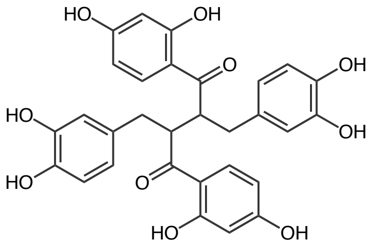
Synthesis of Racemic Hirsutene

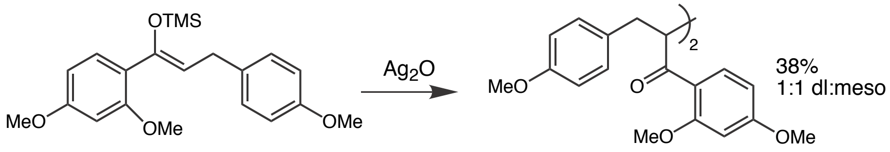


- Isolated as a single diastereomer; proof by conversion to hirsutene.

Cohen, T. *JOC*, **1992**, *57*, 1968

Studies Toward the Synthesis of Brackenin



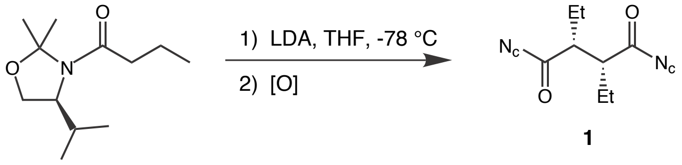


- "Use of Li enolates [for coupling] proved to be unsatisfactory."

Drewes, S.E. *JCS Perk. Trans 1*, **1989**, 1585

Stereoselective Synthesis of Succinamides

Oxazolidine Auxiliary Experiments



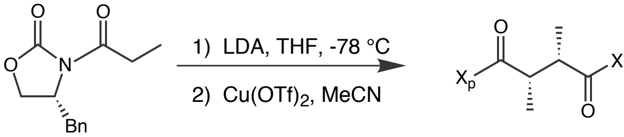
1

Oxidant	Yield	**1**: Σ others
I_2	40-50%	92:8
$CuCl_2$	50-55%	98:2

- No model for induction proposed

Porter, N.A. et al. *TL*, **1993**, *34*, 4457

Oxazolidinone Auxiliary Experiments



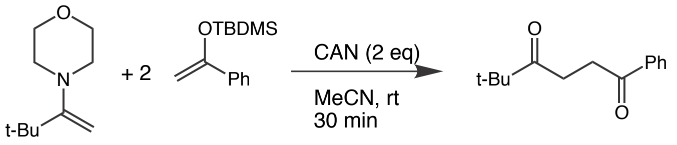
50% yield
5:1 dl mixture

- Also obtained ca. 30% yield of meso dimer

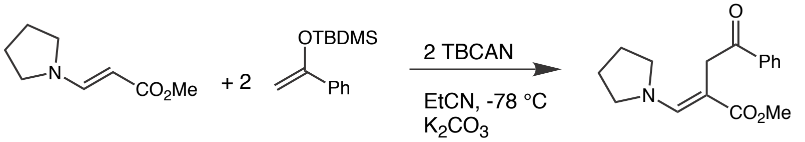
J. Ellman and M. Dart, unpublished results

Oxidative Coupling of Enamines

Silyl Enol Ether Trapping

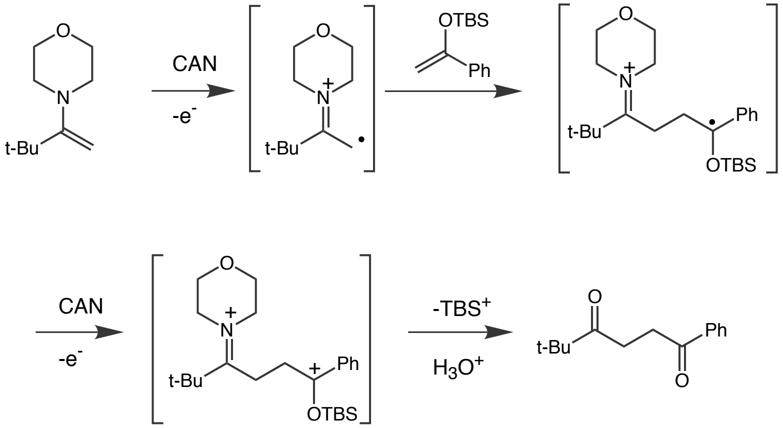


63%



91%

Proposed Mechanism



Narasaka, K. et al. *Chem. Letters* **1992**, 2099

Chemistry 206

Advanced Organic Chemistry

Handout–28A

*O*xidative Coupling of Enolates & Enol Derivatives

Chuck Scales

Evans Group Seminar, March, 1995

D. A. Evans

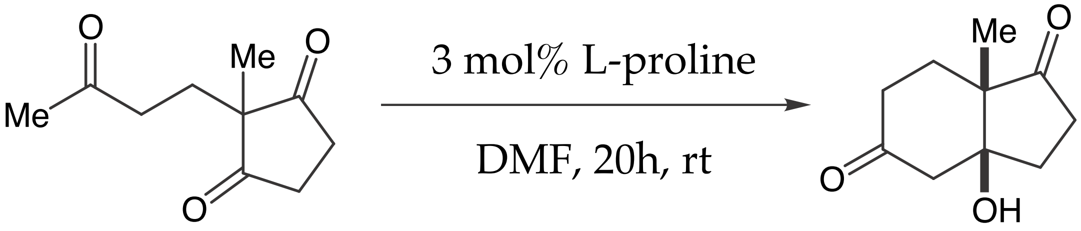
Friday ,
November 21, 2003

Chemistry 206

Advanced Organic Chemistry

Handout–28B

Asymmetric Organocatalysis Using Chiral Amines



93% ee

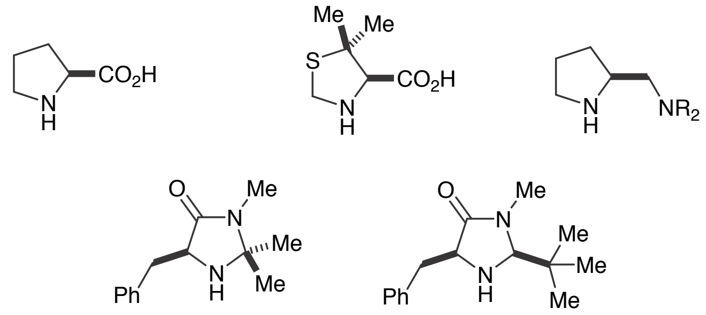
An Evans Group Friday Seminar
Jonathan Lawrence
November 14th 2003

D. A. Evans

Friday ,
November 21, 2003

Asymmetric Organocatalysis Using Chiral Amines

<ins>Contents</ins>:
- Background
- Aldol reactions
- Mannich reactions
- Amination/Oxidation reactions
- Michael reactions
- Cycloaddition reactions
- Alkylation reactions



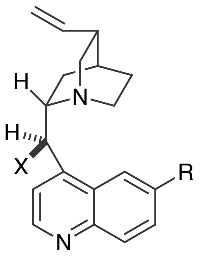
An Evans Group Friday Seminar
Jonathan Lawrence
November 14th 2003

Revent Reviews:
- List, B. "Proline Catalyzed Asymmetric Reactions", *Tet.* **2002**, *58*, 5573-5590
- Miller, S. "Amino Acids and Peptides as Asymmetric Organocatalysts", *Tet.* **2002**, *58*, 2481-2495
- List, B. "Asymmetric Aminocatalysis", *Synlett* **2001**, *11*, 1675-1686
- Dalko, P. "Enantioselective Organocatalysis", *ACIEE* **2001**, *40*, 3726-3748

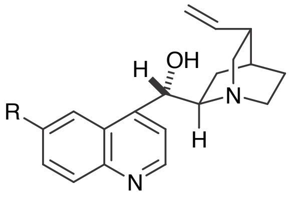
Other Chiral Amines

Cinchona alkaloids:

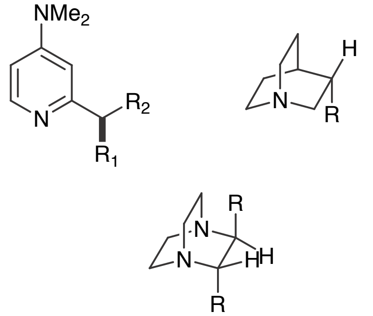
The "nucleophilic" catalysts



R = OMe, X = OH [(-)-quinine]
R = H, X = OH [(-)-cinchonidine]



R = OMe [(+)-quinidine]
R = H [(-)-cinchonine]

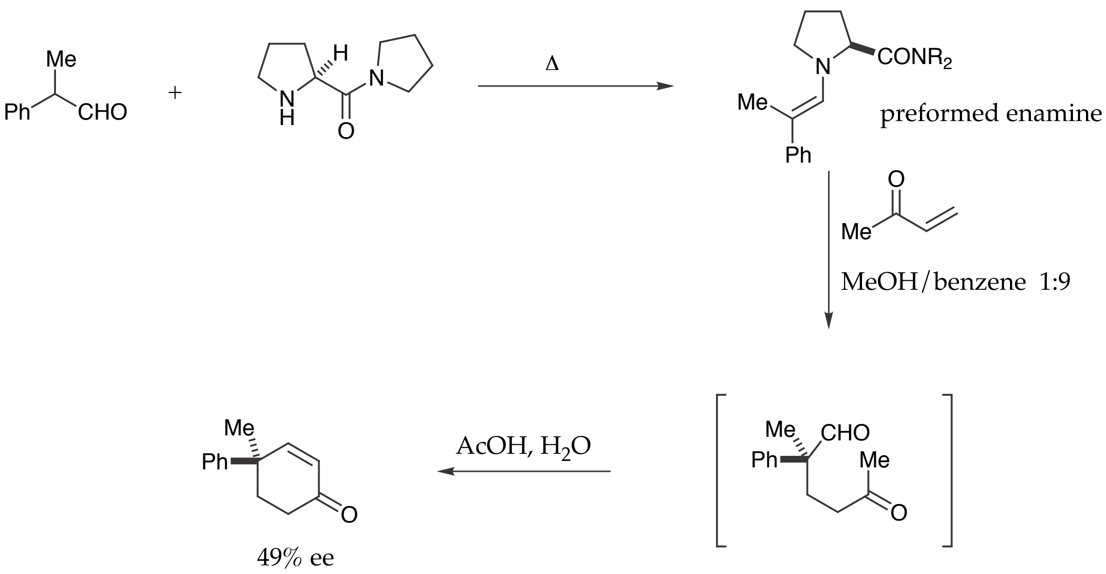


Reviews:
- Pracejus, H. *Fortschr. Chem. Forsch*, **1967**, *8*, 493.
- Morrison, J., Mosher, H. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, **1971**.
- Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.

Relevant Group Seminars:
- Karl Scheidt, *Asymmetric Catalysis with Chiral Lewis Bases (Part I),* March 2001
- Hemaka Rajapakse, *Nonmetal-Based Asymmertic Catalysis (Part II),* March 2001
- Essa Hu, *Asymmetric Catalysis with Chiral Lewis Bases* (*Part III*), March 2001
- Jake Janey, *Asymmetric Catalysis with Chiral Lewis Bases (Part IV),* March 2001

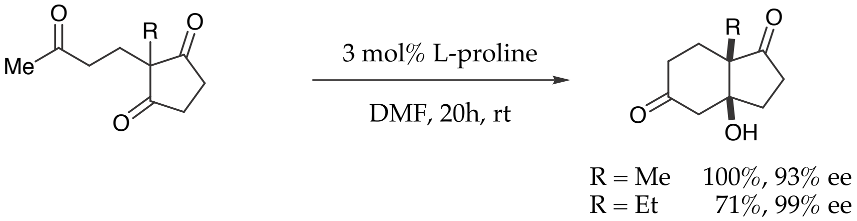
Preliminary Findings

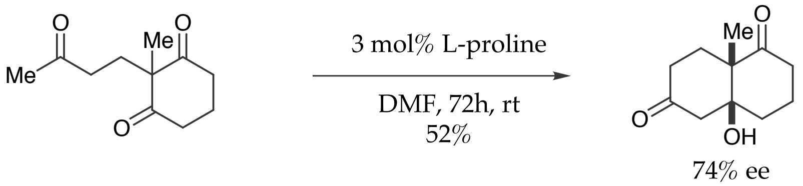
Yamada, 1969:



Yamada, S. *TL* **1969**, *10*, 4237.

The Seminal Experiments

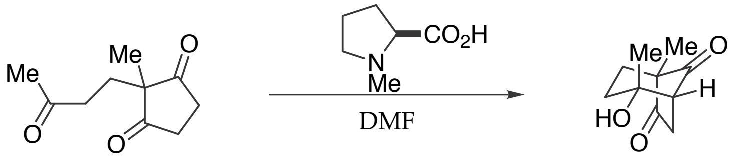




- the use of protic solvents severly diminishes enantioselectivity
- other amino acids as catalysts lead to decreased chemical yield and enantioselectivity
- Eder, Sauer, and Weichert obtained the corresponding aldol condensation products in similar optical purity using 47 mol% L-proline and 1N $HClO_4$

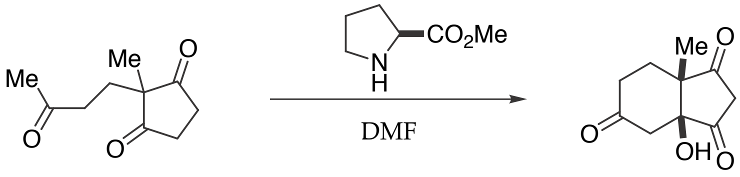
Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.
Eder, U., Sauer, G., Weichert, R. *ACIEE* **1971**, *10*, 496.

Effect of the Catalyst



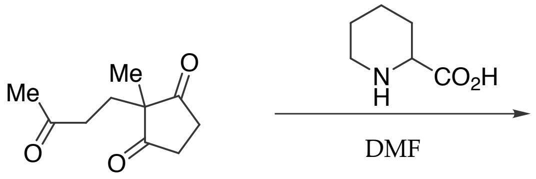
racemic

"major product"



racemic

"major product"

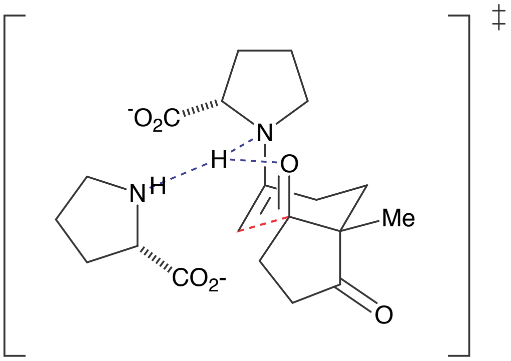


no reaction

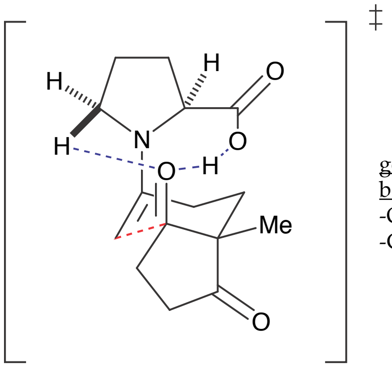
Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.

Transition States

Agami, 1984-1986



Houk, 2001-2003



general hydrogen bond energies
-OH - - O 3.0-8.0 kcal
-CH - - O 0.5-3.8 kcal

- favorable (enamine) N-H---O hydrogen bond
- N-H *anti* to carboxylate electrostatically favored
- reaction is second-order in proline (non-linear effect observed)
- second proline acts as a proton shuttle, allowing enamine to be nucleophilic

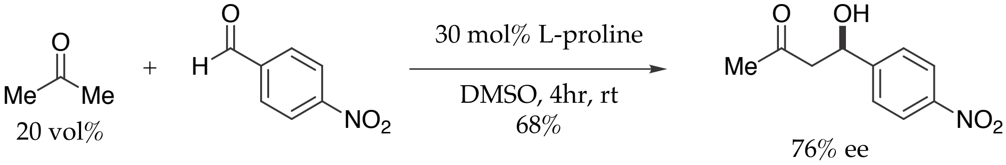
Agami, C. *TL* **1986**, *13*, 1501.
Houk, K. *JACS* **2001**, *123*, 12911.
Houk, K., List, B. *JACS* **2003**, *125*, 16.

- N-H---O hydrogen bond does not lower energy of transition state
- favorable O-H---O hydrogen bond
- additional NC-H---O hydrogen bond further stabilizes system
- reaction is first order in proline (supported by kinetic data) and no non-linear effect observed

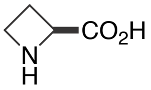
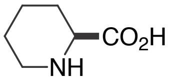
for a discussion on R_3N+-C-H---O=C bonds, see:
Houk, K. *JACS*, **2002**, *124*, 7163.

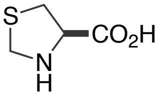
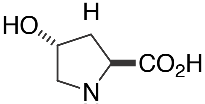
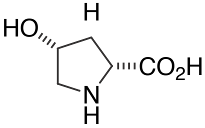
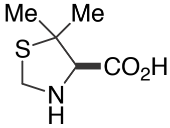
Direct Aldol Addition 1

The initial reaction:



Catalyst screen:
(selected examples)

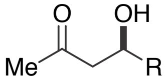
compound	% yield	% ee
(L)-His, (L)-Val (L)-Tyr, (L)-Phe	< 10	--
	55	40
	< 10	--

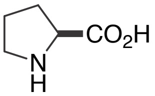
compound	% yield	% ee
	67	73
	85	78
	> 50	- 62
	66	86 *

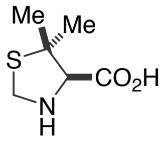
List, B., Barbas, C. *JACS*, **2000**, *122*, 2395-2396
*Barbas, C. *JACS*, **2001**, *123*, 5260-5267

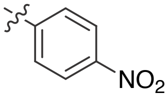
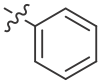
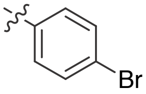
Direct Aldol Addition 2

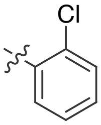
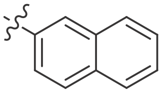
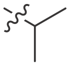
Substrate scope:
variation of the aldehyde




1


2

product R =	cat.	% yield	% ee
	**1**	68	76
	2	60	86
	**1**	62	60
	2	60	89
	**1**	74	65
	2	65	67

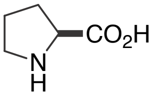
product R =	cat.	% yield	% ee
	**1**	94	69
	2	71	74
	**1**	54	77
	2	60	88
	**1**	97	96
	2	61	94

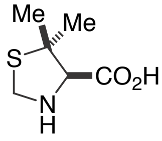
- DMTC **2** is catalyst of choice for aromatic aldehydes, although chemical yield decreases due to slower rate of reaction
- α–unbranched aldehydes yield no appreciable amount of product with proline catalyst **1** due to enolization and self-aldolization under reaction conditions (DMSO/acetone = 4:1)

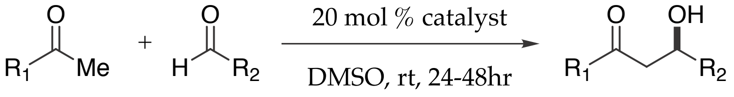
List, B. *JACS*, **2000**, *122*, 2395.
Barbas, C. *JACS*, **2001**, *123*, 5260.

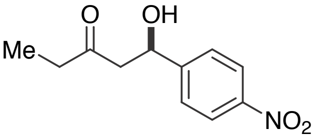
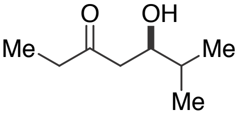
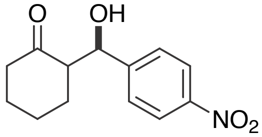
Direct Aldol Addition 3

Substrate scope:
variation of the ketone donor


1


2

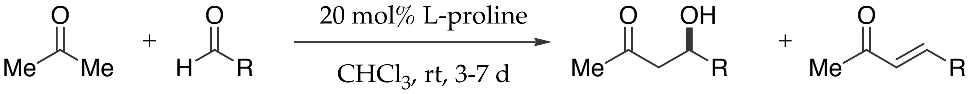


product R =	cat.	% yield	% ee
	**1** **2**	65 57	77 74
	**1** **2**	60 <5	80 ---
	**1** **2** 	*syn* 24 *anti* 35 *syn* 21 *anti* 41	67 90 69 89

Barbas, C. *JACS*, **2001**, *123*, 5260.

Direct Aldol Addition 4

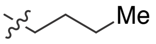
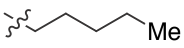
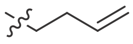
Substrate scope:
use of α-unbranched aldehydes

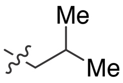
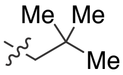


20 mol%

1

2

product R=	% yield **1**	% yield **2**	% ee
	29 31	0 38	70 67 *
	35	40	73 *
	34	35	72

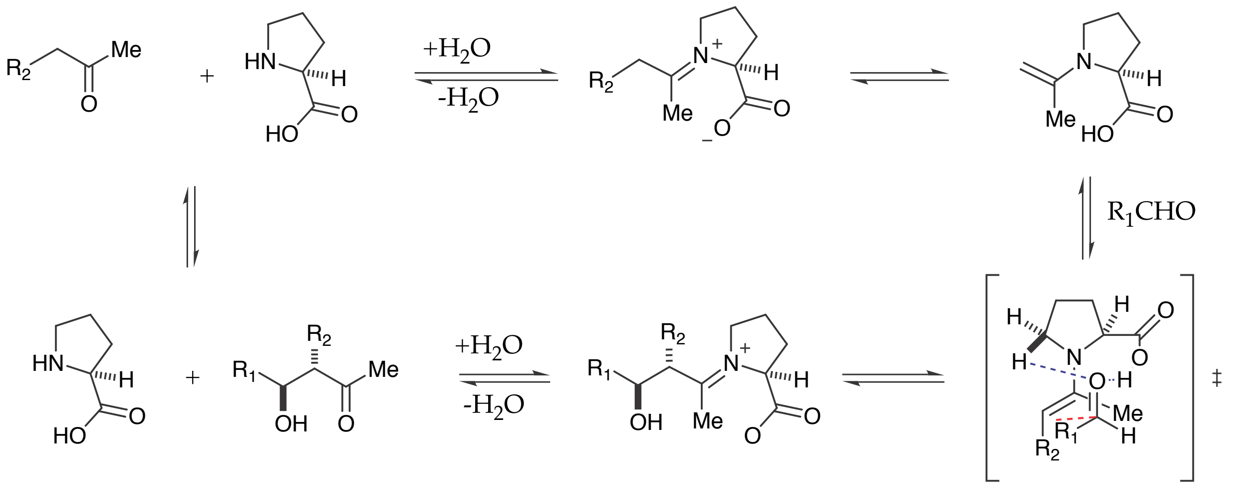
product R=	% yield **1**	% yield **2**	% ee
	23 34	46 42	61 73 *
	22	50	36

* reaction performed neat in acetone

- use of cyclic ketones (cyclopentanone, cyclohexanone) result in moderate yield and diastereoselectivity, and up to 95% ee
- enone products arise from a Mannich addition-elimination sequence

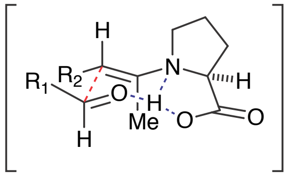
List, B. *OL* **2001**, *3*, 573.

Direct Aldol Reaction Mechanism



Houk's calculated T.S.

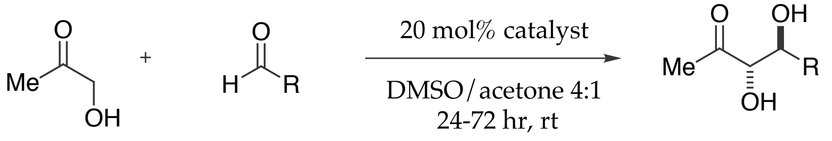
previously proposed T.S.:
metal-free Zimmerman-Traxler model

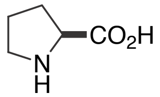


- synclinal approach of aldehyde
- R_1 in pseudo-eqitorial position
- C-H - - O distance ~ 2.4 A
- DFT calculations in DMSO

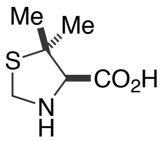
List, B. *JACS* **2000**, *122*, 2395.
List, B., Houk, K. *JACS* **2003**, *125*, 2475.

Synthesis of *Anti*-1,2-Diols

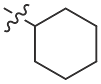
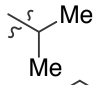
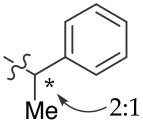
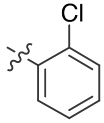


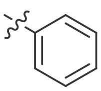
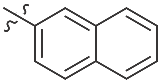
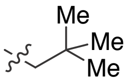
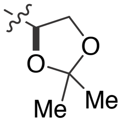


1



2

product R =	cat.	dr	% yield	% ee
	**1**	>20:1	60	>99
	2	>20:1	45	95
	**1**	>20:1	62	>99
	2	---	<5	---
	**1**	>20:1	51	>99
	2	---	<5	---
	**1**	3:2	95	67 (32)
	2	3:2	60	92 (78)

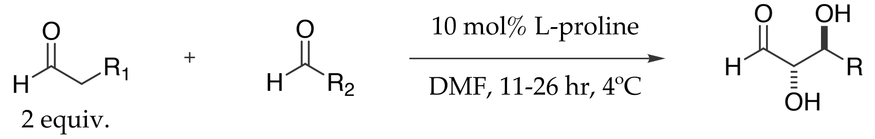
product R =	cat.	dr	% yield	% ee
	**1**	1:1	83	80 (n.d.)
	2	1:1	52	95 (50)
	**1**	3:1	62	79 (33)
	2	---	<5	---
	**1**	1.7:1	38	>97 (84)
	2	---	<5	---
	**1**	2:1	40	>97 (97)
	2	---	<5	---

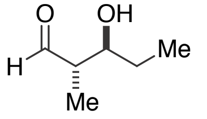
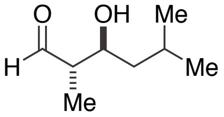
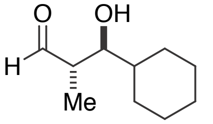
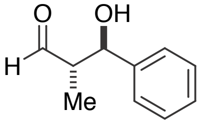
List, B. *JACS*, **2000**, *122*, 2395.
Barbas, C. *JACS*, **2001**, *123*, 5260.

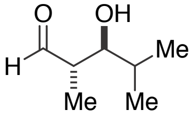
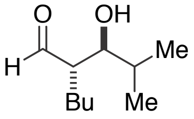
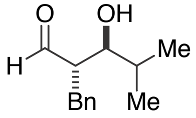
more substituted enamine formed due to:

- increased acidity of proton removed
- increased stability of enamine due to $O_{n.b.}$ --> π^* C=C

Use of Aldehydes as Donors in Direct Aldol



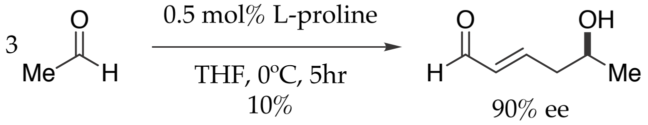
product R =	dr	% yield	% ee
	4:1	80	99
	3:1	88	97
	14:1	87	99
	3:1	81	99

product R =	dr	% yield	% ee
	24:1	82	>99
	24:1	80	98
	19:1	75	91

- reaction requires lower catalyst loading, shorter times, and only 2 equivalents of aldehyde donor

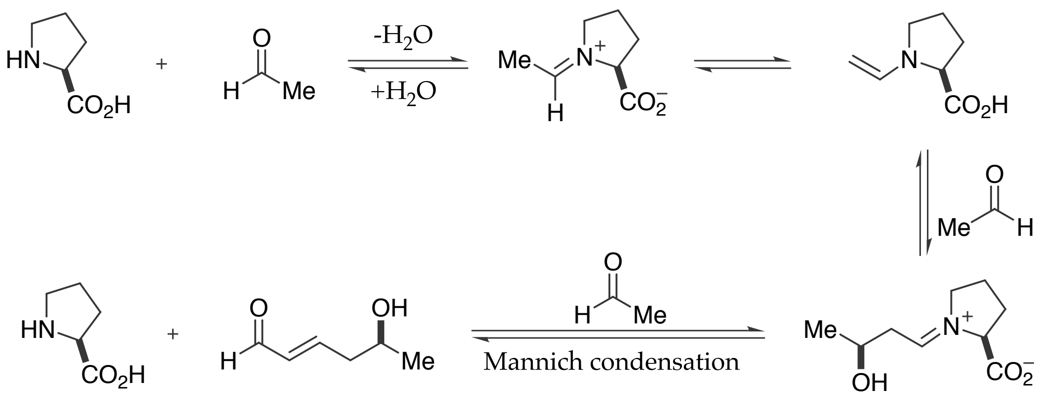
MacMillan, D. *JACS*, **2002**, *124*, 6798.

Trimerization of Acetaldehyde



- THF at 0ºC was found to be the optimal conditions for yield and ee (DMSO @ rt = 13% y, 57% ee, $CHCl_3$ @ rt = $_2$% y, $_{68}$% ee)

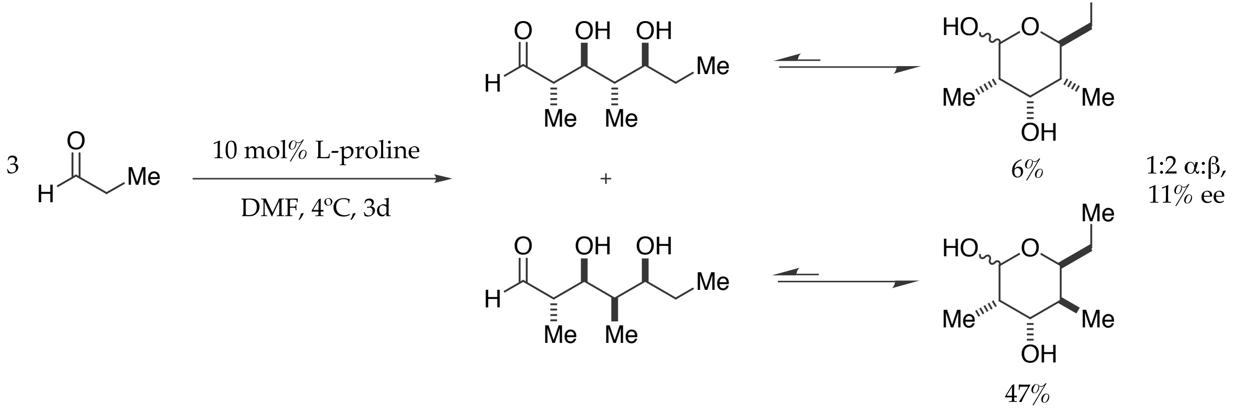
Mechanism:



Barbas, C. *JOC*, **2002**, *67*, 301.

Propionaldehyde Trimerization

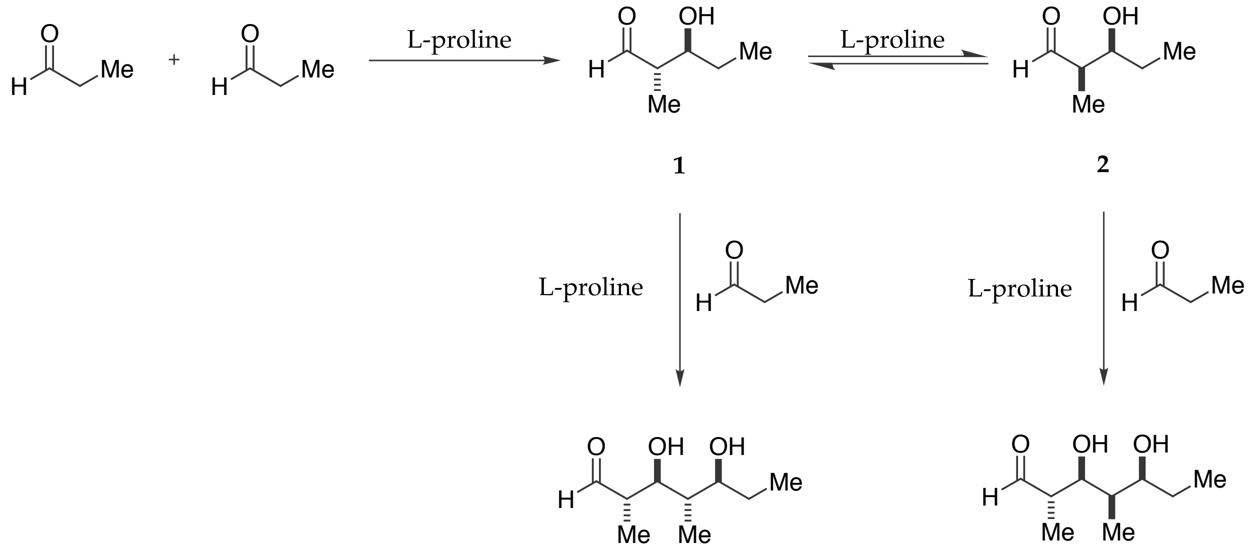
A method for carbohydrate assembly



- reaction analygous to an aldolase enzyme that furnishes the minor product shown above
- propionaldehyde added slowly dropwise in order to obtain trimer over dimer products
- enantioselectivity erodes with longer reaction times (after 10 hr product ee = 47%)
- substituent at C-6 variable by using 1 eq. of corresponding aldehyde and 2 eq. of propionaldehyde

Barbas, C. *TL*, **2002**, *43*, 9591.

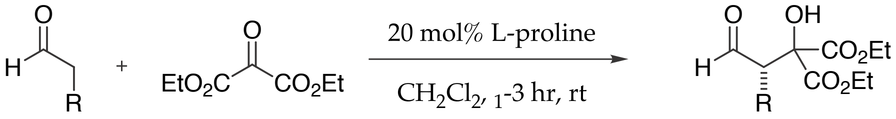
Mechanism of Propionaldehyde Trimerization

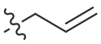


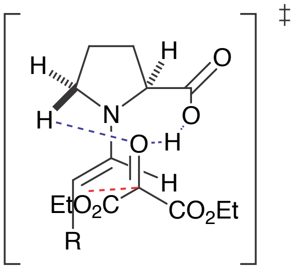
- incubating isolated **1** with L-proline led to formation of **2** through epimerization (1:1 ratio of **1**:**2** after 96 hr)

Barbas, C. *TL* **2002**, *43*, 9591.

Aldehyde Aldol Addition to Activated Carbonyl Compounds



product R =	% yield	% ee
Me	90	90
Et	91	85
i-Pr	88	85
	94	88
n-Hex	91	84
Ph	97	0



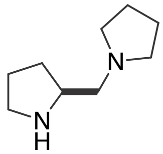
Jorgensen, K. *Chem. Comm.* **2002**, 620.

◆ protection of the aldehyde as the dioxolane prevents epimerization of the α center during column chromatography

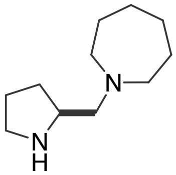
---

Other Chiral Amine Catalysts for the Direct Aldol Addition

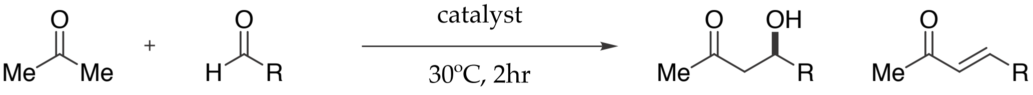
Chiral diamines:



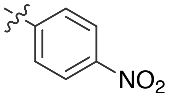
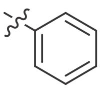
1



2



3 **4**

product R =	cat.	% yield **3**	% ee	% yield **4**
	1.5 mol% **1**◆2TfOH + 1.5 mol% **1**	60	88	7
	3 mol% **2**	72	93	7
	1.5 mol% **1**◆2TfOH + 1.5 mol% **1**	37	83	32
	3 mol% **2**	13	91	25

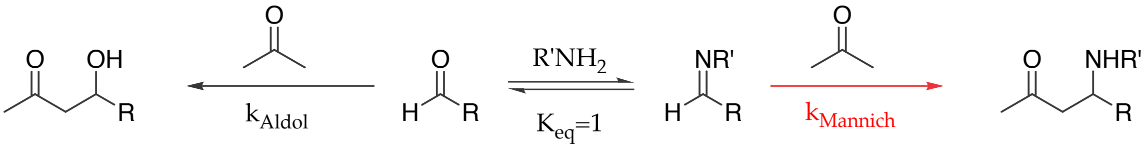
◆ proposed mechanism similar to that of proline catalyzed reactions, with proton transfer from protonated tertiary N to O

Yamamoto, *Tet.* **2002**, *58*, 8167.

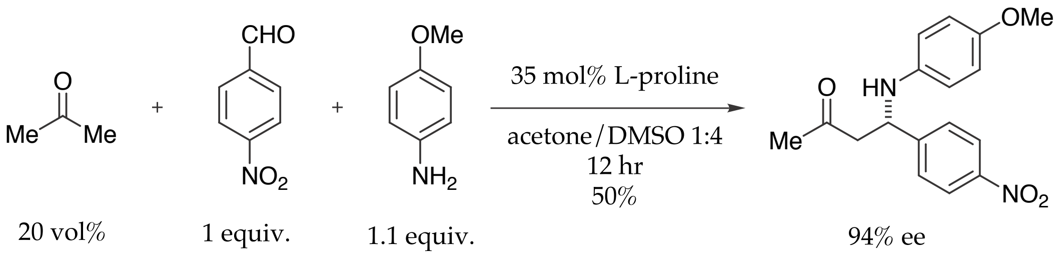
Mannich Reaction: First Report

Required Conditions:

- enamime addition must be faster to the imine than to the corresponding aldehyde
- formation of the aldimine from a primary amine must be faster than the aldol addition
  - NMR studies show that Keq(aldehyde ⇌ imine) = 1



3-component reaction verifies hypotheses:



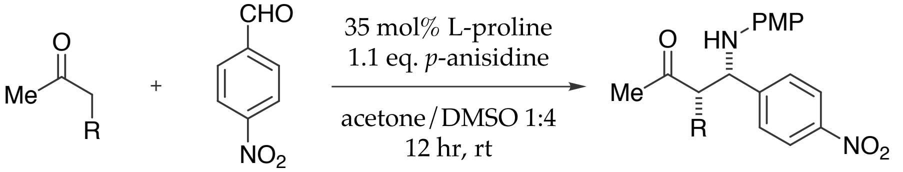
(+ <20% aldol product)

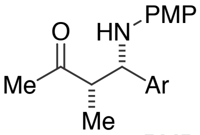
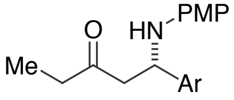
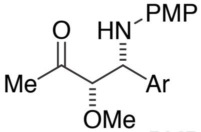
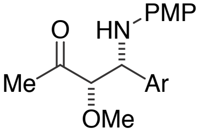
- 10 mol% proline and 1.3 eq ketone used without loss of efficiency

List, B. *JACS*, **2000**, *122*, 9336.

Mannich Reaction: Scope

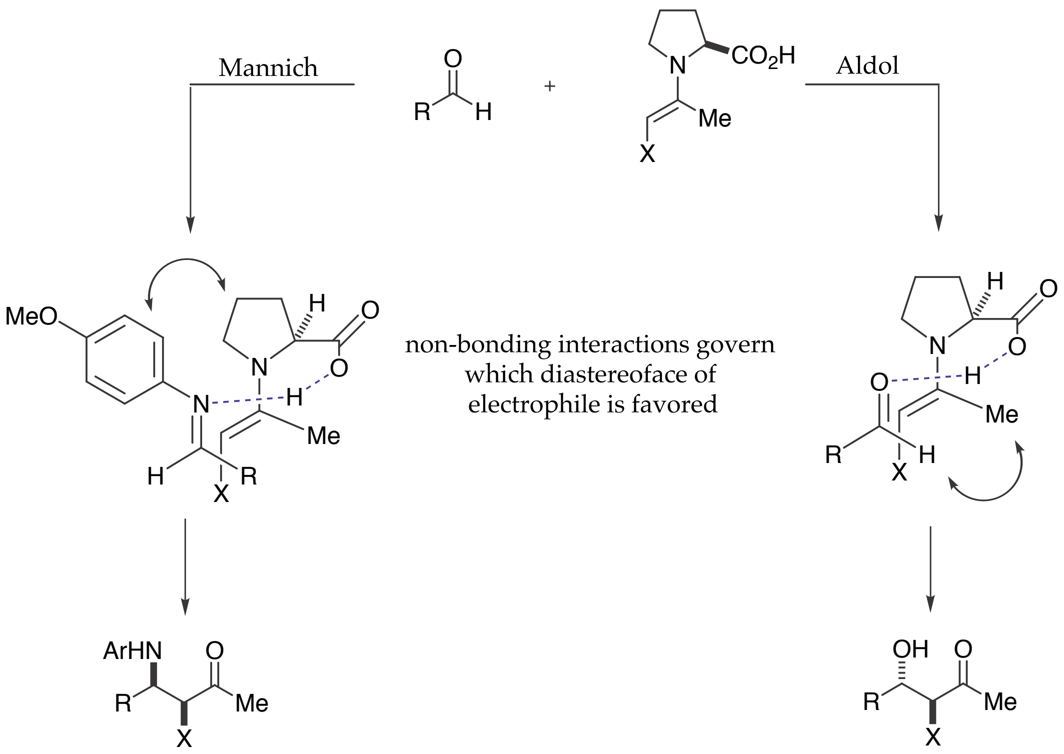
Variation of the ketone donor:



R =	product		% yield	dr	% ee
Me		2.5	95	>20:1	99
		1	---	>20:1	94
OMe			93	>20:1	98
OH			92	>20:1	>99

List, B. *JACS*, **2000**, *122*, 9336.

Mannich Reaction: Transition States



non-bonding interactions govern which diastereoface of electrophile is favored

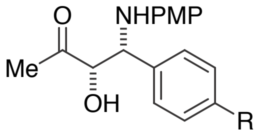
List, B. *JACS* **2002**, *124*, 827.

Mannich Reaction: Scope 2

Variation of the aldehyde:

- aliphatic aldehydes, including α-unbranched are good substrates (60-90% yield, 73-93% ee)
- aromatic aldehydes are excellent substrates, (79-92% yield, 61-99% ee)

Effect of electron donation from the aldehyde:

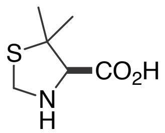


R =	% yield	dr	% ee
CN	88	15:1	99
H	83	9:1	93
Me	85	5:1	86
OMe	88	3:1	61

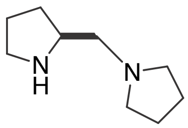
Variation of the catalyst:

- proline proves to be the best catalyst, with other catalysts affording reduced yield and optical purity.

Reaction of acetone with isovaleraldehyde:



60% y., 16% ee



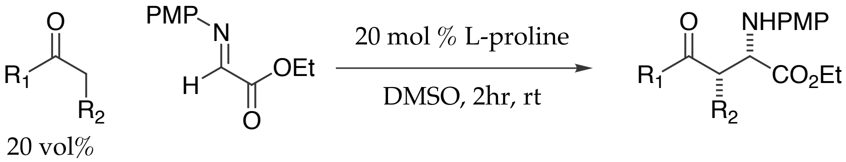
26% y., 0% ee

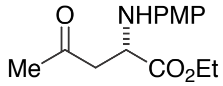
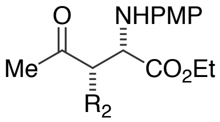
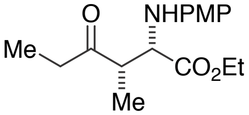
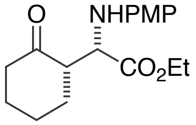
List, B. *JACS* **2002**, *124*, 827.

α-Imino Ethyl Glyoxylate as Mannich Acceptor 1

An entry to α-amino acids

Addition of ketones:



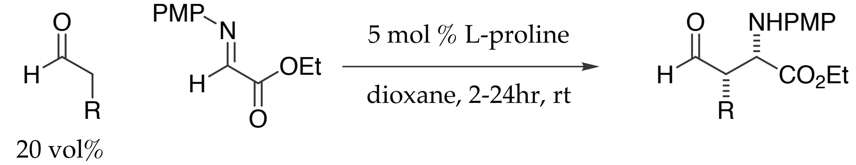
product	R_2 =	% yield	dr	% ee
		86	---	99
	Me	72	>19:1	>99
	allyl	79	>19:1	>99
	OH	62	>19:1	99
		47	>19:1	>99
		81	>19:1	>99

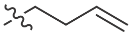
Barbas, C. *JACS* **2002**, *124*, 1842

α-Imino Ethyl Glyoxylate as Mannich Acceptor 1

An entry to α-amino acids

Addition of aldehydes:



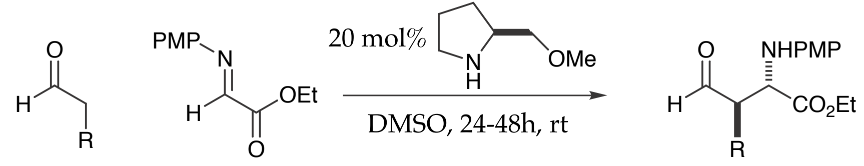
R =	% yield	dr	% ee
Me	72	1.1:1	99
Et	57	1.5:1	99
i-Pr	81	>10:1	93
n-Bu	81	3:1	99
n-Pent	89	>19:1	>99
	71	>19:1	>99

- aqueous workup or column chromatography may lead to decreased diastereoselectivities
- reaction has been performed in aqueous media (Barbas, *TL* **2003**, *44*, 1923)

Barbas, C. *JACS* **2002**, *124*, 1866.

Anti-Selective Mannich Reaction

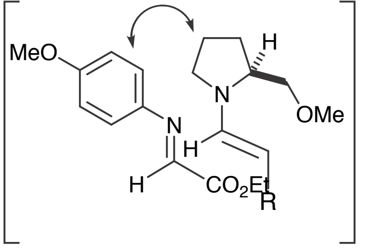
Addition of aldehydes:



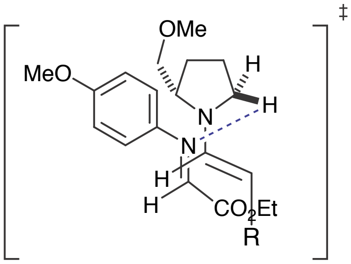
20 vol%

R =	% yield	dr	% ee
Et	44	1:1	75
i-Pr	52	10:1	82
n-Bu	54	10:1	74
t-Bu	57	>10:1	92
n-Pent	78	>10:1	76
n-Hex	68	>19:1	76

proposed transition state



bettter?

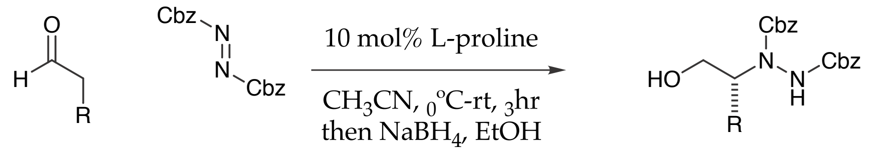


For a review of SMP use in asymmetric synthesis, see:
Enders, D. *Synthesis* **1996**, 1403.

Barbas, C. *TL* **2002**, *43*, 7749.

Direct α–Amination 1

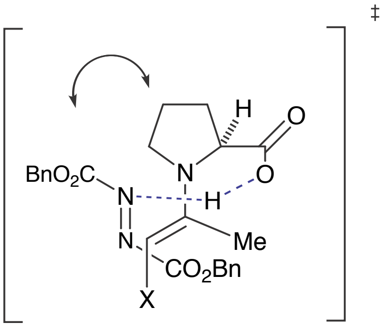
Addition of aldehydes:



1.5 equiv.

1 equiv.

R =	% yield	% ee
Me	97	>95
n-Pr	93	>95
n-Bu	94	97
i-Pr	99	96
Bn	95	>95

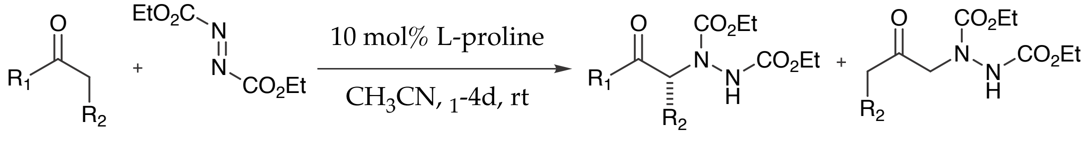


- longer reaction time leads to epimerization, so aldehyde is reduced *in situ*

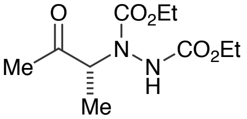
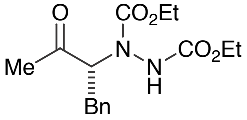
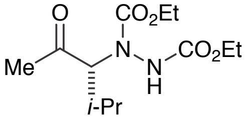
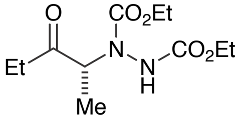
List, B. *JACS* **2002**, 124, 5656.

Direct α–Amination 2

Addition of ketones:



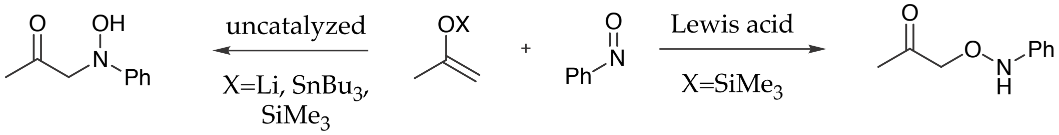
1 **2**

product **1**	ratio **1**:**2**	% yield (**1**+**2**)	% ee
	10:1	80	95 (93)
	4.5:1	92	98 (94)
	3:1	99	99 (99)
	---	79	94 (93)

Jorgensen, *JACS* **2002**, *124*, 6254.

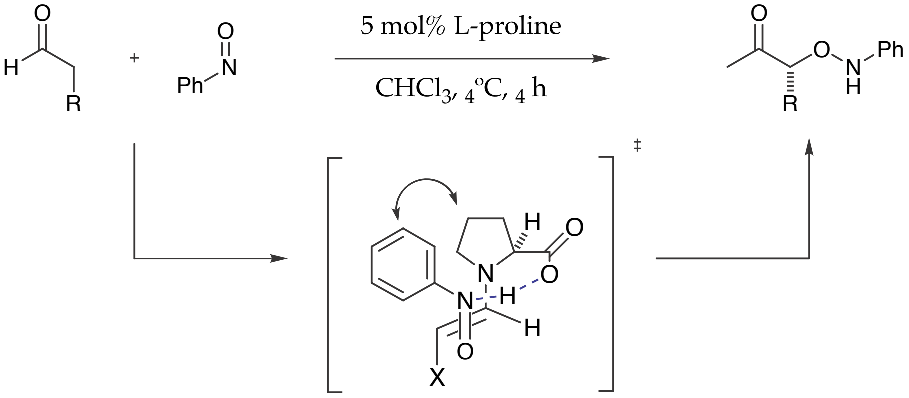
α–Oxidation of Aldehydes with Nitrosobenzene 1

The choice of reaction conditions determine N or O selelctive addition:



Yamamoto, H. *OL*, **2002**, *4*, 3579.

Larger basicity of nitrogen allows proline to catalyze O-nucleophilic addition:

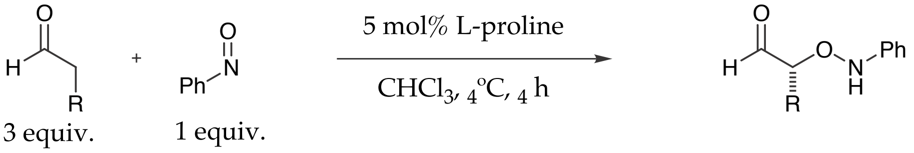


a possible transition state

MacMillan, D. *JACS* **2003**, *125*, 10808.

α–Oxidation of Aldehydes with Nitrosobenzene 2

Aldehyde scope:



R =	% yield	% ee
Me	88	97
n-Bu	79	98
i-Pr	85	99
$CH_2CH{=}CH_2$	99	96

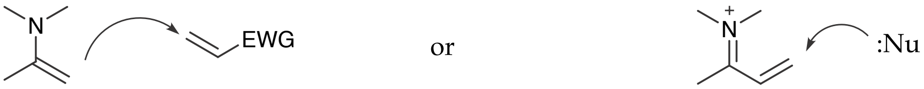
R =	% yield	% ee
Bn	95	97
Ph	60	99
$(CH_2)_3$OTIPS	76	98
CH_2-(3'-N-methyl indole)	83	98

- product most easily isolated as the primary alcohol ($NaBH_4$ reduction)

MacMillan, D. *JACS* **2003**, *125*, 10808.

Asymmetric Organocatalysis of the Michael Reaction

Two mechanistic possibilities exist:



enamine

imminium

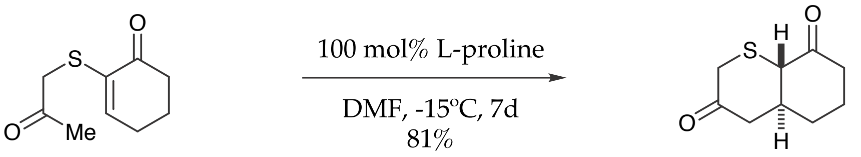
Examples include:

additions to:
    alkylidene malonates
    α,β–unsaturated nitroalkenes

additions of:
    malonate esters
    nitroalkanes
    aromatics (Friedel-Crafts reactions)
    silyloxy furans
Diels-Alder reaction
Dipolar cycloaddition

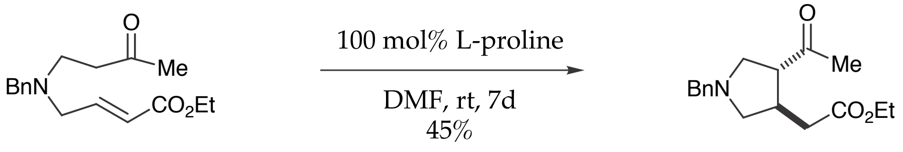
Michael Additions using Enamine Catalysis:

Moderate Success has been Achieved



28% ee

Kozikowski, A. *JOC*, **1989**, *54*, 2275.



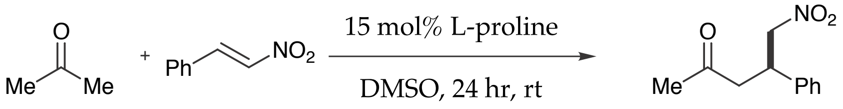
34% ee

Momose, T. *J.Chem.Soc.*, *Perkin Trans.*, **1992**, 509.

Enamine Catalysis: Examples 2

Recent examples:

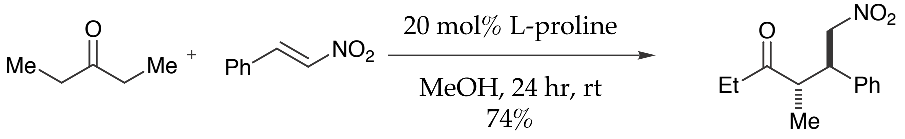
List:



7% ee

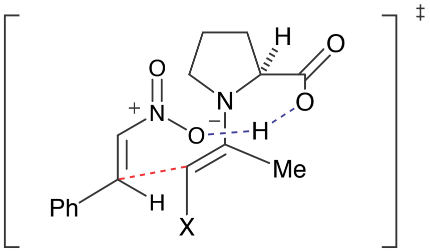
List, B. *OL* **2001**, *3*, 2423.

Enders:



73% ee, dr=7.3:1

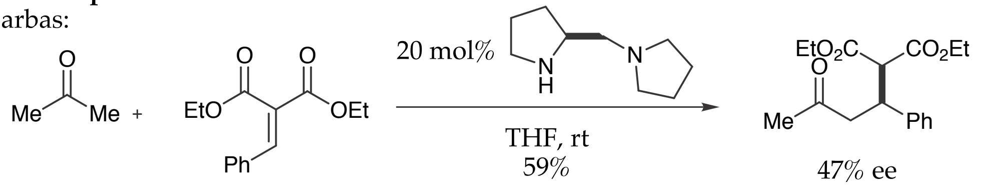
- use of MeOH as solvent increases ee



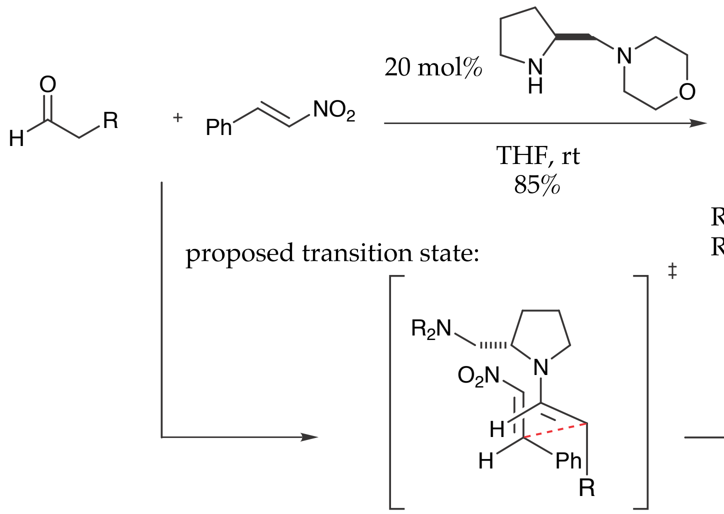
Enders, *Synlett* **2002**, 26.

Enamine Catalysis: Examples 3

Recent examples:
Barbas:



Barbas, C. *TL*, **2001**, *42*, 4441.

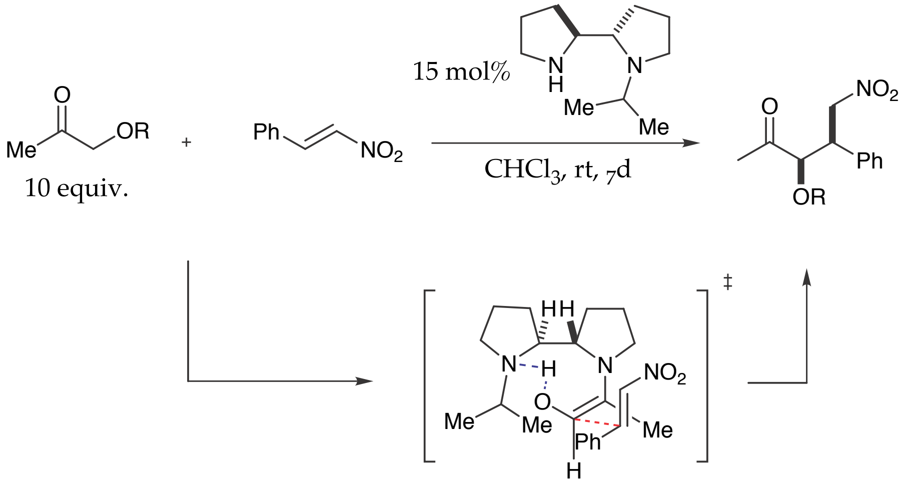


R = Me 56% ee, dr=9:1
R = *i*-Pr 72% ee, dr=11:1

Barbas, C. *OL* **2001**, *3*, 3737.

A Highly Enantioselective Michael Addition Using Enamines

A New Chiral Diamine Catalyst



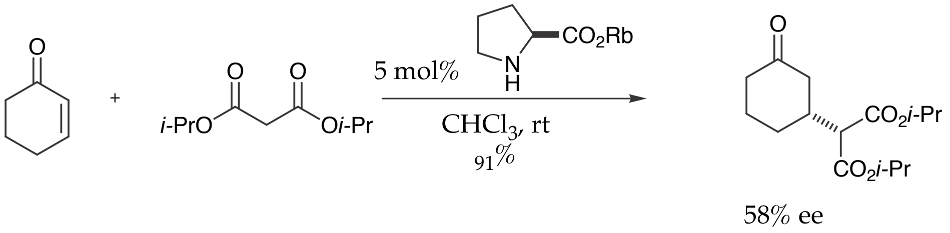
		syn/anti	
R	yield	dr	ee
Me	75	1:5	69
H	79	5:1	98

- with variation of aromatic group on nitroolefin:
  - ee = 96-98%
  - dr = 3.5:1 - 19:1
- selection of aromatic groups used:
  - tolyl, *p*-methoxyphenyl, *p*-chlorophenyl, 2-thienyl

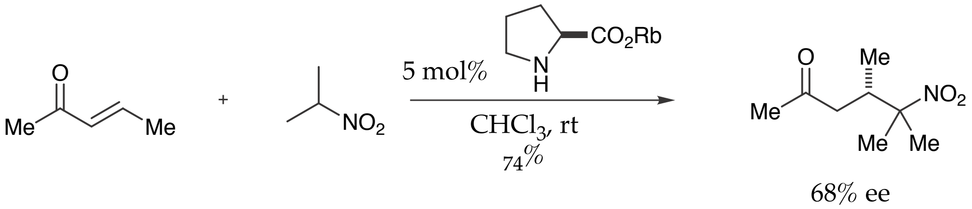
Alexakis, A. *OL*, **2003**, *5*, 2559.

Imminium Catalysis of Conjugate Additions 1

Proline has been used with only mild success:



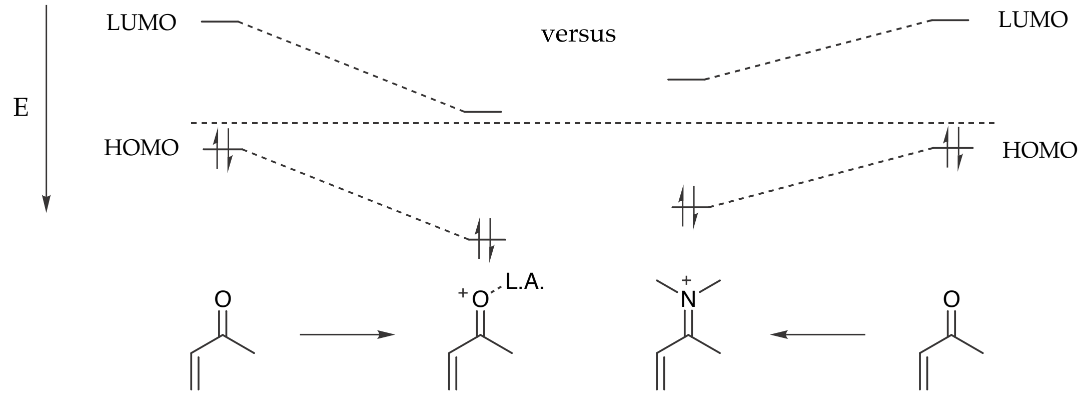
- Proline rubidium salt gives lower ee in the Hajos-Parrish-Weichert reaction



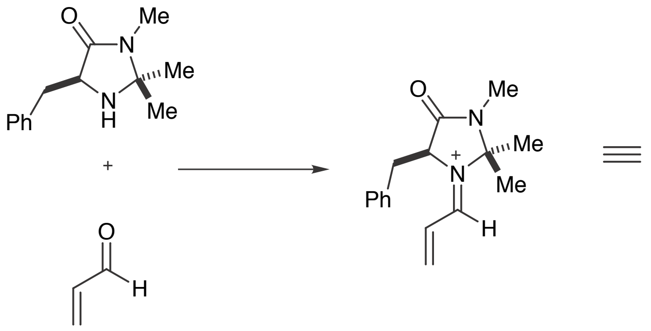
Yamaguchi, *JOC* **1996**, *61*, 3520.

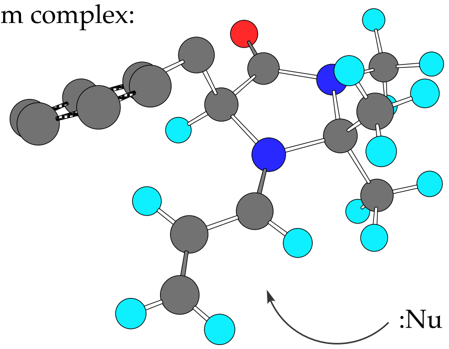
MacMillan Introduces A New Catalyst

Imminium ion formation lowers the LUMO of the system and allows catalysis to occur:



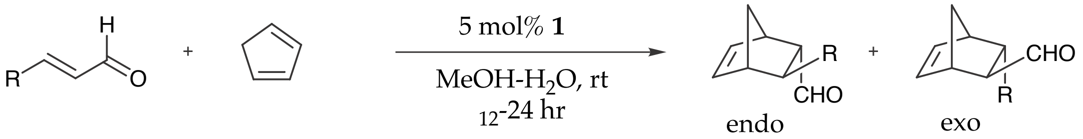
Consensation of an aldehyde with the catalyst produces an imminium complex:





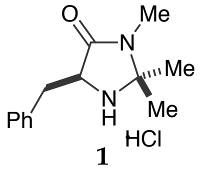
PM3 minimized structure

Diels-Alder Cycloaddition 1



Dienophile scope:

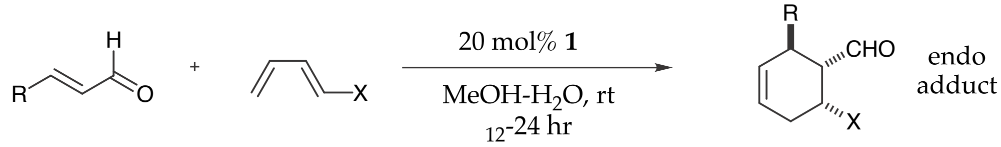
R =	% yield	endo:exo	% ee(endo)	% ee(exo)
Me	75	1:1	86	90
n-Pr	92	1:1	86	90
i-Pr	81	1:1	84	93
Ph	99	1.3:1	93	93
Furyl	89	1:1	91	93



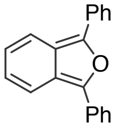
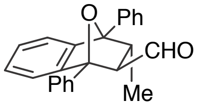
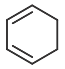
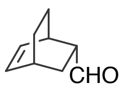
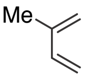
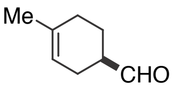
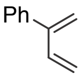
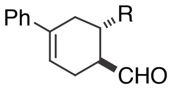
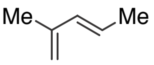
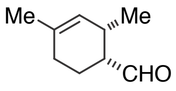
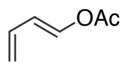
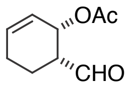
1

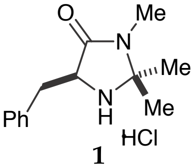
MacMillan, D. *JACS* **2000**, *122*, 4243.

Diels-Alder Cycloaddition 2



Diene scope:

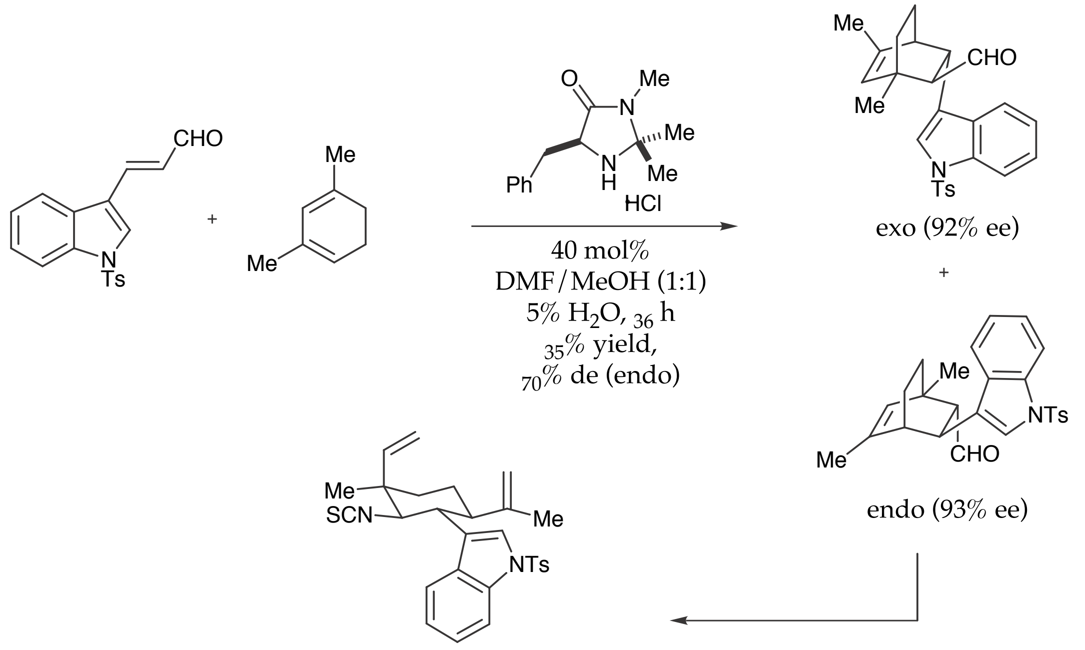
diene	R	product	% yield	exo:endo	% ee
	Me		75	35:1	96
	H		82	1:14	94
	H		84	---	89
	H Me		90 75	--- ---	83 90
	H		75	1:5	90
	H		72	1:11	85



1

MacMillan, D. *JACS* **2000**, *122*, 4243.

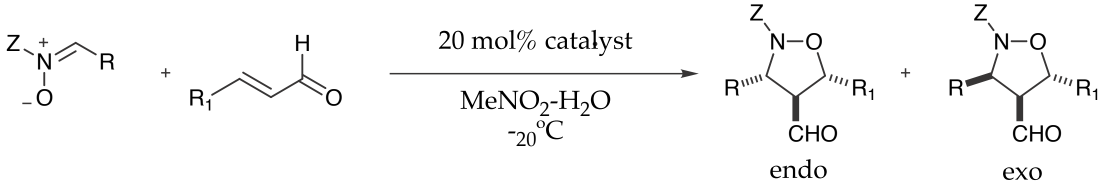
Application to Complex Synthesis



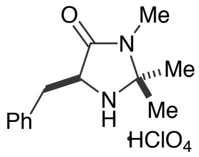
Kerr, M. *JACS* **2003,** ASAP

(+)-Hapalindole Q

Nitrone Cycloaddition



Z	R	R_1	endo:exo	yield	ee (endo)
Bn	Ph	Me	94:6	98	94
allyl	Ph	Me	93:7	73	98
Me	Ph	Me	95:5	66	99
Bn	C_6H_4Cl-4	Me	92:8	78	95
Me	C_6H_4Cl-4	Me	93:7	76	94
Bn	C_6H_4OMe-4	Me	98:2	93	91
Me	C_6H_4Me-4	Me	93:7	82	97
Bn	2-napth	Me	95:5	98	93
Bn	*c*-Hex	Me	99:1	70	99
Bn	Ph	H	81:19	72	90
Bn	Ph	H	86:14	80	92
Bn	C_6H_4Cl-4	H	85:15	80	90
Bn	C_6H_4Cl-4	H	80:20	80	91
Bn	2-napth	H	81:19	82	90
Bn	C_6H_4OMe-4	H	91:9	83	90

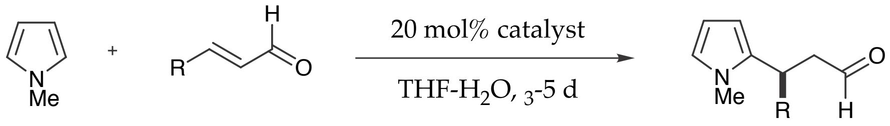


catalyst

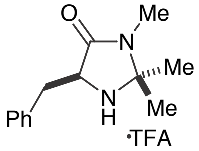
- $HClO_4$ proved to be the best Bronsted acid cocatalyst to promote only enantioselective catalysis
- high endo selectivity attributed to to favorable placement of R group away from geminal dimethyl substituents on catalyst

MacMillan, D. *JACS* **2000**, *122*, 9874

Friedel-Crafts Alkylation 1: Pyrroles



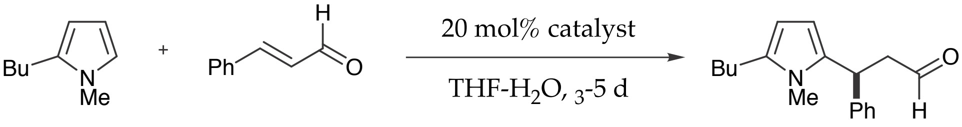
R	temp(°C)	yield	ee
Me	-60	83	91
n-Pr	-50	81	90
i-Pr	-50	80	91
Ph	-30	87	93
PMP	-30	79	91
CH_2OBn	-60	90	87
CO_2Me	-50	72	90



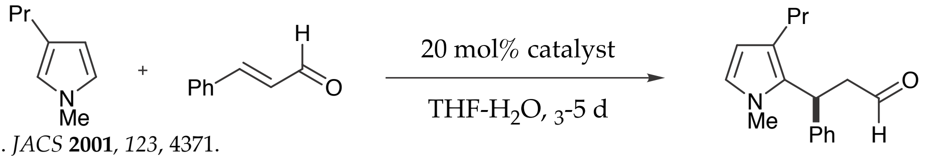
catalyst

- use of *N*-benzyl pyrrole and *N*-allyl pyrrole give similar results

Substitution on the pyrrole is also possible:



87% y, 90% ee

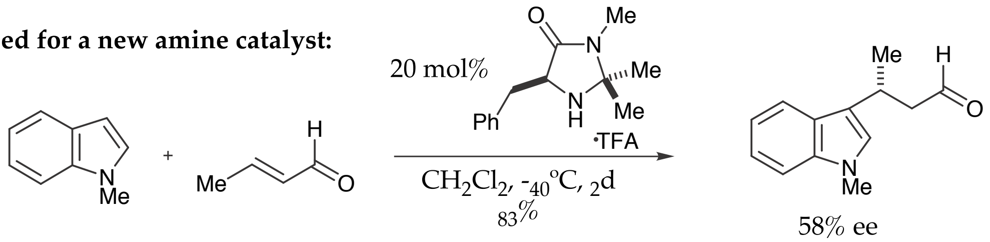


68% y, 97% ee

MacMillan, D. *JACS* **2001**, *123*, 4371.

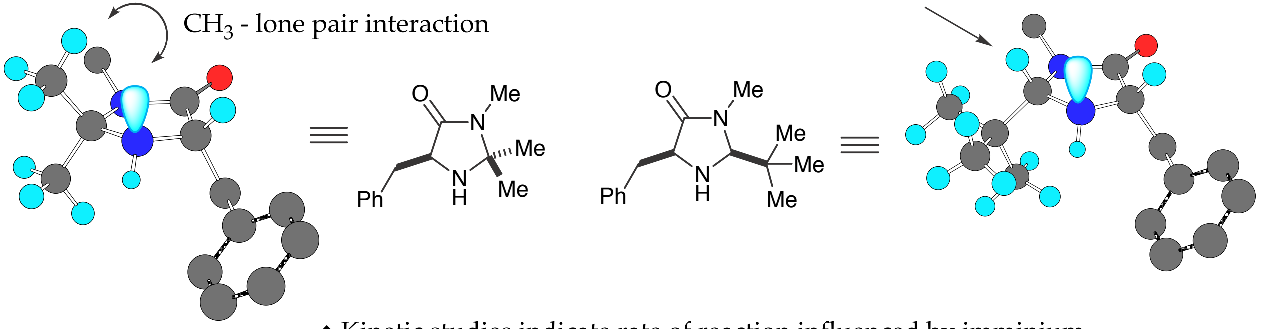
Alkylation of Indoles 1

The need for a new amine catalyst:



- Indole is less electron-rich than pyrrole, so is less nucleophilic toward conjugate addition

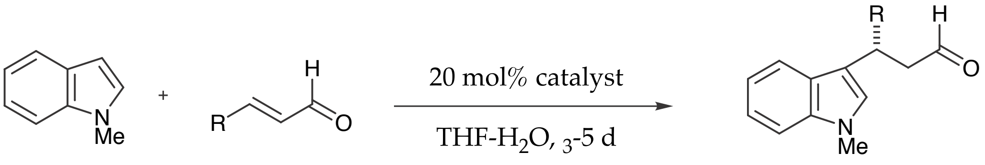
Second generation catalyst: a more reactive variant

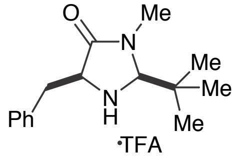


- Kinetic studies indicate rate of reaction influenced by imminium formation as well as carbon-carbon bond forming event

MacMillan, D. *JACS* **2002**, *124*, 1172.

Alkylation of Indoles 2



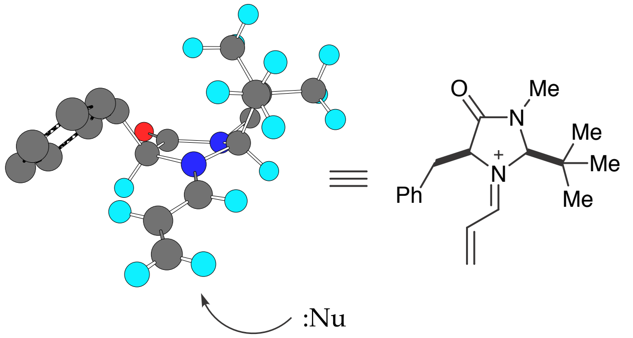


catalyst

R	temp(ºC)	yield	ee
Me	-83	82	92
n-Pr	-60	80	93
i-Pr	-50	74	93
Ph	-55	84	90
CH_2OBz	-83	84	96
CO_2Me	-83	89	91

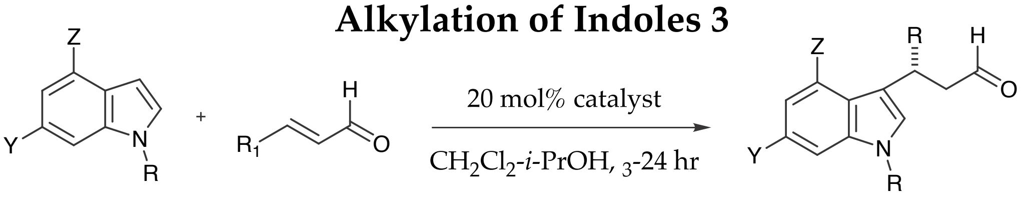
MacMillan, D. *JACS* **2002**, *124*, 1172.

An increase in rate of reaction and enantioselectivity:



- increased top-face coverage
- nucleophile-geminal dimethyl interation removed

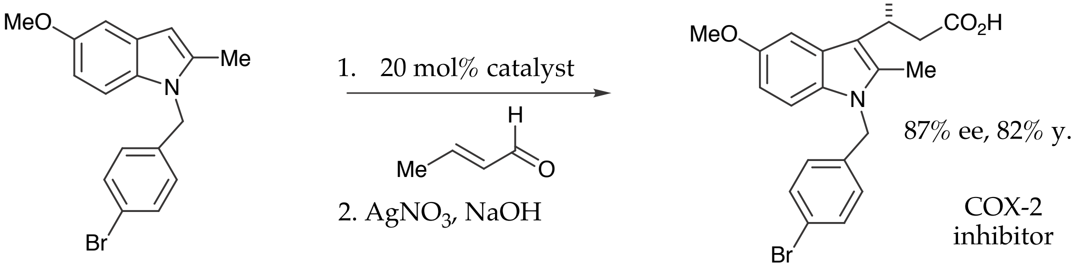
Alkylation of Indoles 3



Indole Scope:

R	Y	Z	R$_1$	temp(ºC)	% yield	% ee
Me	H	H	Me	-87	82	92
H	H	H	Me	-60	72	91
allyl	H	H	Me	-72	70	92
Bn	H	H	Me	-60	80	89
H	H	Me	$-CH_2OBz$	-60	94	94
Me	H	OMe	$-CH_2OBz$	-87	90	96
H	Cl	H	$-CH_2OBz$	-60	73	97

Application to Simple Synthesis:

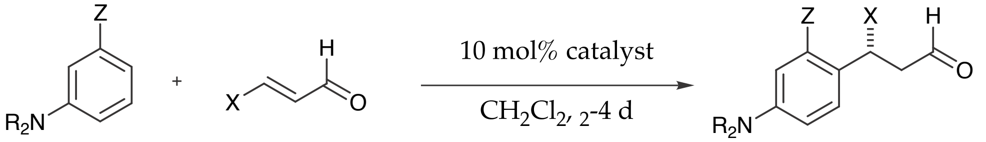


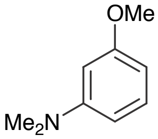
87% ee, 82% y.

COX-2
inhibitor

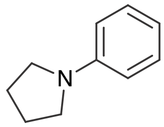
MacMillan, D. *JACS* **2002**, *124*, 1172.

Alkylation of Benzenes

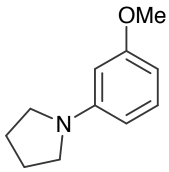




1

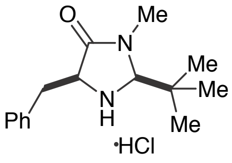


2



3

aniline	X	temp(°C)	% yield	% ee
1	Me	-40	86	89
2	Me	-20	70	87
1	Et	-50	68	88
1	CH_2OBz	-20	89	92
2	CH_2OBz	+20	73	90
1	CO_2Me	-20	90	92
2	CO_2Me	-20	97	97
3	Ph	-50	82	84
3	*p*-ClPh	-10	87	92
1	*p*-NO_2-Ph	-10	87	92
2	*p*-NO_2-Ph	-20	82	90



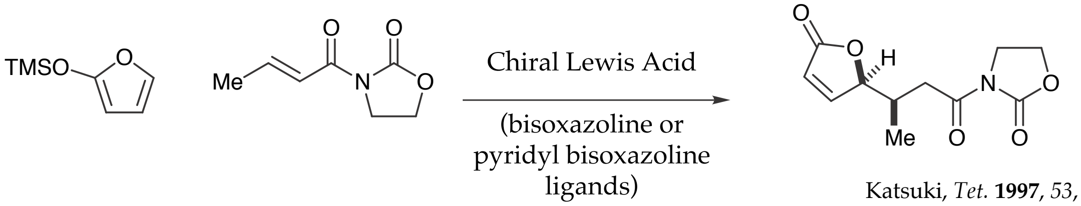
catalyst

- other substituted anilines used with similar results
- catalyst loading can be lowered to 1% without significant loss of yield and enantioselectivity

MacMillan, D. *JACS* **2002**, *124*, 7894.

Mukaiyama-Michael Reaction 1

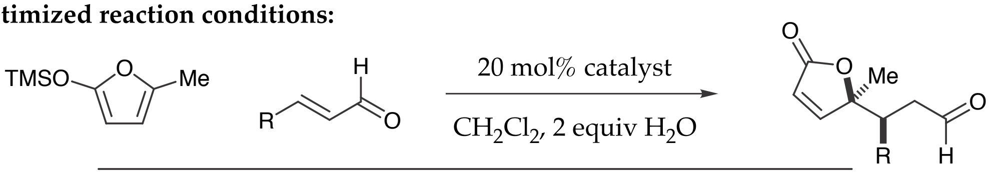
Previous Michael additions with silyloxy furans:



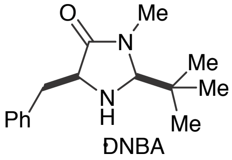
Katsuki, *Tet.* **1997**, *53*, 17015
Desimoni, G. *Tet.* **2001**, *57*, 10203

- note that Lewis acids promote 1,2-addition products when possible, such as α,β–unsaturated enals

Optimized reaction conditions:



R	temp (°C)	% yield	syn:anti	% ee
Me	-70	81	22:1	92
n-Pr	-50	87	31:1	84
i-Pr	-20	80	7:1	98
Ph	-40	77	1:6	99
CH_2OBz	-70	86	20:1	90
CO_2Me	-60	84	11:1	99

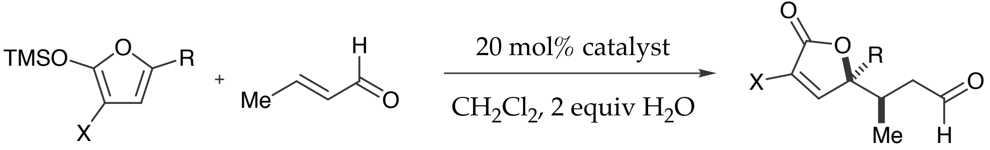


catalyst

MacMillan, D. *JACS* **2003**, *125*, 1192.

Mukaiyama-Michael Reaction 2

Variation of the silyloxy furan

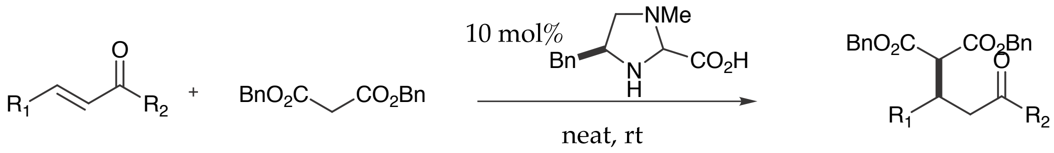


R	X	% yield	*syn:anti*	% ee	
H	H	87	8:1	90	
Me	H	80	22:1	92	
Et	H	83	16:1	90	
CO_2Me	H	86	6:1	98	TFA as cocatalyst
CO_2Me	H	83	1:7	98	TfOH as cocatalyst
Me	Me	73	24:1	90	

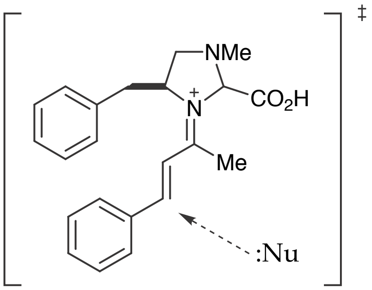
MacMillan, D. *JACS* **2003**, *125*, 1192.

Another Chiral Amine Catalyst

Asymmetric Michael Additions



R_1	R_2	% yield	% ee
p-NO_2Ph	Me	84	89
p-NMe_2Ph	Me	58	77
2-furyl	Me	75	92
2-pyridyl	Me	95	88
n-Bu	Me	61	91
i-Pr	Me	33	84
MeO_2C	Me	59	59
Ph	Me	86	99
Ph	Et	66	95
Ph	*i*-Pr	2	94

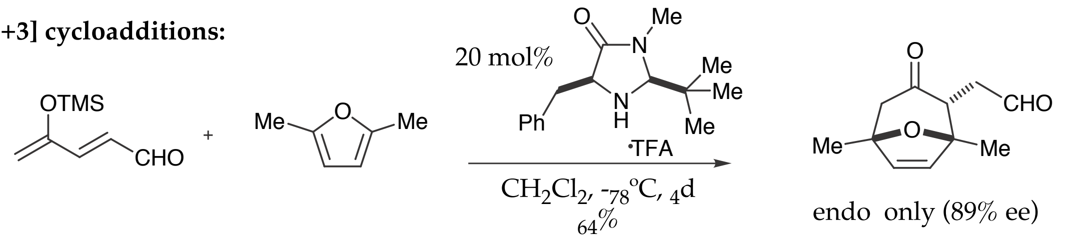


- Nitroalkane additions to α,β–unsaturated ketones has also been performed in good to excellent selectivity (Jorgensen, K. *JOC* **2002**, *67*, 8331.)

Jorgensen, K. *ACIEE* **2003**, *42*, 661.

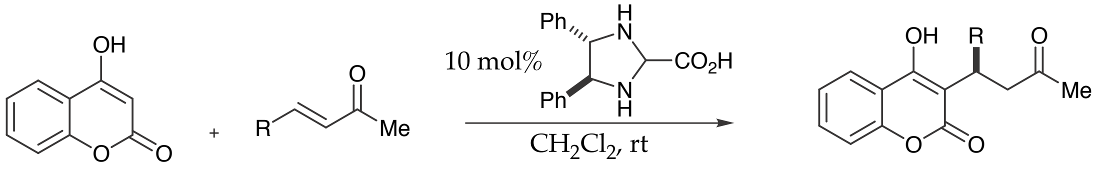
A Listing of Other Asymmetric Organocatalytic Reactions

[4+3] cycloadditions:



Harmata, M. *JACS*, **2003**, *125*, 2058.

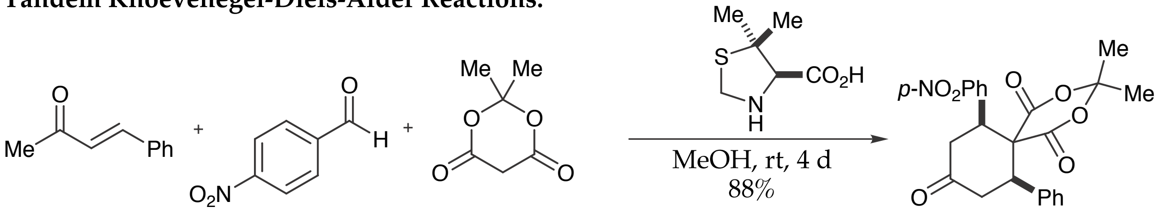
Michael Reactions:



75 - 88% ee

Jorgensen, K. *ACIEE* **2003**, *42*, 4955

Tandem Knoevenegel-Diels-Alder Reactions:



86% ee

Barbas, C. *ACIEE* **2003**, *42*, 4233

Summary

- Reactions are direct:
  - Donors can be used without modification -- no need to deprotonate or silylate prior to reaction
  - Electrophiles can be generated *in situ* (Mannich reaction) most of the time

- Catalysts are:
  - inexpensive
  - commerially available or easily prepared in both enantiomeric forms
  - non-toxic
  - recoverable

- Many reactions can be run at room temperature, under an aerobic atmosphere, with wet solvents

- Many types of reactions can be catalyzed; for some reactions, organocatalysis is the only highly efficient way known (Mannich and Mukaiyama-Michael additions)

- Reaction yield and enantioselectivity is highly dependent on solvent system so require "fine tuning"

- Only reactions that use ketones or aldehydes as donors (electrophiles for Michael additions) can be catalyzed

Organocatalysis using small molecules is a field that has emerged only within the past decade. It is bound to receive increasing attention in the future; as a result, new catalysts will emerge which will allow for the catalysis of reactions previously unutilized in the realm of organocatalysis.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 29

Ambiphilic Functional Groups–3
Sulfur-Based Activating Groups

- Sulfur-Ylides
- Sulfur-Stabilized Carbanions: Structure
- Sulfone-Based Transformations
- Pummerer Rearrangement

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

"Chemical Chameleons: Organosulfones as Synthetic Building Blocks"
B. M. Trost, *Bull. chem. Soc. Japan,* **1988**, *61*, 107-124 **(handout)**

D. A. Evans

Monday,
November 24, 2003

Relevant Background Reading

General: Simpkins, N.S. *Sulphones in Organic Synthesis*, Pergamon Press, New York, 1993.

General: Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019.

Julia: Blakemore, *J. Chem. Soc. Perkin Trans I*. **2002**, 2563.

Electrophilic Properties: Trost, B.M. *Bull.Chem. Soc. Jpn.* **1988**, *61*, 107.

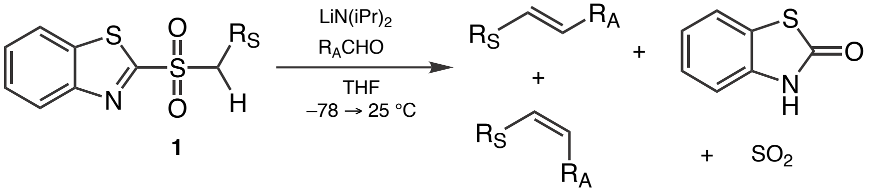
SO_2 Extrusion: Vogtle, F.; Rossa, L. *ACIEE* **1979**, *18*, 515.

Ramberg-Bäcklund Rxn: Paquette, L.A. *Org. Reactions* **1977**, *25*, 1.

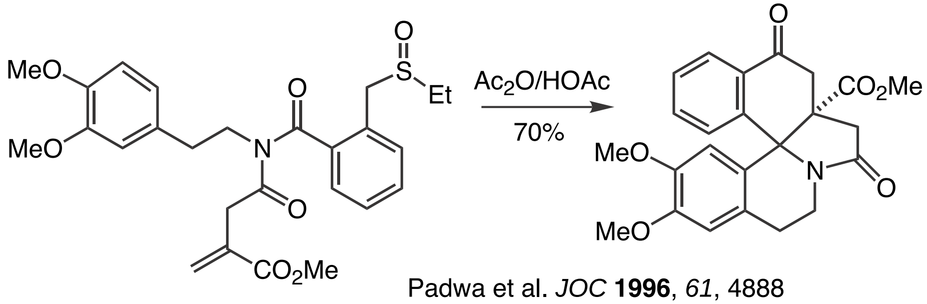
Triflones: Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.

Sulfoximides: Johnson, C.R. *Tetrahedron* **1984**, *40*, 1225

Cum Question, 1998: The stereoselective construction of trans olefins through carbanion-mediated condensation processes has still not been rendered general. One transformation that may be used in certain circumstances is the "one-step" Julia transformation illustrated below. PPProvide a mechanism for this transformation.



The cruel mechanistic problems that you should be prepared for in Chem 206



Padwa et al. *JOC* **1996**, *61*, 4888

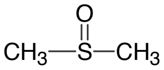
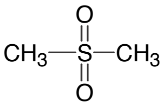
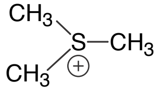
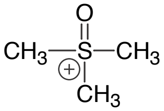
Sulfur-Based Functional Groups-1

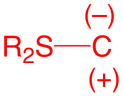
Relevant Background Reading

General:	Simpkins, N.S. *Sulphones in Organic Synthesis*, Pergamon Press, New York, 1993.
General:	Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019.
Julia:	Blakemore, *J. Chem. Soc. Perkin Trans I.* **2002**, 2563.
Electrophilic Properties:	Trost, B.M. *Bull.Chem. Soc. Jpn.* **1988**, *61*, 107.
SO_2 Extrusion:	Vogtle, F.; Rossa, L. *ACIEE* **1979**, *18*, 515.
Ramberg-Bäcklund Rxn:	Paquette, L.A. *Org. Reactions* **1977**, *25*, 1.
Triflones:	Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.
Sulfoximides:	Johnson, C.R. *Tetrahedron* **1984**, *40*, 1225

Acidities of Sulfur-based Functional Groups

Bordwell, F. G.; Zhang, X.-M. *Acc. Chem. Res.* **1993**, *26*, 510-17.

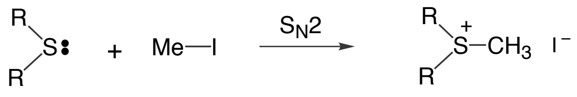
		pKa (DMSO)	
CH_3-S-CH_3	Sulfide	(45)	← CH_4 pKa (~56)
 $CH_3-\overset{O}{\overset{\|}{S}}-CH_3$	Sulfoxide	~35	← NH_3 pKa (~41)
 $CH_3-\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}-CH_3$	Sulfone	~ 31	← HOH pKa 31
 $(CH_3)_2\overset{+}{S}-CH_3$	Sulfonium Salt	18.2	
 $CH_3-\underset{CH_3}{\overset{O}{\overset{\|}{\overset{+}{S}}}}-CH_3$	Oxo-Sulfonium Salt		


$R_2S-\underset{(+)}{\overset{(-)}{C}}$

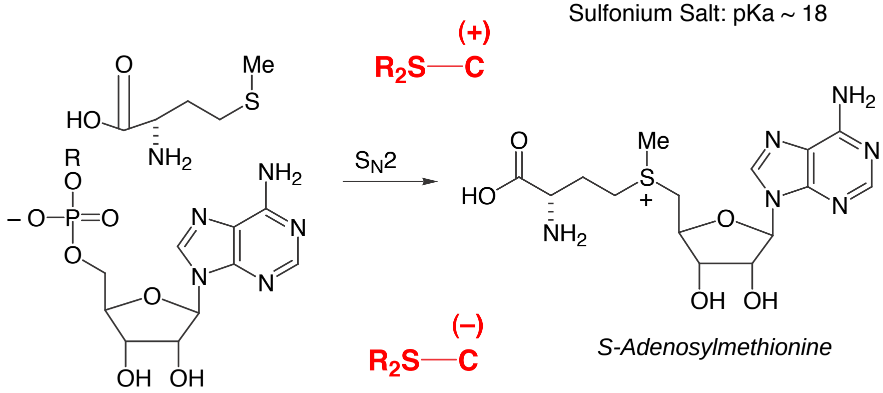
Reactivity Pattern Nonalternate

Reactions of Sulfonium Ylids

■ Synthesis:

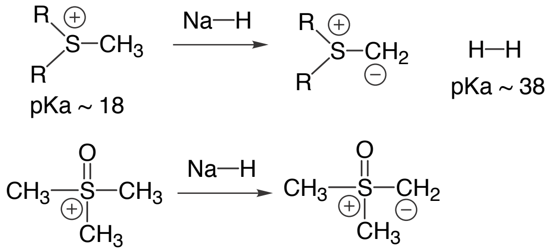


Sulfonium Salt: pKa ~ 18

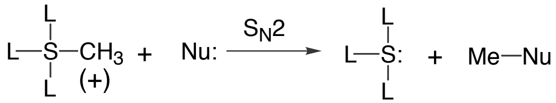


S-Adenosylmethionine

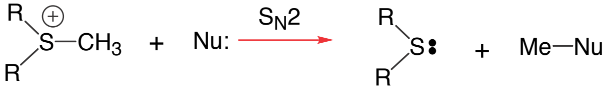
■ Deprotonation:



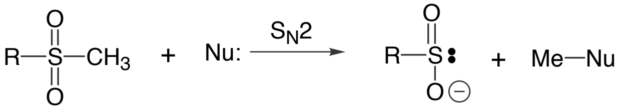
■ **Leaving Group Potential:** R_2S—C(+)



Excellent LG



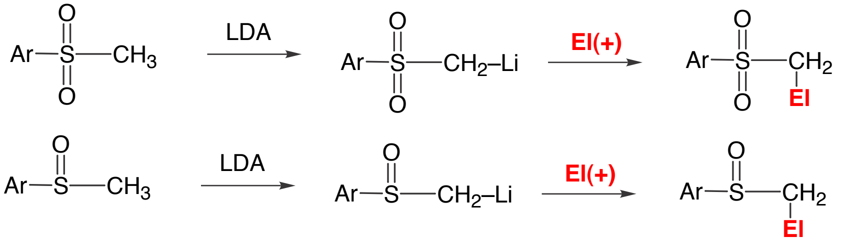
Good LG



X-ray Structures of Metallated Sulfones & Sulfoxides

Sulfone- & Sulfoxide Based Carbanions: Structure

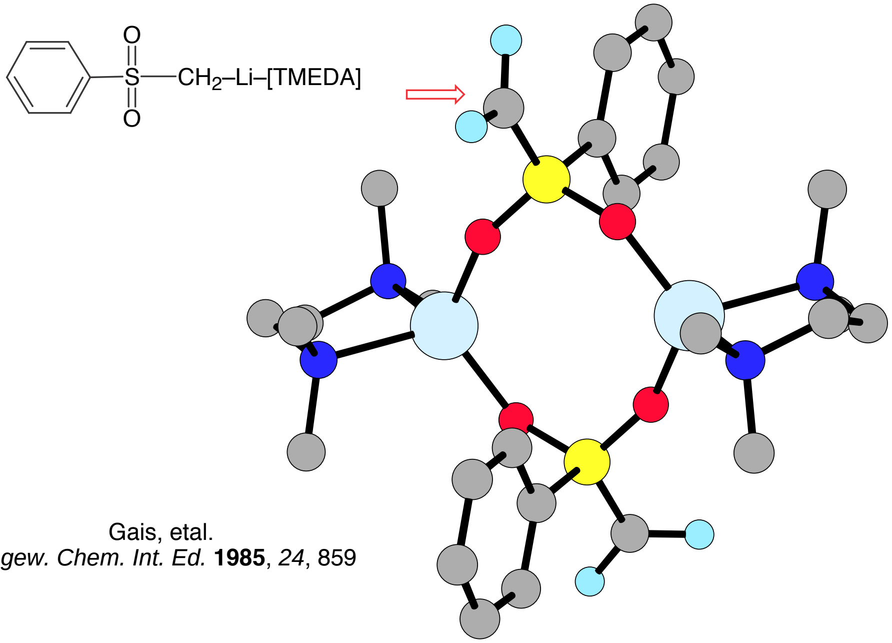
- Sulfone- and sulfoxide-stabilized carbanions are extremely useful carbon nucleophiles in organic synthesis.



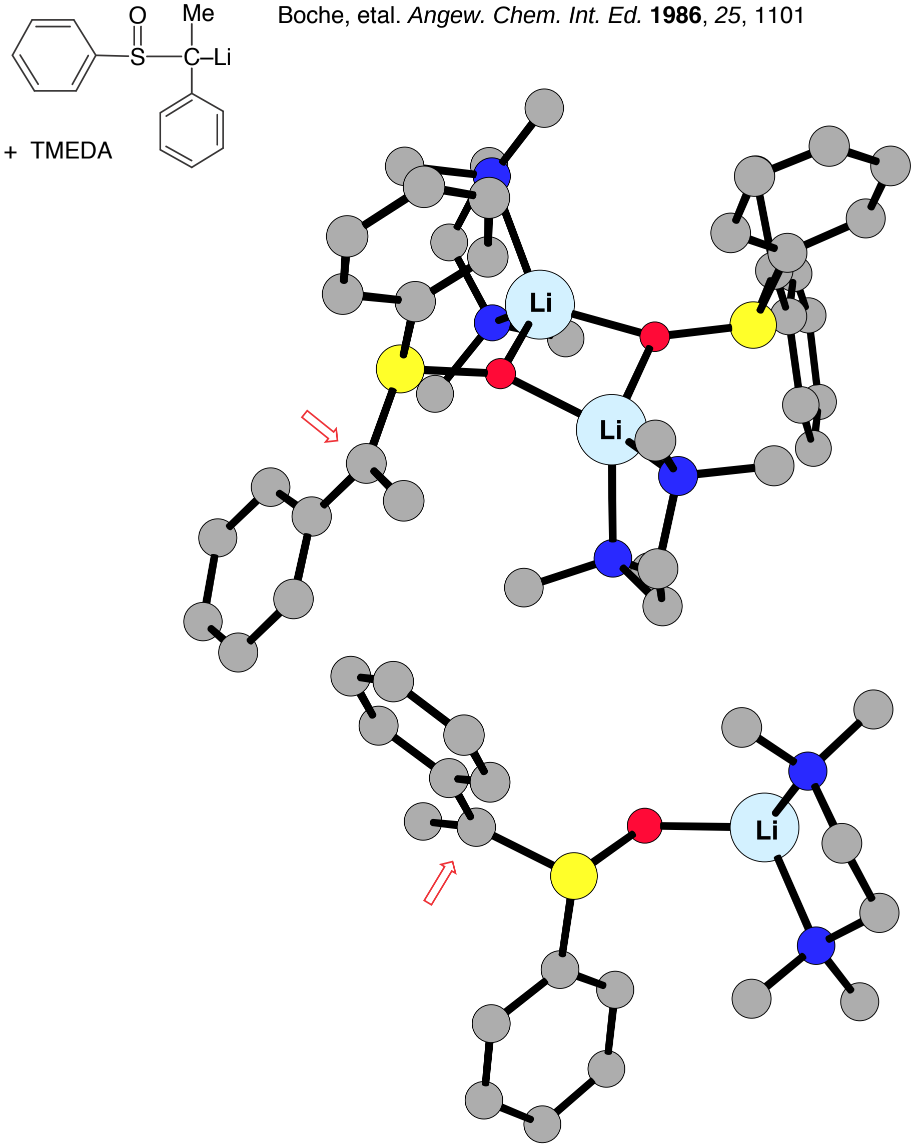
However, until recently little information was available on the solid state structures of these species:

> "The Structure of Lithium Coumpounds of Sulfones, Sulfoximides, Sulfoxides, Thioethers, 1,3 Dithianes, Nitriles, Nitro Compounds, and Hydrazones."
> Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

Here are several examples taken from the Boche review:



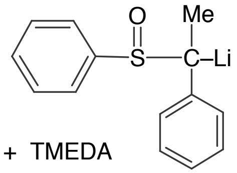
Gais, etal.
Angew. Chem. Int. Ed. **1985**, *24*, 859

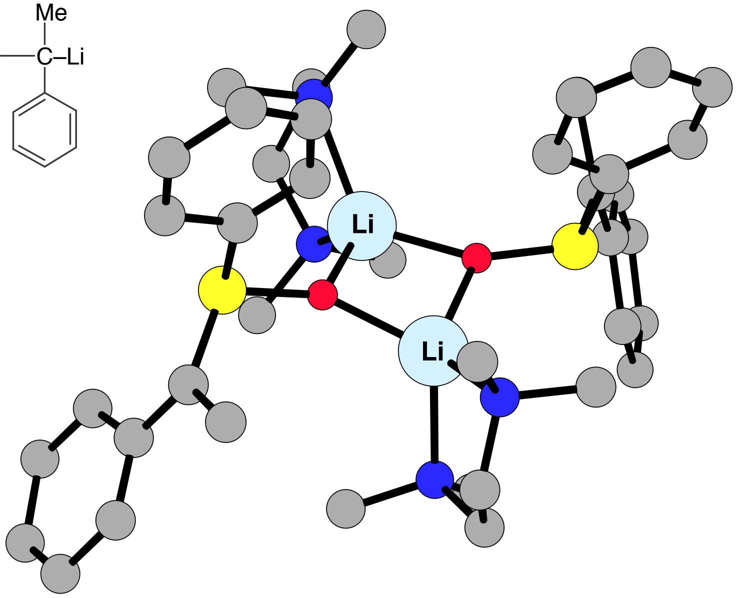


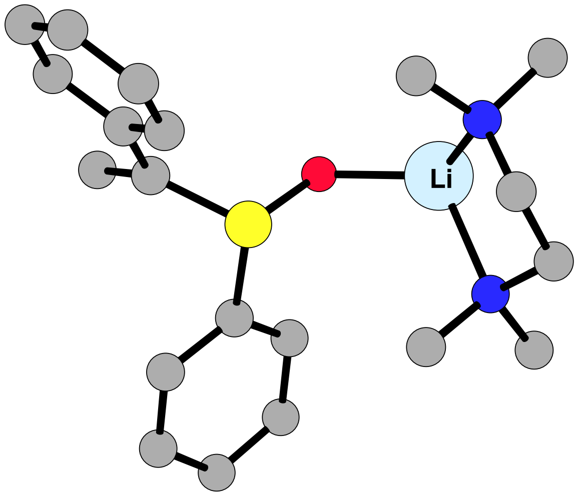
Boche, etal. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101

- The Li counterions are not associated with the charged carbon.
- The carbanions are largely trigonal.

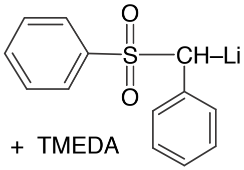
X-ray Structures of Phenylsulfinyl Carbanions

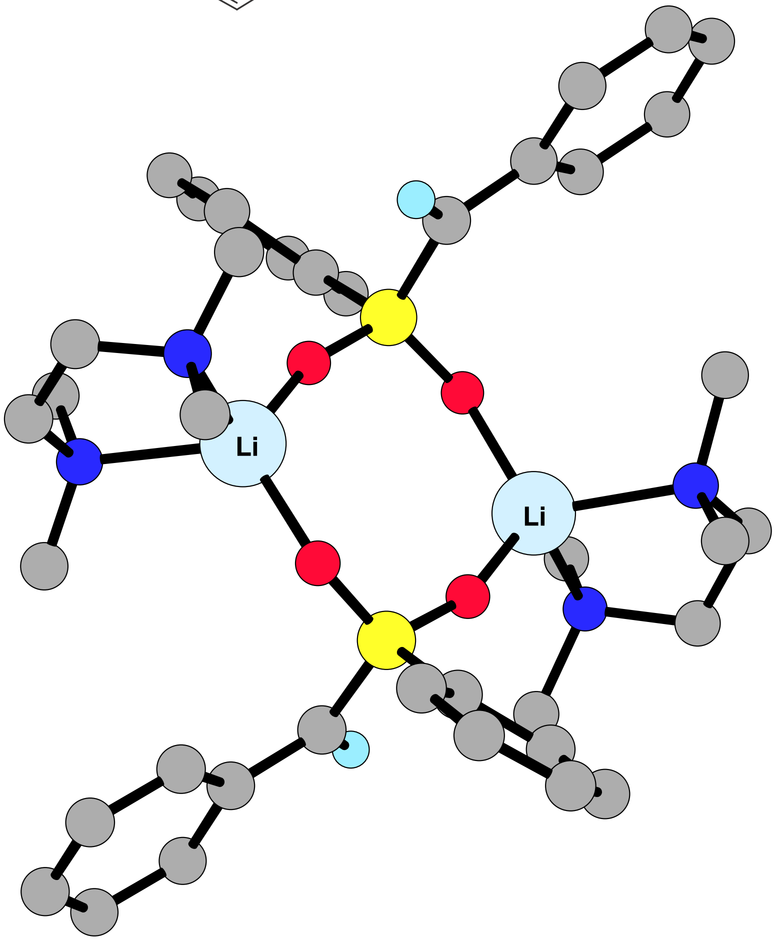






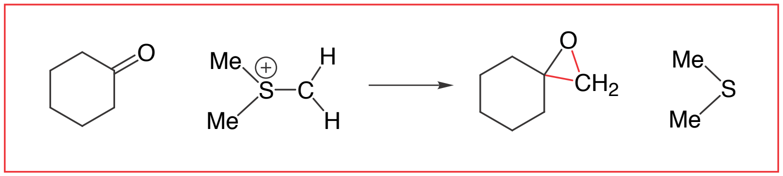
Boche, etal. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101



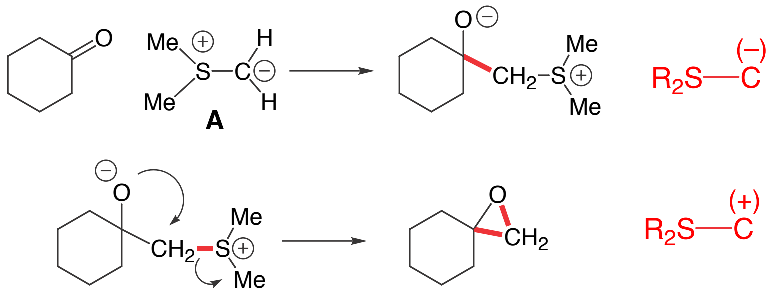


Boche, etal. *Angew. Chem. Int. Ed.* **1985**, *24*, 573

Reactions with ketones: $R_2S-\overset{(\mp)}{C}$ Reactivity Pattern: Nonalternate

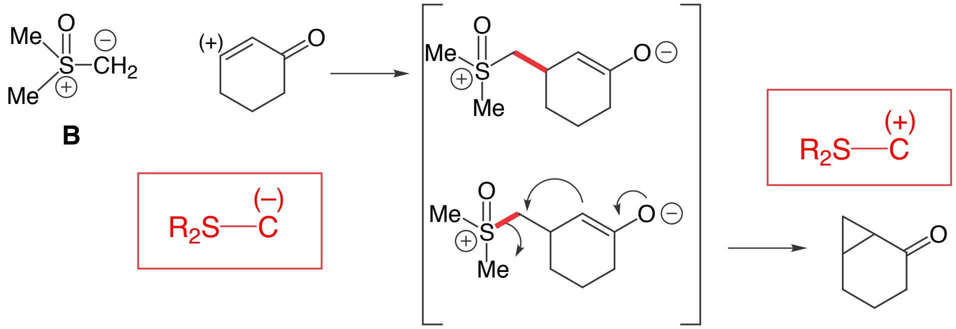


Corey & Chaycovski, *JACS* **1965**, *87*, 1353-1364. **(Handout)**

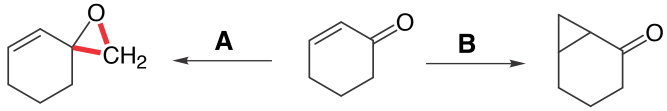


"Twenty-five Years of Dimethylsulfoxonium Methylide (Corey's Reagent).", Gololobov, Y. G.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609.
(electronic handout)

Reactions of OxoSulfonium Ylids: Conjugate Addition

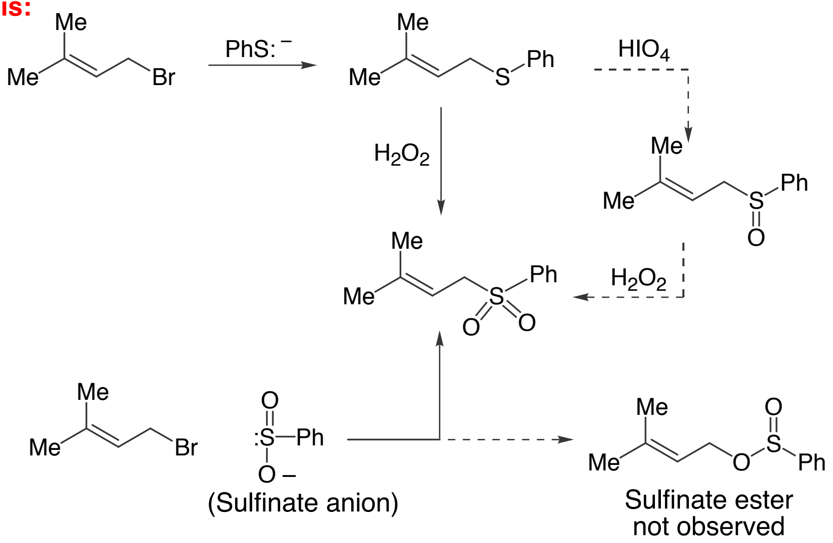


Nonalternate reactivity pattern revealed in consecutive reactions



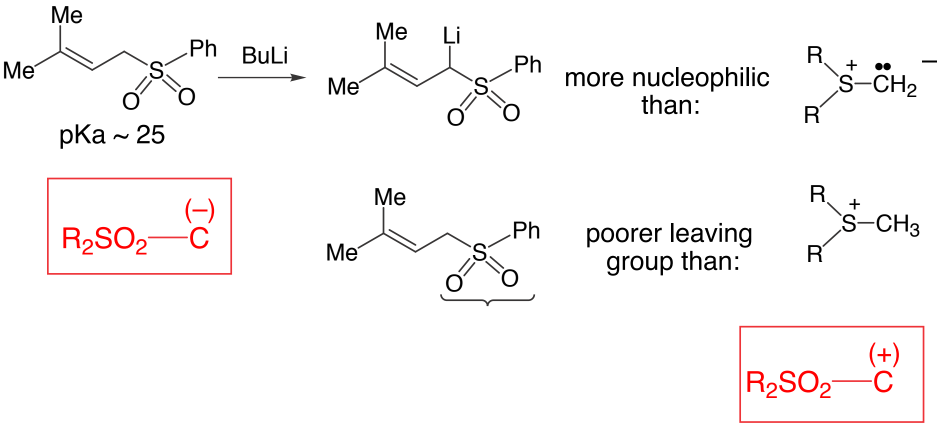
Reactions of Sulfones

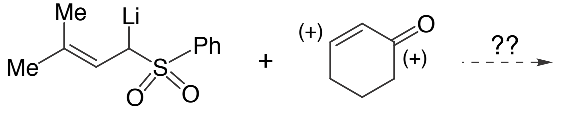
Synthesis:



Good review article: Magnus, *Tetrahedron* **1977**, *33*, 2019-2045.

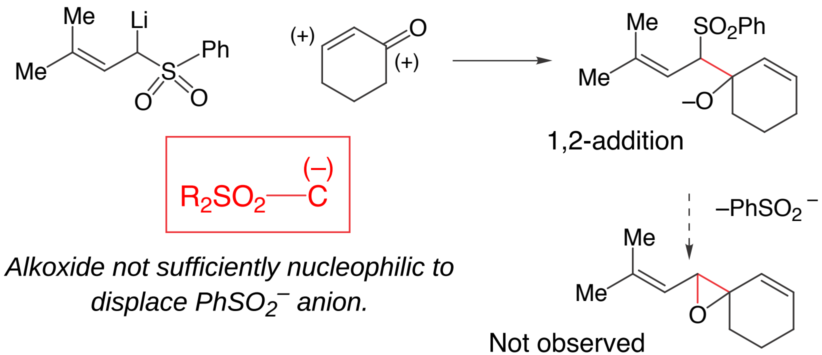
Reactions of Sulfones





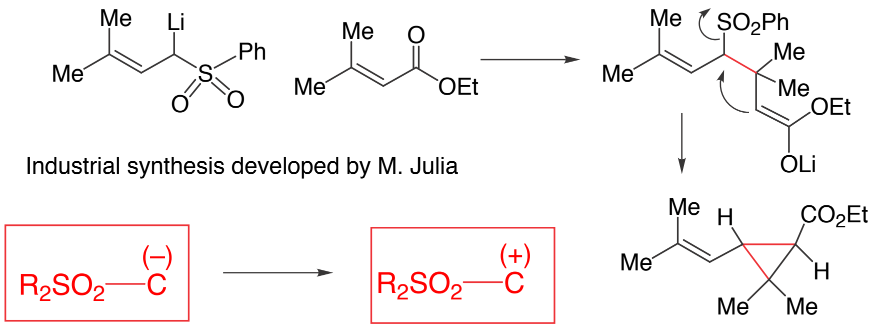
1,2- vs 1,4-addition ??

Will function as LG ??



Alkoxide not sufficiently nucleophilic to displace $PhSO_2^-$ *anion.*

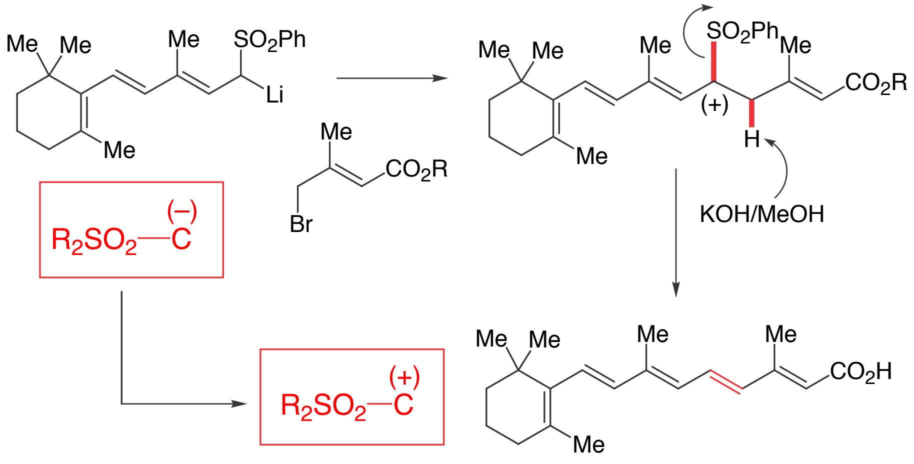
However!!


Me
Li
Ph
Me
S
O
O
Me
O
Me
OEt
Me
SO2Ph
Me
Me
Me
OEt
OLi
$R_2SO_2\text{—}\overset{(-)}{C}$
$R_2SO_2\text{—}\overset{(+)}{C}$
Me
H
CO2Et
Me
H
Me
Me

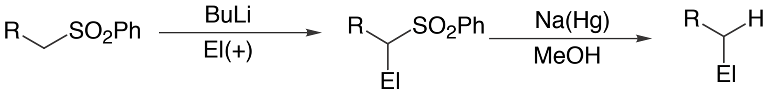
Industrial synthesis developed by M. Julia

trans chrysanthemic acid

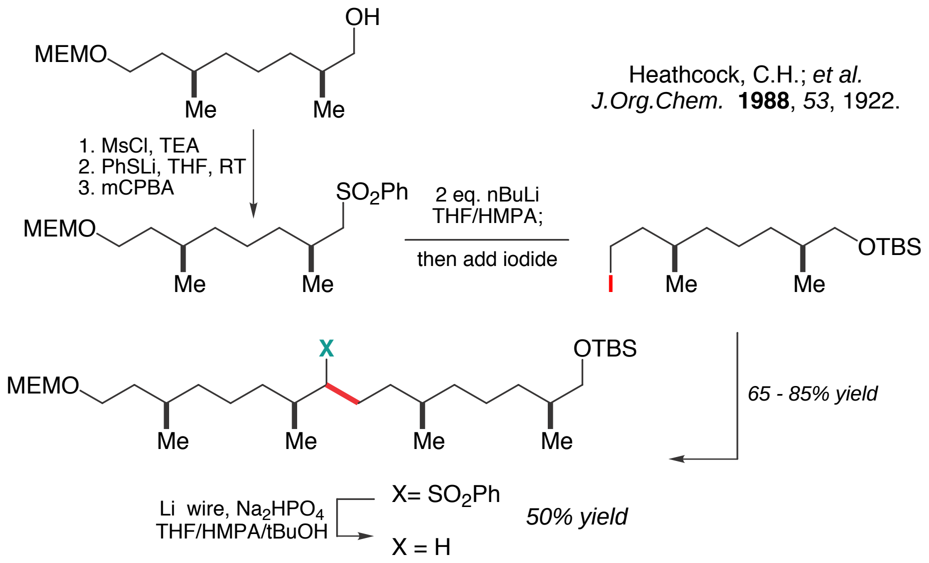
Synthesis of Vitamin A: Julia & Co-workers, *Bull. Soc. Chim. Fr*. **1985**, 130



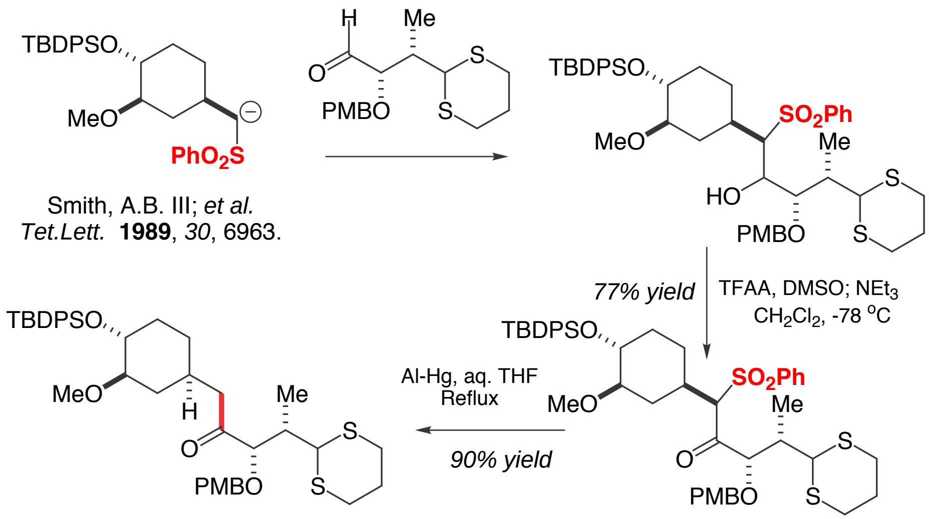
The Sulfone group may also be readily removed reductively:



Fragment Coupling with Sulfonyl Carbanions

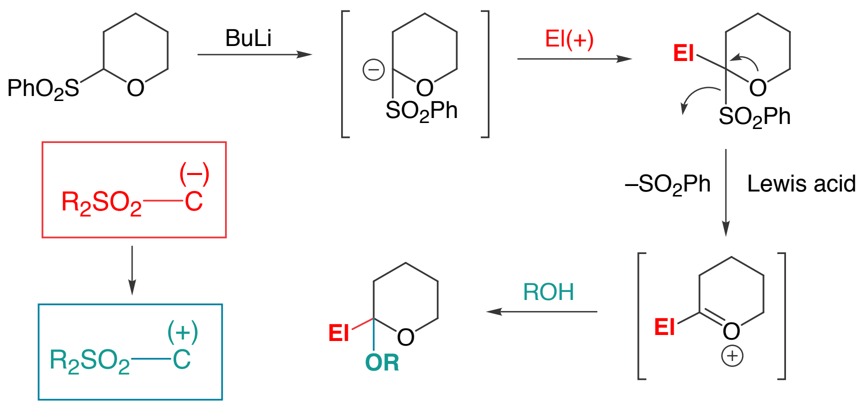


Heathcock, C.H.; *et al.*
J.Org.Chem. **1988**, *53*, 1922.



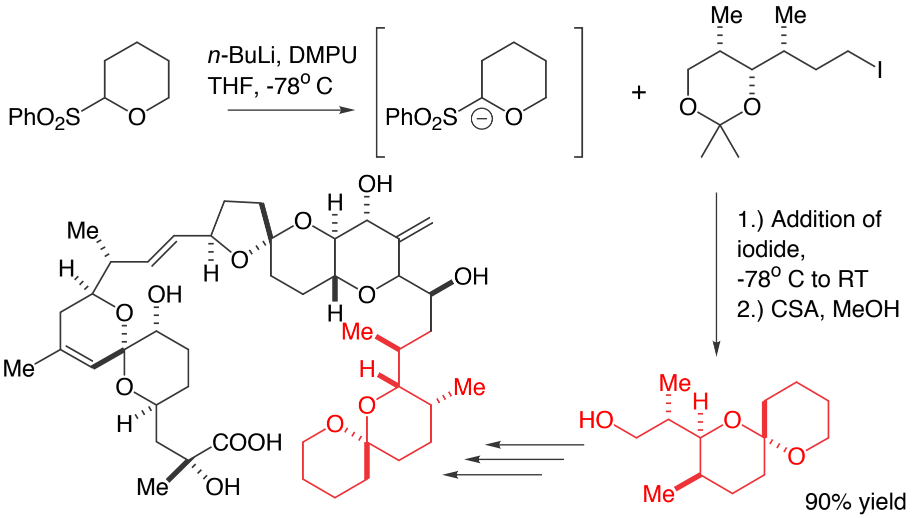
Smith, A.B. III; *et al.*
Tet.Lett. **1989**, *30*, 6963.

Functionalization of cyclic Ethers



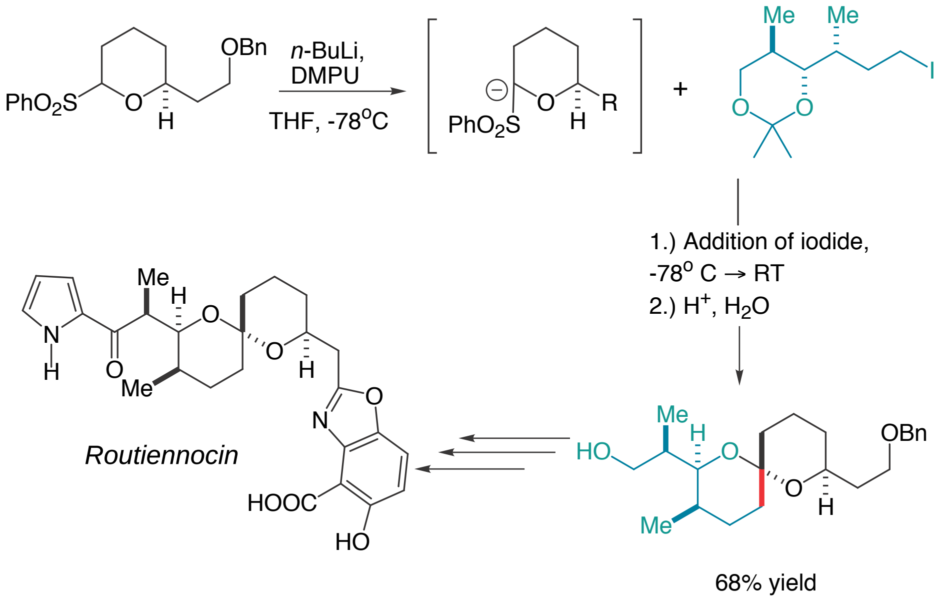
Ley *et al*, *Synlett*, **1992**, 395; Ley *et. al*, *Tetrahedron*, **1992**, *48*, 7899

Total synthesis of Okadaic Acid

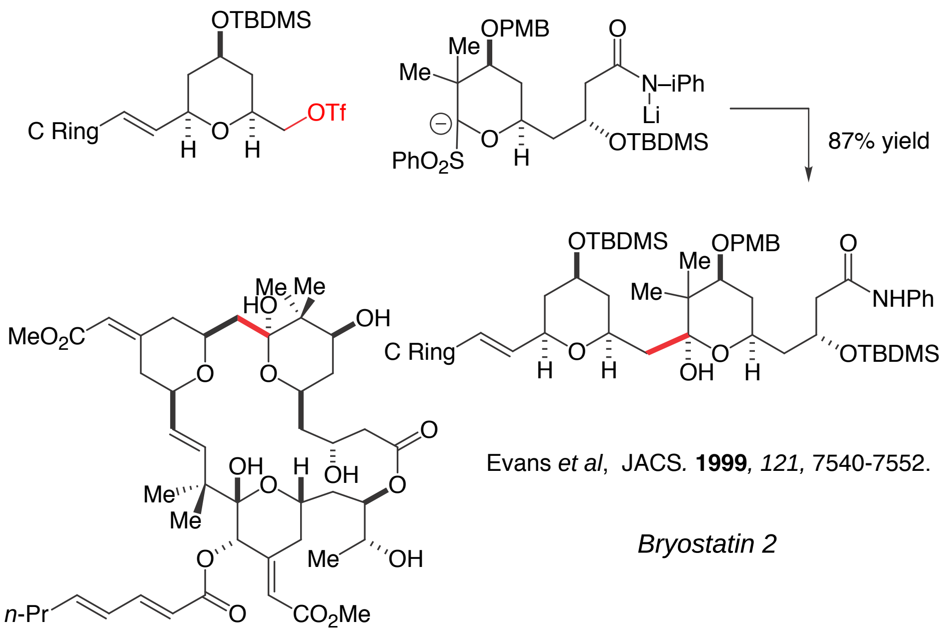


Ley *et al, J. Chem. Soc., Perkin Trans. 1*, **1998**, 3907.

Total Synthesis of Routiennocin (CP-61,405)



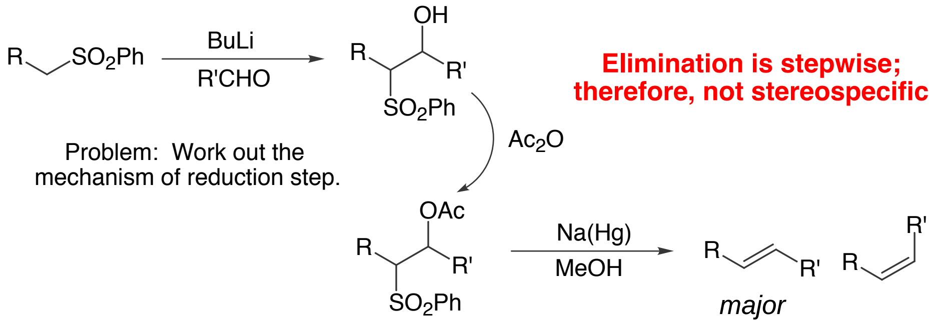
Total synthesis of Bryostatin 2



Evans *et al*, JACS. **1999**, *121*, 7540-7552.

Sulfur-Based Functional Groups-5: Julia Olefin Synthesis

First Generation Julia Trans Olefin Synthesis:



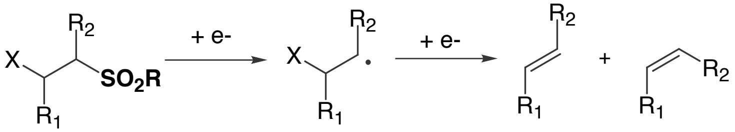
Elimination is stepwise; therefore, not stereospecific

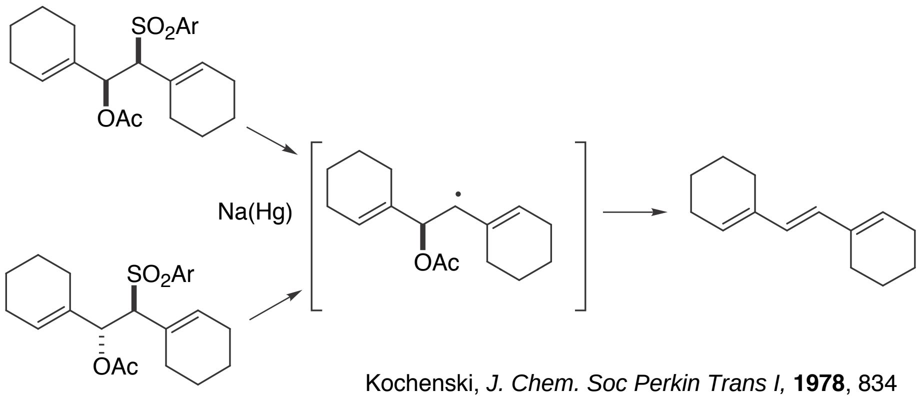
Problem: Work out the mechanism of reduction step.

Good sulfone review: Trost, *Bull Chem. Soc. Japan,* **1988**, *61*, 107-124.

Julia Review,
Blakemore, *J. Chem. Soc. Perkin Trans I*. **2002**, 2563. **(electronic handout)**

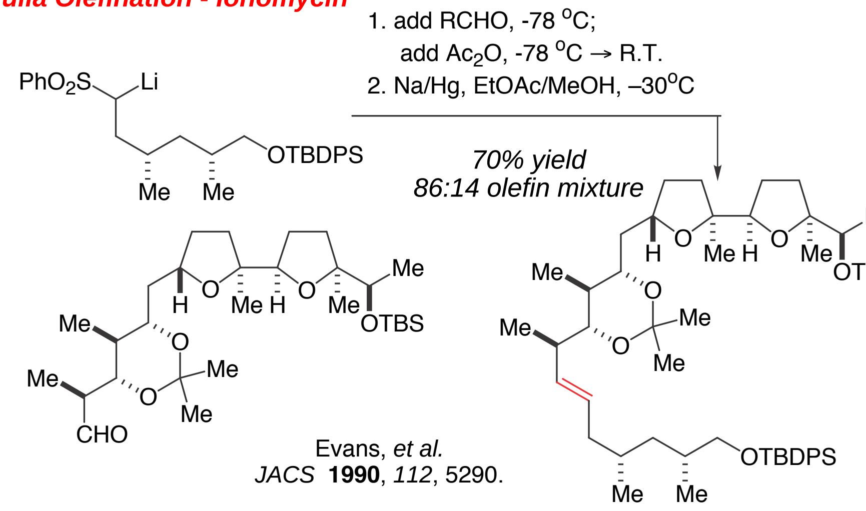
The reduction step is not stereosecific





Kochenski, *J. Chem. Soc Perkin Trans I*, **1978**, 834

Julia Olefination - Ionomycin

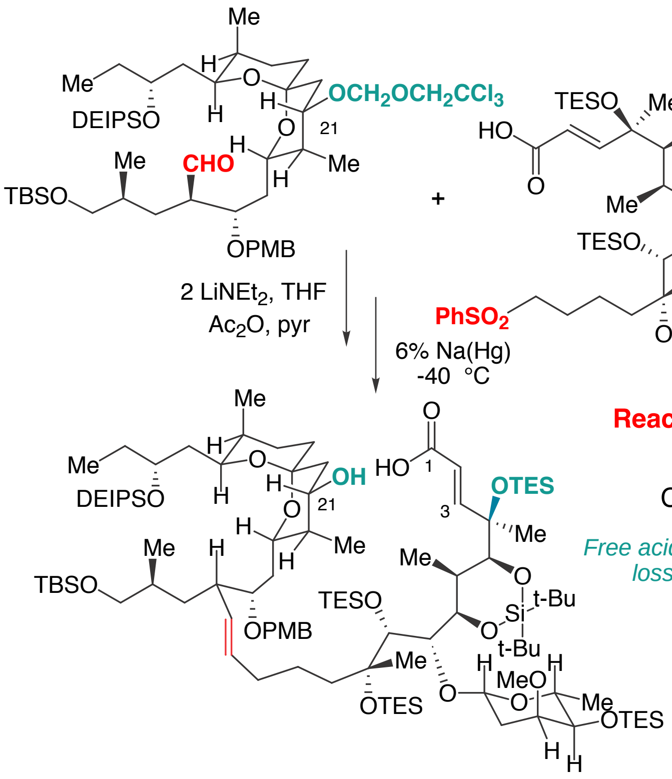


1. add RCHO, -78 °C;
add Ac$_2$O, -78 °C → R.T.
2. Na/Hg, EtOAc/MeOH, –30°C

70% yield
86:14 olefin mixture

Evans, *et al.*
JACS **1990**, *112*, 5290.

Cytovaricin Synthesis: *JACS* **1990**, *112*, 7001



2 LiNEt$_2$, THF
Ac$_2$O, pyr

6% Na(Hg)
-40 °C

Reactions accomplished:

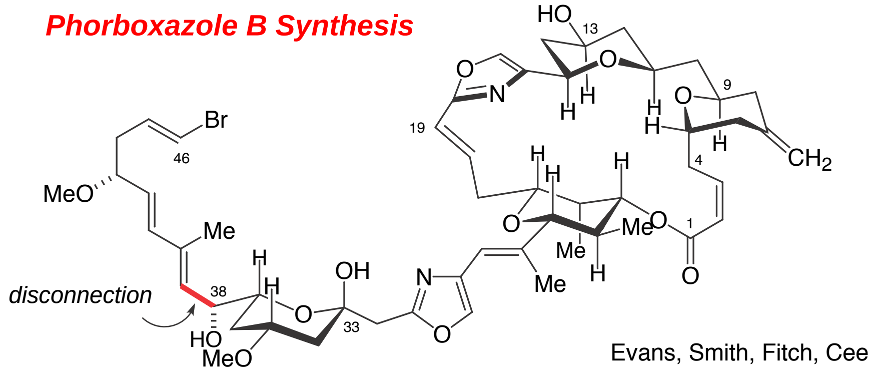
C=C construction
C_{21} OH deprotection

Free acid must be used to prevent loss of C_4 OH in 2nd step

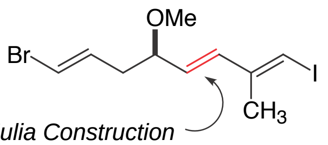
overall yield, 66%

Sulfur-Based Functional Groups-5: Julia Olefin Synthesis-2

Phorboxazole B Synthesis

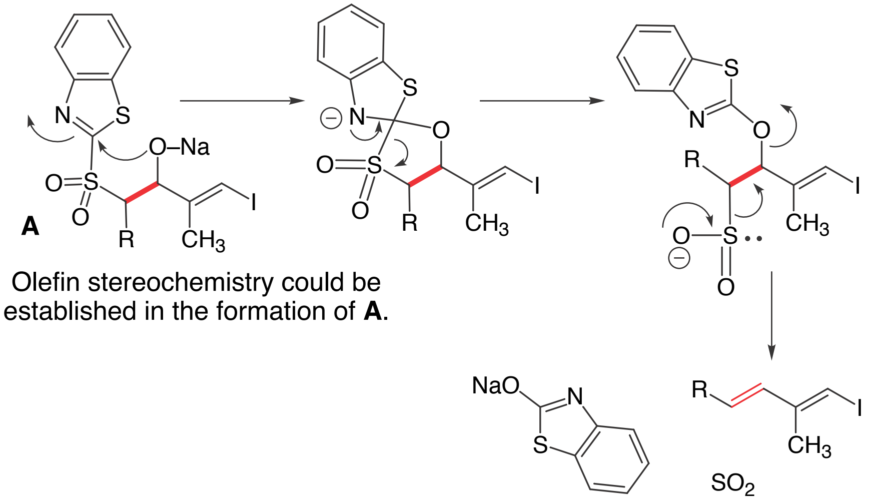


Evans, Smith, Fitch, Cee
JACS **2000**, *122*, 10033-10046.

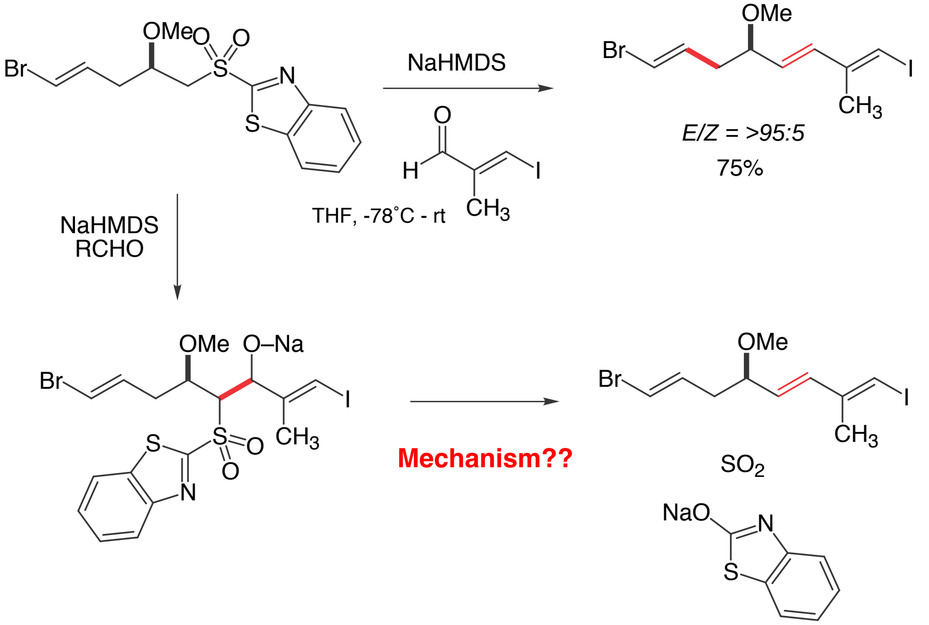


C_{39}–C_{46} Synthon

The Mechanism:



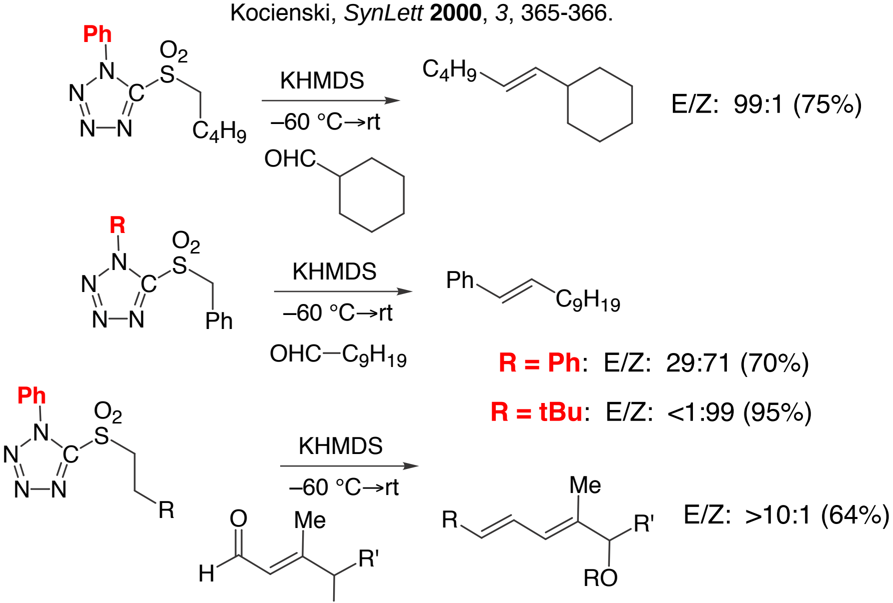
Olefin stereochemistry could be established in the formation of **A**.



Mechanism??

Recent Modifications of the Julia Process:

Kocienski, *SynLett* **2000**, *3*, 365-366.



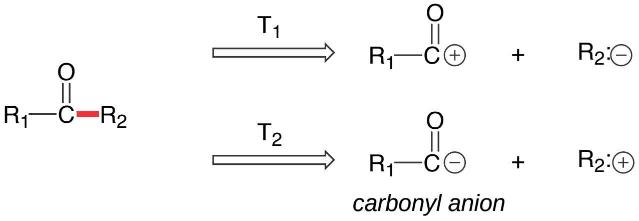
R = Ph: E/Z: 29:71 (70%)

R = tBu: E/Z: <1:99 (95%)

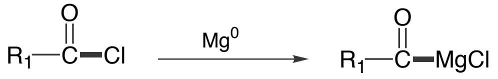
Metternich, *JOC* **1999**, *54*, 9632

Carbonyl Anions: A useful Reversed Polarity Equivalent

Consider the two possible polar disconnections of the C–R_2 bond of the ketone shown below:

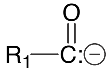


Carbonyl anions are not normally accessible via aldehyde deprotonation

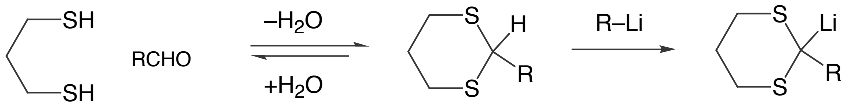


not feasible !! Why??

Operational equivalents to the carbonyl anion are useful in synthesis



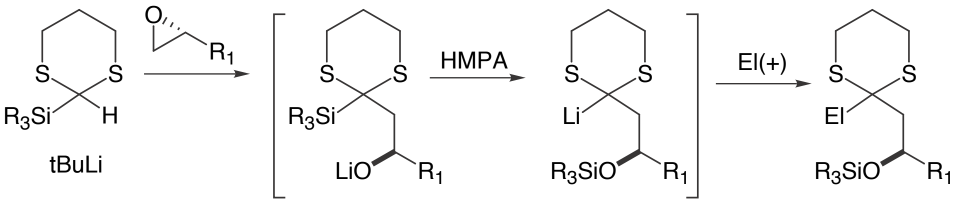
1,3-Dithianes as Carbonyl Anion Equivalents



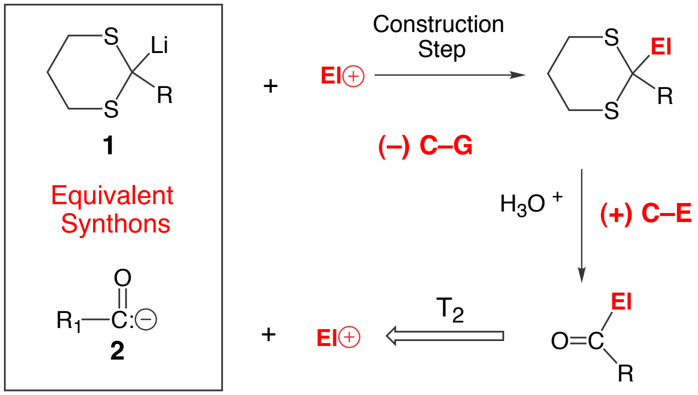
pKa ~ 39

Reactivity Patterns: $(RS)_2$–C(+) $(RS)_2$–C(–)

Latest Innovations: A. B. Smith, *JACS* **2003**, *125*, 14435-14445 (Handout)

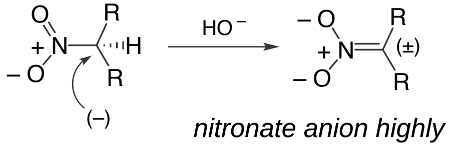


The overall set of reactions which establishes the equivalency of the hypothetical carbonyl anion **1** and its equivalent synthon **2** is shown below:

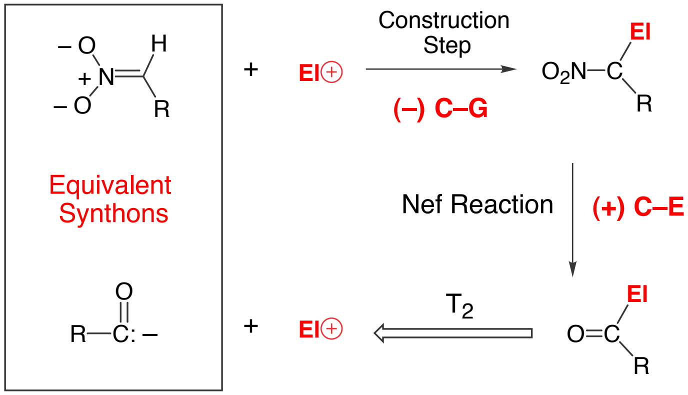


Nitronate Anions are also useful Carbonyl Anions

pKa 18

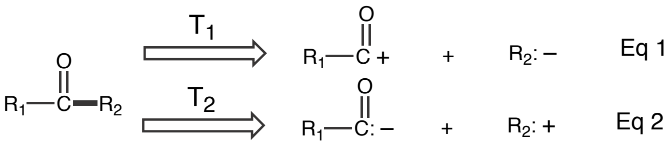


nitronate anion highly stablized



Dithianes anions highly nucleophilic (indiscriminate):
Nitonate anions higly discriminating

Introduction. As you know, transform T_1 conforms to the polar bias mapped on to the carbon skeleton by =O, while transform T_2 does not. Although T_1 is the more common transform, sometimes, because of the presence other functionality in either R_1 or R_2, the "reversed-polarity" transform is more suitable for the particular synthesis at hand.

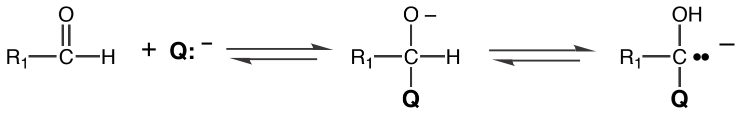


Reversed Polarity Synthon

Ideally, one might visualize a catalytic agent (**Q**) which might react reversibly with an aldehyde in conjunction with inverting its charge affinity pattern. Nature has designed such reagents.

General Scheme

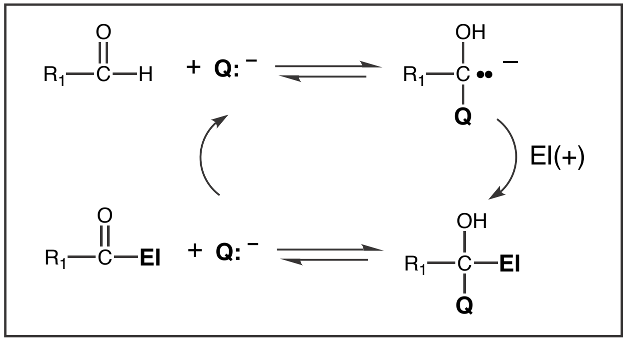
Charge Affininty Inversion Step: The structural constraints on (Q) are that it must be nucleophilic, add reversibly to aldehydes, and stabilize an adjacent carbanionionic center.



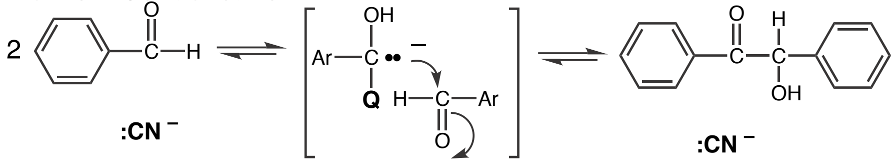
Lets call (Q) a charge affininty inversion operator since in operates on RCHO and reverses the intrinsic polar reactivity of the RCHO carbon from (+) to (–).

Overall Process:

The Inversion Operator



Benzoin Condensation:

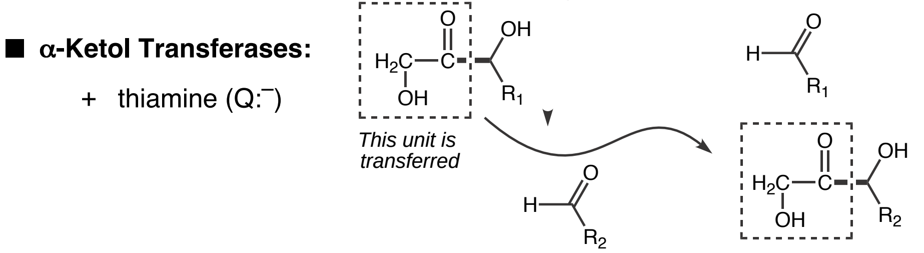


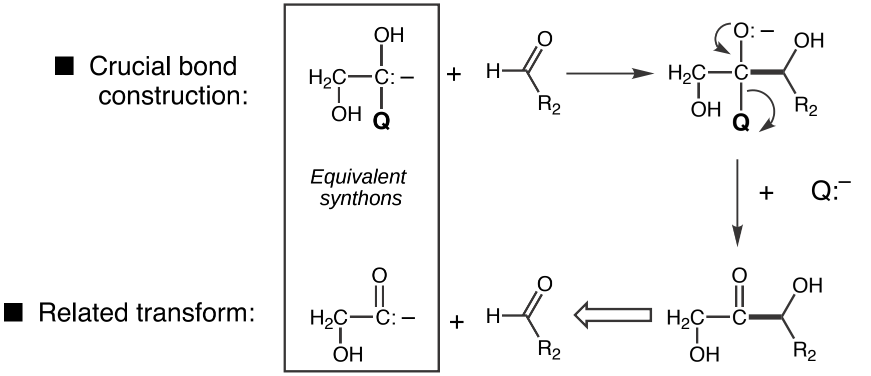
Cyanide ion is the best example of a reagent which functions as an inversion operator. The benzoin reaction is restricted to aromatic aldehydes. Why?

Nature's Inversion Operators

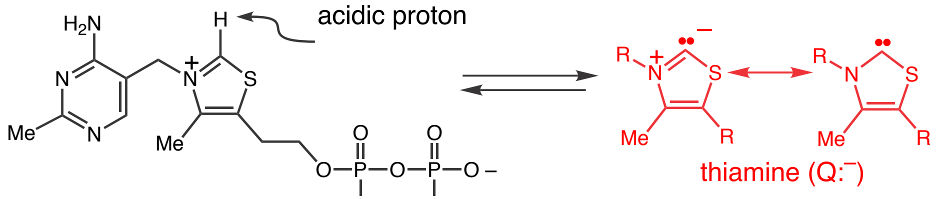
There is a clear need in nature to have both types of polar bond constructions exemplified by Transforms T_1 and T_2 (Eq 1-2). One such reaction is shown below.

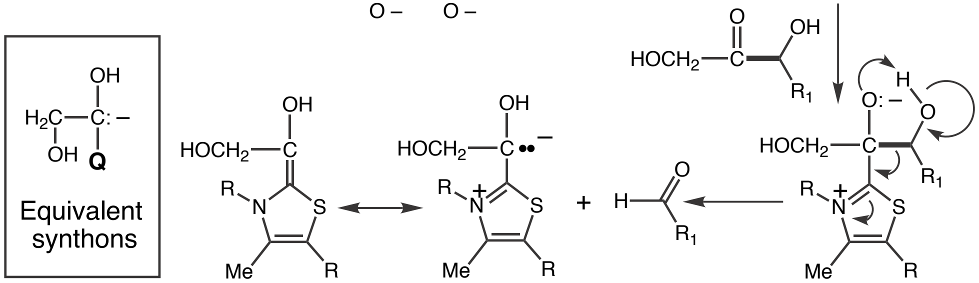
- This reaction, which is enzyme-catalyzed, requires the cofactor thiamine which functions as the inversion operator in these biological processes.





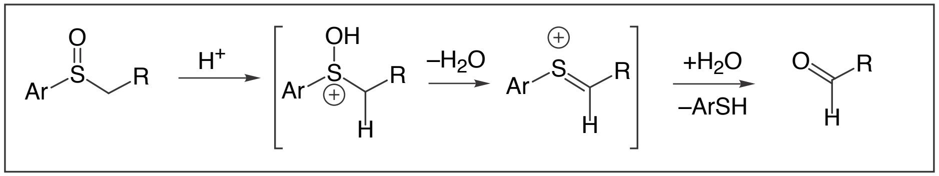
The Thiamine Coenzyme (Virtamin B_1) & how it functions



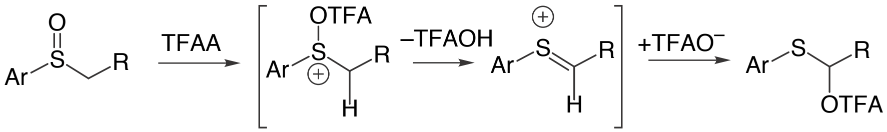


The Pummerer Rearrangement

Basic Transformation:



The Pummerer Rearrangement facilitates the transformation of a sulfinyl → aldehyde transformation. The rearrangement may be initiated by either a Bronsted acid or an anhydride such as trifluoroacetic anhydride (TFAA). With the latter reagent, the transformation occurs at room temperature.



Leading References

De Lucchi, Miotti, et al. (1991). "The Pummerer reaction of sulfinyl compounds." *Organic Reactions* **1991**, *40*: 157.

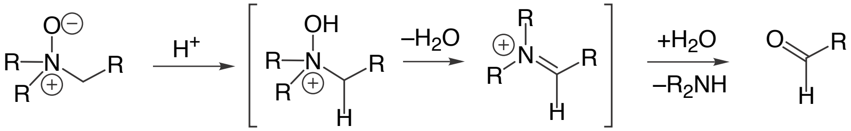
Grierson, and Husson (**1991**). Polonovski- and Pummerer-type Reactions and the Nef Reaction. *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. *6*: 909.

Padwa, A., D. E. Gunn, et al. "Application of the Pummerer reaction toward the synthesis of complex carbocycles and heterocycles." *Synthesis* **1997** 1353-1377.

Carreno, "Applications of sulfoxides to asymmetric synthesis of biologically active compounds." Chem. Reviews **1995** *95*, 1717-1760.

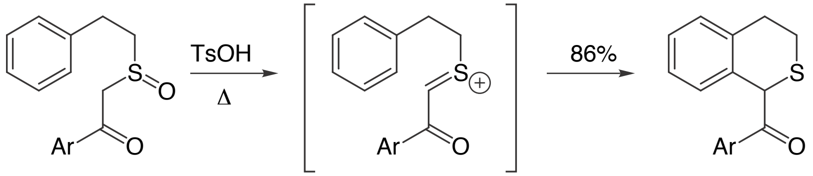
Kita, Y. and N. Shibata (1996). "Asymmetric pummerer-type reactions induced by O-silylated ketene acetals." Synlett(4): 289-296.

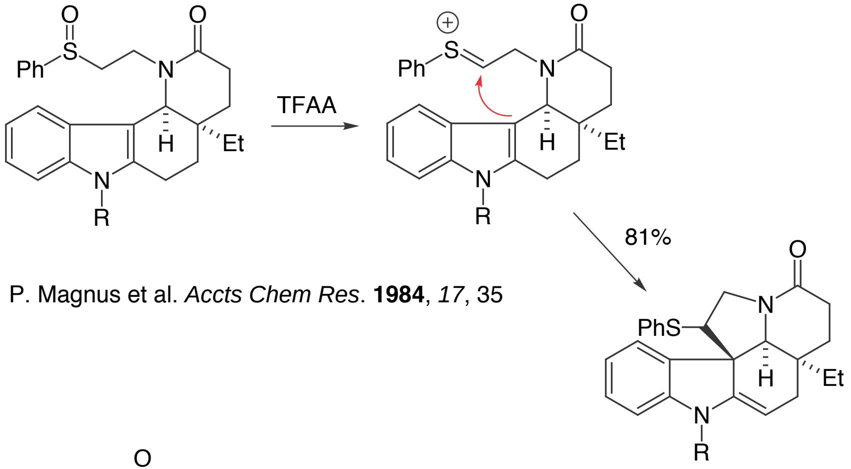
The Related Polonovski Reaction:



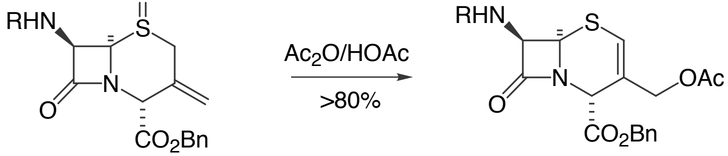
Regioselectivfity: *Depends on the relative kinetic acidy of the α protons*

Transformations Mediated by the Pummer Rearrangement

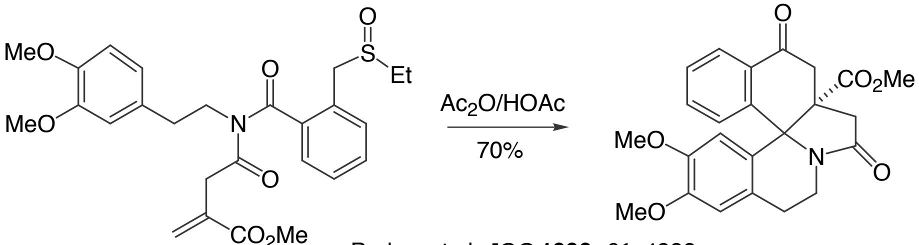




P. Magnus et al. *Accts Chem Res*. **1984**, *17*, 35

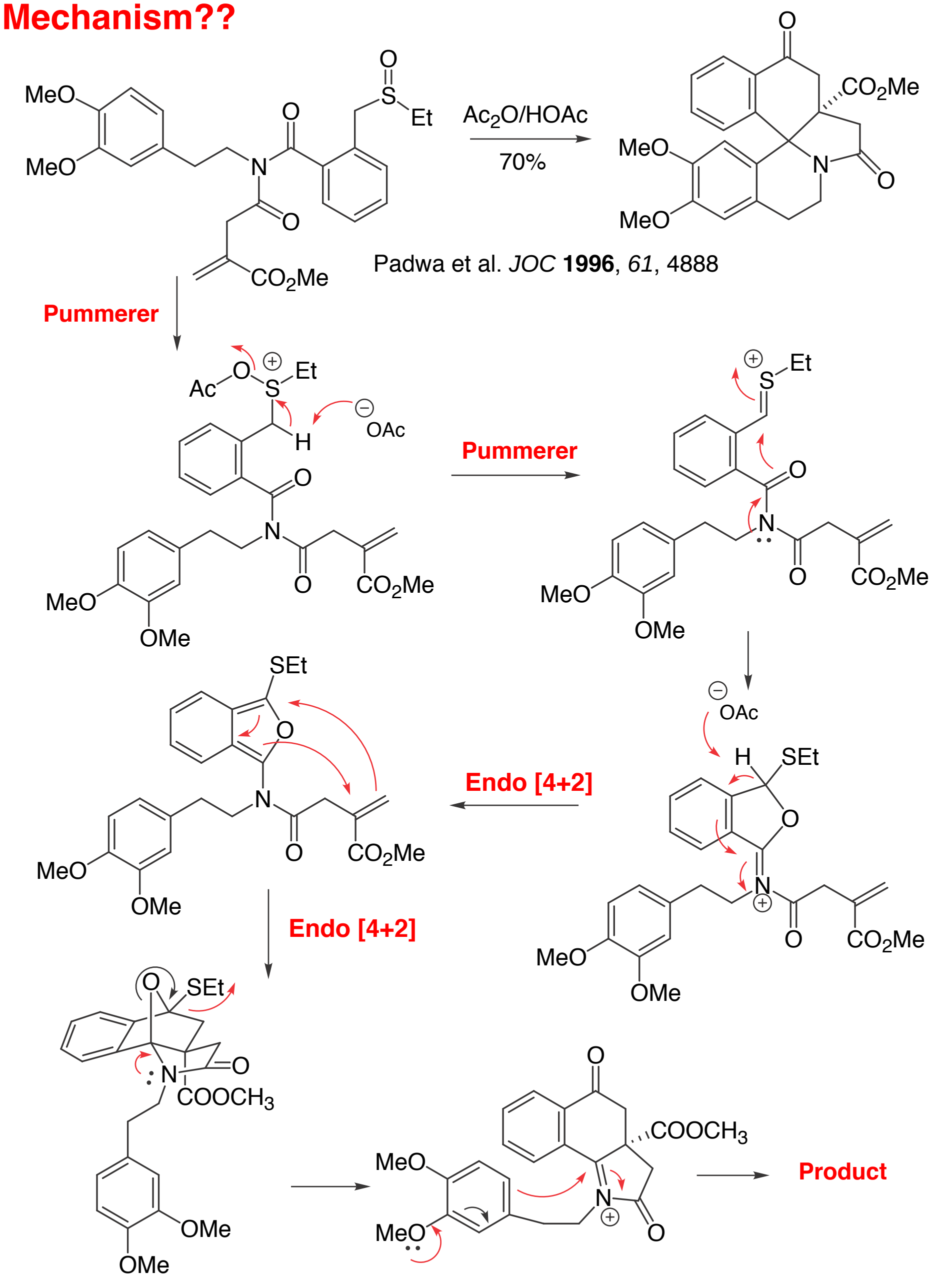


The cruel mechanistic problems that you should be prepared for in Chem 206



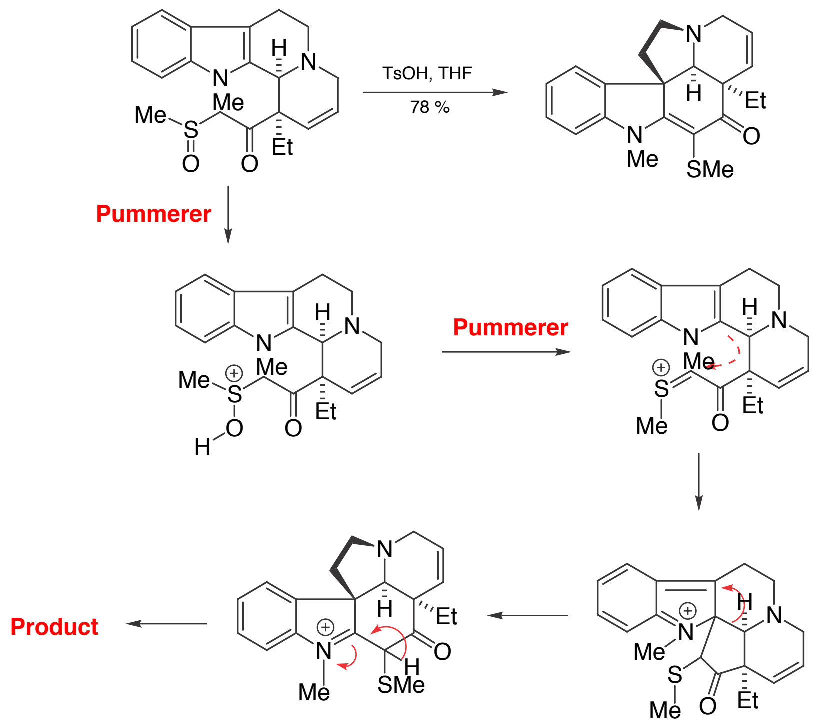
Padwa et al. *JOC* **1996**, *61*, 4888

Mechanism??



Padwa et al. *JOC* **1996**, *61*, 4888

Exam 3, 2000: Question 5 (11 points). An interesting rearrangement which also results in the construction of this same ring system (Question 4) has been reported by Langlois & coworkers (*J.Org. Chem.* **1985**, *50*, 961). This rearrangement is illustrated below. Provide a mechanism for this transformation.



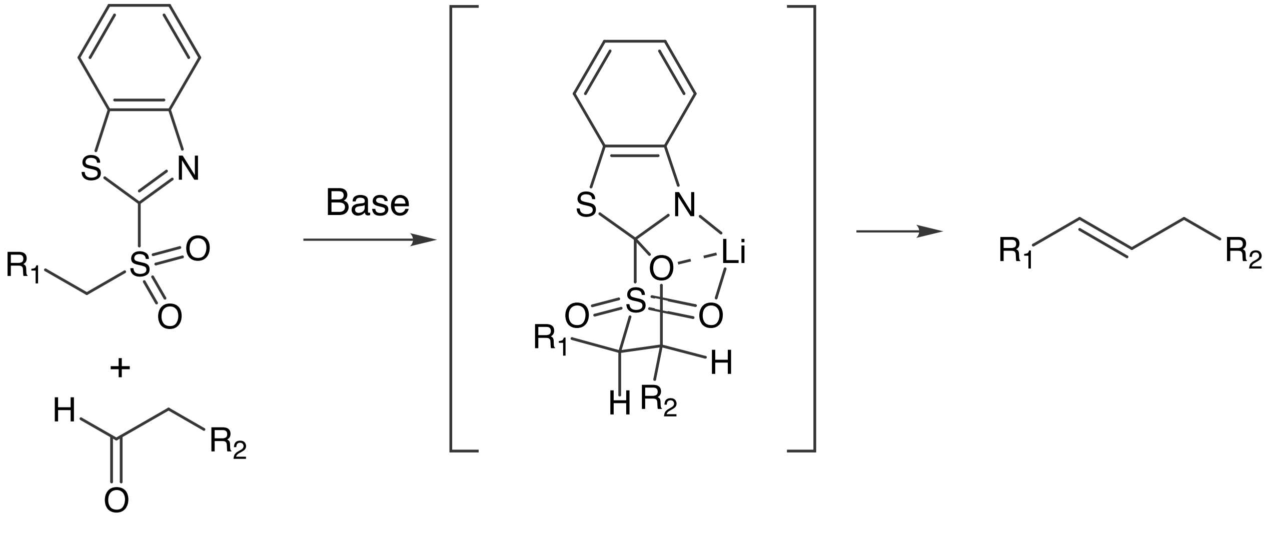
Chemistry 206

Advanced Organic Chemistry

Handout 29A

Overview of the Julia–Kocienski Olefination

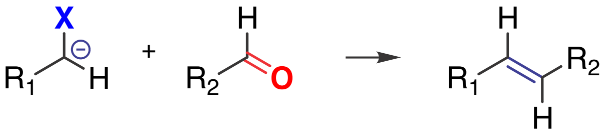
Evans Group Seminar
by
Scott Peterson, September 26, 2003



D. A. Evans

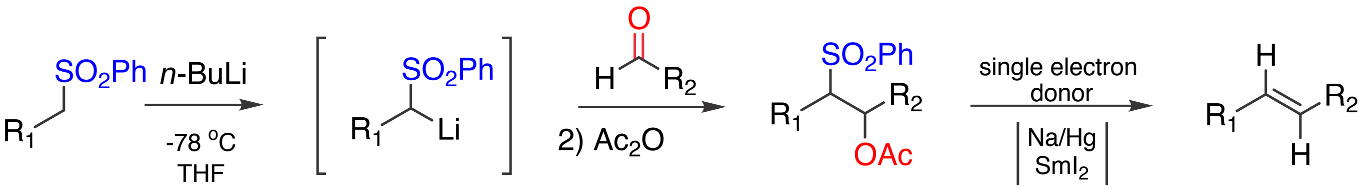
Friday,
November 21, 2003

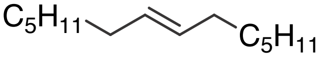
Examples of Direct Olefination from Carbonyl Compounds



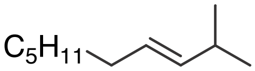
	X	Reaction
B.E Maryanoff, A.B. Reitz, *Chem. Rev.*, 1989, **89**, 863	R_3P^+	*Wittig*
	$R_2P(=O)$	*Horner-Wittig*
	$(RO)_2P(=O)$	*Horner-Wadsworth-Emmons*
L.F. van Staden, D Gravstock, D.J. Ager, *Chem. Soc. Rev.*, 2002, **31**, 195	R_3Si	*Peterson*
	ArS(=O)(=NMe)	*Johnson*
P.R. Blakemore, *J. Chem. Soc., Perkin Trans. 1,* 2002, 2563	$ArSO_2$	*classical Julia*
	$HetSO_2$	*modified Julia*

Classical Julia Olefination

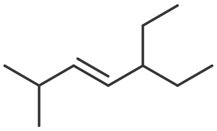




E:Z = 80:20

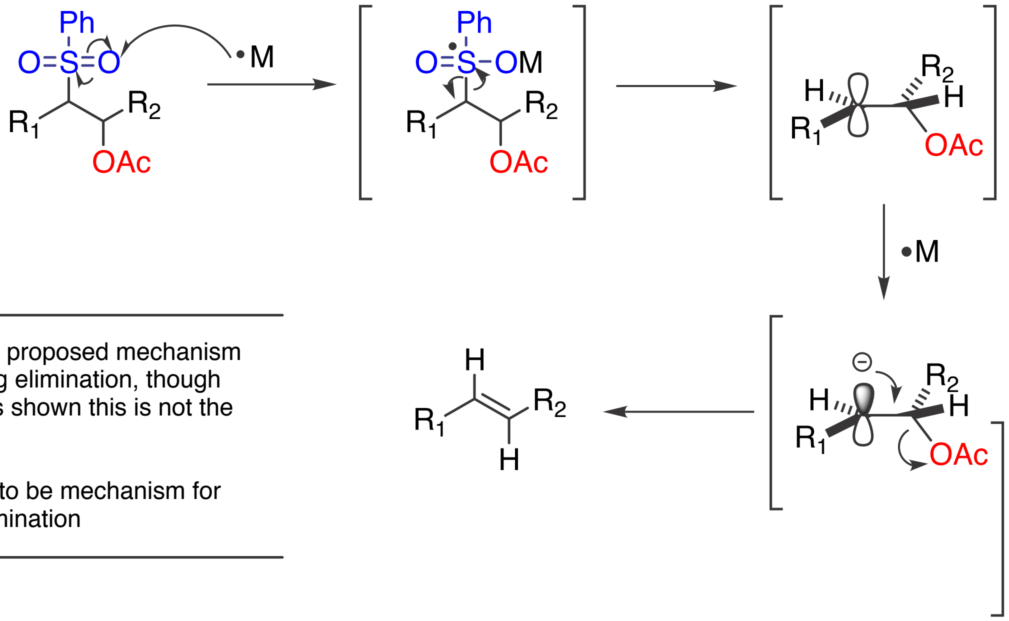


E:Z = 90:10



E:Z = >99:1

Mechanism of Olefin Formation

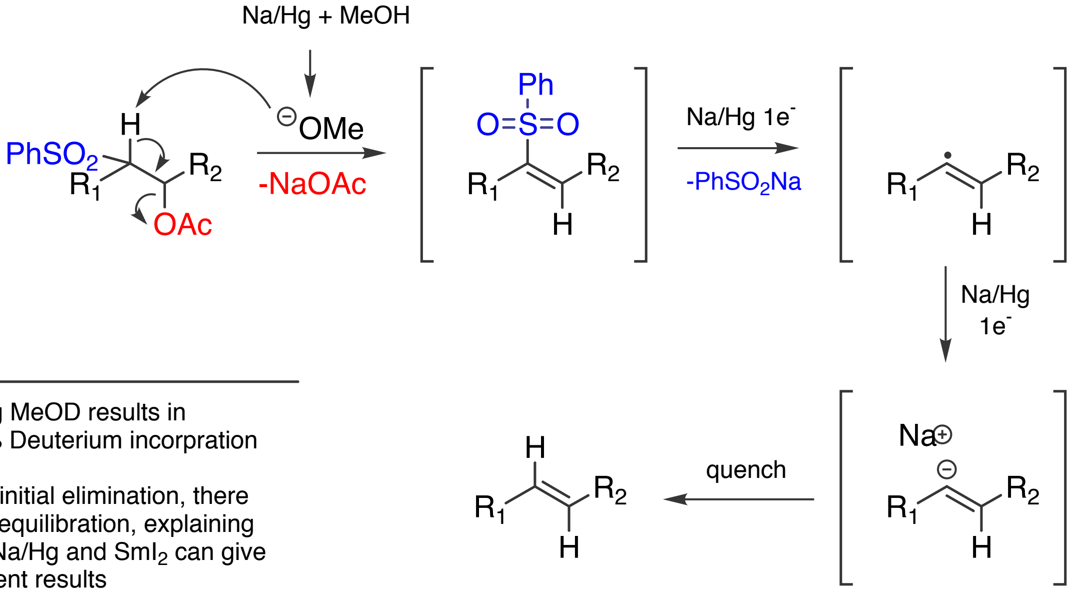


-Originally proposed mechanism for Na/Hg elimination, though Keck has shown this is not the case

-Believed to be mechanism for SmI_2 elimination

G.E. Keck et al., *J. Org. Chem.,* 1995, **60**, 3194

Mechanism of Olefin Formation

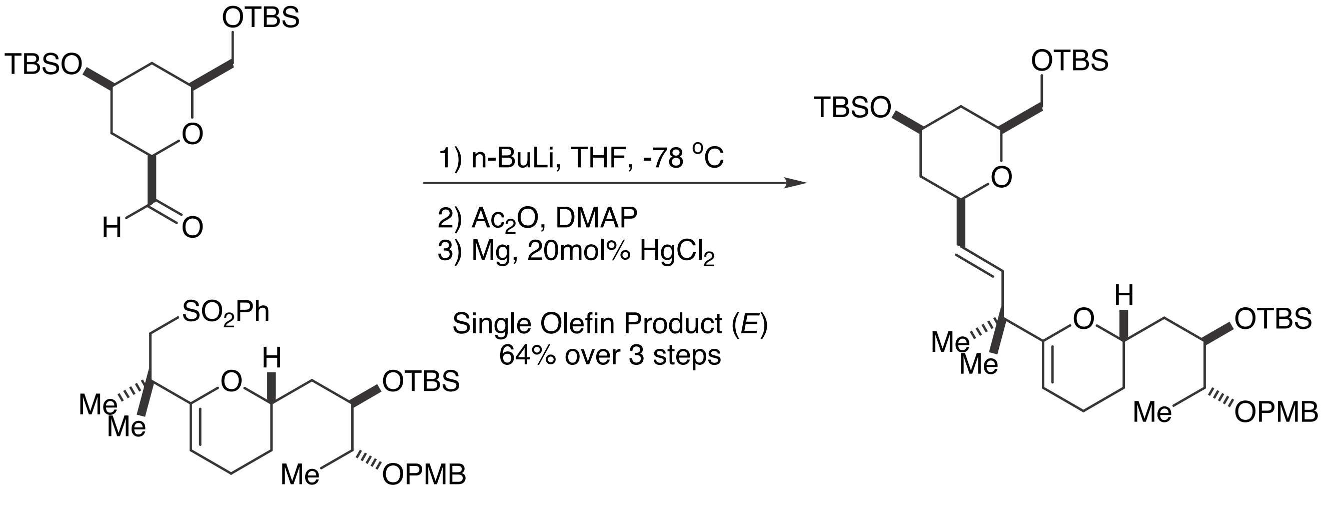


-Using MeOD results in >90% Deuterium incorpration

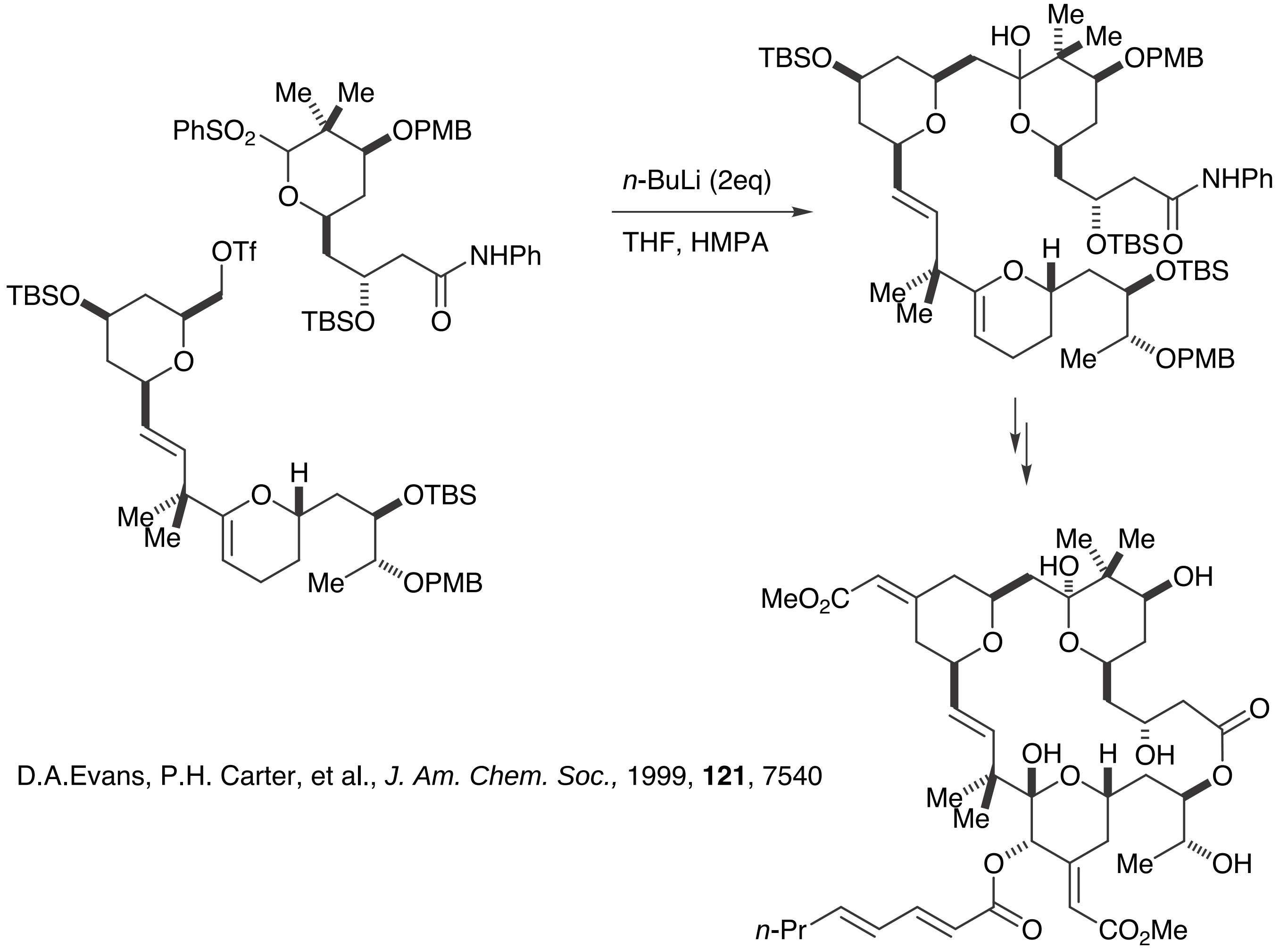
-After initial elimination, there is no equilibration, explaining why Na/Hg and SmI_2 can give different results

G.E. Keck et al., *J. Org. Chem.,* 1995, **60**, 3194

Synthesis of Bryostatin 2

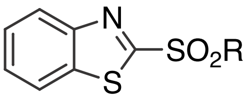


D.A.Evans, P.H. Carter, et al., *J. Am. Chem. Soc.,* 1999, **121**, 7540

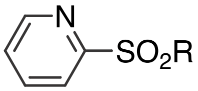


D.A.Evans, P.H. Carter, et al., *J. Am. Chem. Soc.,* 1999, **121**, 7540

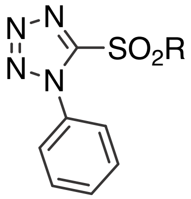
Modified Julia Olefination



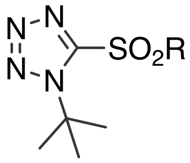
BT



PYR

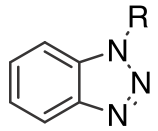


PT



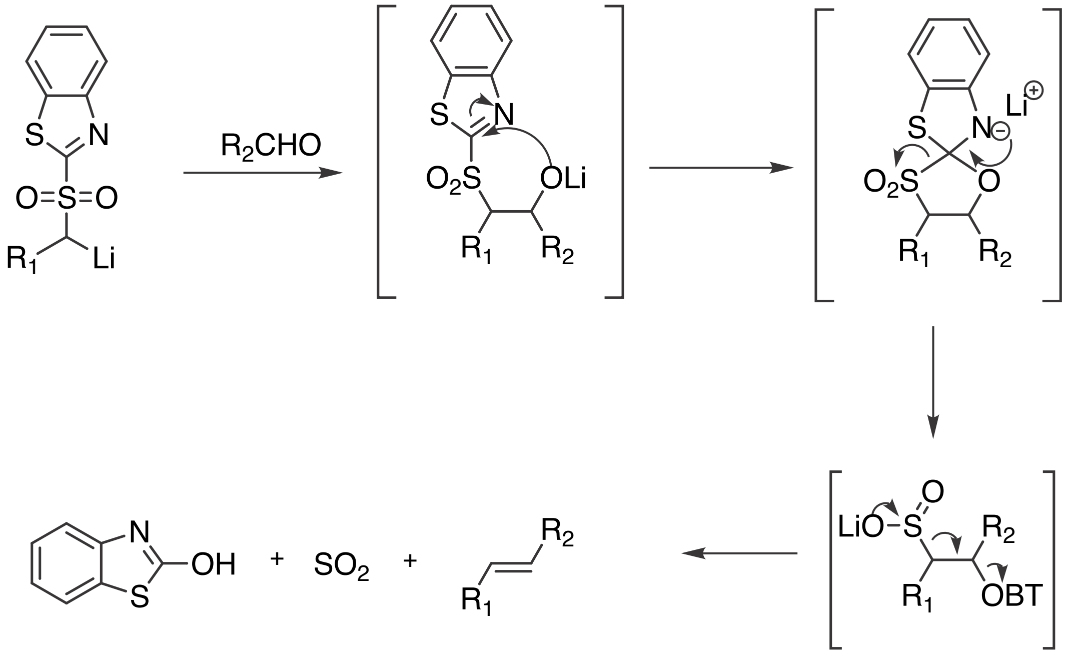
TBT

Bt =

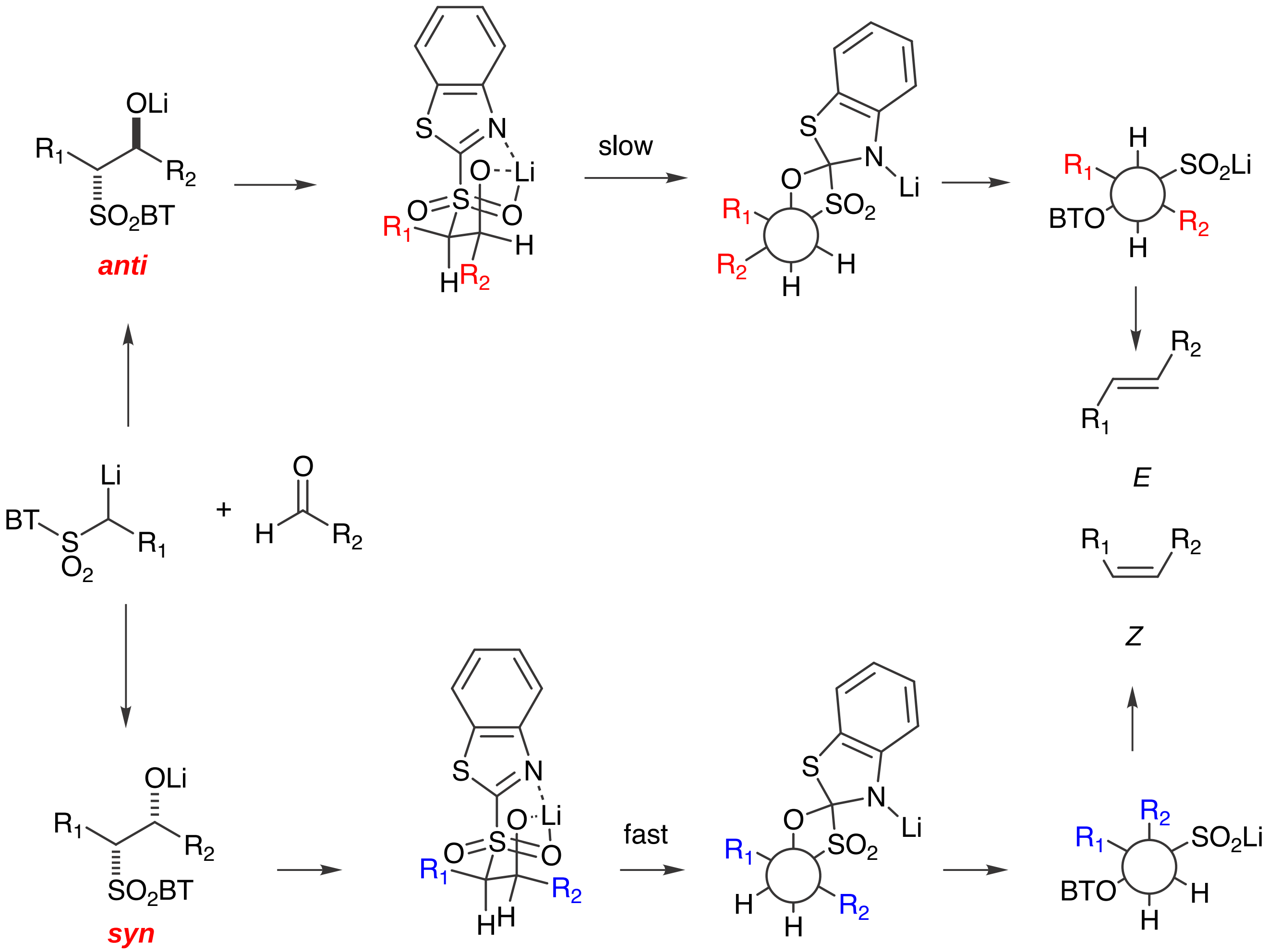


(benzotriazole)

Modified Julia Olefination - Smiles Rearrangement

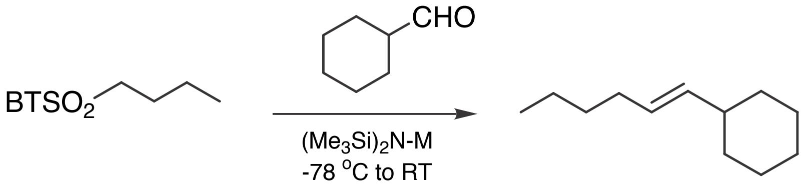


Diastereoselectivity of BT-Sulfones



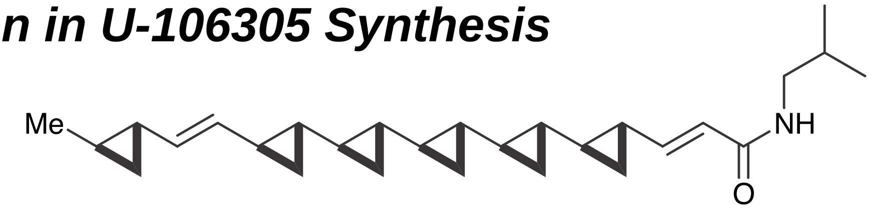
J.B. Baudin, *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

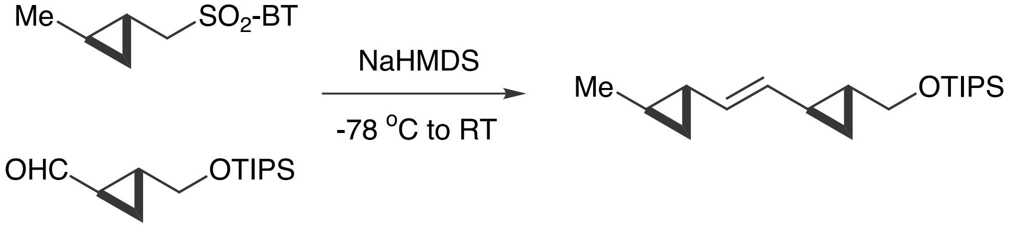
Effects of Solvent and Counterion with BT-Sulfone



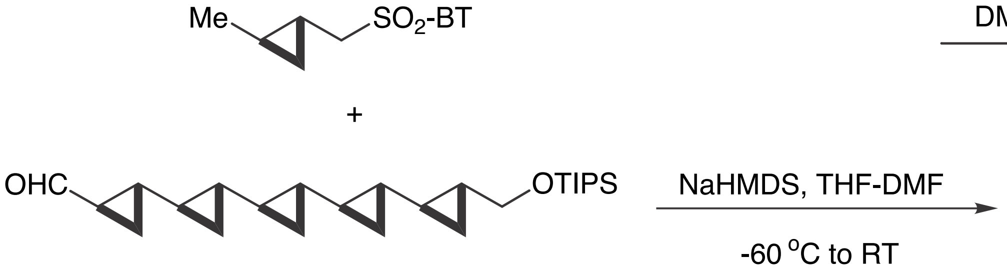
M	Toluene	Et_2O	THF	DME
Li	50:50	49:51	66:34	70:30
Na	54:46	50:50	62:38	75:25
K	54:46	51:49	54:46	76:24

Solvent Screen in U-106305 Synthesis





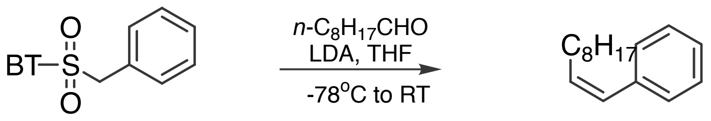
solvent	*E:Z*
toluene	9:91
CH_2Cl_2	9:91
Et_2O	11:89
THF	52:48
DME	71:29
DMF	78:22



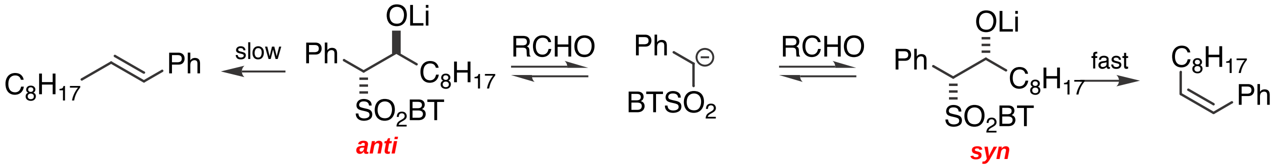
92% **81:19**

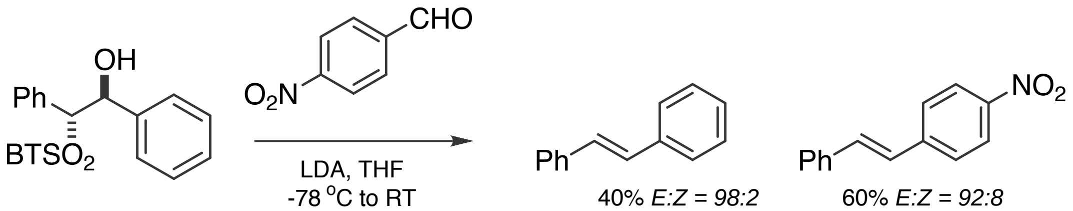
A.B. Charette, et al., *J. Am. Chem. Soc.*, 1996, **118**, 10327

Retroaddition - Addition with BT-Sulfone



E:Z = 23:77



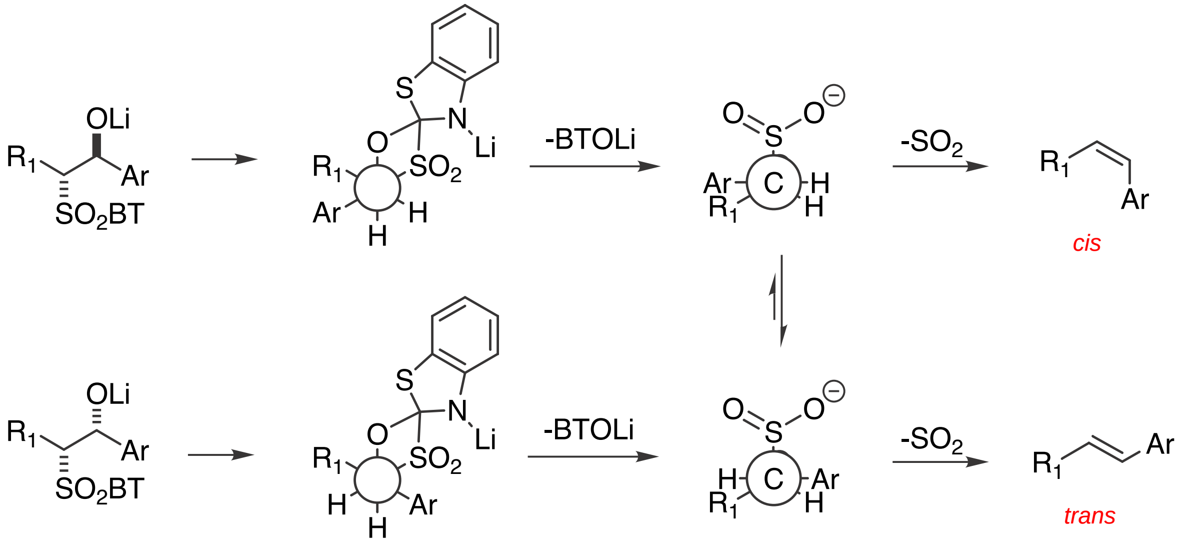


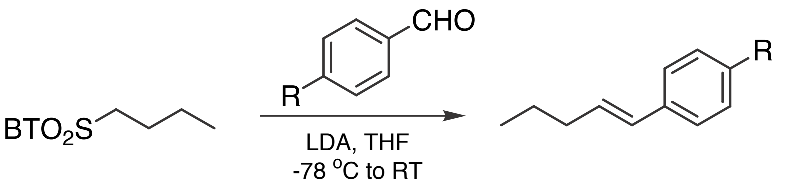
40% *E:Z = 98:2*

60% *E:Z = 92:8*

P.R. Blakemore, Ph.D. Thesis, University of Glasgow, Glasgow, 1999

Aromatic Aldehydes with BT-Sulfones



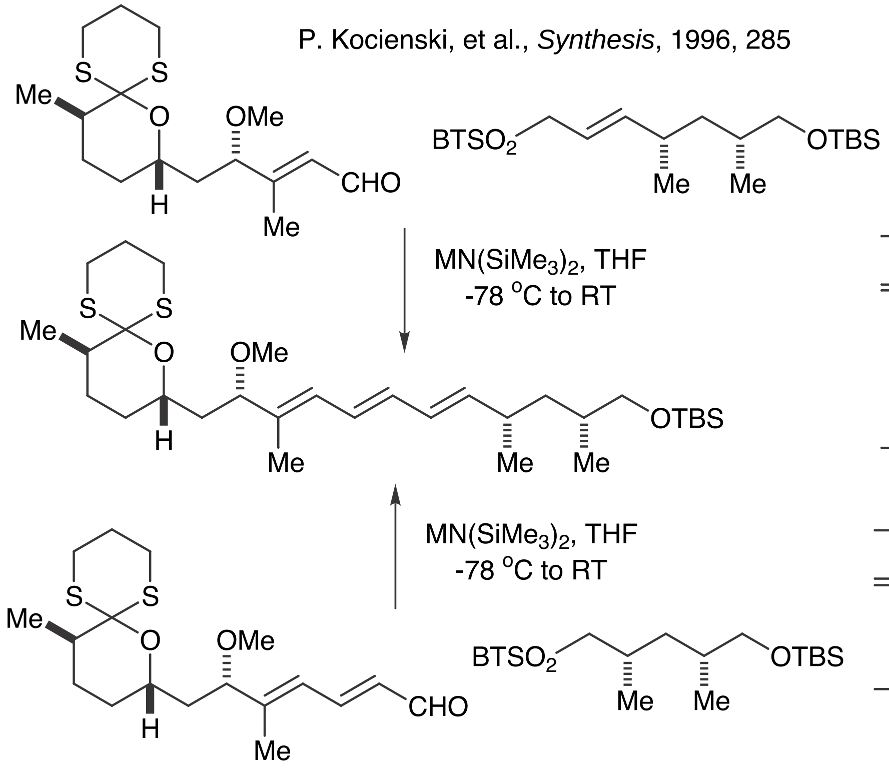


R	yield	E:Z
OMe	95%	99:1
H	68%	94:6
Cl	51%	77:23

J.B. Baudin, et al. *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

Reversibility in Rapamycin Synthesis

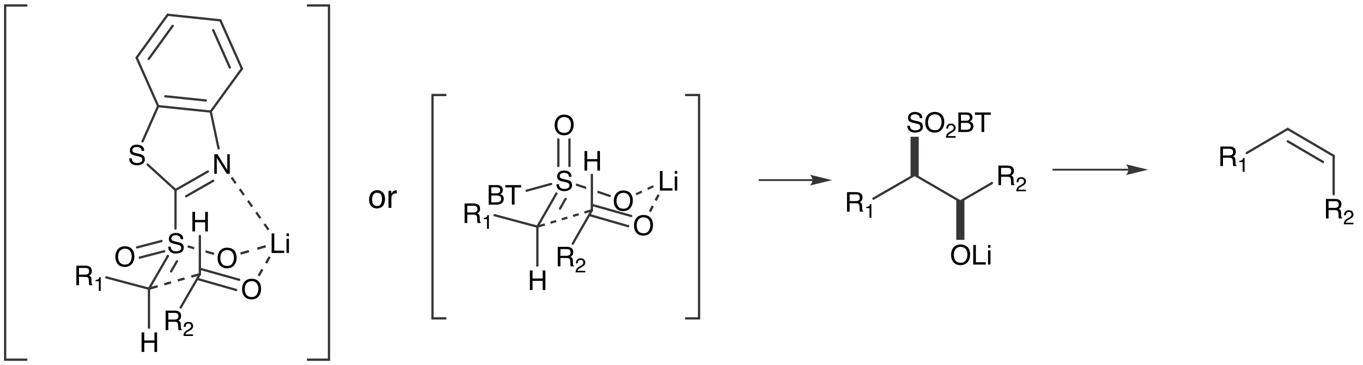
P. Kocienski, et al., *Synthesis*, 1996, 285



M	yield	*E:Z*
Li	75%	29:71
Na	79%	43:57
K	--	18:82

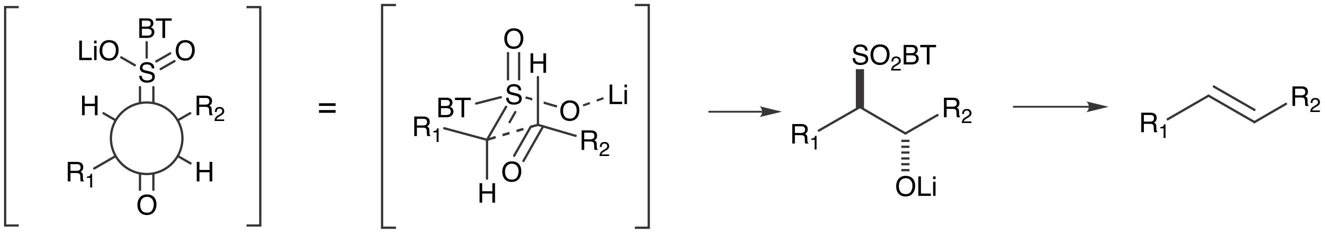
M	yield	*E:Z*
Li	68%	95:5
Na	21%	78:22

Possible Explanation for Diastereoselctivity



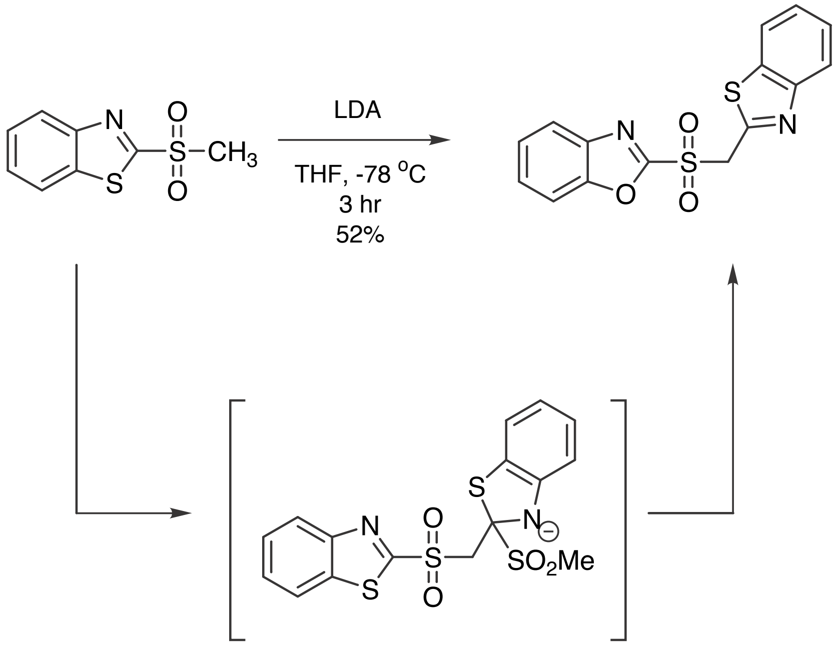
Chelate (closed) Transition State favored for non-polar solvents, small counter-ions (Li)

Non-chelate (opened) Transition State favored for polar solvents, large counter-ions (K)



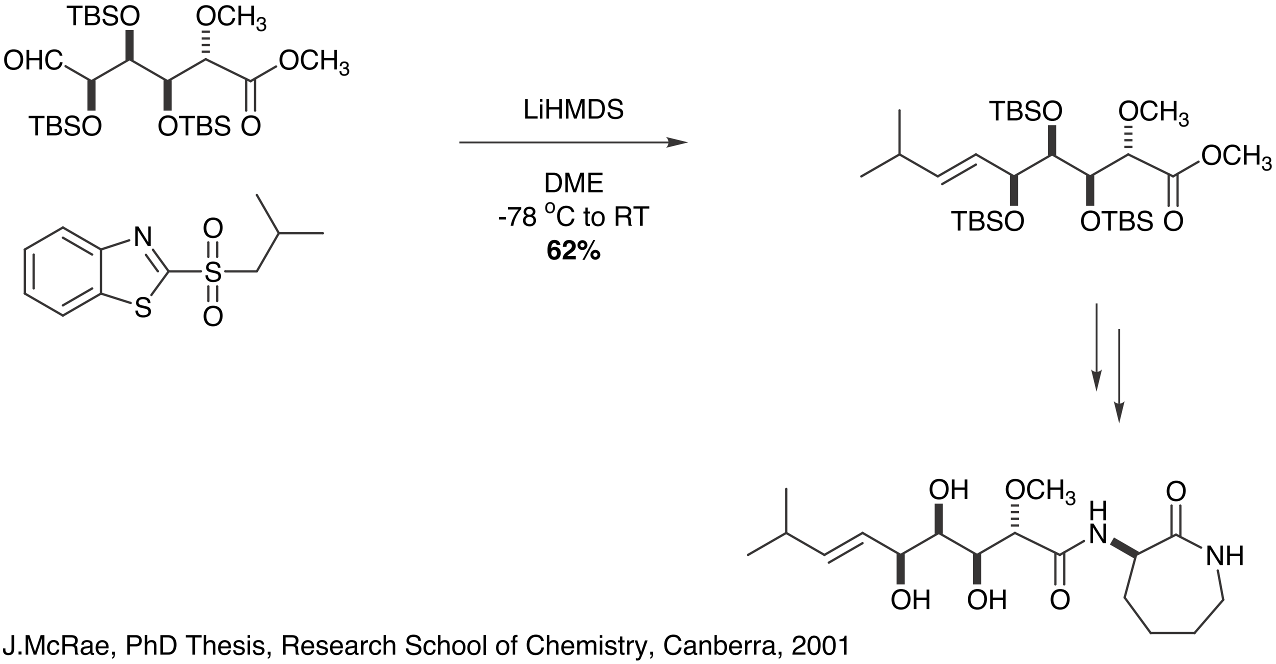
S. Peterson, *Meandering Thoughts*, 2003

Ipso Substitution with BT-Sulfones



J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

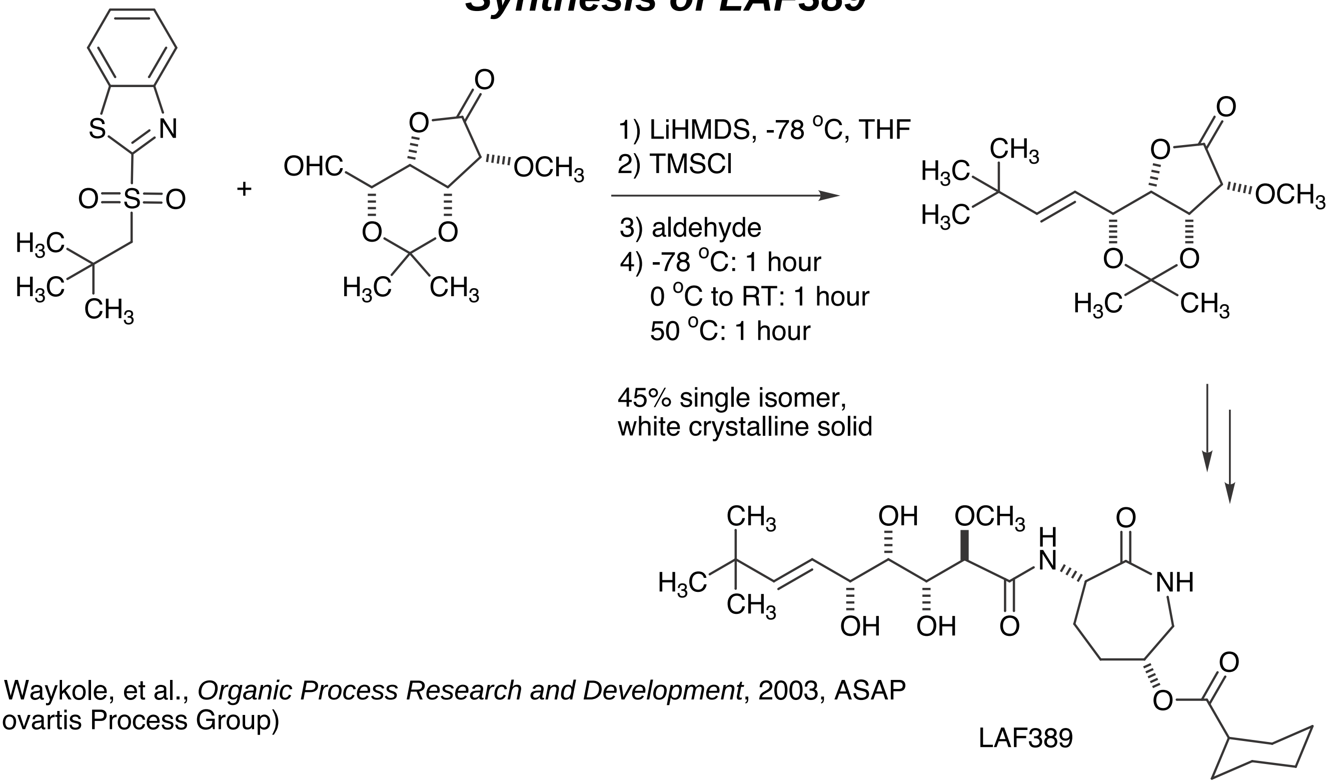
Synthesis of ent-*Bengamide E*



ent-Bengamide E

K.J.McRae, PhD Thesis, Research School of Chemistry, Canberra, 2001
J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

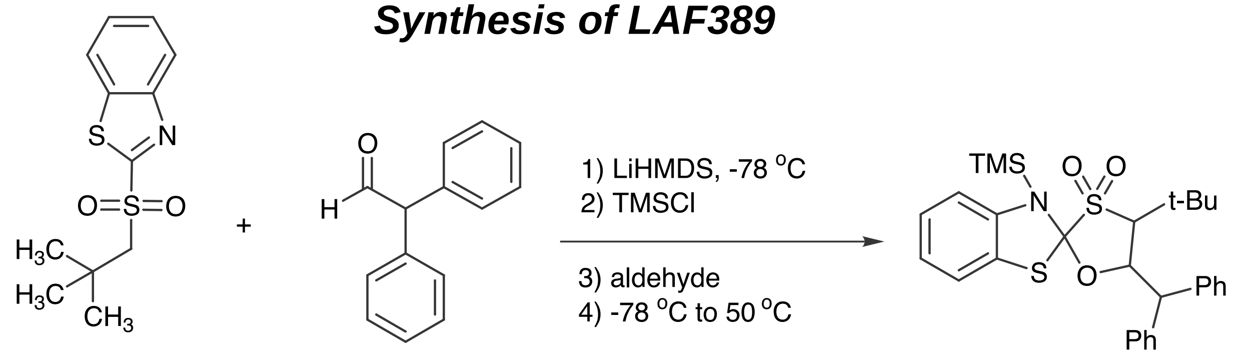
Synthesis of LAF389

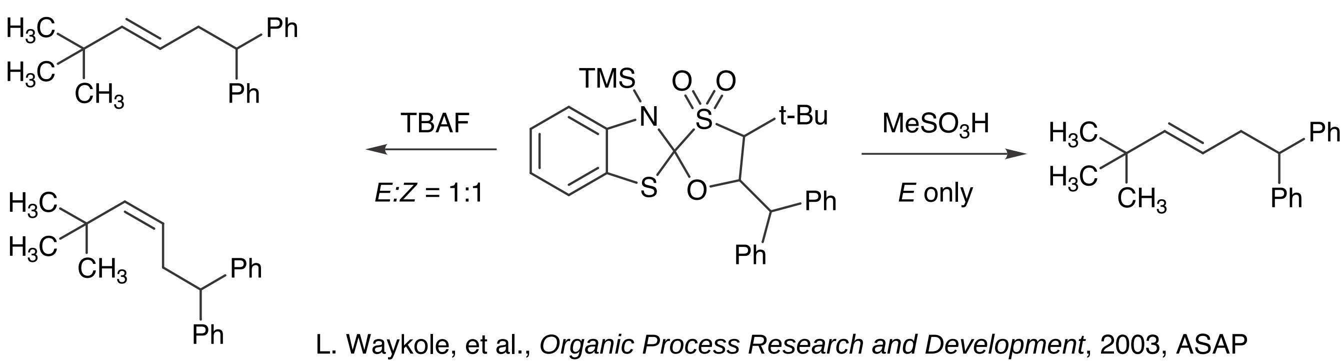


LAF389

L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

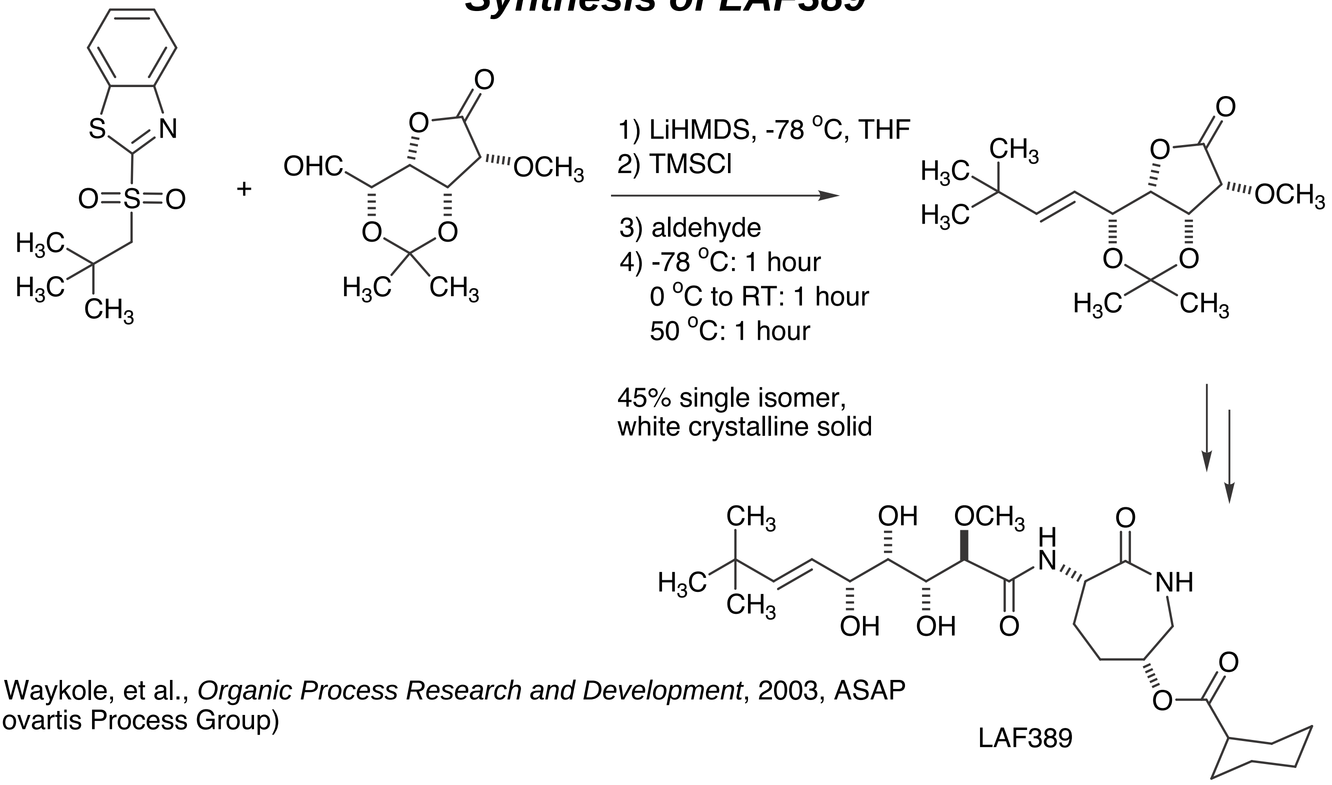
Synthesis of LAF389





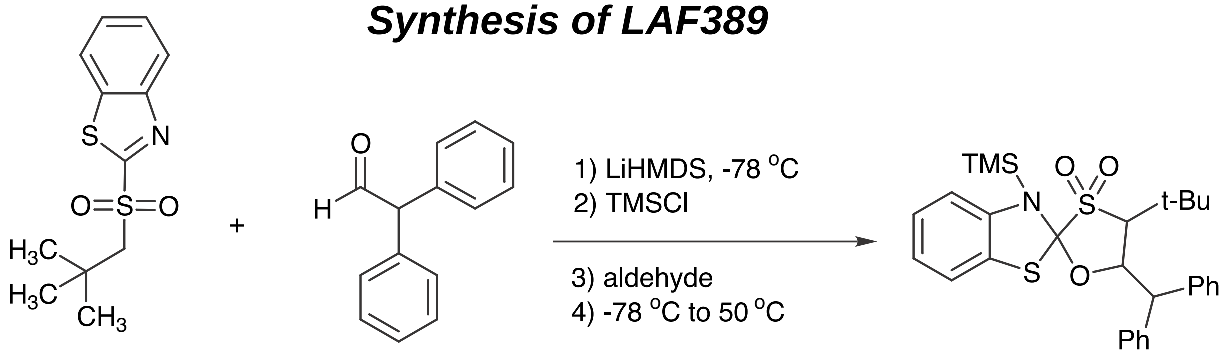
L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

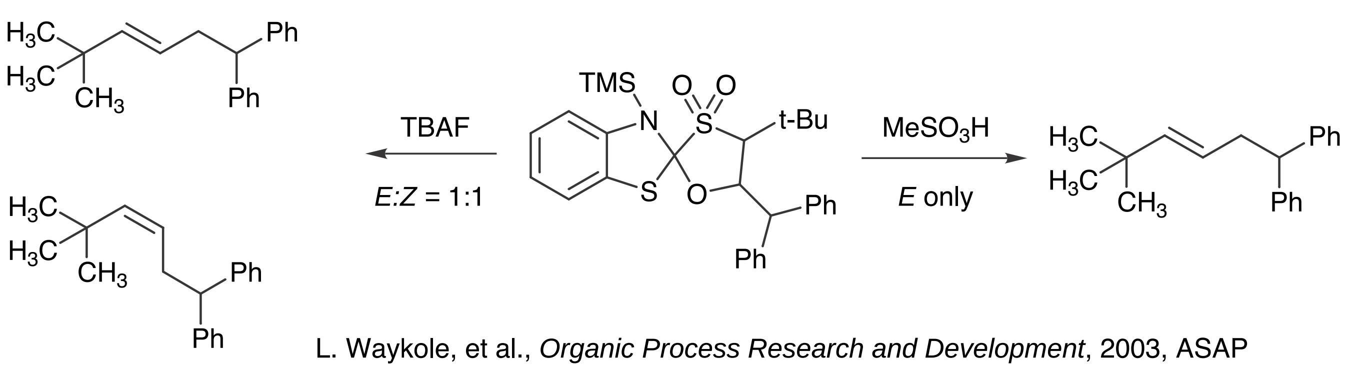
Synthesis of LAF389



L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

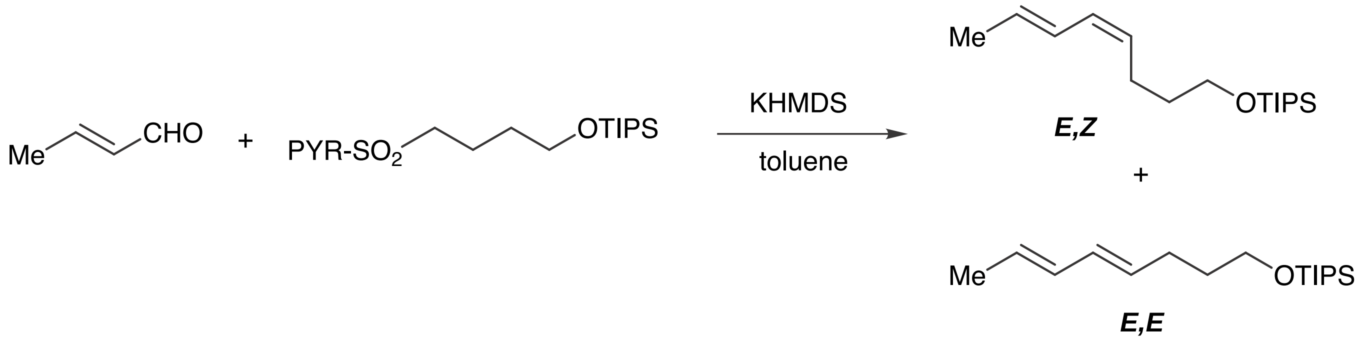
Synthesis of LAF389





L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

Pyridinyl (PYR) Sulfones Examples

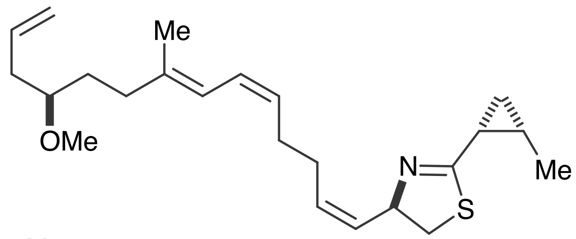


temp	yield	Ratio *E,Z* : *E,E*
-78 °C	35%	84:16
0 °C	53%	90:10
25 °C	67%	91:9

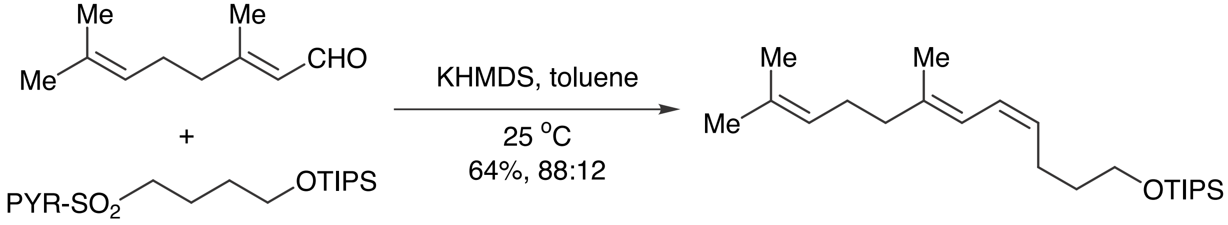
Potassium metallate is stable at RT for 5 min!

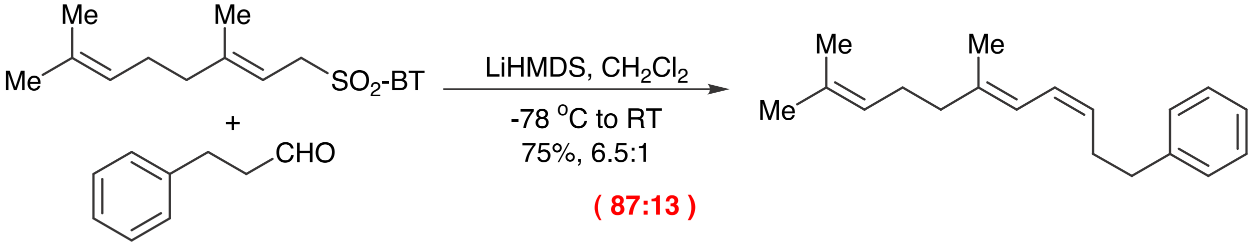
A. B. Charette, et al., *Tet Lett*, 2001, **42**, 5149

Pyridinyl (PYR) Sulfones Examples



Curacin B

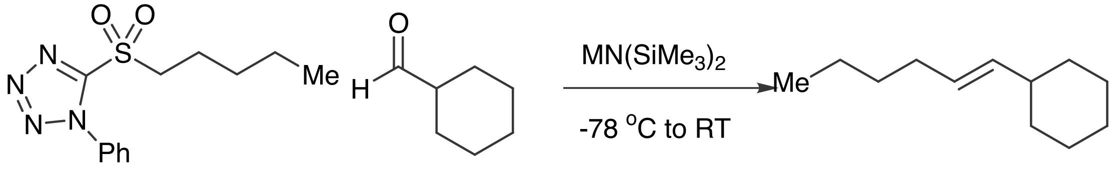




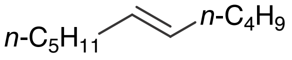
(87:13)

A. B. Charette, et al., *Tet Lett*, 2001, **42**, 5149

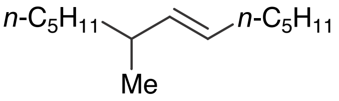
1-Phenyl-1H-tetrazol-5-yl Sulfones



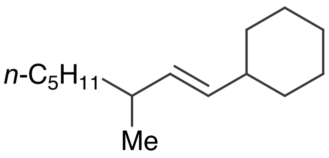
M	toluene	Et_2O	THF	DME
Li	51:49	61:39	69:31	72:28
Na	65:35	65:35	73:27	89:11
K	77:23	89:11	97:3	99:1



E:Z = 94:6



E:Z = 96:4

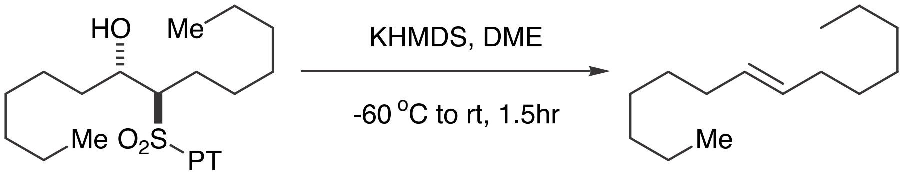


E:Z = 99:1

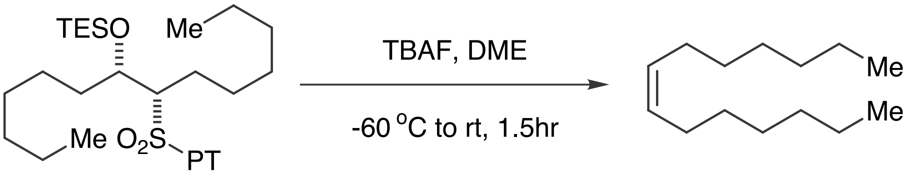
1.5eq aldehyde, KHMDS, DME -78 °C to RT

P.J. Kocienski, et al., *Synlett*, 1998, 26

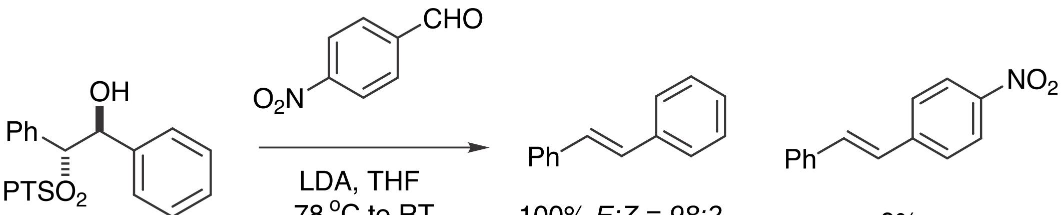
Kinetically Controlled Diastereoselectivity - Irreversible



91%, *E:Z* = 98:2



91%, *E:Z* = 2:98

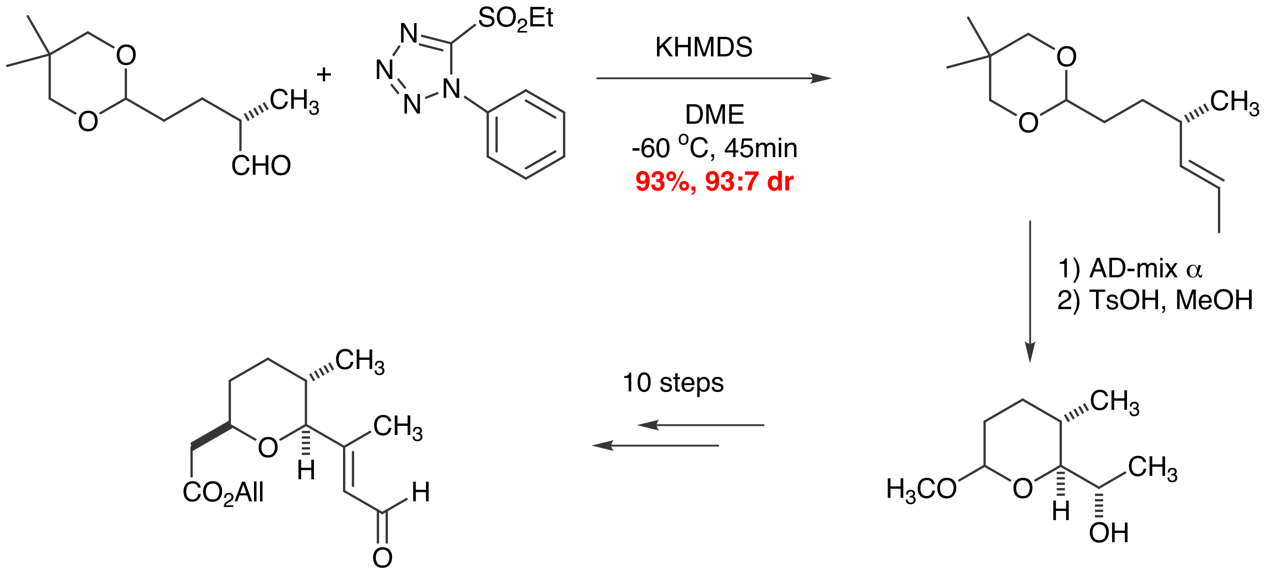


100% *E:Z = 98:2*

0%

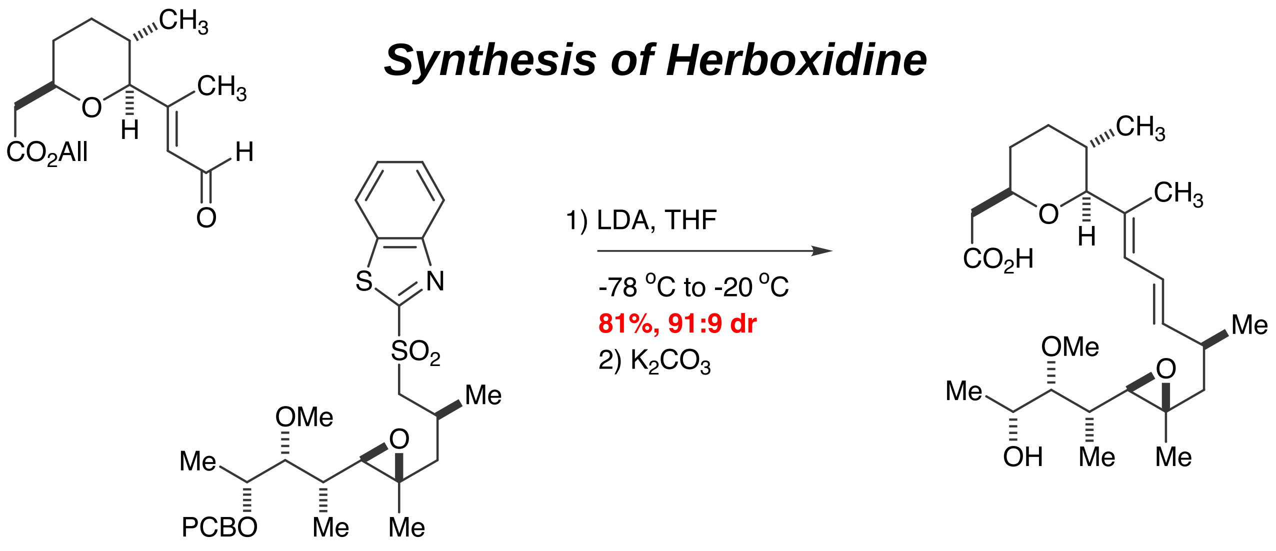
P.R. Blakemore, Ph.D. Thesis, University of Glasgow, Glasglow, 1999

Synthesis of Herboxidine



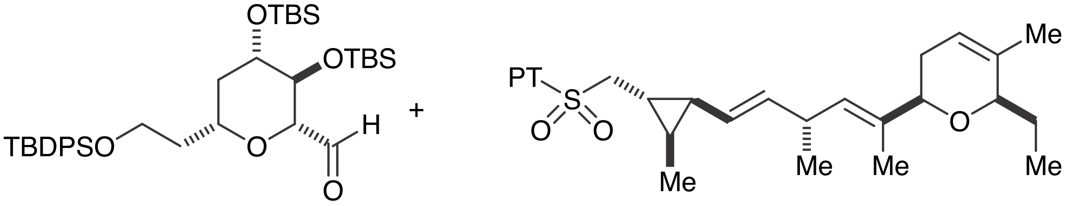
P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1,* 1999, 955

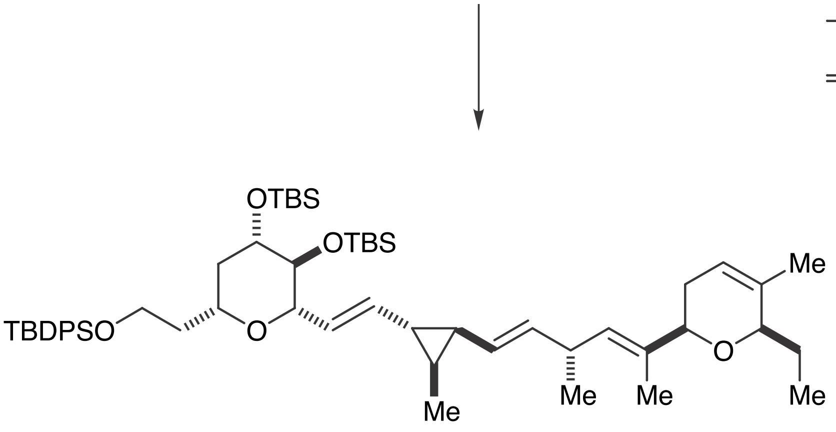
Synthesis of Herboxidine



P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1,* 1999, 955

Synthesis of (+)-Ambruticin

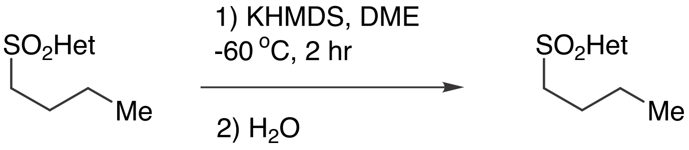




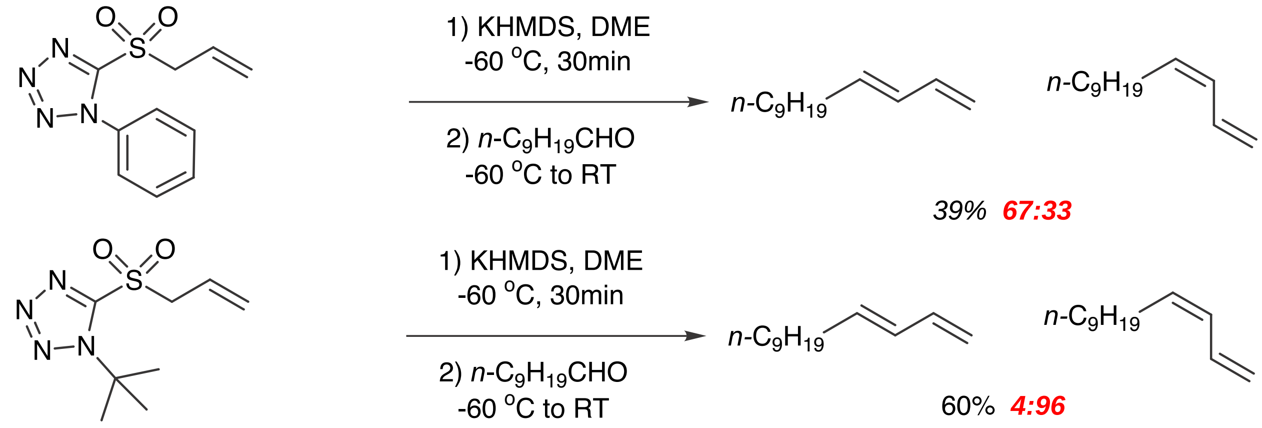
M-HMDS	solvent	temp	*E : Z*
Na	THF	-78 °C	1:8
Na	THF	-35 °C	1:6
K	DMF	-60 °C	1:1
K	DME/18-c-6	-60 °C	1:3
Li	THF/HMPA	-60 °C	3:1
Li	DMF/HMPA	-35 °C	>30:1
Li	DMF/HMPU	-35 °C	>30:1

E.N. Jacobsen, P. Liu, *J. Am. Chem. Soc.*, 2001, **123**, 10772

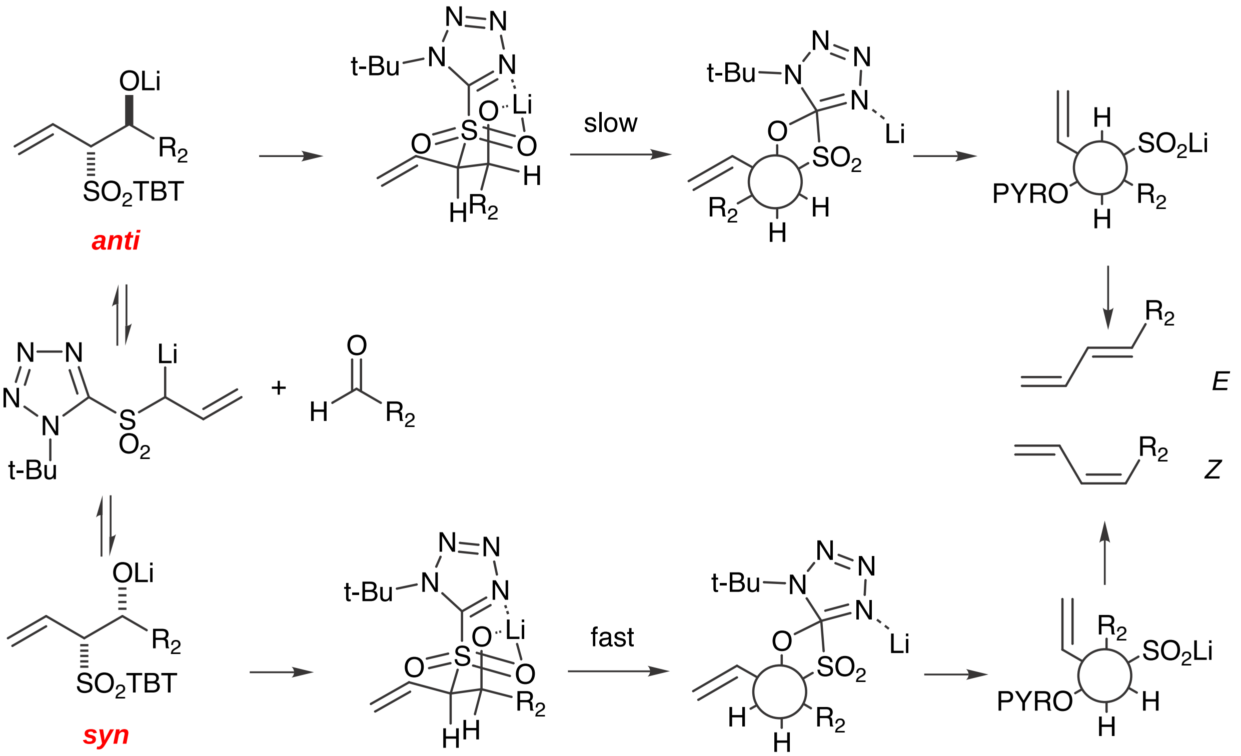
tert-*Butyl-1H-tetrazol-5-yl Sulfones*



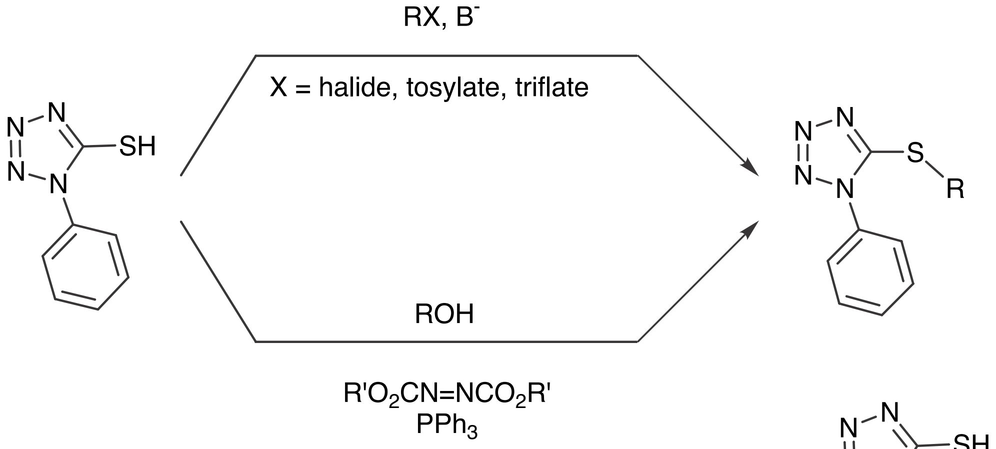
Het	yield
BT	0%
PT	20%
TBT	91%

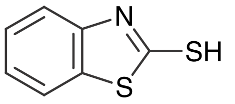


Diastereoselectivity of TBT-Sulfones

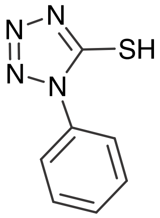


Sulfone Synthesis

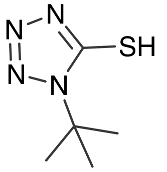




2-mercaptobenzothiazole
100g = $18.00



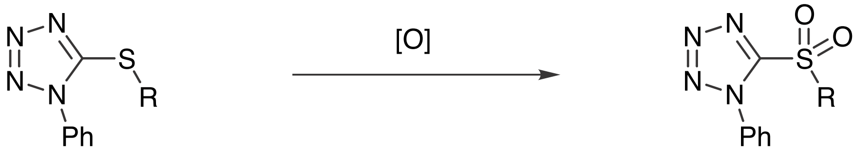
1-phenyl-1-*H*-tetrazole-5-thiol
25g = $22.60



t-Bu—N=C=S + NaN$_3$

tert-butyl isothiacyanate; 25g = $57.80
Sodium azide; 25g = $51.90

Sulfone Synthesis



MCPBA

$(NH_4)_6Mo_7O_{24}$-$4H_2O$ / H_2O_2 Mo(VI)

Na_2WO_4-$2H_2O$ / H_2O_2 W(VI)

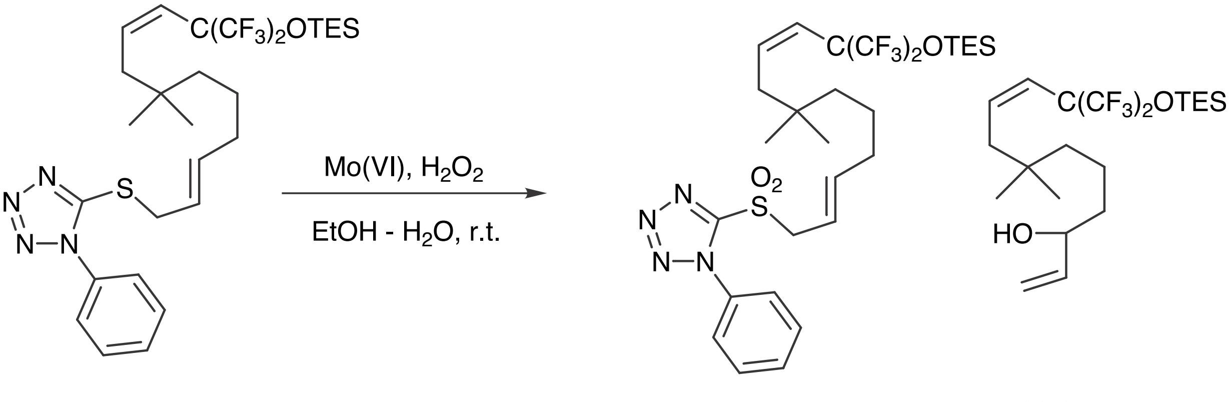
Oxone

CH_3CO_3H

$KMnO_4$

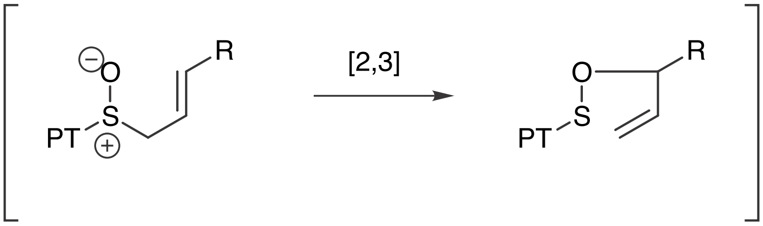
P.R. Blakemore, *J. Chem. Soc., Perkin Trans. 1,* 2002, 2563

Oxidation Problems - Allylic Sulfones



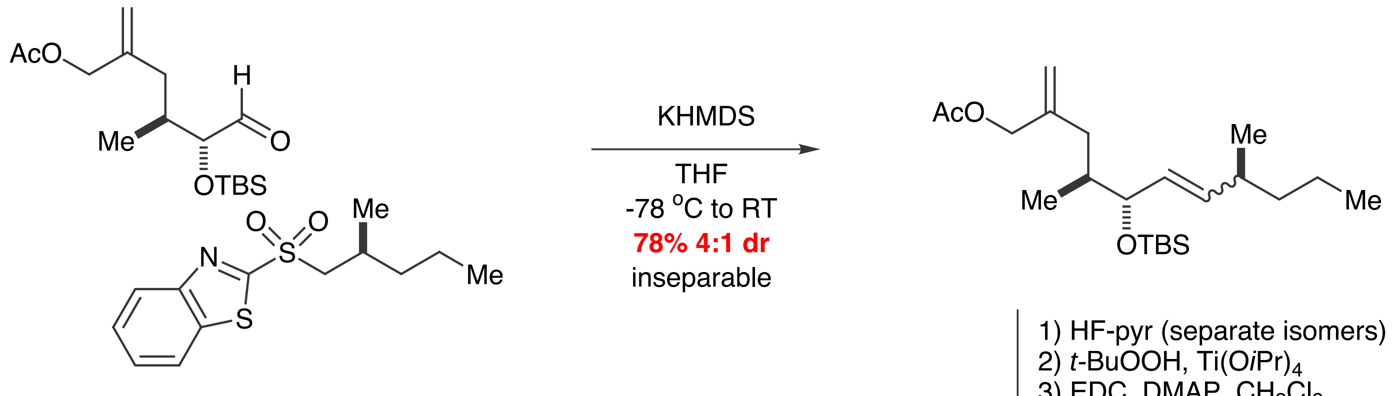
38%

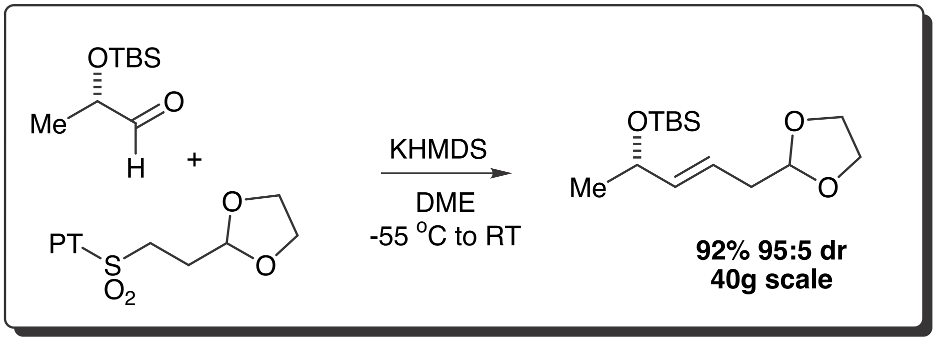
11%

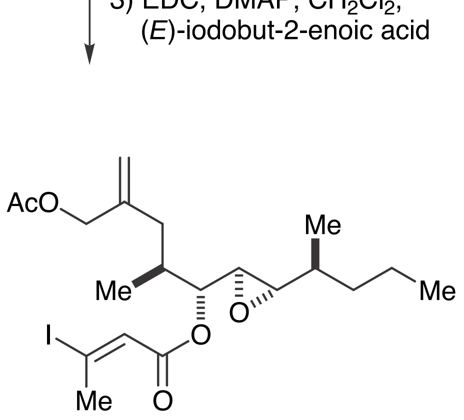


H. Hilpert, B. Wirz, *Tetrahedron*, 2001, **57**, 681
D.A. Evans, G.C. Andrews, *Acc. Chem. Res.*, 1974, **7**, 147

Synthesis of the Proposed Structure of Amphidinolide-A

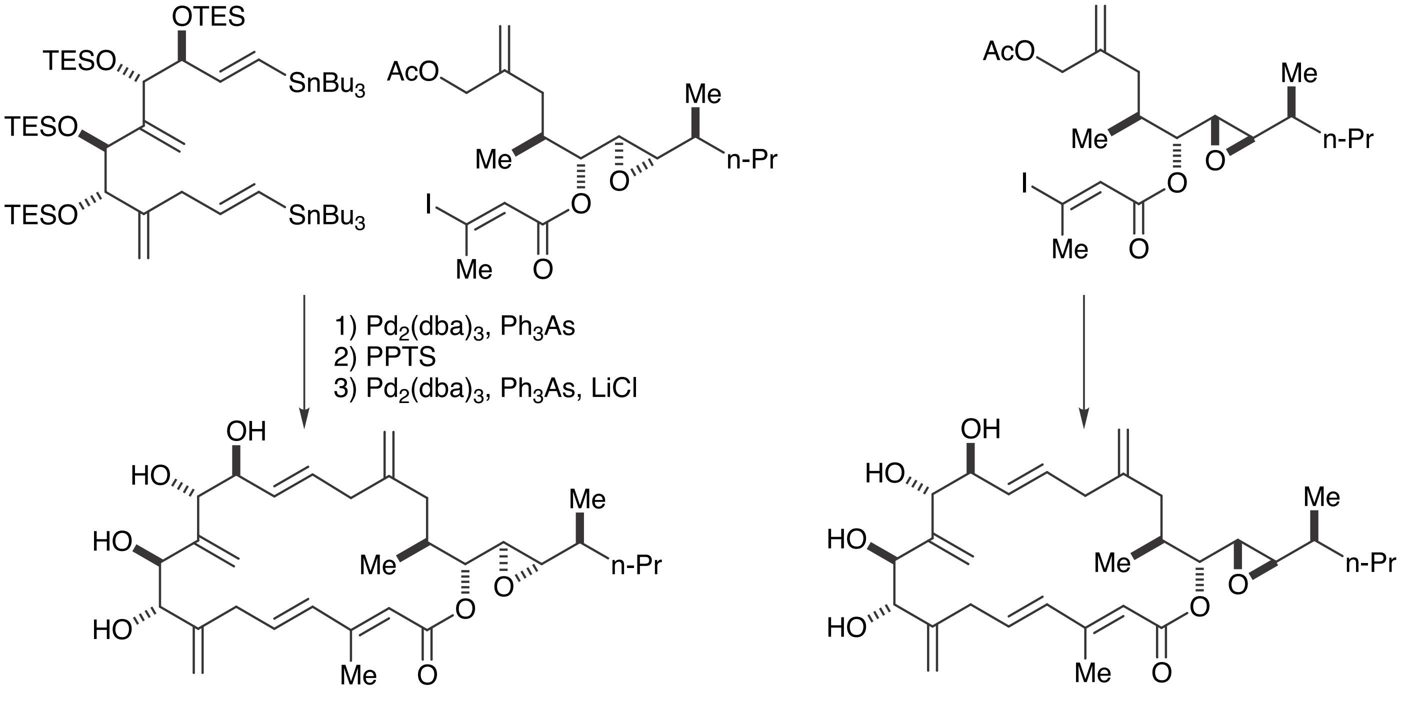






G.Pattenden, H.W.Lam, *Angew. Chem. Int. Ed.*, 2002, **41**, 508
M. Hirama, *Tet. Lett.*, 1999, **40**, 4897

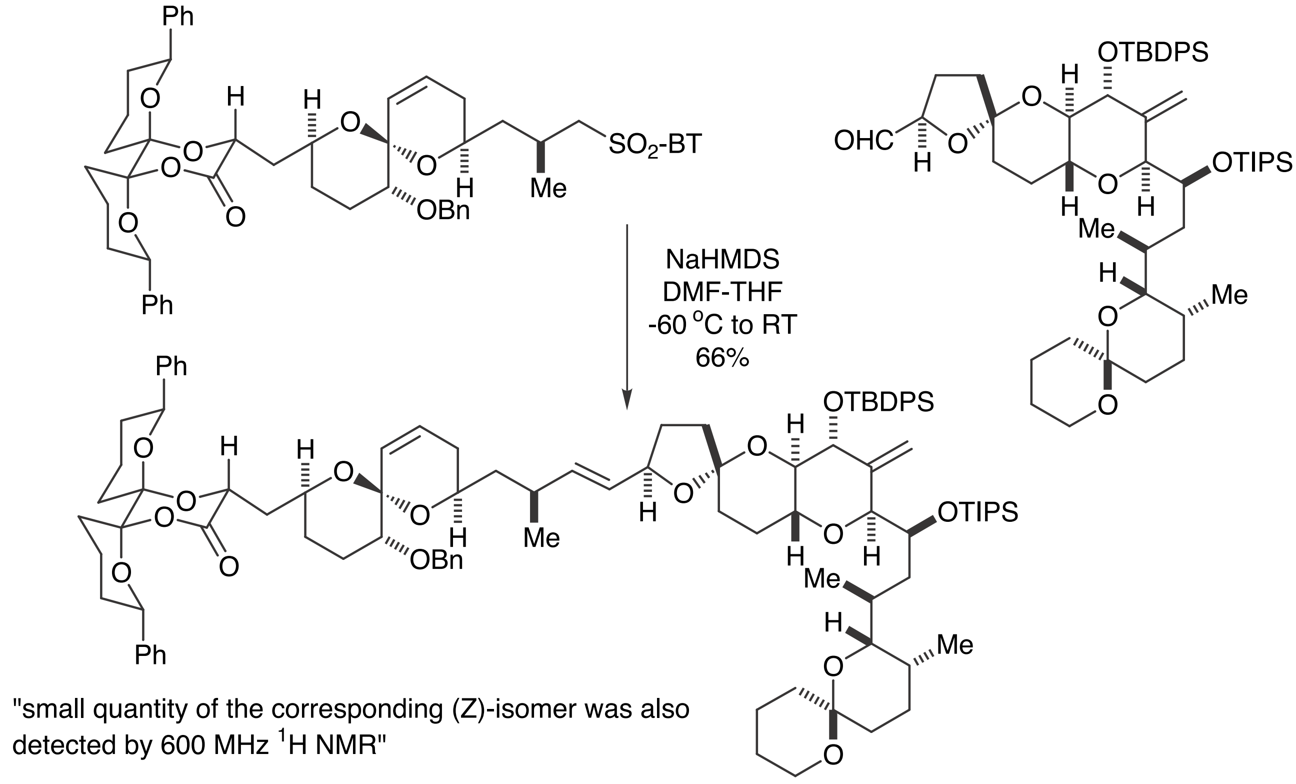
Synthesis of Proposed Structure of Amphidinolide-A



NOT Amphidinolide-A **NOT Amphidinolide-A**

G.Pattenden, H.W.Lam, *Angew. Chem. Int. Ed.*, 2002, **41**, 508

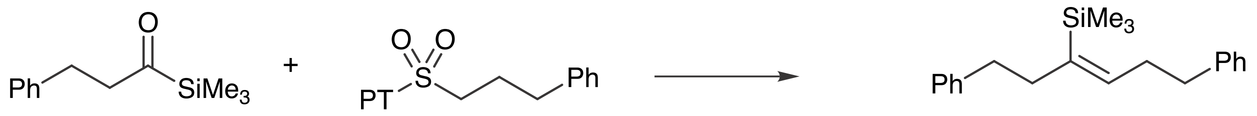
Synthesis of Okadaic Acid

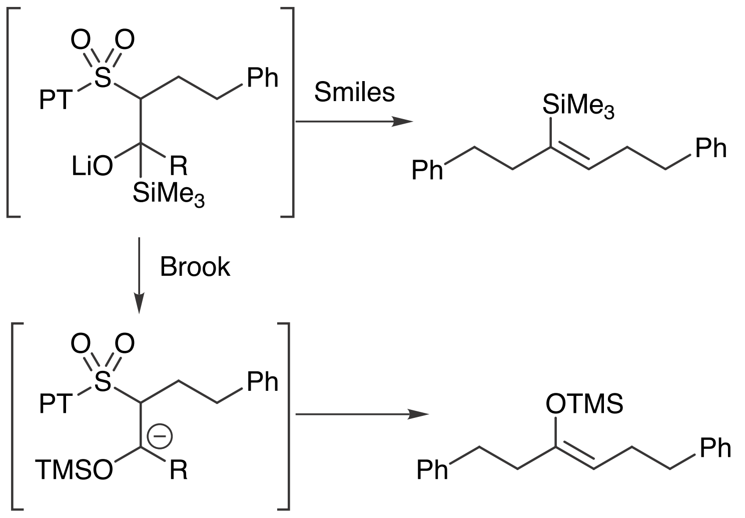


"small quantity of the corresponding (Z)-isomer was also detected by 600 MHz ^{1}H NMR"

S.V. Ley, et al., *J. Chem. Soc., Perkin Trans. 1,* 1998, 3907

Synthesis of Vinylsilanes





M-HMDS	temp	yield	*E : Z*
Li	-78 °C	93%	64:36
Li	-85 °C	89%	74:26
Li	-95 °C	84%	75:25
Na	-78 °C	50%	59:41
K	-78 °C	NA	NA

J. Wicha, et al., *Org. Lett.,* 2003, **5**, 2789

Conclusions

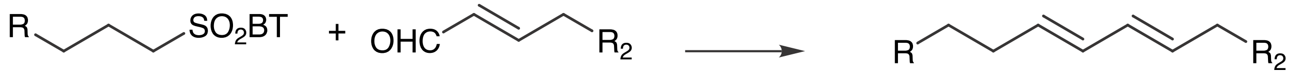
BT and PT sulfones have become useful funtional groups for the synthesis of olefins from aldehydes

inexpensive starting materials
sulfones can be made in high yield from alcohols
olefination reactions occur under mild conditiions, and are typically high yielding and selective

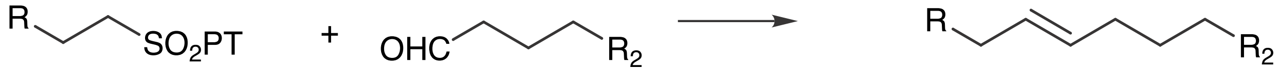
Stereochemical outcome is kinetically controlled in most cases. Though reaction conditions can often influence selectivities

Polar solvents with soft counter ions often favor *E* olefins
Non-polar solvents with hard counter ions often favor *Z* olefins

BT sulfones are most useful for the synthesis of conjugated dienes through reaction with α,β–unsaturated aldehydes



PT sulfones are most useful for the synthesis of non-conjugated (*E*) olefins



PYR and TBT sulfones both produce high levels of *cis* selectivity, though yields are typically lower than BT reactions

Definitely more to come in the future

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 30

Ambiphilic Functional Groups–4

- Construction of Consonant & Dissonant FG Relationships
- Charge Affinity Inversion Operators

Lecture 27 and handout 27A

Handout 30A: Homoenolates: Synthesis & Applications

Mesembrine Syntheses: Keely, S. L.; Tahk, F. C. *JACS*. **1968**, *90*, 5584.
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580 **(handouts)**

Stetter, *The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds. Org. React. (N.Y.)* ***1991****, 40, 407.*

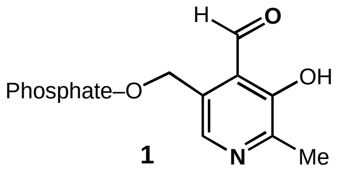
Ahlbrecht, "Stereoselectivity of chiral homoenolate equivalents." *Synthesis* **1999**, 365-390.

D. A. Evans

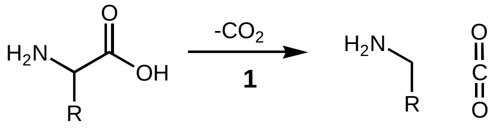
Monday,
December 1, 2003

Relevant Questions

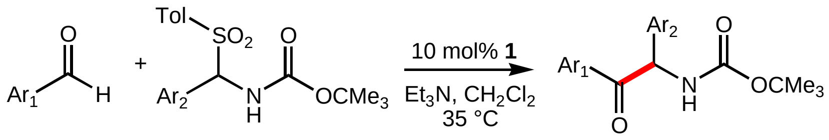
The pyridoxal co-factor (Vitamin B_6) 1, facilitates the decarboxylation of α-amino acids. Provide a mechanism by which **1** carries out this transformation.

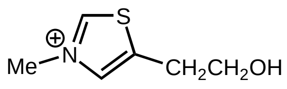


1



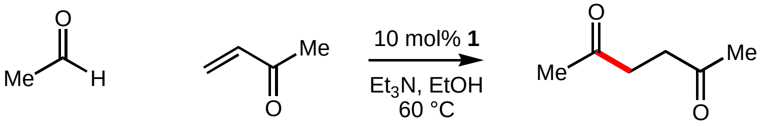
Cume Question, Fall 2001. The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group (*JACS* **2001**, *123*, 9696-9697). Provide a mechanism for this transformation.





1 (used as catalyst)

The nucleophilic addition of aldehydes to electrophilic double bonds catalyzed by thiazolium salt **1** is referred to as the Stetter Reaction (Stetter, H.; Kuhlmann, H. *Org. Reactions* **1991**, *40*, 407). Provide a mechanism for this transformation.



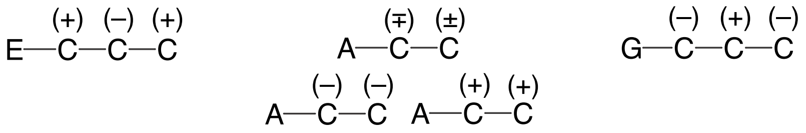
Summary of Functional Group Classification Scheme

Classification of Functional Groups

Each substituent attached to carbon activates that carbon toward a polar reaction by either resonance or induction or both.

	F_1—C	F_2—C	F_3—C	F_4—C
Induction	(+)	(+)	(–)	(–)
Resonance	(+)	(–)	(+)	(–)
Symbol	E—C (+)	A—C (±)		G—C (–)

Charge Affinity Patterns



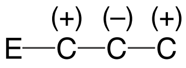
$\mathrm{E{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}}$ $\mathrm{A{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}}$ $\mathrm{G{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}}$

$\mathrm{A{-}\overset{(-)}{C}{-}\overset{(-)}{C}}$ $\mathrm{A{-}\overset{(+)}{C}{-}\overset{(+)}{C}}$

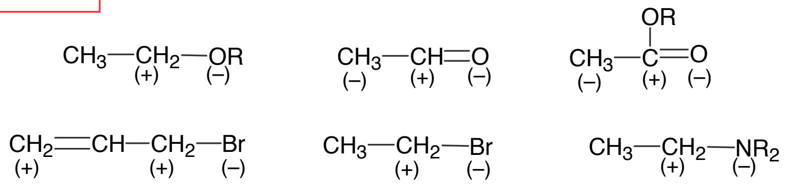
Real functional groups are assigned to a class designation by inspection of the chemistry of that FG, along with that of its conjugate acid and conjugate base

Charge affinities of real functional groups form a subset of the ideal FG classes.

E-Functions



$\mathrm{E{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}}$

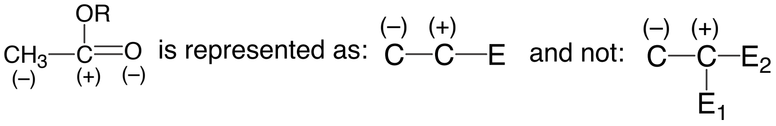


$\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}\underset{(-)}{OR}}$ $\mathrm{\underset{(-)}{CH_3}{-}\underset{(+)}{CH}{=}\underset{(-)}{O}}$ $\mathrm{\underset{(-)}{CH_3}{-}\underset{(+)}{\overset{OR}{C}}{=}\underset{(-)}{O}}$

$\mathrm{\underset{(+)}{CH_2}{=}CH{-}\underset{(+)}{CH_2}{-}\underset{(-)}{Br}}$ $\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}\underset{(-)}{Br}}$ $\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}\underset{(-)}{NR_2}}$

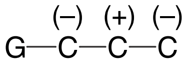
- Note that the issue of oxidation state in not explicitly incorporated. This issue is subordinate to that of defining site reactivity.

For example,



$\mathrm{\underset{(-)}{CH_3}{-}\underset{(+)}{\overset{OR}{C}}{=}\underset{(-)}{O}}$ is represented as: $\mathrm{\overset{(-)}{C}{-}\overset{(+)}{C}{-}E}$ and not: $\mathrm{\overset{(-)}{C}{-}\underset{E_1}{\overset{(+)}{C}}{-}E_2}$

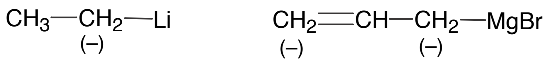
G-Functions



$\mathrm{G{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}}$

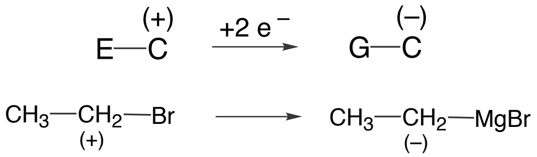
- Those ideal FGs which create nucleophilic carbon at point of attachment.
- Exhibit strictly alternate charge affinity patterns.

These are your metallic FGs such as Li, Mg, etc.



$\mathrm{CH_3{-}\underset{(-)}{CH_2}{-}Li}$ $\mathrm{\underset{(-)}{CH_2}{=}CH{-}\underset{(-)}{CH_2}{-}MgBr}$

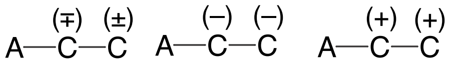
- Note that a 2-electron reduction (or oxidation) will transform an E-Class FG to a G-Class FG.



$\mathrm{E{-}\overset{(+)}{C}} \xrightarrow{+2\,e^-} \mathrm{G{-}\overset{(-)}{C}}$

$\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}Br} \longrightarrow \mathrm{CH_3{-}\underset{(-)}{CH_2}{-}MgBr}$

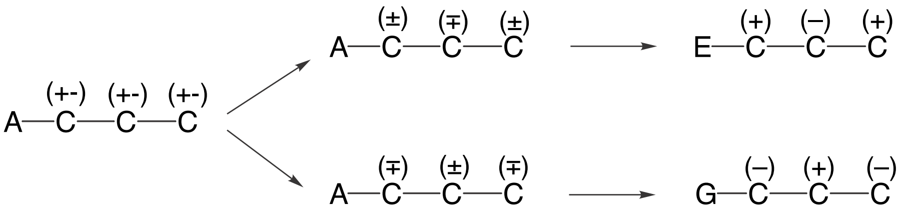
A-Functions



$\mathrm{A{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}}$ $\mathrm{A{-}\overset{(-)}{C}{-}\overset{(-)}{C}}$ $\mathrm{A{-}\overset{(+)}{C}{-}\overset{(+)}{C}}$

- All sites activated equally for electrophilic & nucleophilic reactivity.
- Those ideal FGs which exhibit nonalternate polar site reactivity are included.

One might visualize a process wherein A-functions are gradually polarized towards either E– or G– behavior in response to changes in inductive and resonance effects.



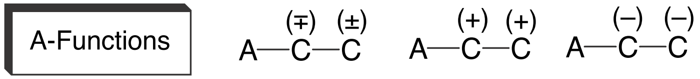
$\mathrm{A{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}} \nearrow \mathrm{A{-}\overset{(\pm)}{C}{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}} \longrightarrow \mathrm{E{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}}$

$\mathrm{A{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}} \searrow \mathrm{A{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}{-}\overset{(\mp)}{C}} \longrightarrow \mathrm{G{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}}$

A-functions are some of the most useful FGs in organic synthesis because of the unique reactivity provided.

Pairwise Functional Group Relationships

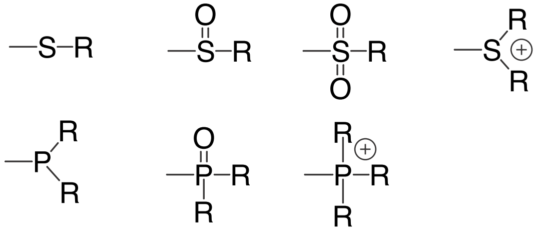
A-Functions: Real Examples



- A-functions are composed of polyatomic arrangements of N & O.

$-NO_2$ $=NOH$ $=NNR_2$ $-N{=}NR_2$ $=N(O)R$ $=N{=}N$ $\equiv N$

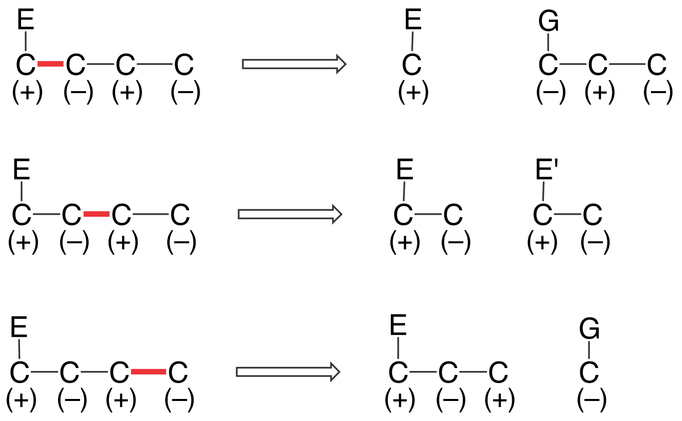
- A-functions are composed of second-row elements such **S** and **P**.



- Functional groups derived from many of the transition elements

Synthesis of Targets containing E-Functions

Transforms utilizing target E-function in synthesis plan given highest priority.



G–FG lost
in construction

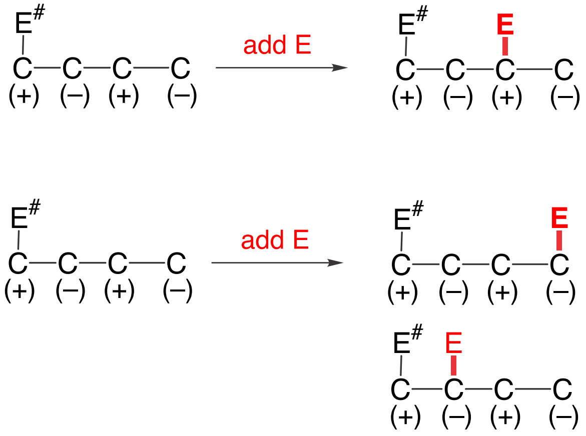
E'–FG lost
in construction

G–FG lost
in construction

Given the resident E-function, the charge affinity pattern dictates the nature of the polar coupling process and thus functional groups to be employed in synthesis.

Classification of Pairwise Difunctional Relationships

Consider the paired relationships of E-functions. There are two relationships.



Charge affinity patterns
are "matched."

Pairwise relationship is "consonant".

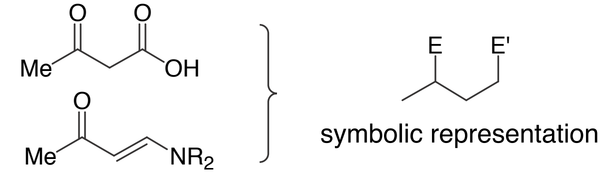
Charge affinity patterns
are "unmatched."

Pairwise relationship is "dissonant".

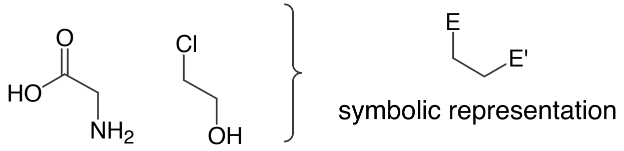
Consonant & dissonant relationships may be established with E-E, E-G, or G-G pairings.

Most target structures are composed of E-functions.

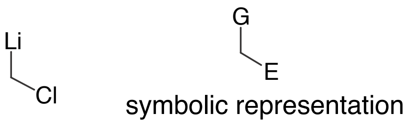
Representative difunctional relationships



Classification: 1,3-C



Classification: 1,2-D

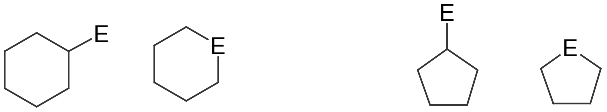


Classification: 1,1-D

Pairwise Functional Group Relationships–2

Classification of Pairwise Difunctional Relationships

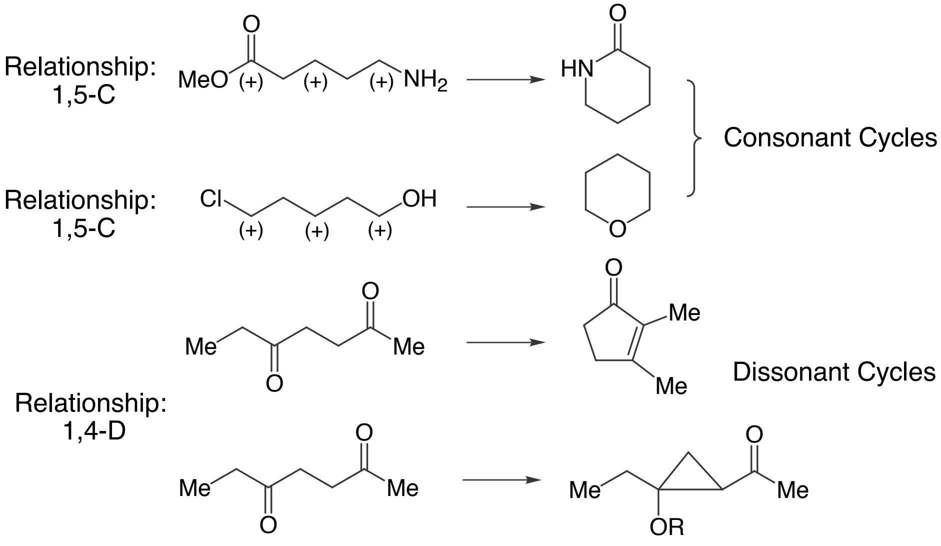
- A single FG residing either in or appended to a cycle may establish a FG relationship with itself.



Consonant cycles   Dissonant cycles

Consonant & Dissonant Relationships: Path-Cycle Interconversions

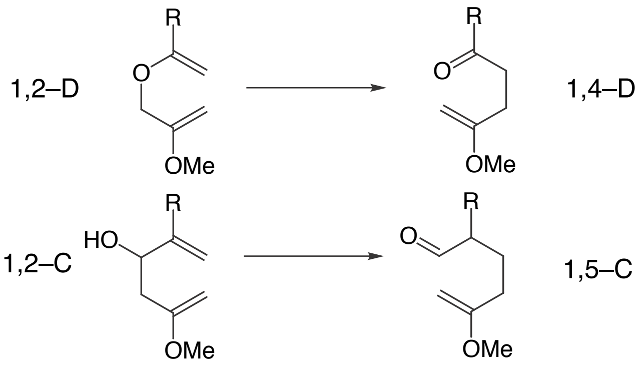
Linear molecules may be transformed into cycles & vice-versa:



Path-cycle interconversions such as those illustrated permute, but do not eliminate the relationship. i.e. D-bond paths are transformed into D-cycles.

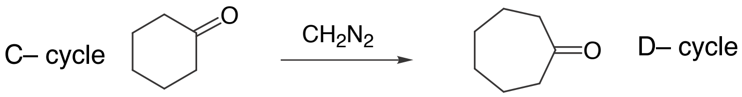
Pairwise Relationships: Path-Path Interconversions via Sigmatropic Rearrangements

[3,3] Sigmatropic Rearrangements:

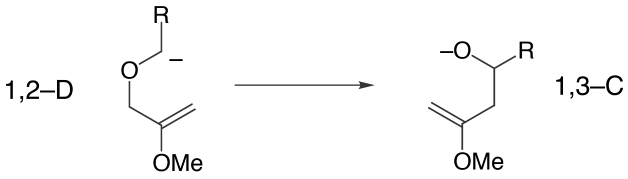


- For these rearrangements, C→C', D→D' but C→D not possible

[1,2] Sigmatropic Rearrangements:



[2,3] Sigmatropic Rearrangements:



General Rule For [m,n] Sigmatropic Rearrangements:

When the sum of m+n is even, the FG relationship is maintained, e.g. C→C'
When the sum of integers is odd, the FG relationship is changed, e.g. C→D

Pairwise Functional Group Relationships–3

Pairwise Relationships in Inorganic Reagents

■ E-functions in their most stable oxidation states (HO^-, NH_3, Cl^-) are represented as E(–).

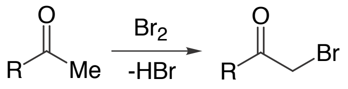
There exist an important family of reagents which have E-FGs directly coupled:

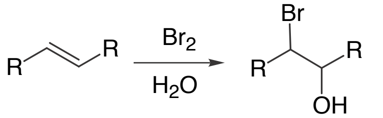
E–E Reagents

Br—Br HO—NH_2
HO—OH H_2N—NH_2

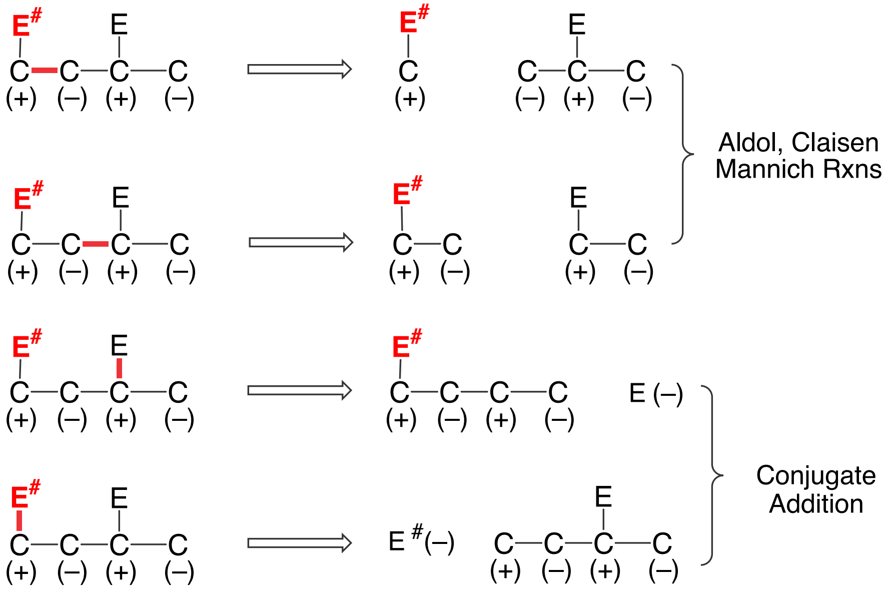
In each of these reagents there is a 0,0-D relationship

These reagents are used to construct D-Relationships:





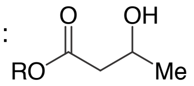
Synthesis of Targets containing Consonant Pairwise Relationships



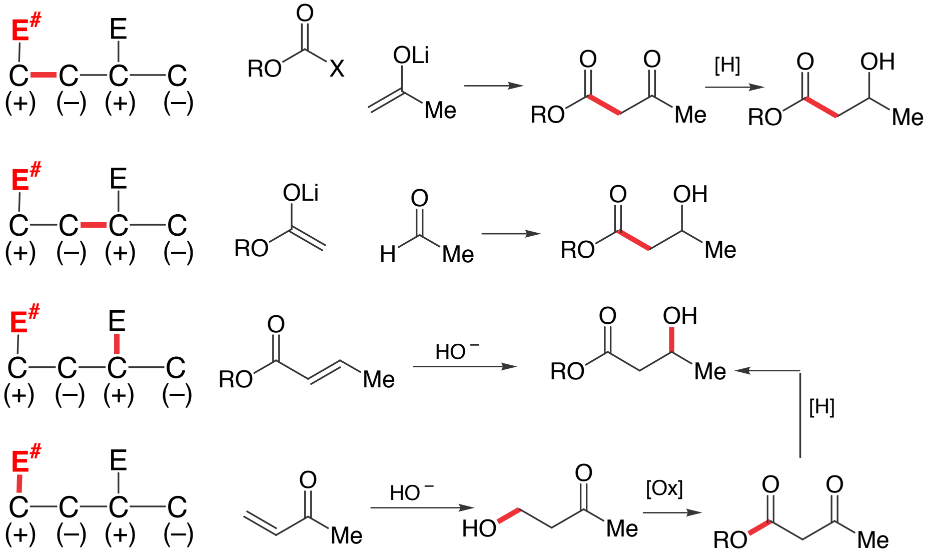
Consonant difunctional relationships can be constructed from just the functions illustrated & polar bond constructions.

A Specific Case

Target structure:



Step I: There are 4 bonds interconnecting E & E'. Hence generate the 4 transforms leading to mono-functional precursors:

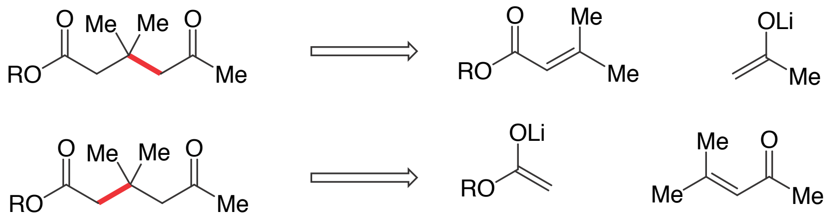


Step II: Evaluate the efficiency of the 4 plausible routes to the target from available precursors.

Given the oxidation state in the target, the second synthesis looks the best and the fourth looks the worst.

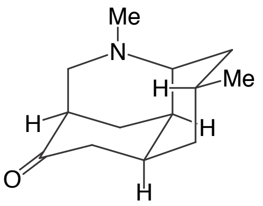
The Constraint of Quaternary Centers

If a quaternary center occurs along the consonant bond path, one is limited to bond constructions on either side of that restriction



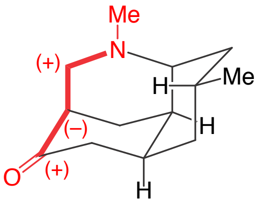
Pairwise Functional Group Relationships–4

Quaternary Centers & Bridgehead Restrictions

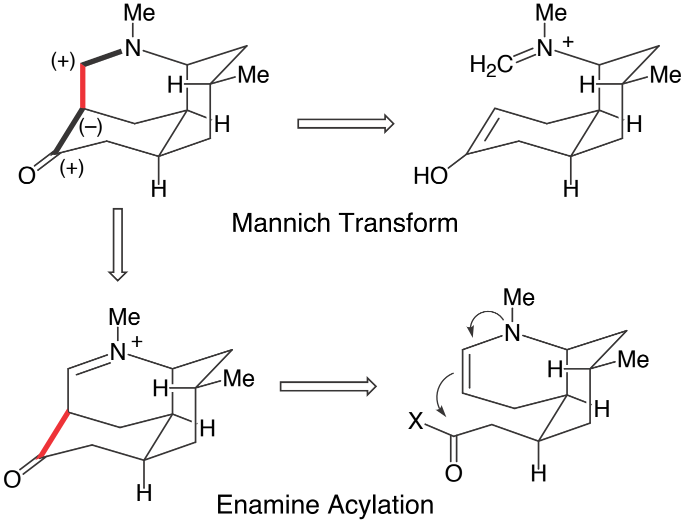


Lucidulene Synthesis: *JACS* **94**, 4779 (1972)

Focus on the shortest consonant bond path:



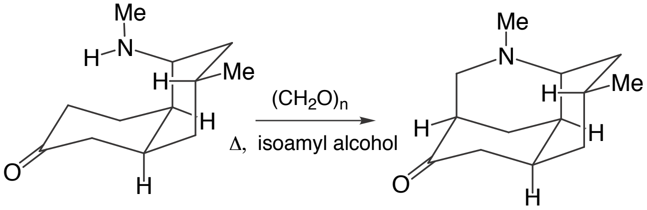
The two permitted bond constructions along illustrated bond path flank the bridgehead carbon



Mannich Transform

Enamine Acylation

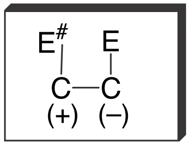
Option Selected:

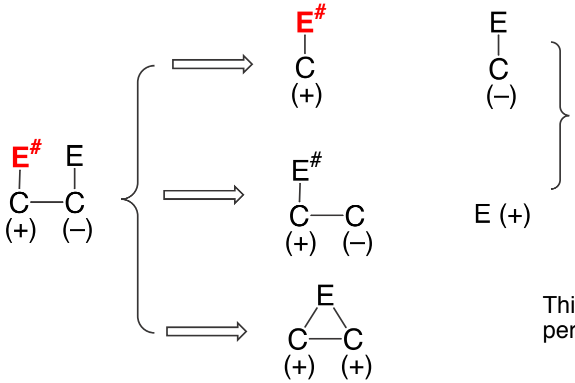


- Corrolary: π-conjugation cannot be extended through bridgehead or quaternary centers

Synthesis of Dissonant Pairwise Relationlships

The pairwise relationship is "unmatched"; hence, the illustrated E-functions cannot be used exclusively to construct the bond path. Let's consider the simplest case: a 1,2-D relationship.





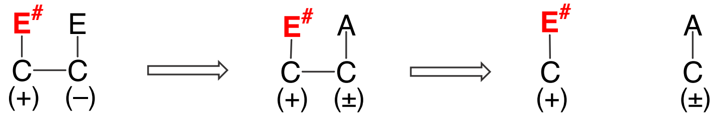
Resident E-functions do not provide required charge affinity pattern for coupling

This transform defined a path-cycle permutation of the D-relationship

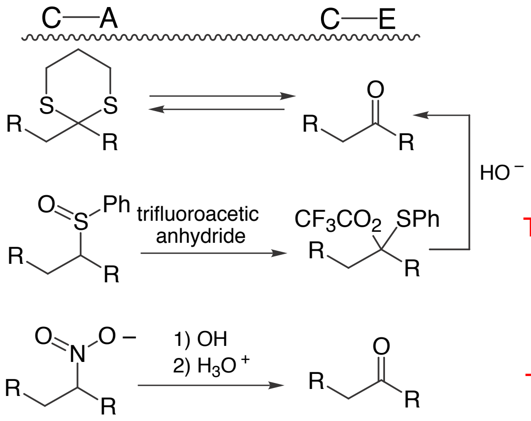
In the illustrated polar disconnections, one of the fragments may exploit the charge affinity pattern of the resident FG while the other may not.

Hence dissonant pairwise relationships may not be constructed via just the functions present in the target.

Dissonant Pairwise Relationlships via A-Functions



In implementing this strategy you must know all important **1,1-A↔E FG transformations**



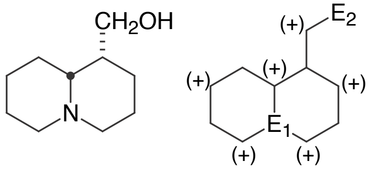
The Pummerer Rearrangement

"The Pummerer reaction of sulfinyl compounds.", De Lucchi, etal. *Org. Reactions* **1991**, *40*, 157.

The Nef Reaction

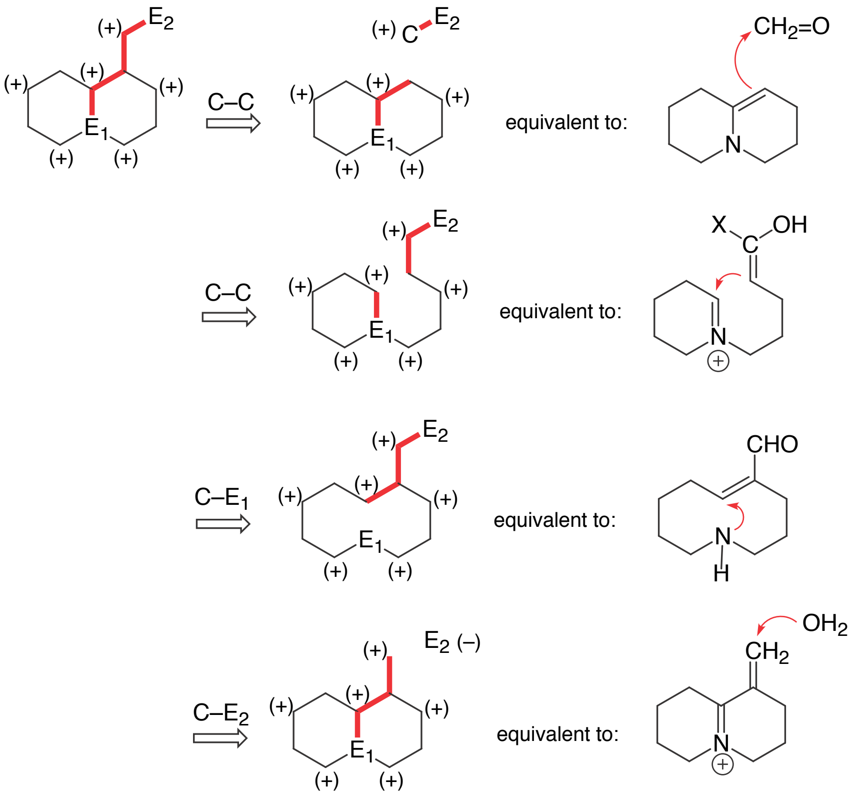
Bond path analysis of simple alkaloids

lupinine

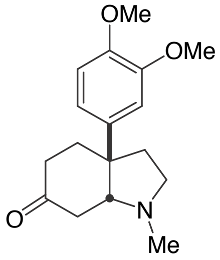


Every complex polyfunctional molecule may be analyzed structurally in terms of its individual consonant or dissonant construction paths or cycles. For example, in the alkaloid lupinine all possible construction paths interconnecting E1 and E2 are consonant. Consonant paths within the polyatomic framework define seams in the structure that may be constructed using aldol and related processes.

Begin the disconnection process by focusing on the shortest consonant bond path. In this case, there are 4 bonds, hence 4 disconnections.



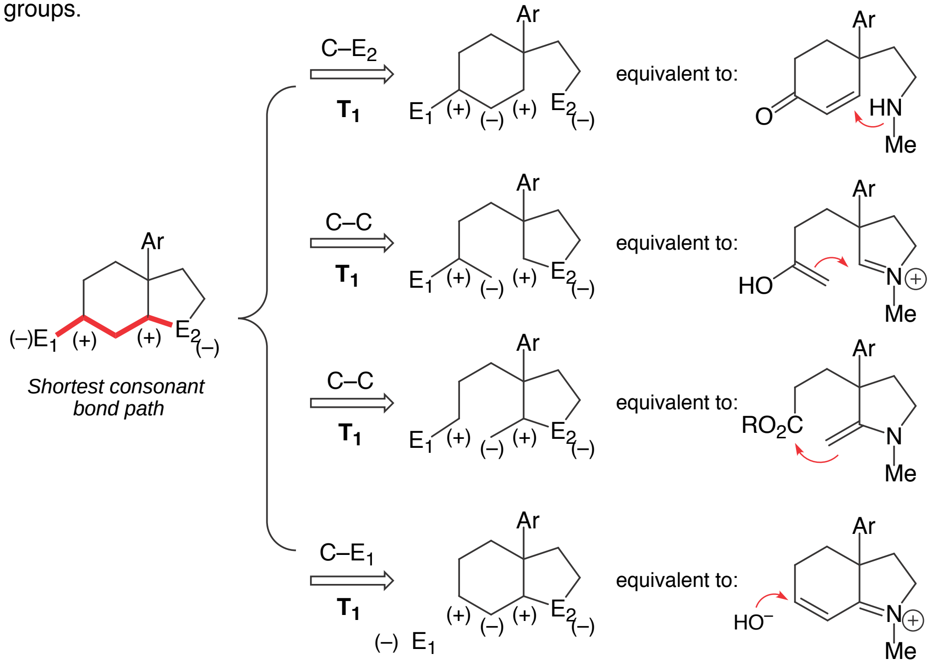
Note that oxidation states of precursors is not yet considered.



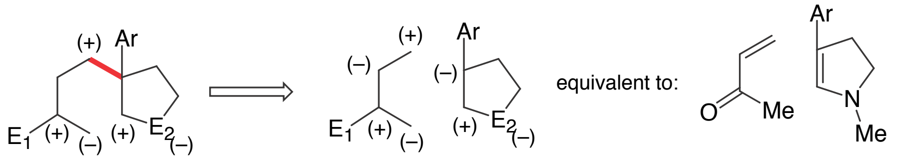
Mesembrine

Curphey, T. J.; Kim, H. L. *Tetrahedron Lett*. **1968**, 1441.
Keely, S. L.; Tahk, F. C. *JACS*. **1968**, *90*, 5584.
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580
Shamma, M.; Rodrigues, H. R. *Tetrahedron* **1968**, *24*, 6583

In the analysis of potential routes to structures like **mesembrine**, identify the shortest consonant bond path and then proceed to carry out all polar disconnections along that bond path. Since there four bonds interconnecting =O and N (E1 and E2), there will be four associated transforms which one may execute using the illustrated functional groups.



Now consider further analysis of T_1: Again, select the shortest E_1-E_2 bond path and disconnect next to quaternary center. Dissonant element is localized in 5-membered enamine



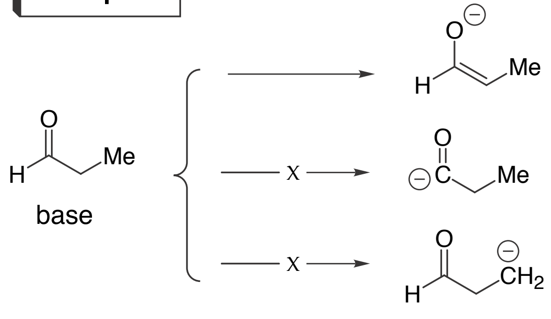
Handouts

Keely, S. L.; Tahk, F. C. *JACS*. **1968**, *90*, 5584.
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580

Inversion Operators-1: The Electronic Characteristics of Cyanide Ion

Inaccessible Reactivity Modes in Carbonyl Deprotonation

Example:

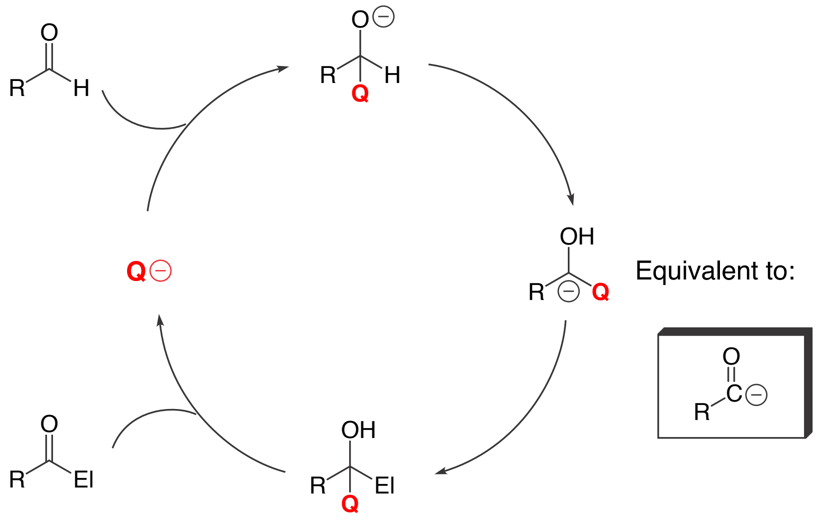


carbonyl anion inaccessible

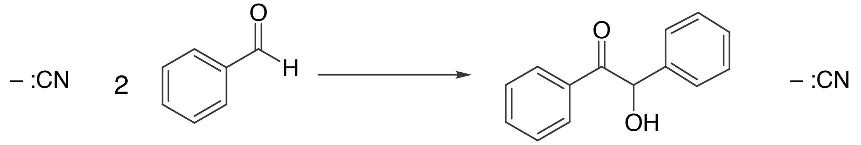
homoenolate anion inaccessible

Can one design "catalysts" which will provide access to carbonyl anion equivalents in situ??

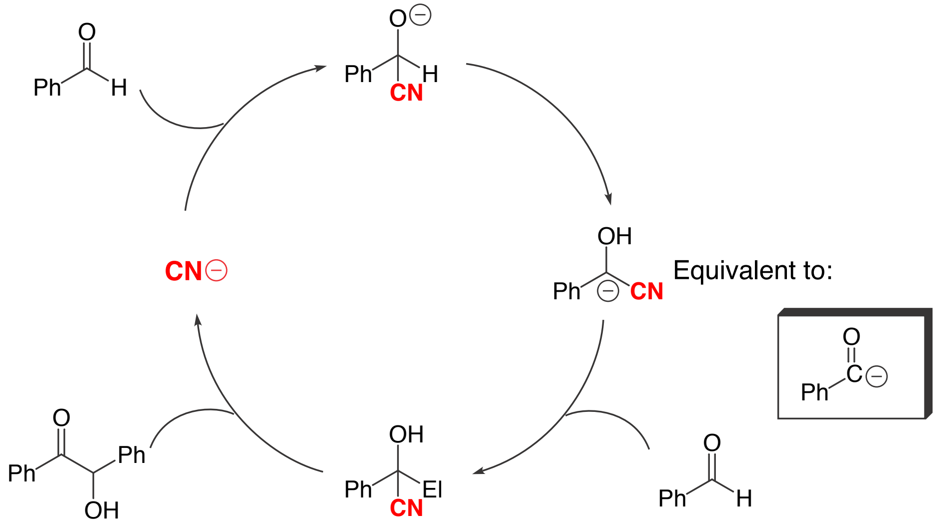
Let Q – be such a catalyst, we will call it an "inversion operator"



The Benzoin Condensation



- Cyanide ion is such a "catalyst"

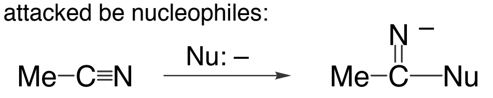


How do we classify the $\equiv N$ functional group?

- Hydrogen cyanide is a fairly good Bronsted acid (pKa$_{HOH}$ 9.5)

$$H{-}C{\equiv}N \rightleftharpoons H^{+} + {-}\,:C{\equiv}N \qquad \overset{(-)}{C}{-}G$$

- Acetonitrile can be attacked be nucleophiles:



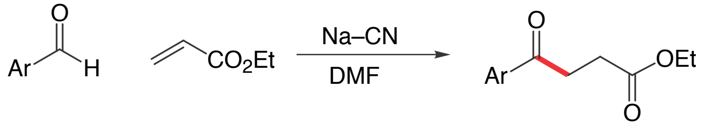
$$Me{-}C{\equiv}N \xrightarrow{Nu:\,-} Me{-}\overset{N^{-}}{\overset{\|}{C}}{-}Nu \qquad \overset{(+)}{C}{-}E$$

- Acetonitrile can be deprotonated by strong bases (pKa $_{DMSO}$ ~ 30)

$$Me{-}C{\equiv}N \rightleftharpoons H^{+} + H_2\bar{C}{-}C{\equiv}N \qquad \overset{(-)}{C}{-}\overset{(+)}{C}{-}E$$

Cyanide-based Carbonyl Anion Equivalents

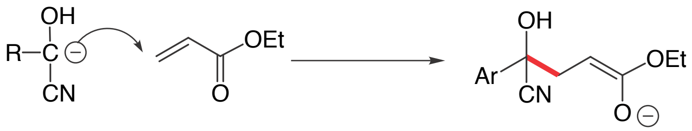
- Extensions of the Benzoin condensation concept are possible in some instances:



44% yield

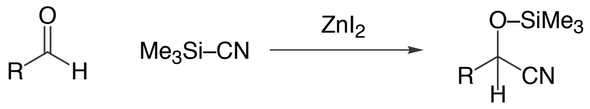
The C–C Bond Construction

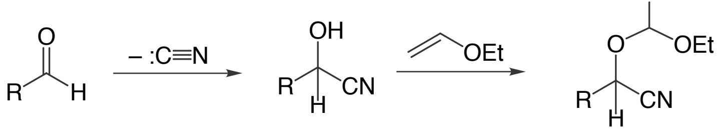
Stetter, *Org. Reactions* **1991**, *40*, 407.



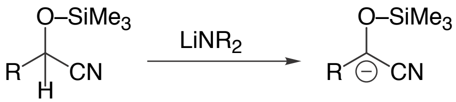
- The in situ use of cyanide ion as an inversion operator is limited. Greater generality may be achieved by multistep alternatives:

Aldehyde Derivatization Step

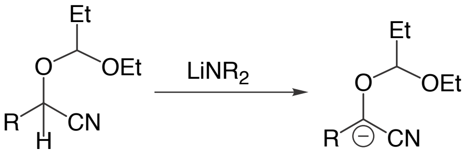




Substrate Deprotonation Step



Deprotonation possible only for R = Ar due to Si migration.

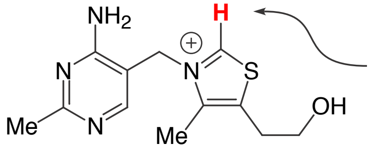


Deprotonation possible for All R groups

G. Stork *JACS* **93**, 5286 (1971)

Thiazolium Salts: Nature's Inversion Operators

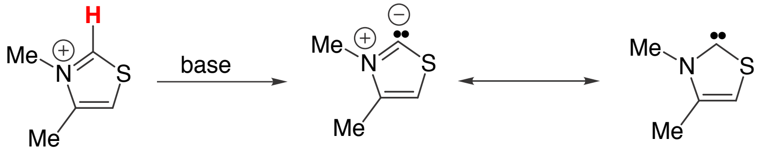
Reactions equivalent to the benzoin are catalyzed by biological co-factors to make (and break) dissonant difunctional heteroatom-heteroaton relationships



The thiamine cofactor

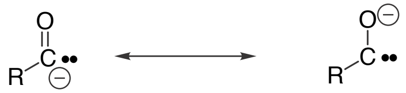
The pka of this proton has been the subject of considerable study. The current estimates are that the value falls in the range of 16-20 but this number is not firm.

F. G. Bordwell *JACS* **113**, 985, (1991)



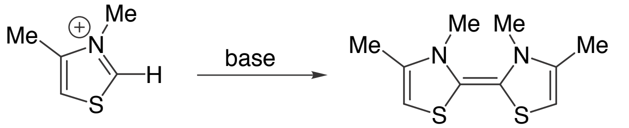
1

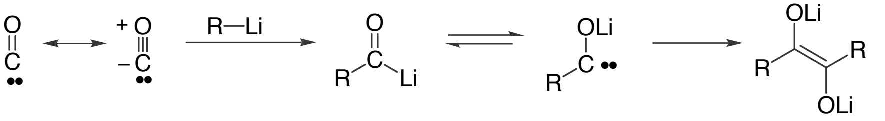
Carbonyl anions might be similarly stabilized



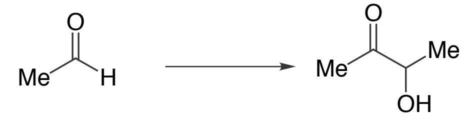
2

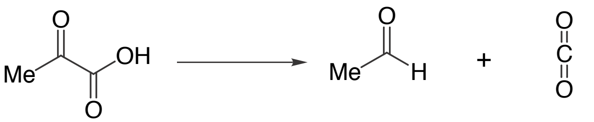
In the absence of electrophiles **1** & **2** dimerize as would be expected for carbene reactivity.





Reactions catalyzed by thiamine

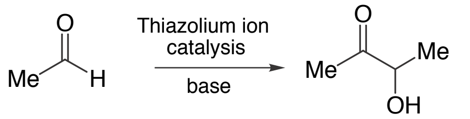




Thiazolium Salts as Inversion Operators–2

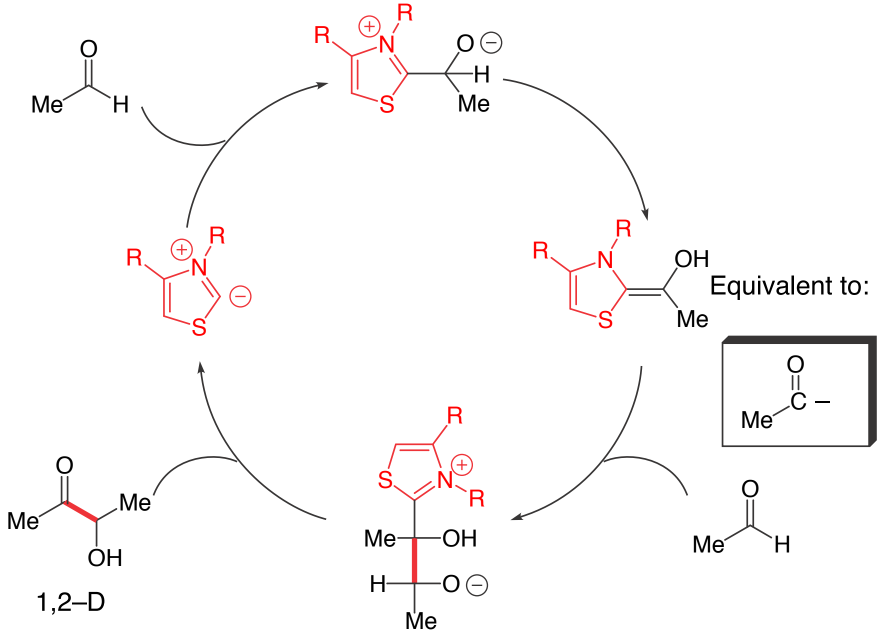
Aldehyde dimerization by Thiazolium Salts

The Reaction

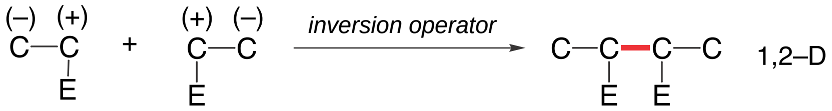


1,2–D

The Catalytic Cycle



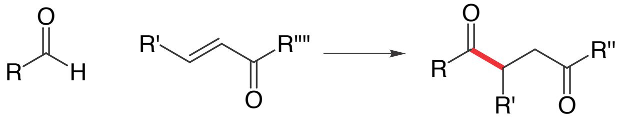
- Hence dissonant relationships may made from E-functions if "inversion operator" is employed



- The is a fundamental strategy for handling the formation and cleavage of D-relationships in nature.

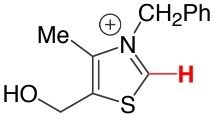
Cataylzed Michael Reactions byThiazolium Salts

The Reaction



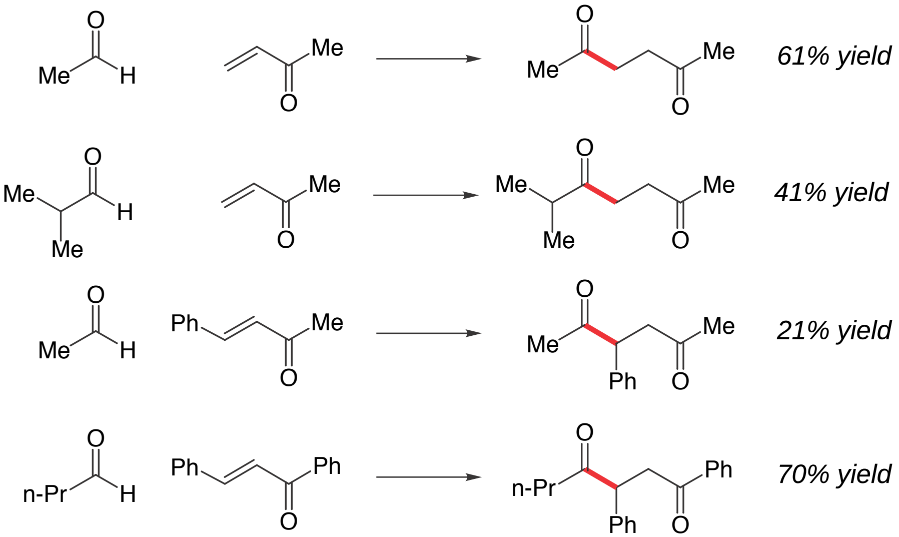
1,4–D

The Catalyst:

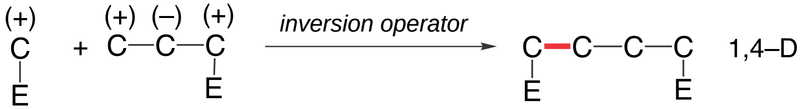


The Conditions:
0.1 equiv catalyst, Et$_3$N or NaOAc,
EtOH or DMF at 60-80 °C

Examples: "The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds.", Stetter, H.; Kuhlmann, H. *Org. Reactions* **1991**, *40*, 407.



- 1,4-D relationships may also be made from E-functions if "inversion operator" is employed.

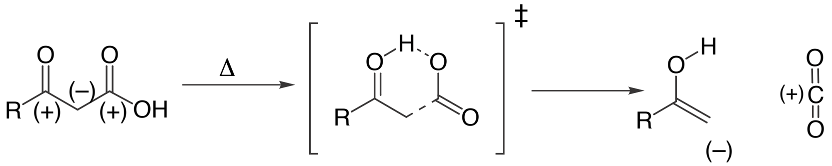


- There is no analogue to this reaction in nature.

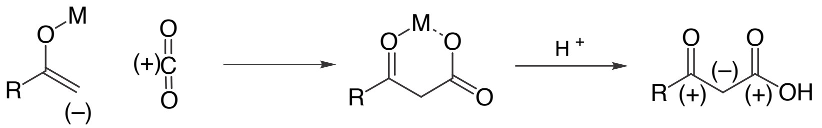
Thiazolium Salts as Inversion Operators–3

Decarboxylation Cataylzed by Thiazolium Salts

- Background: Decarboxylation from consonant difunctional relationships is facile:

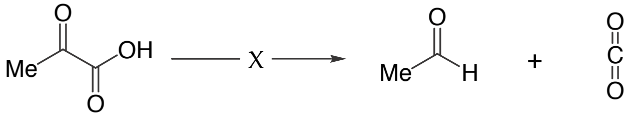


- The reverse processe can be achieved under basic conditions:

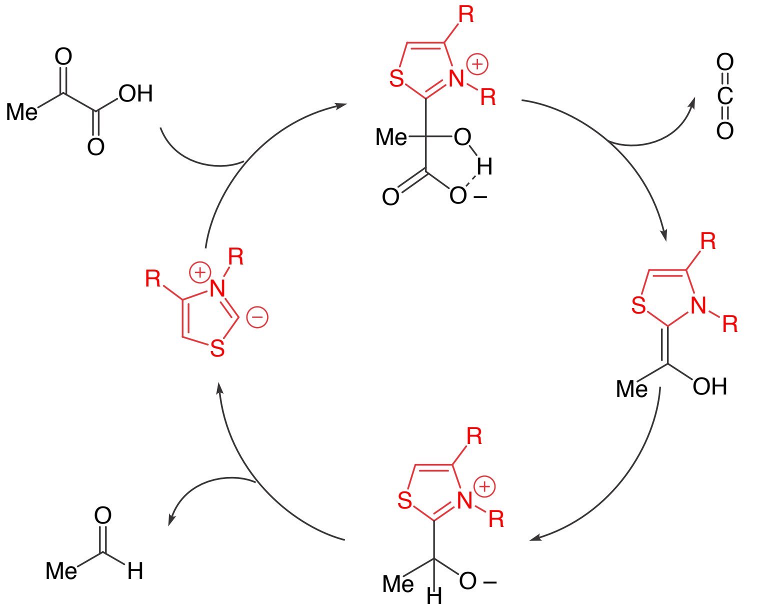


- Such consonant relationships may be readily made (and broken) via the resident functional groups. The analog reactions for dissonant relationships not possible.

For example:



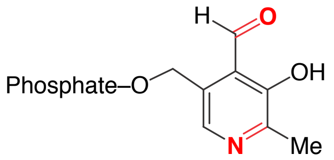
- Nature uses inversion operators to break such 1,2-D relationships



Design Attributes of Inversion Operators

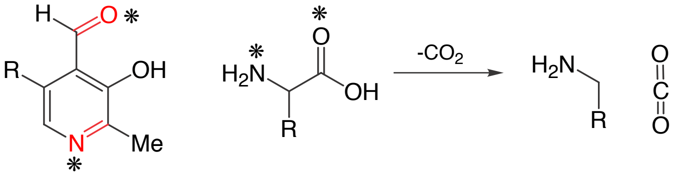
Inversion operators are constructed from A-functions or molecules containing D-relationships.

The pyridoxal Co-factor (Vitamin B_6)



The critical difunctional relationlship is that between =O & =N. This is a 1,4-D relationship

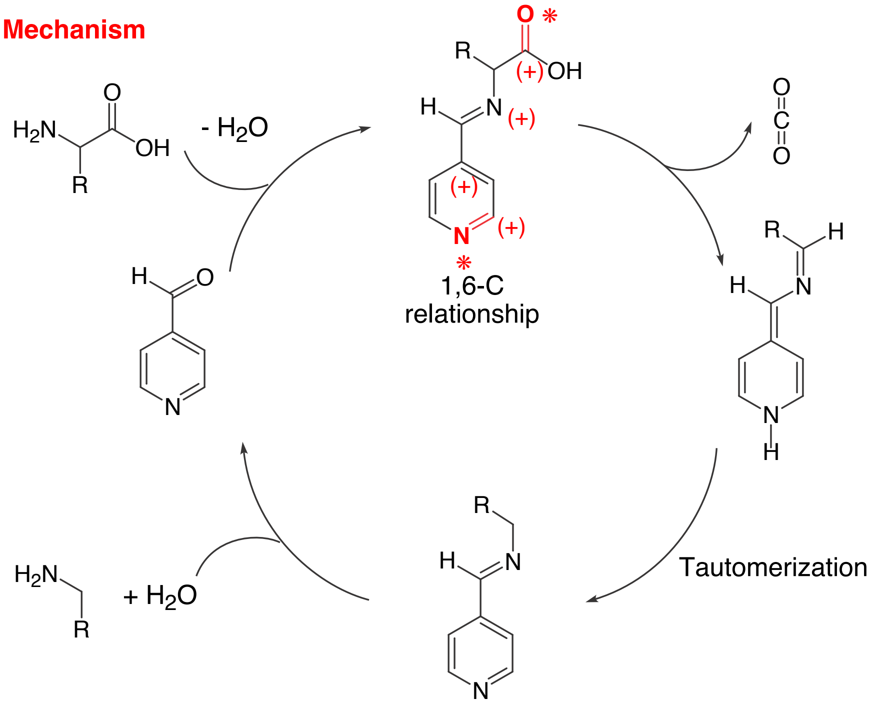
The Reaction



1,4-D relationship

1,2-D relationship

The Mechanism



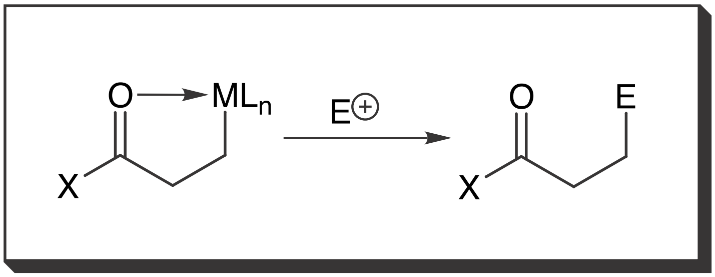
Chemistry 206

Advanced Organic Chemistry

Handout 30A

Homoenolates: Synthesis & Applications

Evans Group Seminar
by
Jason Burch, March 24, 2000



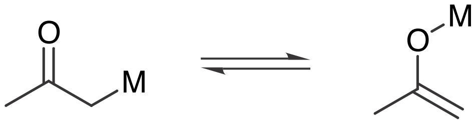
D. A. Evans

Monday,
December 1, 2003

Enolates and Homoenolates

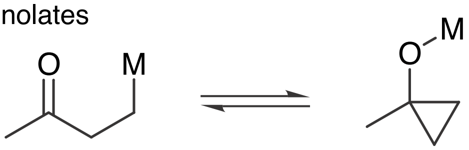
The Tautomerism Problem

- Enolates



- tautomerism is generally not a problem because oxyanionic tautomer still acts as carbon nucleophile

- Homoenolates



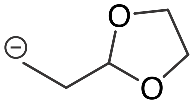
- tautomerism is a much larger problem because it is often irreversible and oxyanioic tautomer rarely acts as a carbon nucleophile

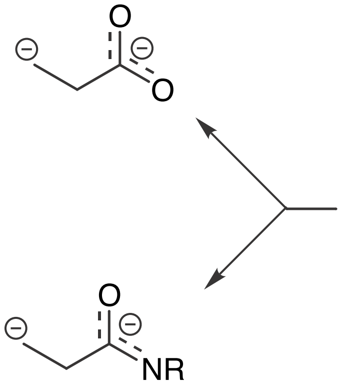
Nakamura in *Comp.Org.Synth.,* **1991**, *2*, 441

Homoenolate Equivalents

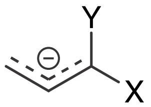
Definition: species containing an ionic carbon β to a moeity which can be converted into a carbonyl group

Examples:





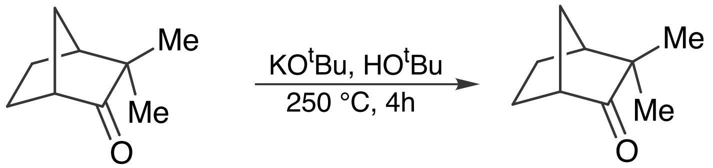
in situ protection



X = OR, NR_2, etc.
Y = H, R, OR, NR_2, etc.

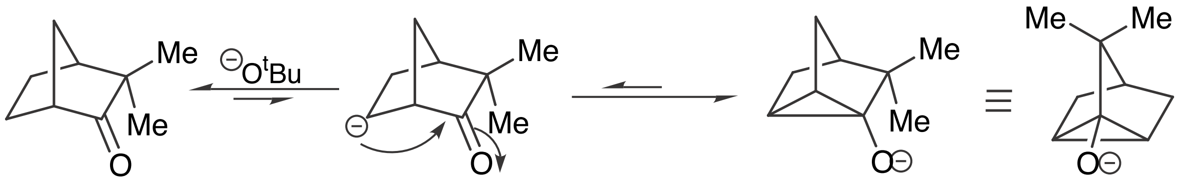
Werstiuk in "Umpoled Synthons", Hase, Ed.;
Wiley: New York, **1987**, Chap. 6
Ahlbrecht, *Synthesis,* **1999**, 365 (chiral examples)

The First "Homoenolate"



(+)-camphenilone **(±)**-camphenilone

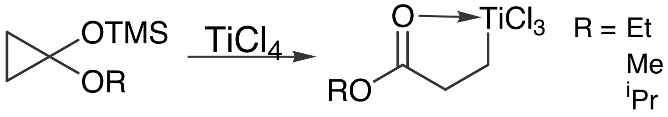
- no racemization occurred in >4 days at 250 °C in the absence of base
- proposed to proceed via a "homoenolate anion"



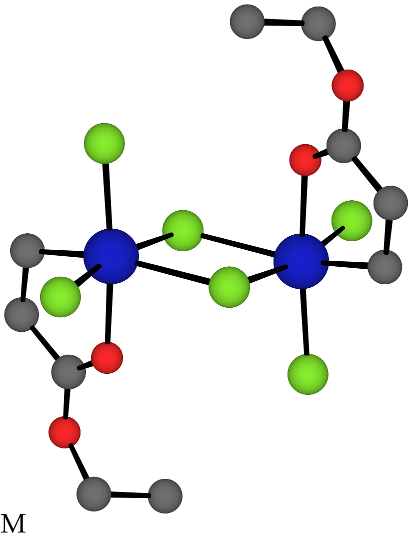
Nickon, *J.Am.Chem.Soc.*, **1962**, *84*, 4604

Cyclopropane Ring Opening

Synthesis of Titanium Homoenolates



- if conducted in $CDCl_3$ leads to a deep wine-red color; precipitates as purple needles in hexanes
- IR spectrum strongly supports coordinated carbonyl ($\nu_{C=O}$ = 1603 for R = ^{i}Pr in benzene)
- molecular weight by cryoscopy is 560-620 indicating dimeric structure
  → later verified in solid state by x-ray crystal structure (Floriani)



Relevant bond lengths (Å):

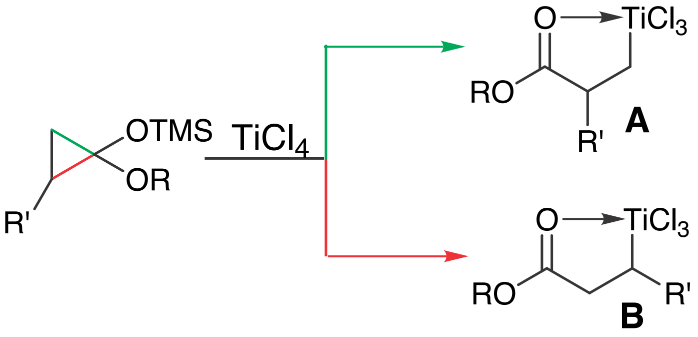
Ti-C	2.081
Ti-O	2.072
C=O	1.235

Nakamura, *J.Am.Chem.Soc.* **1983**, *105*, 651
Floriani, *Organometallics*, **1993**, *12*, 2845

Cyclopropane Ring Opening

Regioselectivity of Ring Cleavage - Titanium

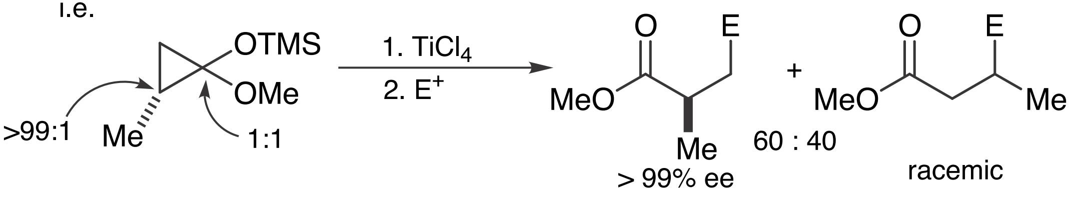
- in general, cleavage occurs selectively at the least substituted cyclopropane bond



R	R'	A : B
^{i}Pr	Me	>95 : 5
Me	Me	60 : 40
Et	Ph	78 : 22

- **A** can be isolated, but **B** is too unstable; only detected by *in situ* quench with electrophiles (i.e. Br_2, RCHO)
- if non-racemic starting material is used, quench with electrophiles indicates non-racemized **A** and totally racemic **B**

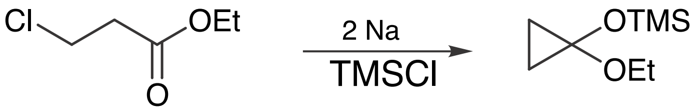
i.e.



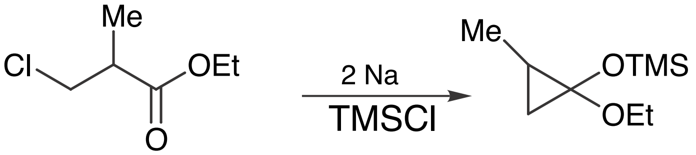
Nakamura, *J.Am.Chem.Soc.*, **1986**, *108*, 3749

Cyclopropane Synthesis

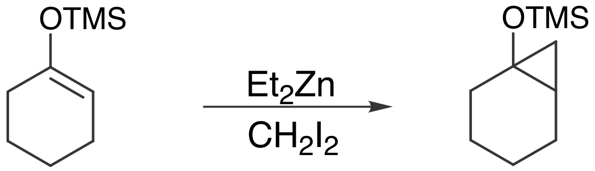
- most common method



- used to prepare substituted cyclopropanes



- use Simmons-Smith for ketone-derived substrates

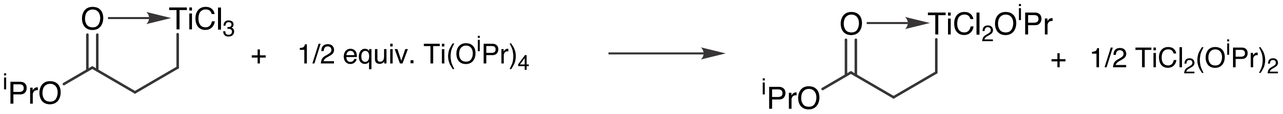


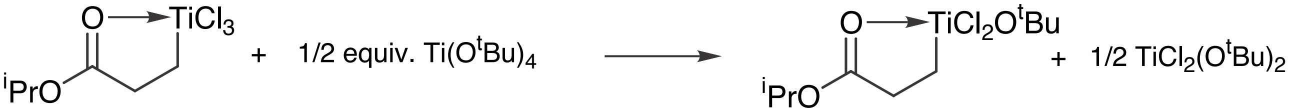
Ruhlmann, *Synthesis* , **1971**, 236.
Salaun, *Org. Synth.*, **1985**, *63*, 147
Murai, *J.Org.Chem.*, **1973**, *38*, 4354

Alkoxide-Modified Homoenolates

Tuning Titanium Homoenolate Reactivity

- Problem: trichlorotitanium homoenolates are not reactive enough for some applications
  can also lead to chlorinated byproducts
- Idea: replace 1 or more chlorides with alkoxides to increase nucleophilicity





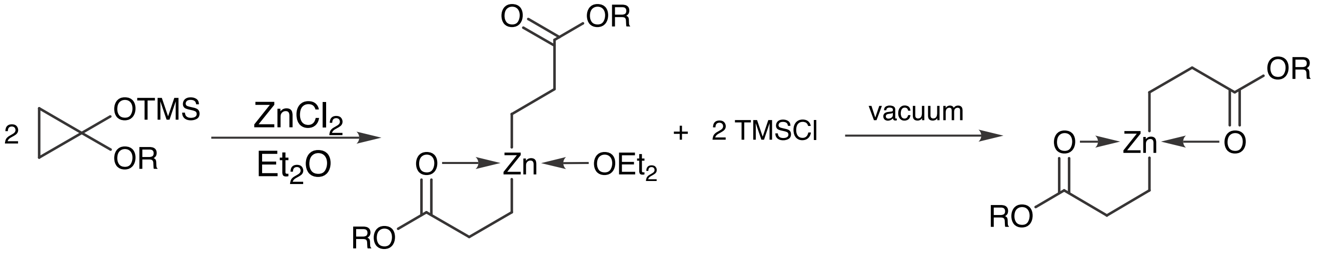
- Have not been characterized to the detail of the trichlorohomoenolates
- Appear to have "significant contribution from monomeric forms" (from molecular weight data)
- Are more reactive than trichloro homoenolates towards homoaldolisation

Nakamura, *J.Am.Chem.Soc.*, **1986**, *108*, 3745

Cyclopropane Ring Opening

Zinc Homoenolates

- Zinc homoenolates can be prepared in a similar method to titanium



$\nu_{C=O} = 1662\ cm^{-1}$
$1740\ cm^{-1}$

4 inequivalent
methylene groups
in ^1H-NMR

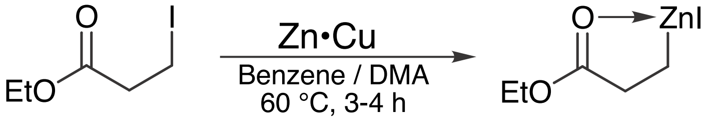
$\nu_{C=O} = 1645\ cm^{-1}$

2 inequivalent
methylene groups
in ^1H-NMR

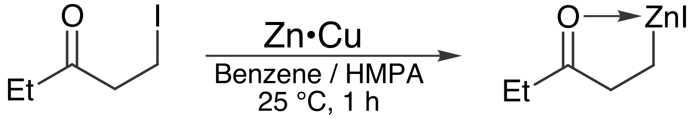
Nakamura, *Organometallics*, **1985**, *4*, 641

Direct Oxidative Addition

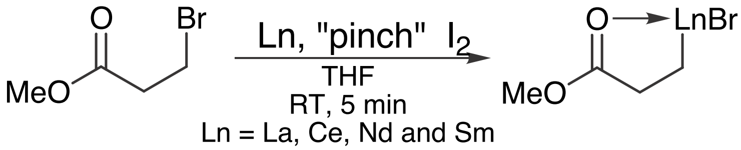
Zinc and Lanthanide Homoenolates



Quantitative



Poor yield (~50%)

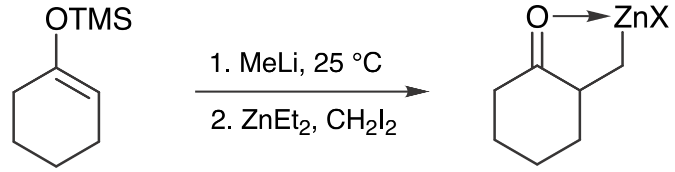


Poor yields of
homoaldolate (50-60%)
due to competition with
McMurray coupling of
aldehyde

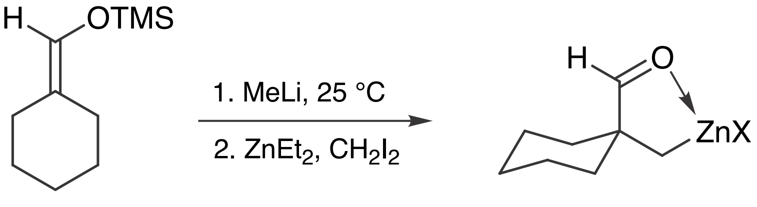
Yoshida, *Tetrahedron Lett.*, **1985**, *26*, 5559
Yoshida, *Angew.Chem.,Int.Ed.Engl.*, **1987**, *26*, 1157
Fukuzawa, *Chem. Commun.*, **1986**, 475

Enolate Homologation

Synthesis of Zinc Homoenolates



- less reactive than most zinc homoenolates
- can also be used to form aldehyde homoenolates

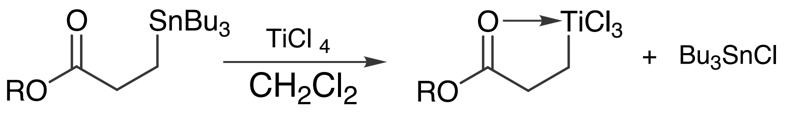


Knochel, *J.Org.Chem.*, **1993**, *58*, 2694

Direct Tin-Titanium Exchange

New Route to Titanium Homoenolates

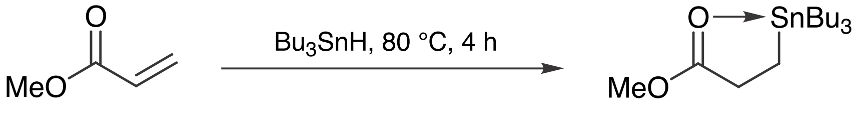
- Treatment of β–tri-n-butylstannyl esters with $TiCl_4$ directly forms titanium homoenolate

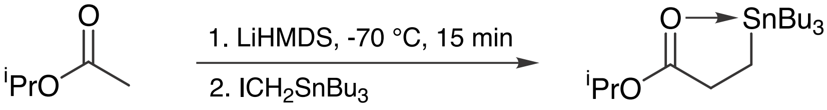


R = Me, ${}^{i}Pr$

- Isotope labelling studies showed rxn does not proceed via cyclopropane

- Substrates can easily be prepared by two methods:

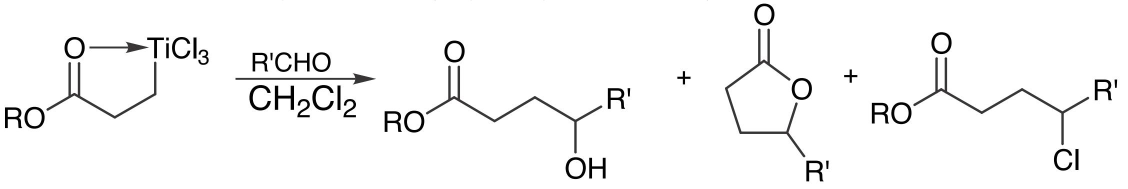


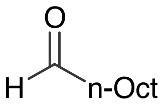
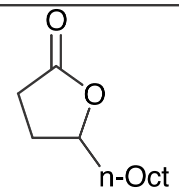
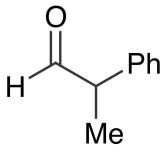
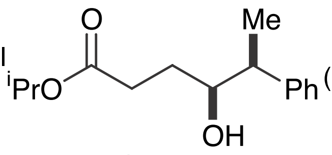
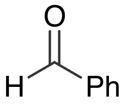
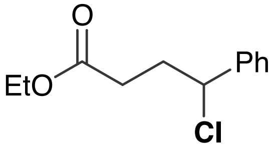


Goswami, *J.Org.Chem.*, **1985**, *50*, 5907
van der Kirk, *J. Appl. Chem.*, **1957**, *7*, 356
Still, *J.Am.Chem.Soc.*, **1978**, *100*, 1481

The First Homoaldol Reaction

Synthesis of γ-hydroxyesters and γ-lactones

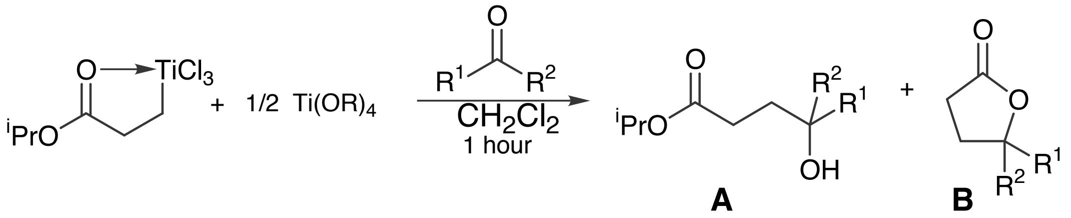


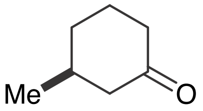
Aldehyde	R	Temp (°C)	Time (h)	Workup	Product	Yield
	Et	0	1	Acidic		81
	${}^{i}Pr$	0	2.5	Neutral		67 (85:15)
	Et	0	1.5	Neutral		90

Nakamura, *J.Am.Chem.Soc.*, **1977**, *99*, 7360

Homoaldol Reactions with Alkoxide-modified Homoenolates

Homoaldol Reactions with Aromatic Aldehydes and Ketones

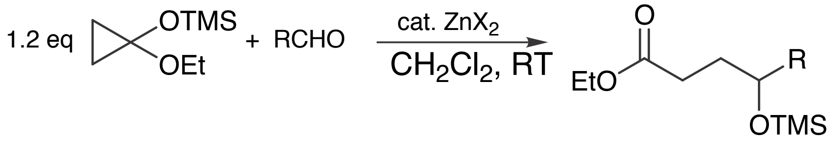


Electrophile	R	Temp(°C)	Yield (**A** or **B**)
Benzaldehyde	^{i}Pr	0	90(**A**)
Crotonaldehyde	^{i}Pr	0	88(**A**)
Acetophenone	^{i}Pr ^{t}Bu	20 20	66(**A**), 12(**B**) 93(**B**)
Cyclohexanone	^{i}Pr ^{t}Bu	20 20	62(**B**) 91(**B**)
	^{t}Bu	20	91(**B**) dr = 88 : 12 equatorial attack

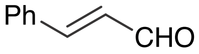
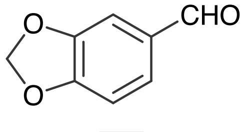
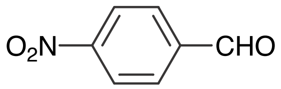
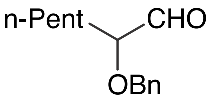
Nakamura, *J.Am.Chem.Soc.*, **1986**, *108*, 3745

Homoaldol Reactions of Zinc Homoenolates

First Catalytic Homoaldol Reactions



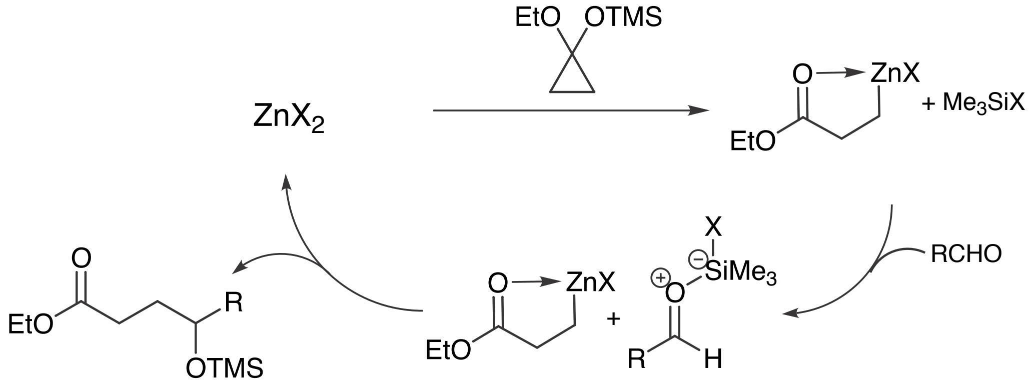
- TMSCl generated is essential (i.e. no reaction if removed *in vacuo* for stoichiometric case)

Aldehyde	**Catalyst, yield** **ZnCl$_2$ (30-50 mol%)**	 **ZnI$_2$ (0.1-1 mol%)**
PhCHO	84	89
	94	84
	91	95
	--	84
	79 93:7 *syn : anti* chelation product	--

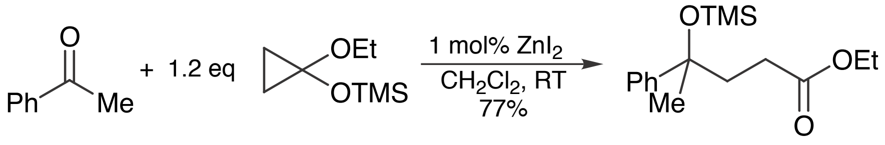
Nakamura, *J.Am.Chem.Soc.*, **1987**, *109*, 8056

Homoaldol Reactions of Zinc Homoenolates

Proposed Catalytic Cycle



- with ZnI_2, the homoenolate is reactive enough to add to ketones:

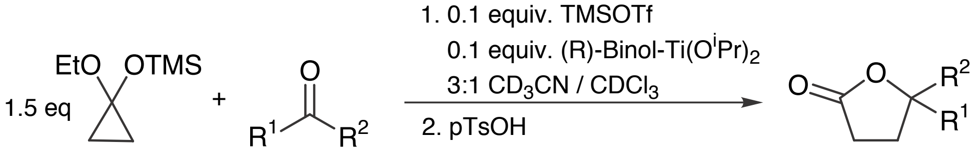


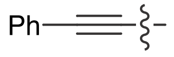
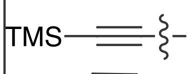
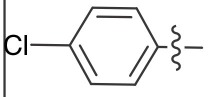
- no reaction even with stoichiometric $ZnCl_2$

Nakamura, *J.Am.Chem.Soc.*, **1987**, *109*, 8056

Gleason's Homoaldol reaction

First Catalytic Titanium Homoaldol Reaction



R^1	**R^2**	**Conditions**	**Yield**
Ph	H	0 °C, 24 h	99
	H	0 °C, 36 h	76
	H	0 °C, 36 h	82
	H	0 °C, 80 h	84
^tBu	H	45-50 °C, 54 h[a]	52
Ph	Me	45-50 °C, 60 h[a]	78

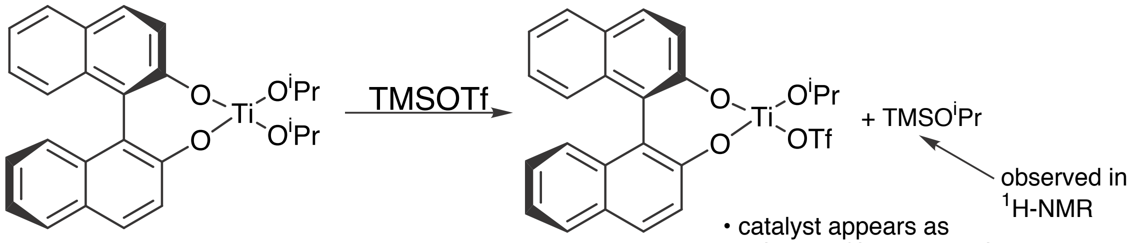
[a] 2 equiv. of cyclopropane used

Gleason, *Org. Lett.*, **1999**, *1*, 1643

Gleason's Homoaldol reaction

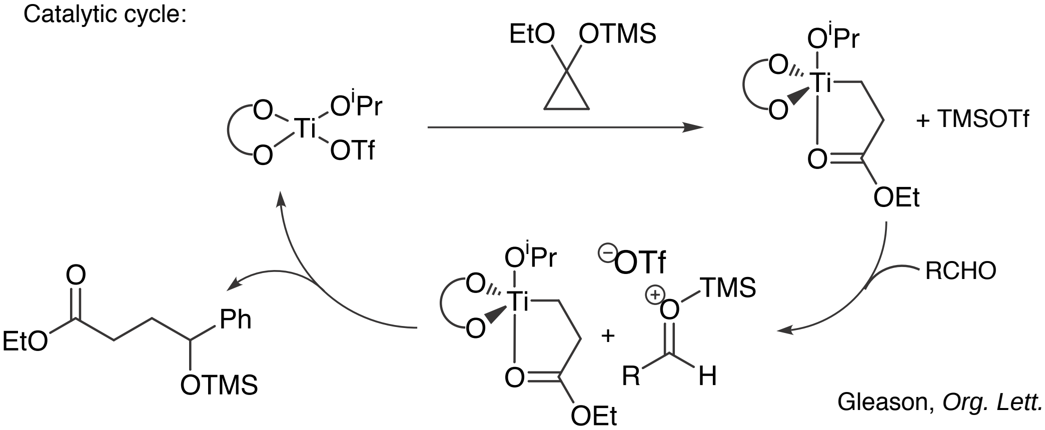
Proposed Catalyst and Catalytic Cycle

Catalyst:



- catalyst appears as mixture of interconverting species in NMR at RT

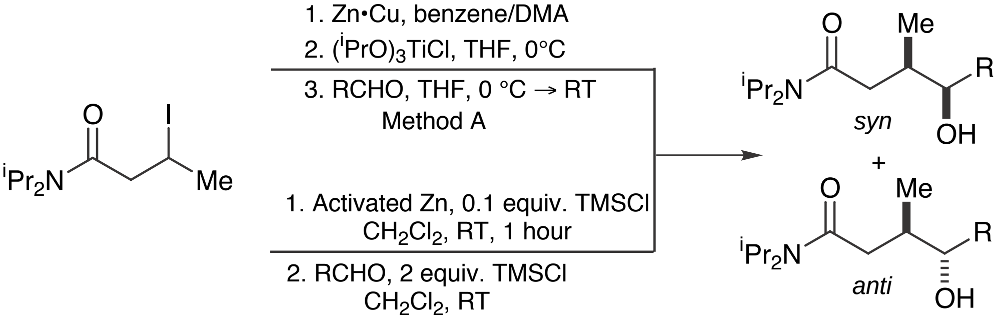
Catalytic cycle:



Gleason, *Org. Lett.*, **1999**, *1*, 1643

Diastereoselective Homoaldol Reactions of Amide-homoenolates

Synthesis of *syn*- or *anti*-β-methyl-γ-hydroxyamides



1. Zn•Cu, benzene/DMA
2. (^iPrO)₃TiCl, THF, 0°C
3. RCHO, THF, 0 °C → RT
Method A
1. Activated Zn, 0.1 equiv. TMSCl CH₂Cl₂, RT, 1 hour
2. RCHO, 2 equiv. TMSCl CH₂Cl₂, RT
Method B
^iPr₂N
I
Me
syn
anti
R
OH

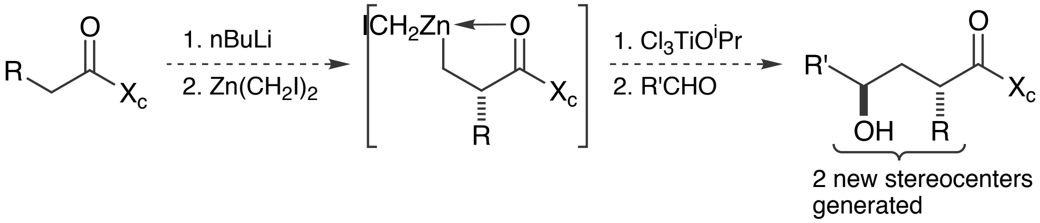
R	Method	Time (h)	Yield	***syn:anti***
Ph	A	3	79	94 : 6
	B	2.5	82	13 : 87
o-MeOPh	A	3	87	85 : 15
	B	0.6	95	25 : 75
2-furyl	A	0.5	61	96 : 4
	B	0.6	60	38 : 62

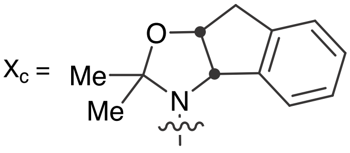
Asaoka, *J.Chem.Soc. Perkin Trans. 1*, **1995**, 285

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

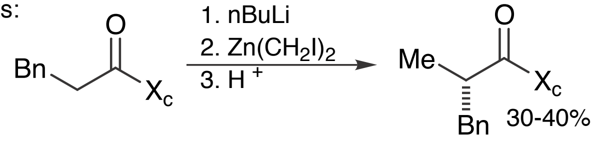
Asymmetric Synthesis of α-alkyl, γ-hydroxy Carbonyl Compounds

- idea:





- initial results:



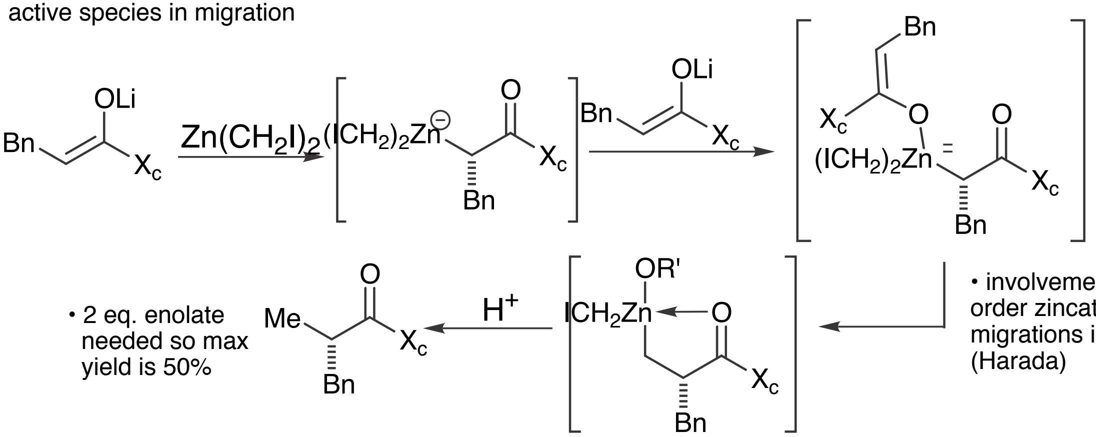
But ReactIR showed disappearance of enolate and appearence of new species

McWilliams, *J.Am.Chem.Soc.*, **1996**, *118*, 11970

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of α-alkyl, γ-hydroxy Carbonyl Compounds

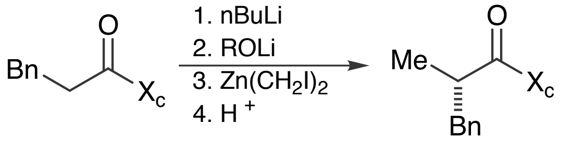
- proposal: zinc enolate unreactive towards homolagation; higher order zincate (zincate + extra enolate) active species in migration



- 2 eq. enolate needed so max yield is 50%

- involvement of higher order zincates in 1,2-migrations is known (Harada)

- idea: add an equivalent of alkoxide to take the place of the enolate in the higher order zincate



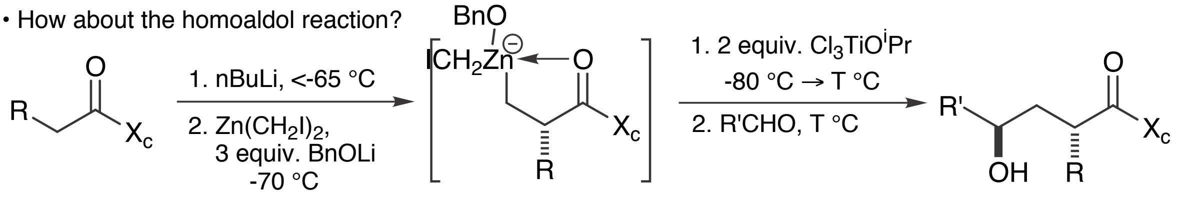
ROLi	Conversion
EtOLi	35
nPrOLi	74
BnOLi	82 (78% isolated)
$LiO(CH_2)_2OLi$	31

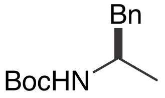
McWilliams, *J.Am.Chem.Soc.*, **1996**, *118*, 11970
Harada, *J.Org.Chem.*, **1993**, *113*, 2958

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of α-alkyl, γ-hydroxy Carbonyl Compounds

- How about the homoaldol reaction?

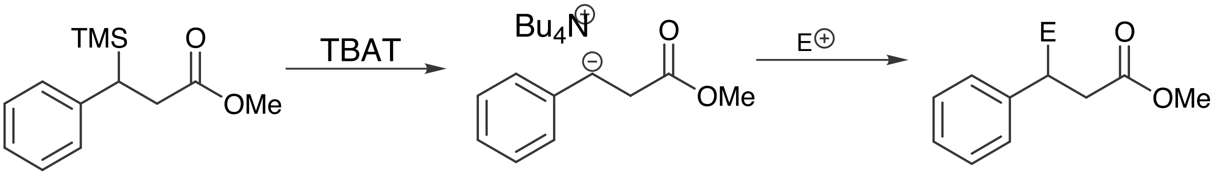


Aldehyde (R')	R	T (°C)	de (%)	Yield
	Bn	-20	≥99	59
	Me	-20	82	58
phenyl	Bn	-40	82	50
phenyl	Me	-40	80	44
iso-propyl	Bn	-50	76	53
n-butyl	Bn	-20	64	53

McWilliams, *J.Am.Chem.Soc.*, **1996**, *118*, 11970

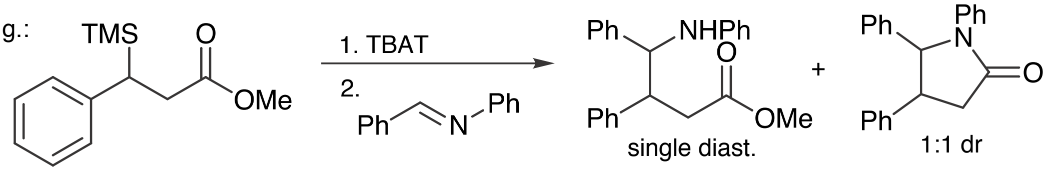
Reactive Homoenolates

First Synthesis of a Metal-free Homoenolate



- reactive enough to add to imines, as well as aldehydes and ketones

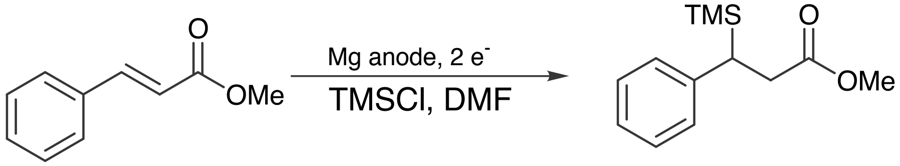
e.g.:



single diast.
22%

1:1 dr
60%

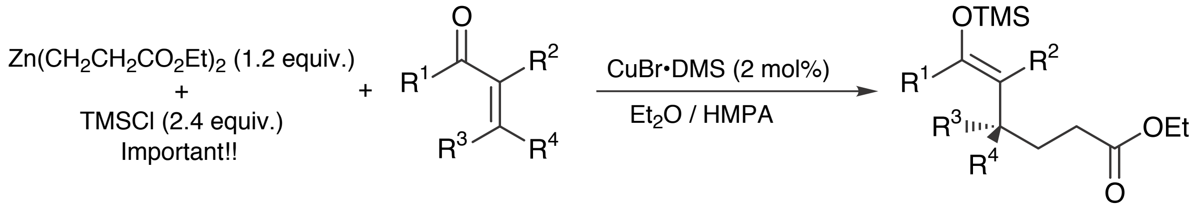
- substrate made easily using Nishiguchi method

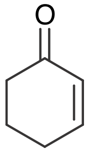
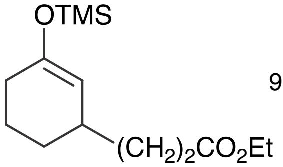
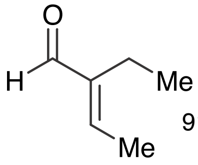
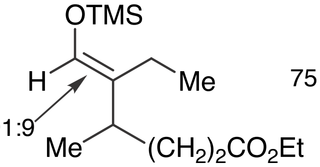
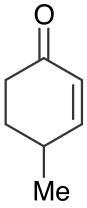
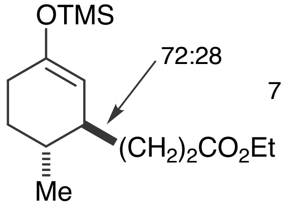
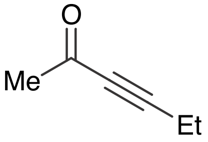
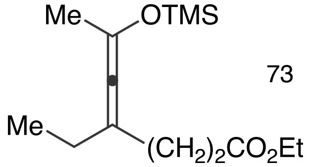


Fry, *Tetrahedron Lett.*, **1999**, *40*, 7945
Nishiguchi, *Tetrahedron Lett.*, **1992**, *33*, 5515

Conjugate Addition of Zinc Homoenolates

Synthesis of δ,ε-(silylenolether)-esters

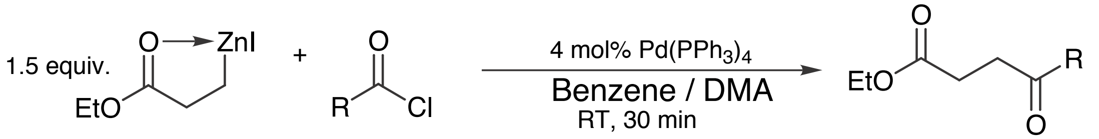


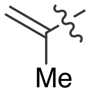
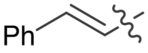
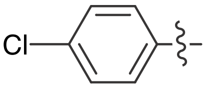
Enone	Product	Yield	Enone	Product	Yield
		93			75
		78			73

Nakamura, *J.Am.Chem.Soc.*, **1987**, *109*, 8056
Nakamura, *Org. Synth.*, **1987**, *66*, 43

Acylation of Zinc Homoenolates

Synthesis of γ-ketoesters - Yoshida

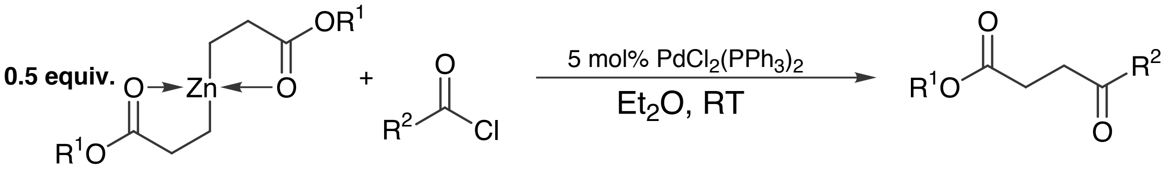


R	Yield
Ph	100
	90
	92
	100

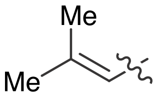
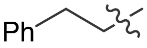
Yoshida, *Tetrahedron Lett.*, **1985**, *26*, 5559

Acylation of Zinc Homoenolates

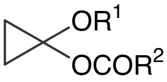
Synthesis of γ-ketoesters - Nakamura



- note: only 0.5 equiv. of Zn species needed so both homoenolates are transferred

R^1	R^2	Yield
Et	Ph	93
^{i}Pr		81
Et		83
^{i}Pr	^{t}Bu	50

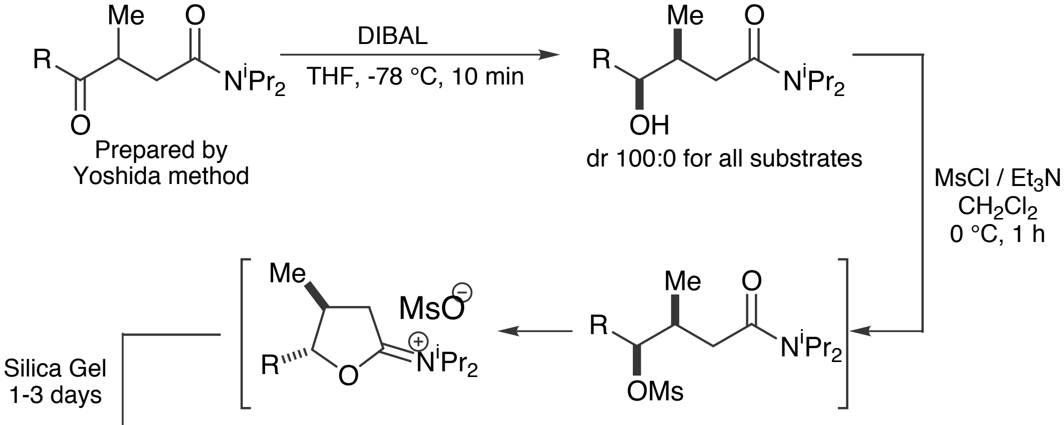
- when carried out in $CDCl_3$ got quantitative O-acylation (with or without Pd)

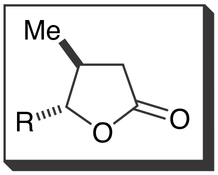
i.e. 

Nakamura, *J.Org.Chem.*, **1987**, *26*, 8056

Application of Homoenolate Acylation

Synthesis of α,β-disubstituted γ-butyrolactones by Diastereoselective Reduction



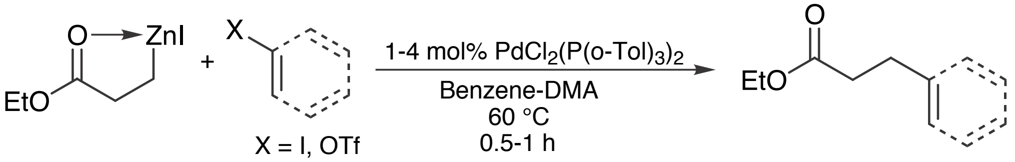


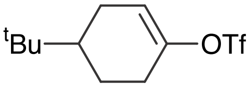
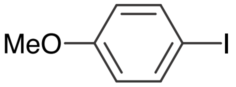
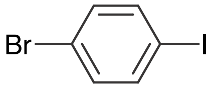
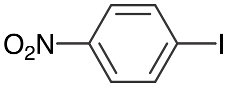
R	Yields	
	Reduction	Cyclization
Ph	87	82
p-ClPh	93	95
p-MeOPh	90	92
Bn	62	83

Asaoka, *Heterocycles*, **2000**, *52*, 227

Arylation and Vinylation of Zinc Homoenolates

Synthesis of β-vinyl and β-aryl esters - Yoshida



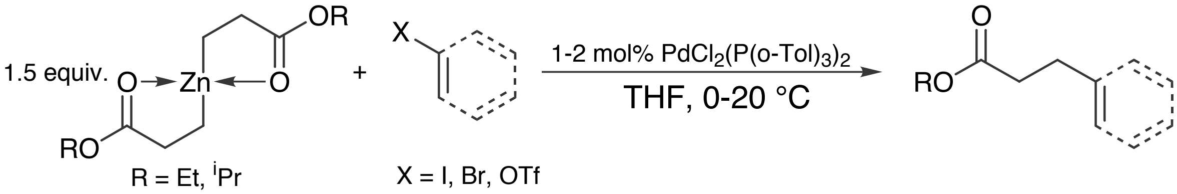
Coupling Partner	Yield
	74
	96
	67
	80

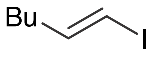
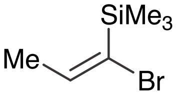
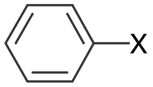
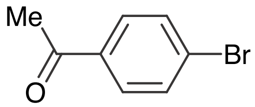
← Only vinylation example given

Yoshida, *Tetrahedron Lett.*, **1986**, *27*, 955

Arylation and Vinylation of Zinc Homoenolates

Synthesis of β-vinyl and β-aryl esters - Nakamura

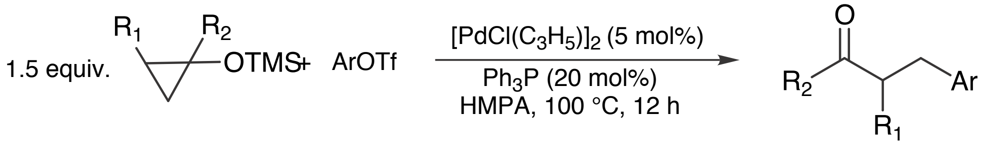


Coupling Partner	Yield
	90
	87
 X = OTf Br I	0 67 79
	49

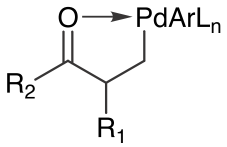
Nakamura, *J.Org.Chem.*, **1987**, *26*, 8056

Arylation of Palladium Homoenolates

Catalytic Formation of β–aryl Ketones



- proposed to proceed via

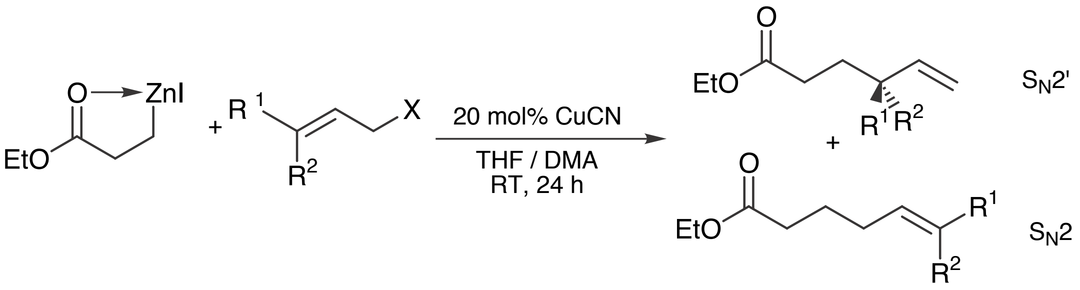


R_1	R_2	Ar	Yield
$-CH_2CH_2CH_2CH_2-$		1-napthyl	84
$-CH_2CH_2CH_2CH_2-$		p-NO_2Ph	68
H	p-OMePh	Phenyl	65
n-Heptyl	H	1-napthyl	58

Nakamura, *J.Am.Chem.Soc.*, **1988**, *110*, 3296

Allylation of Zinc Homoenolates

Synthesis of δ,ε-unsaturated Esters - Yoshida

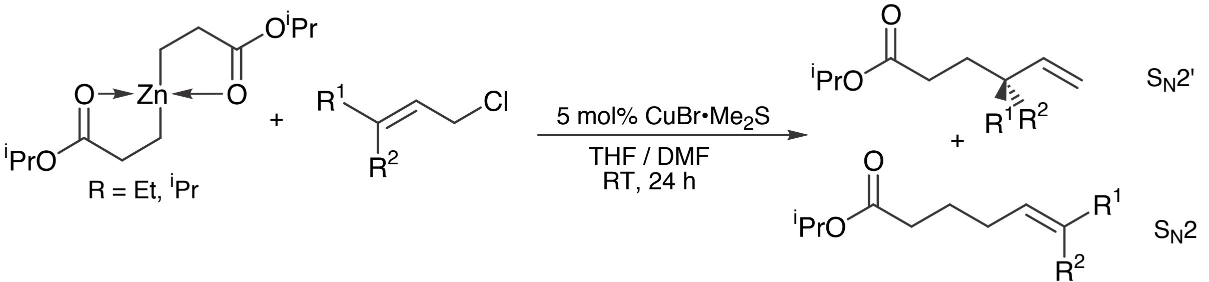


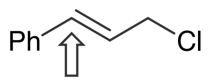
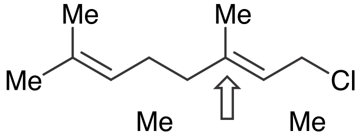
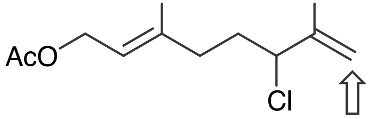
R^1	R^2	X	Yield	S_N2' : S_N2
H	H	OTs	89	--
Ph	H	OTs Br Cl	80 93 99	87 : 13 88 : 12 87 : 13
CO_2Me	H	Br	80	100 : 0

Yoshida, *J.Org.Chem.*, **1987**, *52*, 4418

Allylation of Zinc Homoenolates

Synthesis of δ,ε-unsaturated Esters - Nakamura



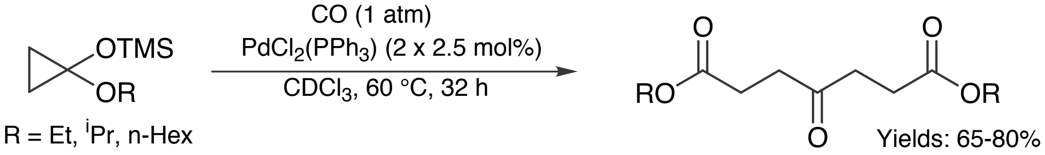
Allyl chloride	Yield	$S_N2' : S_N2$
	97 65	96 : 4 1 : 99
	81	88 : 12
	72	100 : 0

← Catalyst changed to 5 mol% $NiCl_2$•dppe

Nakamura, *J.Am.Chem.Soc.*, **1987**, *109*, 8056

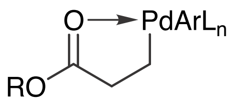
Carbonylative Symmetrical Coupling of Palladium Homoenolates

Catalytic Synthesis of 4-keto Pimelates

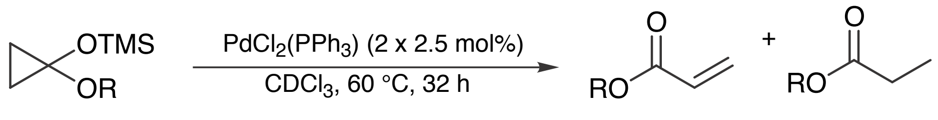


Yields: 65-80%

- proposed to proceed via



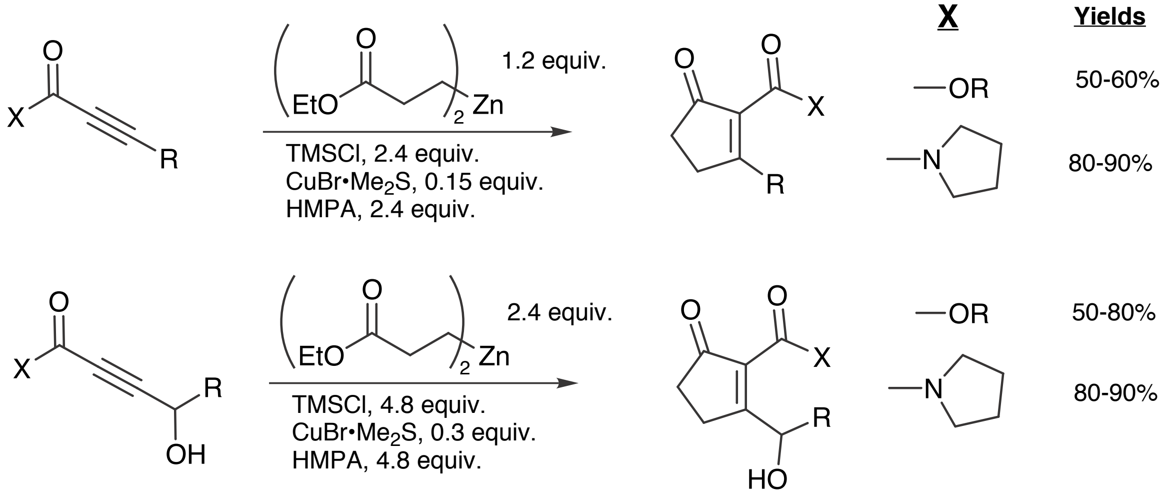
- evidence



Nakamura, *Tetrahedron Lett.*, **1988**, *29*, 1541

Crimmins' Cyclopentenone Synthesis

Introduction and Generality

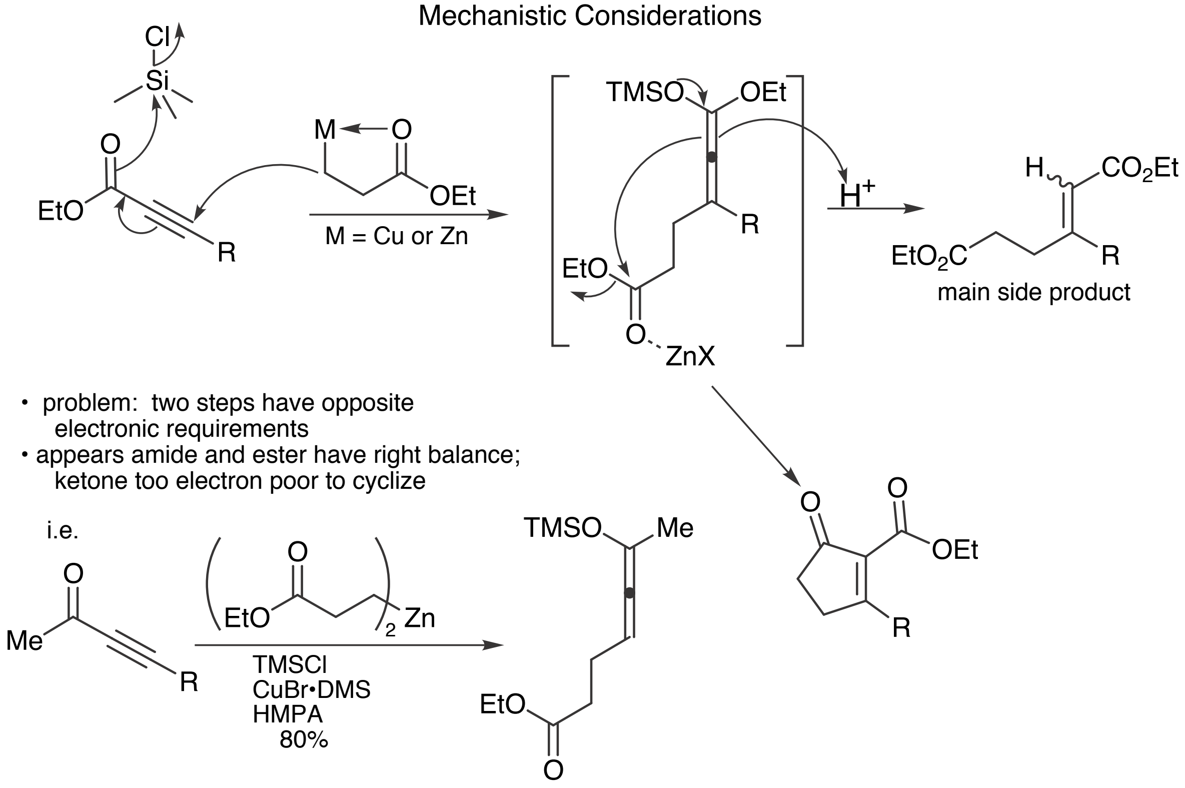


Functionality supported in R: ethers, epoxides, furans, α,β unsaturated esters

Crimmins, *J.Org.Chem.*, **1993**, *58*, 1038

Crimmins' Cyclopentenone Synthesis

Mechanistic Considerations



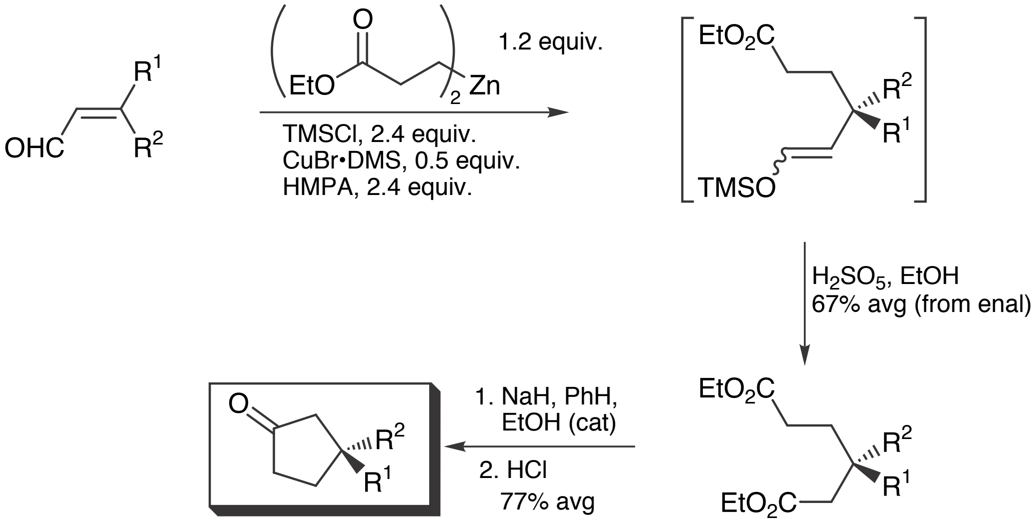
- problem: two steps have opposite electronic requirements
- appears amide and ester have right balance; ketone too electron poor to cyclize

i.e.

Crimmins, *J.Org.Chem.*, **1993**, *58*, 1038

Leahy Cyclopentannulation

Synthesis of 3,3-disubstituted cyclopentanones



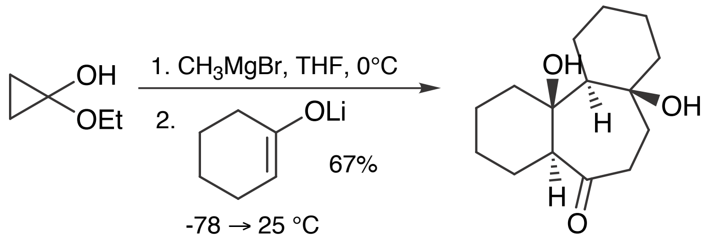
Substrates studied:

$R^1 = R^2 = n$-Bu
$R^1 = R^2 =$ Ph
$R^1 =$ Ph, $R^2 =$ Me
$R^1 =$ Ph, $R^2 =$ H

Leahy, *J.Org.Chem.*, **1994**, *59*, 5496

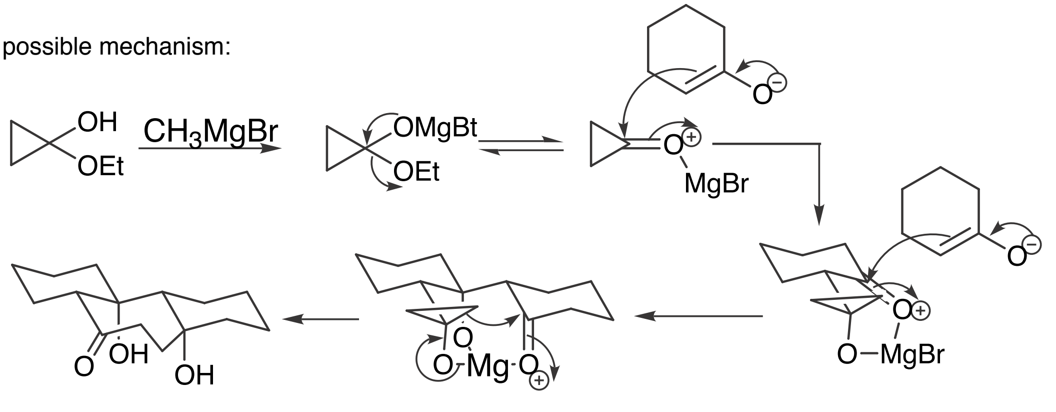
Tandem Aldol / Aldol / Homoaldol Reaction

One-pot synthesis of a 6,7,6-tricycle



Relative stereochemistry verified by x-ray crystallography

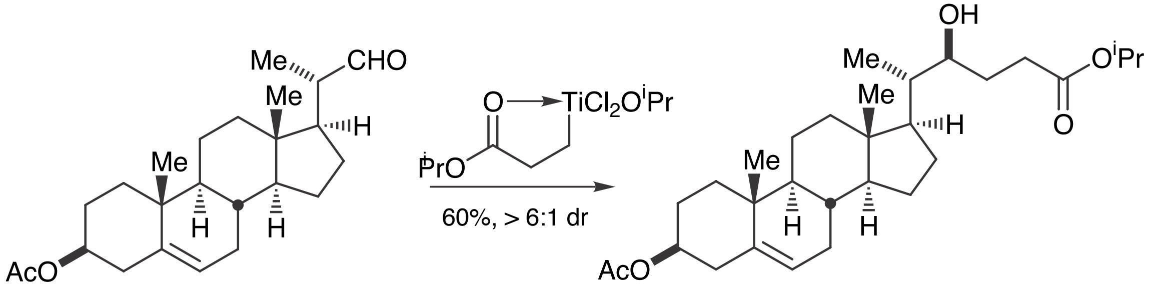
A possible mechanism:



Helquist, *J.Am.Chem.Soc.*, **1986**, *108*, 8313

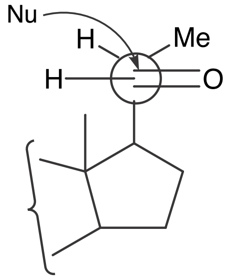
Synthetic Examples

Depresosterol



- trichlorotitanium homoenolate is not reactive enough to add to hindered aldehyde

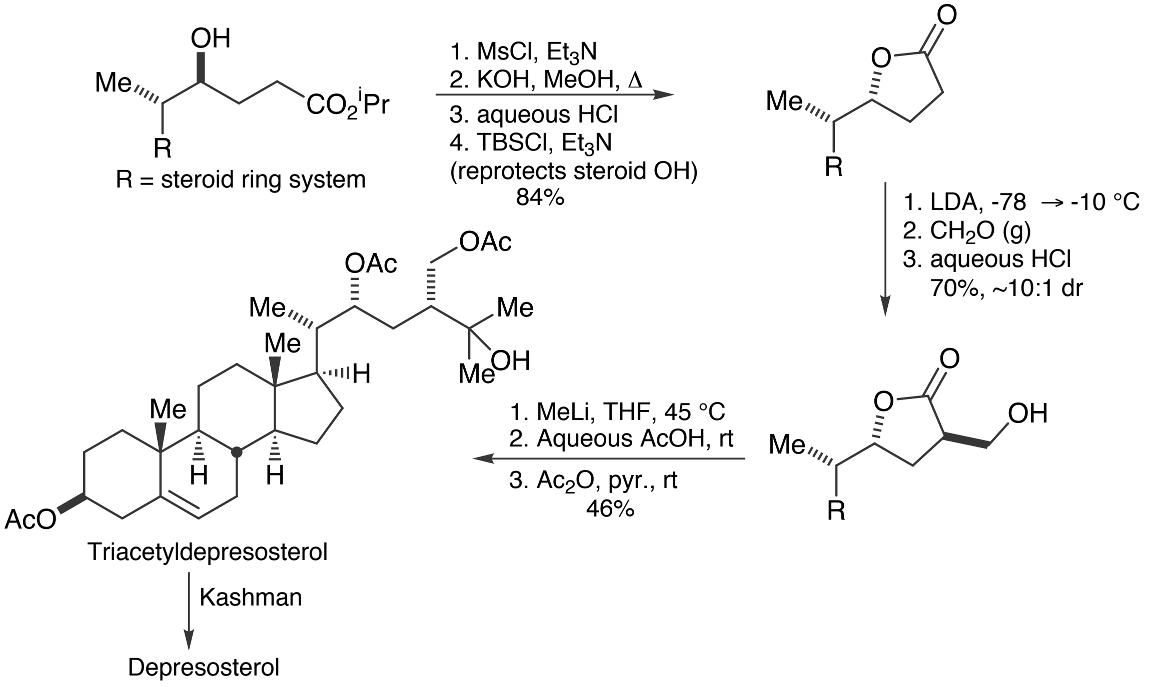
Via



Nakamura, *J.Am.Chem.Soc.*, **1985**, *107*, 2138

Synthetic Examples

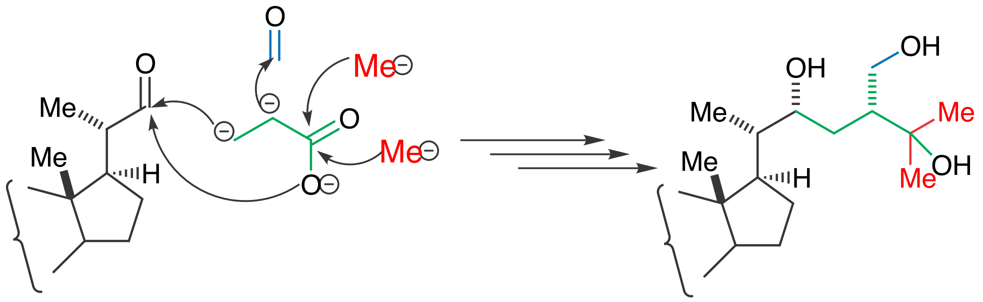
Depresosterol - completion of the formal synthesis



Nakamura, *J.Am.Chem.Soc.*, **1985**, *107*, 2138
Kashman, *Tetrahedron*, **1981**, *37*, 2397

Synthetic Examples

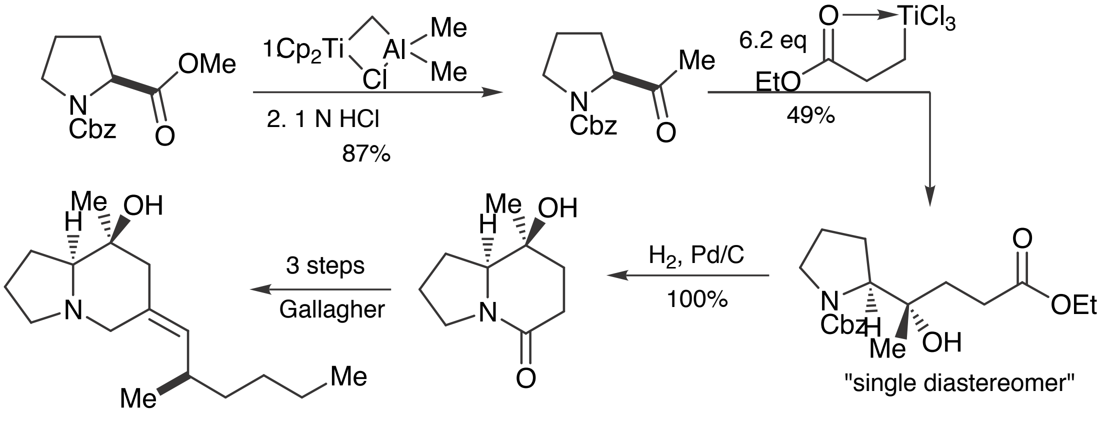
Depresosterol - Maximizing Homoenolate Functionality



Nakamura, *J.Am.Chem.Soc.*, **1985**, *107*, 2138

Synthetic Examples

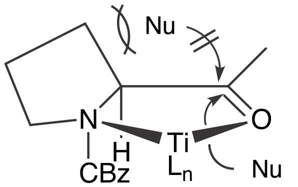
Pumiliotoxin 251D



"single diastereomer"

Pumiliotoxin 251D

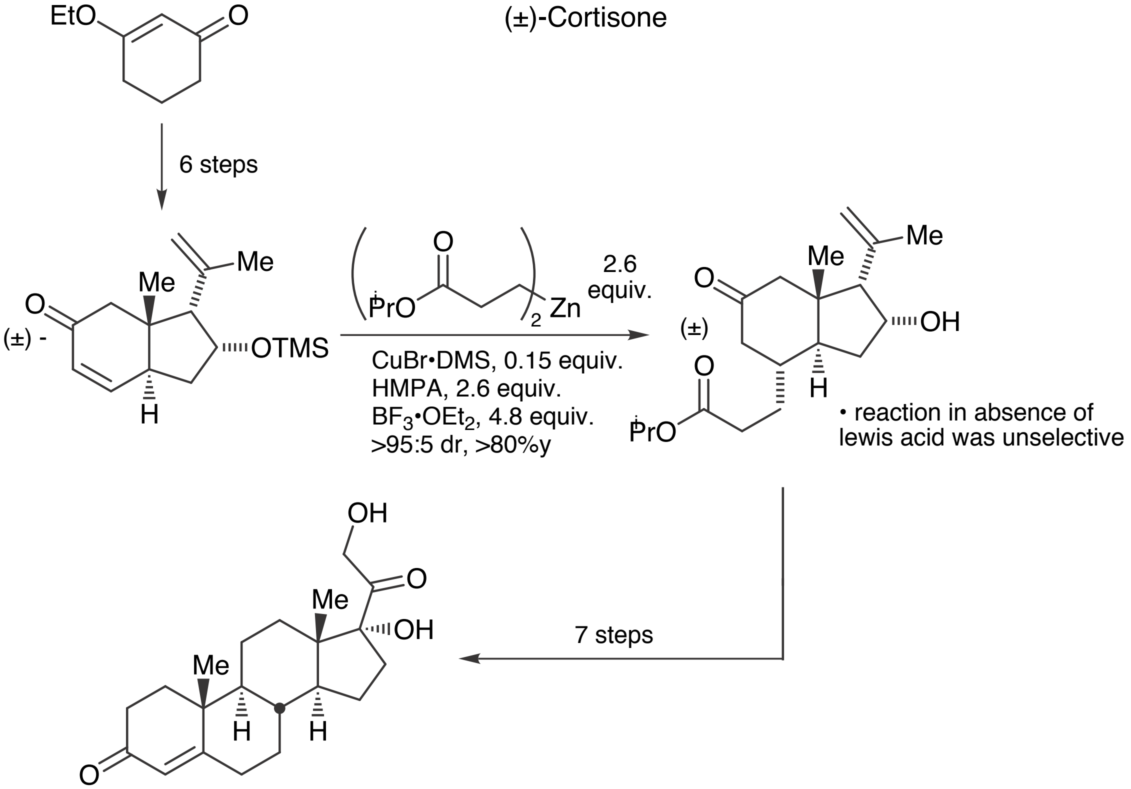
via:



Barrett, *J.Org.Chem.*, **1999**, *64*, 1410
Gallagher, *J.Am.Chem.Soc.*, **1991**, *113*, 2652

Synthetic Examples

(±)-Cortisone

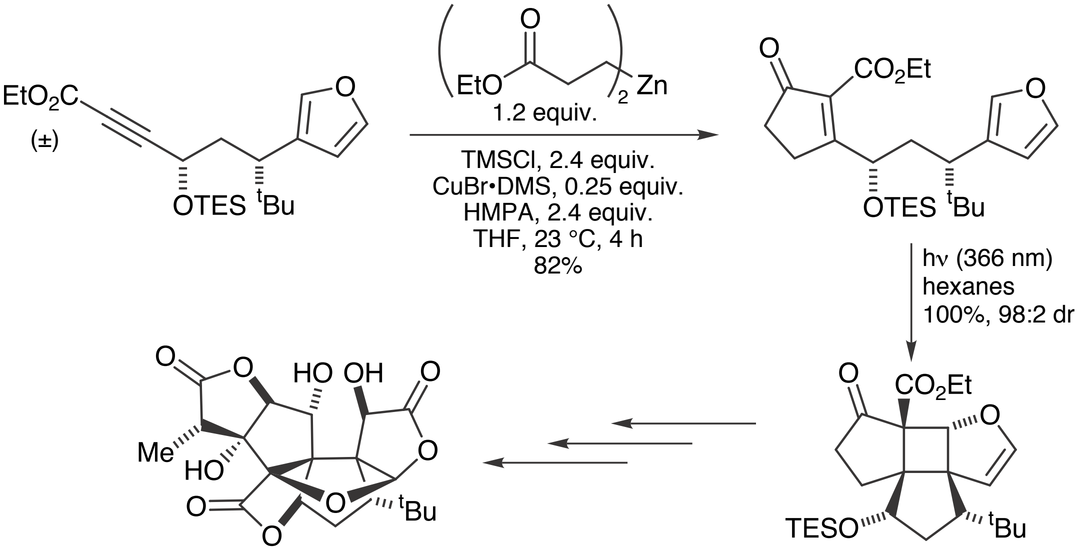


(±)-cortisone

Nakamura, *J.Org.Chem.*, **1986**, *51*, 4324

Synthetic Examples

(±)-Ginkgolide B



(±)-Ginkgolide B

Crimmins, *J.Am.Chem.Soc.*, **1999**, *121*, 10249

Carbocations: Stability & Structure

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 30

Introduction to Carbonium Ions

- Carbocation Stabilization
- Carbocation Structures by X-ray Crystallography
- Vinyl & Allyl Carbonium Ions

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Birladeanu, L. (**2000**). "The Story of the Wagner-Meerwein Rearrangement." *J. Chem. Ed.* **2000**, *77*, 858. **(handout)**

Olah, G. A. (**2001**). "100 Years of Carbocations and their Significance in Chemistry." *J. Org. Chem.* **2001**, *66*, 5944-5957. **(handout)**

Walling, C. (**1983**). "An Innocent Bystander Looks at the 2-Norbornyl Cation." *Acc. Chem. Res.* **1983**, *16*, 448. **(handout)**

Laube (**1995**). "X-Ray Crystal Structures of Carbocations Stabilized by Bridging or Hyperconjugation." *Acc. Chem. Res.***1995**, *28*,: 399 **(handout)**

D. A. Evans

Wednesday,
December 3, 2003

Other Relevant Background Reading

March, *Advanced Organic Chemistry*, 4th Ed. Chapter 5, pp165-174.

Lowery & Richardson, *Mech. & Theory in Org, Chem.*, 3rd Ed. pp 383-412.

Arnett, Hoeflich, Schriver in *Reactive Intermediates* **Vol 3**, Wiley, 1985, Chapter 5, p 189.

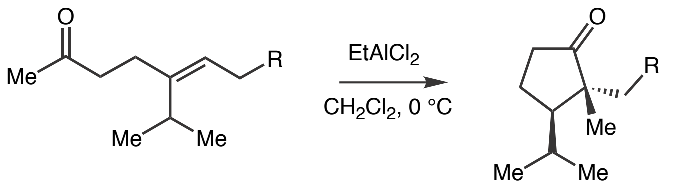
Saunders, M. and H. A. Jimenez-Vazquez (**1991**). "Recent studies of carbocations." Chem. Rev. 91: 375.

Stang, P. J. (**1978**). "Vinyl Triflate Chemistry: Unsaturated Cations and Carbenes." Acc. Chem. Res. 11: 107.

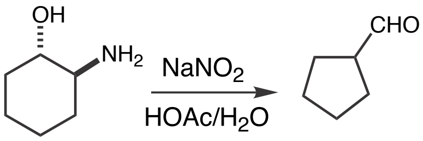
Olah, G. A. and G. Rasul (**1997**). "Chemistry in superacids .26. From Kekule's tetravalent methane to five-, six- and seven-coordinate protonated methanes." Acc. Chem. Res. 30(6): 245-250.

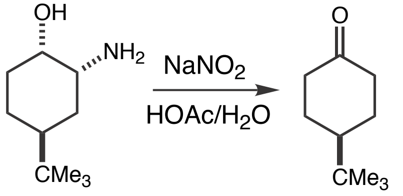
Olah, G. A. (**1995**). "My search for carbocations and their role in chemistry (Nobel lecture)." *Angew. Chem., Int. Ed. Engl.* **34**, 1393-1405

Qumulative Exam Question Fall, 2001. The reaction illustrated below was recently reported by Snider and co-workers (*Org. Lett.* **2001**, *123*, 569-572). Provide a mechanism for this transformation. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.



Carey & Sundberg-A, p 337: Provide mechanisms for the following reactions.

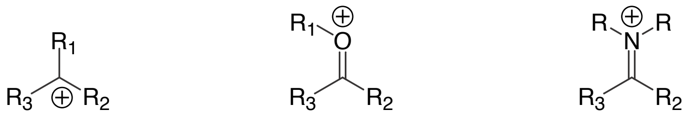




Carbocations: Stability

Carbocation Subclasses

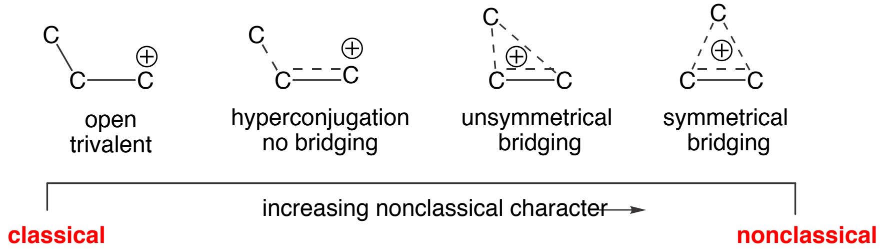
Carbon-substituted **Heteroatom–stabilized**



R–R_3 = alkyl or aryl   R–R_3 = alkyl or aryl   R–R_3 = alkyl or aryl

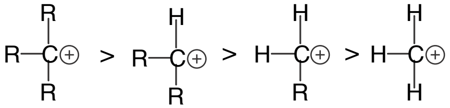
The following discussion will focus on carbocations unsubstitutred with heteroatoms

Classical vs nonclassical carbonium ions



Stability: Stabilization via alkyl substituents (hyperconjugation)

Order of carbocation stability: 3˚>2˚>1˚



Due to increasing number of substituents capable of hyperconjugation

The relative stabilities of various carbocations can be measured in the gas phase by their affinity for hydride ion.

$$R^{\oplus} + H^{\ominus} \longrightarrow R{-}H + HI$$

Hydride Affinity = –ΔG°

ΔHI increases → C(+) stability decreases

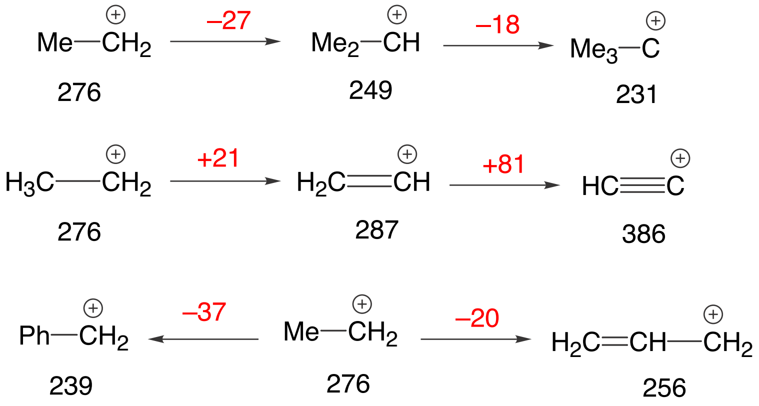
Note: As S-character increases, cation stability decreases due to more electronegative carbon.

J. Beauchamp, *J. Am. Chem. Soc.* **1984**, *106*, 3917.

	Hydride ion affinities
CH_3^+	314
$CH_3CH_2^+$	276
$(CH_3)_2CH^+$	249
$(CH_3)_3C^+$	231
$H_2C{=}CH^+$	287
$H{-}C{\equiv}C^+$	386
$PhCH_2^+$	239

Carey & Sundberg–**A**, pp 276-

Hydride ion affinities (HI)

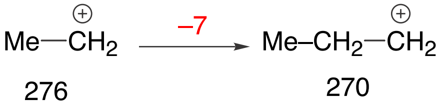


$$\underset{276}{Me{-}\overset{\oplus}{C}H_2} \xrightarrow{-27} \underset{249}{Me_2{-}\overset{\oplus}{C}H} \xrightarrow{-18} \underset{231}{Me_3{-}\overset{\oplus}{C}}$$

$$\underset{276}{H_3C{-}\overset{\oplus}{C}H_2} \xrightarrow{+21} \underset{287}{H_2C{=}\overset{\oplus}{C}H} \xrightarrow{+81} \underset{386}{HC{\equiv}\overset{\oplus}{C}}$$

$$\underset{239}{Ph{-}\overset{\oplus}{C}H_2} \xleftarrow{-37} \underset{276}{Me{-}\overset{\oplus}{C}H_2} \xrightarrow{-20} \underset{256}{H_2C{=}CH{-}\overset{\oplus}{C}H_2}$$

The effect of beta substituents: Rationalize



$$\underset{276}{Me{-}\overset{\oplus}{C}H_2} \xrightarrow{-7} \underset{270}{Me{-}CH_2{-}\overset{\oplus}{C}H_2}$$

Hydride ion affinities versus Rates of Solvolysis

	$PhCH_2$–Br	CH=CH–CH_2–Br	Me_2CH–Br
rel rate	100	52	0.7
HI	239	256	249
Δ-HI	0	+17	+10

Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

Conclusion:
Gas phase stabilities do not always correlate with rates of solvolysis

Carbocation Stability: The pK_{R+} value

Definition: $R^+ + H_2O \rightleftharpoons ROH + H^+$

$$K_{R+} = \frac{a_{ROH} \cdot a_{H+}}{a_{R+} \cdot a_{H2O}}$$

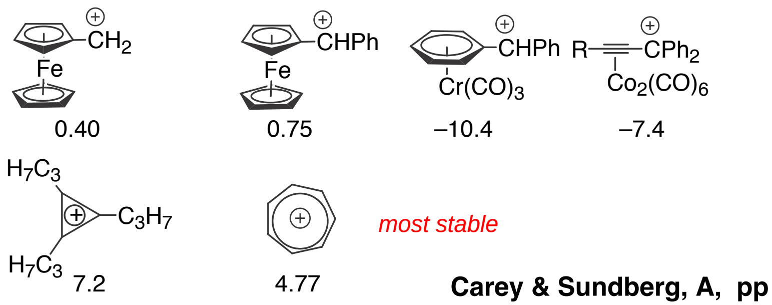
a = activity

$$\boxed{pK_{R+} = -\log K_{R+}}$$

Carey & Sundberg, A, p 277

***Table*: pK_{R+} values of some selected carbenium salts**

$(4\text{-MeO-}C_6H_4)_3C^{\oplus}$	$Ph_3C^{\oplus}$	$(3\text{-Cl-}C_6H_4)_3C^{\oplus}$	$Ph_2\overset{\oplus}{C}H$	*least stable*
0.82	– 6.63	– 11.0	– 13.3	



0.40 0.75 –10.4 –7.4

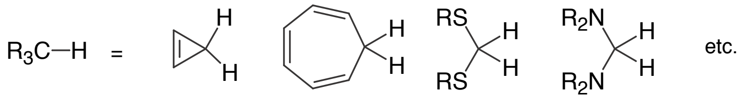
7.2 4.77 *most stable*

Carey & Sundberg, A, pp 276-

Carbocation Generation

Hydride abstraction from neutral precursors

$$\boxed{R_3C{-}H \quad + \quad \text{Lewis-Acid} \longrightarrow R_3C^{\oplus}}$$



Lewis-Acid: $Ph_3\overset{\oplus}{C}\ \overset{\ominus}{B}F_4$, BF_3, PCl_5

Removal of an energy-poor anion from a neutral precursor via Lewis Acids

$$\boxed{R_3C{-}X \quad + \quad \textbf{LA} \longrightarrow R_3C^{\oplus} \quad + \quad LA{-}X^{\ominus}}$$

LA: Ag , $AlCl_3$, $SnCl_4$, $SbCl_5$, $\mathbf{SbF_5}$, BF_3, $FeCl_3$, $ZnCl_2$, PCl_3, PCl_5, $POCl_3$
...

X: F, Cl, Br, I, OR

Acidic dehydratization of *secondary* and *tertiary* alcohols

$$\boxed{R_3C{-}OH \quad + \quad H{-}X \xrightarrow{-\,H_2O} R_3C^{\oplus} \quad + \quad X^{\ominus}}$$

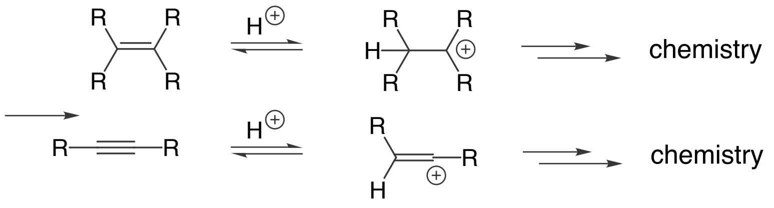
R: Aryl + other charge stabilizing substituents
X: SO_4^{2-}, ClO_4^-, FSO_3^-, $CF_3SO_3^-$

From neutral precursors via heterolytic dissociation (solvolysis) - First step in S_N1 or E1 reactions

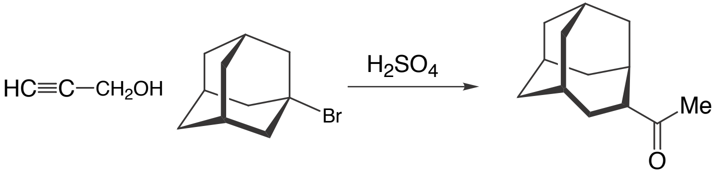
$$R_3C{-}X \xrightarrow{\text{solvent}} R_3C^{\oplus} \quad + \quad X^{\ominus}$$

Ability of X to function as a leaving group:
$-N_2^+ > -OSO_2R' > -OPO(OR')_2 > -I \geq -Br > Cl > OH_2^+$ ...

Addition of electrophiles to π-systems

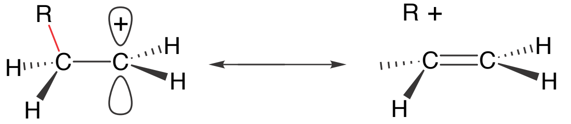


Provide a Mechanism of this transformation



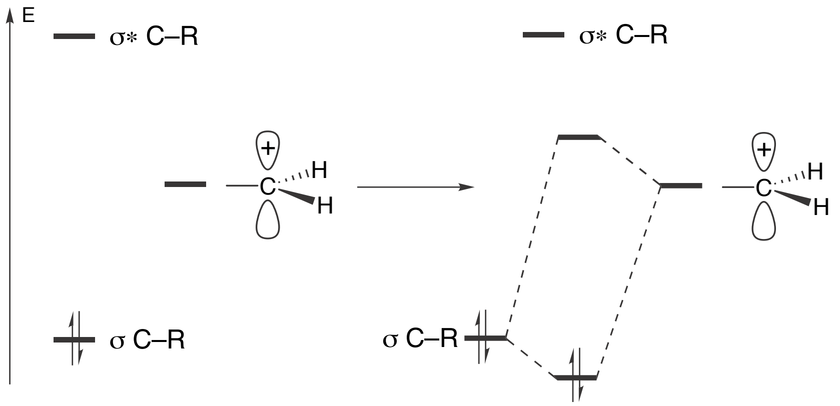
J.C.S.,CC **1971**, 556

Carbocation Stabilization Through Hyperconjugation



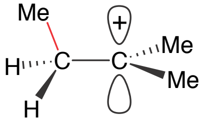
■ **FMO Description**

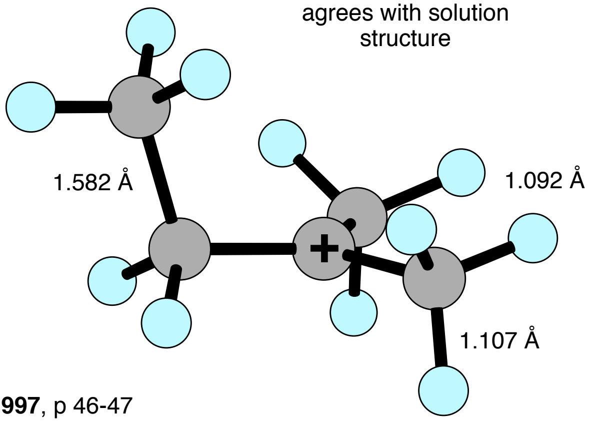
Take linear combination of σ C–R (filled) and C p_z-orbital (empty):



Syn-planar orientation between interacting orbitals

C–H versus C–C Hyperconjugation: The t-Pentyl Cation





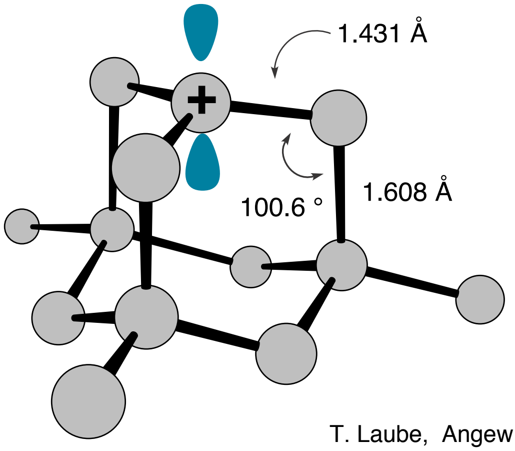
Calculated carbocation agrees with solution structure

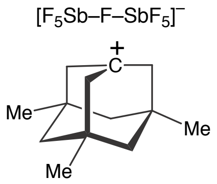
R. P von Schleyer in
Stable Carbocation Chemistry, **1997**, p 46-47

Physical Evidence for Hyperconjugation: The Adamantyl Cation

Bonds participating in the hyperconjugative interaction, e.g C–R, will be lengthened while the C(+)–C bond will be shortened.

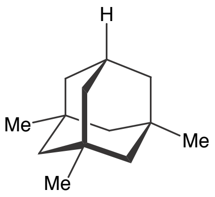
First X-ray Structure of an Aliphatic Carbocation

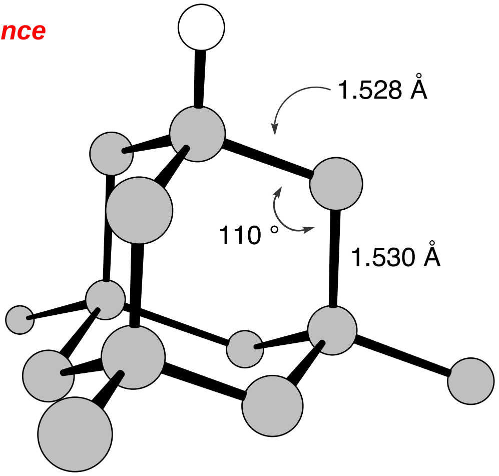




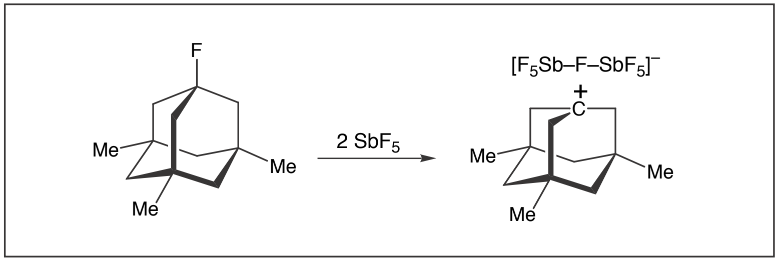
T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

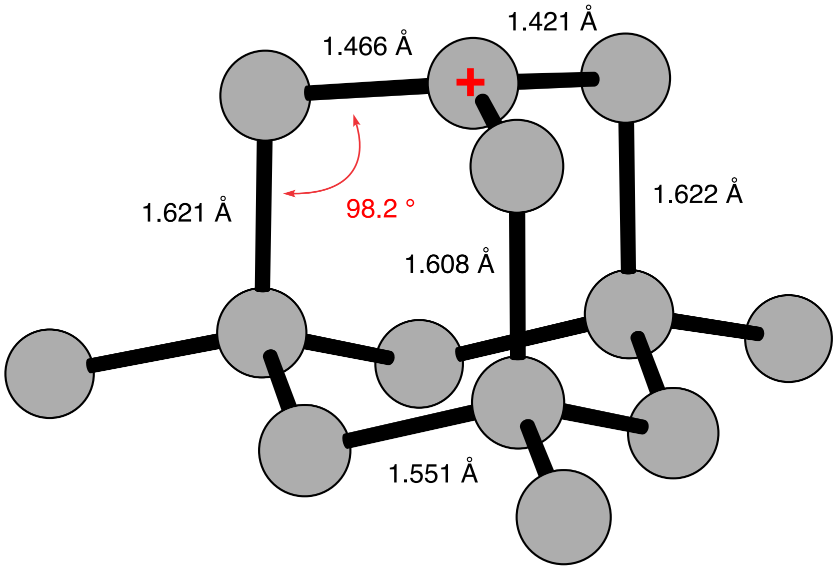
The Adamantane Reference (MM-2)





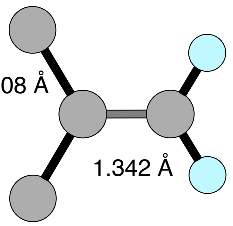
Carbocations: Structure

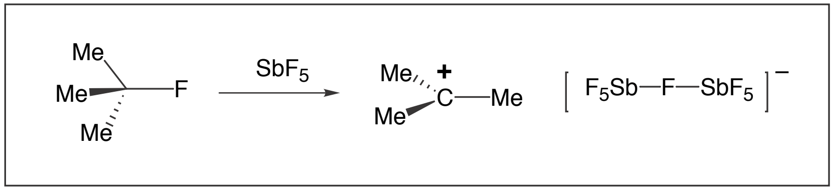


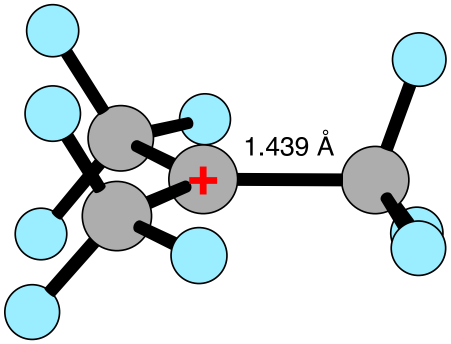


T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

reference structure:
CSP3–Csp2 bond length

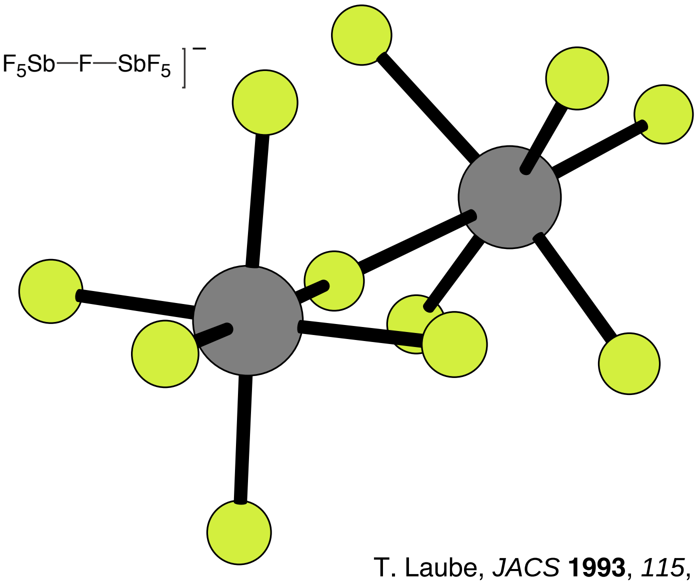






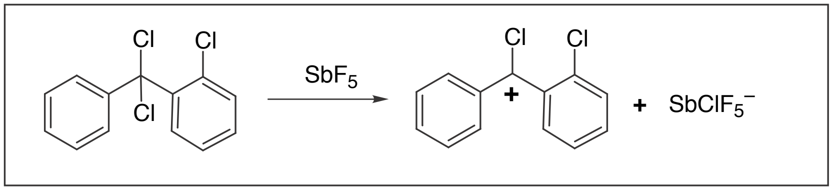
C–C$_1$: 1.439 Å
C–C$_2$: 1.446 Å
C–C$_3$: 1.442 Å

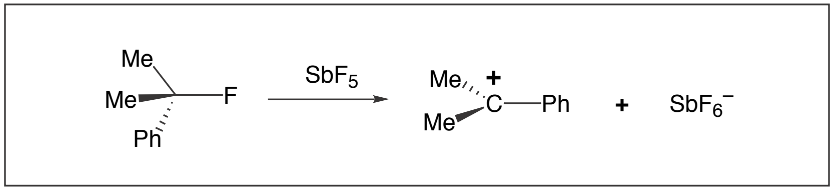
[F$_5$Sb—F—SbF$_5$]$^-$

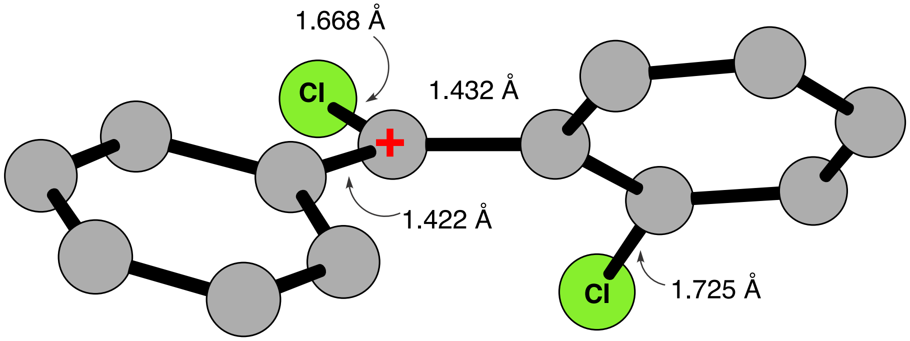


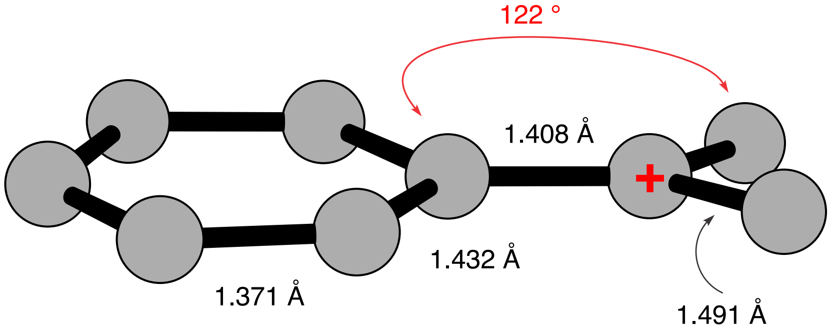
T. Laube, *JACS* **1993**, *115*, 7240

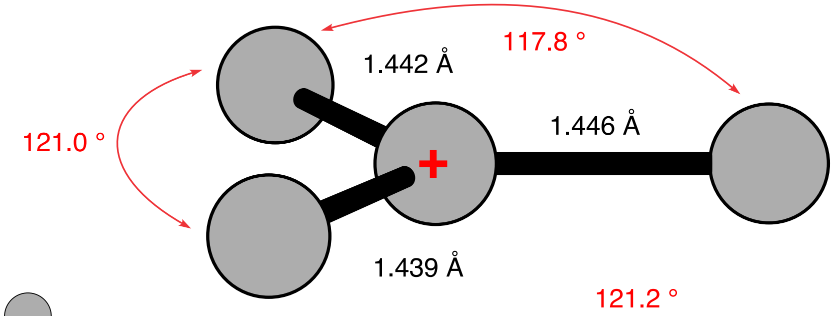
Carbocations: Structure

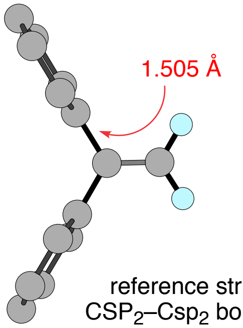




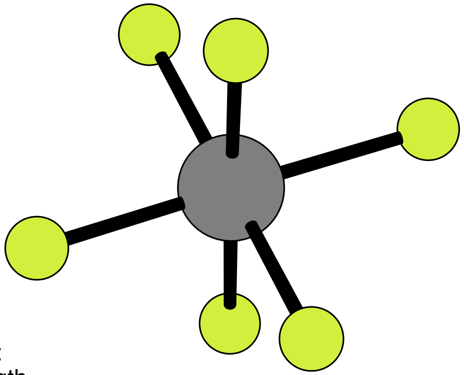


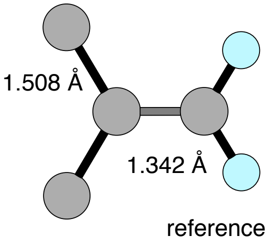






reference structure:
CSP_2–Csp_2 bond length

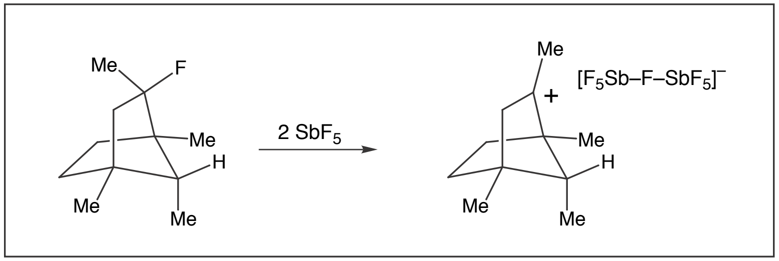




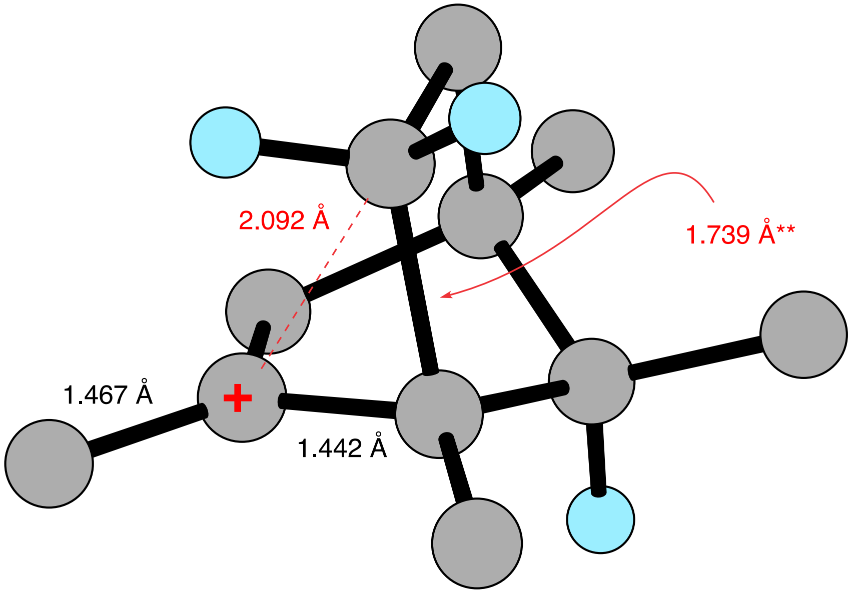
reference structure:
CSP_3–Csp_2 bond length

T. Laube, *JACS* **1993**, *115*, 7240

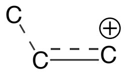
Carbonium Ion X-ray Structures: Bridged Carbocations



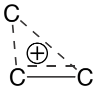
T. Laube, Angew. *Chem. Int. Ed.* **1987**, *26*, 560



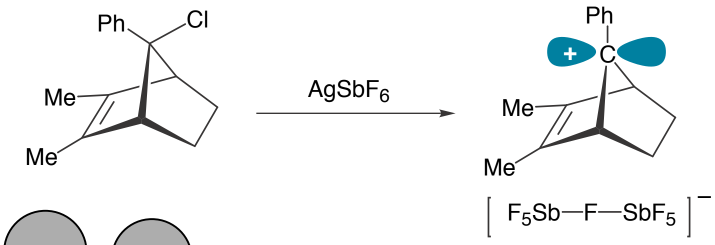
**One of the longest documented C–C bond lengths.

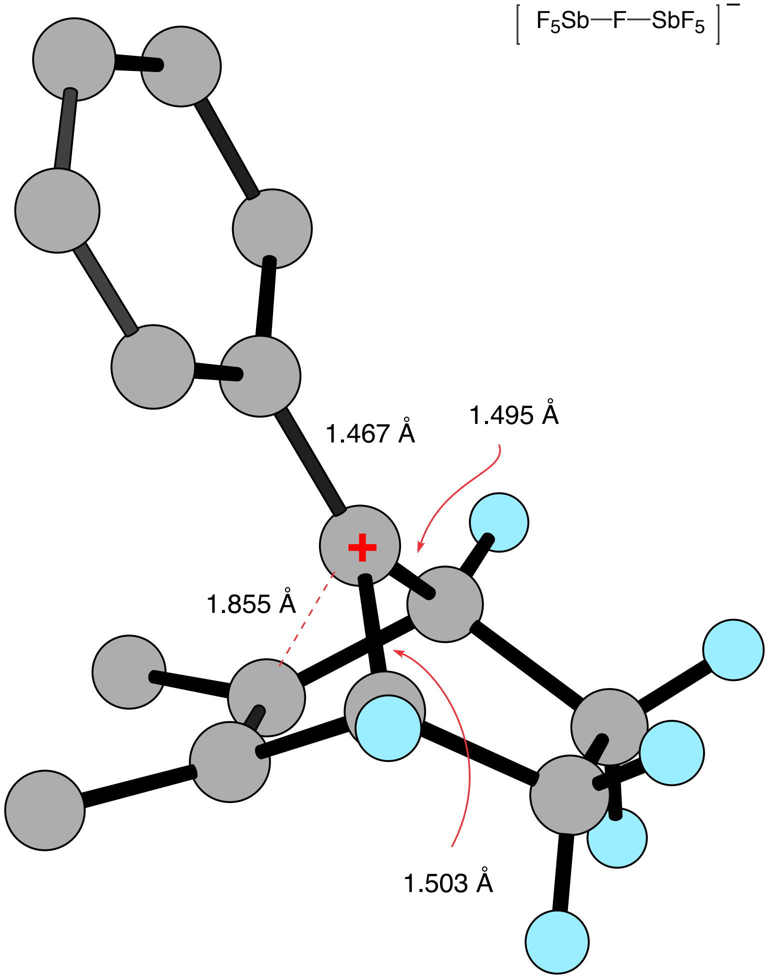


hyperconjugation
no bridging



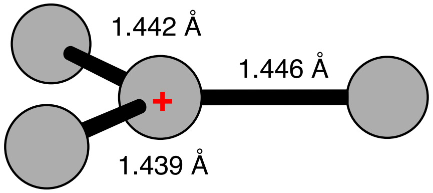
unsymmetrical
bridging



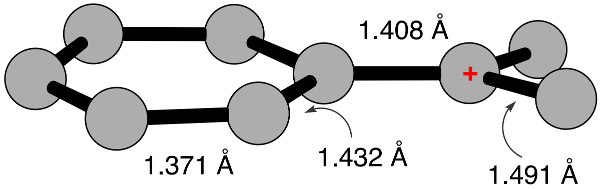


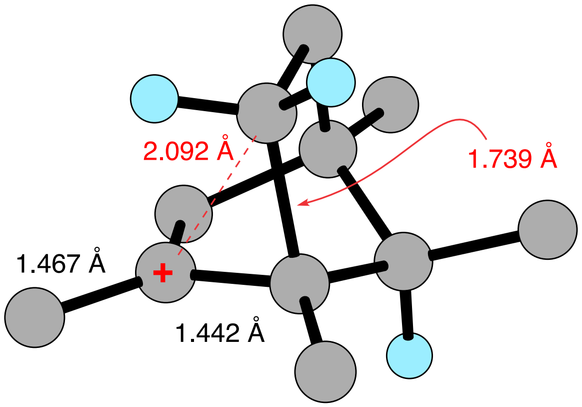
T. Laube, *JACS* **1989**, *111*, 9224

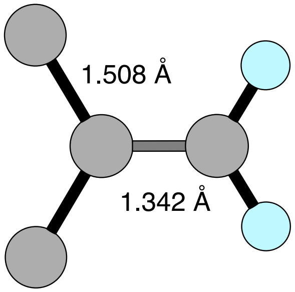
Carbonium Ion X-ray Structures: A Summary

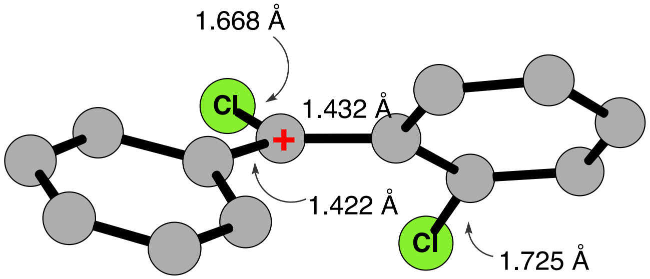


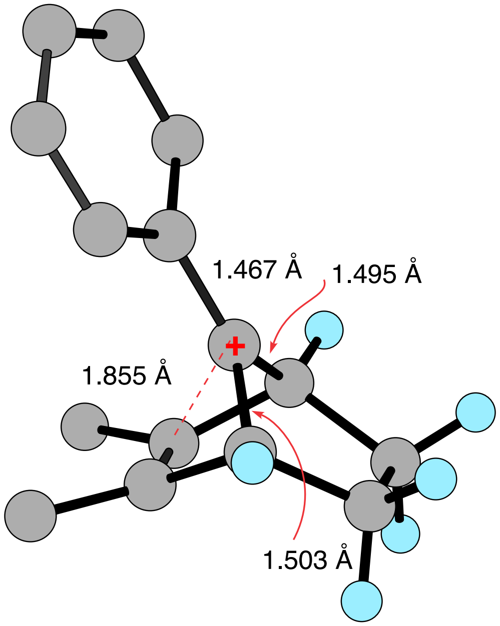
(ref 1.513 Å)Ph–C(Me)=CH2

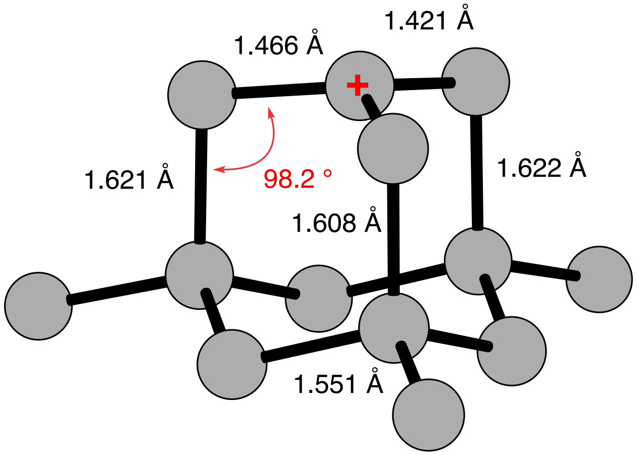




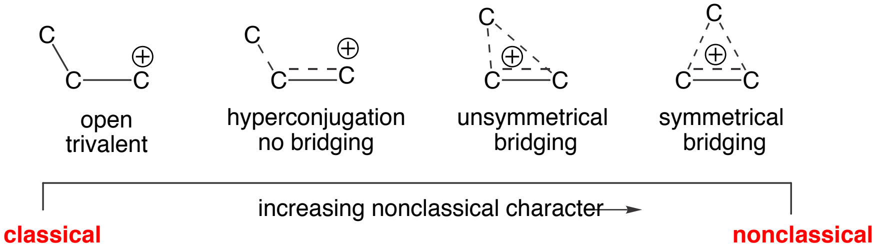








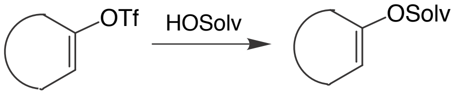
Nomenclature: classical vs nonclassical



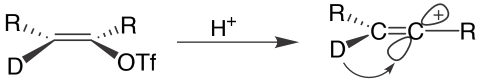
Vinyl & Allyl Carbocations

Vinyl & Phenyl Cations: Highly Unstable

Evidence suggests that vinyl cations are linear.



As ring size decreases, the rate of hydrolysis also diminishes. Implying that the formation of the linear vinyl cation is disfavored due to increasing ring strain.



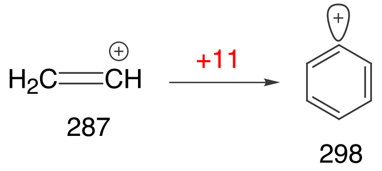
Hyperconjugation

A secondary kinetic isotope effect was measured to be K_H/K_D = 1.5 (quite large) indicating strong hyperconjugation and an orientation of the vacant p orbital as shown above.

P. J. Stang *J. Am. Chem Soc.* **1971**, *93*, 1513; P. J. Stang *J.C.S. PT II* **1977,** 1486.

Hydride ion affinities (HI)

$$\underset{276}{H_3C{-}\overset{\oplus}{C}H_2} \xrightarrow{+21} \underset{287}{H_2C{=}\overset{\oplus}{C}H} \xrightarrow{+81} \underset{386}{HC{\equiv}\overset{\oplus}{C}}$$

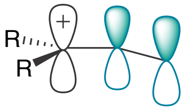


Phenyl Cations

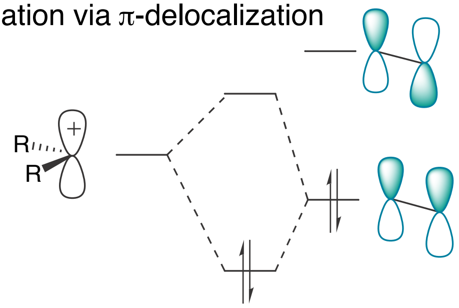
The ring geometry opposes rehybridization (top) so the vacant orbital retains sp^2 character. Additionally, the empty orbital lies in the nodal plane of the ring, effectively prohibiting conjugative stabilization.

Allyl & Benzyl Carbocations

Carbocation Stabilization via π-delocalization



allyl cation



■ Stabilization by Phenyl-groups

The Benzyl cation is as stable as a t-Butylcation. This is shown in the subsequent isodesmic equations:

	ΔH^0_r [kcal/mol]
$(CH_3)_3\overset{\oplus}{C} + PhCH_3 \rightleftharpoons (CH_3)_3CH + Ph\overset{\oplus}{C}H_2$	3.8
$(CH_3)_3\overset{\oplus}{C} + PhCH_2Cl \rightleftharpoons (CH_3)_3CCl + Ph\overset{\oplus}{C}H_2$	- 0.8

Hydride ion affinities (HI)

$$\underset{239}{Ph{-}\overset{\oplus}{C}H_2} \xrightarrow{-8} \underset{231}{Me_3{-}\overset{\oplus}{C}}$$

Hydride ion affinities versus Rates of Solvolysis

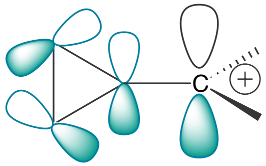
	$PhCH_2$–Br	**Me_2CH**–Br	**CH=CH–CH_2**–Br
	100	0.7	52
HI	239	249	256
Δ-HI	0	+10	+17

Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

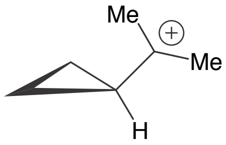
Cyclopropyl-carbinyl & Bridgehead Carbocations

Carbocation Stabilization via Cyclopropylgroups



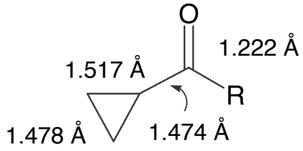
See Lecture 5, slide 5-05 for discussion of Walsh orbitals

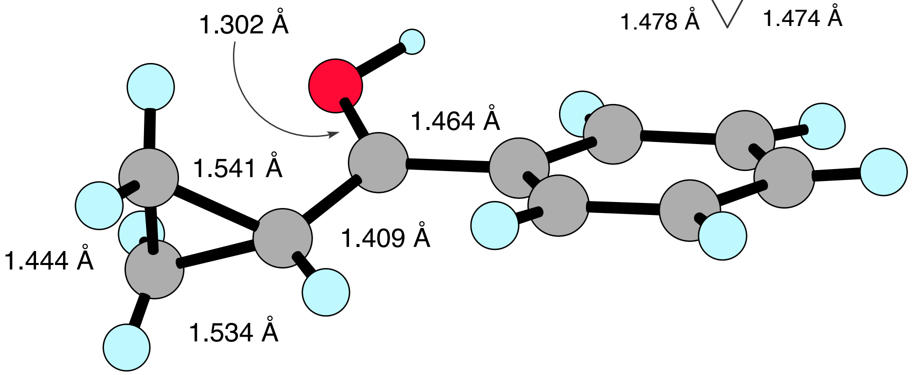
A rotational barrier of about 13.7 kcal/mol is observed in following example:

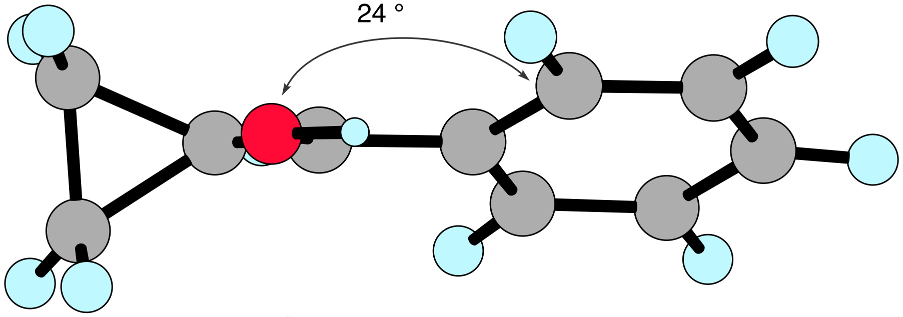


NMR in super acids
δ(CH_3) = 2.6 and 3.2 ppm

X-ray Structures support this orientation

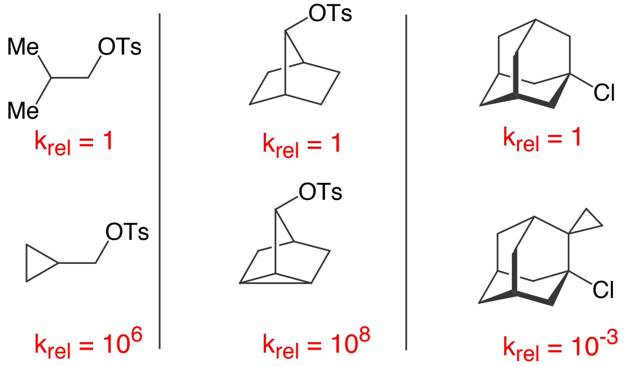






R. F. Childs, *JACS* **1986**, *108*, 1692

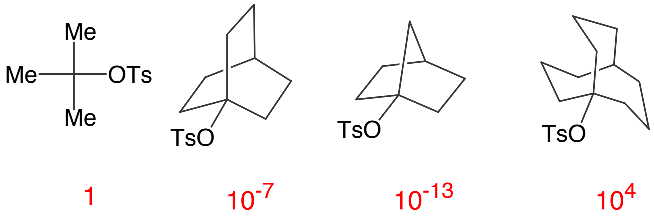
Solvolysis rates represent the extend of that cyclopropyl orbital overlap contributing to the stabiliziation of the carbenium ion which is involved as a reactive intermediate:



Why??

Carey–A, p 286

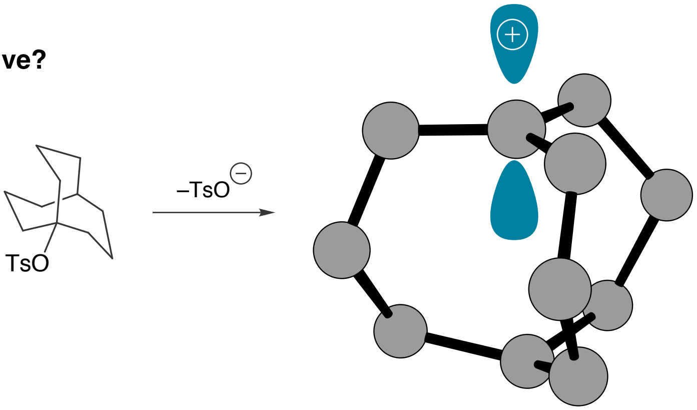
Bridgehead Carbocations



why so reactive?

Bridgehead carbocations are highly disfavored due to a strain increase in achieving planarity. Systems with the greatest strain increase upon passing from ground state to transition state react slowest.

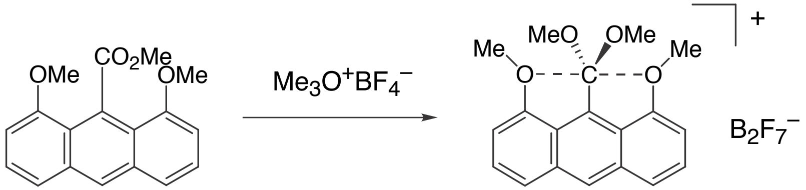
why so reactive?



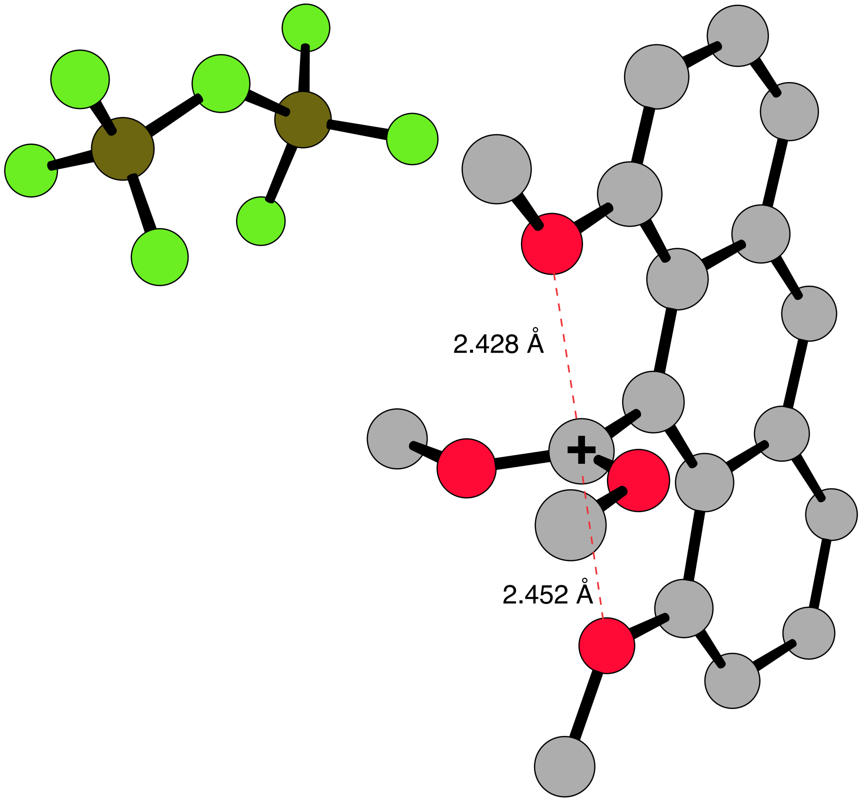
A Stable Hypervalent Carbon Compound ?

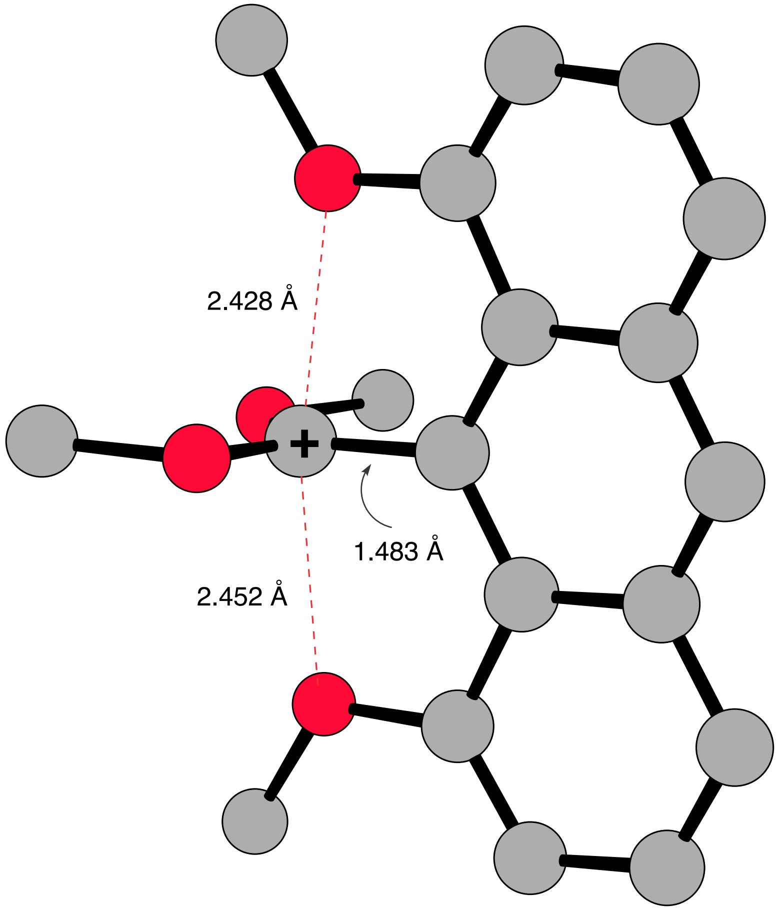
"The Synthesis and Isolation of Stable Hypervalent Carbon Compound (10-C-5) Bearing a 1,8-Dimethoxyanthrecene Ligand"

Akibe, et al. *JACS* **1999**, *121*, 10644-10645



"The relevant C–O distances are longer than a covalent C–O bond (1.43 Å) but shorter than the sum of the van der Waals radii (3.25 Å)."



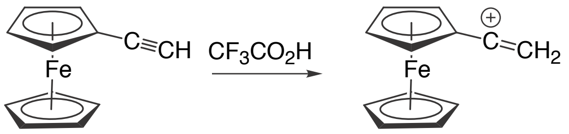


For a recent monograph on hypervalent Compounds see:
"Chemistry of Hypervalent Compounds", K. Akiba, Wiley-VGH, 1999

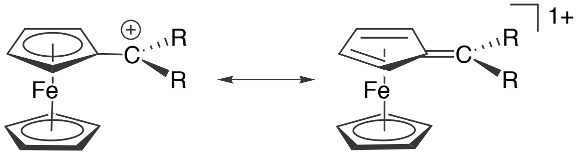
Transition Metal-Stablized Carbocations-1

Carbocation Stabilization - d(π) stabilization via Transition metal Fragments

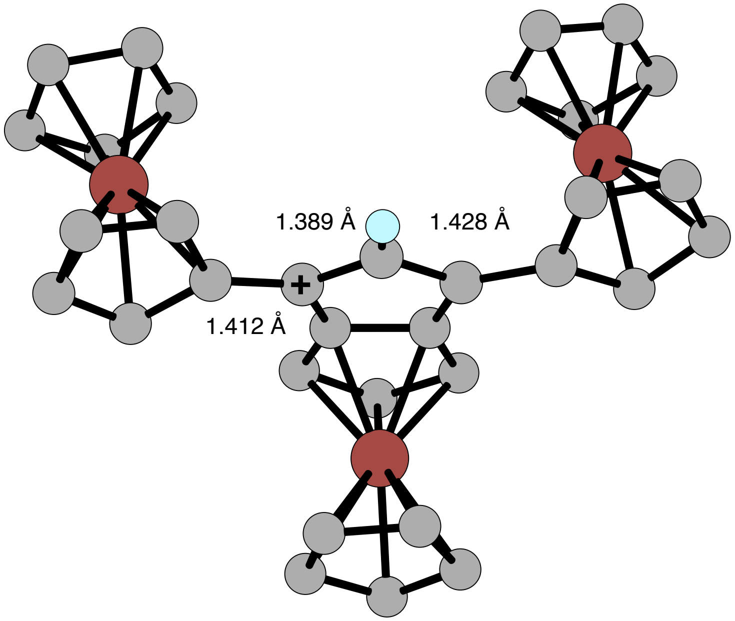
- Transition metal not bound directly to carbenium ion: **Ferrocenes**



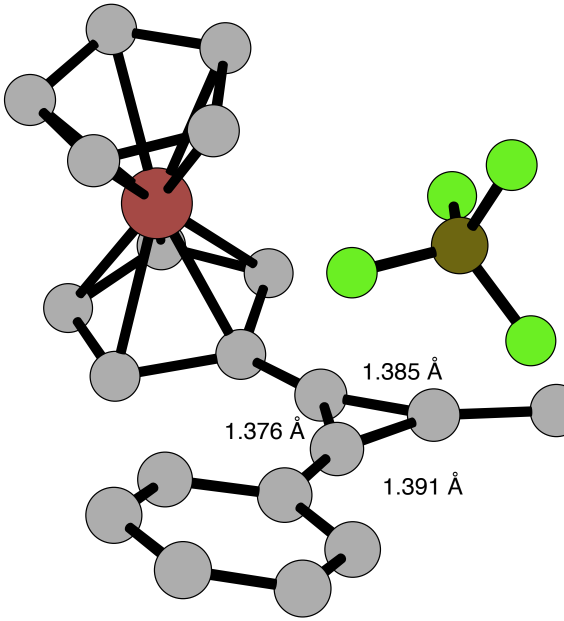
stable in CF_3COOH

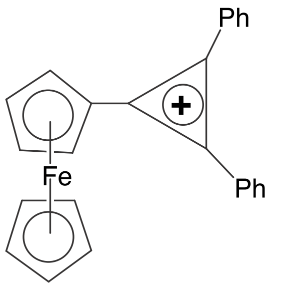


an important resonance contribution

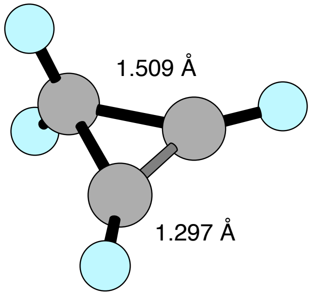


J. Lukasser, etal. *Organometallics* **1995**, *14*, 5566-5578



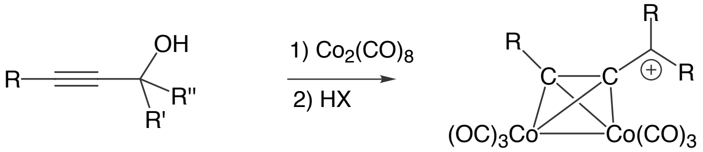


R. L. Sime, etal. *JACS* **1974**, *96*, 892



Cyclopropene
MM 2

- Transition metal not bound directly to carbenium ion: **Colbalt-Acetylenes**



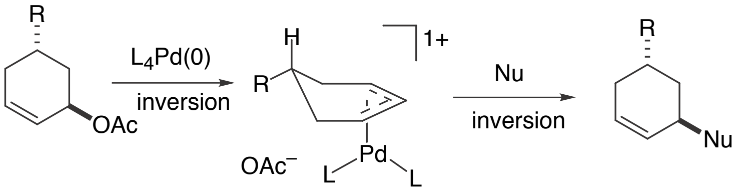
isolable,
basis of the Nicholas reaction

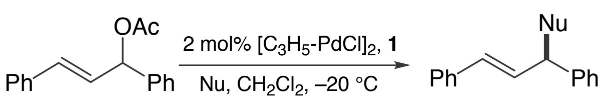
See Houk etal. *JACS* **1999**, *121*, 3596-3606

Transition Metal-Stablized Carbocations-Pd Catalysis

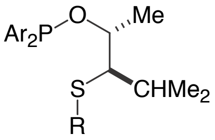
Carbocation Stabilization - d(π) stabilization via Transition metal Fragments

Transition metals bound to carbenium ions: π–Allyl Pd(II) Complexes

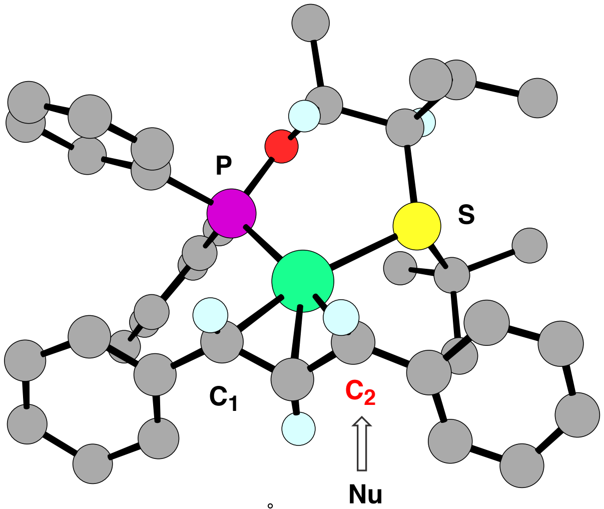




Nu = $CH(CO_2Me)_2$ 98% ee
Nu = BnNH 95% ee

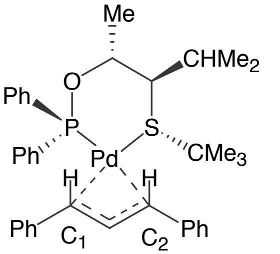


1a Ar = Ph



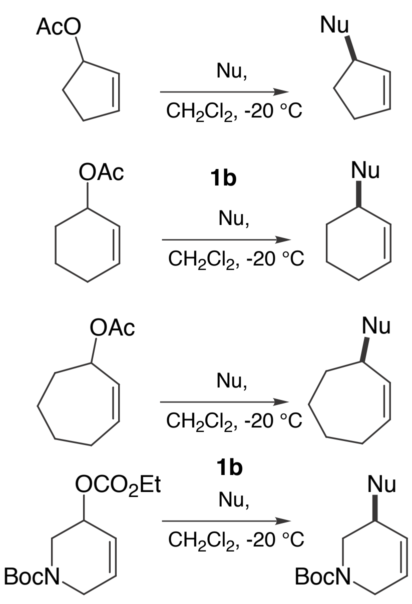
Pd-C_1, 2.16Å

Pd-C_2, 2.28Å

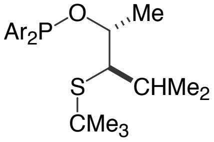


Selected Bond Lengths:
Pd-C_1, 2.16Å; Pd-C_2, 2.28Å
Pd-P, 2.29 Å; Pd-S, 2.38 Å

Evans, Campos,Tedrow, Michael, Gagné,
JACS **2000**, *122*, 7905

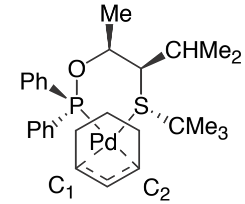


Nu = $CH(CO_2Me)_2$	Nu = BnNH
94% ee	91% ee
94% ee	91% ee
96% ee	97% ee
94% ee	94% ee

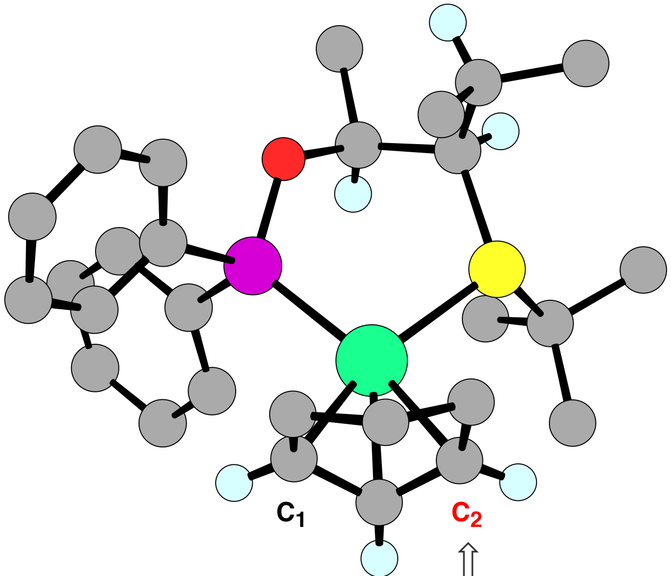


1b, Ar = α-naphthyl

conditions: 2 mol% $[C_3H_5\text{-}PdCl]_2$, **2b**



Selected Bond Lengths:
Pd-C_1, 2.17Å; Pd-C_2, 2.26Å
Pd-P, 2.25 Å; Pd-S, 2.36 Å



Pd-C_1, 2.17Å

Pd-C_2, 2.26Å

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 32

Introduction to Carbonium Ions–2

- Allyl- & Vinylsilanes: The β-Silicon Effect
- Carbonium Ion Rearrangements

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Walling, C. (**1983**). “An Innocent Bystander Looks at the 2-Norbornyl Cation.” *Acc. Chem. Res. 16*: 448. **(handout)**

Birladeanu (**2000**). “The Story of the Wagner-Meerwein Rearrangement.” *J. Chem. Ed. 77*: 858. **(handout)**

Lambert, (**1999**). “The β effect of silicon and related manifestations of σ conjugation.” *Acc. Chem. Res. 32*, 183-190. **(handout)**

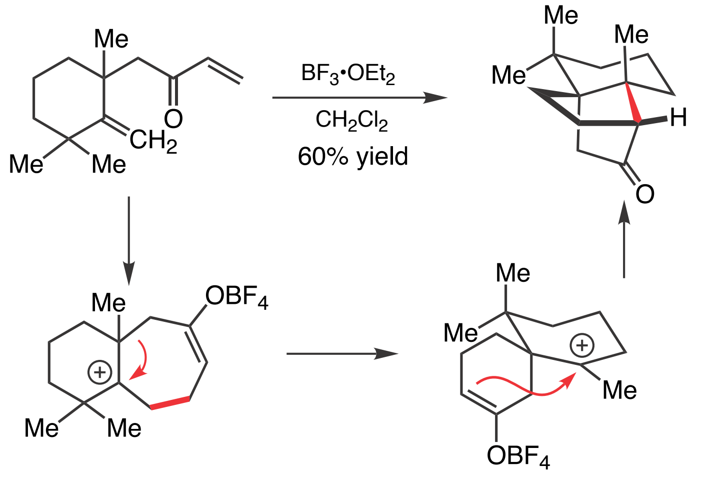
Other Relevant Background Reading

Saunders, M. and H. A. Jimenez-Vazquez (**1991**). “Recent studies of carbocations.” Chem. Rev. 91: 375.

D. A. Evans

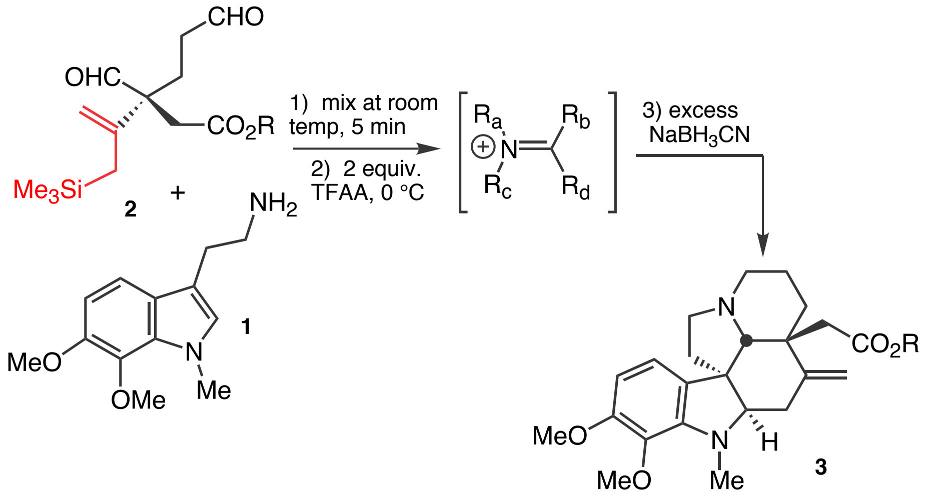
Friday,
December 5 , 2003

Here is a typical carbonium ion question that you should be able to handle by the end of the course. Write out a mechanism for the following transformation.



A. Srikrishna, *Chem Commun* **1994**, 2259

Question 13. Final Exam, 1999. During Corey's synthesis of Aspidophytine (*JACS*, **1999**, *121*, 6771), the pivotal intermediate **3** was assembled by the union of **1** and **2** under the specified conditions. Provide a mechanism for this single-pot transformation.

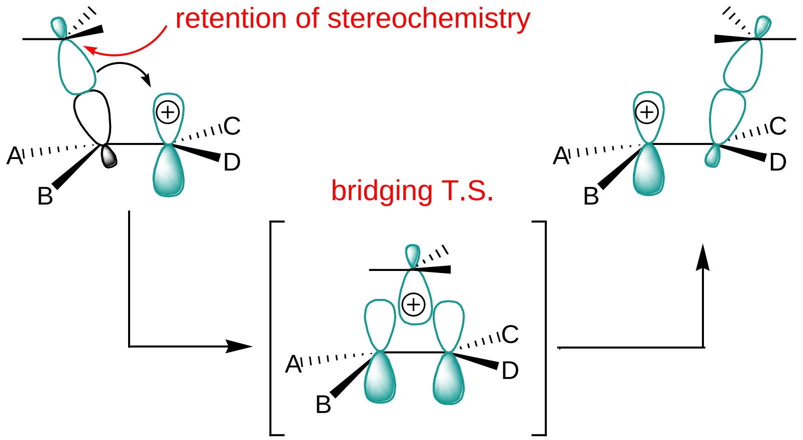


Carbocation [1,2] Sigmatropic Rearrangements

1,2 Sigmatropic shifts are the most commonly encountered cationic rearrangements. When either an **alkyl** substituent or a **hydride** is involved, the term **Wagner-Meerwein shift** is employed to identify this class of rearrangments.

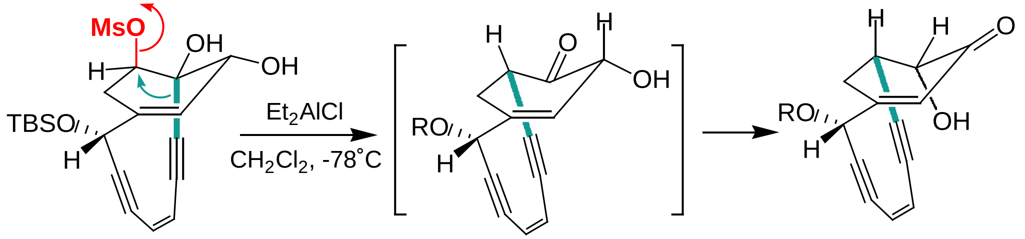
Birladeanu (**2000**). "The Story of the Wagner-Meerwein Rearrangement." J. Chem. Ed. 77: 858. **(handout)**

Stereoelectronic requirement for migration....



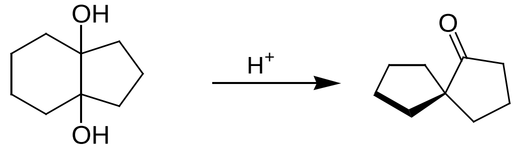
2-electron Huckel transition state

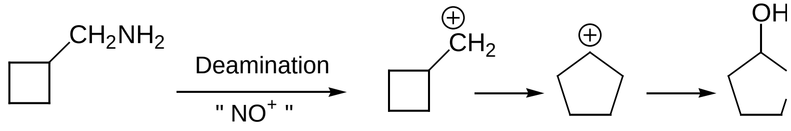
If **migration accompanies ionization**, the migration terminus will be **inverted**. Overlap between the σ C-C (migration origin) and the σ* C-X (migration terminus) will be maximized in an **antiperiplanar** arrangement.



S. L. Schreiber et al. *Tetrahedron Lett.* **1989**, *30*, 3765

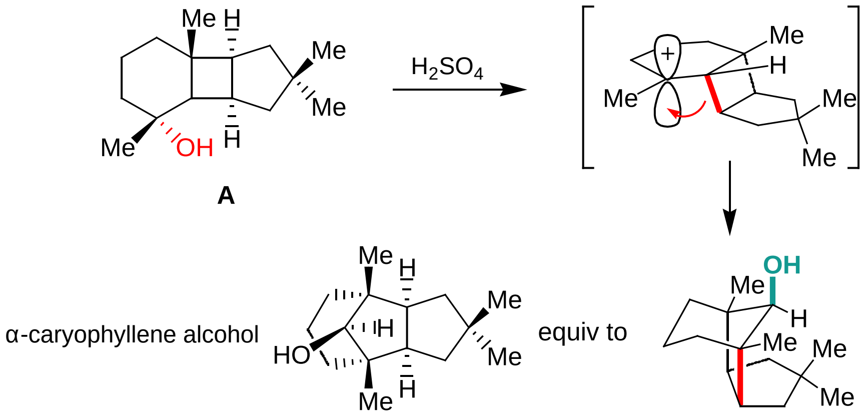
Pinacol rearrangement (vicinal diol): Driving force is the gen. of C=O



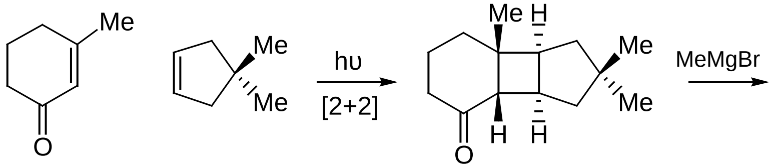


Demjanov-rearrangement (Driving force: relief of ring strain)

Wagner-Meerwein Rearrangements: Application in Total Synthesis

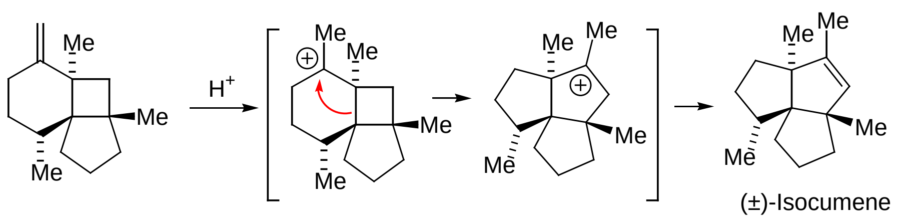


Preparation of A:



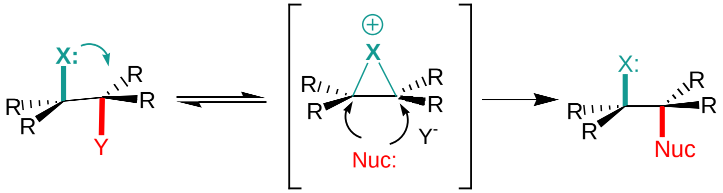
Carbocation Rearrangements-2

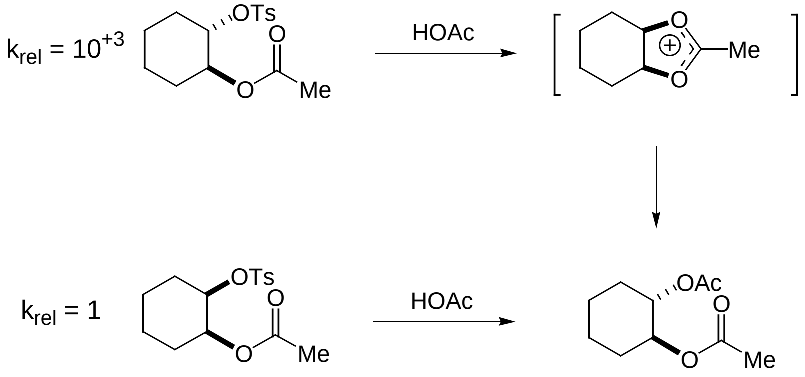
Synthesis of (±)-Isocomene: Pirrung, *JACS* **1979**, 7130; *1981*, 82.

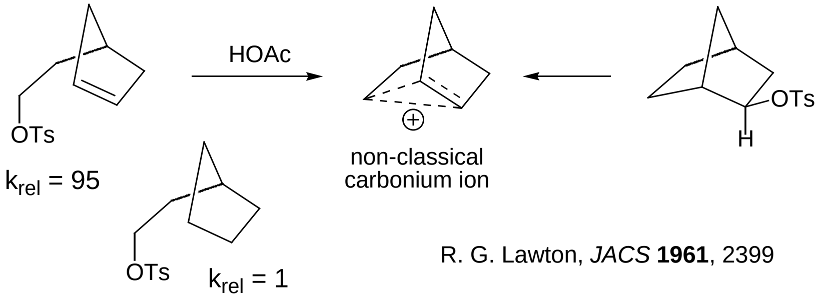


Carbocations: Neighboring Group Participation

- Groups with accessable electron density (heteroatoms, arenes) and the correct stereoelectronic orientation (anti-periplanar) can "assist" in the ionization of a leaving group.

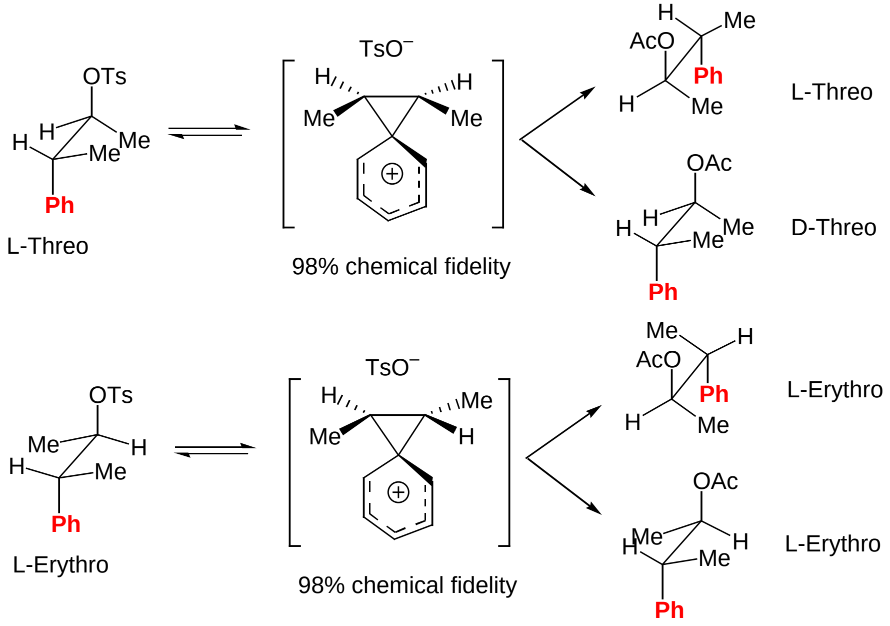




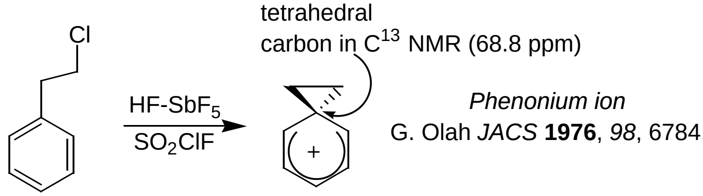


R. G. Lawton, *JACS* **1961**, 2399

The Cram Phenonium Ion Experiments: Cram, *JACS* **1949**, *71*, 3865



Physical Evidence for Neighboring Group Participation



tetrahedral carbon in C^{13} NMR (68.8 ppm)

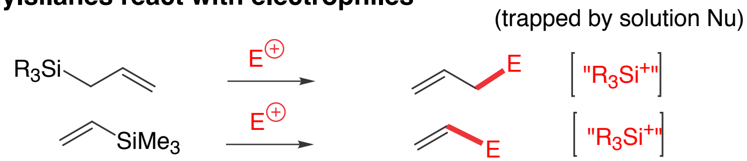
Phenonium ion
G. Olah *JACS* **1976**, *98*, 6784.

See Lowry & Richardson, pp 434-439 for discussion of this controversy

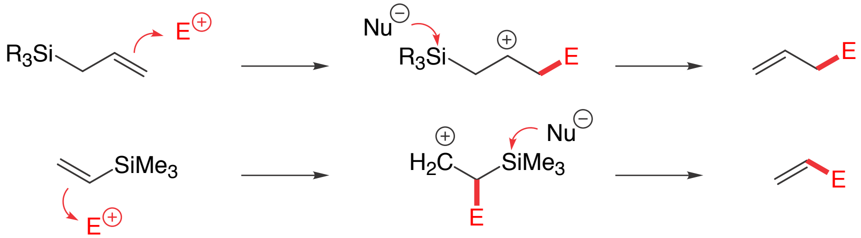
Allyl- & Vinylsilanes: The β-Silicon Effect

References:
Lambert *Acc. Chem. Res.* **1999**, *32*, 183-190
Lambert, *JACS* **1990**, *112*, 8120; **1996**, *118*, 7867.
Fleming, *Organic Reactions* **1989**, *37*, 54.
Fleming, *Chem. Rev.*, **1997**, 2063.

Allyl– & Vinylsilanes react with electrophiles

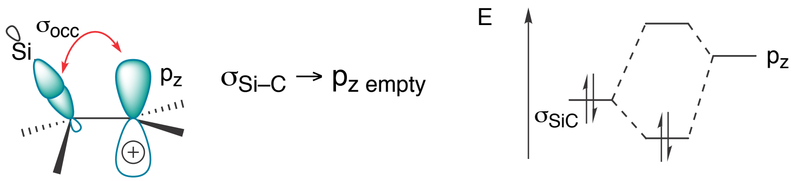


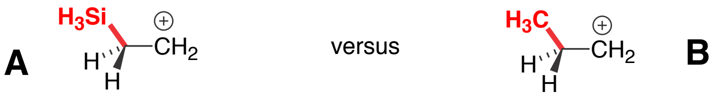
Mechanism - the simple picture: β-Silicon stabilizes carbocation



Fleming, *Organic Reactions* **1989**, *37*, 54.

β-Silicon Effect: the origin of regioselectivity

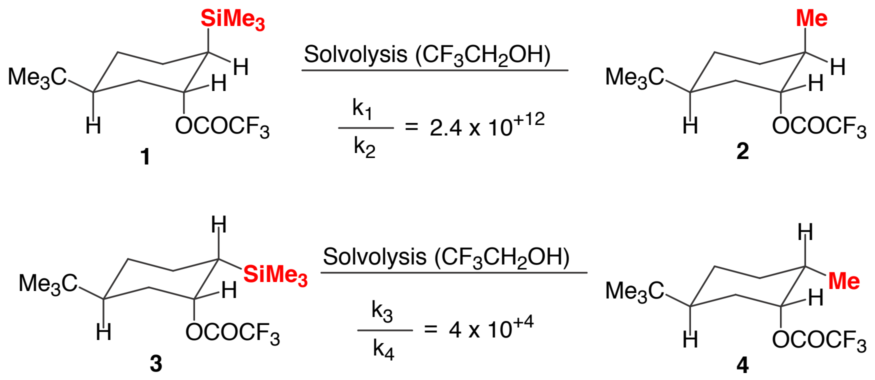




Calculation: A more stable than B by 38 kcal/mol.

Jorgensen *JACS* **1985**, *107*, 1496.

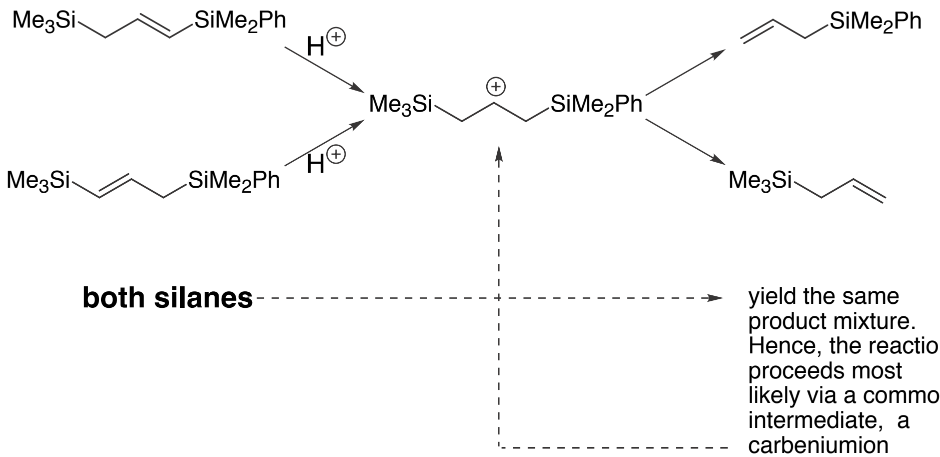
Magnitude of the β-Silicon Effect



"These figures established the β-effect as one of the kinetically strongest in organic chemistry": J. Lambert

Data provide no distinction between open and bridged intermediates

Proof for a stepwise mechanism provided the following protodesilylation experiment:

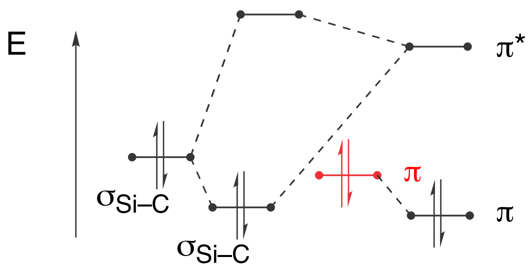


both silanes yield the same product mixture. Hence, the reaction proceeds most likely via a common intermediate, a carbeniumion

Allyl- & Vinylsilanes: The β-Silicon Effect-2

General: Allylsilanes are more nucleophilic than alkenes

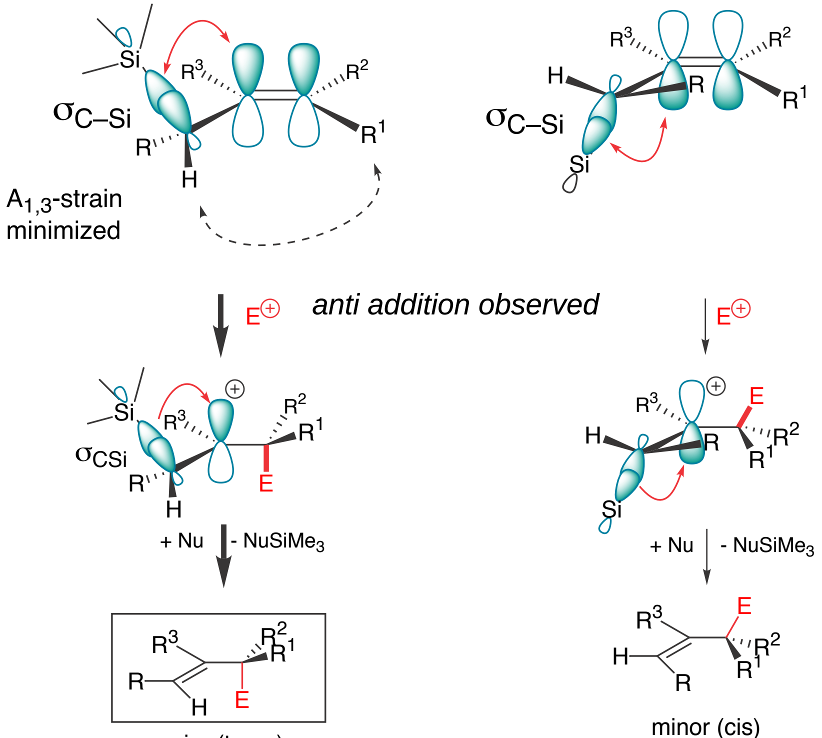
⟹ HOMO is higher in energy due to ***negative hyperconjugation***



$\pi\ (\pi^*) \longleftrightarrow \sigma_{C-Si}$

Houk, *JACS* **1982**, *104*, 7162.

Electrophile Addition - Stereoelectronics



anti addition observed

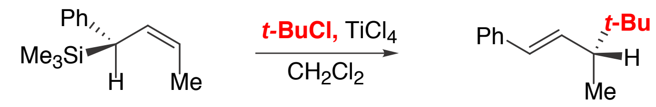
major (trans)

minor (cis)

The stereochemical consequences for the major product are:

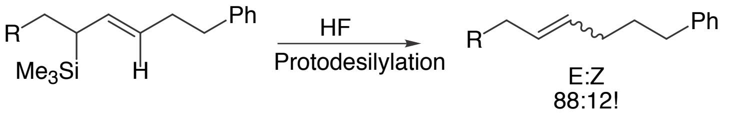
- ❒ trans-alkene:
- ❒ anti-addition of E^+ with respect to SiR_3

Examples:



JACS **1982**, *104*, 4962.

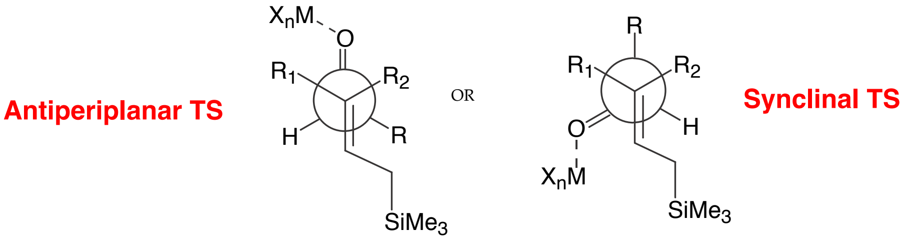
But



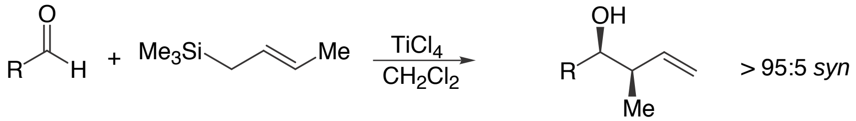
Eschenmoser, *Helv. Chim. Acta* **1979**, *62*, 1922.

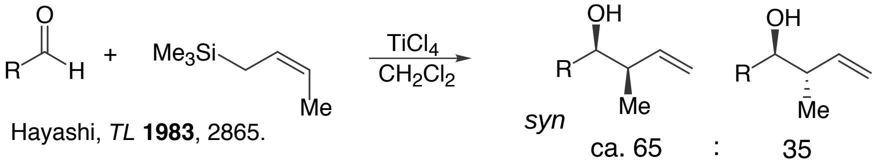
Carbonyl Addition of Allylsilanes: Open Transition States

Me_3Si– is not sufficiently Lewis acidic to activate C=O through pre-association; however $(RO)_2MeSi$– is Lewis acidic enough to activate C=O through pre-association. These allylsilanes add to RCHO througl closed transition states



Calculations by Houk et al. show that the relative energy differences between the antiperiplanar and and synclinal transition states are negligible. Both the antiperiplanar and synclinal models predict a ***syn*** selectivity for the newly formed stereogenic centers.

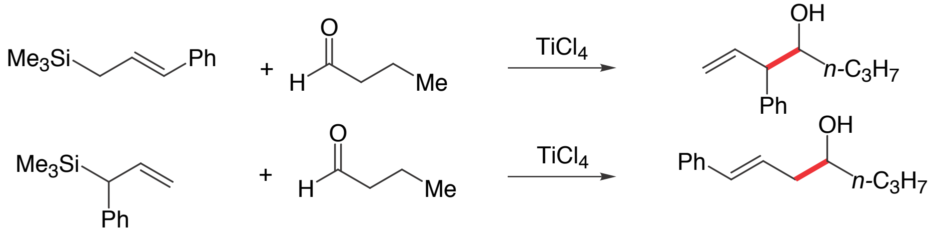




Hayashi, *TL* **1983**, 2865.

Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones, Denmark and Jiping Fu, *Chem. Rev.* **2003,** *103,* 2763-2793 **(handout)**

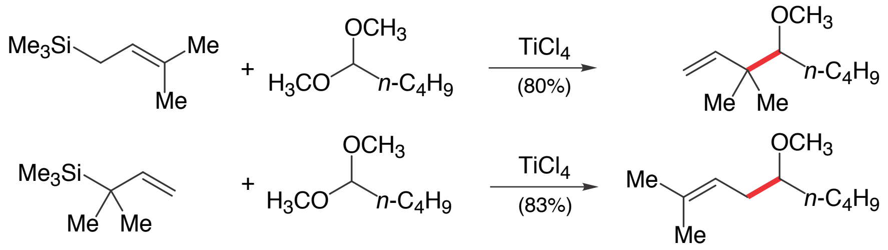
Allylsilanes add to aldehydes and acetals under Lewis acid promotion



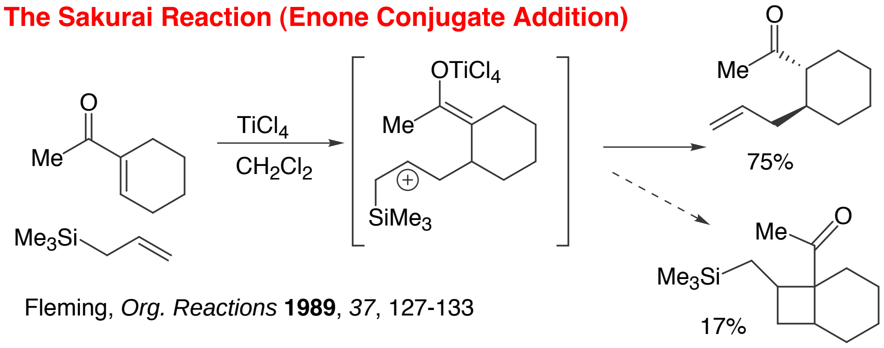
regioselectivity: Allyl inversion

Felkin Selectivity also holds with this class of nucleophiles

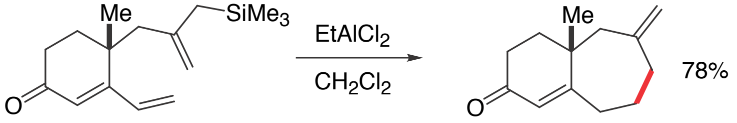
Acetals can be used as well



The Sakurai Reaction (Enone Conjugate Addition)



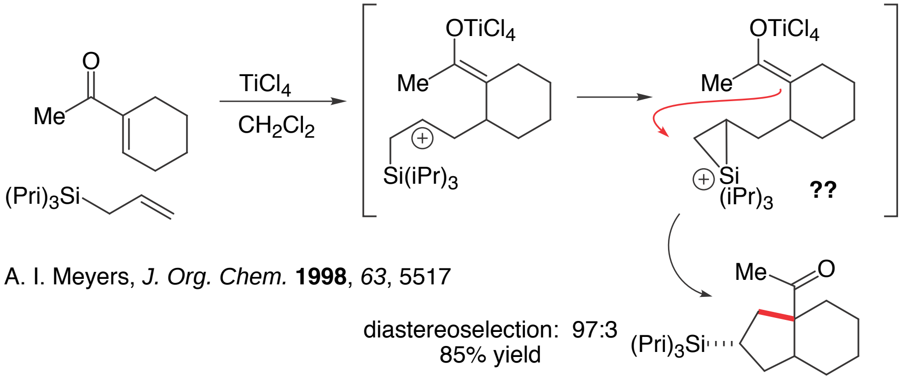
Fleming, *Org. Reactions* **1989**, *37*, 127-133



Majetich, *Tetrahedron* **1987**, *43*, 5621

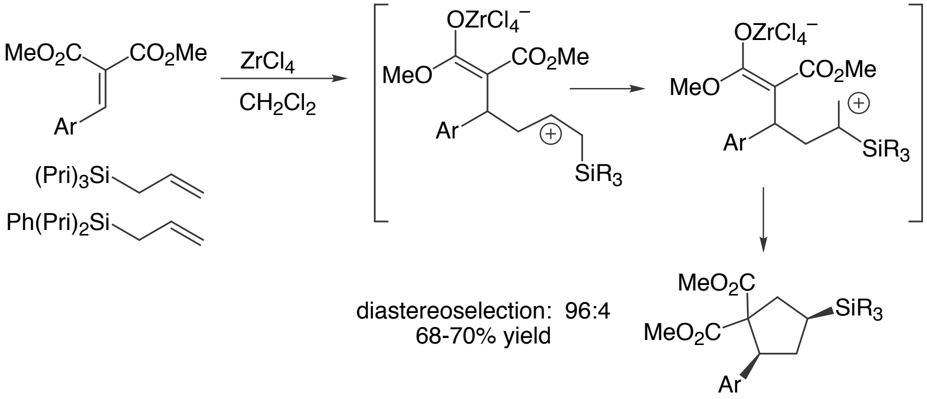
Reactions Proceedilng through Silicon-Migration

Si migration may be promoted by using hindered Si substituents



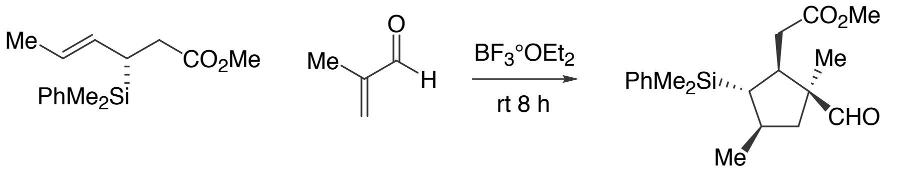
A. I. Meyers, *J. Org. Chem.* **1998**, *63*, 5517

diastereoselection: 97:3
85% yield



diastereoselection: 96:4
68-70% yield

Can you work out the mechanism??



diastereoselection: >30:1
93% yield

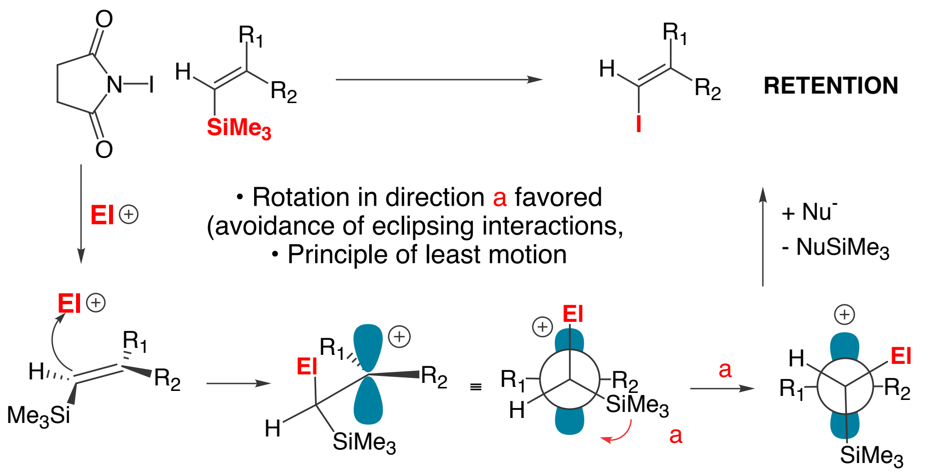
Panek, *J. Org. Chem.* **1993**, *58*, 2345

Vinylsilanes: Reactions with Electrophiles

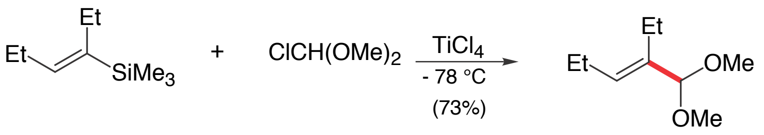
Stereochemistry of Electrophile Addition to Vinylsilanes

Vinyl/Allylsilanes in Organic Synthesis - Selected Examples

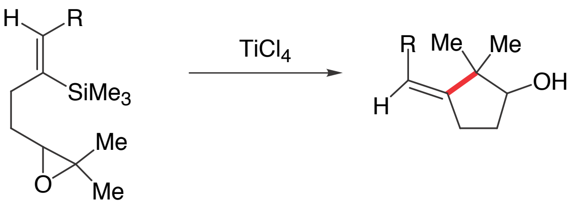
Fleming, *Org. Reactions* **1989**, *37*, 54.



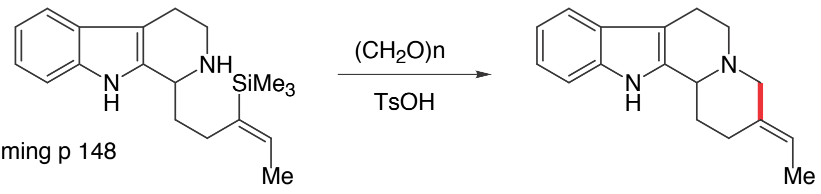
• Rotation in direction a favored
(avoidance of eclipsing interactions,
• Principle of least motion



Fleming p 289

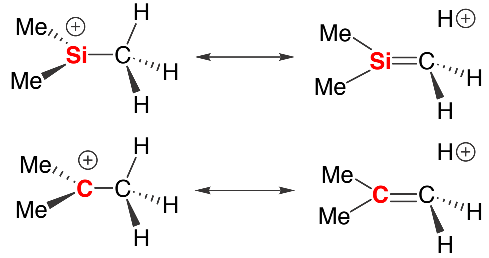


Fleming p 148



Summary Statements

1. Me_3C+ is more stable than Me_3Si+ in spite of the fact that Si is less electronegative than C.



C–Si bond length: 1.87 Å

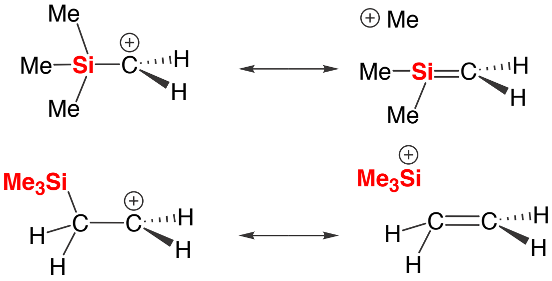
C–C bond length: 1.54 Å

C–Si hyperconjugation is less pronounced than the anaologous C–C hyperconjugation do to the impact of the longer C–Si bond lengths.

2. Carbonium ions α to Si are less stabilized than carbonium ions β to Si.

C(+) α to silicon

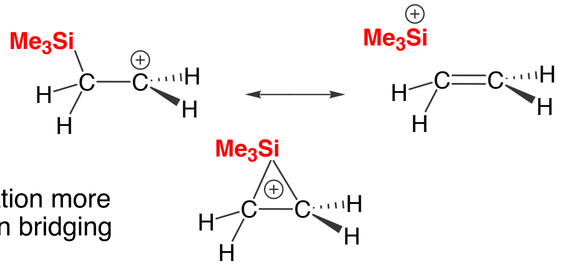
C(+) β to silicon



C–Si hyperconjugation is less pronounced than the anaologous C–C hyperconjugation do to the impact of the longer C–Si bond lengths.

3. According to Lambert, silicon has a propensity to stabilize β carbonium ion via hyperconjugation (vertical stabilization) rather than bridging (nonvertical stabilization.

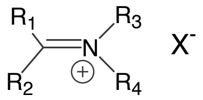
C(+) β to silicon



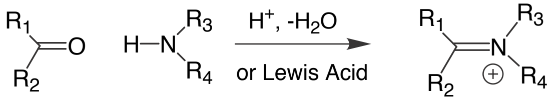
hyperconjugation more important than bridging

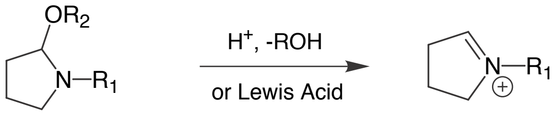
4. Silicon has a lower propensity to undergo Wagner–Meerwein like rearrangements than carbon.

Iminium Ions

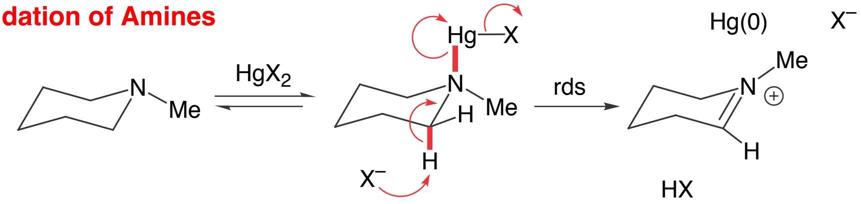


Common Methods of Generation:

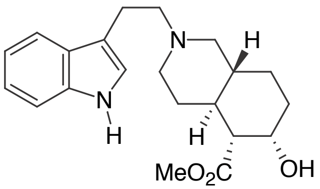




Oxidation of Amines

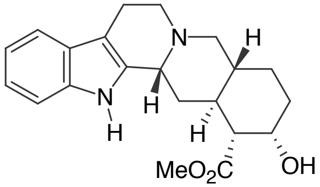


Stereoelectronic Effects on Nu Addition to Iminium Ions

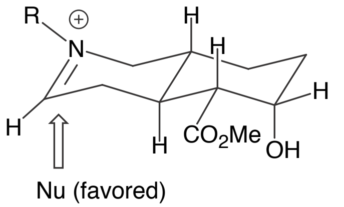


$Hg(OAc)_2/EDTA$

$NaBH_4$

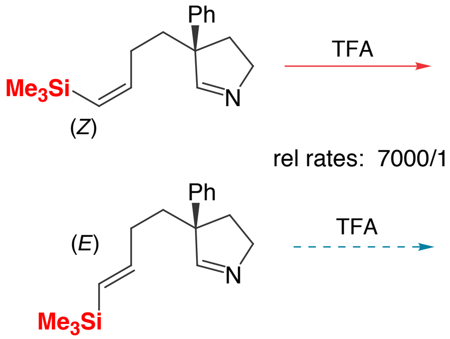


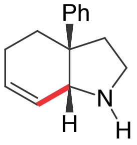
one diastereomer



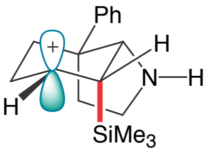
Stork et al. *JACS* **1972**, *94*, 5109.

C=N Stereoelectronic Effects: Lecture 20

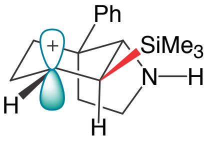




Overman et al. *TL* **1984**, *25*, 5739.

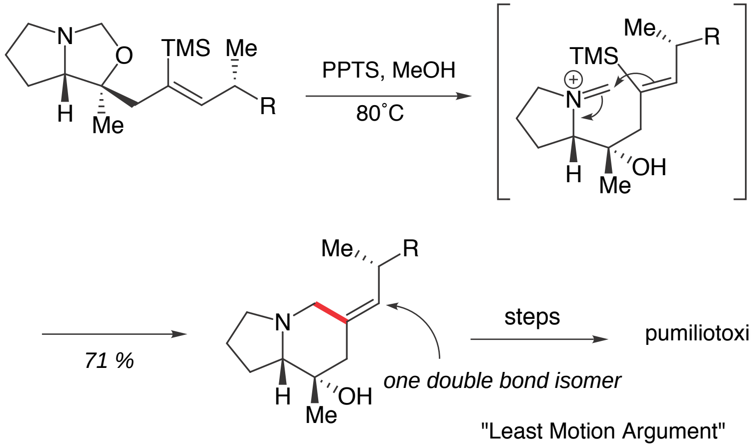


(*Z*) *vinylsilane*)



(*E*) *vinylsilane*)

Only in the case of the (Z) vinylsilane is the emerging p orbital coplanar with C-Si bond. Full stabilization of the empty orbital cannot occur with the (E) vinylsilane.....hence the rate difference.



"Least Motion Argument"

Overman et al. *JOC* **1989**, *54*, 2591.

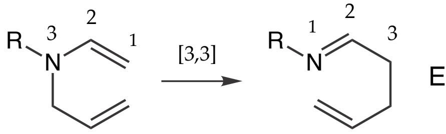
The Aza-Cope Rearrangement

Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

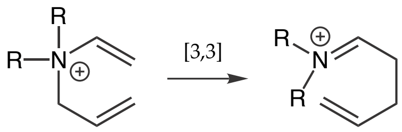
The 3-aza-Cope Rearrangement:

Neutral Variant:



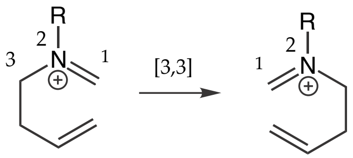
Exothermic as written by ~7-10kcal/mole.

Ammonium Variant:



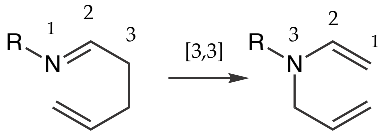
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

2-aza-Cope Rearrangement:



In the simplest case, degenerate. Steric effects, conjugation, or selective trapping of a particular isomer, will drive equilibrium. As with the 3-aza-Cope, the cationic version proceeds under much milder conditions.

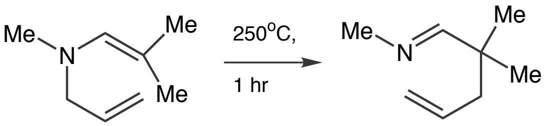
1-aza-Cope Rearrangement:



The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates(i.e., incorporating the imine into a strained ring or by making R an acyl group).

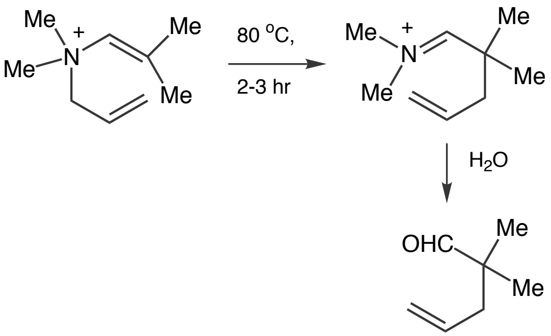
The 3-aza-Cope Rearrangement

First Neutral Case: Hill TL **1967**, 1421.



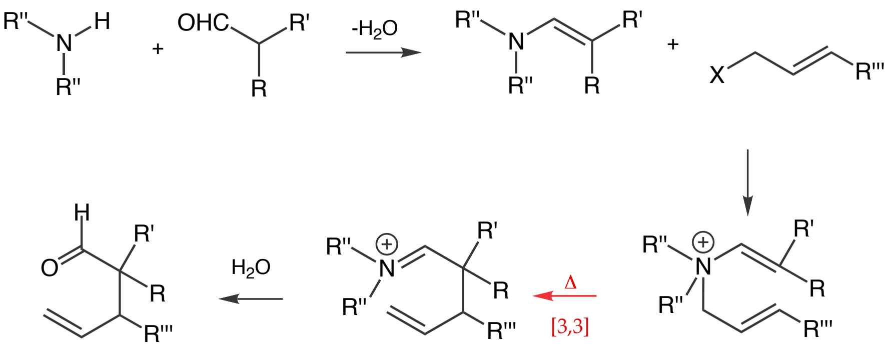
"Practically quantitative", no real yields given.

First Cationic Case: Elkik *Compt. Rend.* **1968**, *267*, 623.



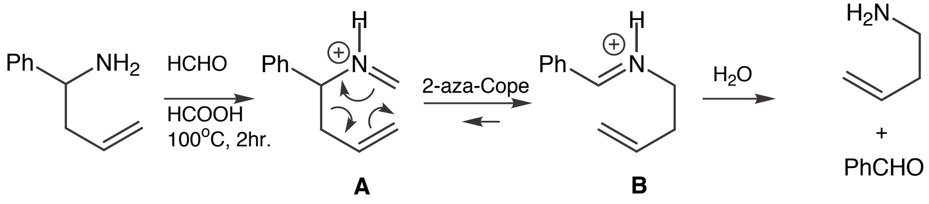
No yields given.

Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, *72*, 169.



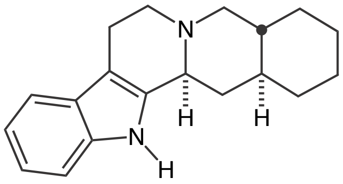
The 2-aza-Cope Rearrangement

First Reported Case: Horowitz JACS 1950, *72*, 1518.

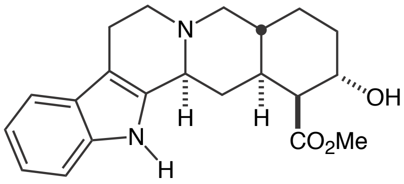


Equilibrium between **A** and **B** driven towards **B** by conjugation of iminium double bond to the aromatic ring in **B**.

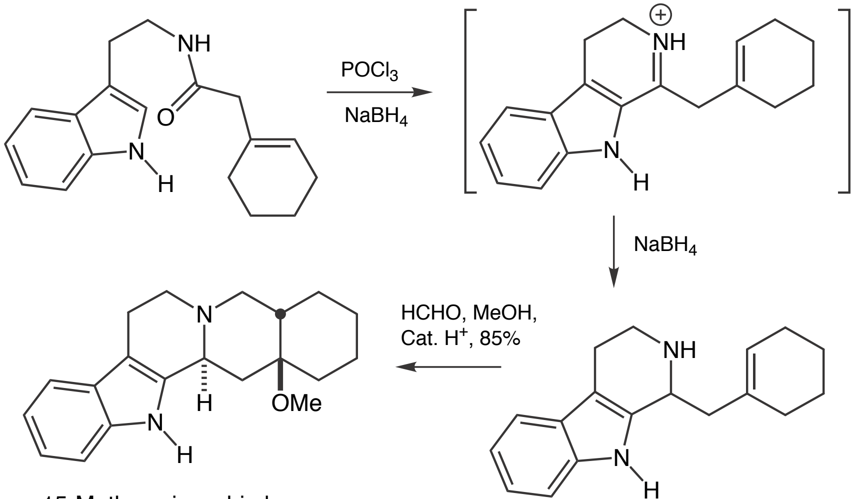
Application to Yohimbine Analog Synthesis: Winterfeldt *Chem. ber.* **1968**, *101*, 2938.



Yohimbane

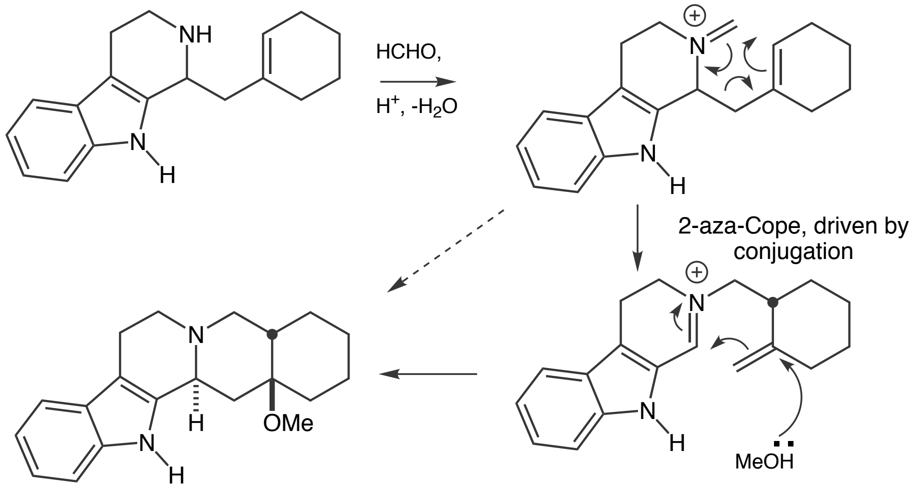


Yohimbine



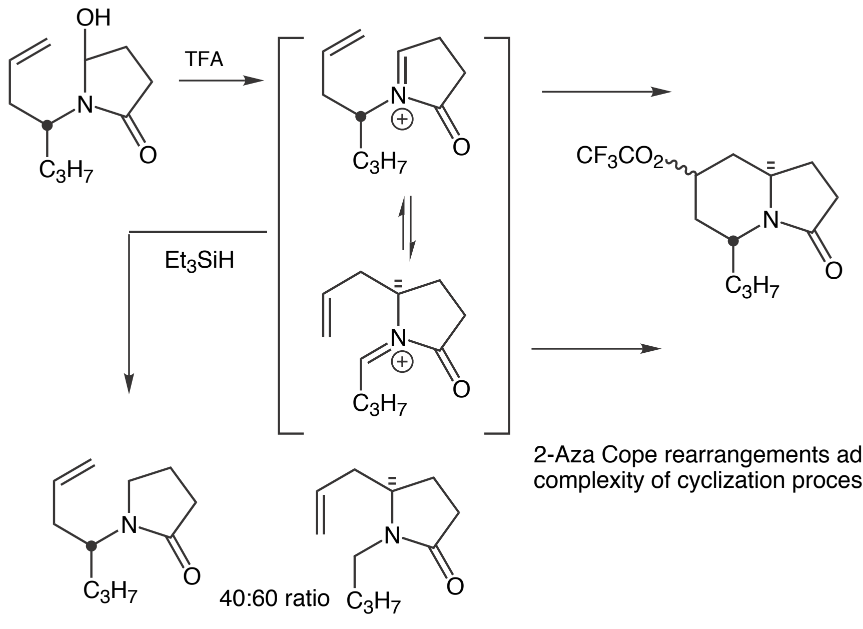
15-Methoxy-isoyohimbane

Mechanism for Yohimbane Analog Formation:



N-Acyliminium Ion Rearrangements: Hart JOC ***1985****, 50, 235.*

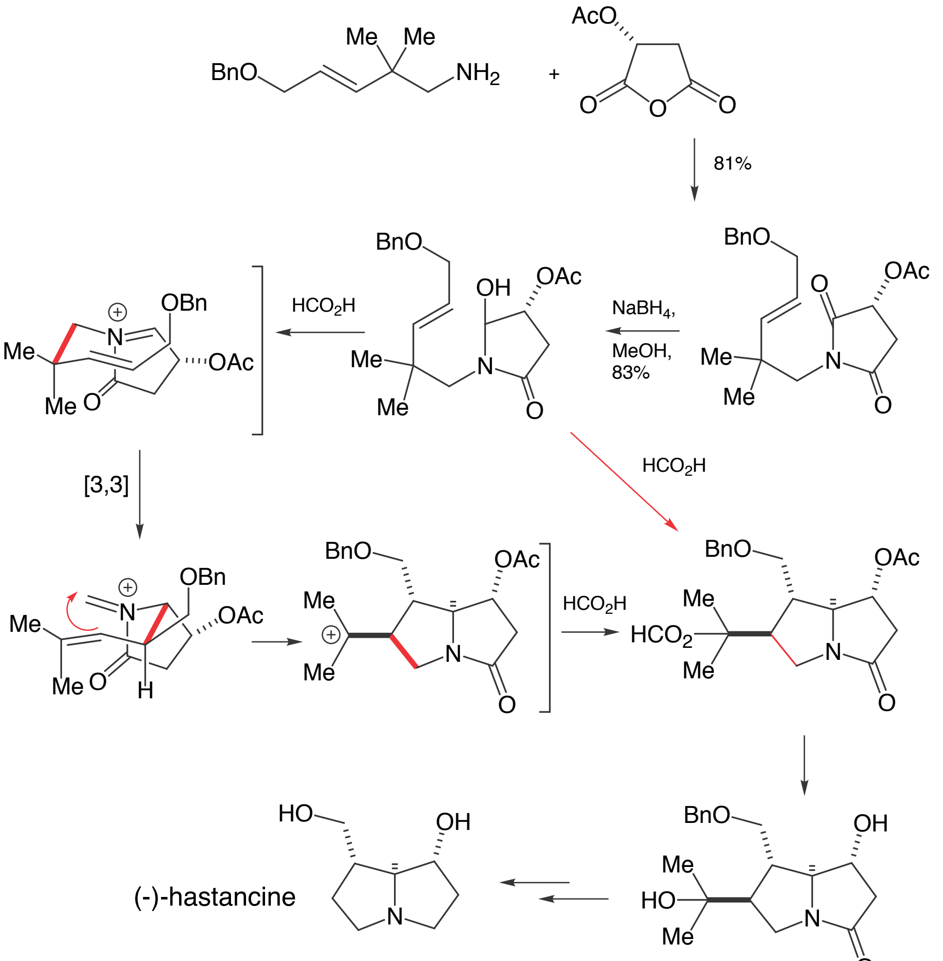
Hart observed an unusual product while trapping the intermediates of N-acyliminium olefi cyclizations.

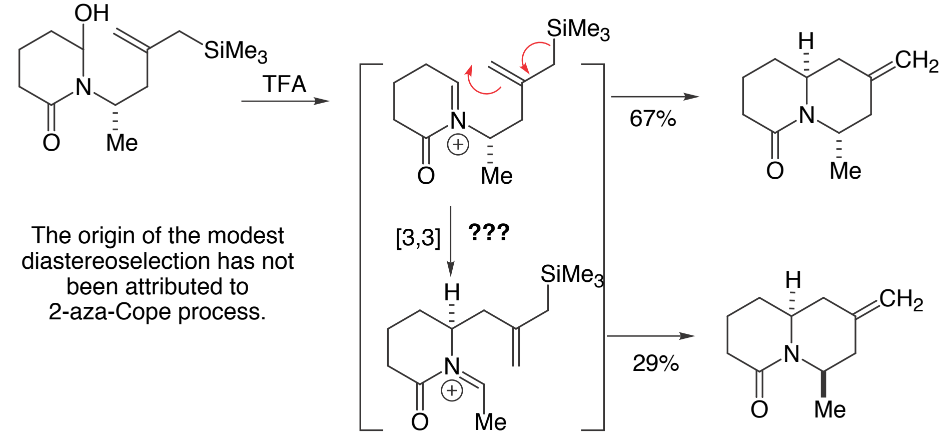


2-Aza Cope rearrangements add to complexity of cyclization process

N-Acyliminium Ion Rearrangements

*Synthesis of (-)-hastanecine: Hart JOC **1985**, 50, 235.*

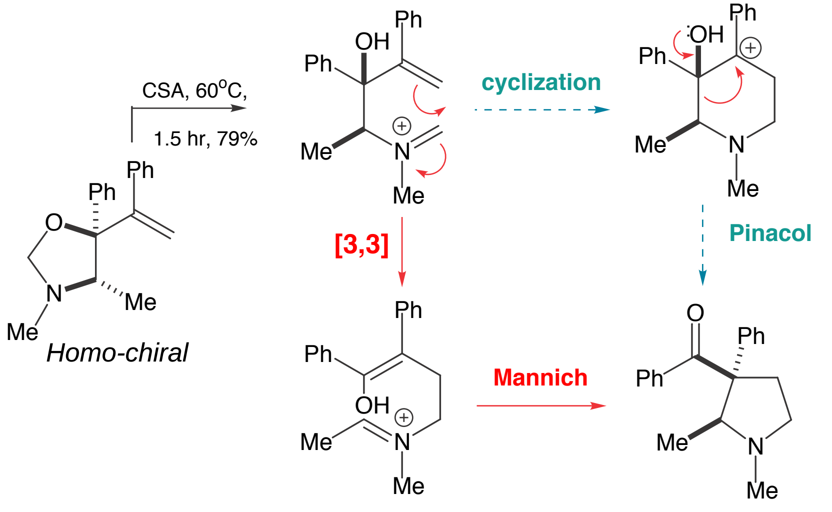




The origin of the modest diastereoselection has not been attributed to 2-aza-Cope process.

Gelas-Mailhe, *Tet. Lett*, **1992**, *33*, 73

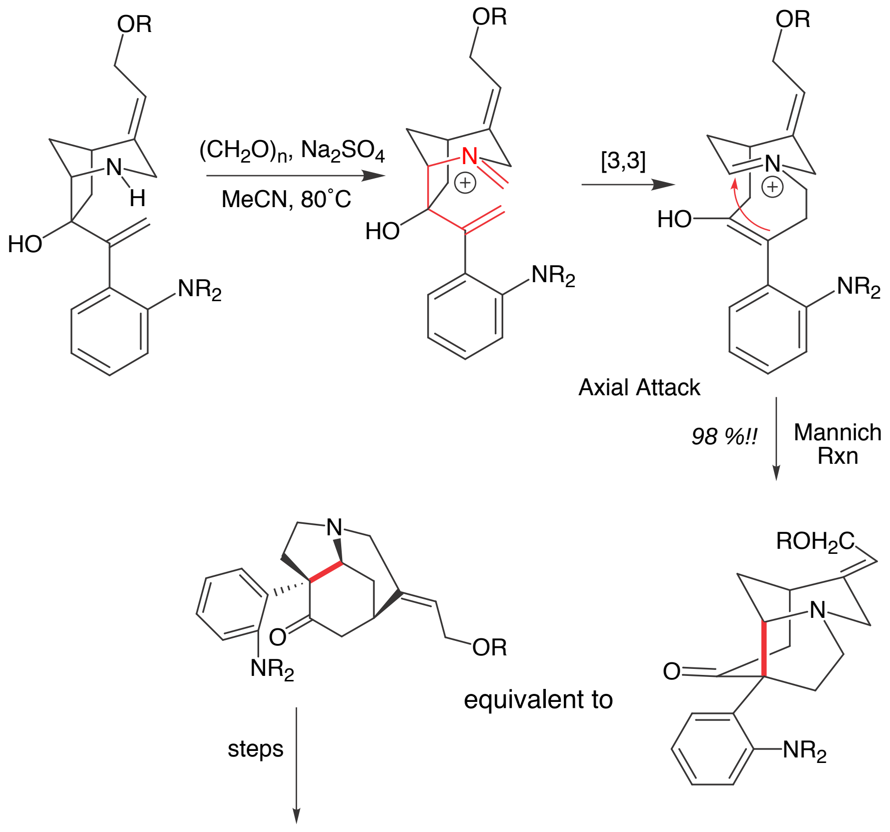
Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??

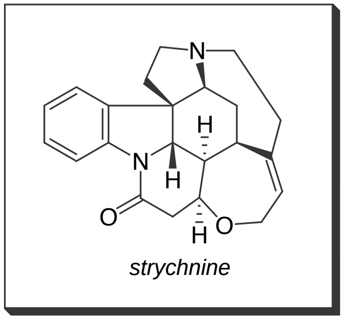


racemic product

Conclusion: 2-aza-Cope rearrangements afford a low-barrier to competing processes

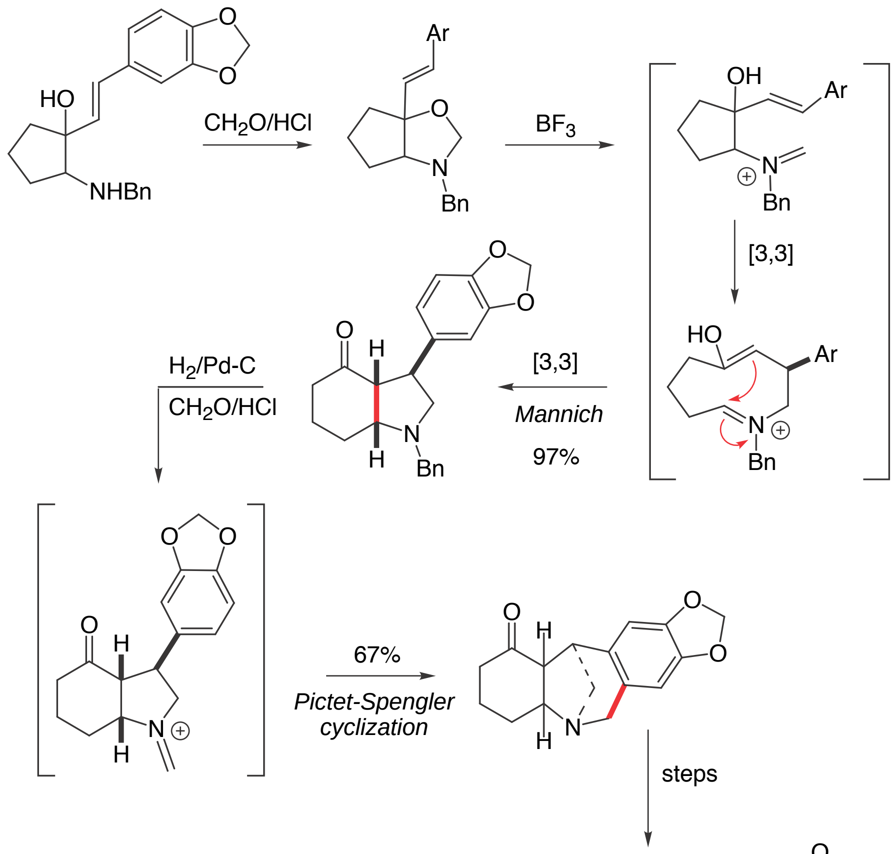
2-Aza-Cope-Mannich sequence:

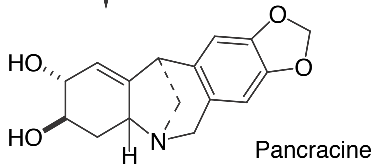




Overman et al. *JACS* **1995**, *117*, 5776.

Another aza-Cope-Mannich sequence:





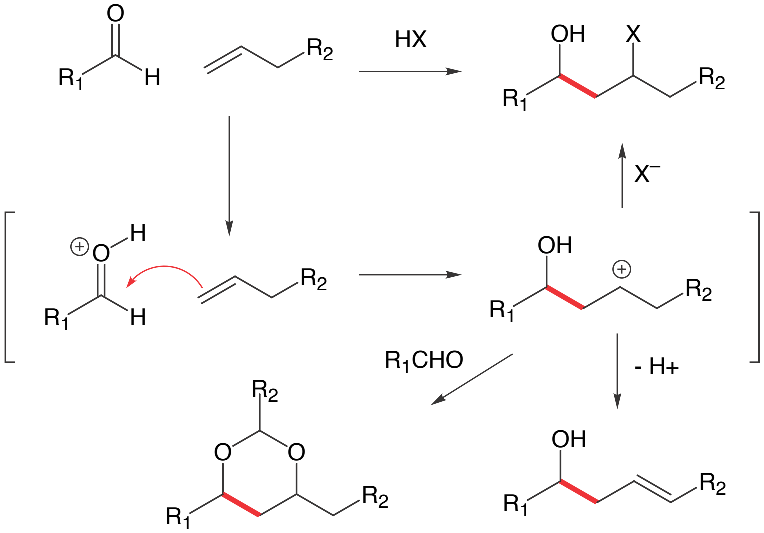
Overman et al. *JOC* **1991**, *56*, 5005

The Prins-Pinacol Reaction

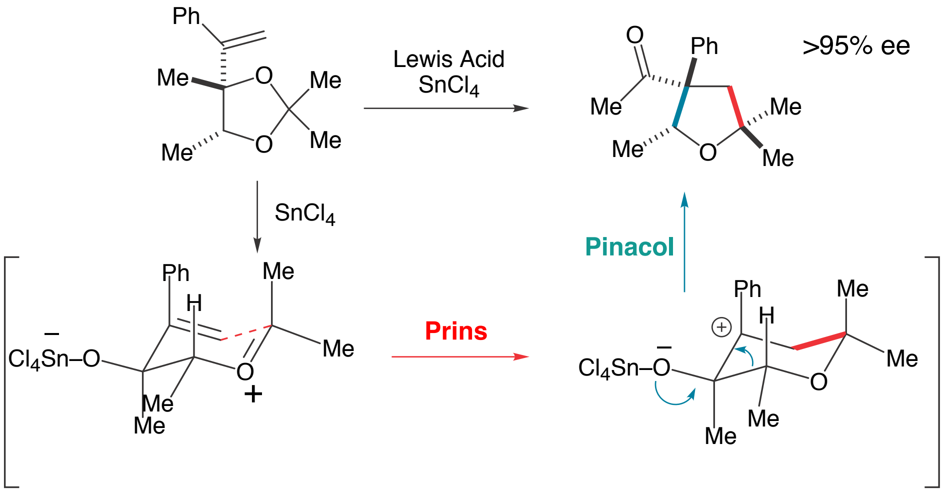
References

Prins reaction: Adams, D.R.; Bhaynagar, S. D. *Synthesis* **1977**, 661
Prins & carbonyl ene reactions: Snider, *Comprehensive Organic Synthesis*, **1991**, *Vol. 2*

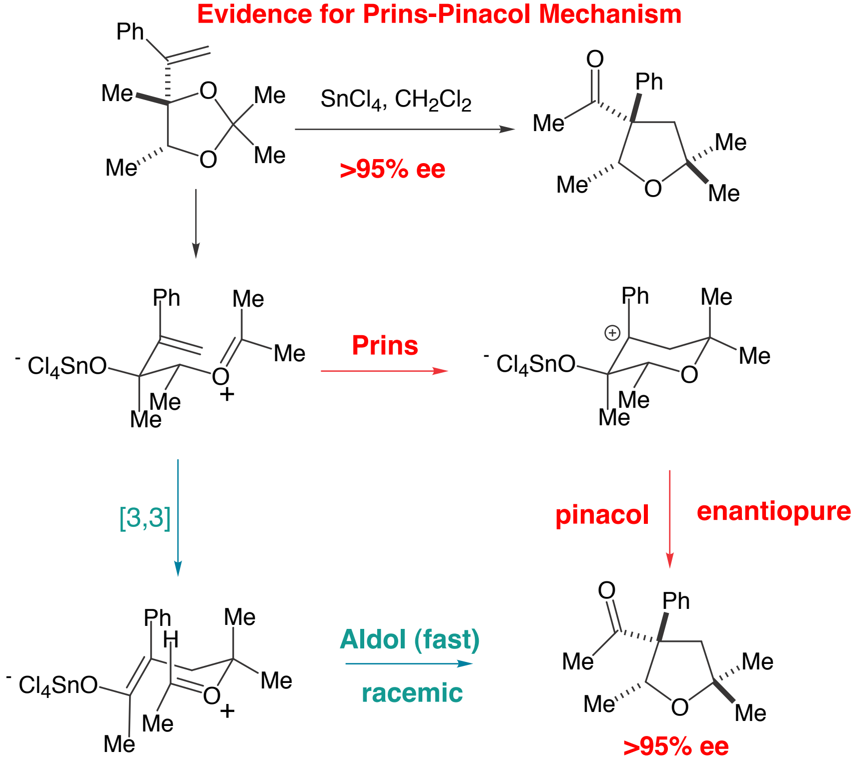
The Prins Process:



The Prins-Pinacol Variant:

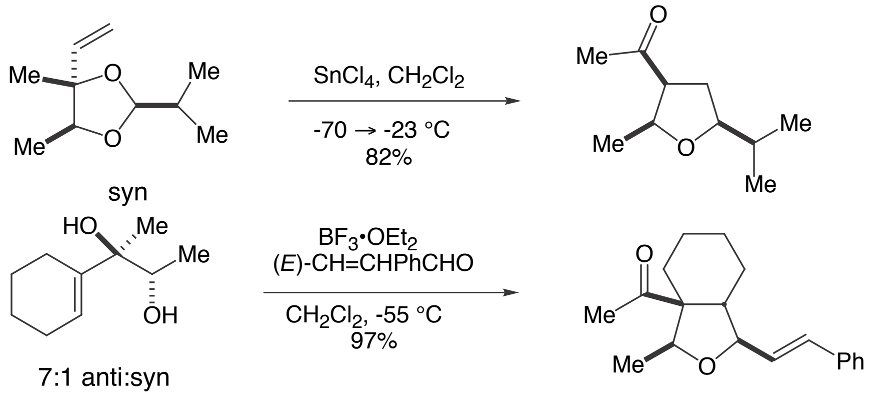


Evidence for Prins-Pinacol Mechanism



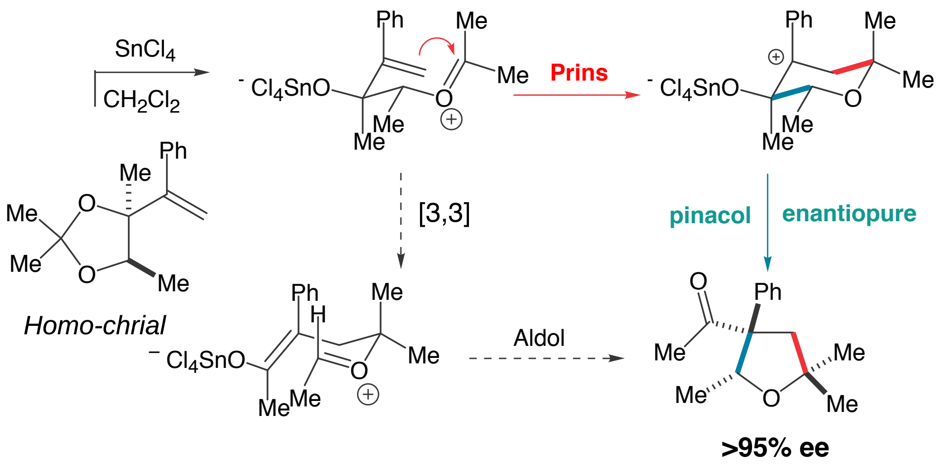
If a [3,3] rearrangement were intervening, the product would be racemic.
Overman, *JACS* **2000**, *122*, 8672
Overman, *Org Lett* **2001**, *3*, 1225

Examples of Stereoselective THF Formation



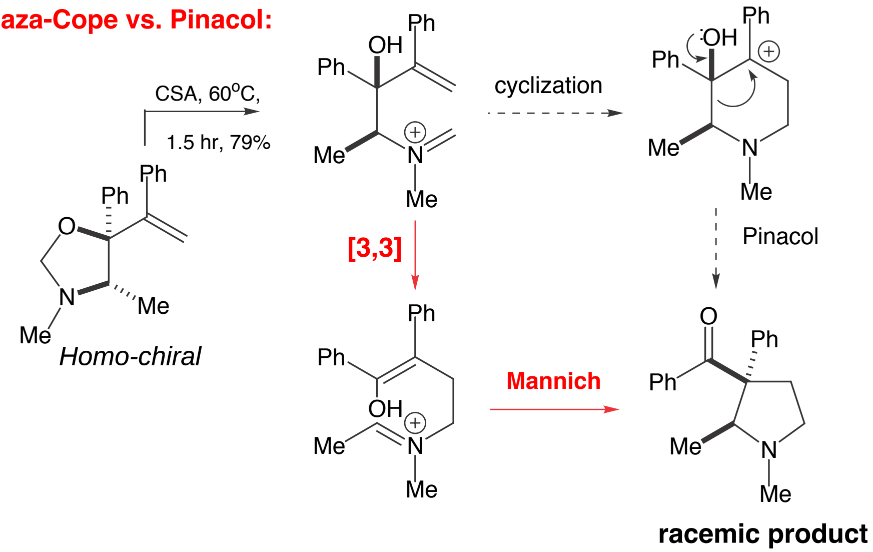
The Prins-Pinacol Reaction

Prins-Pinacol Mechanism



Prins cyclization faster than [3,3] rearrngement

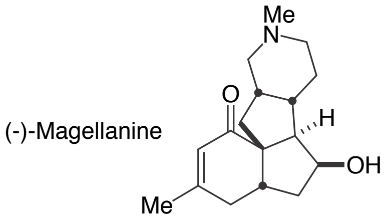
2-aza-Cope vs. Pinacol:



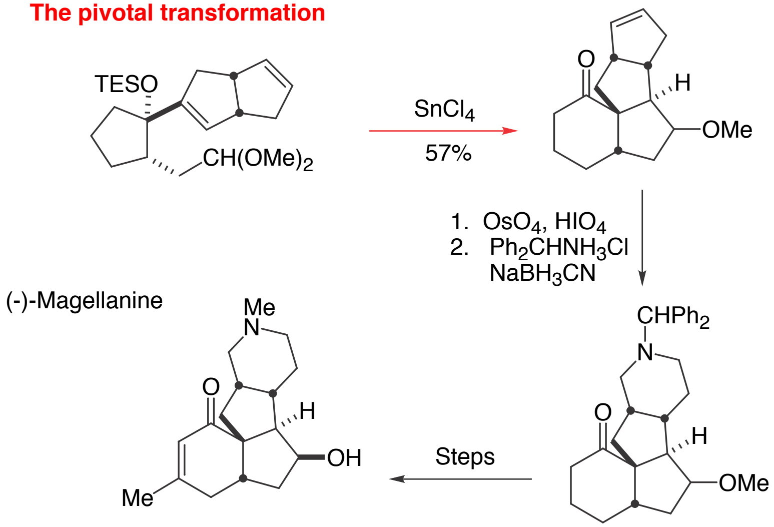
[3,3] rearrngement faster than Mannich cyclization

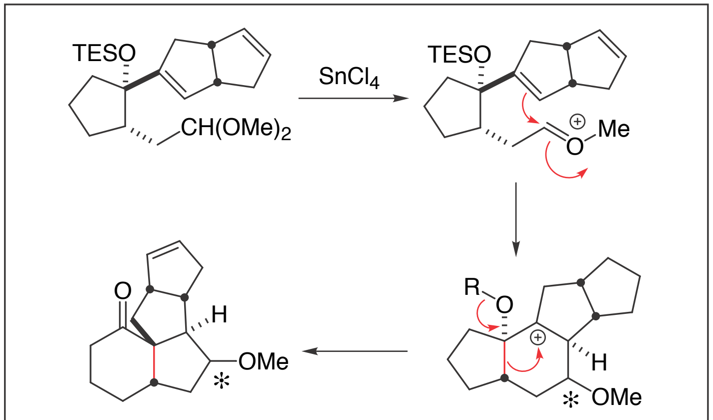
Overman: Magellanine Synthesis

JACS, **1993**, *115*, 2992



The pivotal transformation



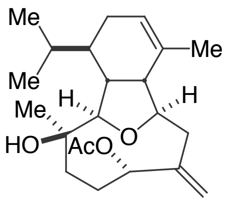


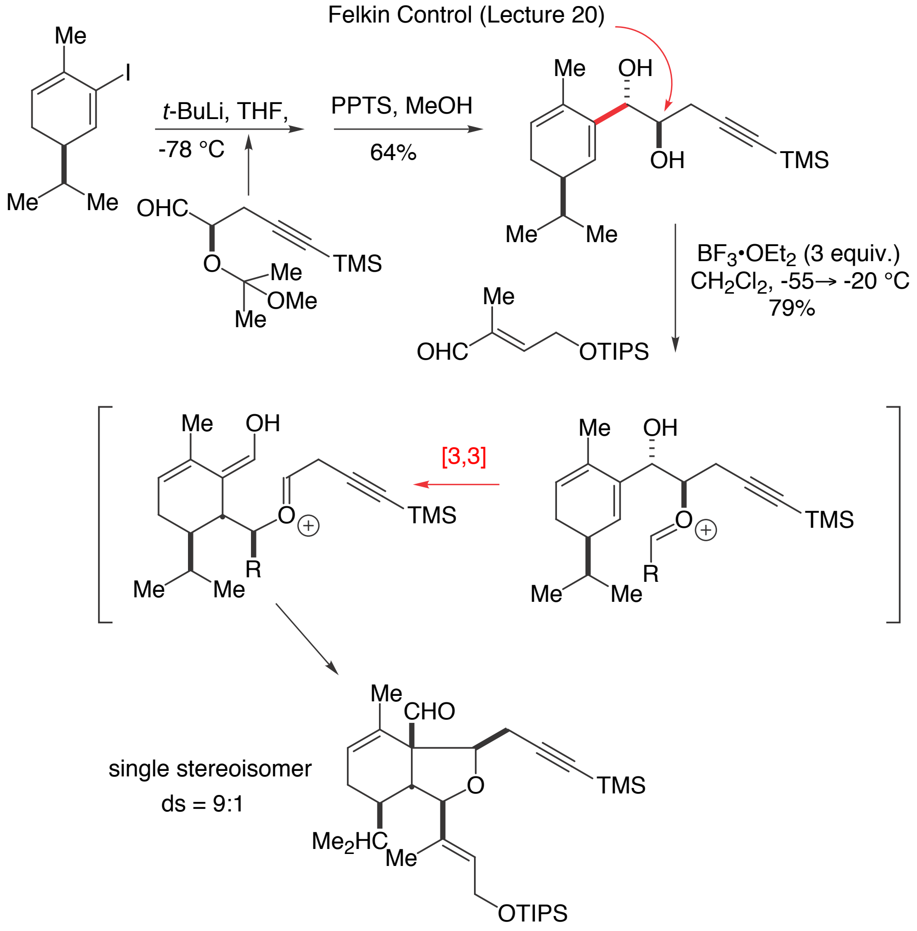
✻ mixture of diastereomers

Overman Synthesis of a Eunicellin Diterpene

Overman & MacMillan JACS, **1995**, *117*, 10391

(-)-7-Deacetoxy-alcyoninacetate



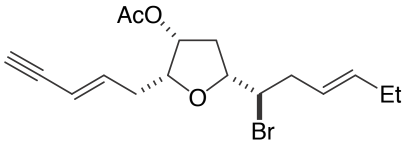


single stereoisomer
ds = 9:1

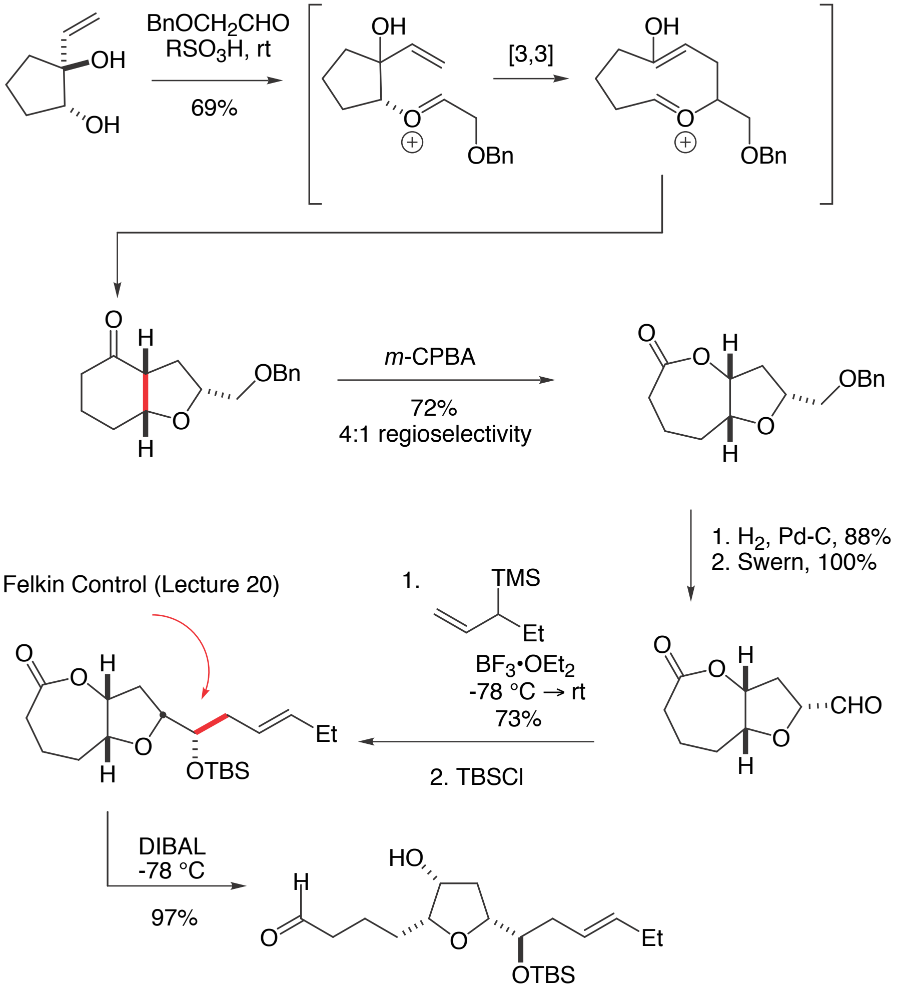
6 steps, 39% yield from (*S*)-carvone

Overman: Synthesis of *trans*-Kumausyne

JACS, **1991**, *113*, 5378



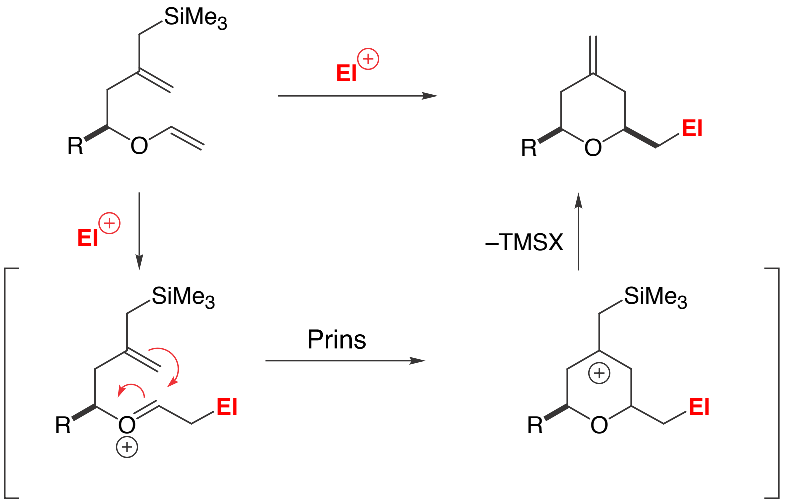
trans-Kumausyne



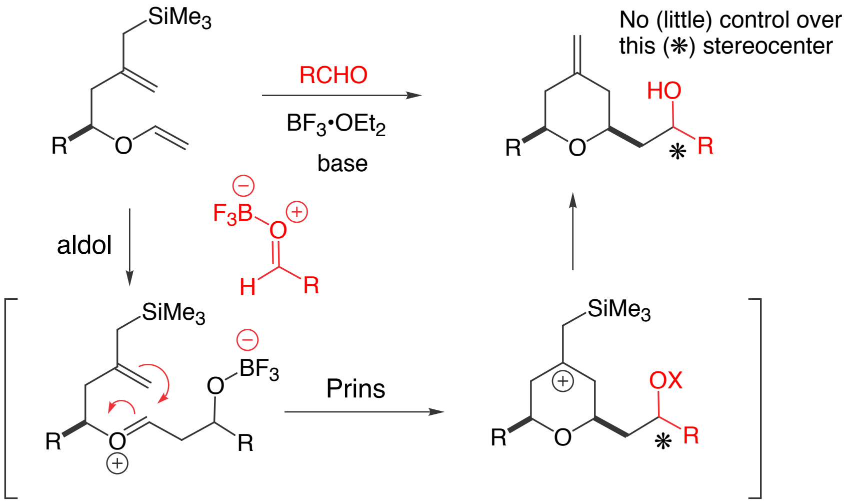
Mukaiyama Aldol–Prins Cascade

Rychnovsky JACS, **2001**, *123*, 8420

The Basic Process

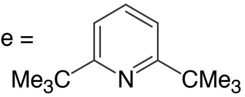


Let El(+) = Lewis acid activated RCHO

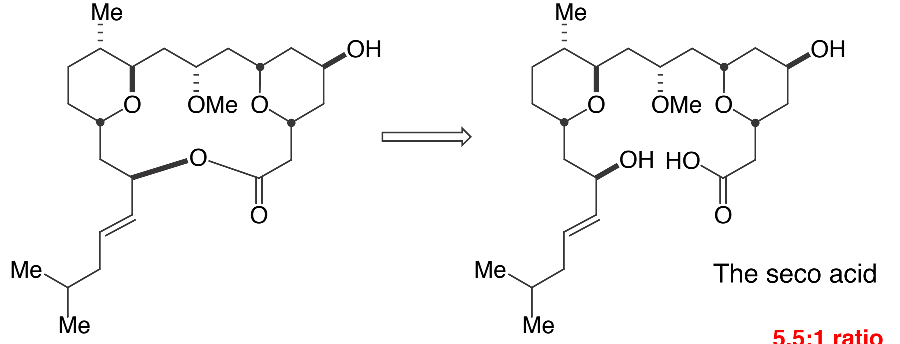


No (little) control over this (✻) stereocenter

base =

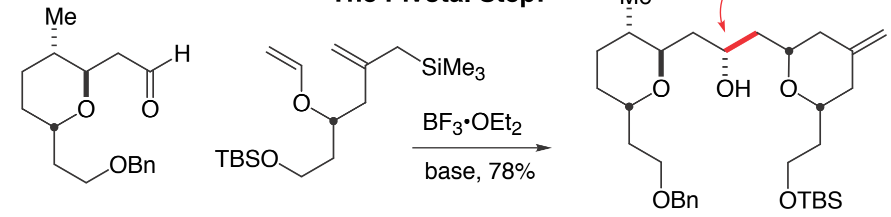


Application to Leucasandrolide



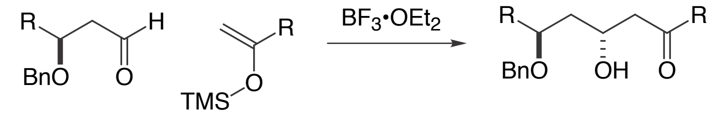
The seco acid

The Pivotal Step:



5.5:1 ratio

Control of hydroxyl center: see Lecture 20

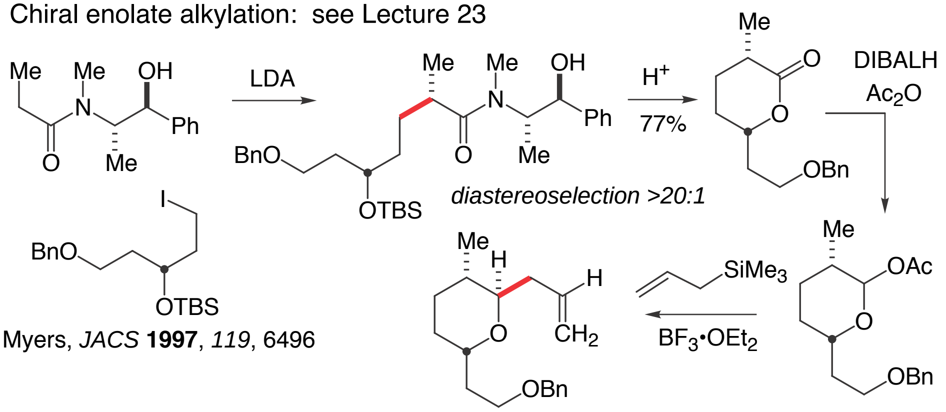


anti selection: ~5–8:1

Evans et al., *JACS* **1996**, *116*, 4322

Aldehyde Synthesis

Chiral enolate alkylation: see Lecture 23

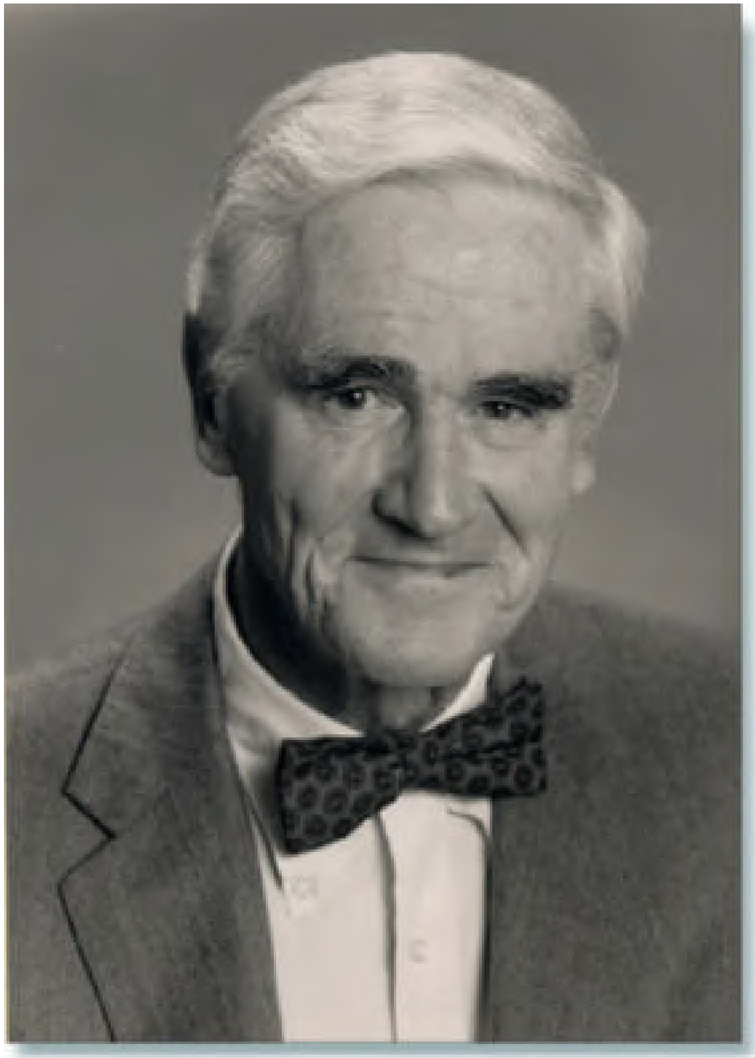


diastereoselection >20:1

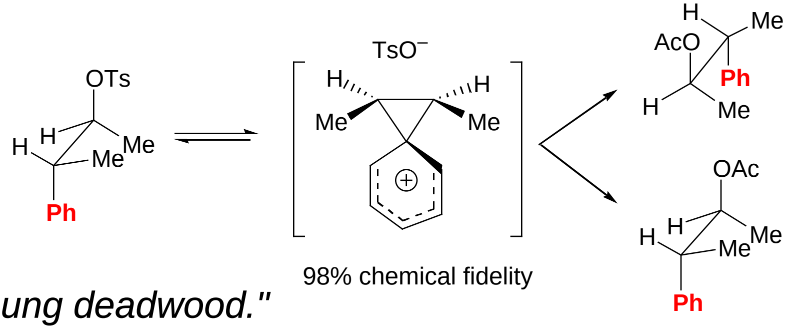
Myers, *JACS* **1997**, *119*, 6496

cyclic oxo-carbenium ion addition: see Lecture 19

Donald J.Cram (1919–2001)



Phenonium Ion Experiments: Cram, *JACS* **1949**, *71*, 3865



98% chemical fidelity

Cram: *"Just remember Dave, old deadwood is better than young deadwood."*

"A View from the Far Side. Memorable Characters and Interesting Places." Evans, D. A. *Tetrahedron* **1999**, *55*, 8589-8608.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 33

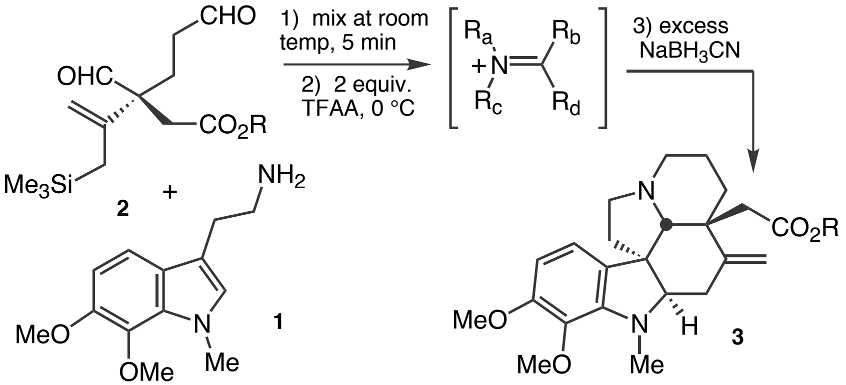
Introduction to Carbonium Ions–3

- Stabilized Carbocations: Iminium Ions ($C{=}NR_2(+)$)
- Stabilized Carbocations: Oxo–Carbenium Ions ($C{=}OR(+)$)
- Stabilized Carbocations: Addition & Rearrangements

Reading Assignment for this Lecture:

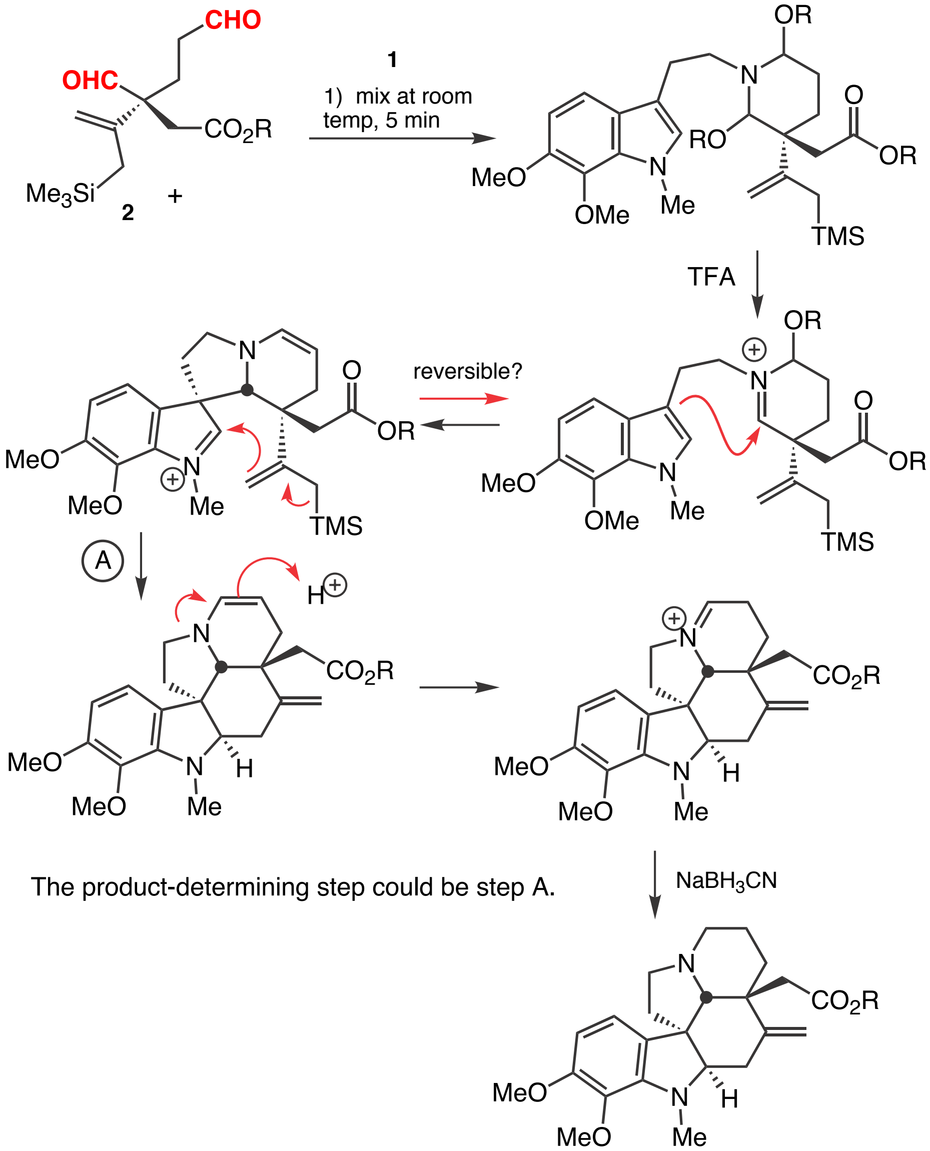
Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Question 13. Final Exam, 1999. During Corey's recent synthesis of Aspidophytine (*JACS*, **1999**, *121*, 6771), the pivotal intermediate **3** was assembled by the union of **1** and **2** under the specified conditions. Provide a mechanism for this single-pot transformation.



D. A. Evans

Monday,
December 8 , 2003



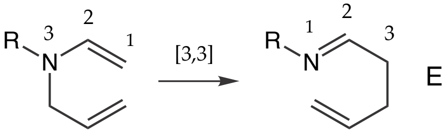
The product-determining step could be step A.

Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

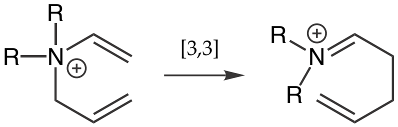
The 3-aza-Cope Rearrangement:

Neutral Variant:



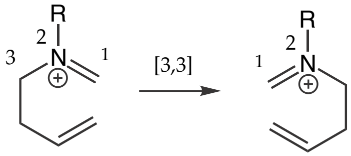
Exothermic as written by ~7-10kcal/mole.

Ammonium Variant:



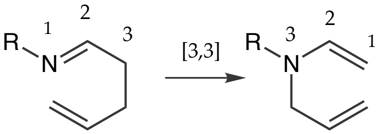
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

2-aza-Cope Rearrangement:



In the simplest case, degenerate. Steric effects, conjugation, or selective trapping of a particular isomer, will drive equilibrium. As with the 3-aza-Cope, the cationic version proceeds under much milder conditions.

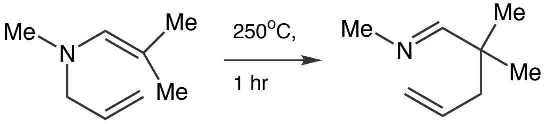
1-aza-Cope Rearrangement:



The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates(i.e., incorporating the imine into a strained ring or by making R an acyl group).

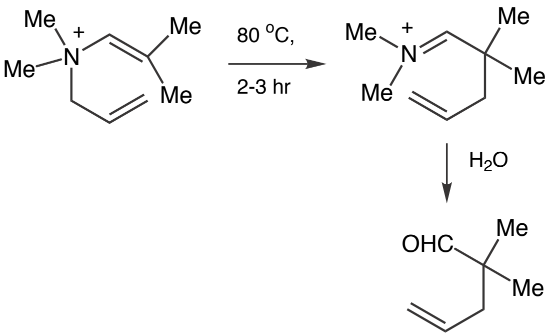
The 3-aza-Cope Rearrangement

First Neutral Case: Hill TL **1967**, 1421.



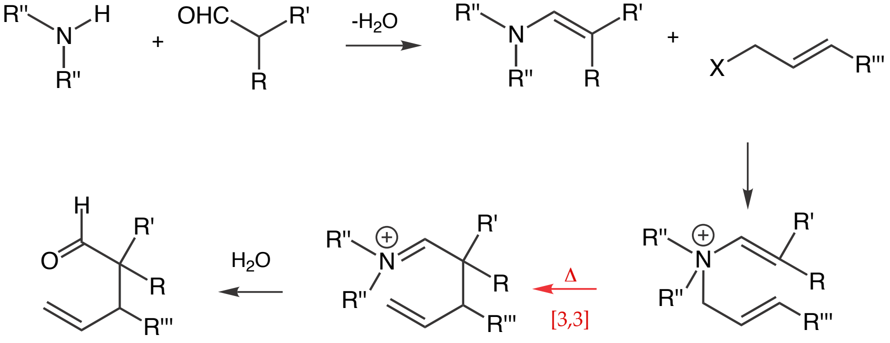
"Practically quantitative", no real yields given.

First Cationic Case: Elkik *Compt. Rend.* **1968**, *267*, 623.



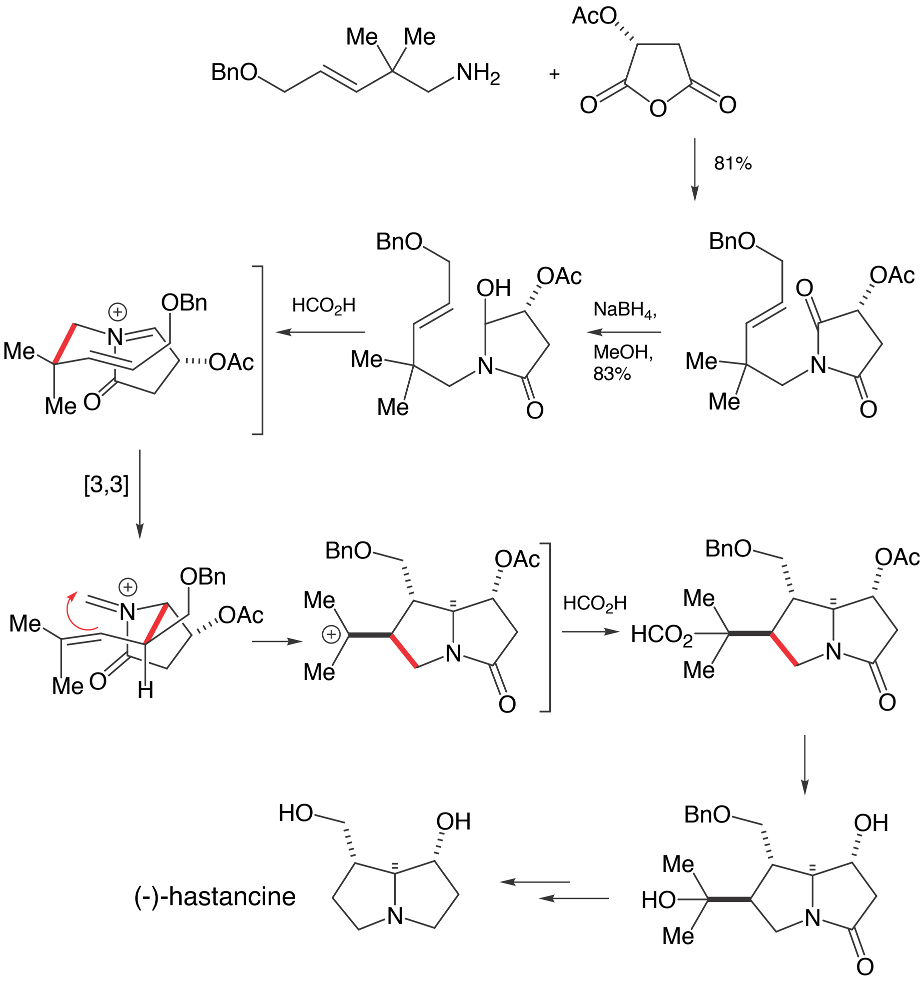
No yields given.

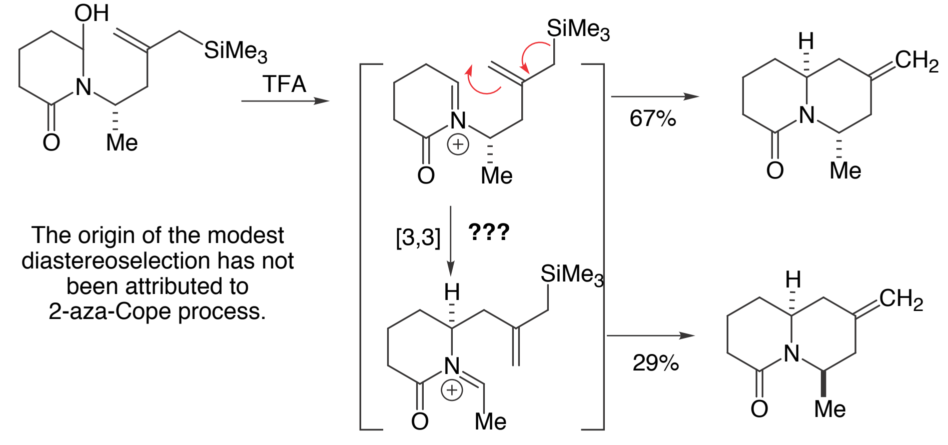
Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, *72*, 169.



N-Acyliminium Ion Rearrangements

*Synthesis of (-)-hastanecine: Hart JOC **1985**, 50, 235.*

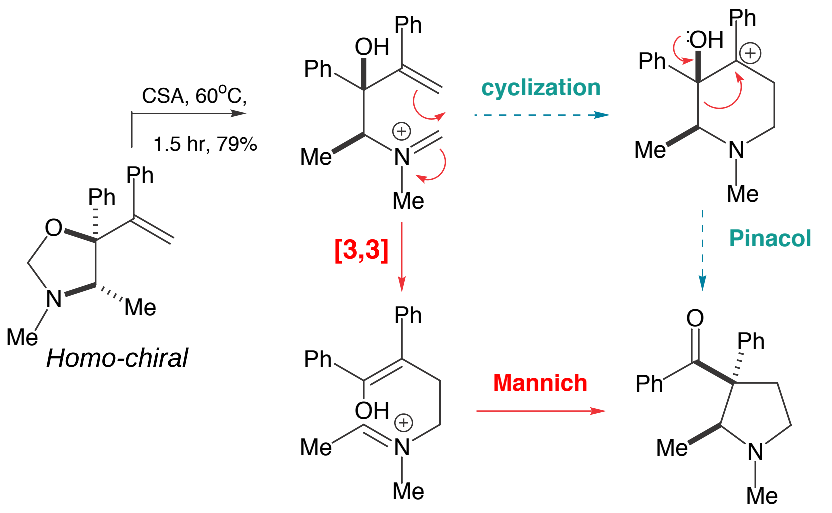




The origin of the modest diastereoselection has not been attributed to 2-aza-Cope process.

Gelas-Mailhe, *Tet. Lett*, **1992**, *33*, 73

Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??

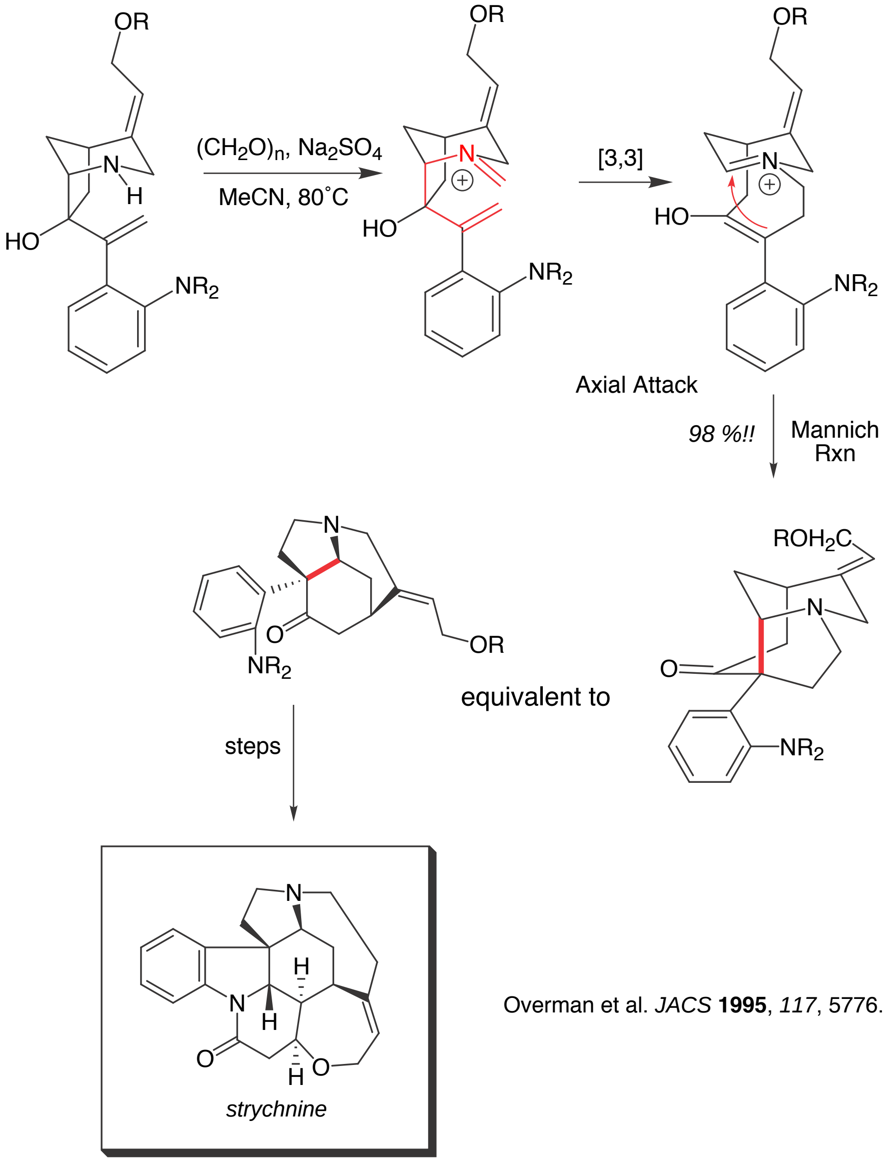


racemic product

Conclusion: 2-aza-Cope rearrangements afford a low-barrier to competing processes

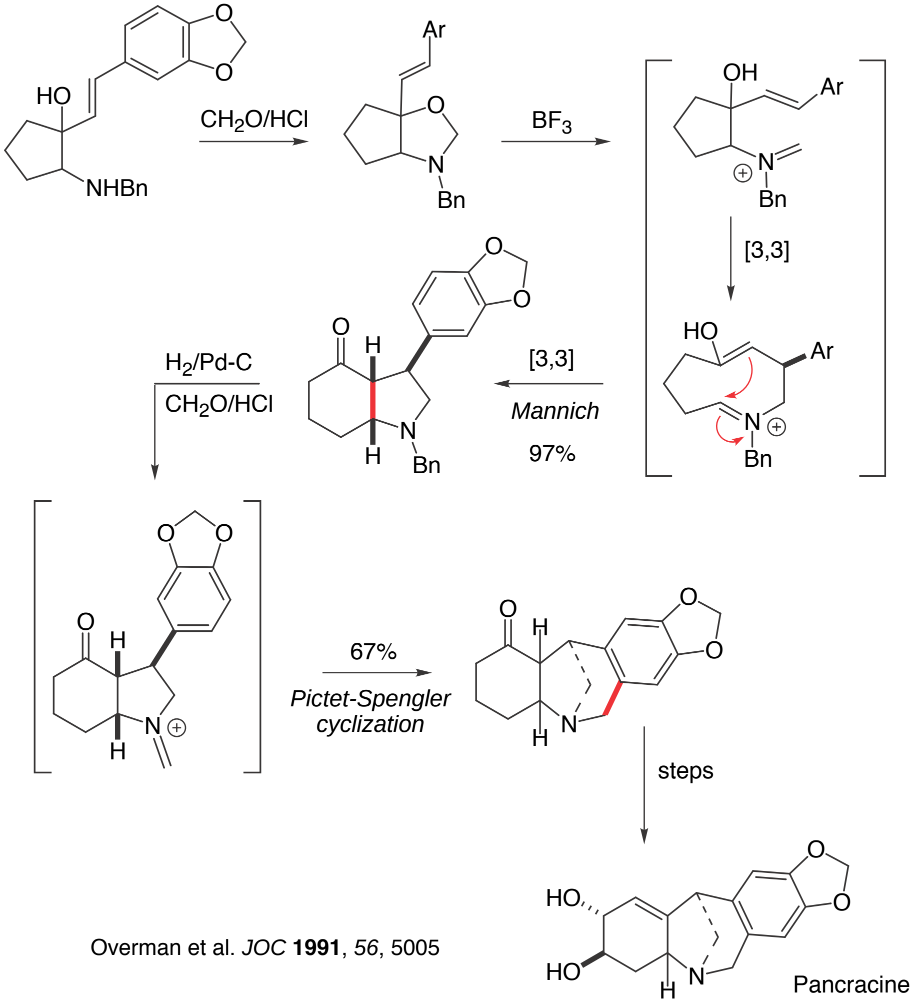
Stabilized Cations: Iminium-Ions 2

2-Aza-Cope-Mannich sequence:



Overman et al. *JACS* **1995**, *117*, 5776.

Another aza-Cope-Mannich sequence:

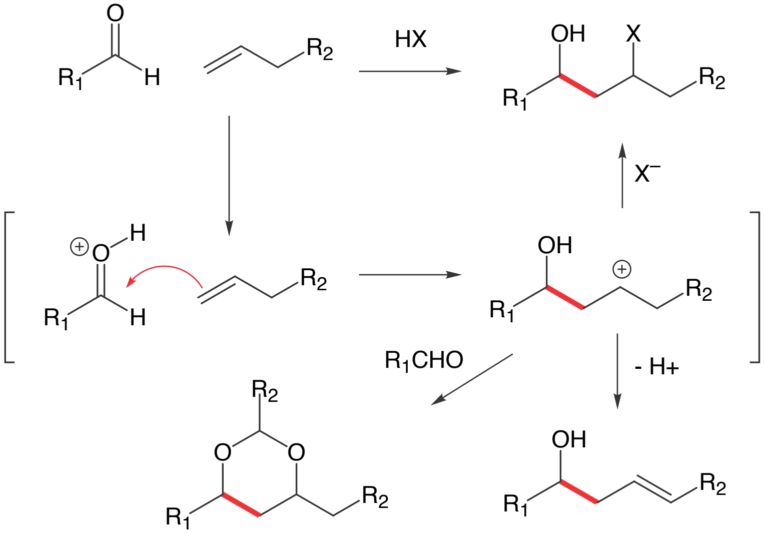


Overman et al. *JOC* **1991**, *56*, 5005

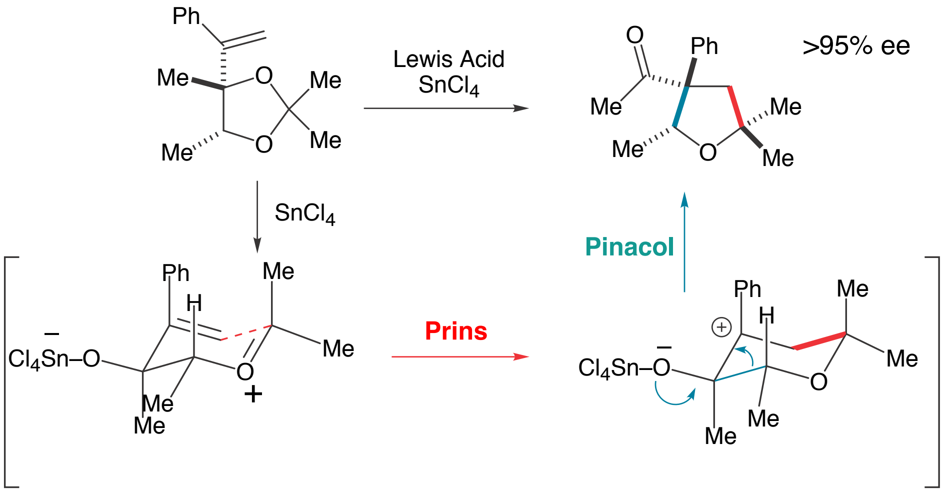
References

Prins reaction: Adams, D.R.; Bhaynagar, S. D. *Synthesis* **1977**, 661
Prins & carbonyl ene reactions: Snider, *Comprehensive Organic Synthesis*, **1991**, *Vol. 2*

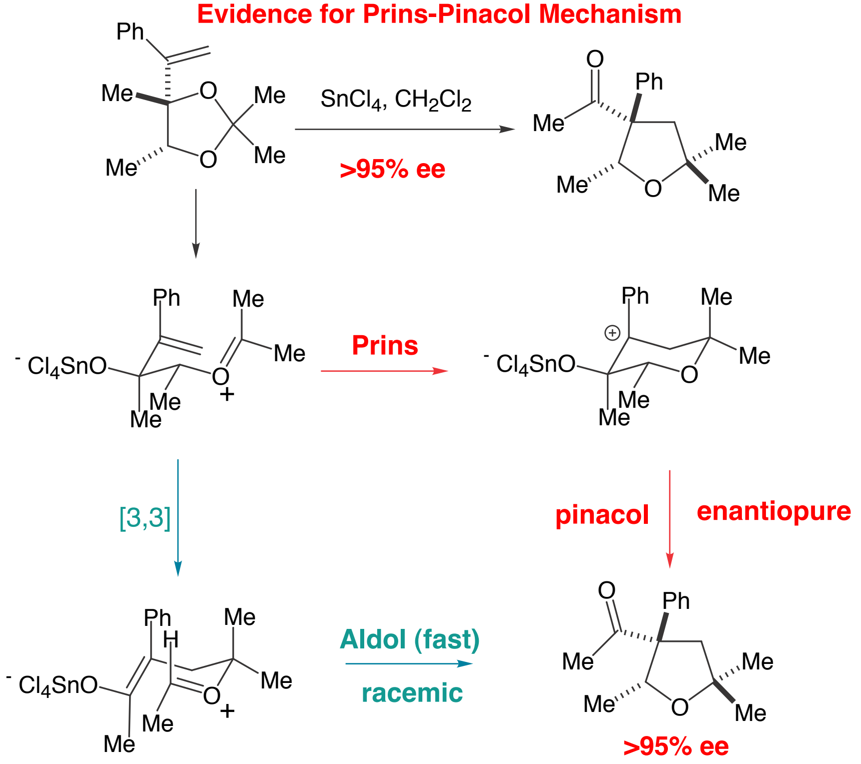
The Prins Process:



The Prins-Pinacol Variant:



Evidence for Prins-Pinacol Mechanism



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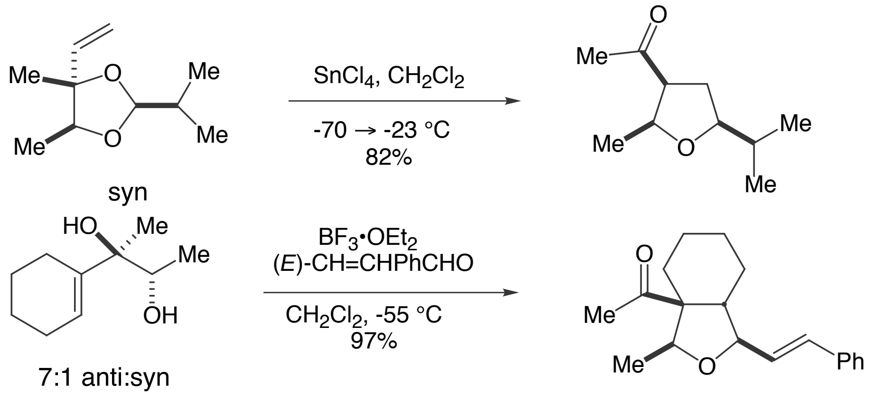
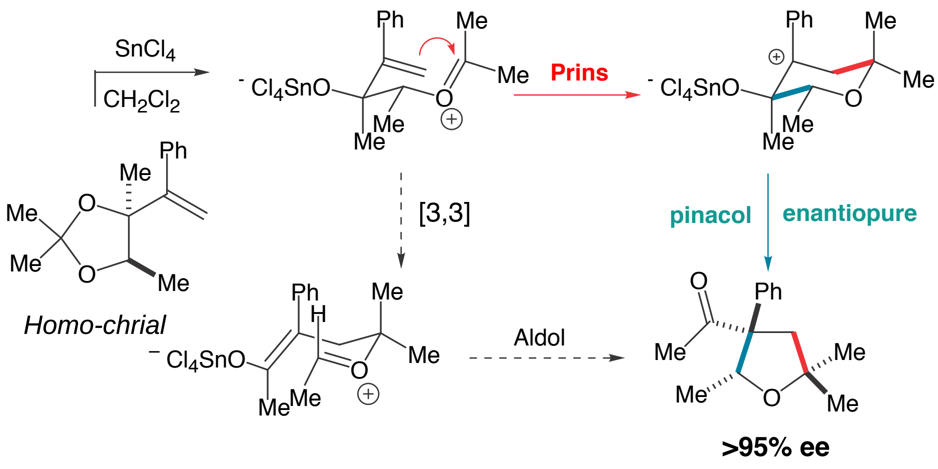
Overman, *JACS* **2000**, *122*, 8672
Overman, *Org Lett* **2001**, *3*, 1225

Examples of Stereoselective THF Formation



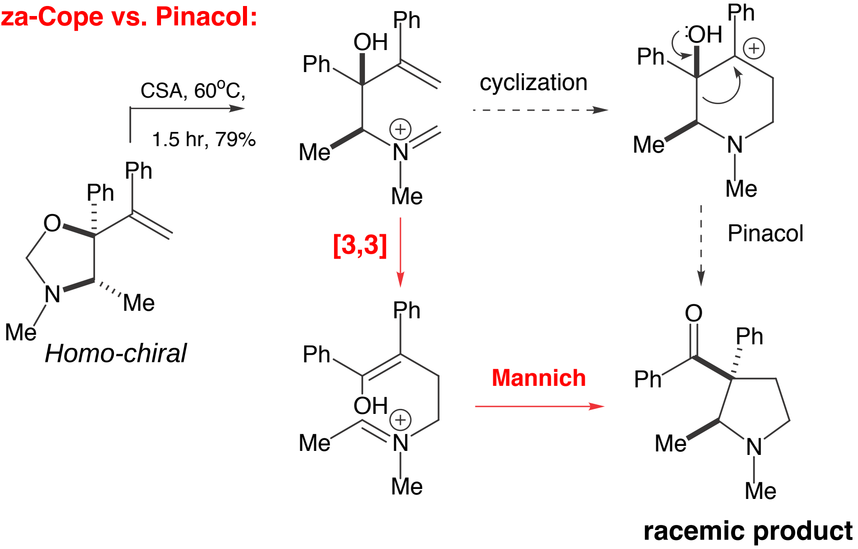
The Prins-Pinacol Reaction

Prins-Pinacol Mechanism



Prins cyclization faster than [3,3] rearrngement

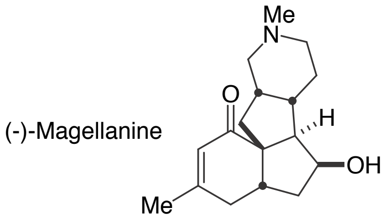
2-aza-Cope vs. Pinacol:



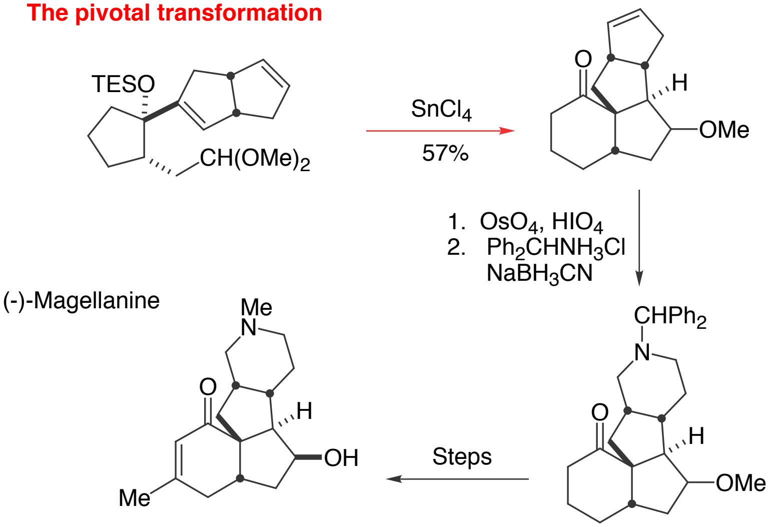
[3,3] rearrngement faster than Mannich cyclization

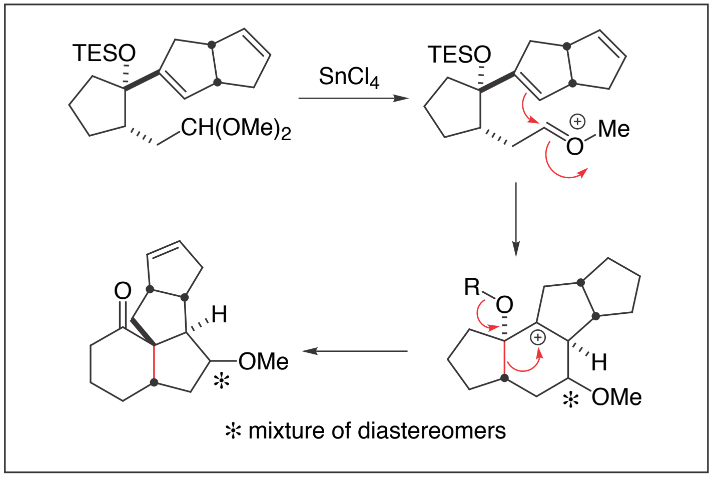
Overman: Magellanine Synthesis

JACS, **1993**, *115*, 2992



The pivotal transformation



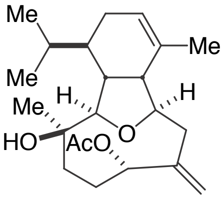


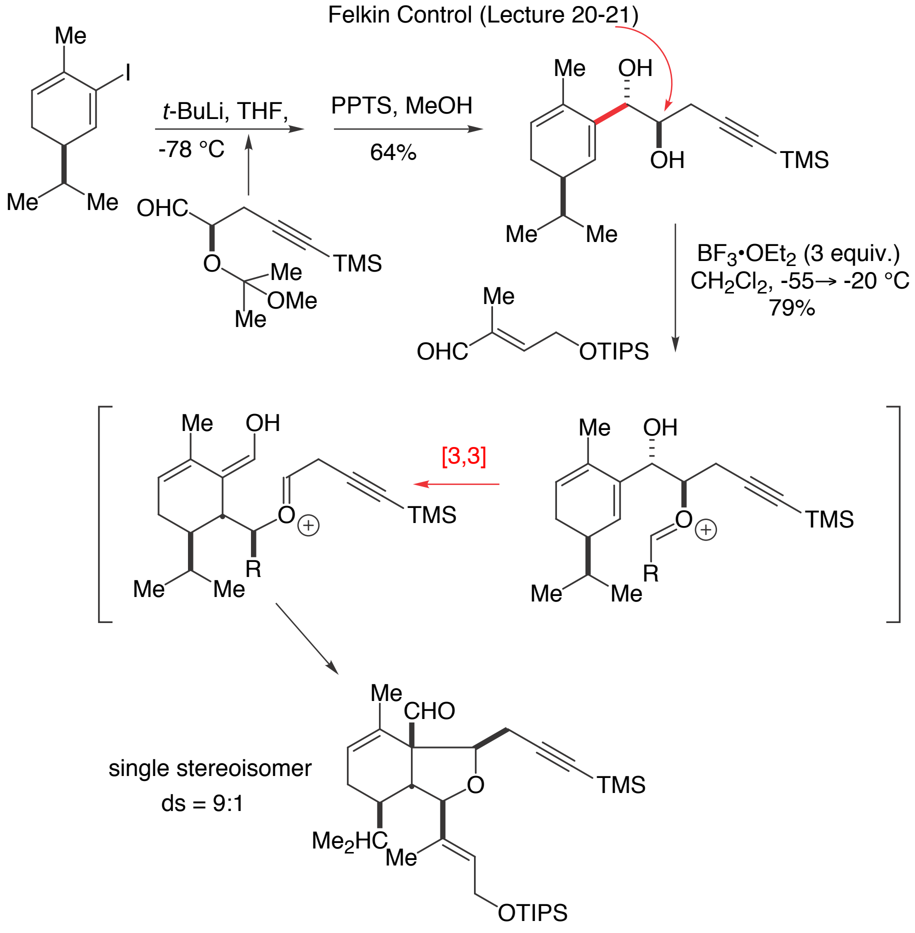
✻ mixture of diastereomers

Overman Synthesis of a Eunicellin Diterpene

Overman & MacMillan JACS, **1995**, *117*, 10391

(-)-7-Deacetoxy-alcyoninacetate





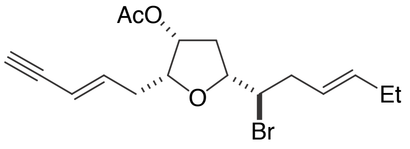
single stereoisomer

ds = 9:1

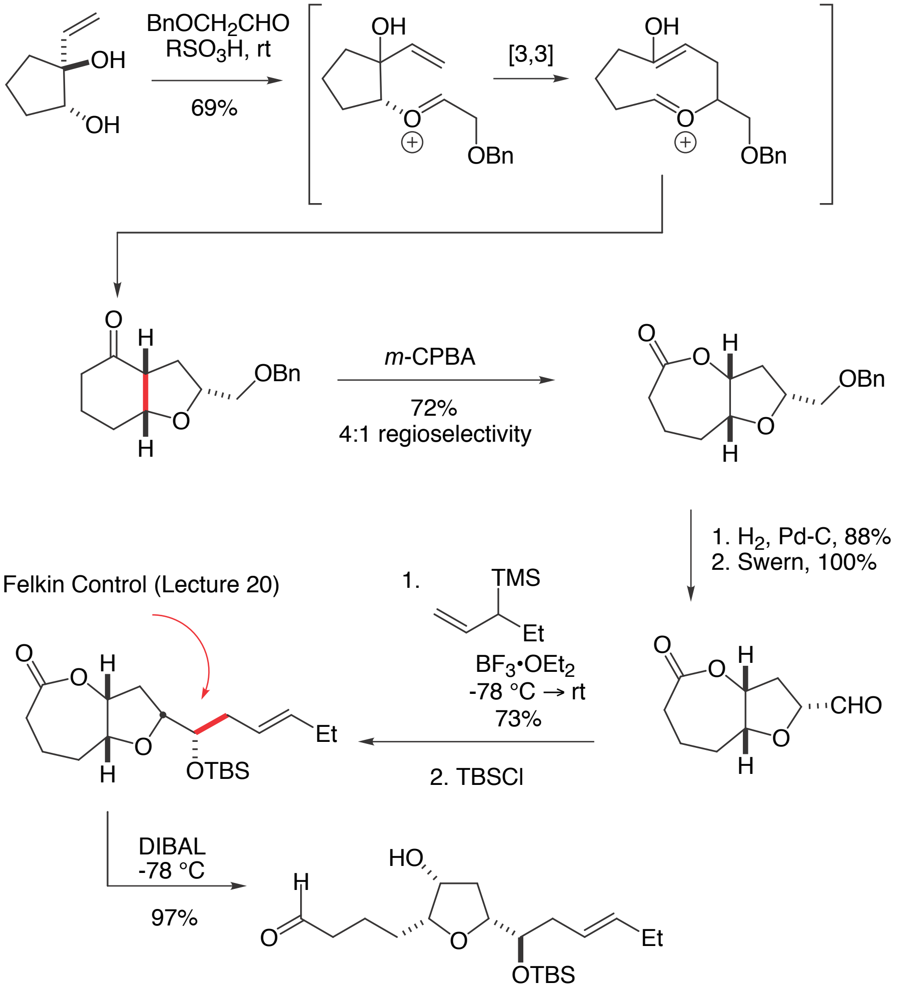
6 steps, 39% yield from (*S*)-carvone

Overman: Synthesis of *trans*-Kumausyne

JACS, **1991**, *113*, 5378



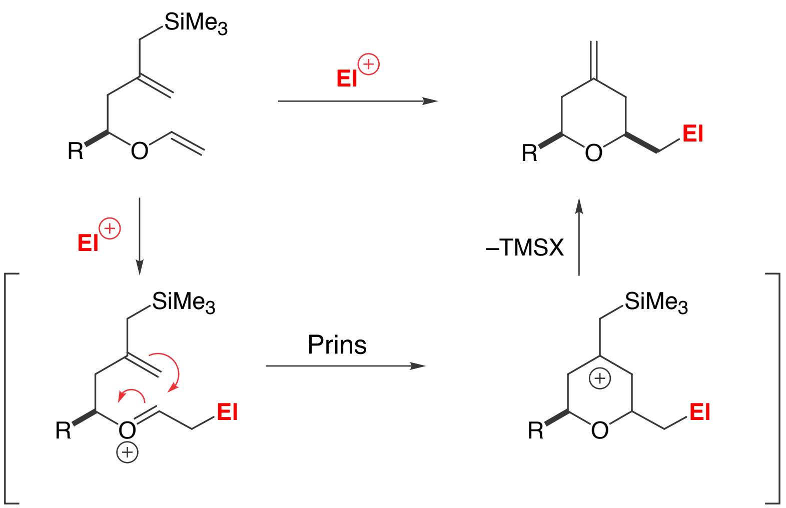
trans-Kumausyne



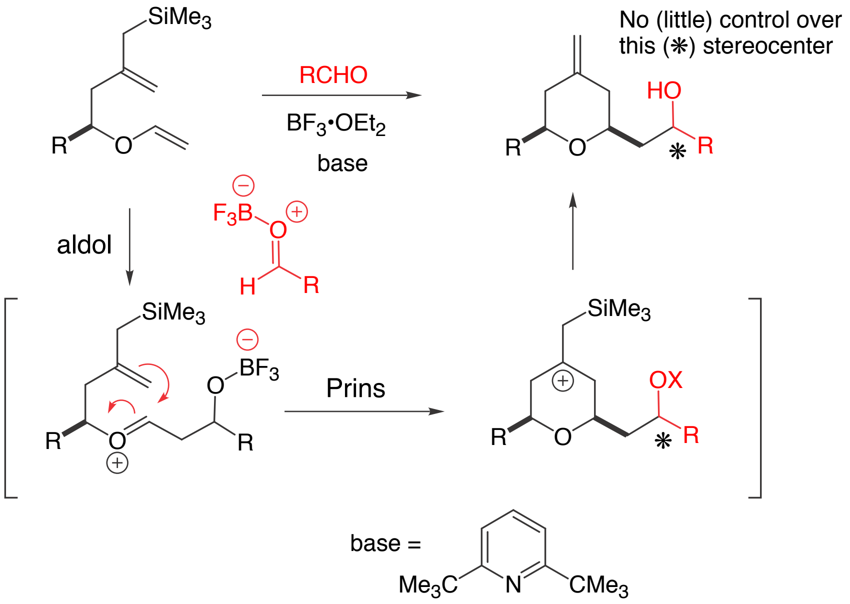
Mukaiyama Aldol–Prins Cascade

Rychnovsky JACS, **2001**, *123*, 8420

The Basic Process

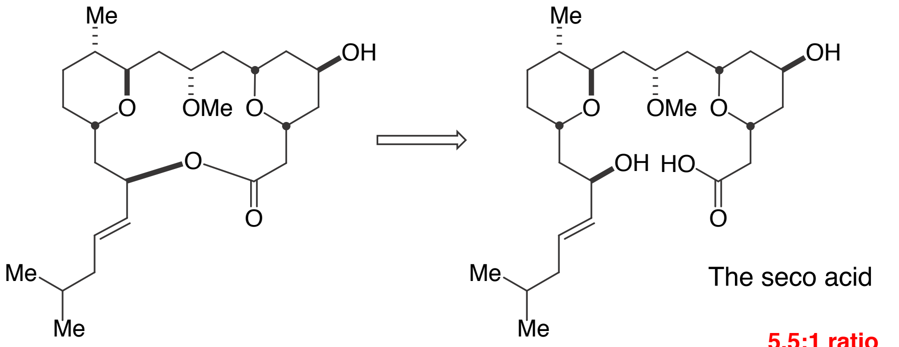


Let El(+) = Lewis acid activated RCHO



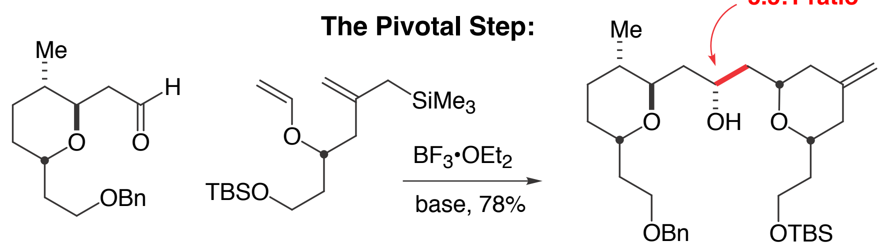
No (little) control over this (✻) stereocenter

Application to Leucasandrolide



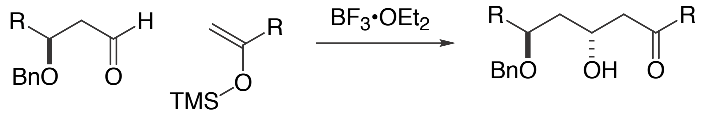
The seco acid

The Pivotal Step:



5.5:1 ratio

Control of hydroxyl center: see Lecture 20-21

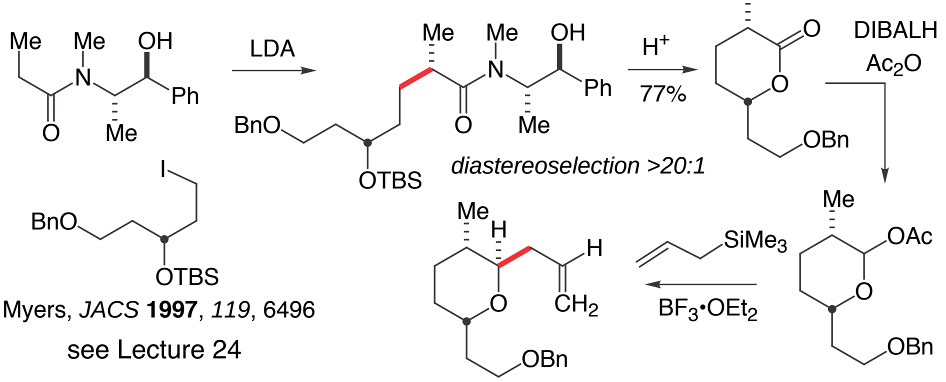


anti selection: ~5–8:1

Evans et al., *JACS* **1996**, *116*, 4322

Aldehyde Synthesis

Chiral enolate alkylation: see Lecture 24



diastereoselection >20:1

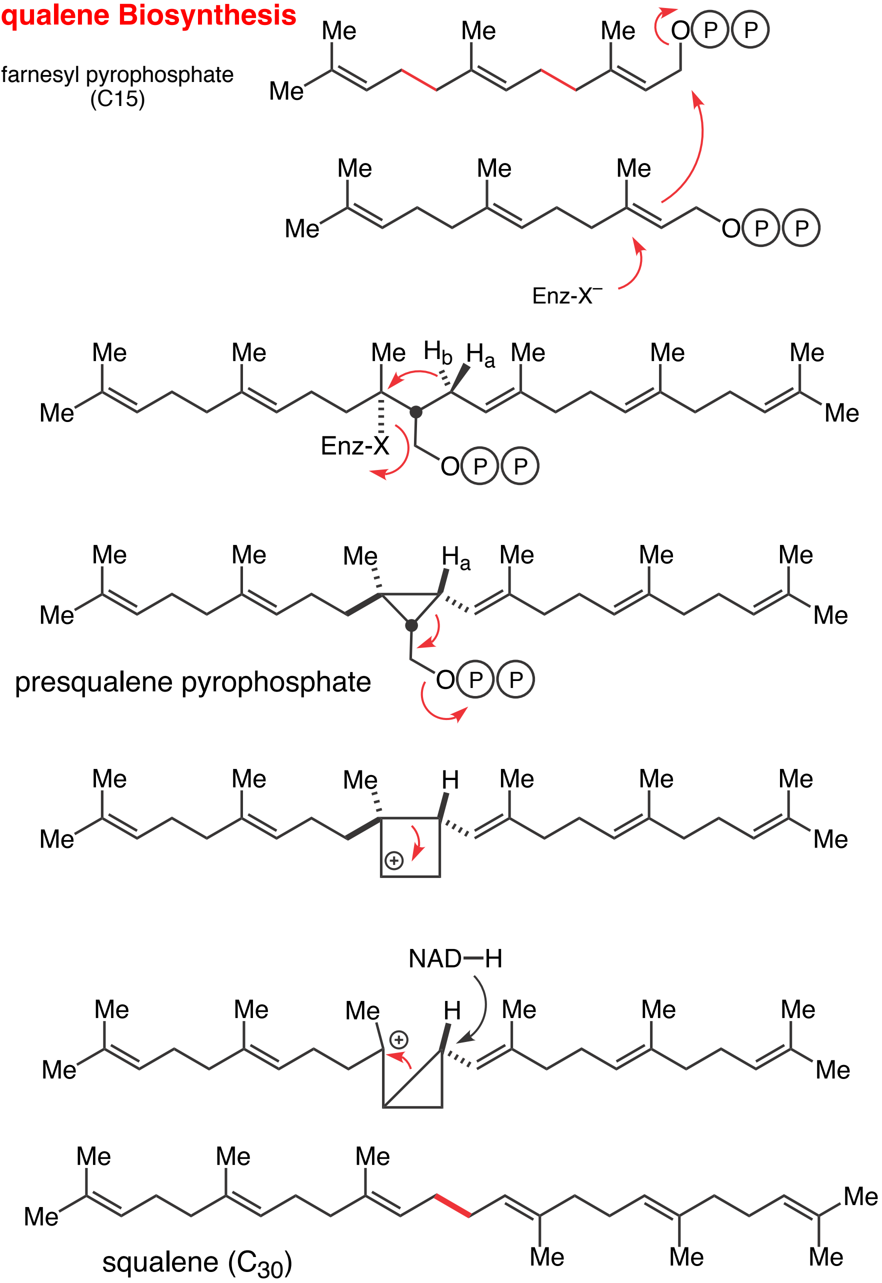
Myers, *JACS* **1997**, *119*, 6496

see Lecture 24

cyclic oxo-carbenium ion addition: see Lecture 20

Squalene Biosynthesis; Squalene Oxide Cyclization

Squalene Biosynthesis


farnesyl pyrophosphate (C15)

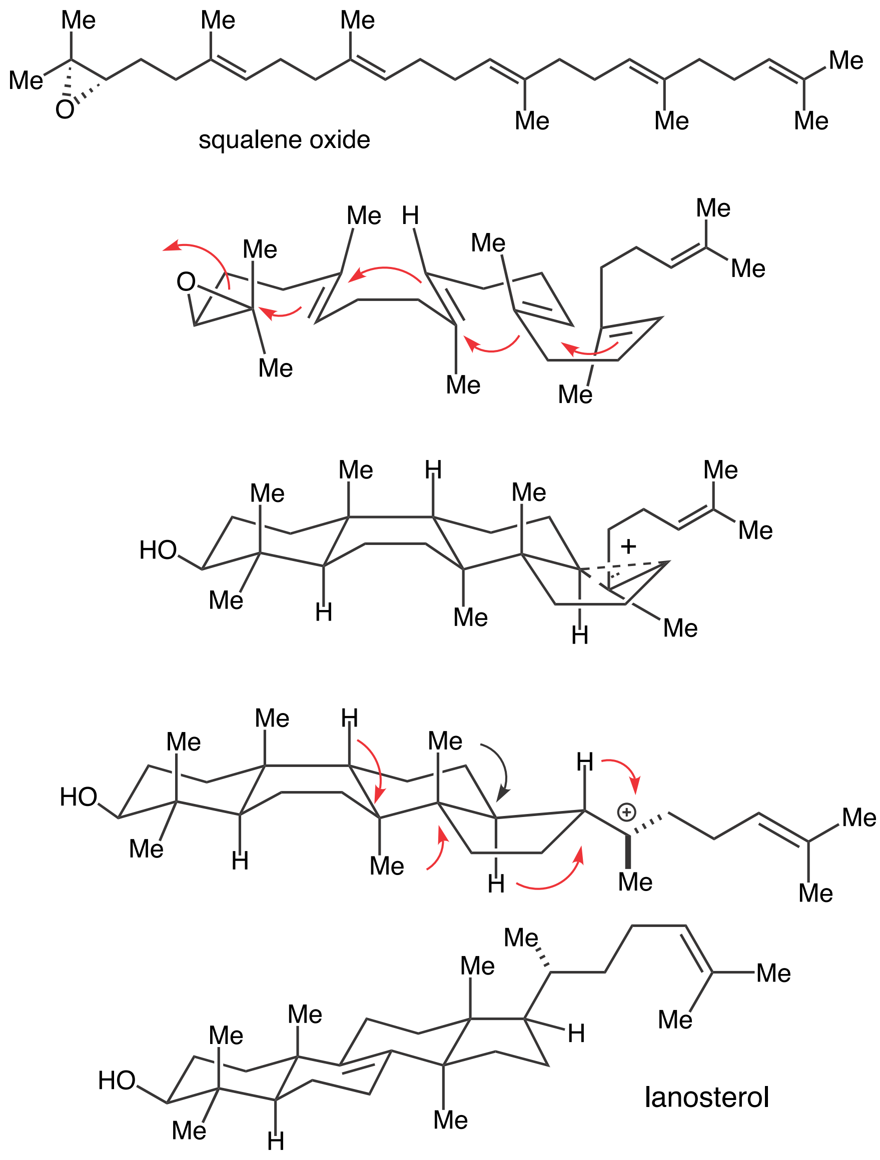
presqualene pyrophosphate

squalene (C_{30})

Squalene Oxide Cyclase

Prestwilch, et. al. *Chem. Rev.* **1993**, *93*, 2189-2206

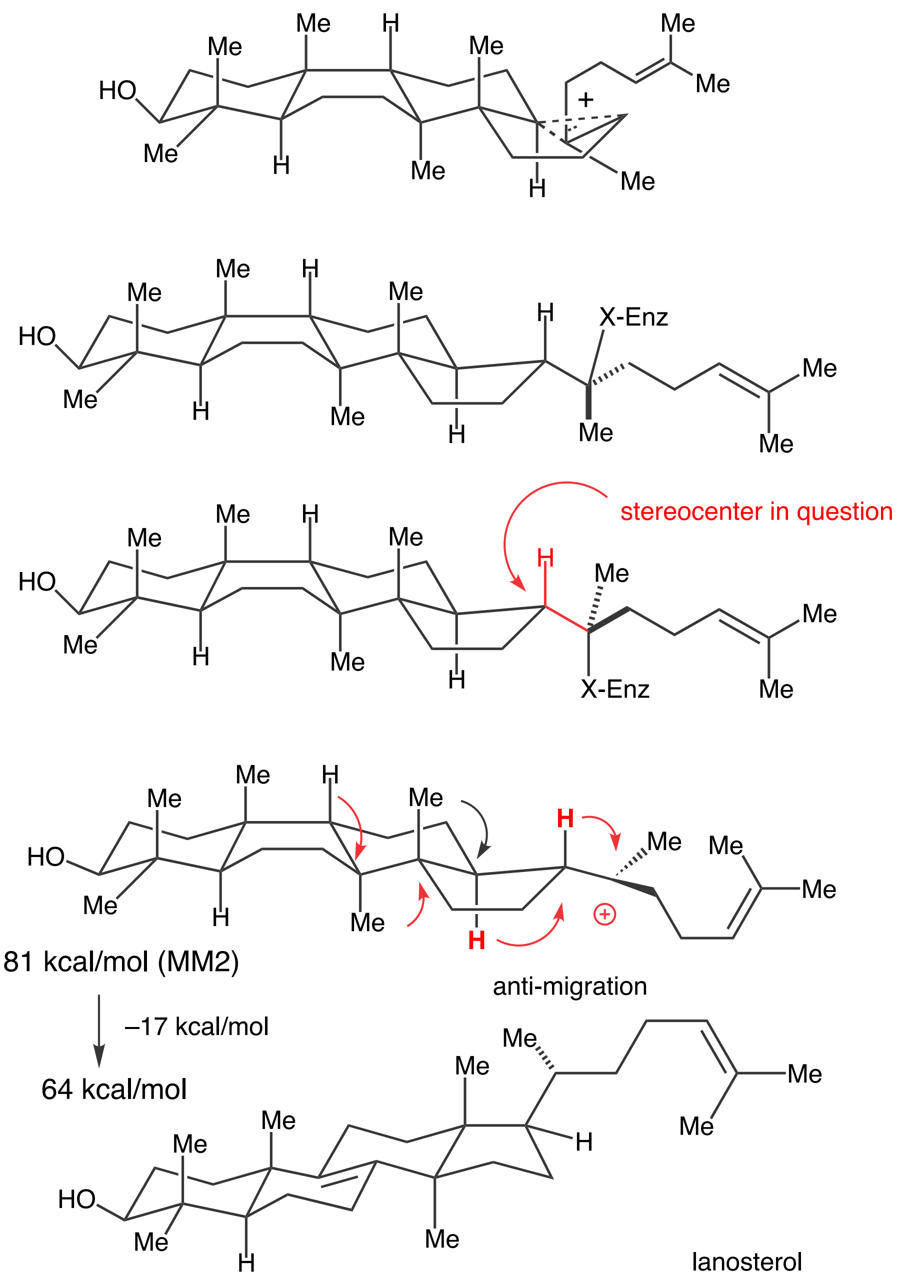
Cornforth Proposal: *ACIEE*, **1968**, 903.


squalene oxide

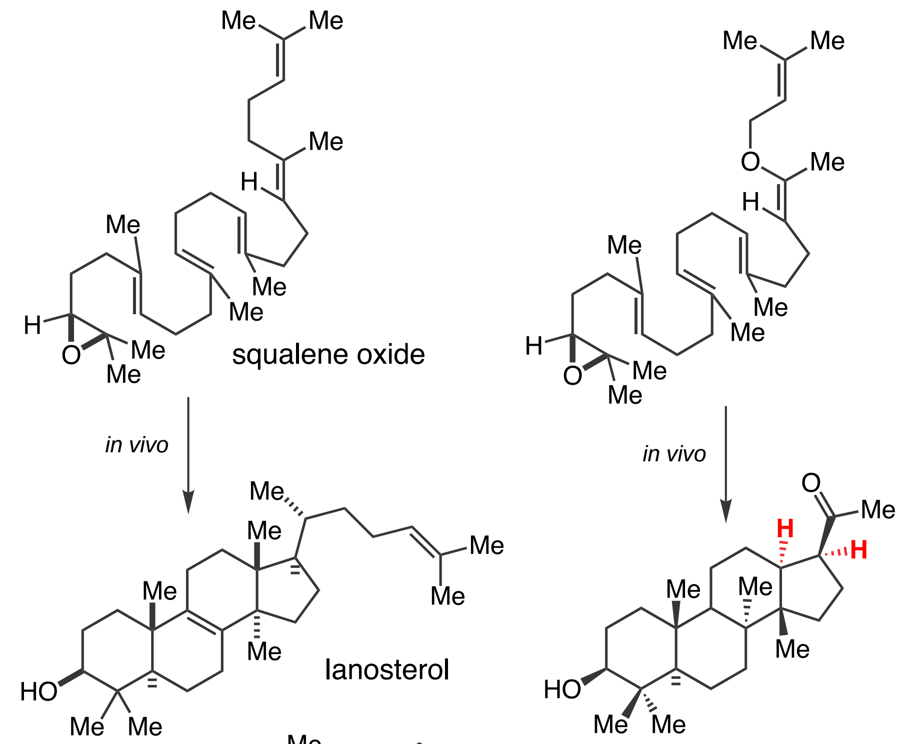
lanosterol

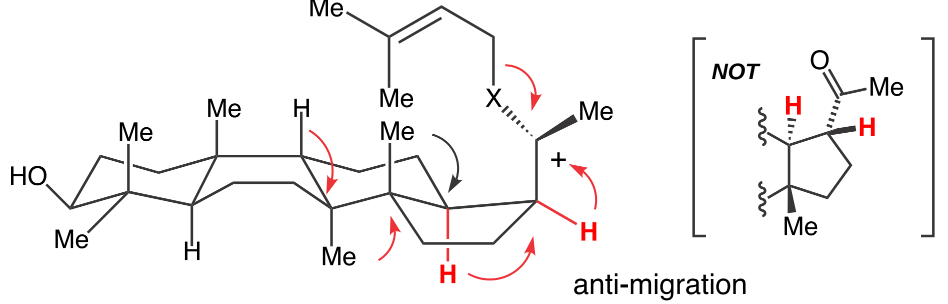
The Corey Addendum to the Cyclization Process

Squalene Oxide Cyclase - Cornforth Proposal: *ACIEE*, **1968**, 903.



Corey–Virgil Revision: *JACS* **1991**, *113*, 4025-4026; 8171-8172





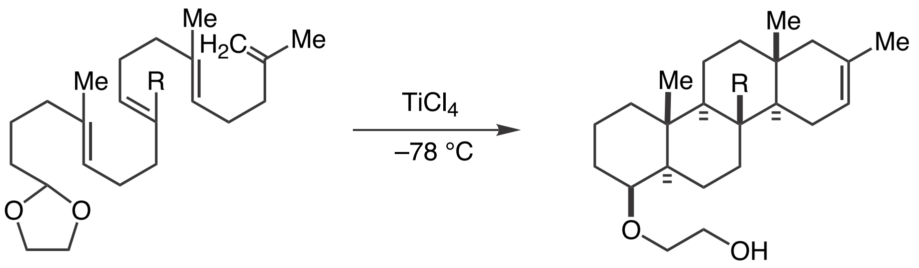
Sir John Cornforth:

"That outpost of empire Australia,
produces some curious mammalia,
the kangaroo rat,
the blood-sucking bat,
and Aurthur J. Birch, inter alia."

If you are anxious for over-exposure,
to prepublication disclosure,
to good food and good drink,
without leisure to think,
try IUPAC symposia."

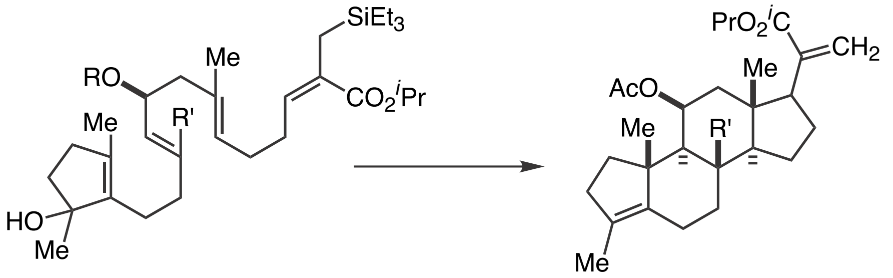
Cationic Cyclizations in the Laboratory

Biomimetic Polyene Cyclizations



Johnson, et al. *JACS* **1987**, *109*, 2517.

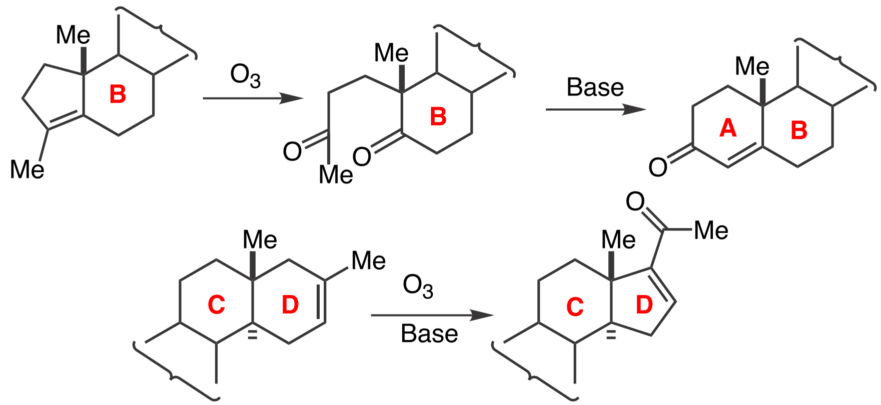
R = H ca. 30%
R = CH=CH$_2$ 77%

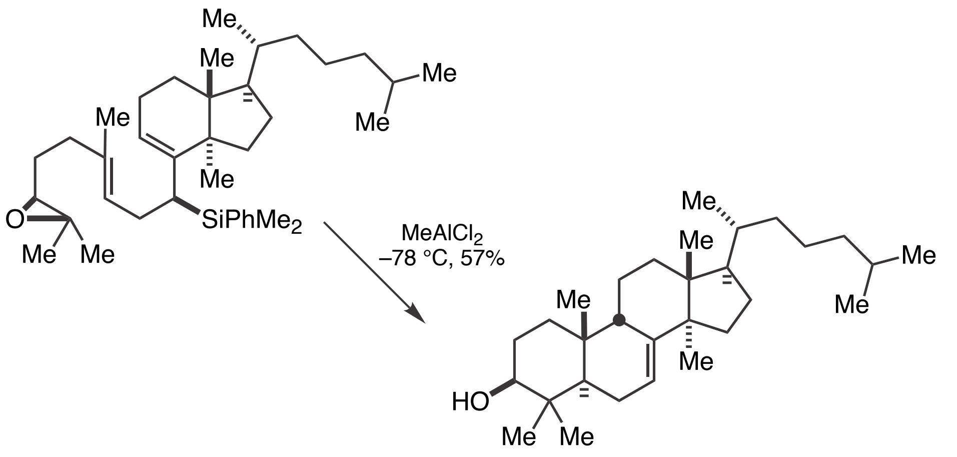


Johnson, et al. *JACS* **1987**, *109*, 5852.

R = OH, R' = H 20%, 24 hr.
R = OAc, R' = CH=CH$_2$ 80%, 1 min.

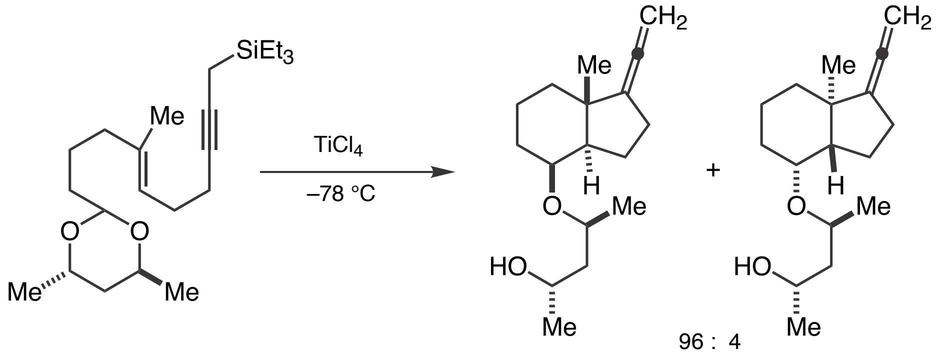
Post cyclization transformation: Johnson





E. J. Corey, et al. *Tetrahedron Lett.* **1994**, *35*, 9149.

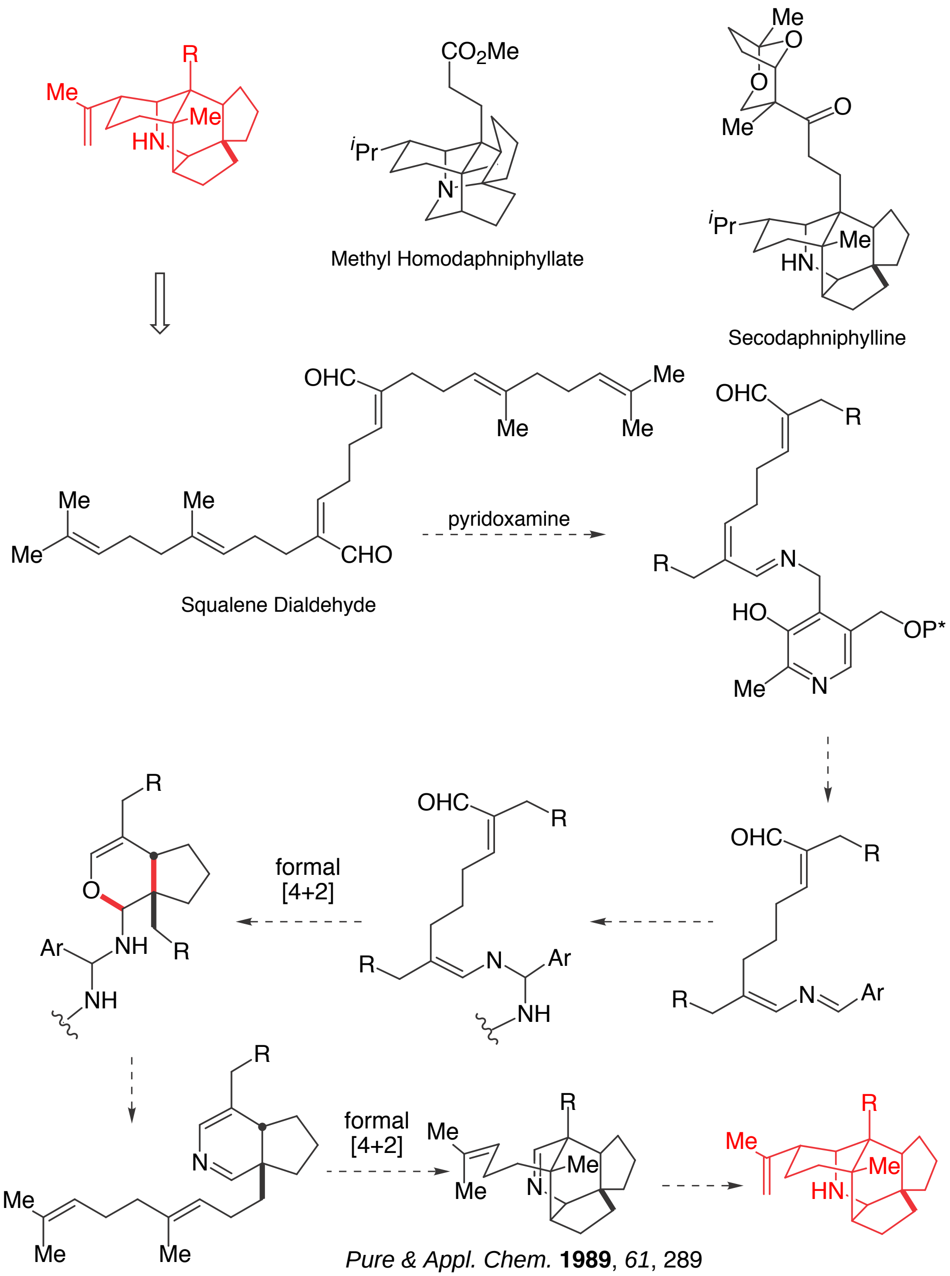
Cyclization to Form Simpler Bicyclics



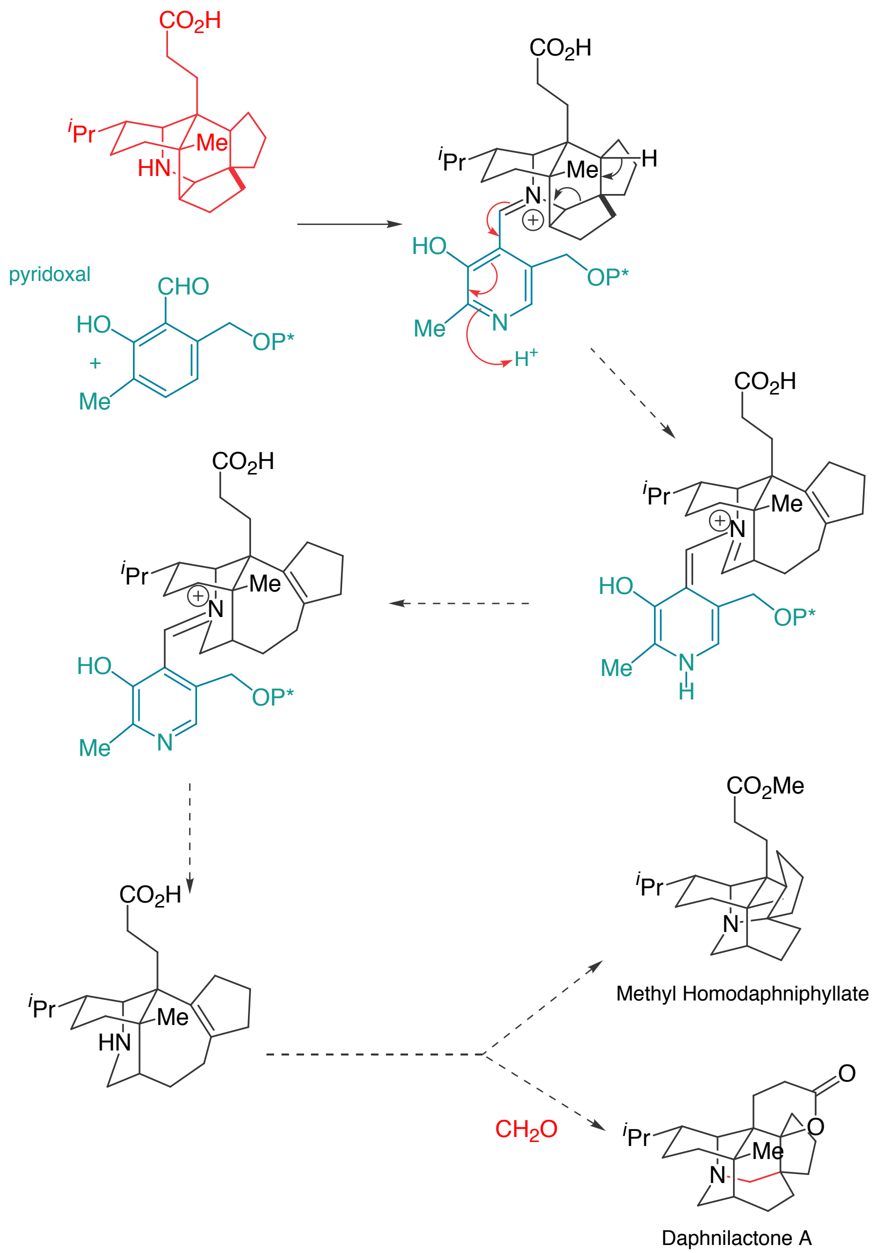
Johnson, et al. *JACS* **1984**, *106*, 1138.

Introduction of chiral auxiliaries for C=O groups

Proposed Biosynthesis of the Daphniphyllum Alkaloids



Pure & Appl. Chem. **1989**, *61*, 289
J. Am. Chem. Soc. **1986**, *108*, 8274



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Handout 33A

Introduction to Carbonium Ions–4

- Stabilized Carbocations: Oxo–Carbenium Ions (C=OR(+))
- Introduction to Terpene Biosynthesis
- Squalene, Lanosterol, & Cholesterol Biosynthesis
- Polyene Cyclizations
- Chiral Acetals as C=O Auxiliaries

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Heathcock, C. H. (1992). “The enchanting alkaloids of Yuzuriha.” Angew. Chem., Int. Ed. Engl. 31: 665. **(handout)**

Other Excellent References

Bartlett, P. A. (**1984**). "Olefin Cyclisation Processes That Form Carbon-Carbon Bonds". *Asymmetric Synthesis. Stereodifferentiating Reactions, Part B.* J. D. Morrison. New York, AP. vol 3: 341.

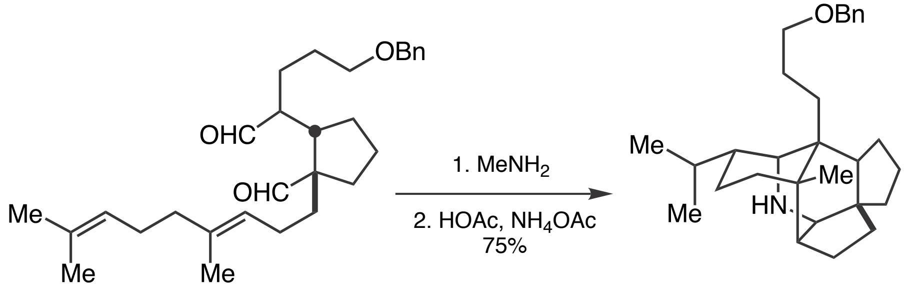
Thebtaranonth, C. and Y. Thebtaranonth (1994). "Cyclization Reactions". Boca Raton, FL, CRC Press.

Corey & Liu, enzyme "Mechanism for Polycyclic Triterpene Formation," *Angew. Chem. Int Ed*. **2000**, *39*, 2812-2833

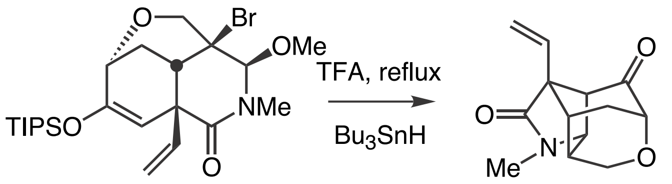
D. A. Evans

Monday,
December 8 , 2003

Several Comp[ex Mechanisms



Angew. Chem. Int. Ed. Engl. **1978**, *17*, 476.
J. Org. Chem. **1990**, *57*, 2544.



A. P. Johnson *et al.*, *JCS Chem. Commun.* **1994**, *6*, 765

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and Aurthur J. Birch, inter alia."

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If you are anxious for over-exposure,
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to good food and good drink,
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Terpene Biosynthesis

Suggested Reading

"An Experimental Demonstration of the Stereochemistry of Enzymic Cyclization of 2,3-Oxidosqualene...."
E. J. Corey, S. C. Virgil *JACS*, **1991**, *113*, 4025.

"New Mechanistic and Stereochemical Insights on the Biosynthesis of Sterols from 2,3-Oxidosqualene Cyclase"
E. J. Corey, et al. *JACS* **1991**, *113*, 8171.

"Enzymatic Cyclization of Squalene and Oxidosqualene to Sterols and Terpenoids" Abe, et al. *Chem. Rev.* **1993**, *93*, 2189.

"Isoprenoid Biosynthesis. Stereochemistry of the Cyclization of Allylic Pyrophosphates." D. E. Cane *Acc. Chem. Res.* **1985**, *18*, 220.

"Biomimetic Polyene Cyclizations"
W. S. Johnson *Angew. Chem. Int. Ed. Engl,* **1976**, *15*, 9.

Interesting Reading

Science, **1997**, v277:
"Structure and Function of the Squalene Cyclase", G. Shultz, p. 1811.

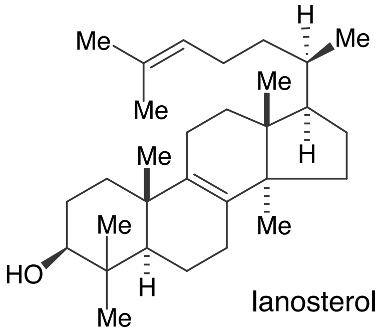
"Structural Basis for Cyclic Terpene Biosynthesis by Tobacco 5-epi-Aristolochene", J. P. Noel, p. 1815.

"Crystal Structure of Pentalene Synthase: Mechanistic Insights on Terpenoid Cyclization Reactions in Biology", D. W. Christianson, p. 1821.

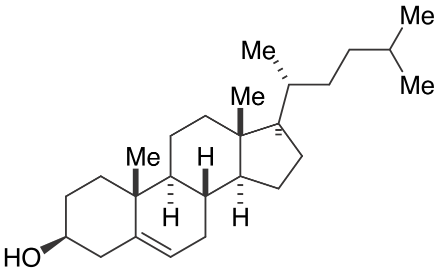
"The Stereochemistry of Allylic Pyrophosphate Metabolism."
D. E. Cane *Chem. Rev.* **1980**, *36*, 1109.

"Biosynthesis of Natural Products" P. Manitto; Wiley&Sons, NY: 1981.

Representative Terpenes

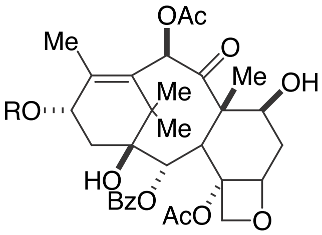


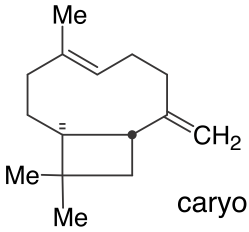
lanosterol



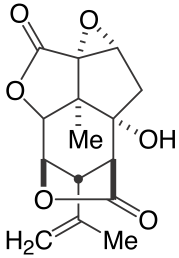
cholesterol

taxol

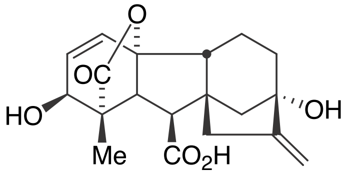




caryophyllene



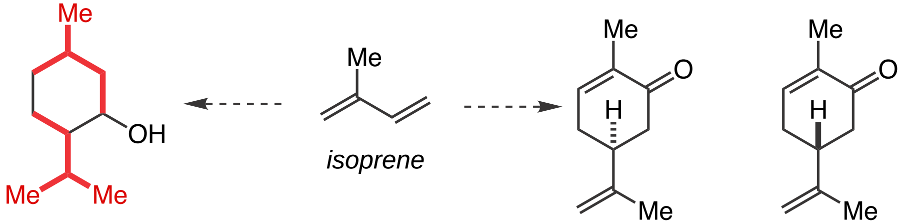
picrotoxinin



gibberellic acid

Terpenes: Occurance in Nature

- Definition: Natural products whose carbon skeletons are built up largely from isoprene subunits:



menthol

isoprene

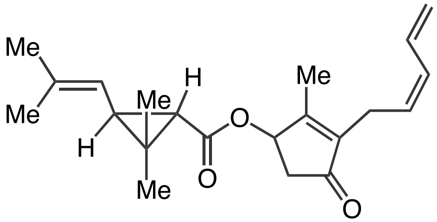
(S)-carvone
caraway

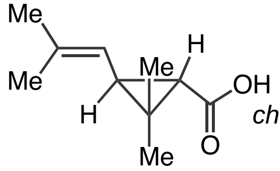
(R)-carvone
spearmint

- Occurance: Plants, insects, higher organisms

- Role in plants: hormones, defense etc.

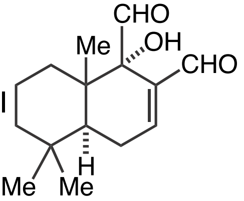
example: pyrethrin insecticides



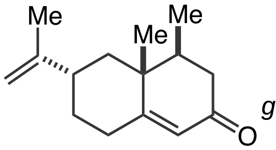


chrysanthemic acid

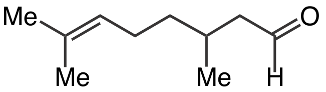
example: antifeedants such as warburganal



example: flavor constituents

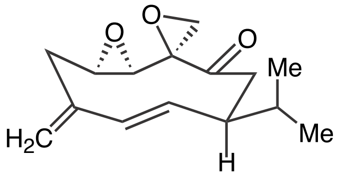


nootkatone
grapefruit flavor

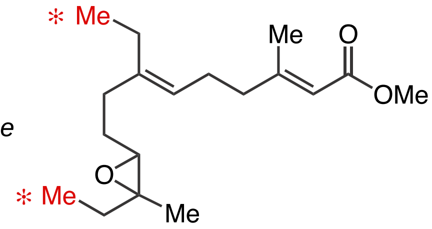


citronellal
lemon oil

- Role in insects: hormones, pheromones (communication chemicals)

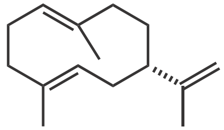


periplanone
sex attractant pheromone of the
American cockroach



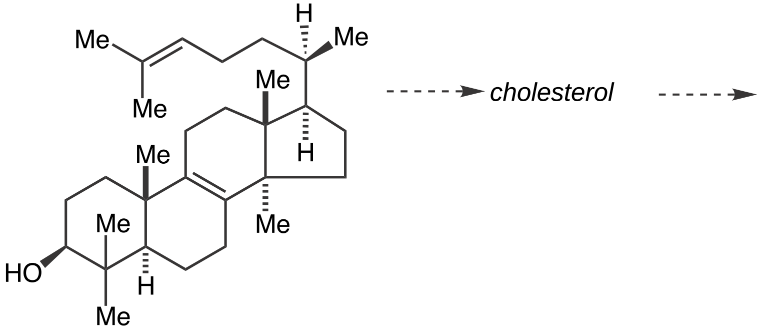
Cecropia junenile hormone
blocks development at larval growth stage

note that the starred methyls are
not derived from isoprene



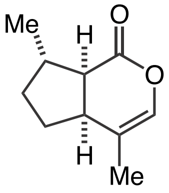
alarm pheromone for aphids

- Role in mammals: hormones, pheromones ??



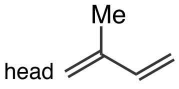
cholesterol

steroid hormones



nepetalactone
oil of catnip
active at nanomolar-femptomolar concentrations
is this related to a feline pheromone?

Isoprene : Building Block of Nature (2)

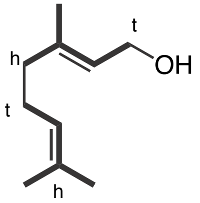


2-methyl-1,3-butadiene
isoprene

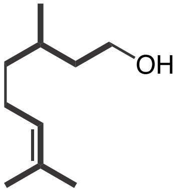
Classification of terpenes

monoterpenes : 10 C-atoms (2 isoprene units)
sesquiterpenes : 15 C-atoms (3 isoprene units)

diterpenes : 20 C-atoms (4 isoprene units)
triterpenes : 30 C-atoms (6 isoprene units)

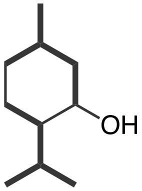


geraniol

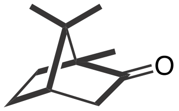


citronellol

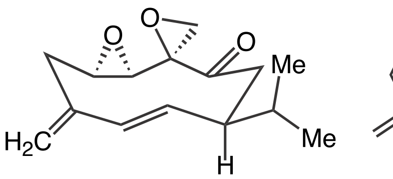
two components in rose oil



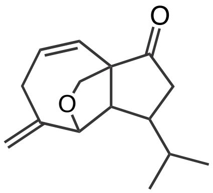
menthol

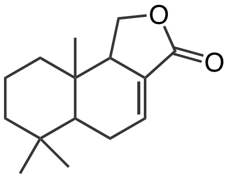


camphor

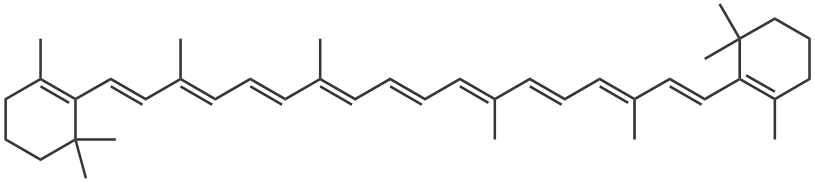


sex attractant pheromone of the American cockroach

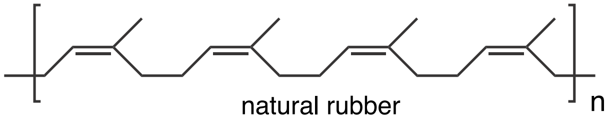




cinnamolide
antifungicide



ß-carotene

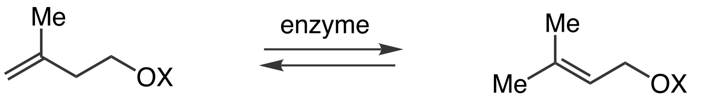


natural rubber

Practice: Recognize the isoprene units in the above structures.

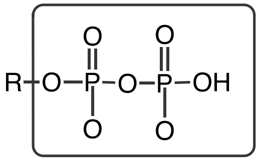
Terpene Biosynthesis

There are two isoprene units which are used to build up terpenes:

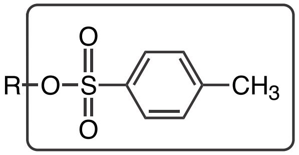


isopentenyl pyrophosphate (IPP)

γ,γ-dimethylallyl pyrophosphate (DMAP)



≡ ROX

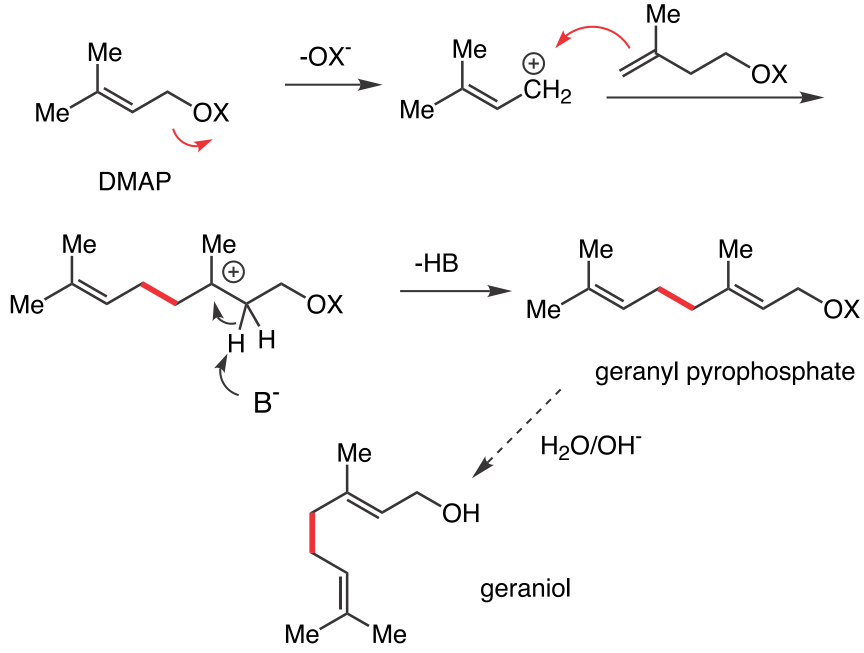


≡ ROTs

pyrophosphate:
nature's leaving group

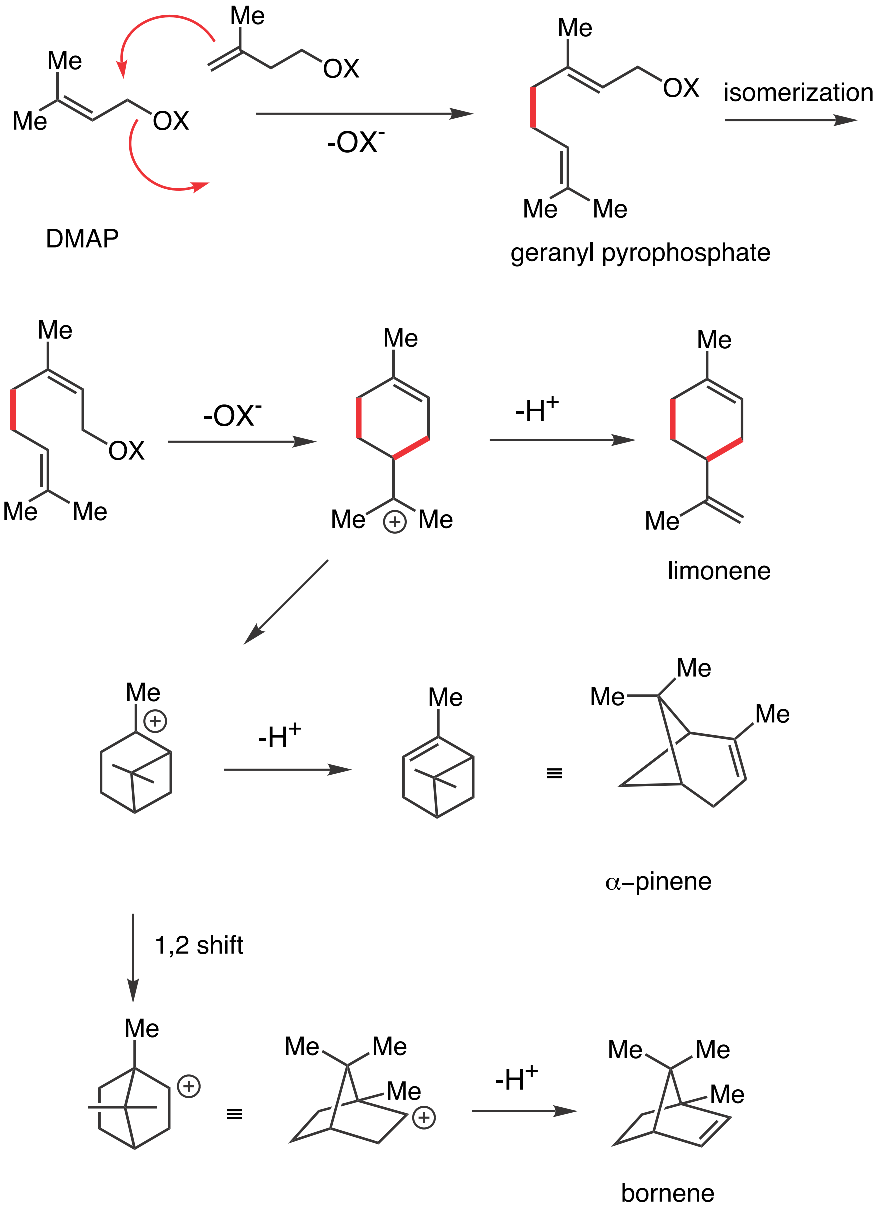
tosylate:
chemist's leaving group

The basic process: alkene addition to electrophiles:

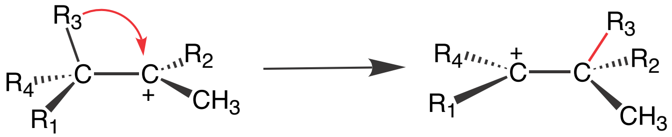


Isoprene : Building Block of Nature (3)

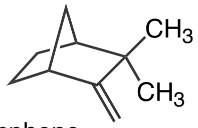
From isoprene to α–pinene and bornene



The Basic Process: 1-2 rearrangement

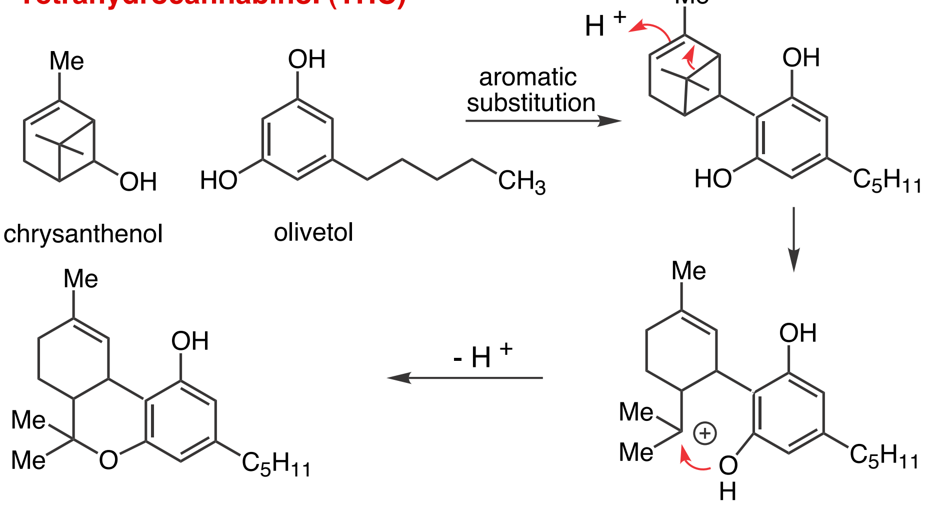


The precursor of bornene could also lead to camphene.
Show the mechanism!

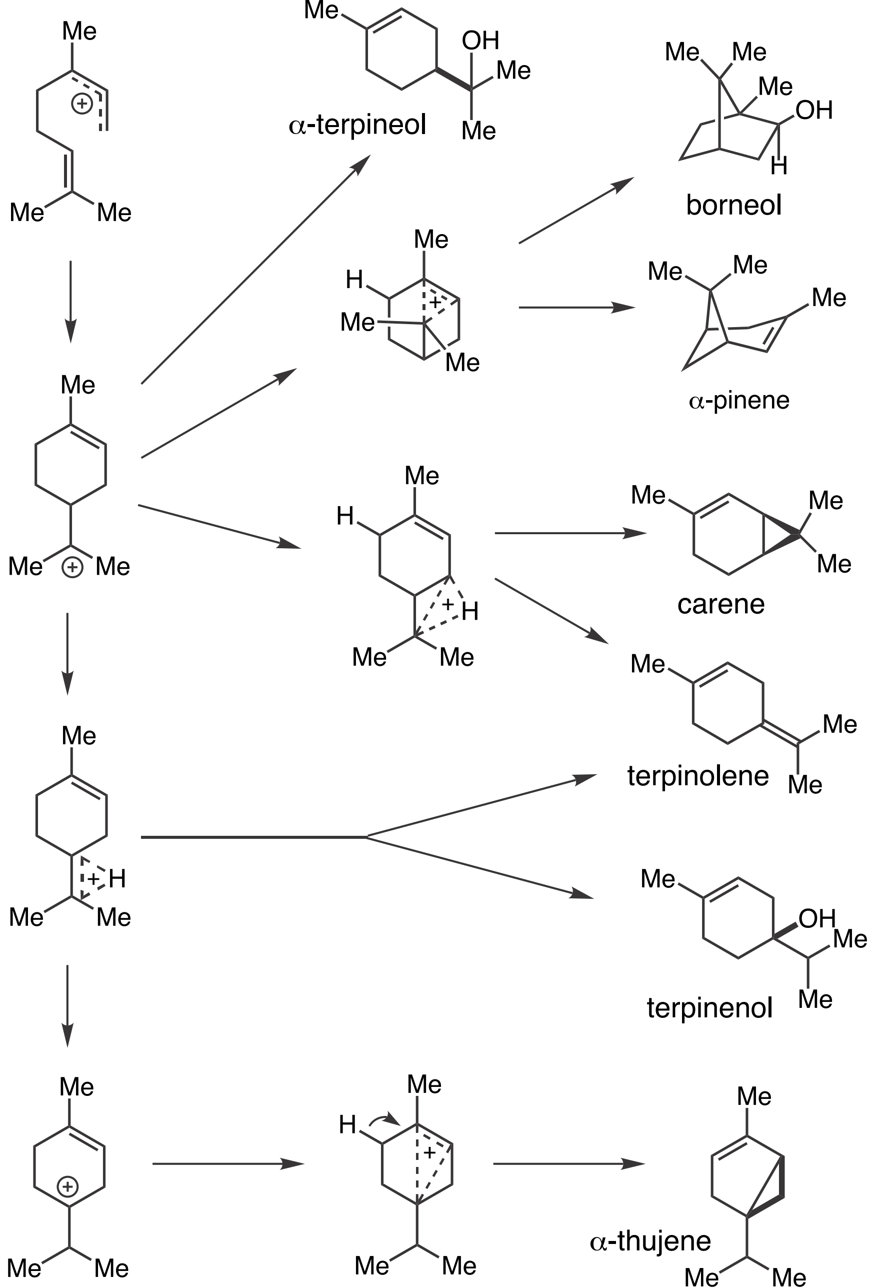


camphene

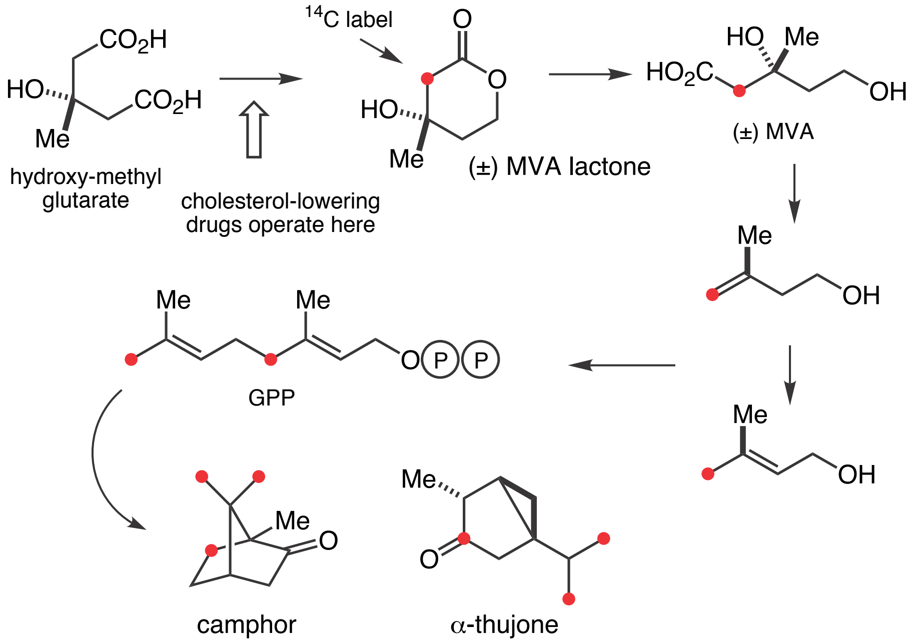
Tetrahydrocannabinol (THC)



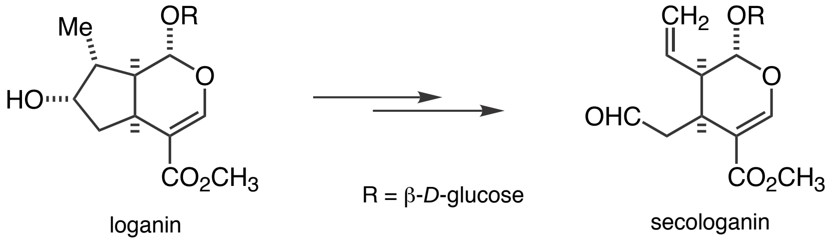
Cyclic Monoterpenes



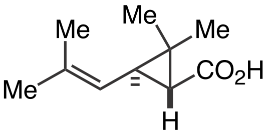
Biosynthetic Study of Monoterpenes



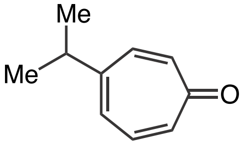
Iridoids and Secoiridoids



Irregular Monoterpenoids

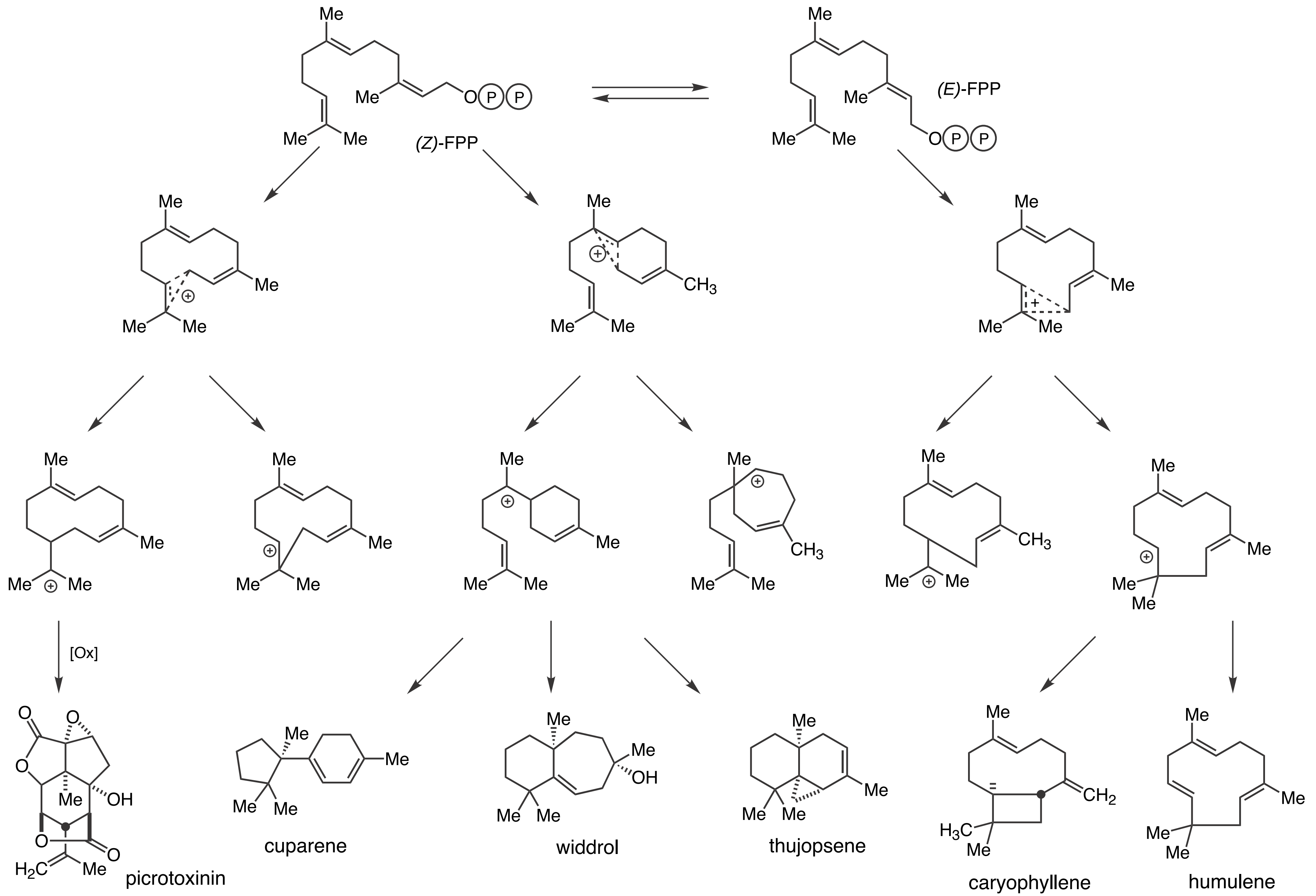


chrysanthemic acid



nezukone

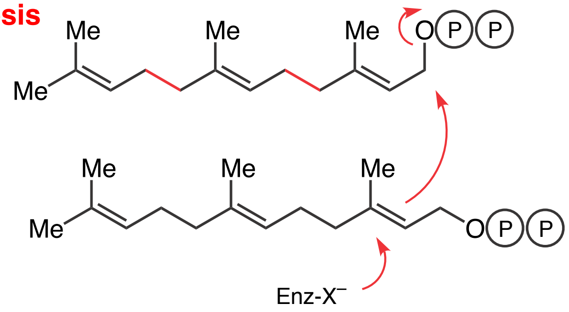
Sesquiterpenes–C$_{15}$ Terpenoids

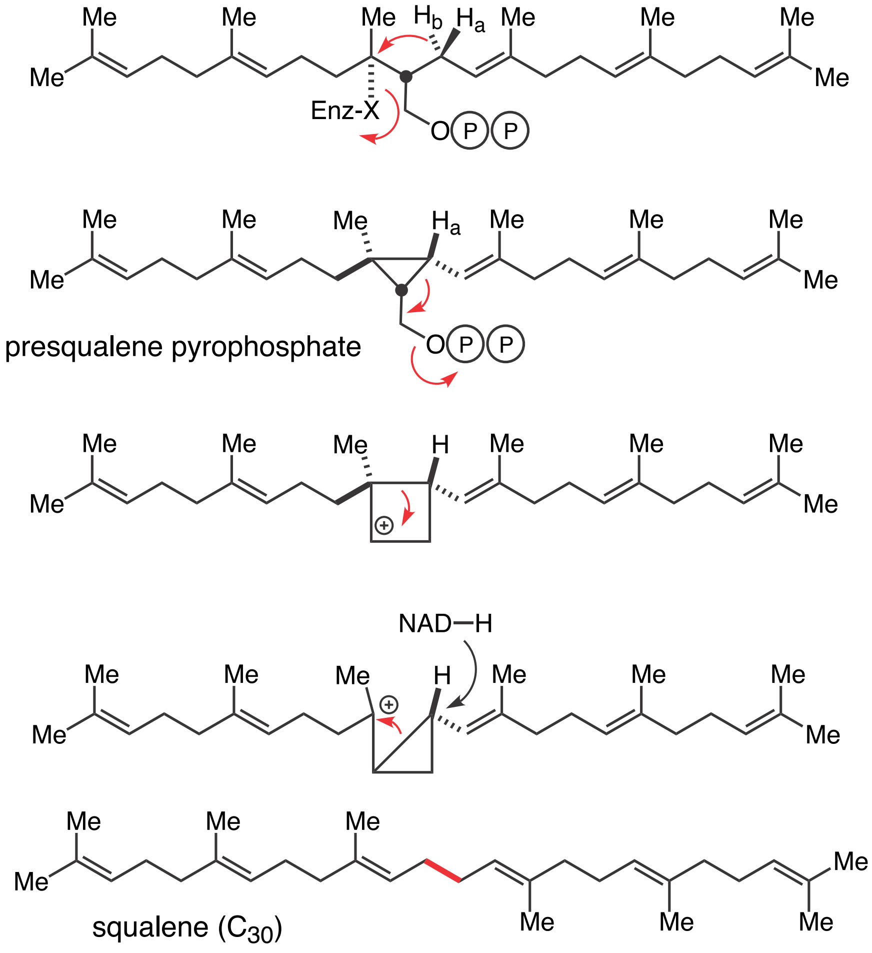


Squalene Biosynthesis; Squalene Oxide Cyclization

Squalene Biosynthesis

farnesyl pyrophosphate
(C15)

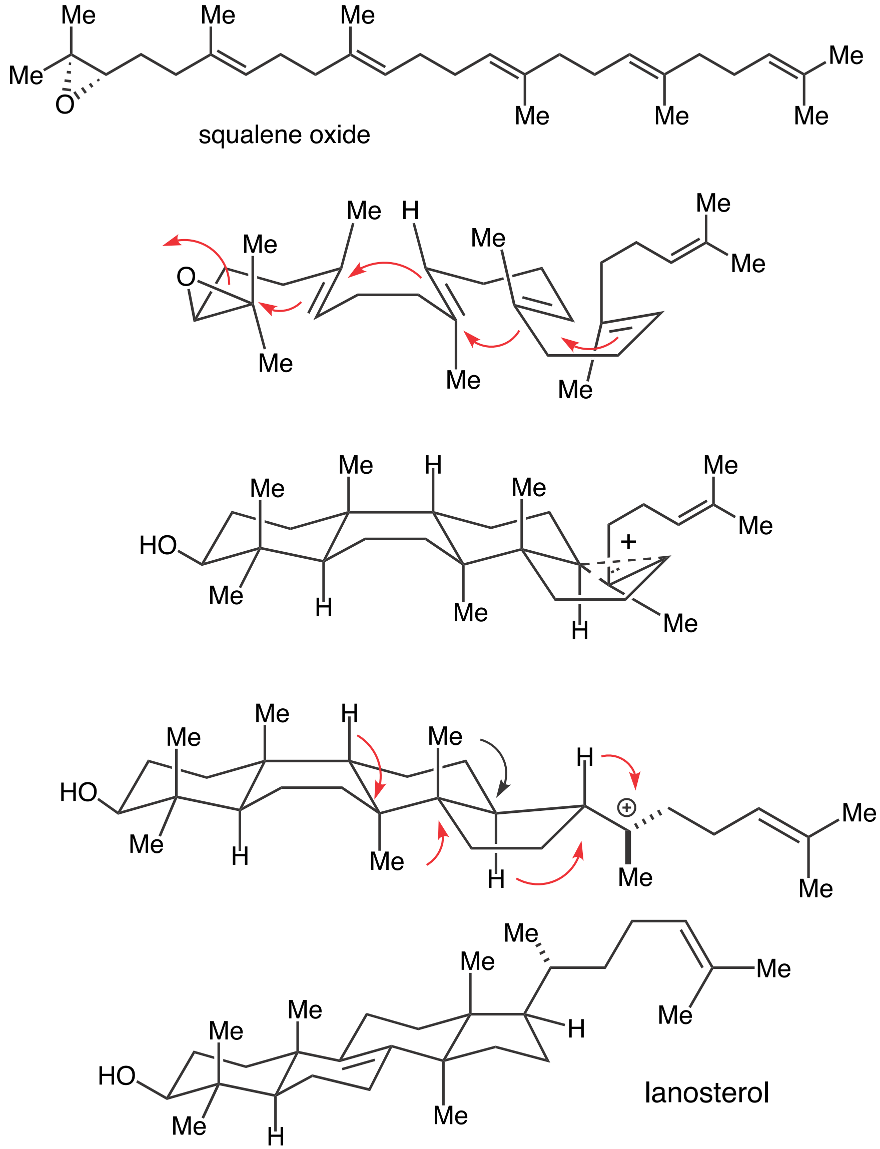




Squalene Oxide Cyclase

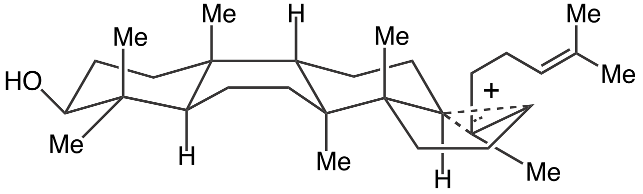
Prestwilch, et. al. *Chem. Rev.* **1993**, *93*, 2189-2206

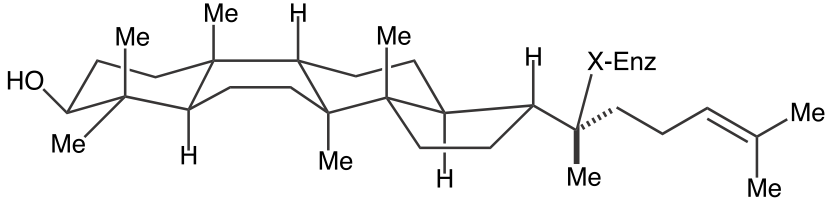
Cornforth Proposal: *ACIEE*, **1968**, 903.

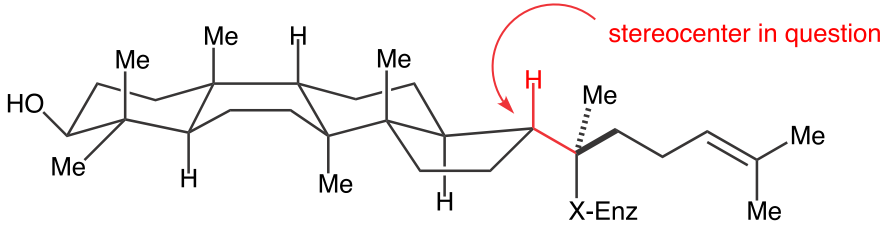


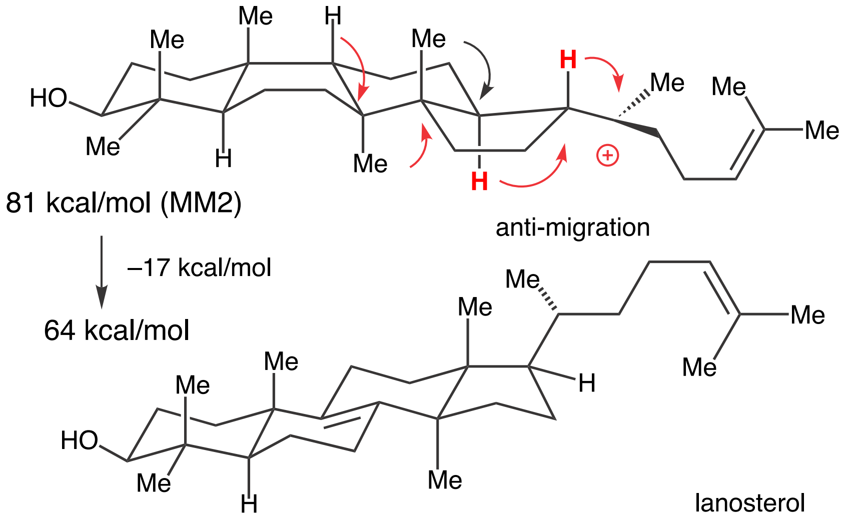
The Corey Addendum to the Cyclization Process

Squalene Oxide Cyclase - Cornforth Proposal: *ACIEE*, **1968**, 903.

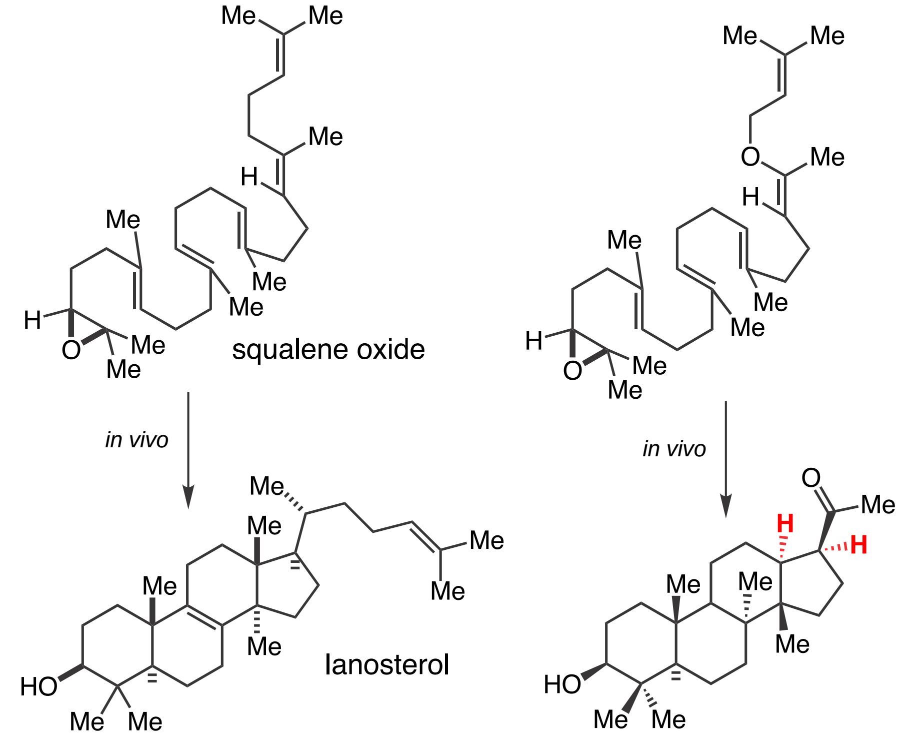


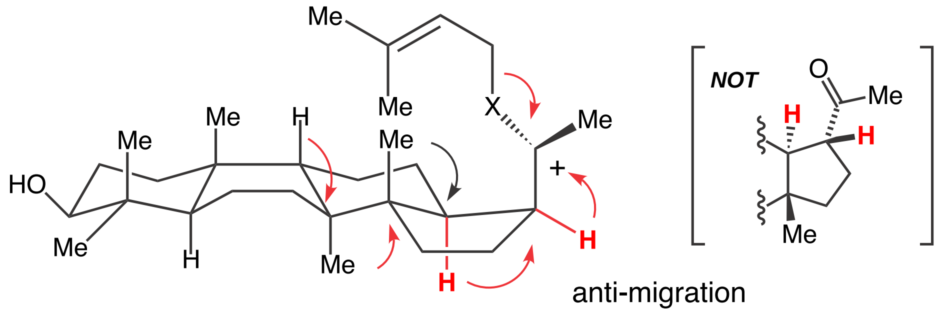






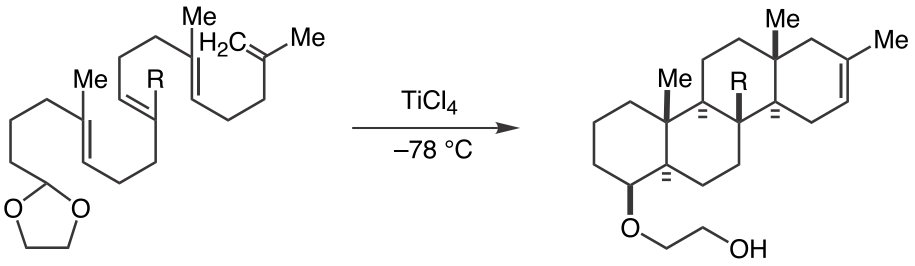
Corey–Virgil Revision: *JACS* **1991**, *113*, 4025-4026; 8171-8172





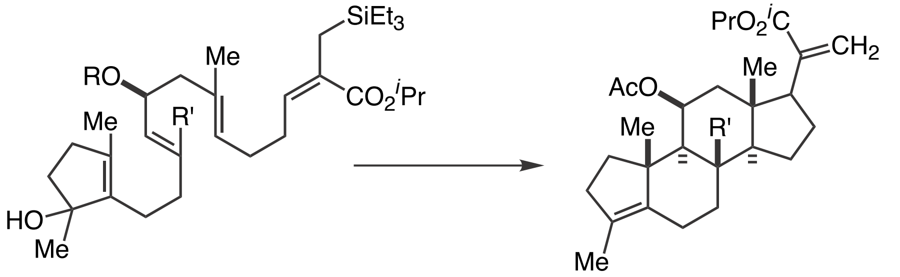
Cationic Cyclizations in the Laboratory

Biomimetic Polyene Cyclizations



Johnson, et al. *JACS* **1987**, *109*, 2517.

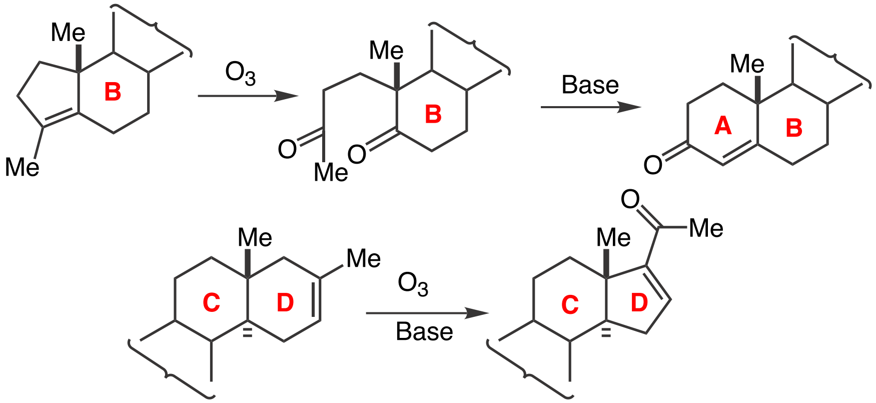
R = H ca. 30%
R = CH=CH$_2$ 77%

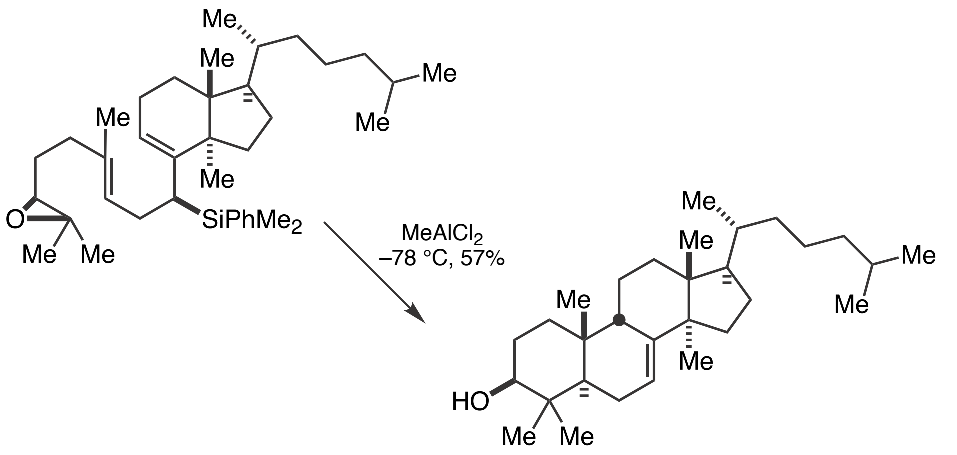


Johnson, et al. *JACS* **1987**, *109*, 5852.

R = OH, R' = H 20%, 24 hr.
R = OAc, R' = CH=CH$_2$ 80%, 1 min.

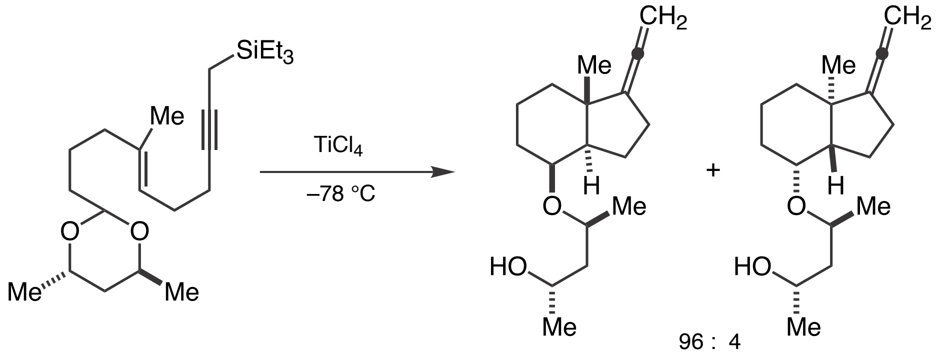
Post cyclization transformation: Johnson





E. J. Corey, et al. *Tetrahedron Lett.* **1994**, *35*, 9149.

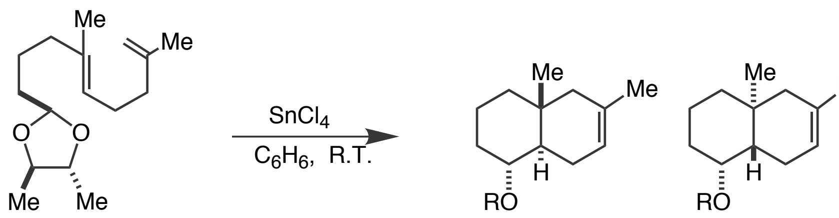
Cyclization to Form Simpler Bicyclics



Johnson, et al. *JACS* **1984**, *106*, 1138.

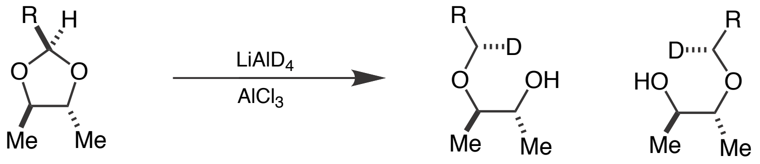
Introduction of chiral auxiliaries for C=O groups

Chiral Acetal Auxiliaries-1



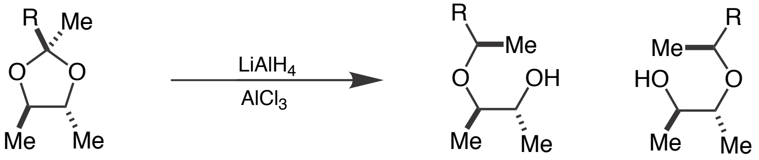
W. S. Johnson & Co-workers,
J. Am. Chem. Soc., **1976**, *98*, 6188.

Ratio = 72 : 28 de = 84%



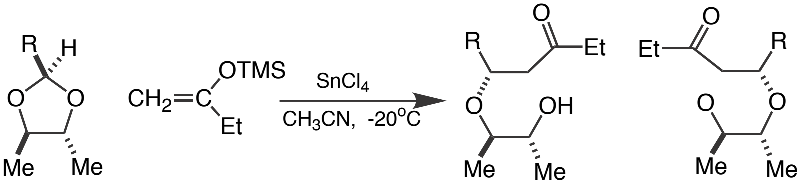
W. J. Richter, *J. Org. Chem.*, **1981**, *46*, 5119.

R	ratio
Et	01:99
t-Bu	22:78
Ph	14:86



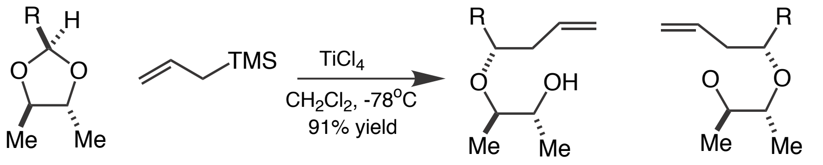
W. J. Richter, *J. Org. Chem.* ,**1981**, *46*, 5119.

R	ratio
Et	73:24
t-Bu	85:15
Ph	51:46



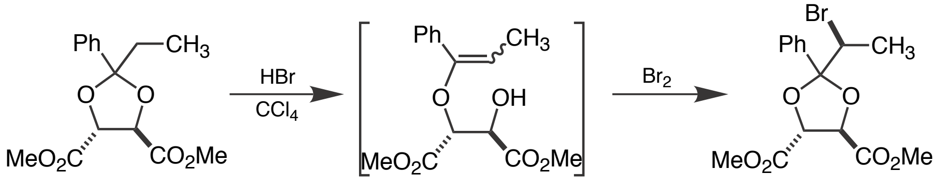
J. M. McNamara, Y. Kishi,
J. Am. Chem. Soc., **1982**, *104*, 7371.

R	ratio
Ph	16:1
n-C$_9$H$_{19}$	03:1



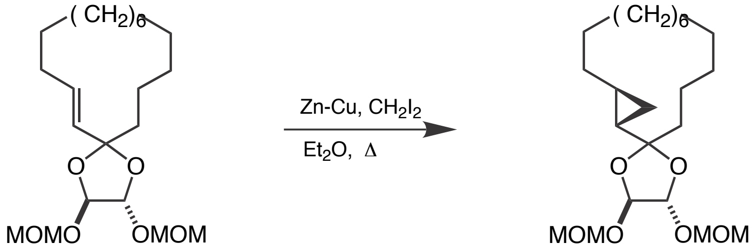
P. A. Bartlett & Co-workers,
J. Am. Chem. Soc., **1983**, *105*, 2088

R = C$_8$H$_{17}$ Ratio = 88 : 12



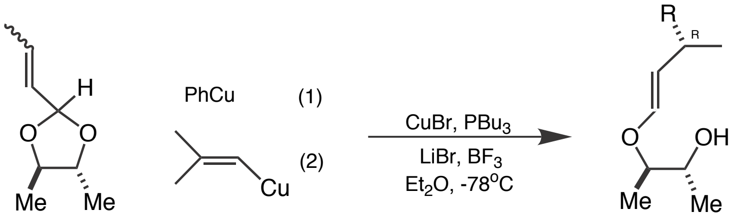
G. Castaldi & Co-workers,
Angew. Chem. I. E., **1986**, *25*, 259.

94 % yield de = 86 %



K. A. Nelson & E. A. Mash,
J. Org. Chem., **1986**, *51*, 2721.

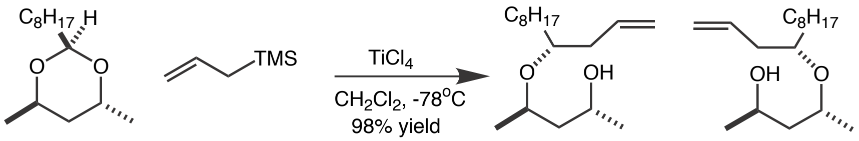
de = >95 %



P. Mangeney & Co-workers,
Tetrahedron Lett., **1987**, *28*, 2363.
(error in R/S nomenclature in paper)

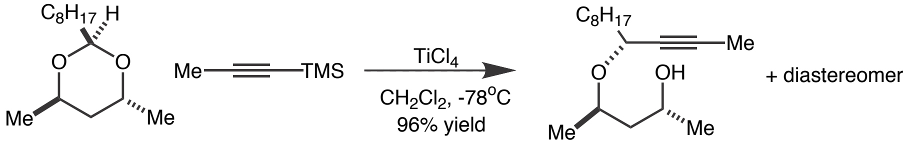
Acetal Isomer	Alkylating Agent (R)	Product E/Z	% Yield	% de
E	(1)	100/0	75	95 (R)
E	(2)	95/5	70	85 (R)
Z	(1)	100/0	75	69 (S)

Chiral Acetal Auxiliaries-2



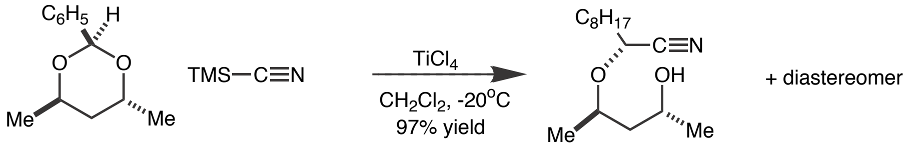
P. A. Bartlett & Co-workers,
J. Am. Chem. Soc., **1983**, *105*, 2088.

Ratio = 87 : 13



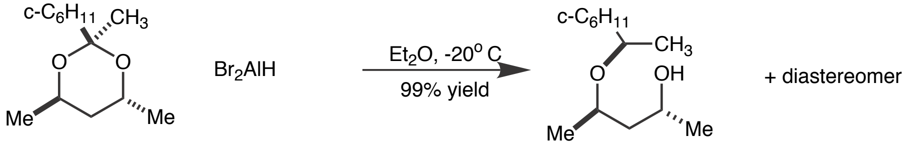
W. S. Johnson & Co-workers,
J. Am. Chem. Soc., **1983**, *105*, 2904.

Ratio = 93 : 7



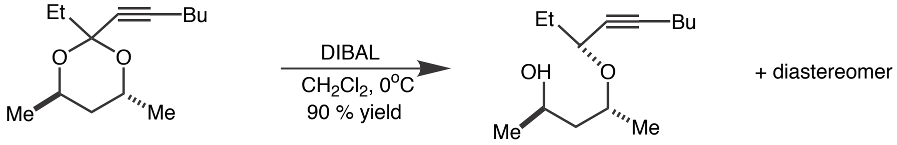
W. S. Johnson & Co-workers,
J. Org. Chem., **1983**, *48*, 2294.

Ratio = 96.5 : 3.5



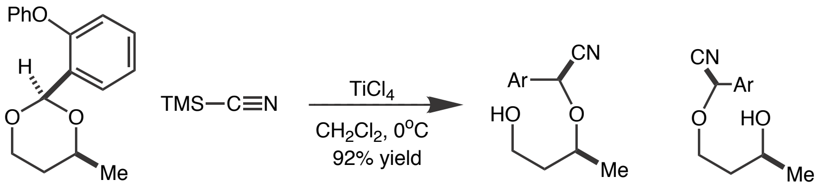
H. Yamamoto & Co-workers,
Tetrahedron Lett., **1983**, *24*, 4581.

Ratio = 23 : 1



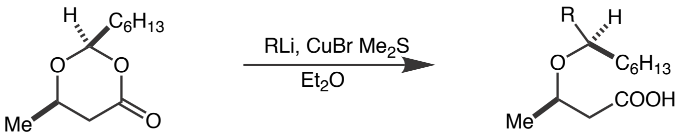
H. Yamamoto & Co-workers,
Tetrahedron Lett., **1986**, *27*, 983.

Ratio = 97 : 3
diastereoselection >99%



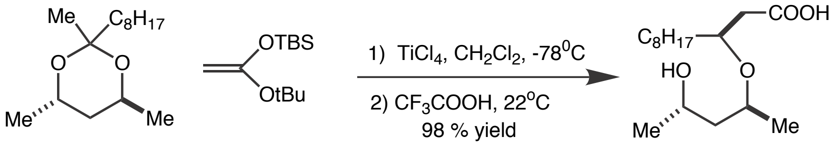
W. S. Johnson & Co-workers,
Tetrahedron Lett., **1984**, *25*, 591.

Ratio = 97 : 3, 88% de



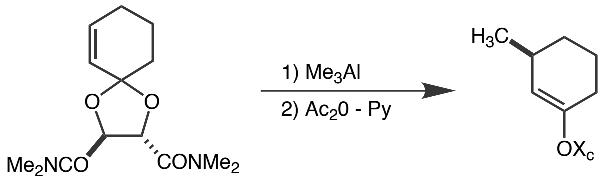
S. L. Schreiber & J. Reagan
Tetrahedron Lett., **1986**, *27*, 2945.

R	Temp.(°C)	% Yield	% de
Me	0	58	94
Ph	-30	90	97



J. D. Elliott & Co-workers,
Tetrahedron Lett., **1985**, *26*, 2535.

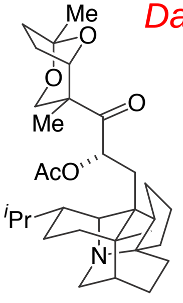
Ratio = 98 : 2

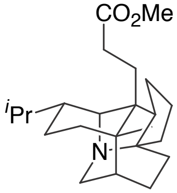


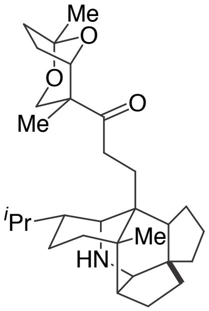
H. Yamamoto & Co-workers,
Tetrahedron Lett., **1984**, *25*, 5911.

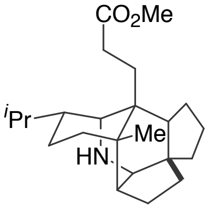
97% yield de = 77%

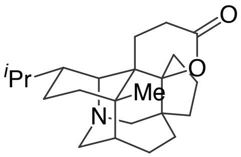
Daphniphyllum Alkaloids

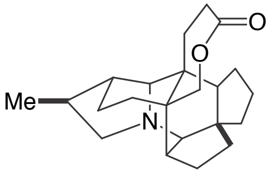

Daphniphylline


Methyl Homodaphniphyllate


Secodaphniphylline


Methyl Homosecodaphniphyllate

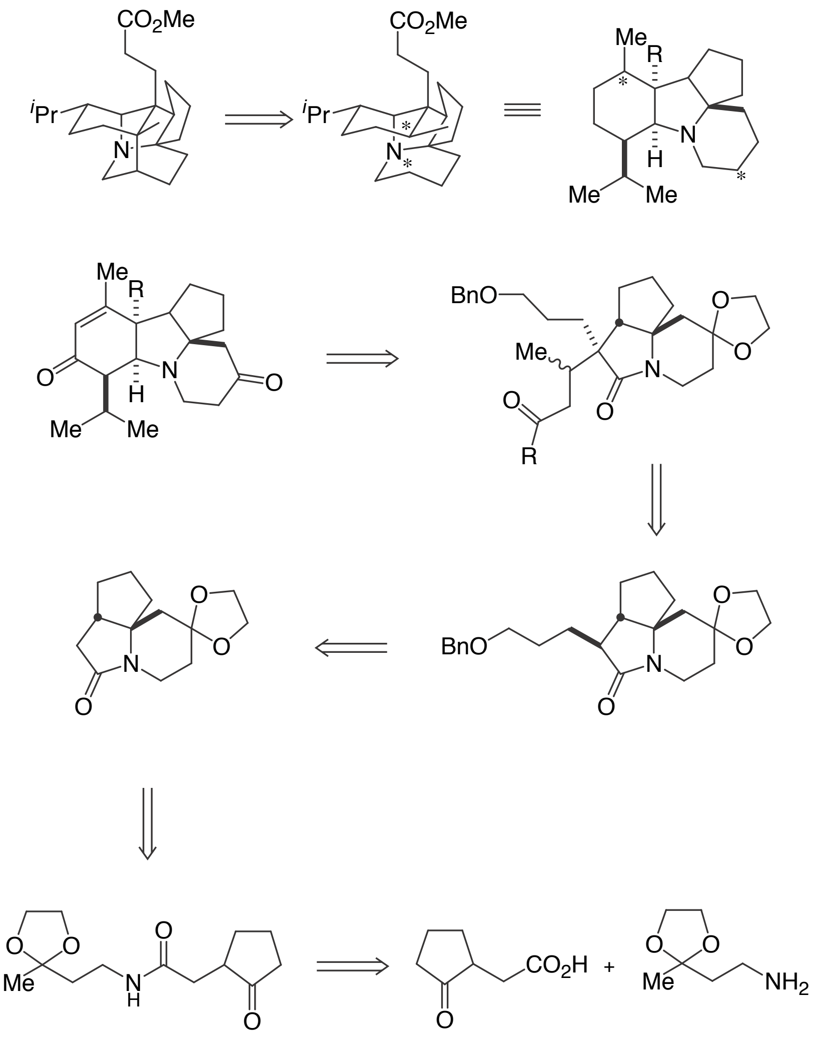

Daphnilactone A


Bukittinggine

- Isolated from bark and leaves of Yuzuriha tree
- Used to cure asthma and vermicide in the early 20th century
- Compounds have been known since 1909. First structure solved in 1965.
- 38 members in this alkaloid family

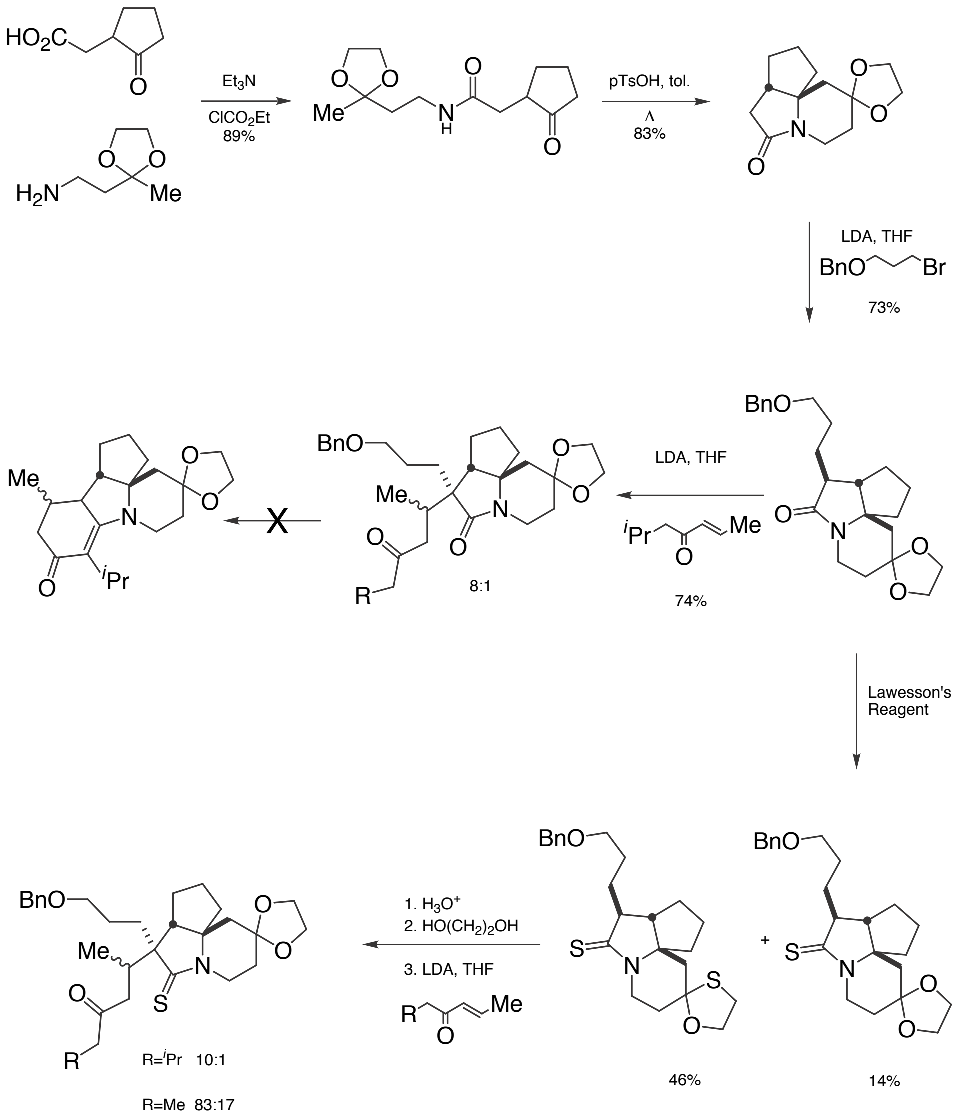
J. Org. Chem. **1992**, *57*, 2531-2594
Kyoto Igaku Zasshi **1909**, *6*, 208
Tet. Lett. **1965**, 965

"Classical" Total Synthesis of Methyl Homodaphniphyllate



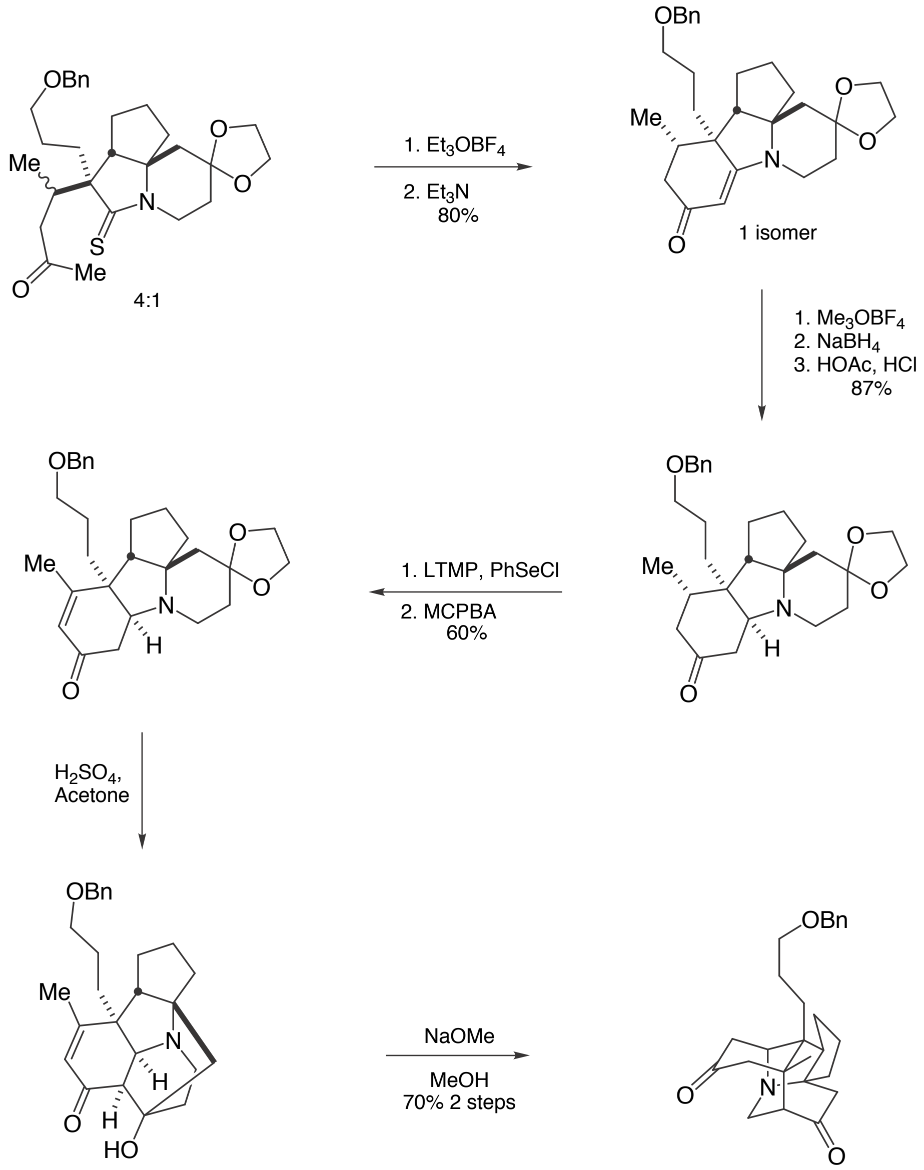
J. Org. Chem. **1992**, *57*, 2531
J. Am. Chem. Soc. **1975**, *97*, 6116
Angew. Chem. Int. Ed. Eng. **1992**, *31*, 665

Synthesis of Methyl Homodaphniphyllate

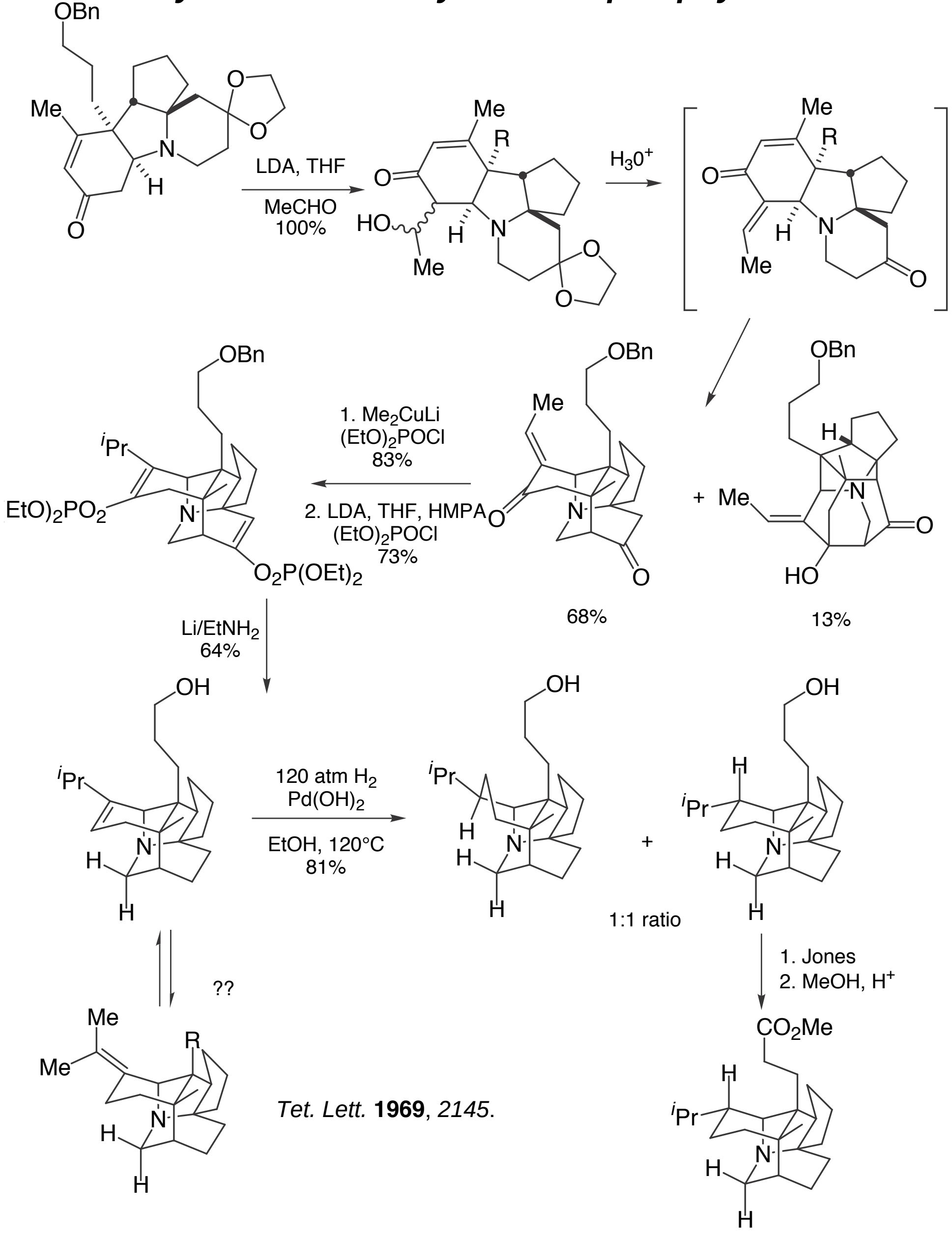


J. Am. Chem. Soc. **1986**, *108*, 5650
J. Org. Chem. **1992**, *57*, 2531
J. Am. Chem. Soc. **1968**, *90*, 6177
Nouv. J. Chem. **1980**, *4*, 47

Construction of the Methyl Homodaphniphyllate Skeleton

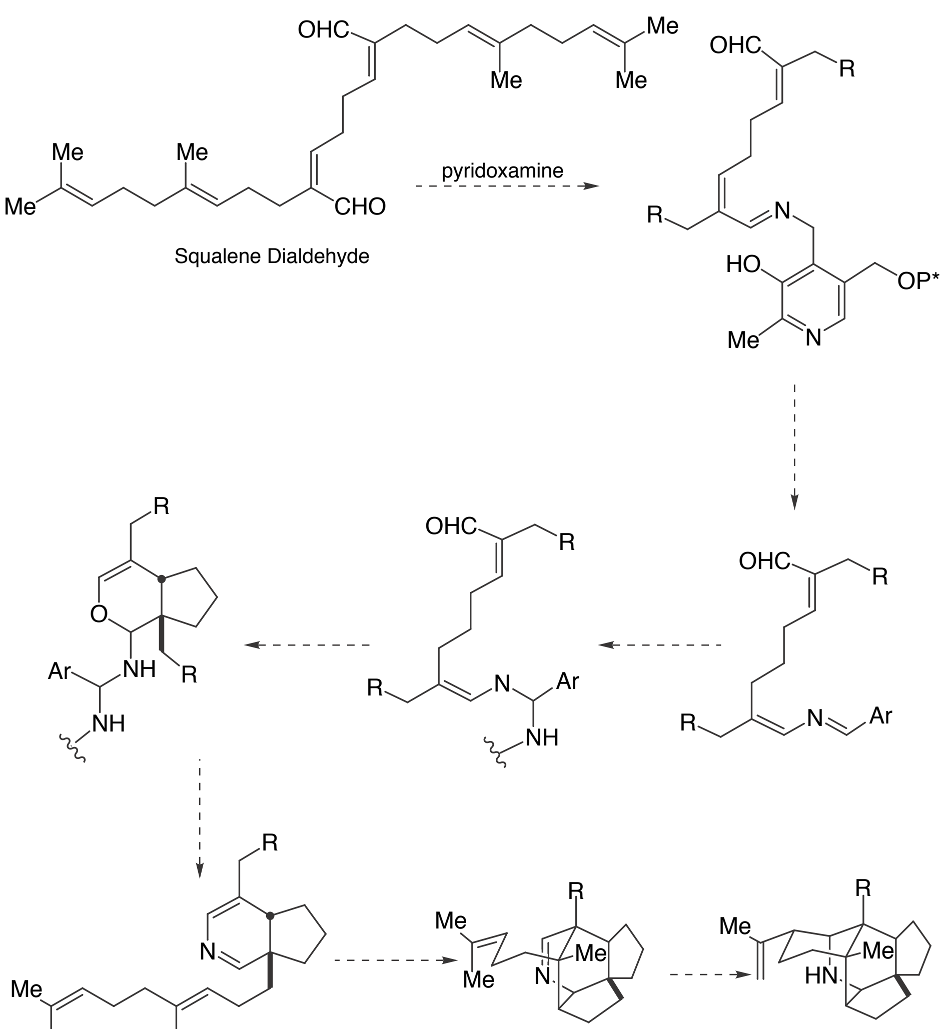


Synthesis of Methyl Homodaphniphyllate cont'd



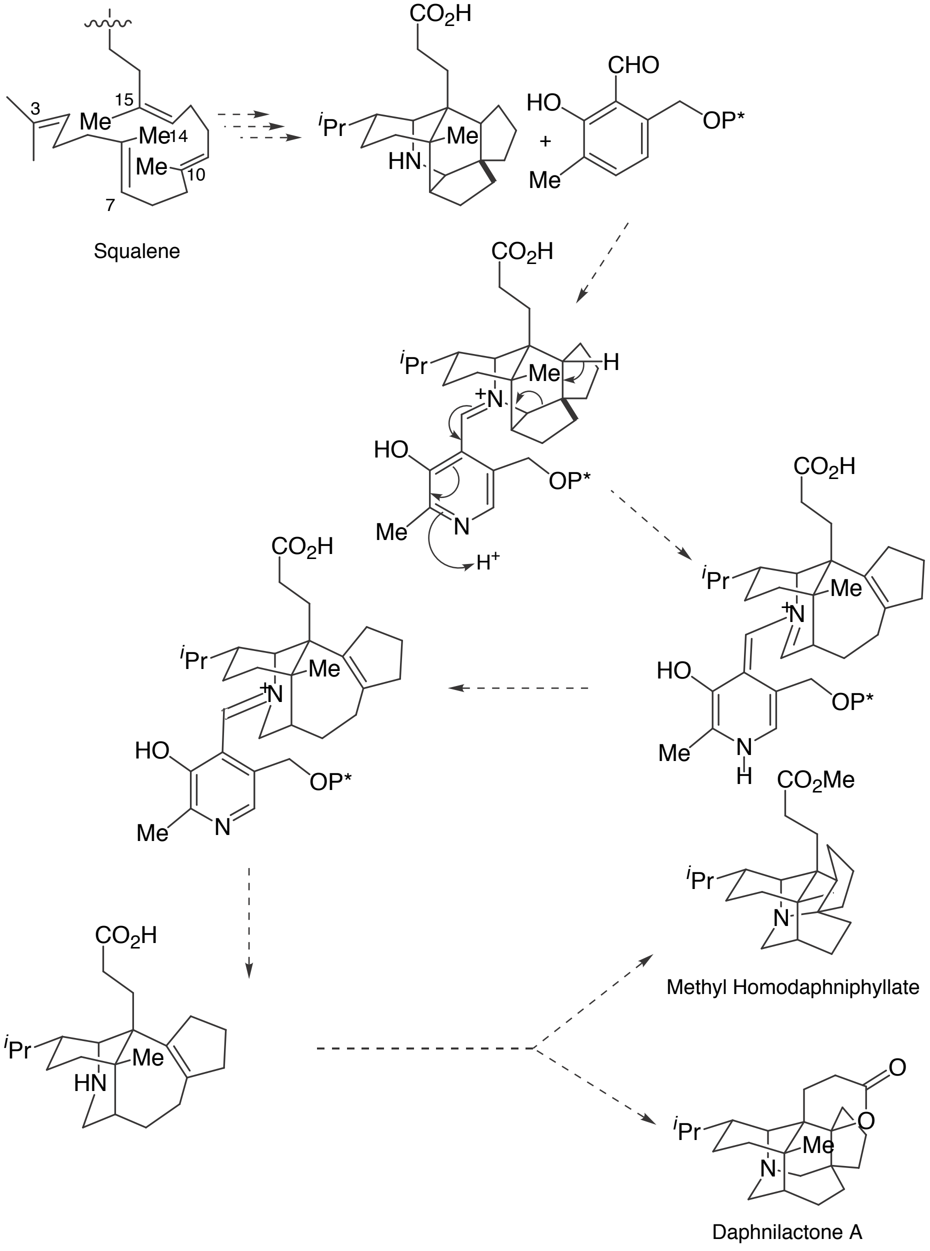
Tet. Lett. **1969**, *2145*.

Proposed Biosynthesis of the Daphniphyllum Alkaloids



Pure & Appl. Chem. **1989**, *61*, 289
J. Am. Chem. Soc. **1986**, *108*, 8274

Proposed Biosynthesis cont'd

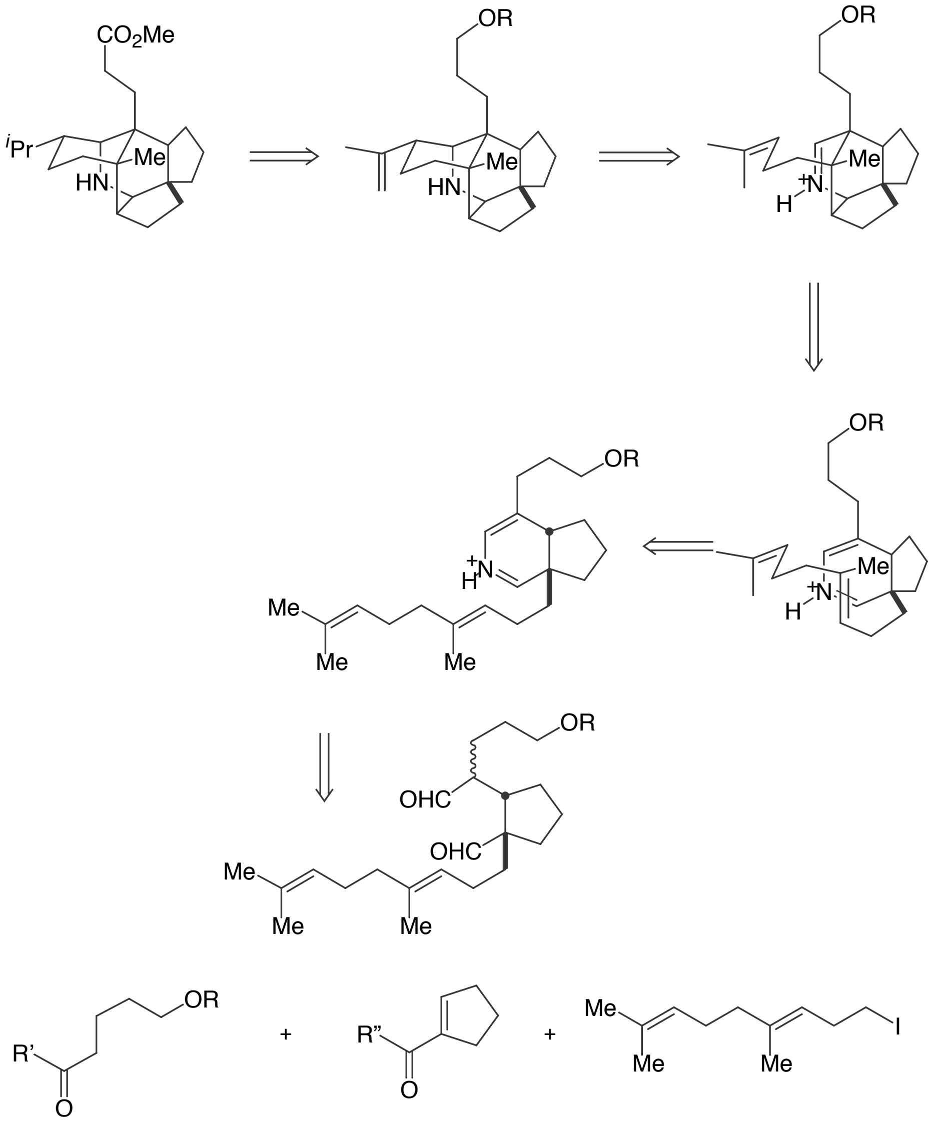


Squalene

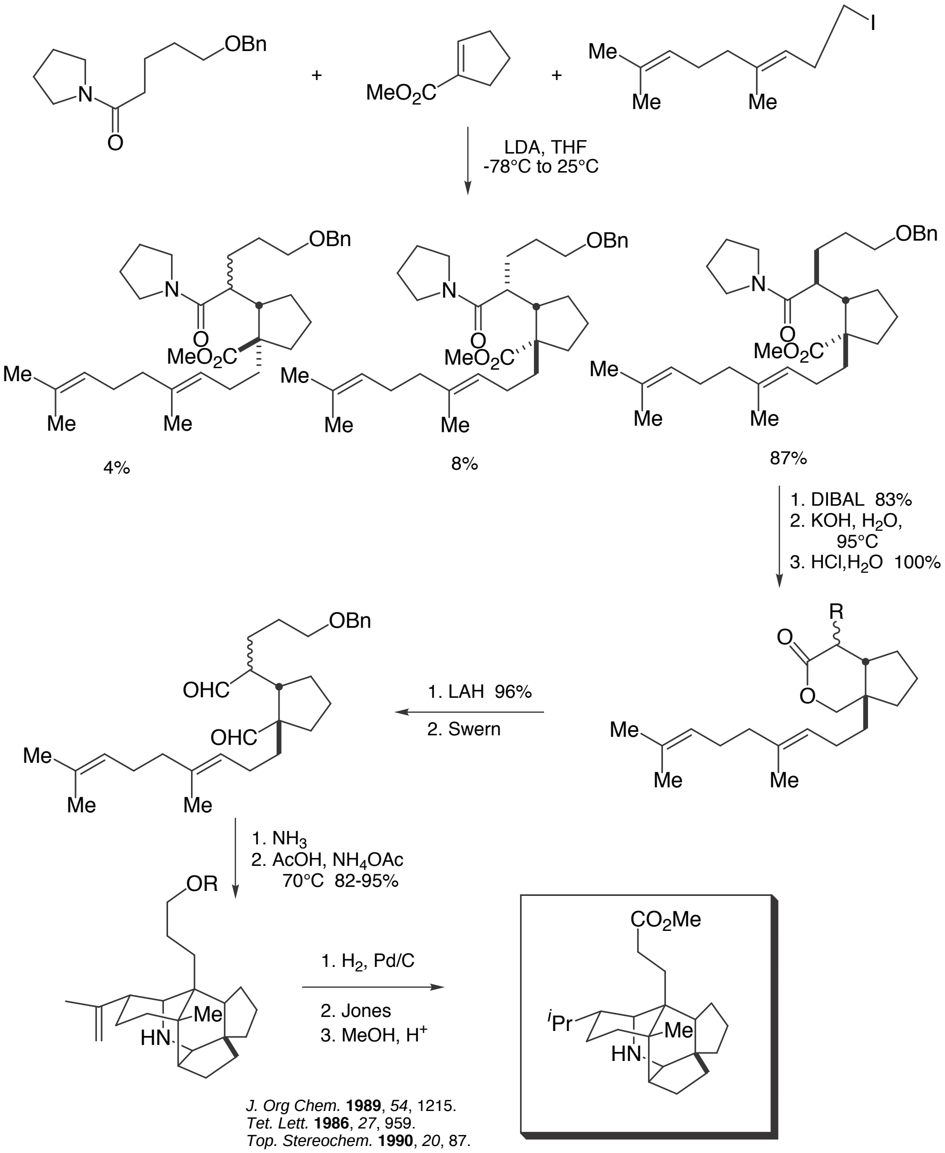
Methyl Homodaphniphyllate

Daphnilactone A

Retrosynthesis of Methyl Homosecodaphniphyllate

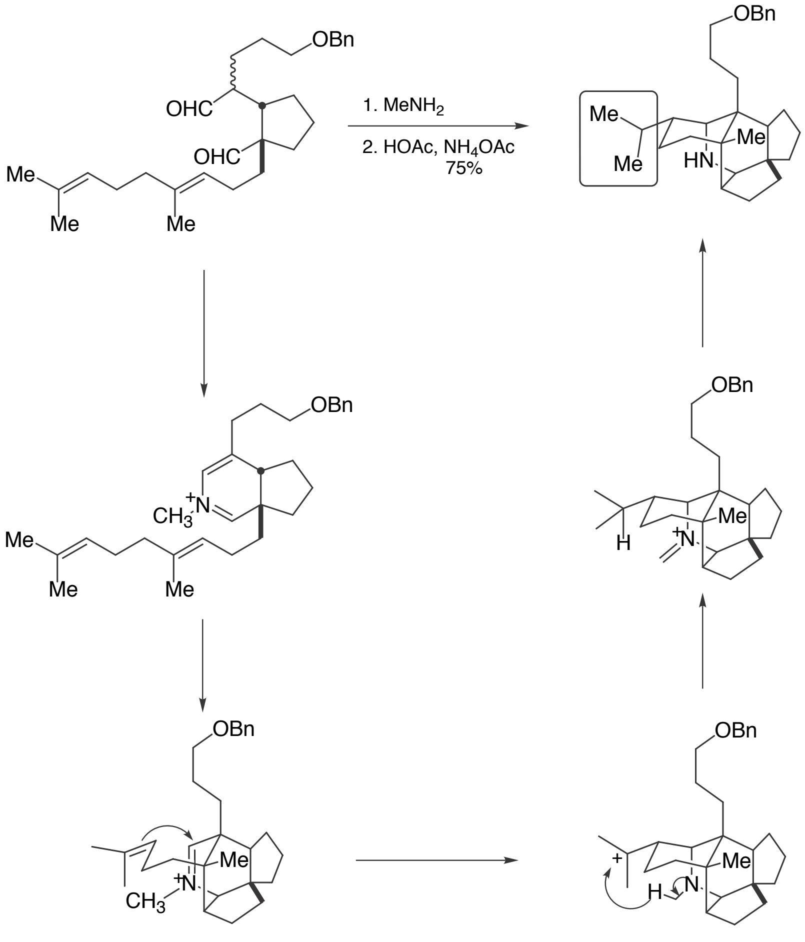


Synthesis of Methyl Homosecodaphnipyllate



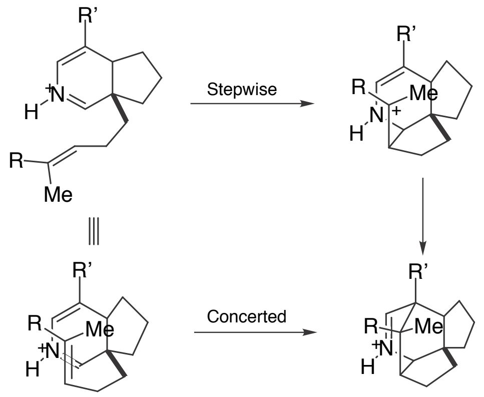
J. Org Chem. **1989**, *54*, 1215.
Tet. Lett. **1986**, *27*, 959.
Top. Stereochem. **1990**, *20*, 87.

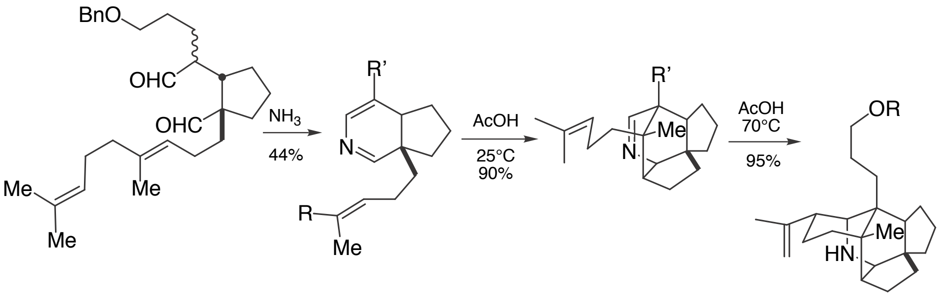
The Vollhardt "Ammonia" Incident

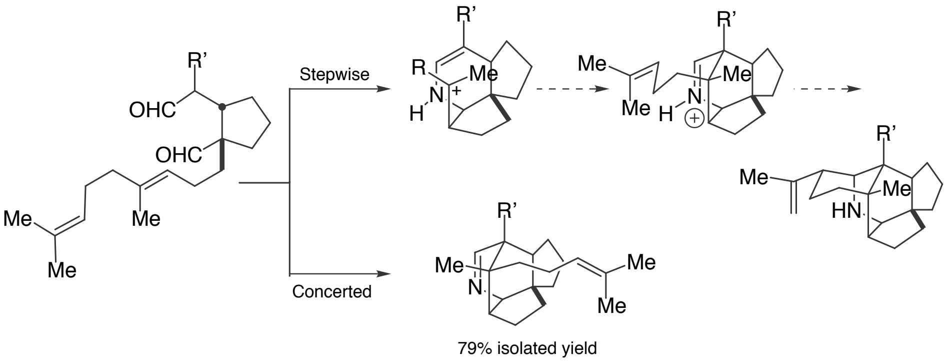


Angew. Chem. Int. Ed. Engl. **1978**, *17*, 476.
J. Org. Chem. **1990**, *57*, 2544.

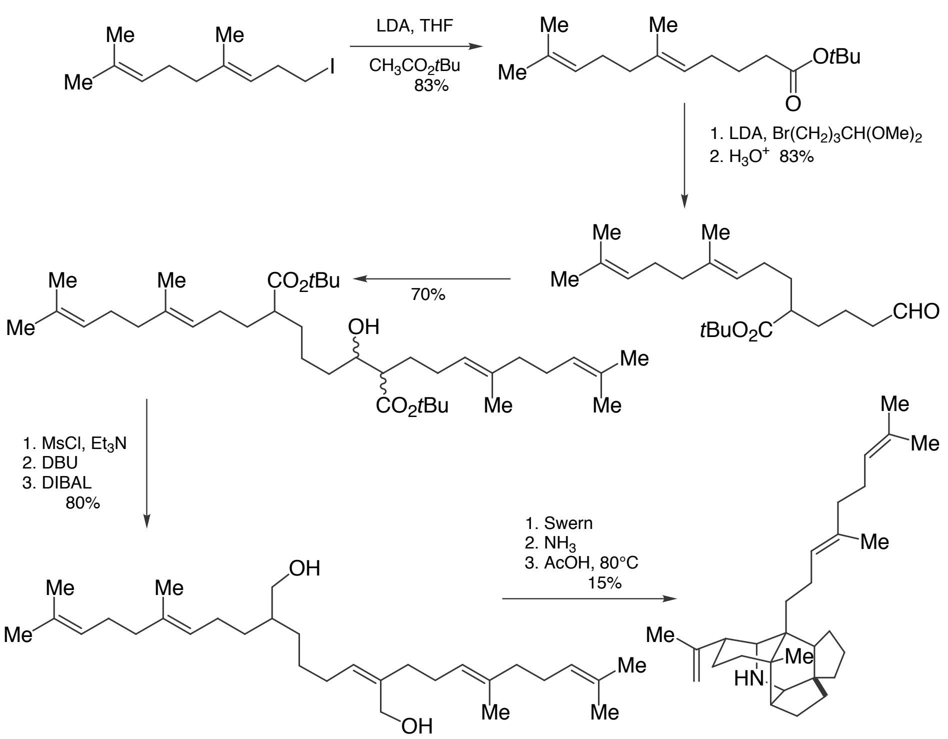
Stepwise vs Concerted Cyclization

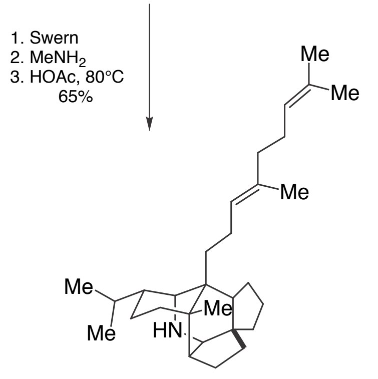






One-Pot Pentacyclization Reaction: Formation of Protodaphniphylline

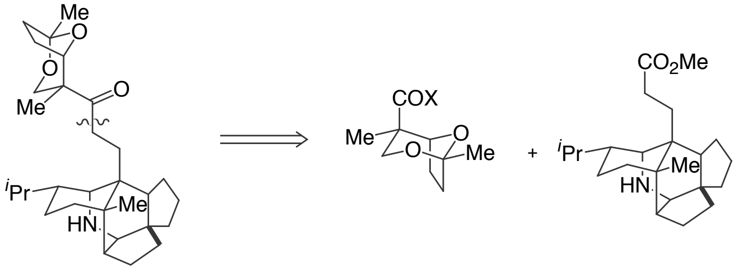


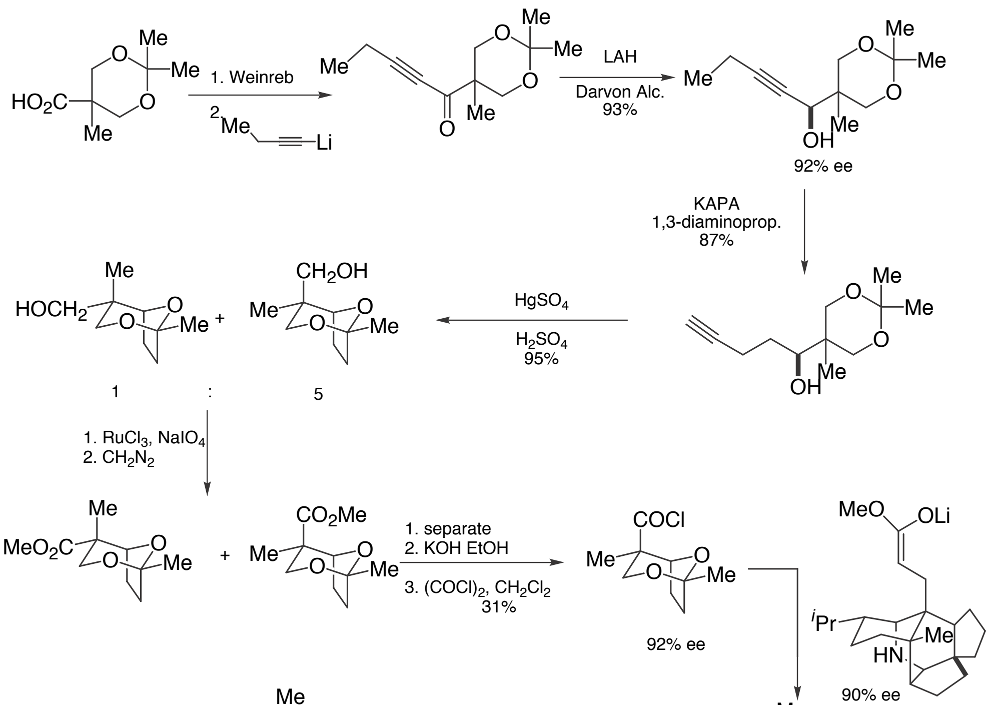


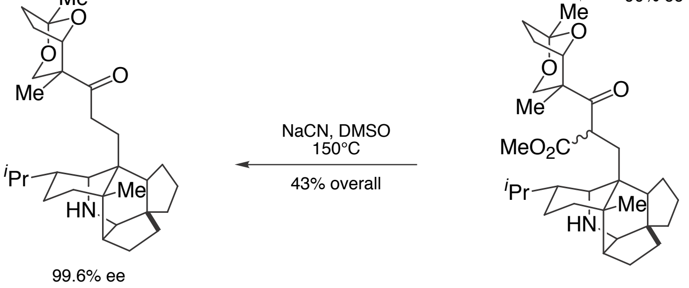
Other amines:

Glycine	38%y
(S)-(+)-Alanine	32%y 1-2%ee
(S)-(+)-Valine	13%y 20-25%ee
(+)-α-Phenylethyl amine	no reaction

Synthesis of (-)-Secodaphniphylline

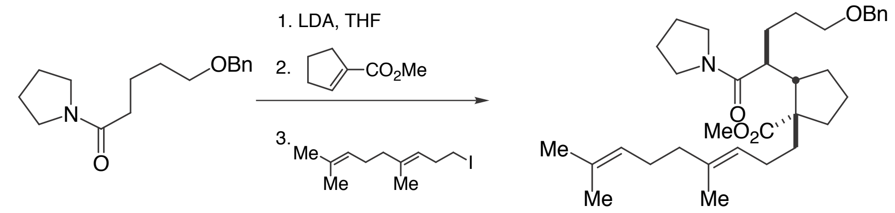


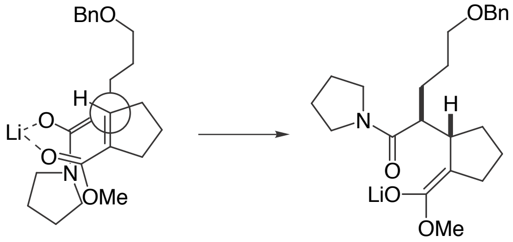


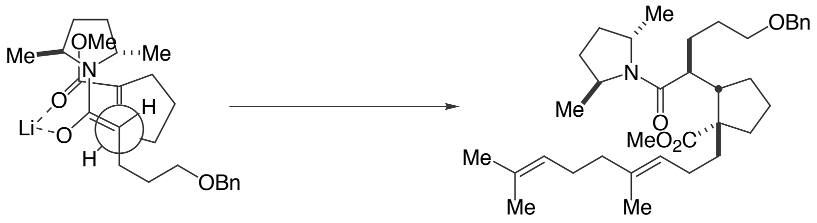


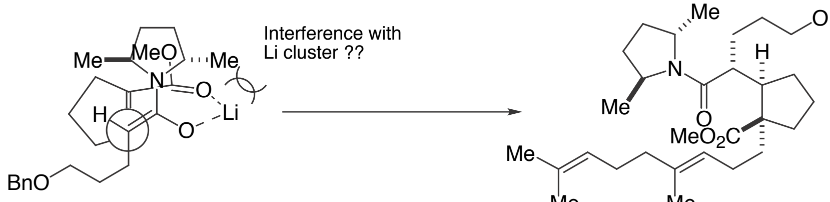
J. Org. Chem. **1980**, *45*, 582
Tet. Lett. **1981**, *22*, 4171
J. Org. Chem. **1981**, *46*, 3936
Tet Lett. **1967**, *8*, 215

Rationale for Stereoselectivity in Michael Additions



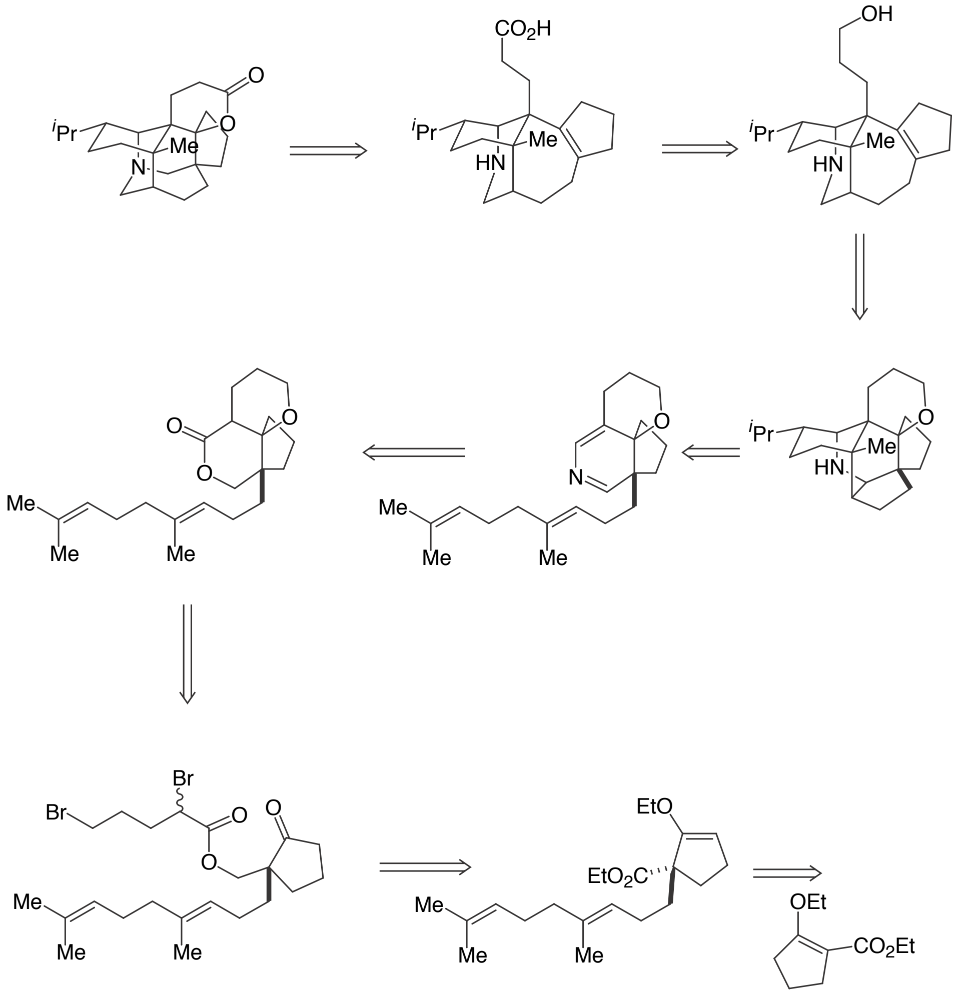






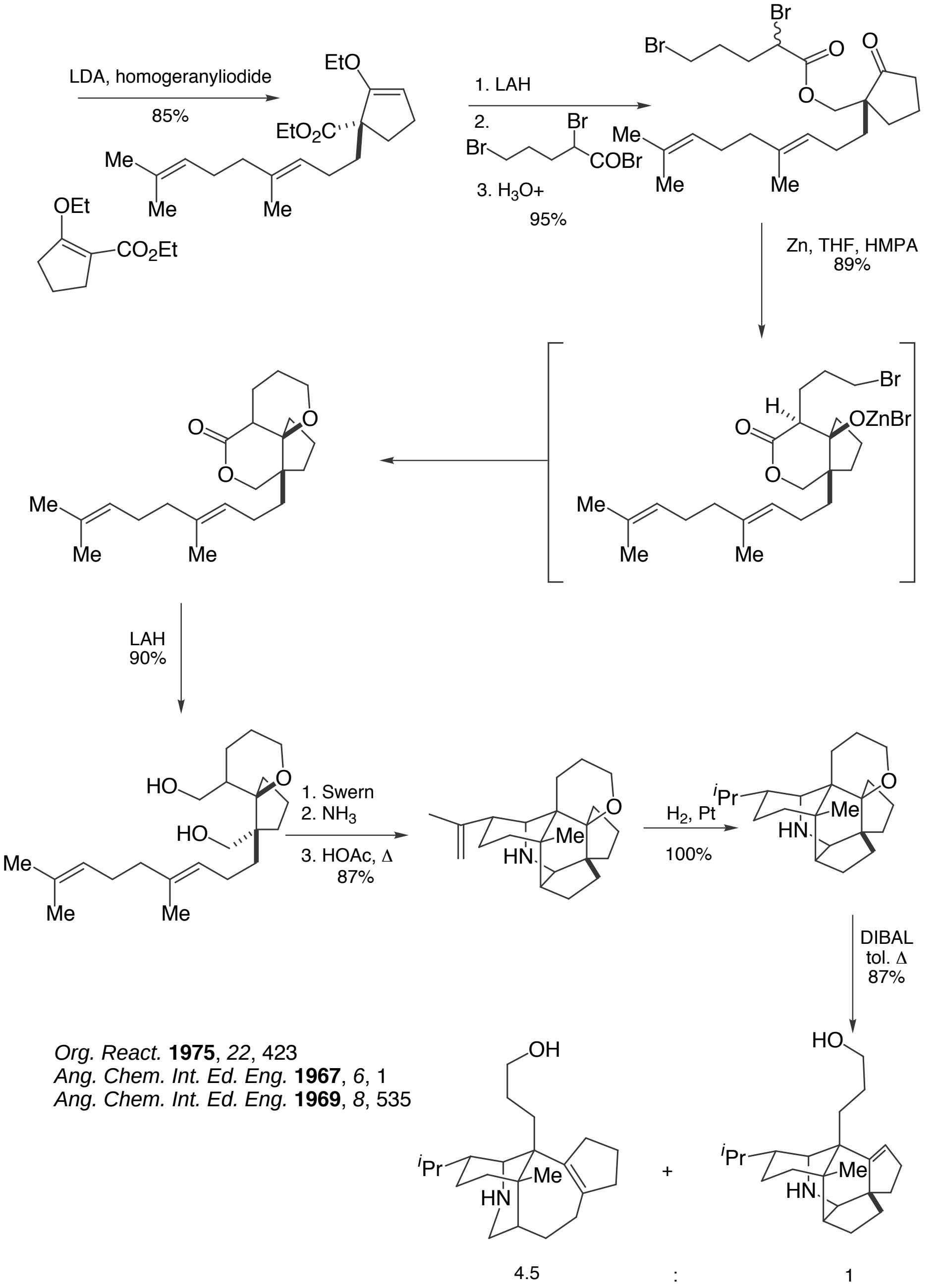
Tet Lett **1986**, *27*, 959
J. Org. Chem. **1990**, *55*, 132
Topics in Stereochemistry **1989**, 227

Retrosynthesis of Daphnilactone A



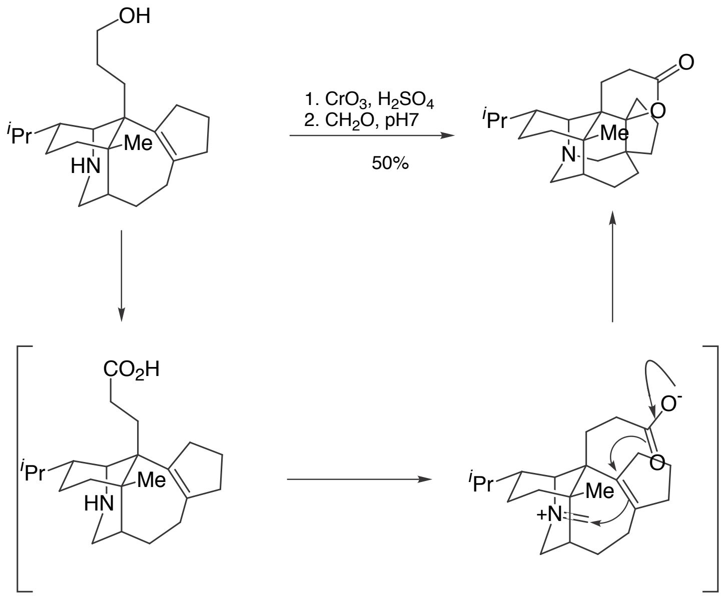
J. Org. Chem. **1992**, *57*, 2585
Angew. Chem. Int. Ed. Engl. **1992**, *31*, 665

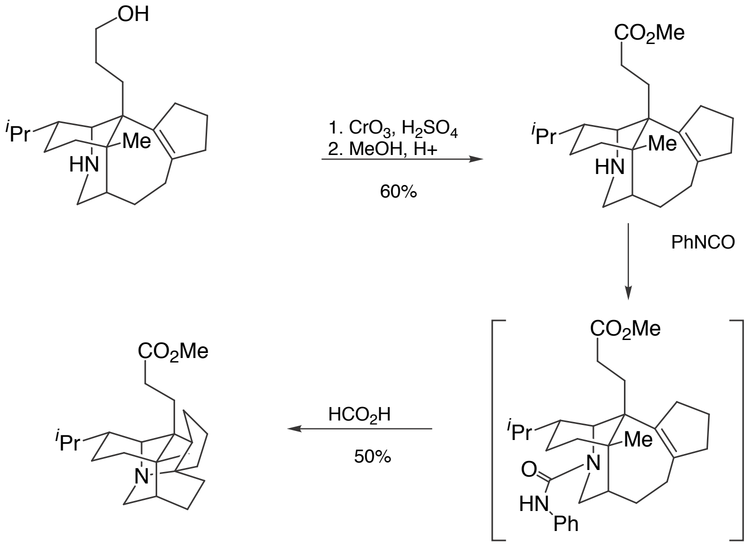
Synthesis of Daphnilactone A



Org. React. **1975**, *22*, 423
Ang. Chem. Int. Ed. Eng. **1967**, *6*, 1
Ang. Chem. Int. Ed. Eng. **1969**, *8*, 535

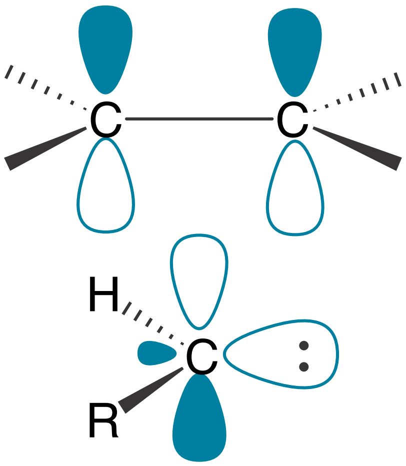
Total Synthesis of Daphnilactone and Conversion to the Daphniphylline Skeleton



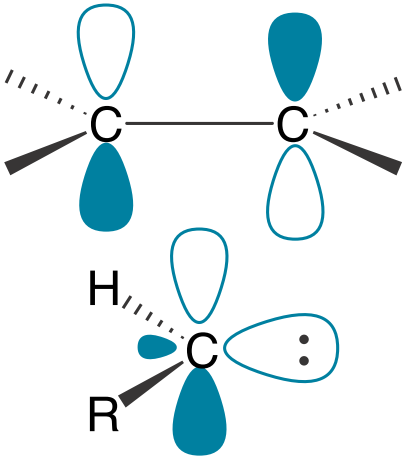


Carfbene–Olefin Cycloaddition: The FMO Analysis

HOMO



LUMO



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 34

Introduction to Carbenes & Carbenoids-1

- Carbene Structure & Electronics
- Methods for Generating Carbenes
- Simmons-Smith Reaction
- Carbene-Olefin Insertions
- Carbene Rearrangements

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part B Chapter 10, "Reactions Involving Highly Reactive Electron-Deficient Intermediates", 595–680.

Handout 09A Simmons-Smith Reaction: Enantioselective Variants
Handout 26B Synthetic Applications of α-Diazocarbonyl Compounds

Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, *29*, 3 **(handout)**

Doyle, Catalytic Methods for Metal Carbene Transformations, *Chem. Rev.* **1986**, *86*, 919-939 **(electronic handout)**

McKervey, Organic Synthesis with α-Diazocarbonyl Compounds, *Chem. Rev.* **1994**, *94*, 1091-1160 **(electronic handout)**

Muller, Catalytic Enantioselective Aziridinations & Asymmetric Nitrene Insertions, *Chem. Rev.* **2003**, *103*, 2905-2919 **(electronic handout)**

Monday,
December 10 , 2003

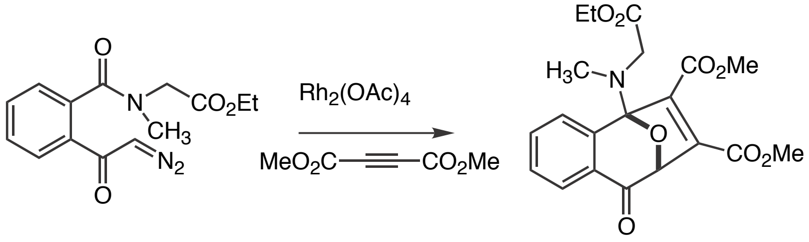
D. A. Evans

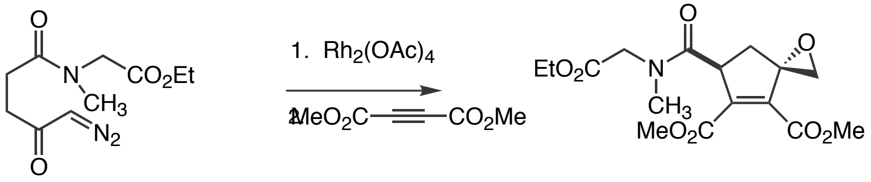
Useful References to the Carbene Literature

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

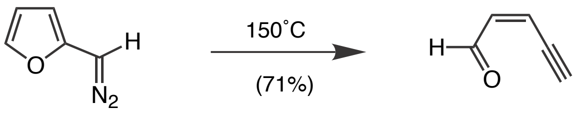
Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

Provide a mechanism for the following transformations.





JACS **1990** 2037



Carbenes: An Introduction

Suggested Reading:

Doyle, *Chem Rev.* **1988,** *86*, 919.
Kodadek, *Science*, **1992**, *256*, 1544.

Recent Review Article:
Chemistry of Diazocarbonyls: McKervey et al. *Chem Rev*. **1994**, *94*, 1091.

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

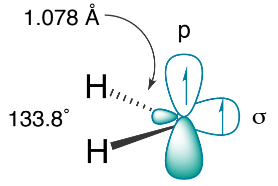
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

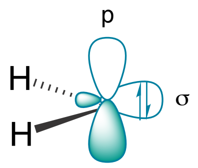
Carbenes: Electronic Structure

■ Carbene Configuration: Triplet vs. Singlet



Triplet (two unpaired e^-)

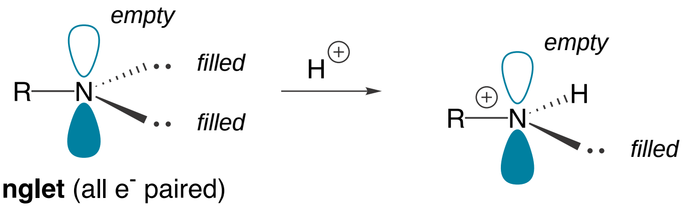
Often has **radical**-like character



Singlet (all e^- paired)

Often has **electrophilic** or **nucleophilic** character: **A**-type (**Ambiphilic)**

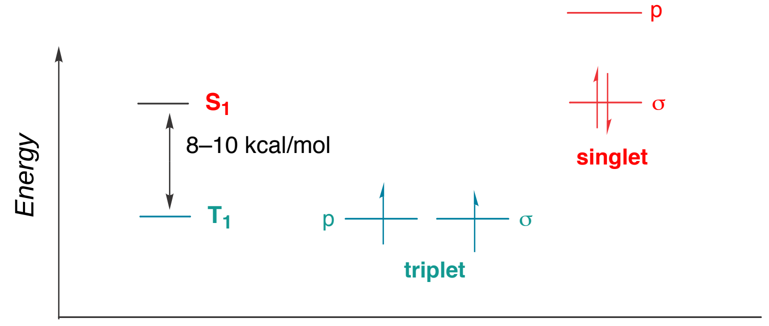
■ Nitrene



Singlet (all e^- paired)

■ Nitrenium ion

■ Carbene Configuration: Triplet vs. Singlet



Due to electron repulsion, there is an energy cost in pairing both electrons in the σ orbital. If a **small energy difference** between the σ and p orbitals exists, the electrons will remain **unpaired (triplet)**. If a **large gap** exists between the σ and p orbitals the electrons will **pair** in the σ orbital (**singlet**).

■ the History of the Singlet-Triplet Gap

Year	**Method**	**Author**	**HCH Angle**	**Grnd State**	**S–T Splitting kcal/mol**
1932	Qual.	Muliken	90-100°	*singlet*	—
1947	Thermochem	Walsh	180°	*triplet*	*small*
1957	Qual. QM	Gallup	160°	*triplet*	30
1969	Ab initio	Harrison	138°	*triplet*	>33
1971	Kinetics	Hase	—	*triplet*	8–9
1971	SCF	Pople	132°	*triplet*	19
1974	MINDO	Dewar	134°	*triplet*	8.7
1976	Expt	Lineberger	138°	*triplet*	19.5
1976	An Initio	Schaeffer	—	*triplet*	19.7
1978	**Expt**	**Zare**	**—**	***triplet***	**8.1**
1982	**Expt**	**Haydon**	**—**	***triplet***	**8.5**

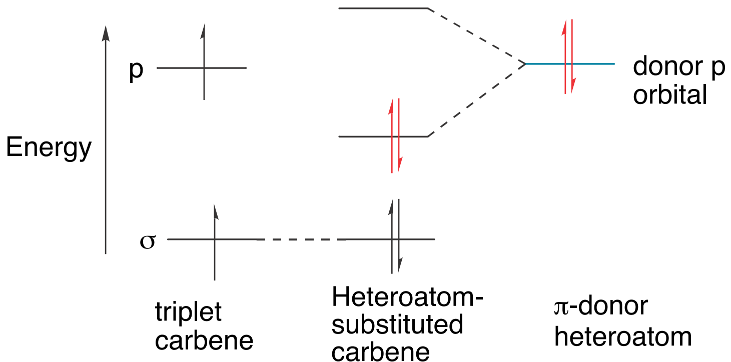
(Wentrup)

Compiler's note: Although a Ph substituent stabilizes the singlet state relative to the triplet, the ground state of PhCH is nevertheless a triplet, with a singlet-triplet gap of 2.75 kcal/mol.

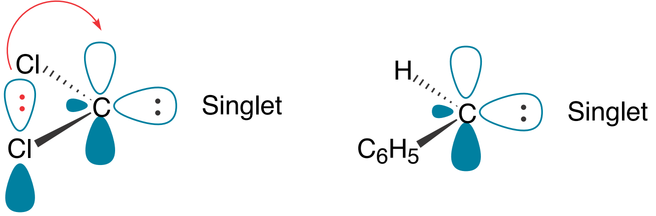
Carbenes: Structure and Generation

Heteroatom-Substituted Carbenes: Singlets

The p orbital of carbenes substituted with **p-donor atoms** (N, O, halogen) is raised high enough in energy to make the pairing of the electrons in the σ orbital energetically favorable. As a result, these carbenes are often in the **singlet** state.

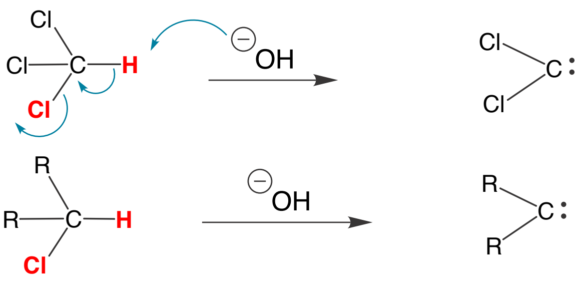


Examples:

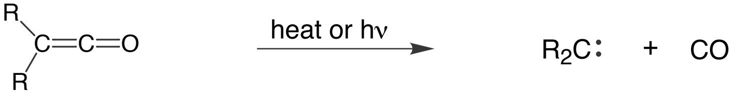


Methods of Synthesis

Alkyl Halides:

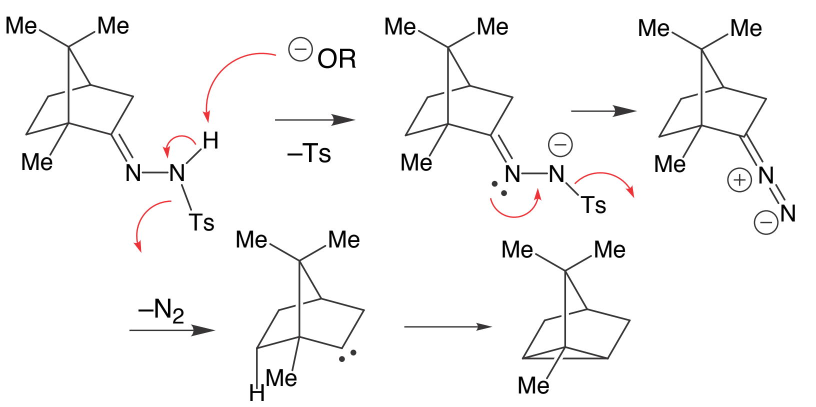


ketenes

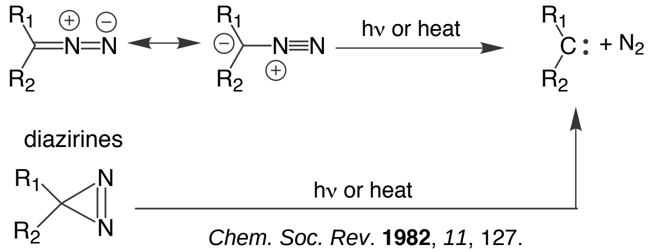


Bamford-Stevens Reaction: See Lecture 28 on Hydrazones

Shapiro *Org. Rxns.* **1976**, *23*, 405.

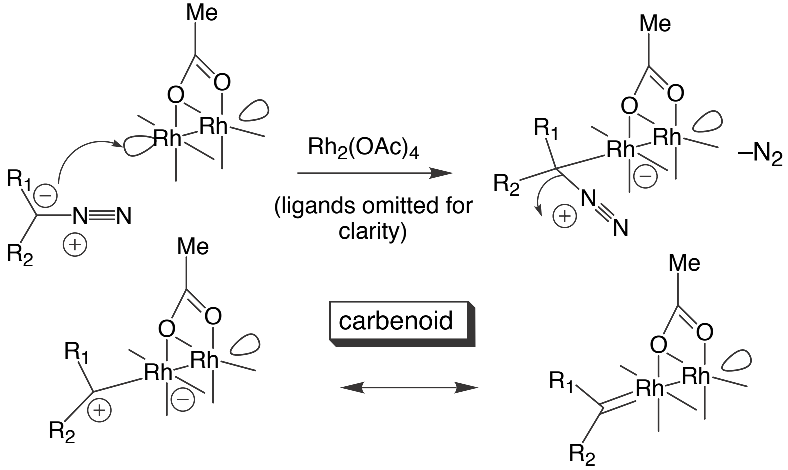


diazo compounds



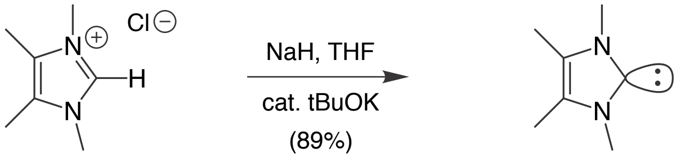
Chem. Soc. Rev. **1982**, *11*, 127.

metal-catalyzed decomposition Doyle *Chem Rev*. **1986**, *86*, 919 **(handout)**

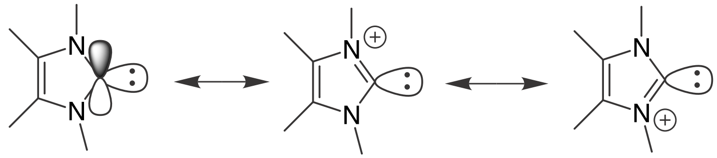


"Stable Carbenes"

"Stable Carbenes–Illusion or reality"?
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674 **(handout)**



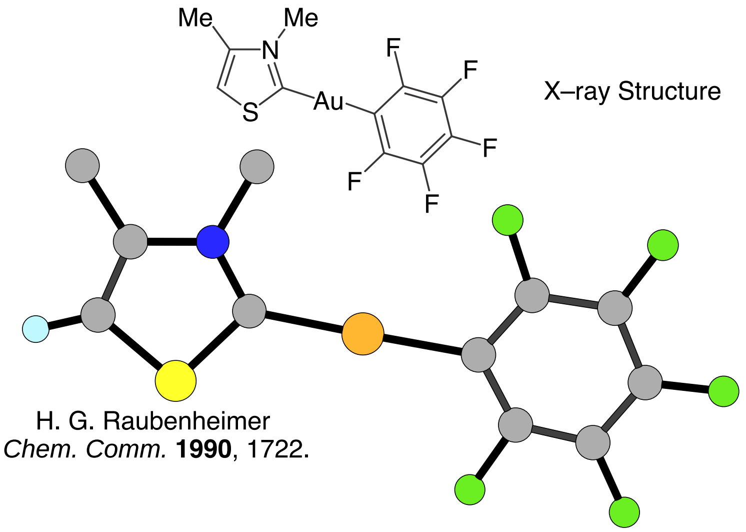
Arduengo et al. *J. Am. Chem. Soc.* **1991**, *113*, 361; **1992**, *114*, 5530.
Arduengo et al. *J. Am. Chem. Soc.* **1994**, *116*, 6812, Neutron diffraction study:



Arduengo argues that these resonance structures are not players based on electron distribution from neutron diffraction.

These are nucleophilic carbenes which display high stability.

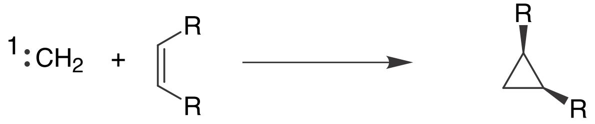
For reviews on the subject, see:
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725.
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674.



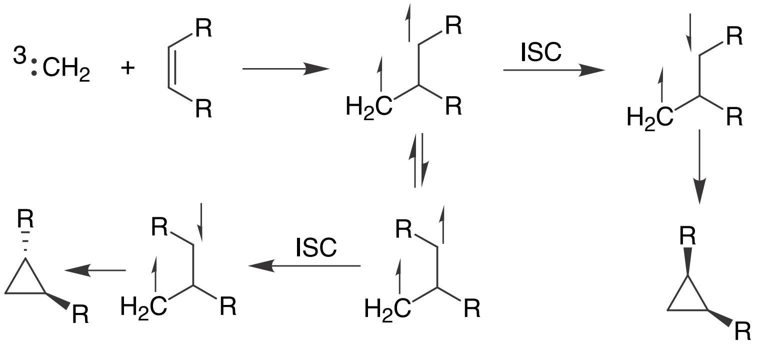
X–ray Structure

H. G. Raubenheimer
Chem. Comm. **1990**, 1722.

Cyclopropanation The Skell Rule:



Singlet carbenes add to olefins **stereospecifically**;

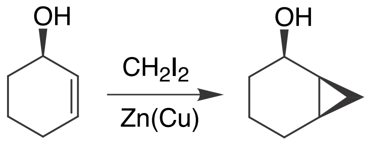


Triplet carbenes add **non-stereospecifically**
Skell and Woodworth *JACS*, **1956**, *78*, 4496.

Synthetic Applications

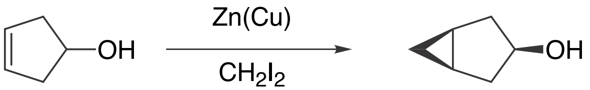
Simmons-Smith Cyclopropanation (See Tedrow hanndout 10B)

Simmons, H.; Smith, R. *J. Am. Chem. Soc.*, **1958**, *80*, 5323.



>99:1 diastereoselectivity

The intermediate organometallic reagent: I–CH$_2$–Zn–I



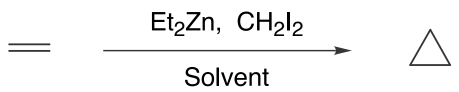
150:1 cis : trans 75% yield

Winstein & Sonnenberg, *JACS* **1961**, *91*, 3235

The Simmons-Smith Reaction

The Furakawa Simmons-Smith Variant

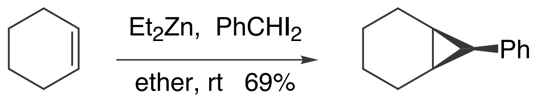
For a recent general review of the Simmons-Smith reaction see: Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



$$Et{-}Zn{-}Et \quad + \quad I{-}CH_2{-}I \rightleftharpoons 2\ \ I{-}CH_2{-}Zn{-}Et$$

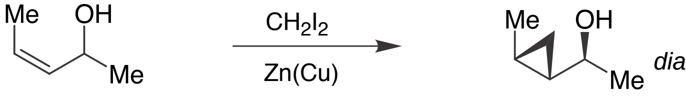
Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron,* **1968,** *24,* 53

Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron,* **1970,** *26,* 243

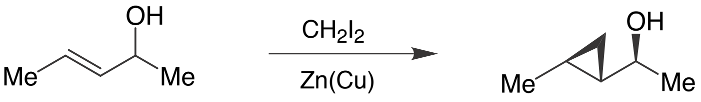


syn : anti
94 : 6

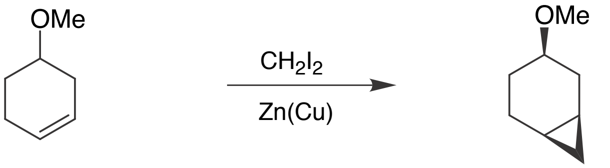
Hydroxyl directivity is a powerful atribute of the S–S Rxn



>99:1 diastereoselectivity

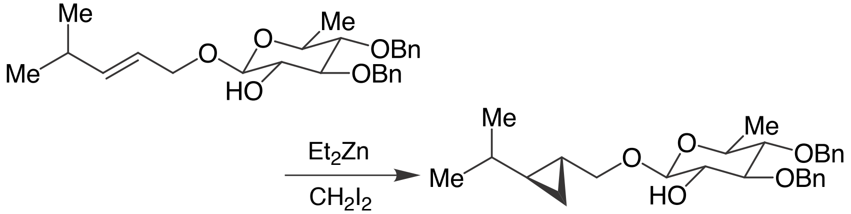


no diastereoselectivity



>99:1 diastereoselectivity

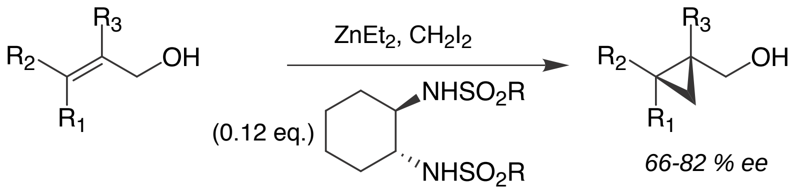
For an review of the directed Simmons-Smith, see:
Evans, D. A.; Hoveyda, A.; Fu, G. *Chem. Rev.* **1993**, *93*, 1307.



Charette, A. B. *JACS* **1991**, *113*, 8166.

>50 : 1 diastereoselection

Catalytic Asymmetric Cyclopropanation:

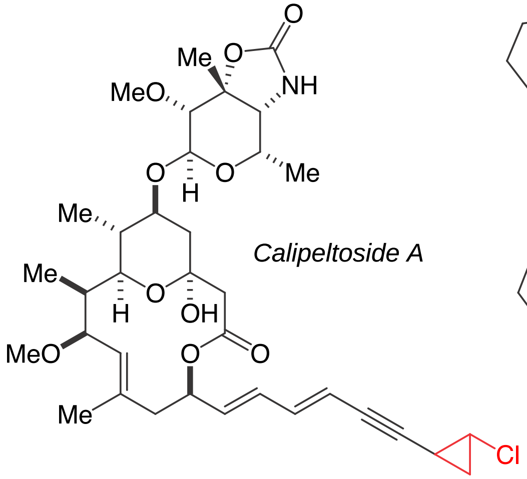


66-82 % ee

Kobayashi, et al. *Tetrahedron Lett*. **1994**, *35*, 7045.

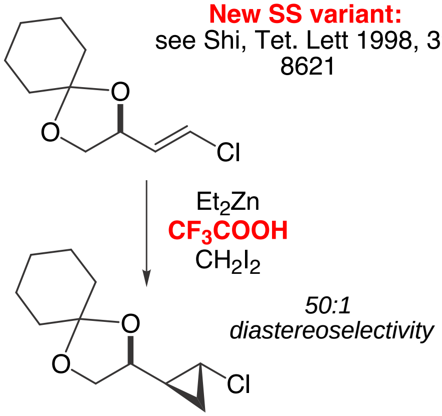
For a Lewis Acid catalyzed process in which the rate of the catalyzed process is faster than the uncatalyzed, see: Charette, A. B. *JACS* **1995**, *117*, 11367.

Applications in Synthesis



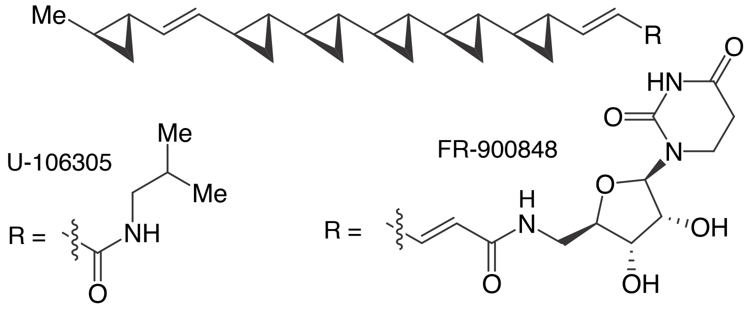
Calipeltoside A

New SS variant:
see Shi, Tet. Lett 1998, 39, 8621



50:1 diastereoselectivity

Evans, Burch
Org. Lett. **2001**, *3*, 503



Charrette, A. B.; *J. Am. Chem. Soc.* **1996**, *118*, 10327.

Falck *J. Am. Chem. Soc.* **1996**, *118*, 6096.

Barrett, *JOC*, **1996**, *61*, 3280.

Tetrahedron Letters 39 (1998) 8621–8624

Exploring New Reactive Species for Cyclopropanation

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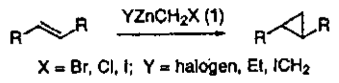
Department of Chemistry, Colorado State University,
Fort Collins, CO 80523
Email: yian@lamar.colostate.edu



(eq. 1)

$$Et_2Zn + 2\,CH_2I_2 \longrightarrow 2EtI + (ICH_2)_2Zn \xrightarrow[\mathbf{2}]{RXH} \underset{\mathbf{3}}{RXZnCH_2I} + CH_3I \qquad \text{(eq. 2)}$$

$$Et_2Zn + \underset{\mathbf{2}}{RXH} \longrightarrow EtH + RXZnEt \xrightarrow{CH_2I_2} \underset{\mathbf{3}}{RXZnCH_2I} + EtI \qquad \text{(eq. 3)}$$

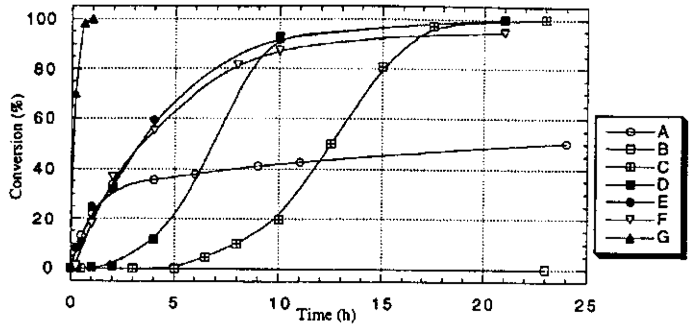
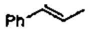
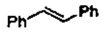
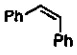
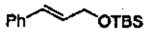
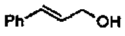
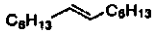
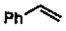
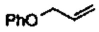
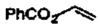
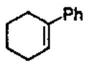


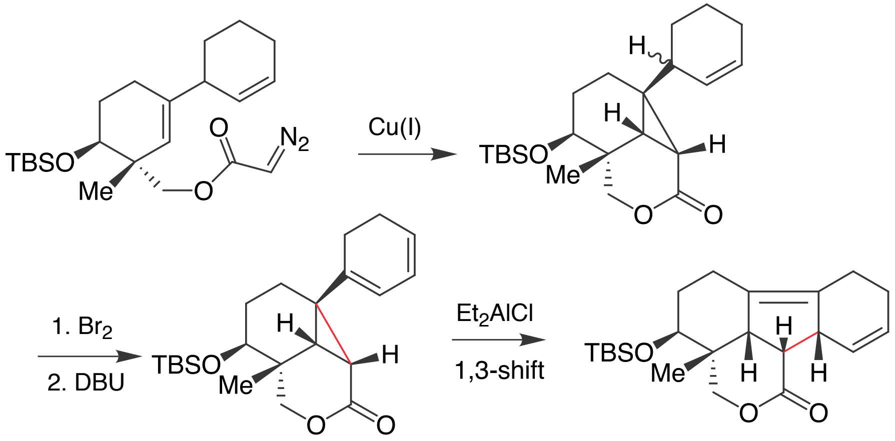
Figure 1. Plot of the conversion of *trans*-β-methylstyrene against time (h). The curves presented are: **(A)** No RXH, **(B)** EtOH or ClCH$_2$CH$_2$OH, **(C)** Cl$_2$CHCH$_2$OH, **(D)** CCl$_3$CH$_2$OH, **(E)** CF$_3$CH$_2$OH, **(F)** PhCO$_2$H, **(G)** CF$_3$CO$_2$H.

Table 1. Cyclopropanation of Representative Olefins Accelerated by CF$_3$CO$_2$H[a]

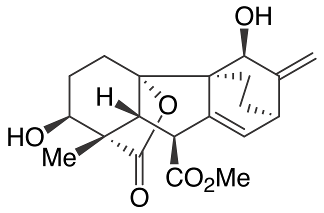
Entry	Substrate	time (min)	Conv. (%)[b]	Yield (%)[c]
1		30	100	77
2		60	>90	70[d]
3		60	nd	72[d]
4		30	100	95
5		40	100	80
6		40	100	99
7		20	100	85
8		30	>97	88
9		150	>90	90
10		30	100	78

Carbenoids: Cyclopropanation

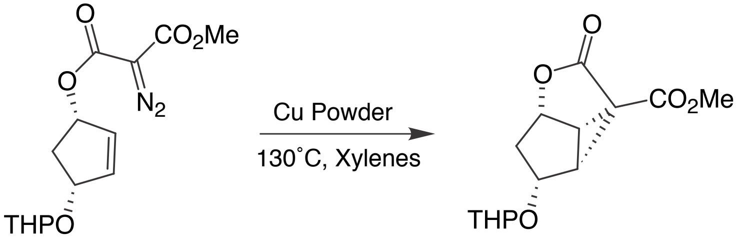
Synthetic Applications

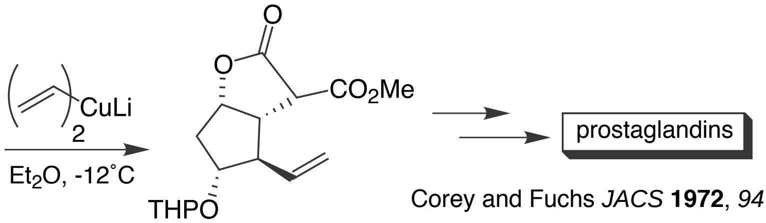


Corey & Myers *JACS* **1985**, *107*, 5574.



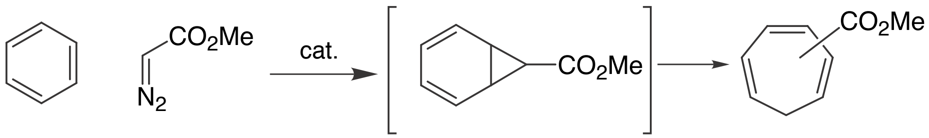
Antheridic Acid

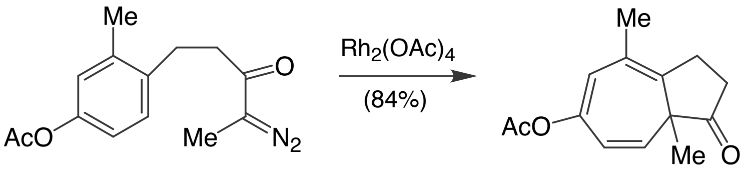


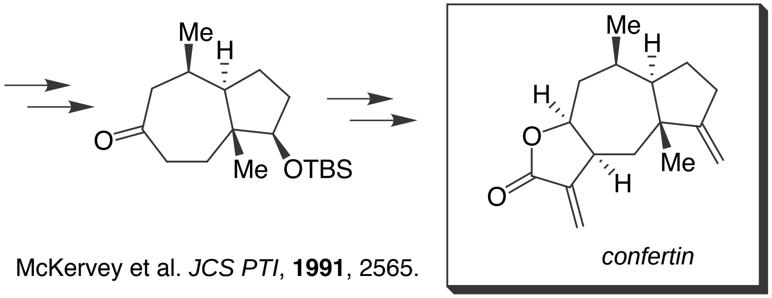


Corey and Fuchs *JACS* **1972**, *94*, 4014.

Buchner Reaction

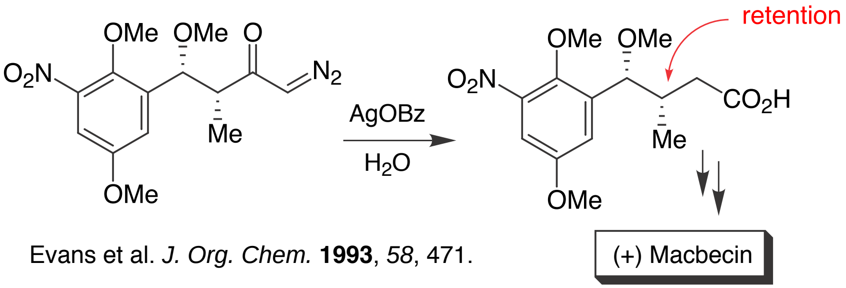






McKervey et al. *JCS PTI*, **1991**, 2565.

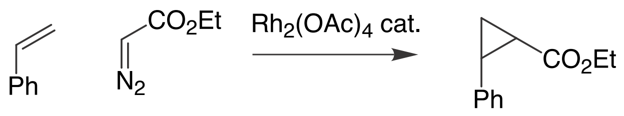
Wolff Rearrangement



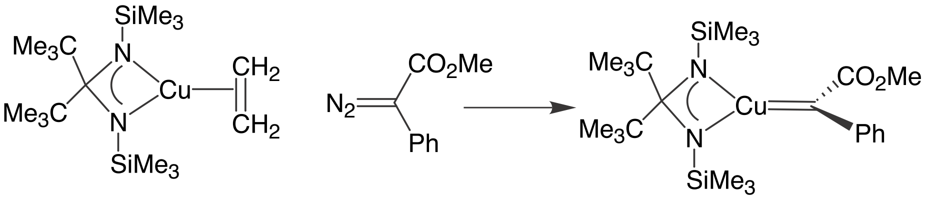
Evans et al. *J. Org. Chem.* **1993**, *58*, 471.

Carbenes: Enantioselective Cyclopropanation

Characterization of metal carbenoid intermediates: not much data!



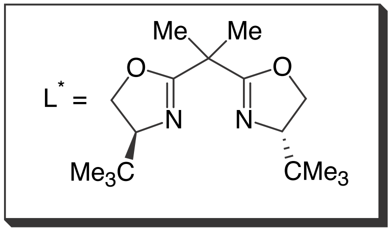
For a detailed mechanistic study which provides supporting evidence for the intermediacy of a Rh carbene, see: Kodakek, *Science*, **1992**, *256*, 1544.

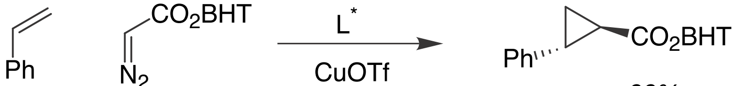


spectroscopically observed

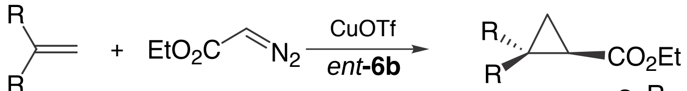
"Copper(I) Carbenes: The Synthesis of Active Intermediates inCu-Catalyzed Cyclopropanation" P. Hoffmann et al, *Angew. Chem. Int. Ed*. **2001**, *40*, 1288-1290

■ Catalytic Asymmetric Variants: Chiral Cu(I) Complexes





99% ee
94:6 trans/cis

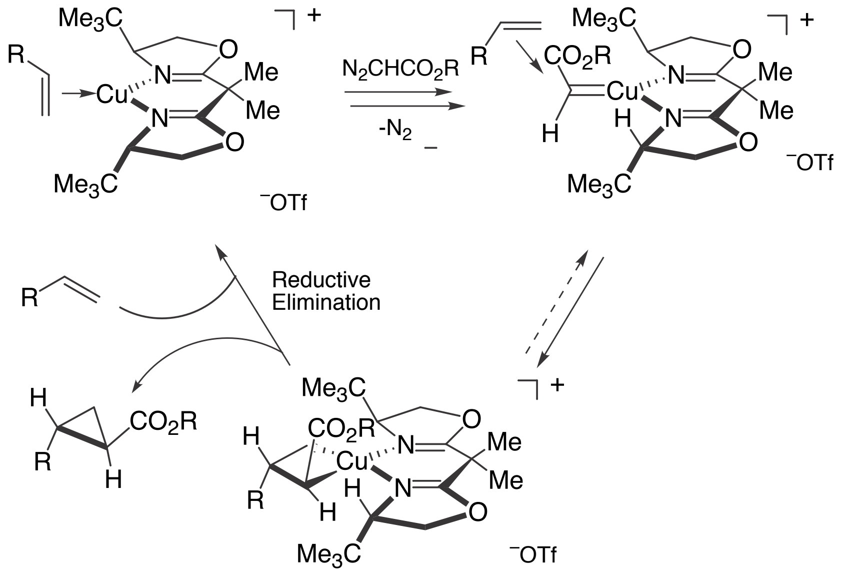


a, R = Ph, >99% ee
b, R = Me, >99% ee

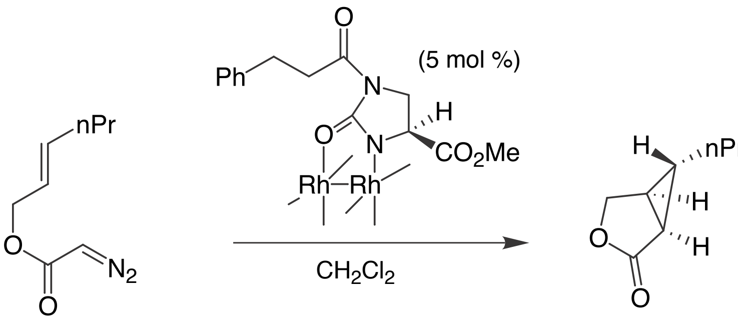
Evans, et al. *J. Am. Chem. Soc.* **1991**, *113*, 726.

■ Mechanism

There is no definitive evidence for metal-catalyzed cyclopropanation and the possibility that metallacyclobutane intermediates are involved cannot be ruled out.



■ Catalytic Asymmetric Variants:Chiral Rh(II) Complexes



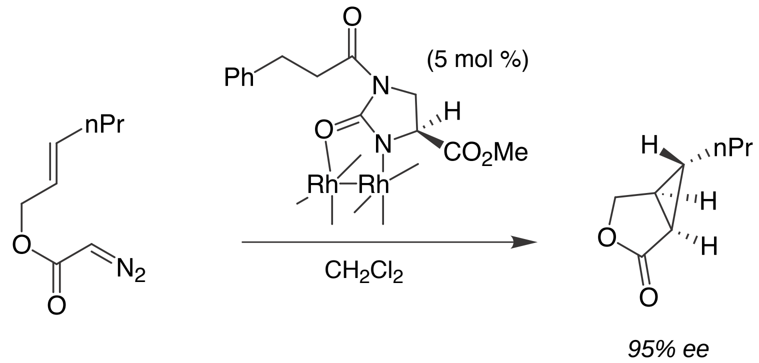
Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.

95% ee

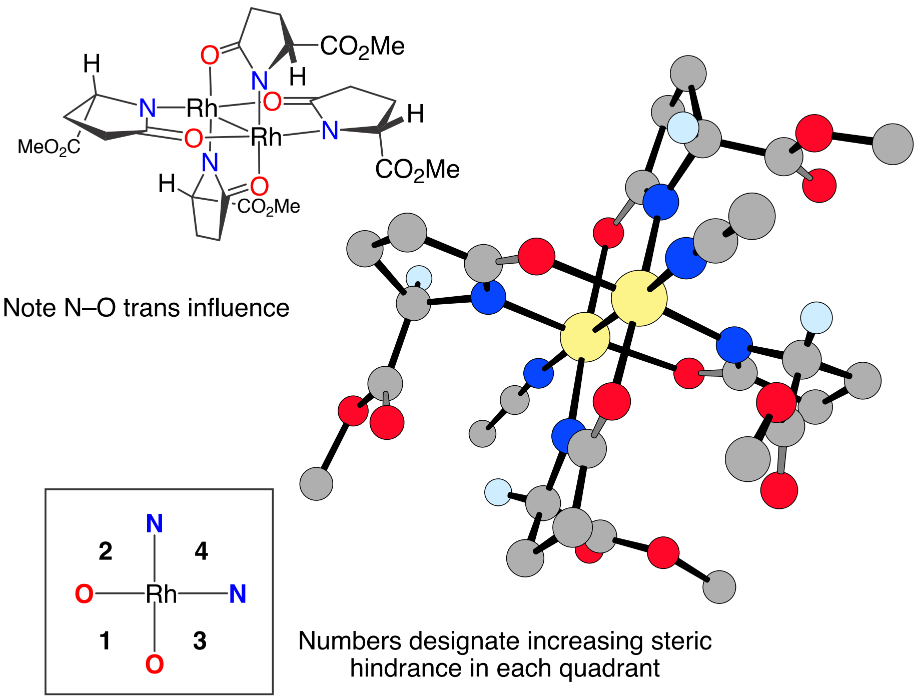
How do these complexes really work??

Carbenes: Enantioselective Cyclopropanation

■ Catalytic Asymmetric Variants: Chiral Rh(II) Complexes



Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.



Note N–O trans influence

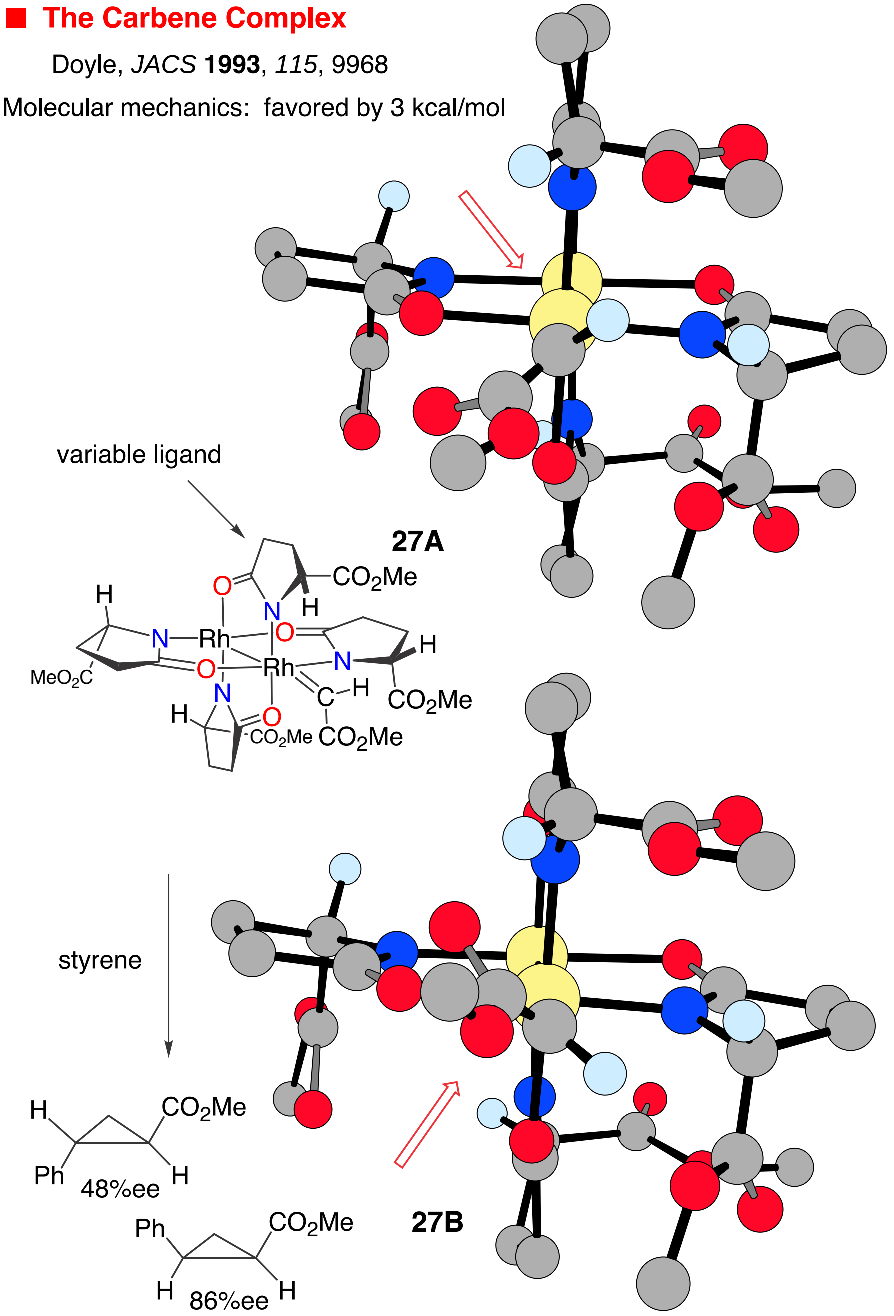
Numbers designate increasing steric hindrance in each quadrant

Doyle, *JACS* **1993**, *115*, 9968

■ The Carbene Complex

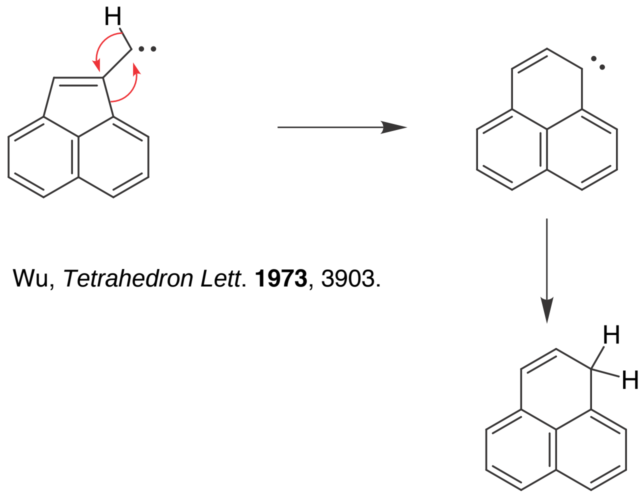
Doyle, *JACS* **1993**, *115*, 9968

Molecular mechanics: favored by 3 kcal/mol



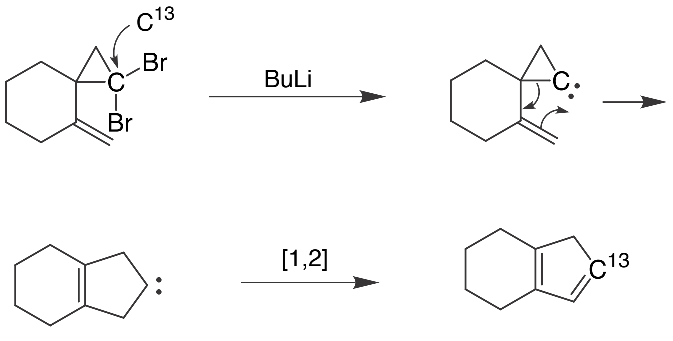
Carbenes: Rearrangements

Carbene-Carbene Rearrangements



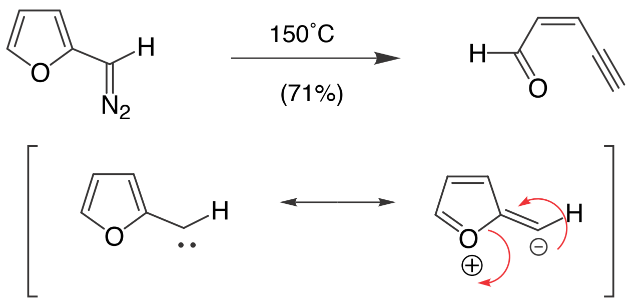
Wu, *Tetrahedron Lett*. **1973**, 3903.

Skattebol Rearrangement

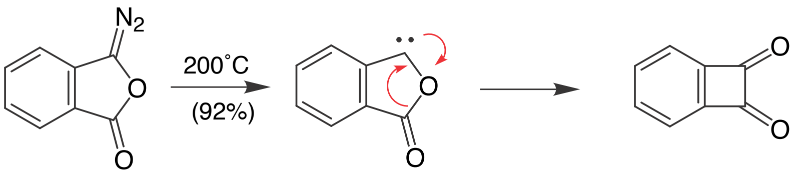


Tetrahedron Lett. **1973**, 2283.

Other Rearrangements



Schecter, *J. Am. Chem. Soc.* **1971**, *93*, 5940.

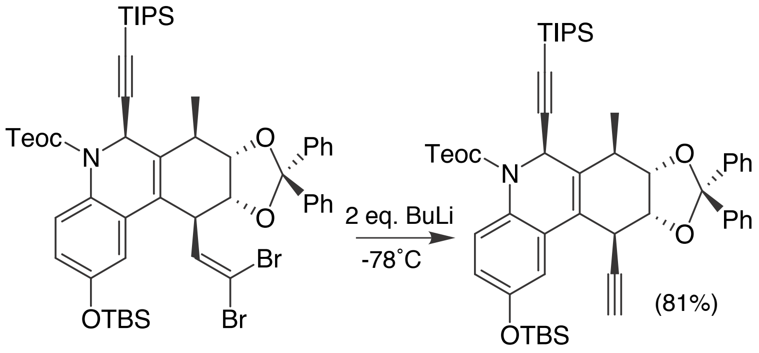


Sammes, *Chem. Comm*. **1975**, 328.

Vinylidenes

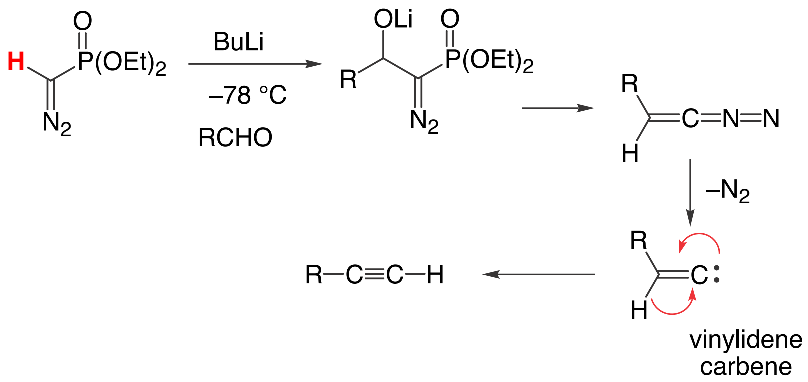
Corey-Fuchs:

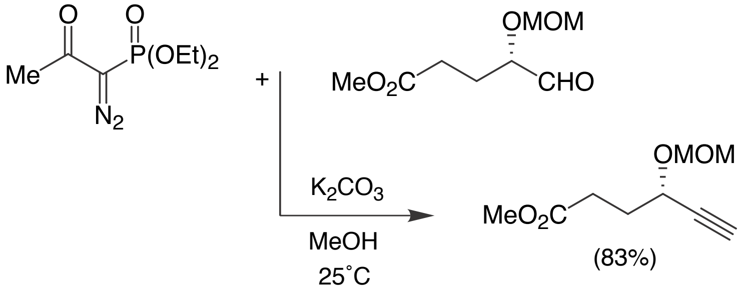
Danishefsky et al.
J. Am. Chem. Soc. **1996**, *118*, 9509.



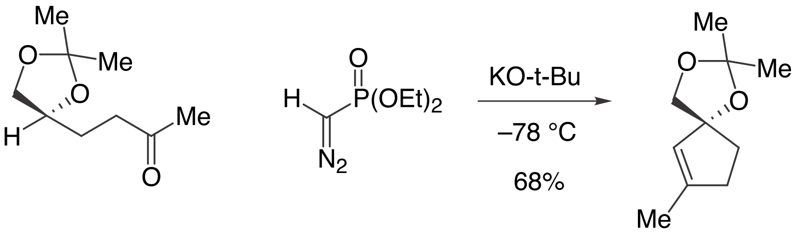
Carbenes: Rearrangements

■ Carbene Rearrangements

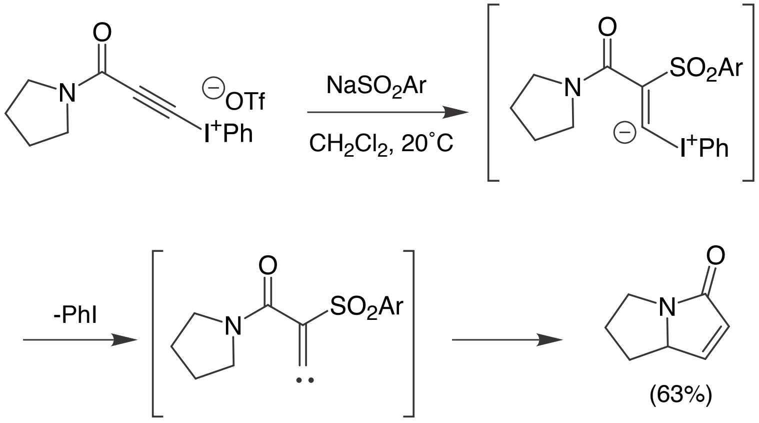




Bestmann, et al. *Synlett* **1996**, 521.

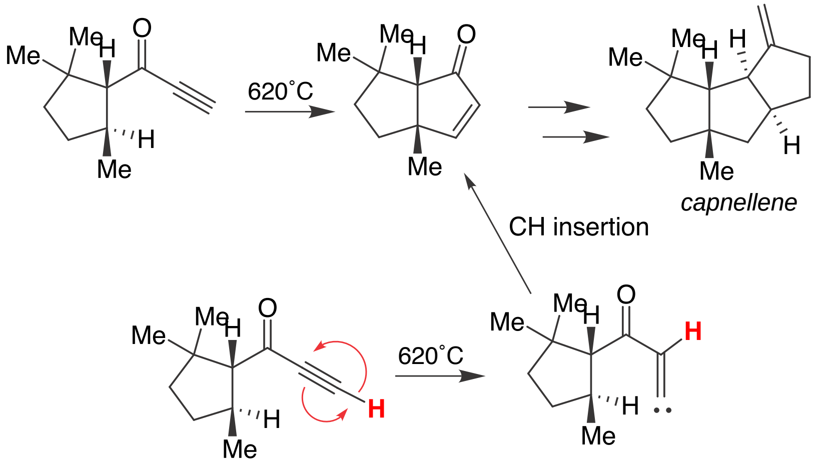


Gilbert, *JOC* **1983**, *48*, 5251



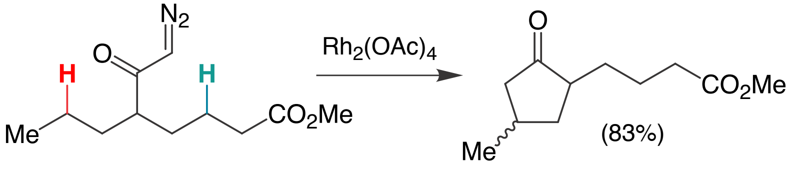
Stang et al. *J. Am. Chem. Soc.* **1994**, *116*, 93.

carbene intermediates are accessible at high temperatures, more later!



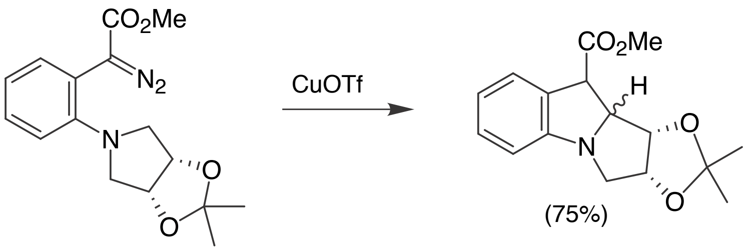
Carbenes: Rearrangements

■ C–H Insertions continued...



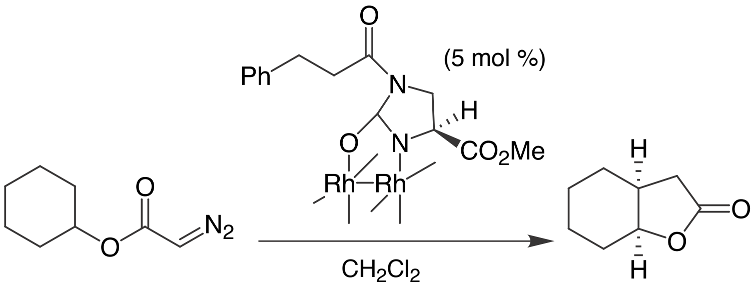
Electrophilic carbenes are very sensitive to electronic effects

Stork *Tetrahedron Lett.* **1988**, *29*, 2283.



Sulikowski, *J. Org. Chem*. **1995**, *60*, 2326.

Enantioselective C-H Insertion

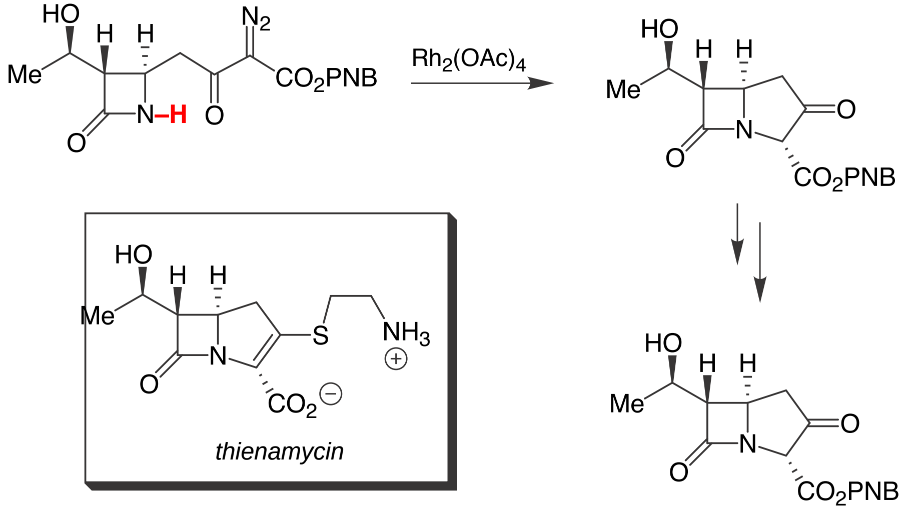


Doyle, *JACS* **1994**, *116*, 4507

99%, 97% ee

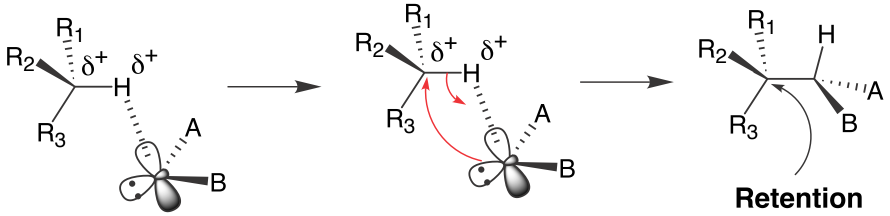
Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, *29*, 3 **(handout)**

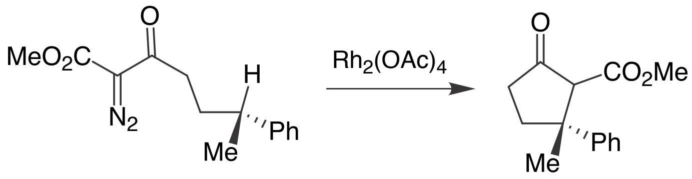
■ N–H Insertions are also possible...



Salzmann, *JACS*, **1980**, *102*, 6163.

Insertions (X-H): Stereochemical outcome

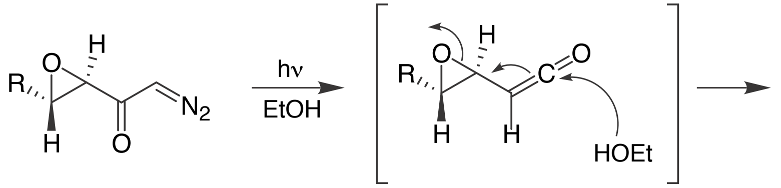


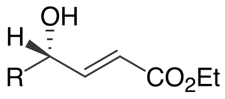


Taber *JACS*, **1996**, *107*, 196.

Carbenes: Rearrangements

Ring Opening

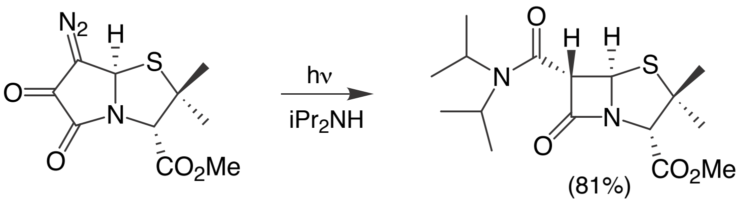




(88%

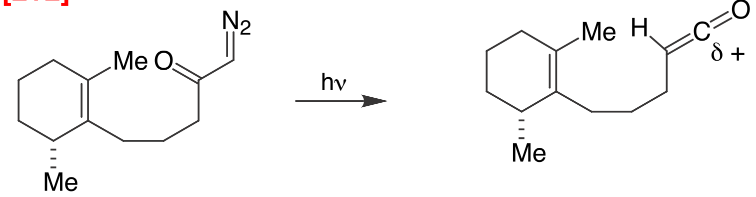
Tetrahedron Lett. **1990**, *31*, 6589.

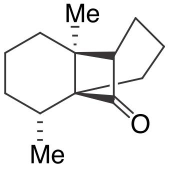
Ring Contraction



Moore et al. *J. Org. Chem.* **1983**, *48*, 3365.

Wolff-[2+2]

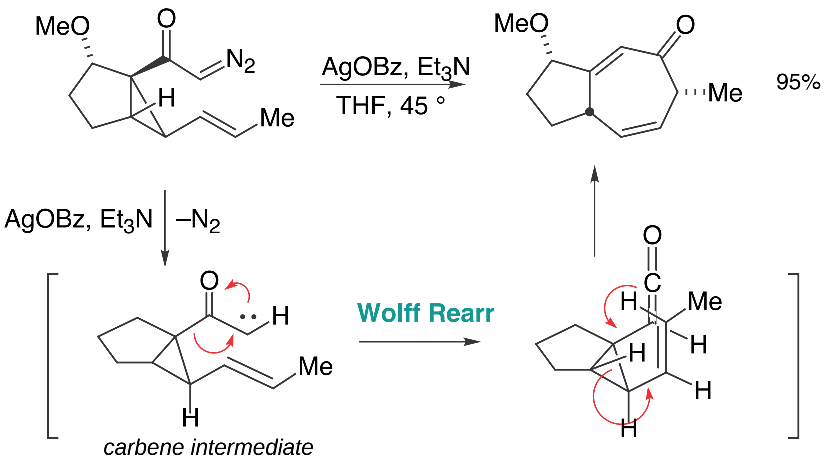




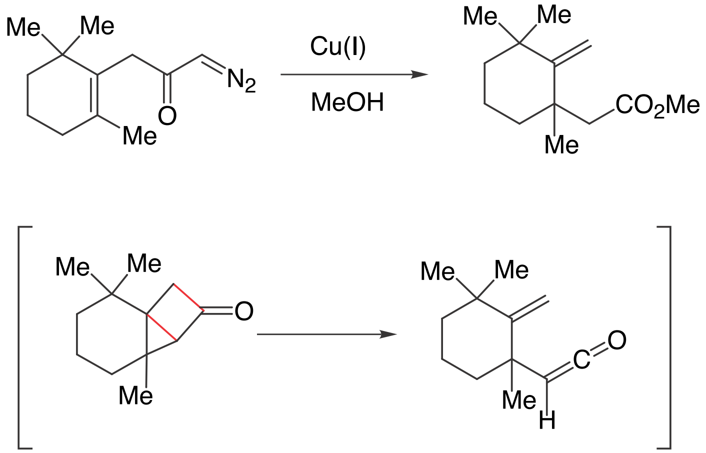
(74%)

J. Org. Chem. **1980**, *45*, 2708.

Problem 332: Wolff Rearrangement Stoltz *ACS* **2003**, *125*, 13624



Vinylolgous Wolff Rearrangement Doyle pp520-521



http://www.courses.fas.harvard.edu/~chem206/

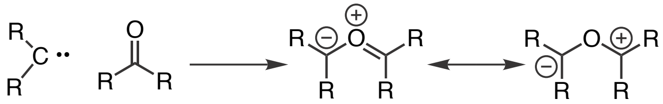
Chemistry 206

Advanced Organic Chemistry

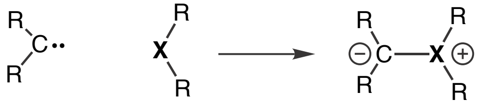
Lecture Number 35

Introduction to Carbenes & Carbenoids-2

- Thermally Induced Carbene Rearrangements
- Carbonyl Ylides and their Reactions



- Oxonium & Sulfonium Ylides and their Reactions



Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 10, "Reactiona Involving Highly Reactive Electron-Deficient Intermediates", 263-350 .

Handout 10B Simmons-Smith Reaction: Enantioselective Variants
Handout 27B Synthetic Applications of α-Diazocarbonyl Compounds
Handout 35A The Use of Fischer Carbenes in Organic Synthesis

D. A. Evans

Friday,
December 12 , 2003

Useful References to the Carbene Literature

Recent Review Article:
Chemistry of Diazocarbonyls: McKervey et al. *Chem Rev*. **1994**, *94*, 1091.

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

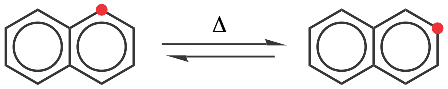
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

The Automerization of Naphthalene (The Cume Question from Hell!)

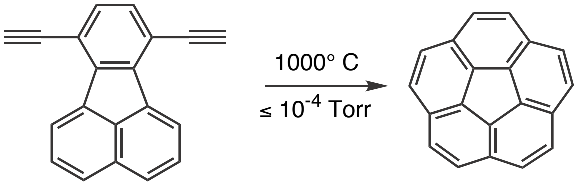
Rationalize



α–^{13}C-labeled $C_{10}H_8$ is isomerized into β–^{13}C-labeled $C_{10}H_8$ at 1035 °C

L. T. Scott, *JACS* **1991**, *113*, 9692.

Provide a Mechanism for this Transformation

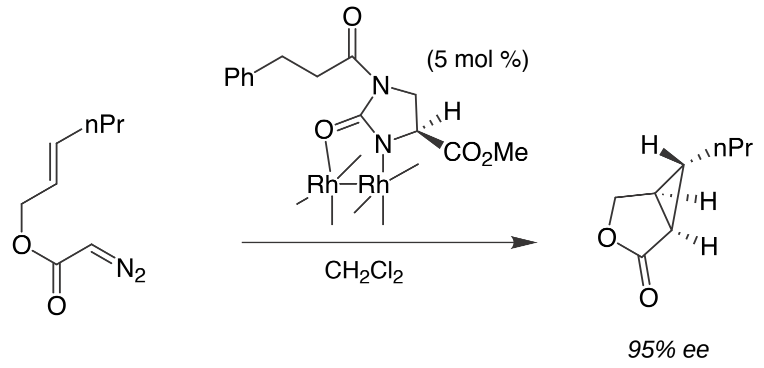


Corannulene 10%

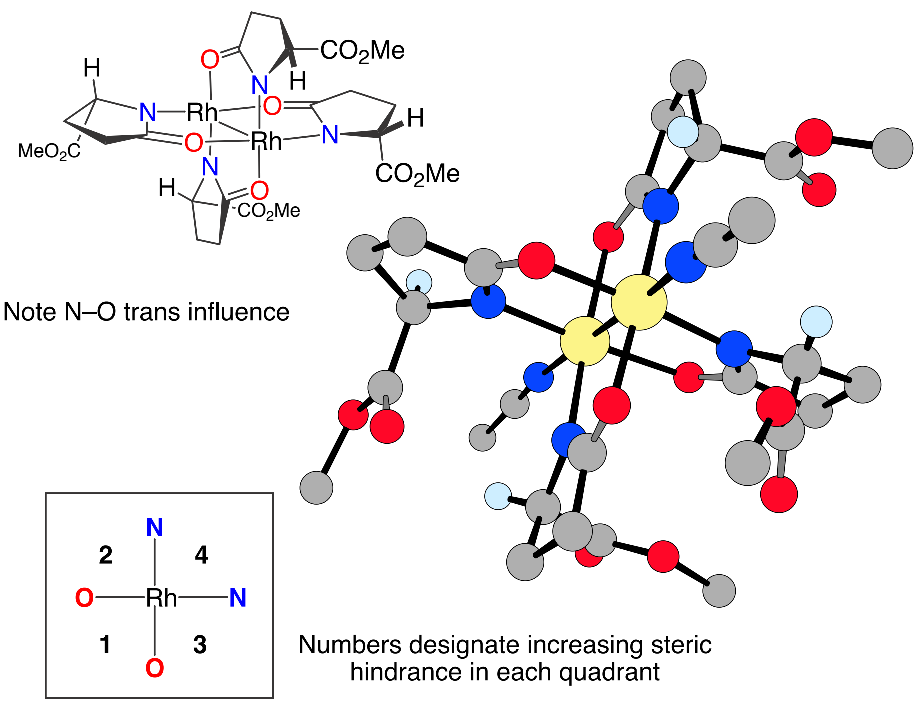
Scott, L.T., et. al., *JACS* **113** 7082 (1991)

Carbenes: Enantioselective Cyclopropanation

■ Catalytic Asymmetric Variants: Chiral Rh(II) Complexes



Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.



Note N–O trans influence

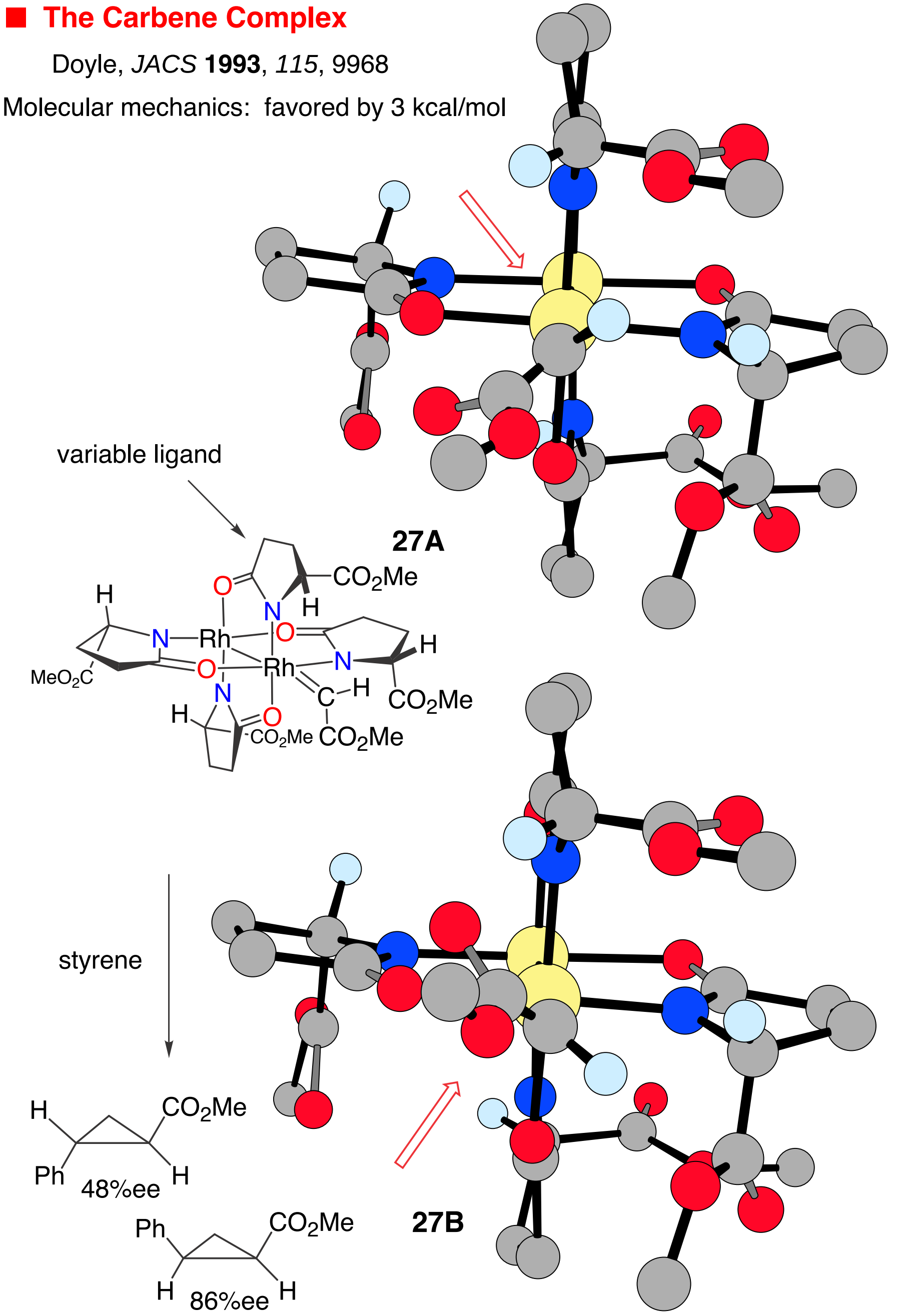
Numbers designate increasing steric hindrance in each quadrant

Doyle, *JACS* **1993**, *115*, 9968

■ The Carbene Complex

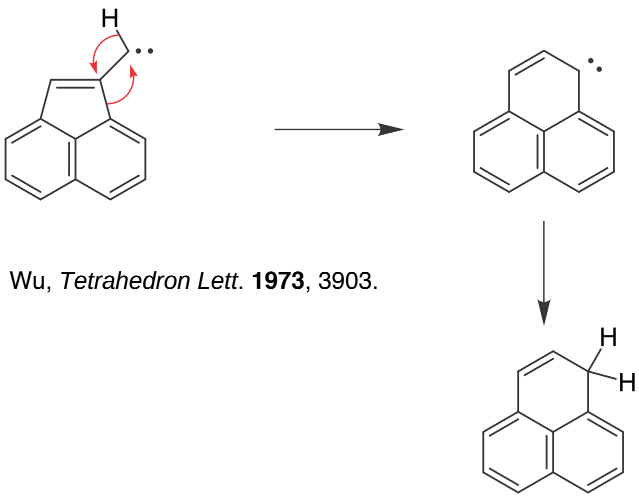
Doyle, *JACS* **1993**, *115*, 9968

Molecular mechanics: favored by 3 kcal/mol



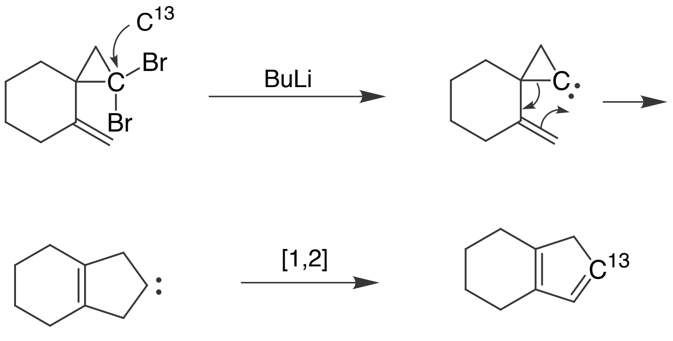
Carbenes: Rearrangements

Carbene-Carbene Rearrangements



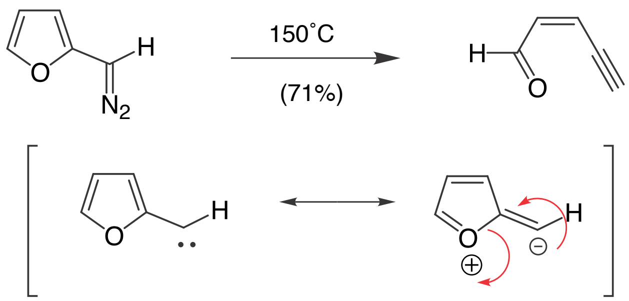
Wu, *Tetrahedron Lett*. **1973**, 3903.

Skattebol Rearrangement

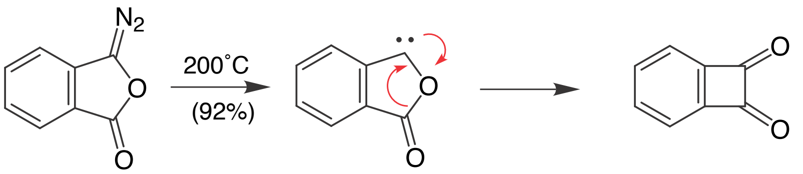


Tetrahedron Lett. **1973**, 2283.

Other Rearrangements



Schecter, *J. Am. Chem. Soc.* **1971**, *93*, 5940.

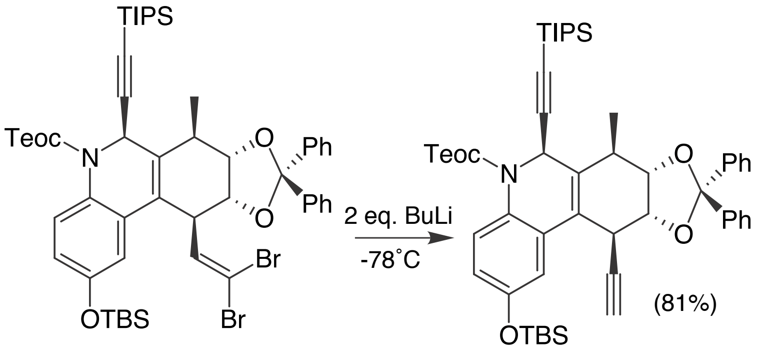


Sammes, *Chem. Comm*. **1975**, 328.

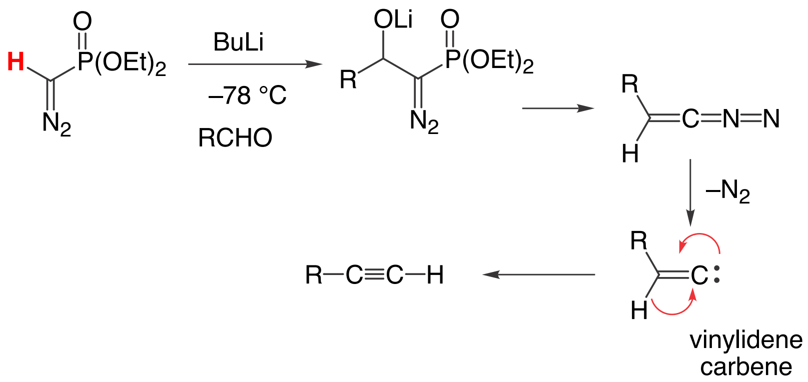
Vinylidenes

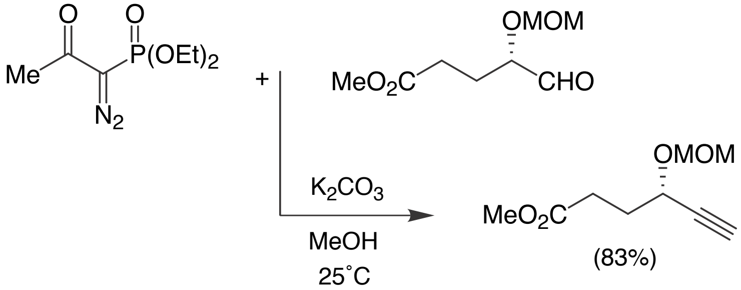
Corey-Fuchs:

Danishefsky et al.
J. Am. Chem. Soc. **1996**, *118*, 9509.

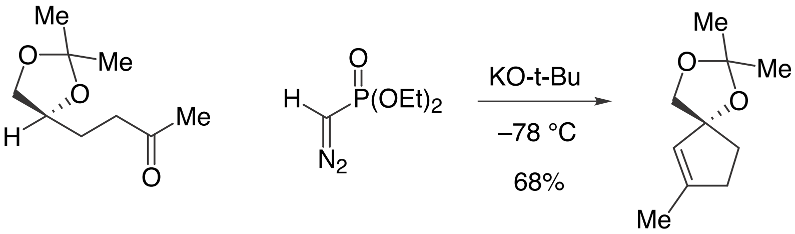


Carbene Rearrangements

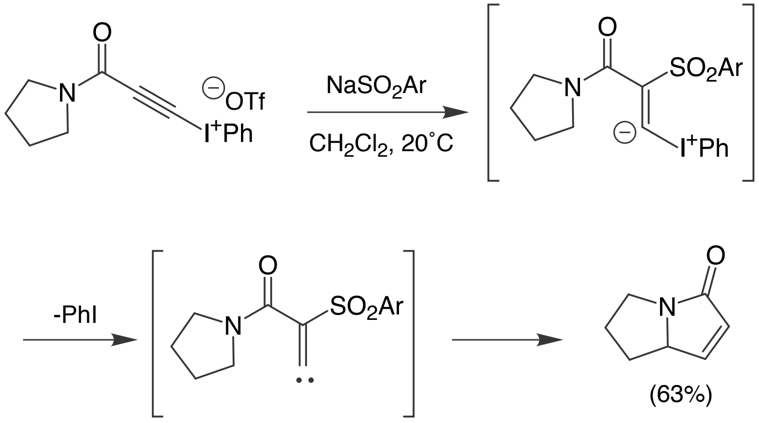




Bestmann, et al. *Synlett* **1996**, 521.

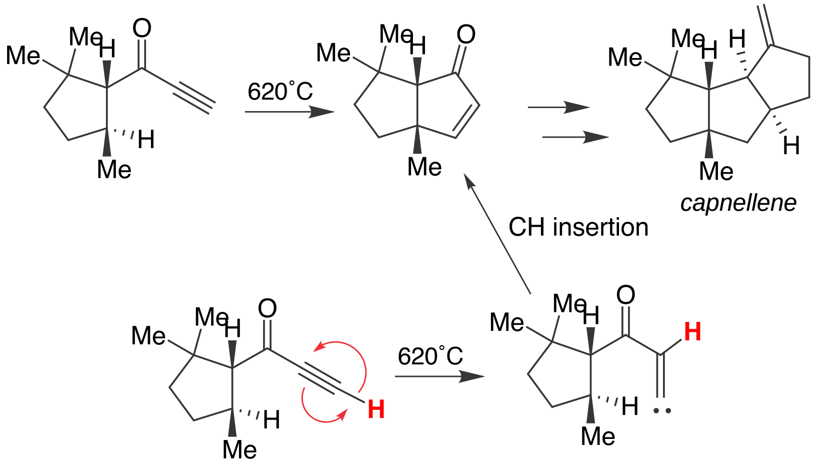


Gilbert, *JOC* **1983**, *48*, 5251



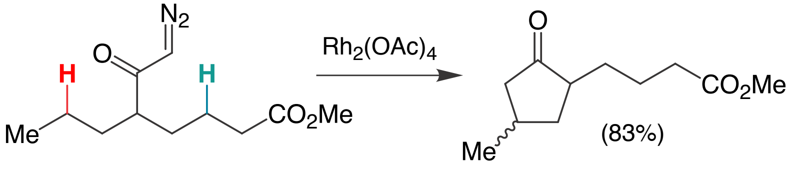
Stang et al. *J. Am. Chem. Soc.* **1994**, *116*, 93.

carbene intermediates are accessible at high temperatures, more later!



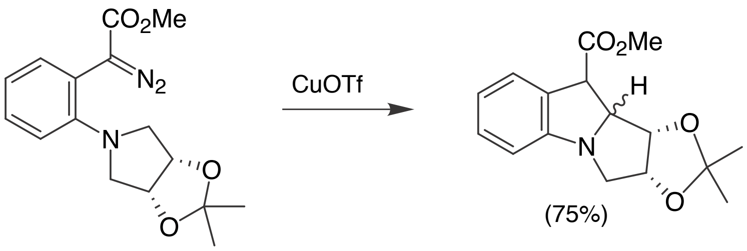
Carbenes: Rearrangements

■ C–H Insertions continued...



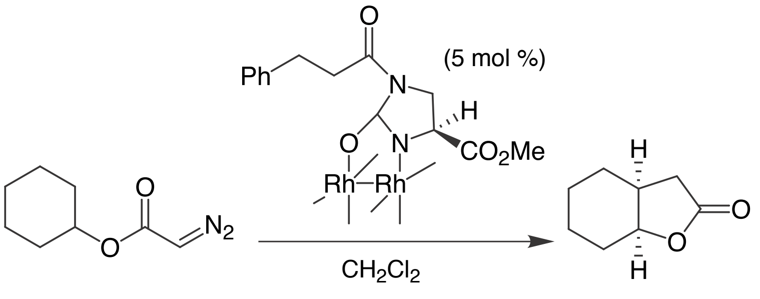
Electrophilic carbenes are very sensitive to electronic effects

Stork *Tetrahedron Lett.* **1988**, *29*, 2283.



Sulikowski, *J. Org. Chem*. **1995**, *60*, 2326.

Enantioselective C-H Insertion

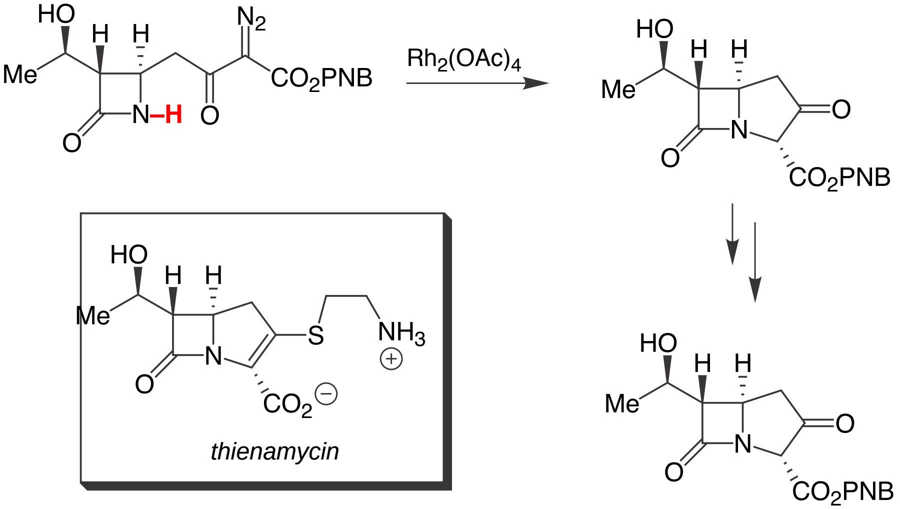


Doyle, *JACS* **1994**, *116*, 4507

99%, 97% ee

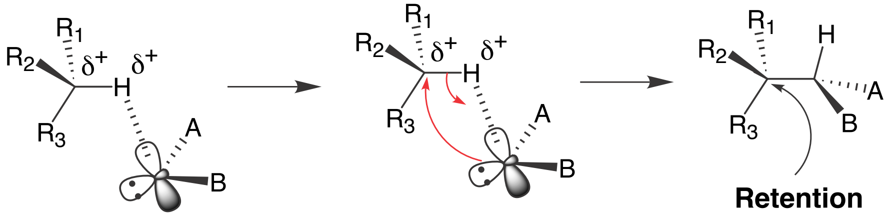
Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, *29*, 3 **(handout)**

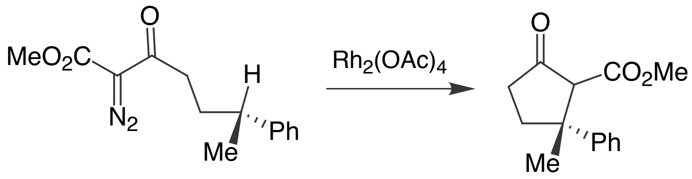
■ N–H Insertions are also possible...



Salzmann, *JACS*, **1980**, *102*, 6163.

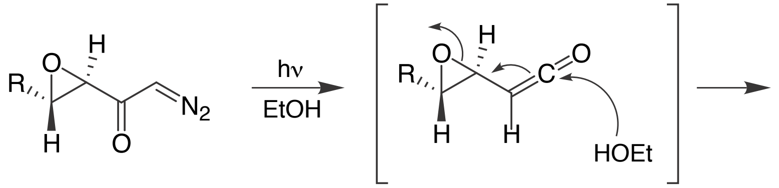
Insertions (X-H): Stereochemical outcome

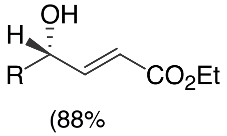




Taber *JACS*, **1996**, *107*, 196.

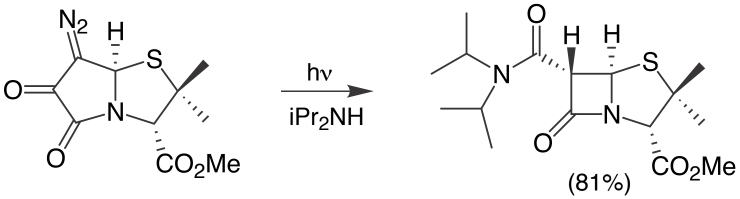
Ring Opening





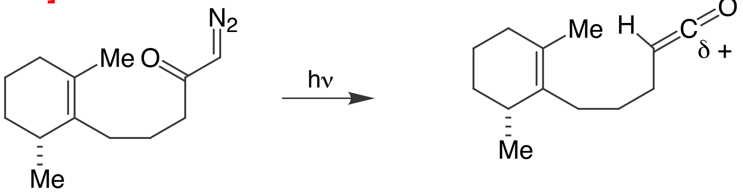
Tetrahedron Lett. **1990**, *31*, 6589.

Ring Contraction

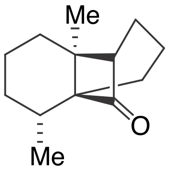


Moore et al. *J. Org. Chem.* **1983**, *48*, 3365.

Wolff-[2+2]

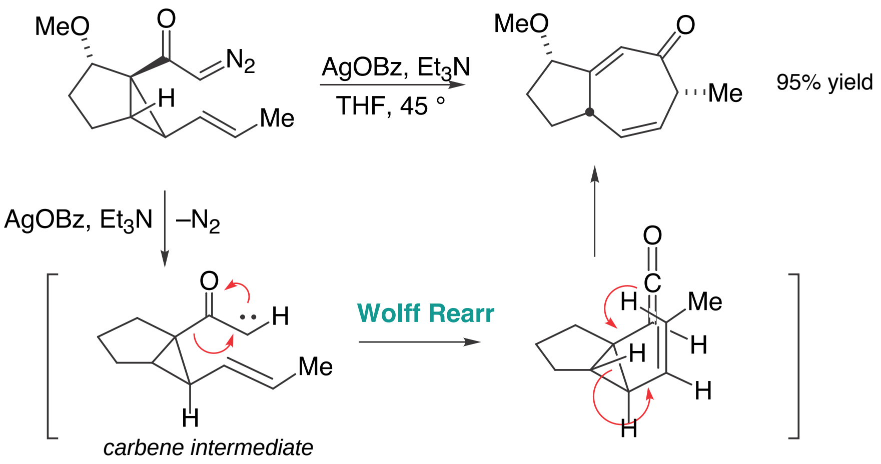


J. Org. Chem. **1980**, *45*, 2708.

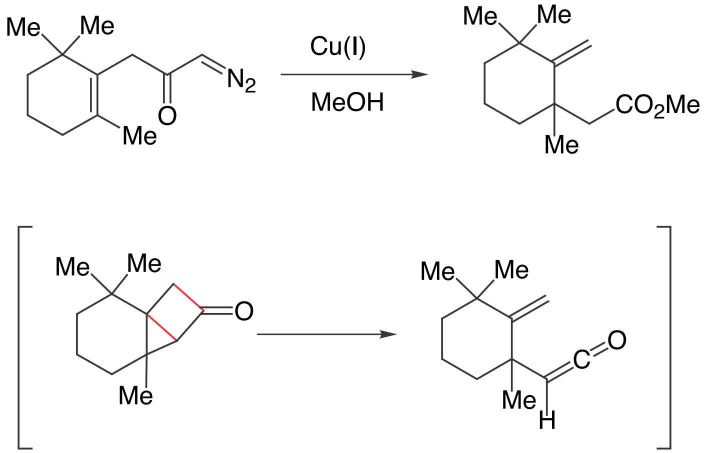


(74%)

Problem 332: Wolff Rearrangement Stoltz *ACS* **2003**, *125*, 13624

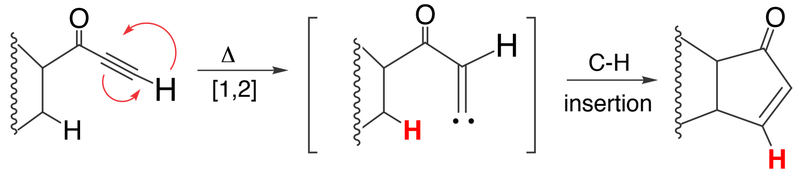


Vinylolgous Wolff Rearrangement Doyle pp520-521

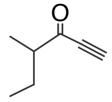
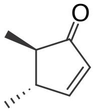
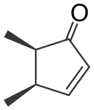
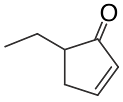
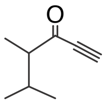
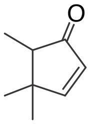
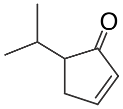
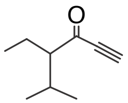
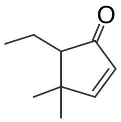
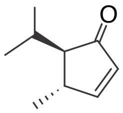
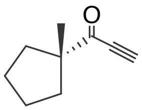
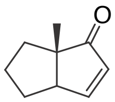
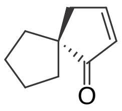


Carbenes are Accessible via Sigmatropic Rearrangement

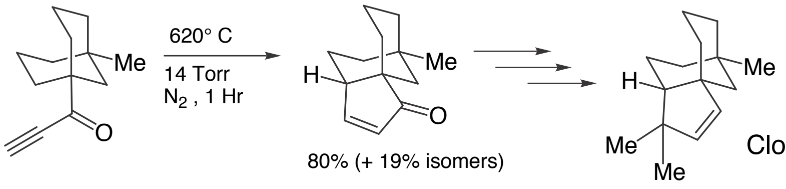
[1,2] Shifts: Alpha-Alkynone Cyclizations



Conditions: 620° C, 12-16 Torr, Quartz filled Quartz Tube

S.M.	3°	2°	1°	Recovery
	–	 60  22	 18	80%
	 87	–	 13	78%
	 54	 46	–	89%
	–	 92	 8	90%

Karpf, M., Dreiding, A., *Helv. Chim. Acta.* **65** 13 (1982)

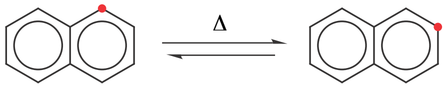


Clovene

Karpf, M., Dreiding, A.S., *Helv. Chim. Acta.* **67** 1963 (1984)

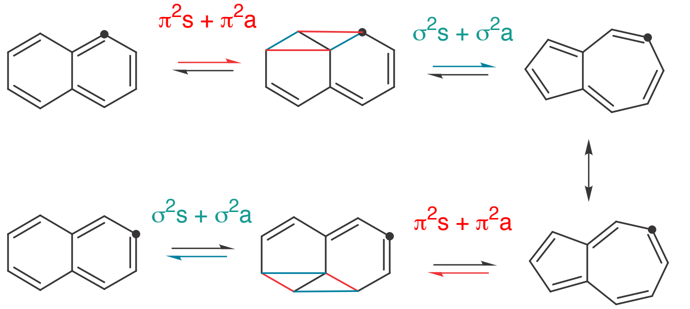
The Automerization of Naphthalene (The Cume Question from Hell!)

Rationalize



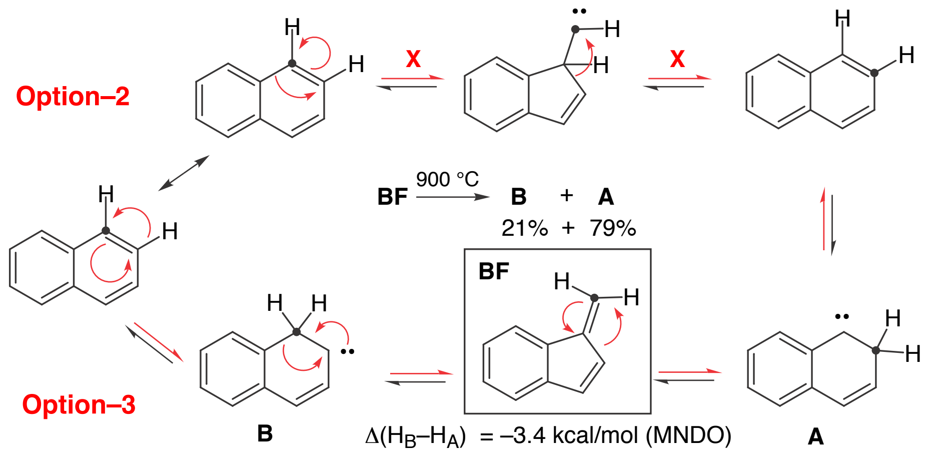
α–^{13}C-labeled $C_{10}H_8$ is isomerized into β–^{13}C-labeled $C_{10}H_8$ at 1035 °C

Mechanism-1: L. T. Scott, *JACS* **1977**, *99*, 4506;



- For the azulene–naphthalene Isomerization: ΔG° = –30.7 kcal/mol (298K)
- The Activation energy for the isomerization: ΔG‡ = +86 kcal/mol

Mechanism-2,3: L. T. Scott, *JACS* **1991**, *113*, 9692.



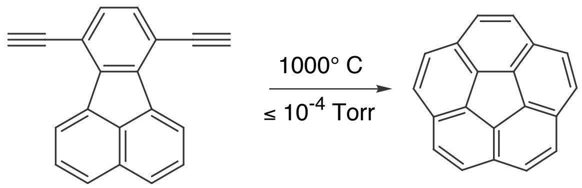
$\mathbf{BF} \xrightarrow{900\ °C} \mathbf{B} + \mathbf{A}$

21% + 79%

$\Delta(H_B–H_A)$ = –3.4 kcal/mol (MNDO)

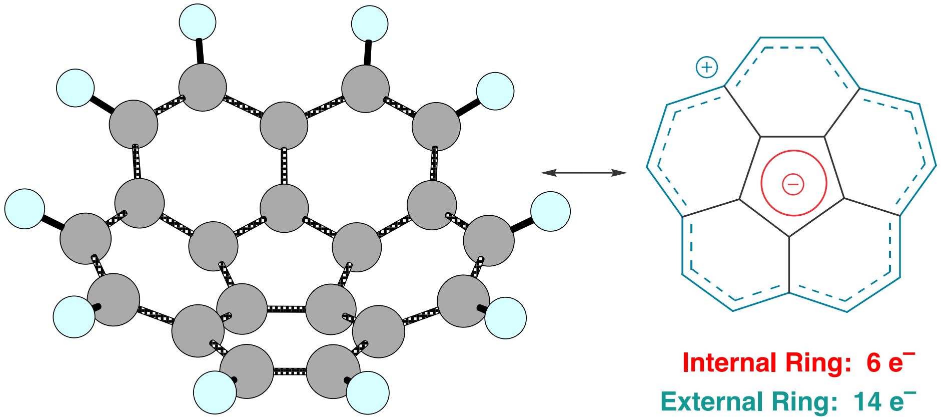
Thermal Generation of Carbene Intermediates

Provide a Mechanism for this Transformation



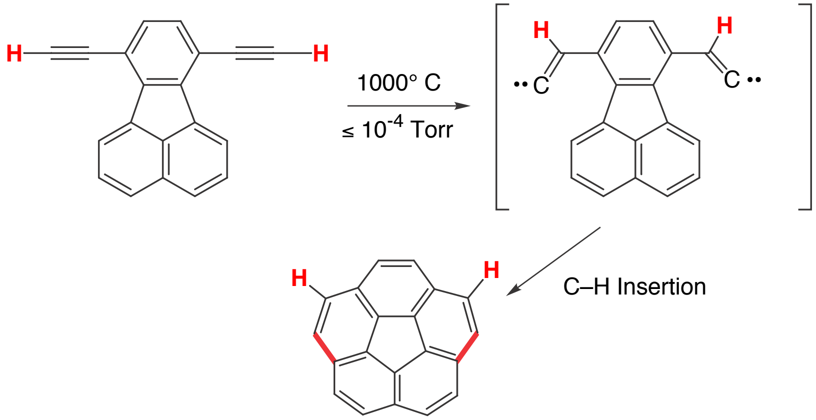
Corannulene 10%

Scott, L.T., et. al., *JACS* **113** 7082 (1991)



Internal Ring: 6 e⁻

External Ring: 14 e⁻



C–H Insertion

Carbenes: Reaction with Heteroatoms

Suggested Reading

Houk and Wu *J. Org. Chem.* **1991**, *56*, 5657.

Padwa and Hornbuckle *Chem. Rev.* **1991**, *91*, 263.

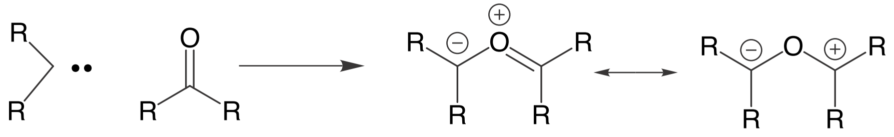
Review Articles

Padwa and Krumpe *Tetrahedron* **1992**, *48*, 5385.

Hoffman, R. W. *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 563.

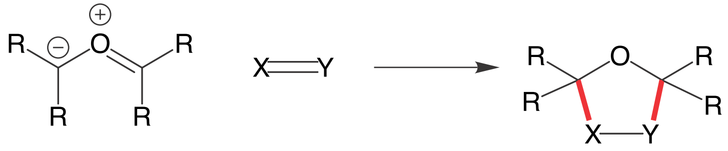
McKervey et al. *Chem. Rev.* **1994**, *94*, 1091.

Ylide Formation by the Interaction of Carbeneoids with Carbonyl Lone Pairs

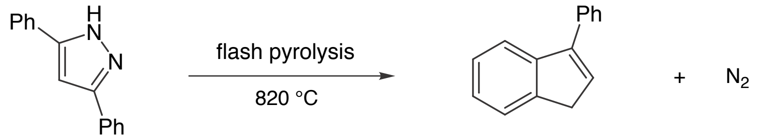


Generally, the carbene precursor of choice is a diazoalkane or, more frequently, an α-diazocarbonyl reagent. These can be decomposed via thermolysis or photolysis. However, the most common method involves catalytic amounts of transition metals, such as copper or rhodium.

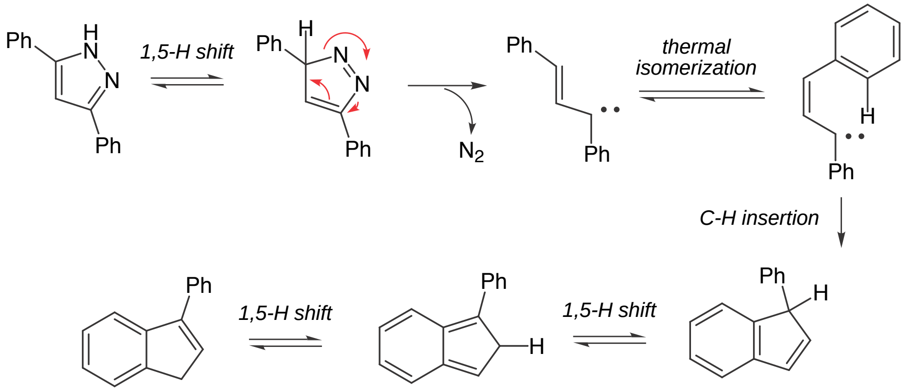
Dipolar Cycloaddition (See Lecture 18)



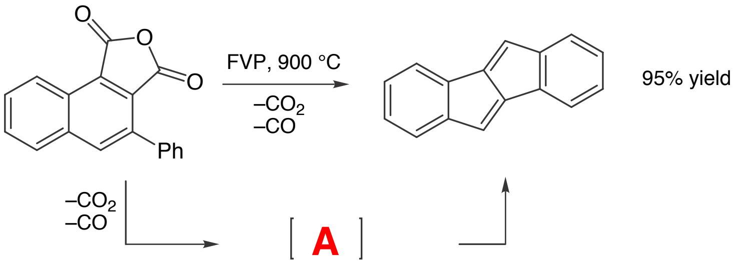
Web Problem 88. Please provide a mechanism for the following high temperature reaction that was reported by Yranzo and co-workers (*J. Org. Chem.* **1998**, *63*, 8188).



Draw a plausible mechanism for the transformation to the major product isomer. *Do not invoke any radical intermediates in your answer.*

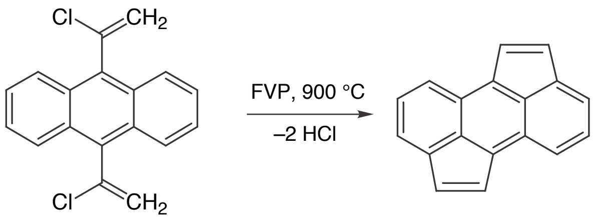


Web Problem 135. Anderson has reported the transformation illustrated below (*Aust J. Chem.* **1990**, *43*, 1137) which is implemented by flash vacuum pyrolysis (FVP). As indicated, this reaction proceeds through intermediate **A**.



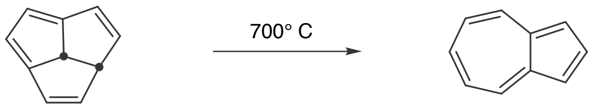
Provide a mechanism for this reaction and identify intermediate **A** in your answer.

Web Problem 172. Scott has recently reported the transformation illustrated below (*Tetrahedron Lett.* **1997**, *38*, 1877) which is implemented by flash vacuum pyrolysis (FVP) at the indicated temperature.

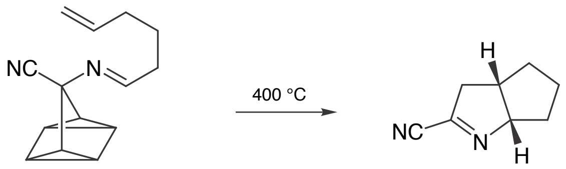


Provide a concise mechanism for this reaction in the space below.

Web Problem 198. Provide a mechanism for the thermal conversion of triquinacene to azulene (*JACS*, **1973**, 2724).



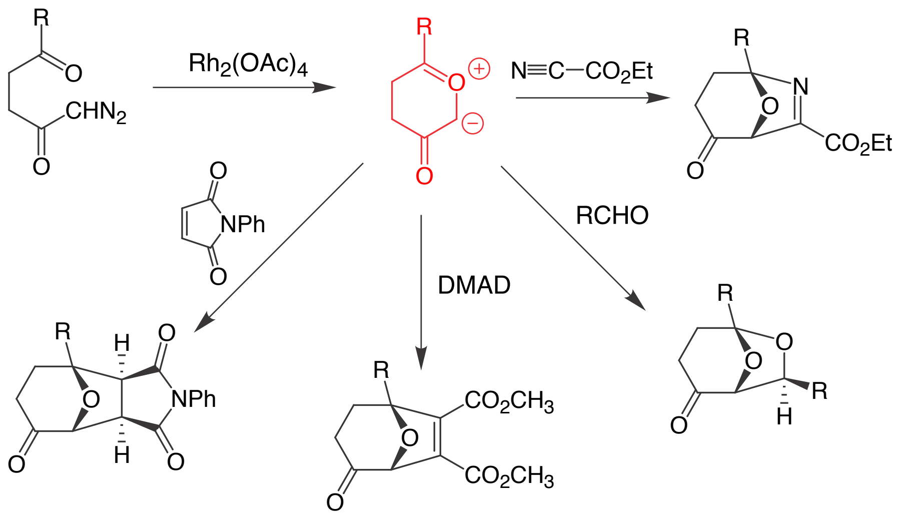
Web Problem 282. Hoffmann has reported the mechanistically interesting thermally induced transformation illustrated below (*Chem. Ber.* **1985**, 634.).



Provide a plausible mechanism for this reaction.

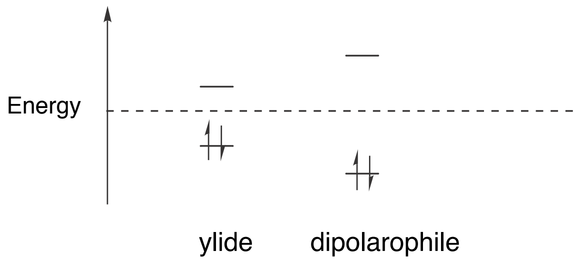
Carbonyl Ylids: Dipolar Cycloaddition

Tandem Intramolecular Cyclization–Intermolecular Cycloaddition

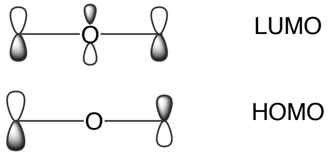


Dipolar-Dipolarophile Cycloadditions: HOMO–LUMO Energies

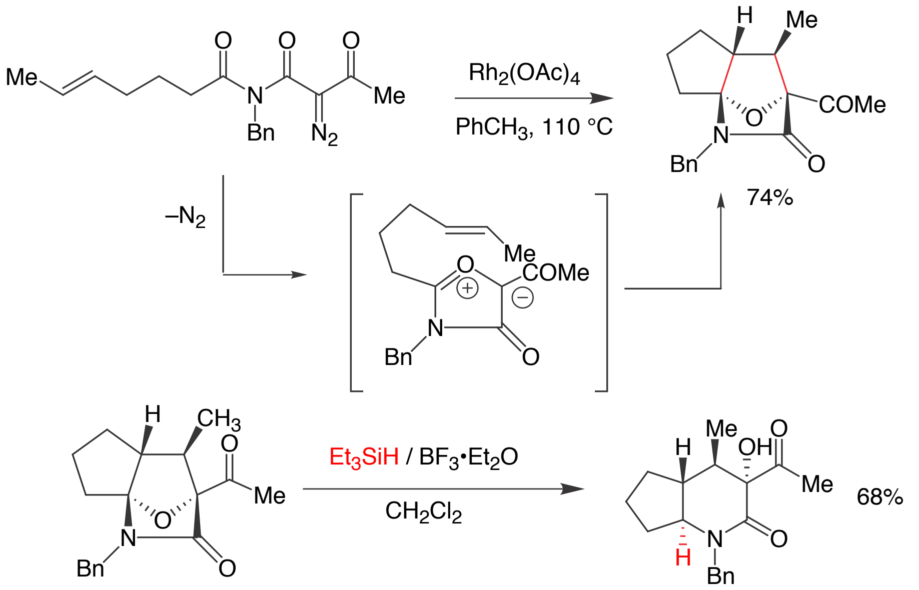
Carbonyl Ylides have very small HOMO-LUMO gaps



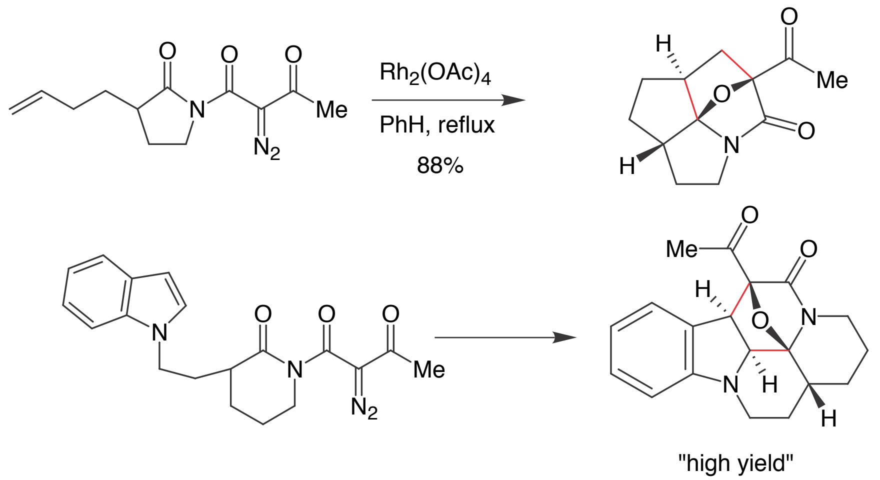
Therefore, either raising the dipolarophile HOMO (electron-donating substituents) or lowering the LUMO (electron-withdrawing) will accelerate the reaction.



Reactions of Diazoimides: [3+2] addition

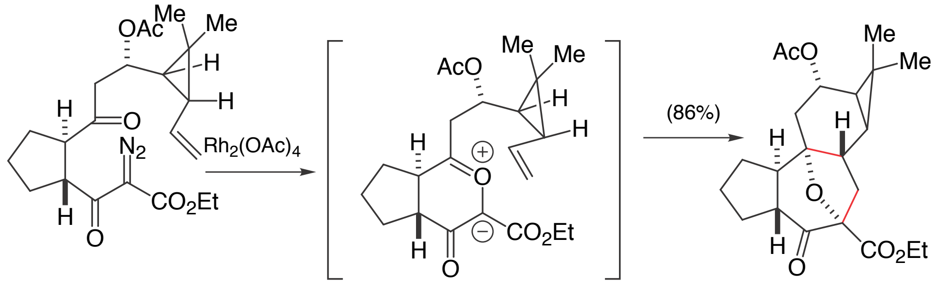


Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677-1680.



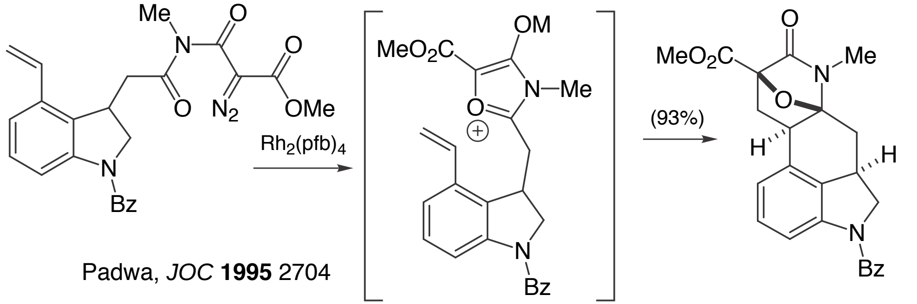
Padwa et. al. *Tetrahedron Lett.* **1992**, *33*, 4731-4734.

Dipolar Cycloadditions: Carbonyl Ylides



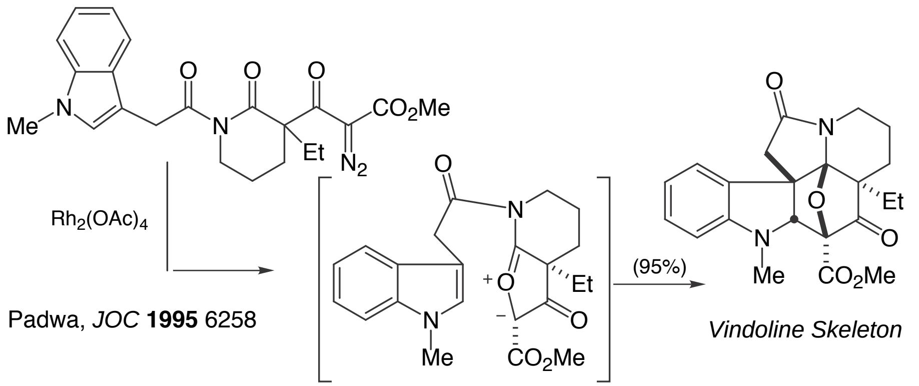
Dauben, *JOC* **1993** 7635

Tigilane Skeleton



Padwa, *JOC* **1995** 2704

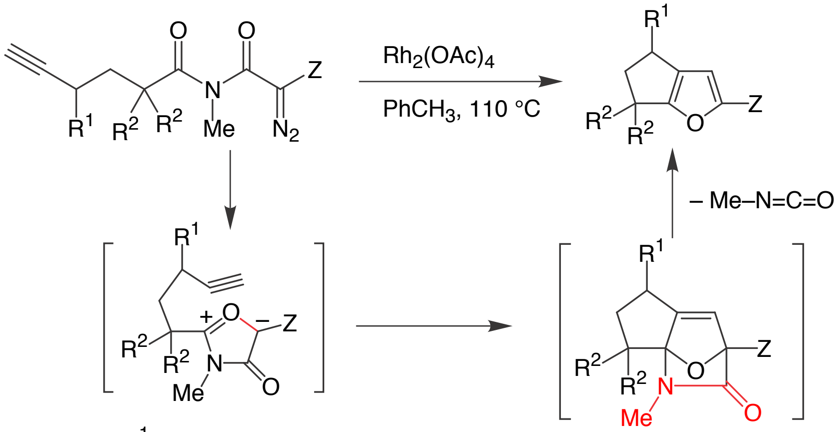
Lysergic Acid Skeleton



Padwa, *JOC* **1995** 6258

Vindoline Skeleton

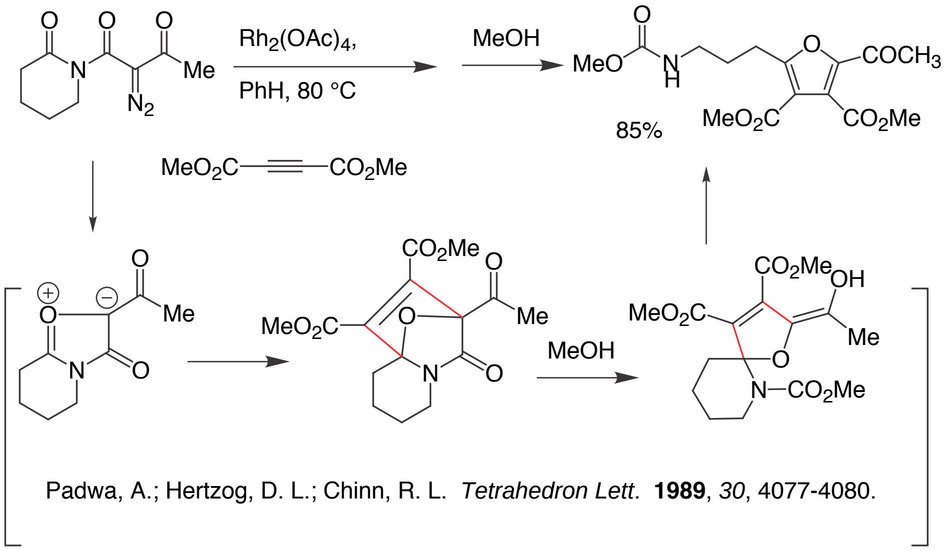
Reactions of Diazoimides: [3+2] addition – [4+2] retroaddition



R^1 = H, OBn
R^2 = H, Me
Z = COMe, CO_2Me

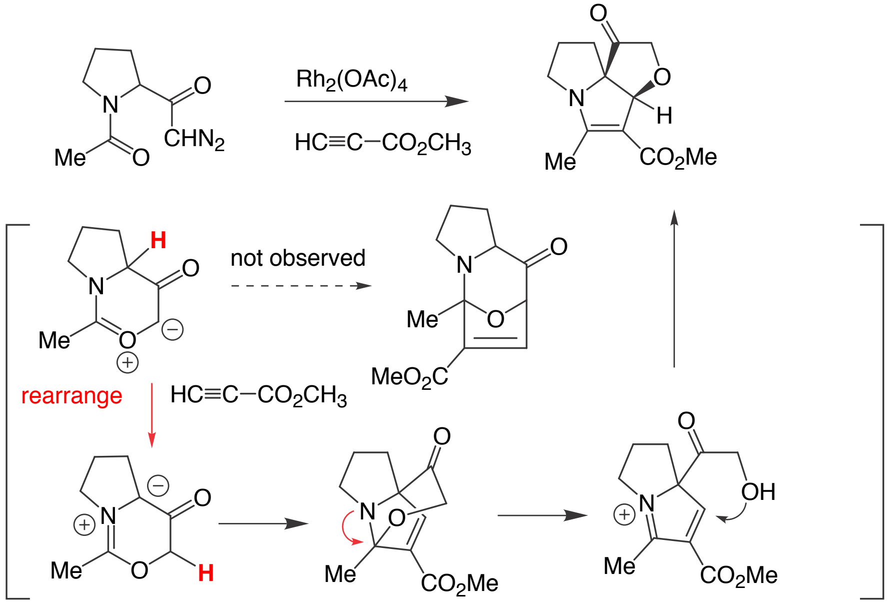
Yields = 44-63%

Maier, M. E.; Schöffling, B. *Chem. Ber*. **1989**, *122*, 1081-1087.



Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett*. **1989**, *30*, 4077-4080.

The Carbonyl Ylide - Azomethine "Dipole Cascade"

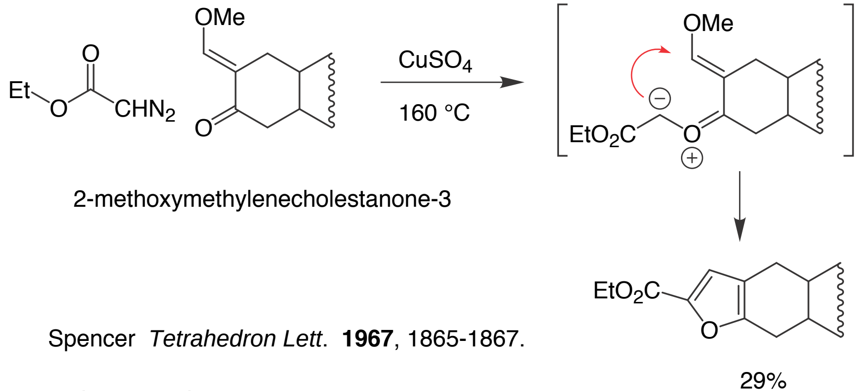


The 1,3-proton shift is catalyzed by trace amounts of water. Azomethine ylide formation requires a proton at the tertiary center.

Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451-6452.
Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593-601.

The Synthesis of Furans

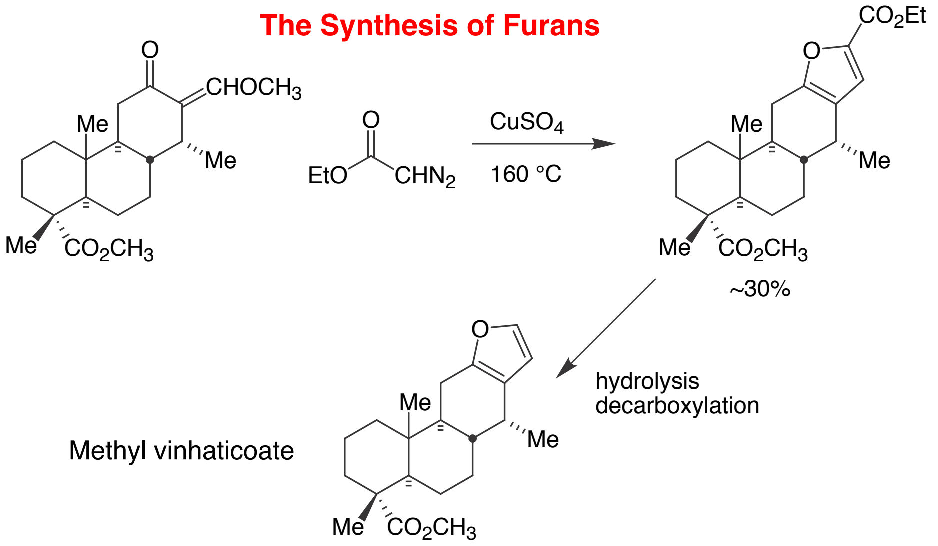
Intermolecular addition to α,β-unsaturated carbonyls



2-methoxymethylenecholestanone-3

Spencer *Tetrahedron Lett.* **1967**, 1865-1867.

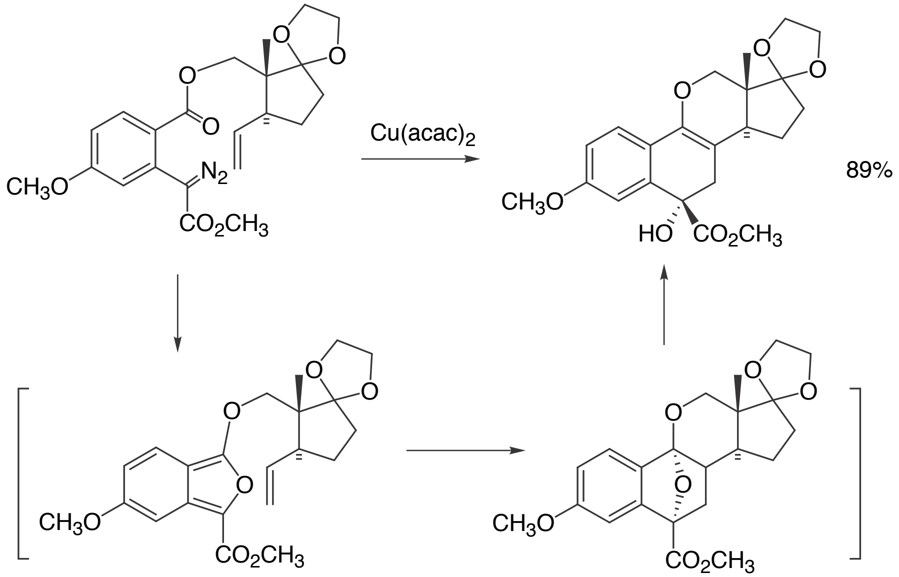
The Synthesis of Furans



Methyl vinhaticoate

Spencer, T. A., *et. al.* *JACS* **1967**, *89*, 5497.

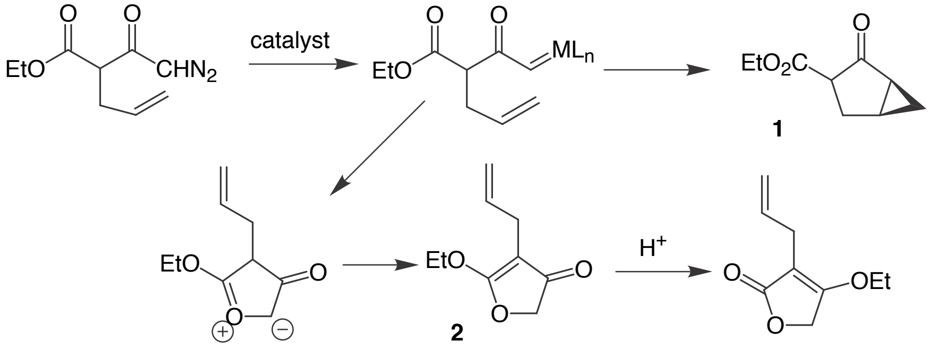
Can you propose a rational mechanism for this transformation?



Hildebrandt, *Tetrahedron Lett.* **1988**, *29*, 2045-2046.

Carbene Heteroatom Transformations: Ylide Formation

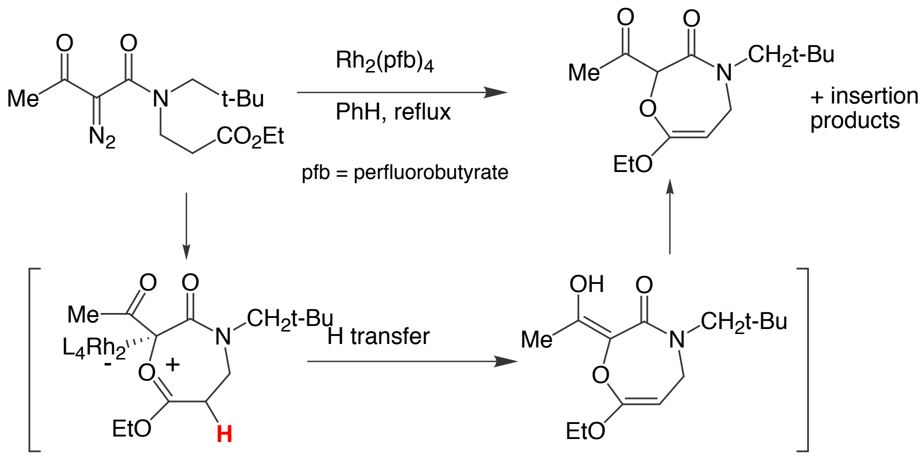
Ylid Formation versus Cyclopropanation



catalyst	Temp (°C)	%1	%2
$Pd_2Cl_2(C_3H_5)_2$	RT	53	3
$Cu(PhCOCHCOMe)_2$	80	50	13
$(MeO)_3PCuI$	RT	3	35
$Rh_2(OAc)_4$	RT	**1**	**58**
None	80	15	54

it is evident that these are reactions of metal carbenoids

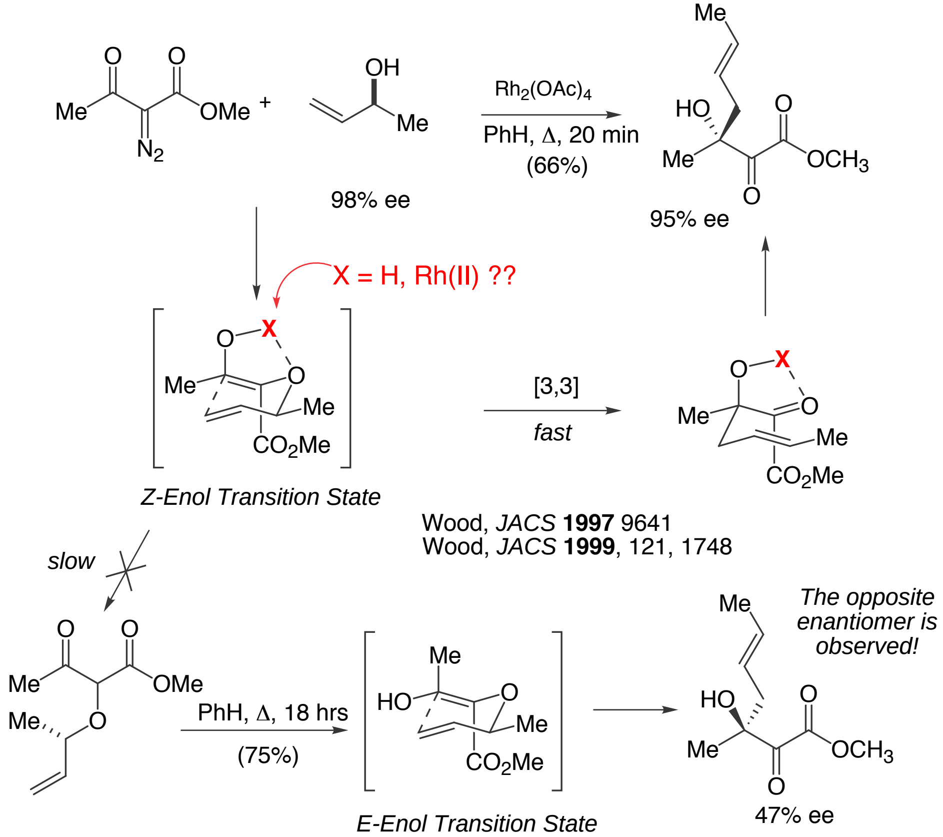
Bien, S.; Gillon, A.; Kohen, S. *J. Chem. Soc. Perkin Trans. I.* **1976**, 489-492



pfb = perfluorobutyrate

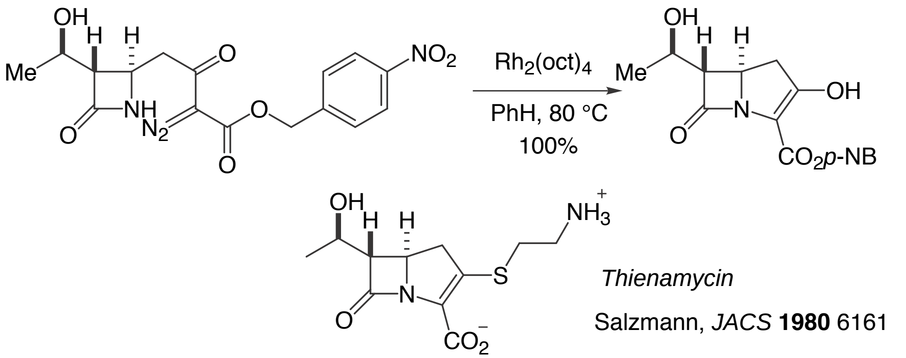
Doyle, M. P., *et al*. *J. Org. Chem*. **1991**, *56*, 820-829.
Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett*. **1989**, *30*, 5397.

Tandem O-H Insertion/Claisen Rearrangement



Wood, *JACS* **1997** 9641
Wood, *JACS* **1999**, 121, 1748

Merck Thienamycin Process

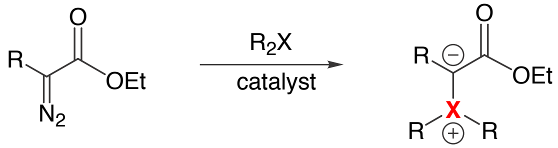


Thienamycin

Salzmann, *JACS* **1980** 6161

Carbene Heteroatom Transformations: Sulfonium & Oxonium Ylids

Ylide Formation

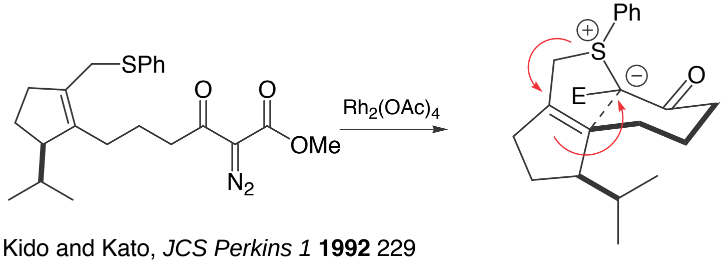


Reviews: Padwa, *Chem. Rev.* **1991** 263
Padwa, *Chem. Rev.* **1996** 223
Barnes, Evening Seminar, March 16, 1993

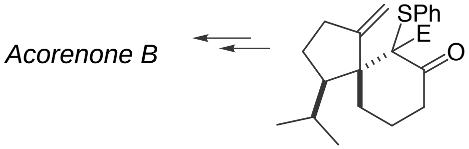
X is generally S, O or N and can be sp^2 or sp^3 hybridized

Ylides often undergo sigmatropic rearrangements or cycloadditions

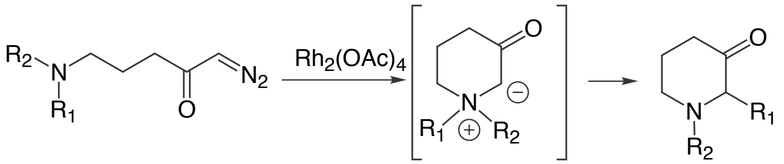
[2,3]-Sigmatropic rearrangement:



Kido and Kato, *JCS Perkins 1* **1992** 229



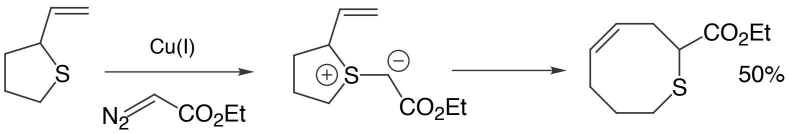
Stevens Rearrangement ([1,2] alkyl shift):

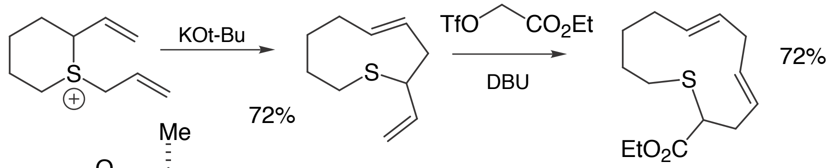


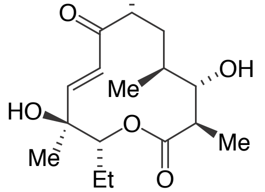
West, *JACS* **1993** 1177

Ring expansion reactions have been investigated

Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358

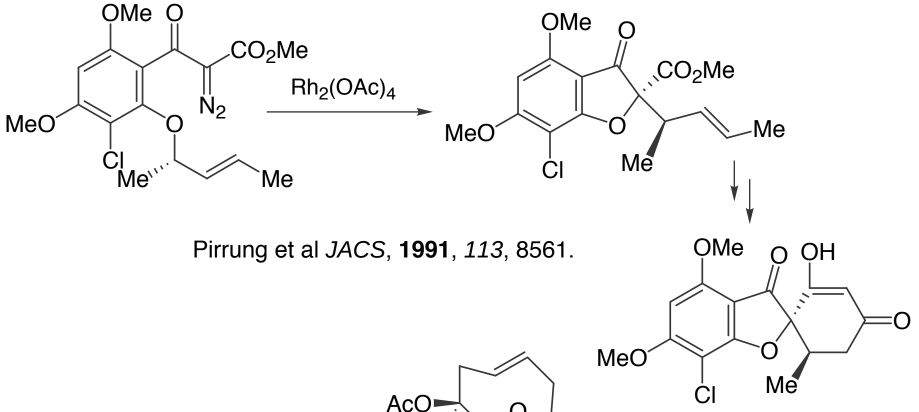






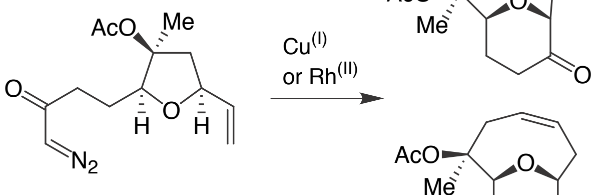
Methynolide has been synthesized by Vedejs using this ring-expansion methodology

Vedejs, *JACS* **1989**, *111*, 8430



Pirrung et al *JACS*, **1991**, *113*, 8561.

griseofulvin



Clark et al.
Tetrahedron Lett. **1996**, *37*, 5605.

Chemistry 206

Advanced Organic Chemistry

Handout–35A

The Use of Fischer Carbenes in Organic Synthesis

"...every synthetic chemist is well advised to follow this fascinating field with appropriate attention."

- Schmalz, H.-G., *ACIEE*, **1994**, 303.

Brian Connell

Evans Group Seminar, February, 1999

D. A. Evans

Friday ,
December 12, 2003

The Use of Fischer Carbenes in Organic Synthesis

"...every synthetic chemist is well advised to follow this fascinating field with appropriate attention."

- Schmalz, H.-G., *ACIEE*, **1994**, 303.

Brian Connell
Evans Group Seminar
2/12/99

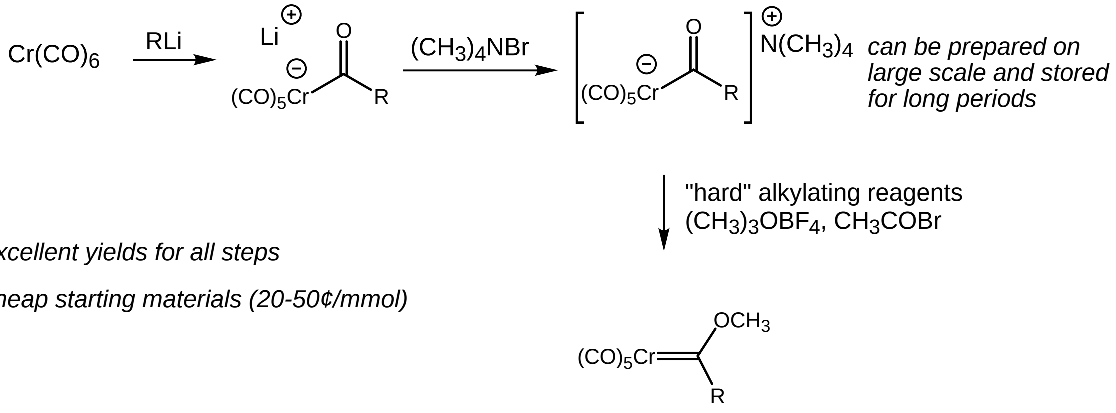
Outline

- Introduction and Fundamentals
- Reactions
  - Cyclopropanation
  - Diels-Alder Cycloaddition
  - Other Cycloadditions
  - Dotz Reaction and Analogs
  - Photochemistry
  - Conjugate Additions
  - Other Reactions

General References:
Wulff,*Organometallics*, **1998**, 3116.
Wulff,C*omprehensive Organic Synthesis*, Vol. 5, Chap 9.2: Metal Carbene Cycloadditions, Pergamon Press, 1991.
Wulff, *Comprehensive Organometallic Chemistry II*, Vol. 12, Chap 5.3: Transition Metal Carbene Complexes: Alkyne and Vinyl Ketene Chemistry, Pergamon Press, 1994.
Hegedus, C*omprehensive Organometallic Chemistry II*, Vol. 12, Chap 5.4: Transition Metal Carbene Complexes: Photochemical Reactions of Carbene Complexes, Pergamon Press, 1994.

Introduction

- Definition: electrophilic, heteroatom stabilized complexes having formal metal-to-carbon double bonds
- Group 6 metals (Cr, Mo, W) are the most common metals used.
- First prepared by Fischer (ACIEE, **1964**, 580):



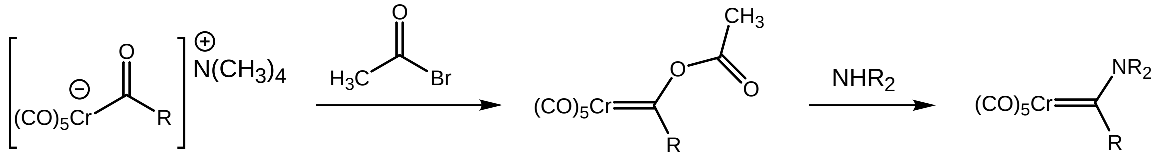
can be prepared on large scale and stored for long periods

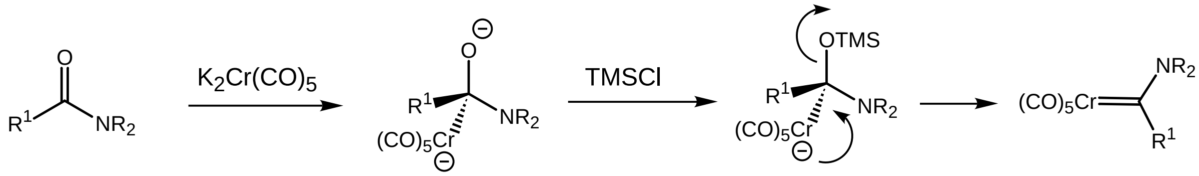
"hard" alkylating reagents
$(CH_3)_3OBF_4$, CH_3COBr

- *excellent yields for all steps*
- *cheap starting materials (20-50¢/mmol)*

- air, silica stable
- crystalline, easy to handle
- colored (yellow to red)

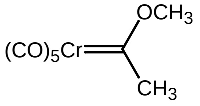
Nitrogen Analogs





Dotz, *Synlett*, **1991**, 381.

Selected Physical Data



Bond Lengths

$\mathrm{C_{carbene}}$ - O = 1.33 Å
$\mathrm{C_{carbene}}$ - Cr = 2.04 Å
Cr - $\mathrm{CO_{cis}}$ = 1.86 - 1.91 Å
Cr - $\mathrm{CO_{trans}}$ = 1.87 Å

IR Frequencies

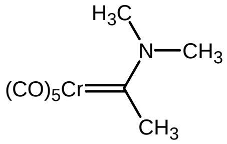
vCO ~2070, 1992, 1953 cm^{-1}

^{1}H NMR

$\mathrm{C_{carbene}}$ - CH_3 = ~5

^{13}C NMR

$\mathrm{C_{carbene}}$ 320-360 ppm



Bond Lengths

$\mathrm{C_{carbene}}$ - N = 1.31 Å
$\mathrm{C_{carbene}}$ - Cr = 2.16 Å
Cr - $\mathrm{CO_{cis}}$ = 1.90 Å
Cr - $\mathrm{CO_{trans}}$ = 1.85 Å

IR Frequencies

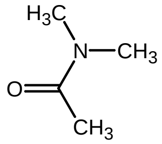
vCO = ~2060, 1970, 1940 cm^{-1}

^{1}H NMR

$\mathrm{C_{carbene}}$ - CH_3 = ~3.2

^{13}C NMR

$\mathrm{C_{carbene}}$ = 250-290 ppm



Bond Lengths

$\mathrm{C_{carbonyl}}$ - N = 1.29 Å
$\mathrm{C_{carbonyl}}$ - O = 1.23 Å

IR Frequencies

vCO = ~1650 cm^{-1}

^{1}H NMR

$\mathrm{C_{carbonyl}}$ - CH_3 = ~2.1

^{13}C NMR

$\mathrm{C_{carbonyl}}$ = ~165 ppm

Major Contributors

Ernst Otto Fischer

I was born in Solln, near Munich, on 10 November 1918 as the third child of the Professor of Physics at the Technical College of Munich, Dr. Karl T. Fischer (died 1953), and his wife, Valentine, née Danzer (died 1935). After completing four years at elementary school I went on to grammar school in 1929, from which I graduated in 1937 with my Abitur. Following a subsequent period of "work service" and shortly before the end of my two years' compulsory military service, the Second World War broke out. I served in Poland, France and Russia. In the winter of 1941/2 I began to study Chemistry at the Technical College in Munich during a period of study leave. I was released by the Americans in the autumn of 1945, and resumed my study of Chemistry in Munich after the reopening of the Technical College in 1946. I graduated in 1949. I took up a position as scientific assistant to Professor Walter Hieber in the Inorganic Chemistry Department, and under his guidance I dedicated myself to working on my doctoral thesis, "The Mechanisms of Carbon Monoxide Reactions of Nickel II Salts in the Presence of Dithionites and Sulfoxylates". After receiving my doctorate in 1952, I was invited by Professor Hieber to continue my activities at the college and consequently chose to specialise in the study of transition metal and organo-metallic chemistry. I wrote my university teaching thesis on "The Metal Complexes of Cyclopentadienes and Indenes". I was appointed a lecturer at the Technical College in 1955 and in 1956 I completed a scientific sojourn of many months in the United States. In 1957 I was appointed Professor at the University of Munich. After turning down an offer of the Chair of Inorganic Chemistry at the University of Jena I was appointed Senior Professor at the University of Munich in 1959 . In 1957 I was awarded the Chemistry Prize by the Göttingen Academy of Sciences. The Society of German Chemists awarded me the Alfred Stock Memorial Prize in 1959. In 1960 I refused an appointment as Senior Professor in the Department of Inorganic Chemistry at the University of Marburg. In 1964 I took the Chair of Inorganic Chemistry at the Technical College of Munich, which had been vacated by Professor Hieber. In the same year I was elected a member of the Mathematics/Natural Science section of the Bavarian Academy of Sciences; in 1969 I was appointed a member of the German Academy of Scientists Leopoldina. In 1972 I was given an honorary doctorate by the Faculty of Chemistry and Pharmacy of the University of Munich.

Lectures on my fields, particularly those on metallic complexes of cyclopentadienes and indenes, metal-pie-complex s of six-ringed aromatics, mono-, di- and oligo-olefins and most recently metalcarbonyl carbene and carbyne complexes, led me on lecture tours of the United States, Australia, Venezuela, Brazil, Israel and Lebanon, as well as numerous European countries, including the former Soviet Union. In 1969 I was Firestone Lecturer at the University of Wisconsin, Madison,Wisconsin, USA; in 1971 Visiting Professor at the University of Florida, Gainesville, USA, as well as the first Inorganic Chemistry Pacific West Coast Lecturer. In the spring of 1973 I held lectures as the Arthur D. Little Visiting Professor at the Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; and that was followed by a period when I was Visiting Distinguished Lecturer at the University of Rochester, Rochester, New York, USA.

Nobel lecture: On the way to carbene and carbyne complexes. *Angew. Chem*. (**1974**), 86(18), 651-63.

Karl Heinz Dotz

Kekule-Institut fur Organische Chemie und Biochemie der Universitat Bonn
Born1943
Ph.D. Technical University of Munich (E.O. Fischer) 1971.
Habilitation Technical University of Munich 1980.
Professor of Organometallic Chemistry University of Marburg 1986-1992, Dean of the Faculty 1990-1991.
Professor of Organic Chemistry University of Bonn since 1992.

Karl's research is focused on the following areas:
- Synthetic Organometallic Chemistry (metal carbenes and planar-chiral arene complexes)
- Physical Organic and Organometallic Chemistry
(distorted fused arenes and cyclophanes: synthesis and structure-chiroptics correlation,transition metal NMR spectroscopy, Ab initio-calculations on organometallic complexes and intermediates)
- Metal-Mediated Organic Synthesis (stereoselective C-C formation via metal carbenes, diastereoselective benzannulation and cyclopentannulation)
- Organometallic Catalysis (chromium-catalyzed cyclopropanation, axial-chiral and redox-active biaryl ligands)
- Transition Metal Modified Sugars (metal glycosylcarbenes and glycosylidenes: synthesis and application in C-glycosidation, disaccharide mimetics,conformation of acyclic metal modified sugars)

Major Contributors

Claude F. Bernasconi

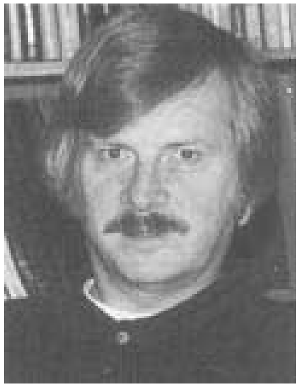
University of California at Santa Cruz

Claude was born in Zurich, Switzerland. He received his undergraduate and Ph.D. degrees from the Swiss Federal Institute of Technology (ETH) with Heinrich Zollinger. Following a postdoctoral year with Manfred Eigen at the Max Planck Institute for Biophysical Chemistry in Gottingen, he joined the chemistry faculty at the University of California at Santa Cruz in 1967, where he has been a professor of chemistry since 1977. His main research interests are in physical organic chemistry and center on problems of mechanism, structure-reactivity relationships, intrinsic barriers of reactions, and catalysis in organic and organometallic reactions, particularly proton transfer reactions, nucleophilic addition to electrophilic alkenes, nucleophilic vinylic substitution and reactions of Fischer carbene complexes.

Charles P. Casey

University of Wisconsin-Madison
Born 1942, St. Louis, MO
B.S. 1963, St. Louis University
Ph.D. 1968, MIT

Chuck received a Ph.D. in organic chemistry from MIT in 1968, where he studied organocopper chemistry under the direction of Professor George M. Whitesides. After spending 6 months at Harvard as an NSF postdoc with Paul D. Bartlett he joined the faculty at Wisconsin. Chuck is interested in studying the mechanisms of organometallic reactions and in developing an understanding of homogeneous catalysis. In addition, he is trying to design new organometallic reagents for synthesis and new heterobimetallic catalysts.



William D. Wulff

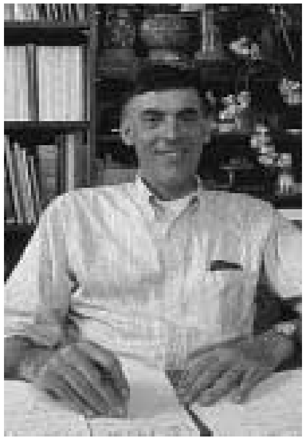
University of Chicago
Born Eau Claire, Wisconsin, 1949
B. S. 1971, University of Wisconsin-Eau Claire
Ph.D. 1979, Iowa State University

Professor Wulff received his Ph.D. degree from Iowa State University in 1979 with Professor Thomas Barton. After NIH postdoctoral work with Martin Semmelhack at Princeton University, he accepted a position at the University of Chicago in 1980. Professor Wulff's research interests are in the applications of organometallics in organic synthesis as both reagents and catalysts.

Jose Barluenga

University of Oviedo

Jose Barluenga obtained his Ph.D. degree (solvomercuration of dienes) at the University of Zaragoza in 1966 under the direction of Professor V. Gomez-Aranda. He spent 3.5 years as a postdoctoral fellow at Max Planck Institut Fur Kohlenforschung, Mulheim, in the group of Professor Hoberg studying aluminum chemistry. In 1970 he took a position as a research associate at the University of Zaragoza, where he was promoted to Associate Professor in 1972. In 1975 he moved to the University of Oviedo as Professor of Organic Chemistry in the Department of Organometallic Chemistry. His major research interest is focused on the development of new synthetic methods in the area of heterocyclic chemistry and functionalized systems.



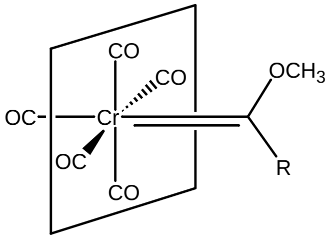
Louis S. Hegedus

Colorado State University
Born Cleveland, Ohio, 1943
B.S, 1965, Penn State University
M.A. 1966, Penn State University
Ph.D., 1970, Harvard

Lou was born in 1943 in Cleveland, Ohio, but grew up in rural Ohio, away from big city temptations. He did his undergraduate studies at Pennsylvania State University, where studied aqueous chromium redox chemistry with Professor Albert Haim. After Ph.D. studies at Harvard on nickel carbonyl chemistry with E. J. Corey (1970), and a NIH postdoctoral year at Stanford with J. P. Collman studying polymer-supported homogeneous catalysis, he moved to Colorado State University, where he remains today as a professor of chemistry. His research interests center on the use of transition metals in organic synthesis.

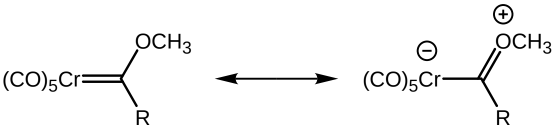
Recurring Themes

The Wall of CO



- $(CO)_5Cr$ is sterically very large

Resonance

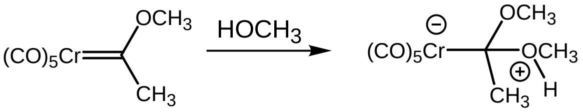


•Rotation about heteroatom carbene bond is restricted by 14-25 kcal/mol

• ^{53}Cr NMR is consistent with strong resonance contribution

Hegedus and Dotz *JACS*, **1988**, 8413.

Kinetic Electrophilicity

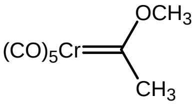


•Formation of tetrahedral intermediate is 10^9 faster than CH_3O^- addition to BnO_2CCH_3.

Bernasconi
Chem. Soc. Rev., **1997**, 299.
JACS, **1998**, *8632*.

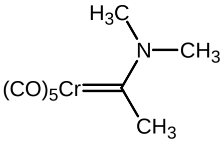
pKa Data

Thermodynamic Acidity

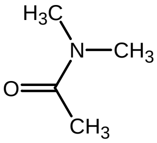


- pK_a(THF) = 8
- pK_a(H_2O) = 12.3

equivalent to p-cyanophenol



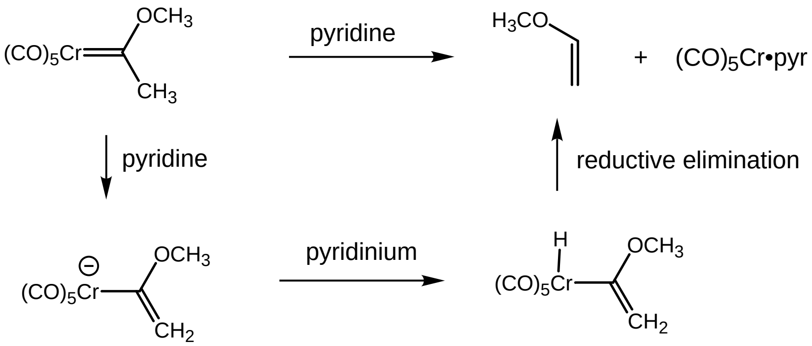
- pK_a = 20.4 (DMSO)



- pK_a = 35 (DMSO)

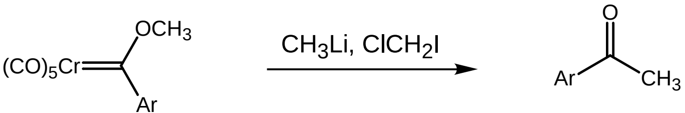
Casey, *JACS*, **1974**, 1230.

Sensitivity to Acid



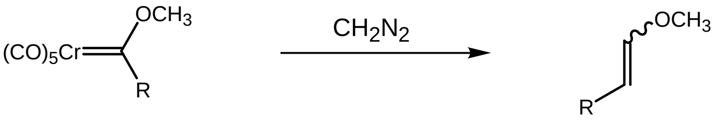
See Hegedus, *JACS*, **1990**, 6255.

Metal Removal and Functionalization

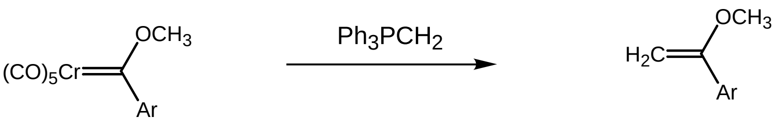


80-90%

Barluenga, *TL*, **1994**, 9471.

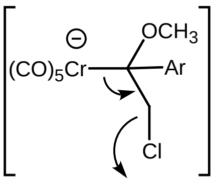


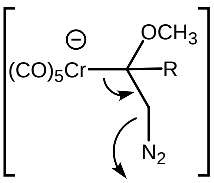
Casey, *TL*, **1973**, 1421.

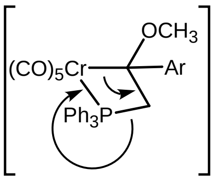


Casey, *JACS*, **1972**, 6543.

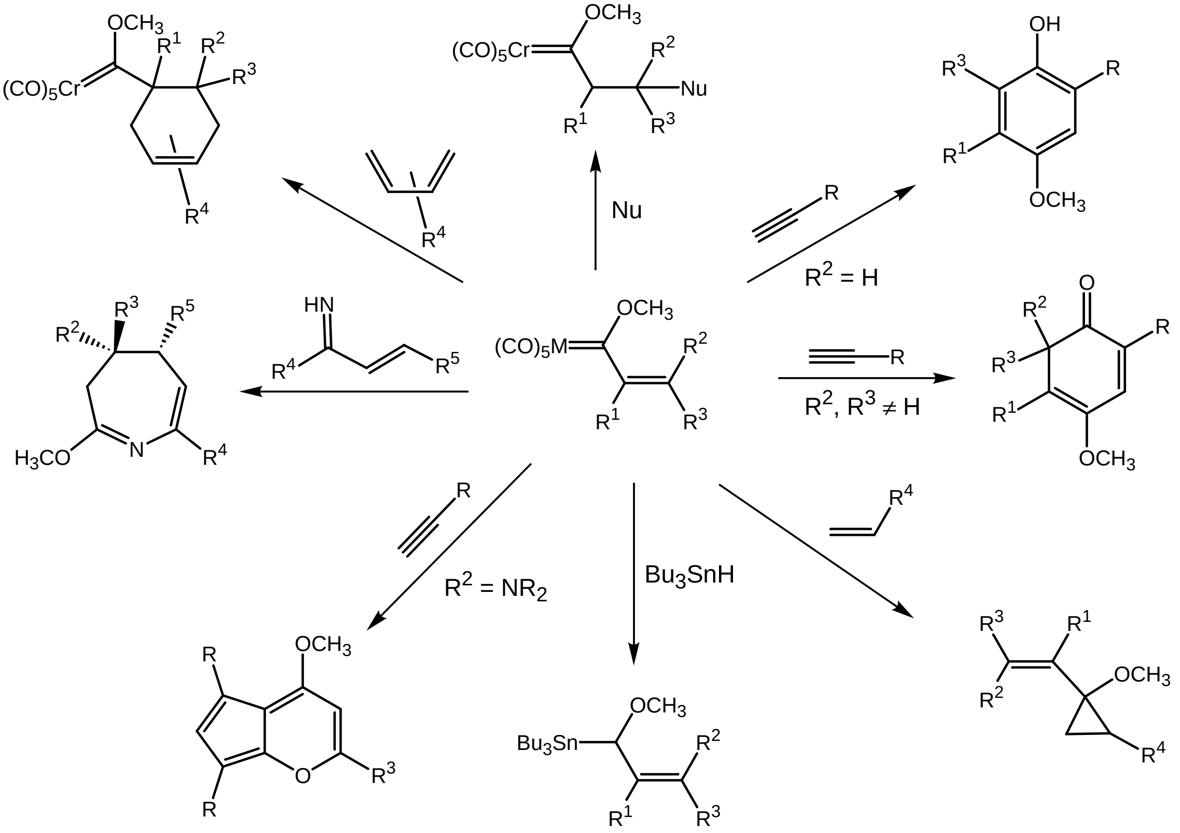
Via similar intermediates:



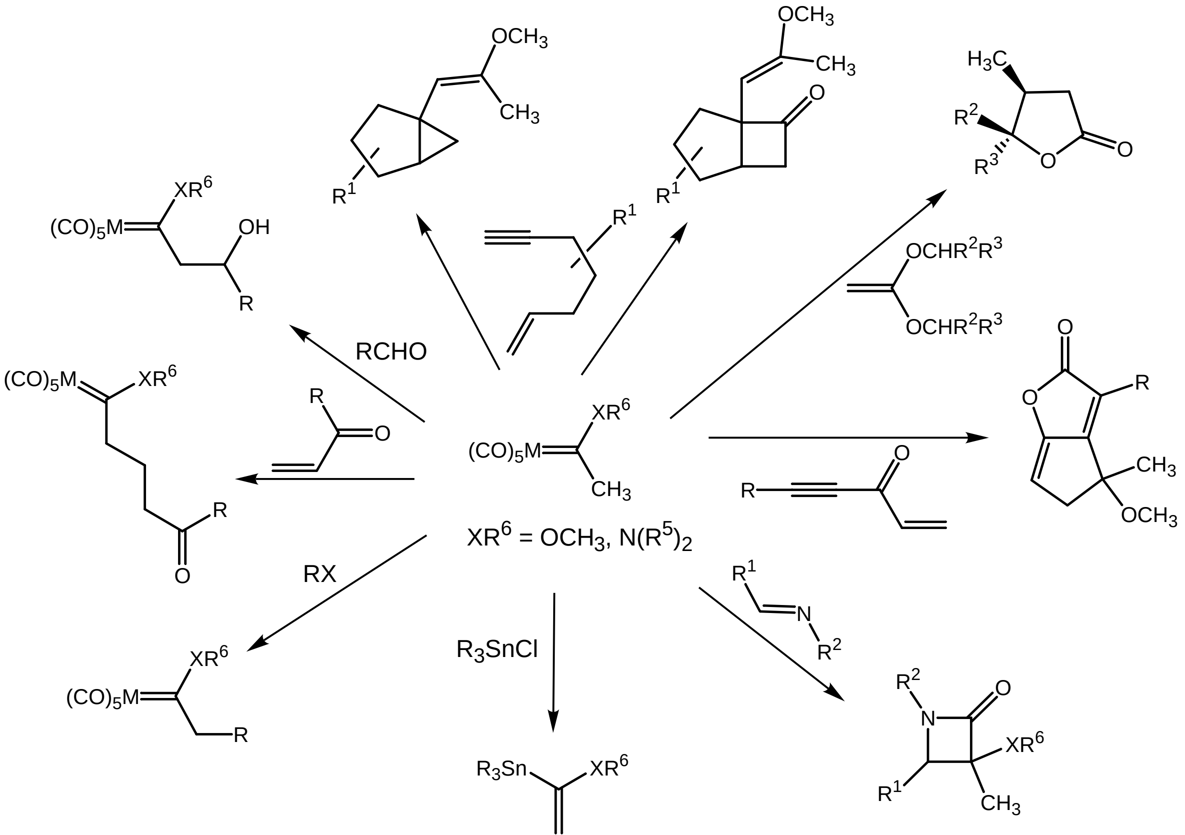




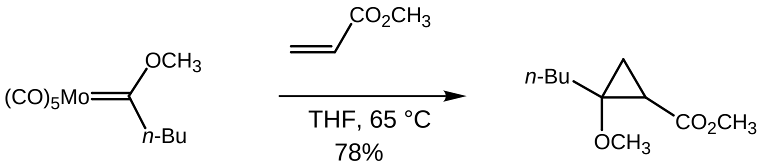
Selected Reactions of Unsaturated Fischer Carbene Complexes



Selected Reactions of Saturated Fischer Carbene Complexes

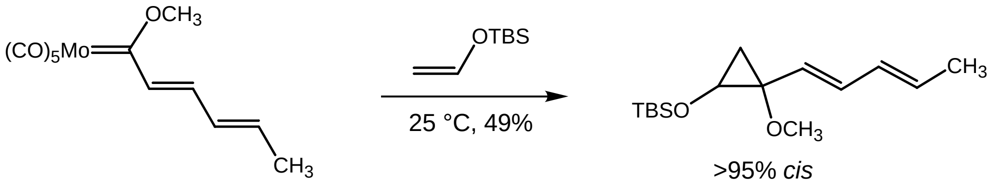


Cyclopropanation



E:Z
1.9:1

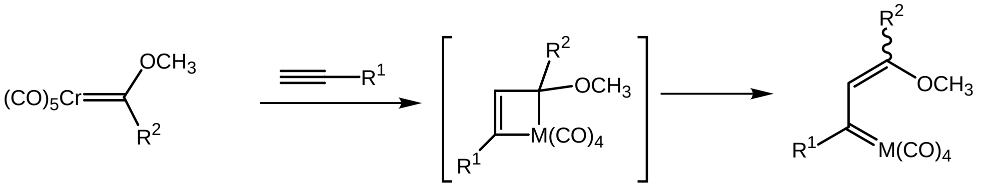
Harvey, *TL*, **1990**, 2529.

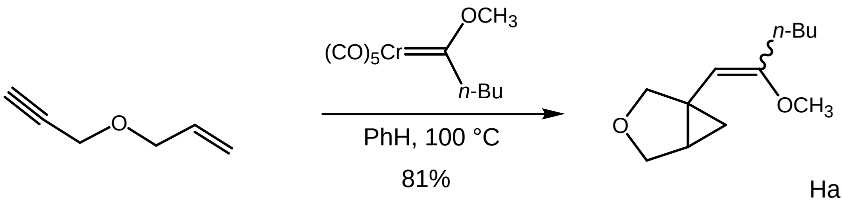


>95% *cis*

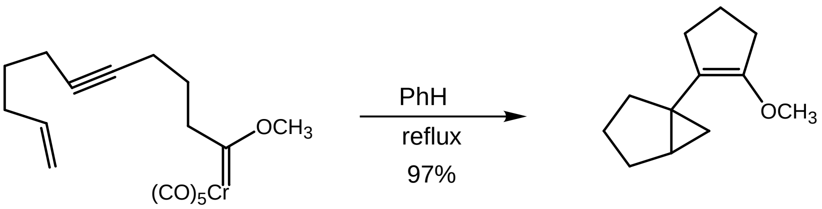
Wulff
Pure Appl. Chem., **1988**, 137.
JACS, **1988**, 2653.

Cyclopropanation
Reaction with Alkynes



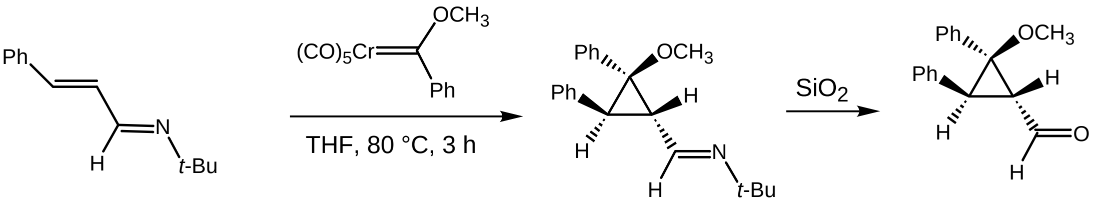


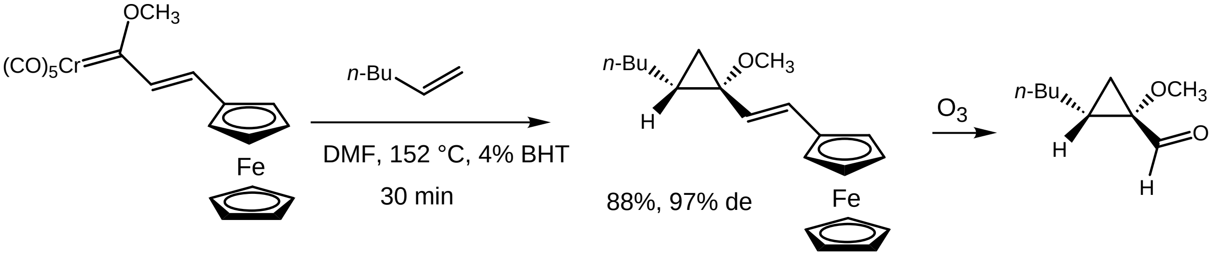
Harvey, *JACS*, **1992**, 8424.



Hoye, *JACS*, **1988**, 2676.

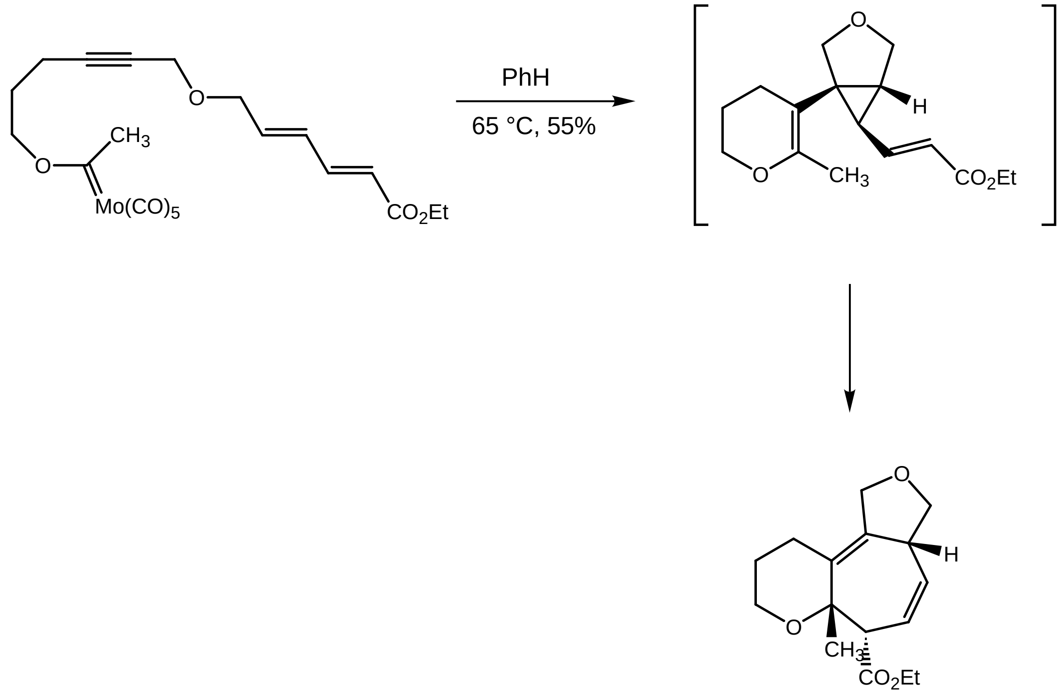
Selective Cyclopropanation





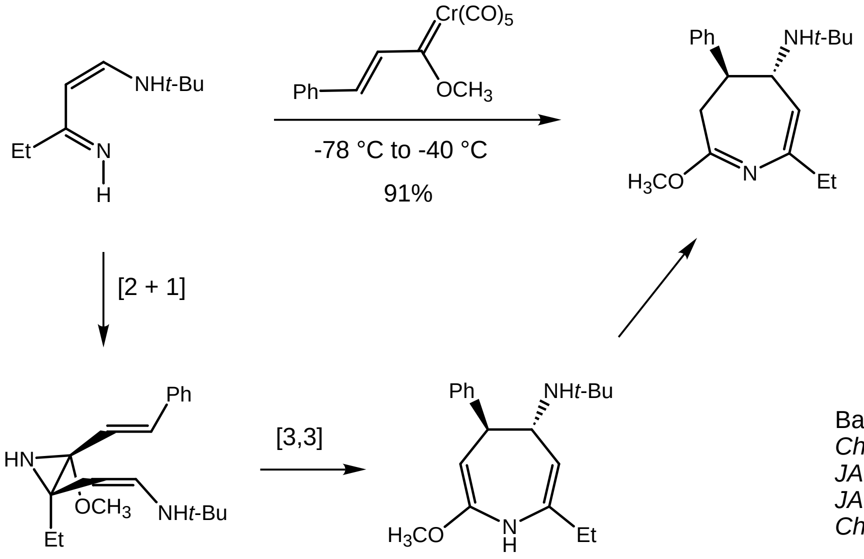
Barluenga
Chem. Commun., **1995**, 665.
JACS, **1997**, 7591.

Cyclopropanation
Reaction with Alkynes



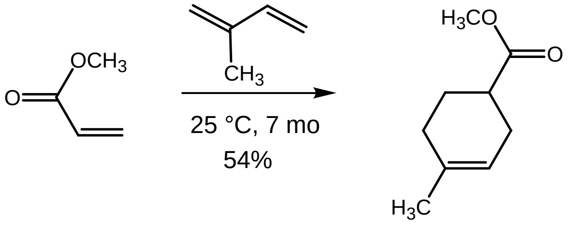
Harvey, *JOC*, **1992**, 5559.

[4 + 3] Annulation



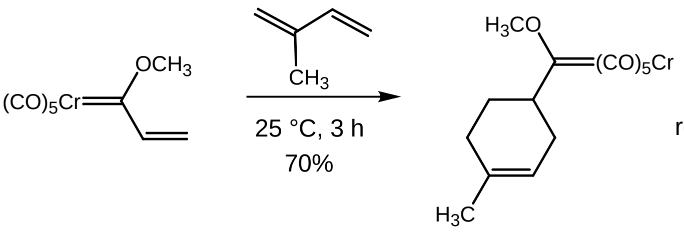
Barluenga
Chem. Commun., **1994**, 321.
JACS, **1995**, 9419.
JACS, **1996**, 695.
Chem. Eur. J., **1996**, 88.

Diels-Alder Cycloaddition



70:30
regioselectivity

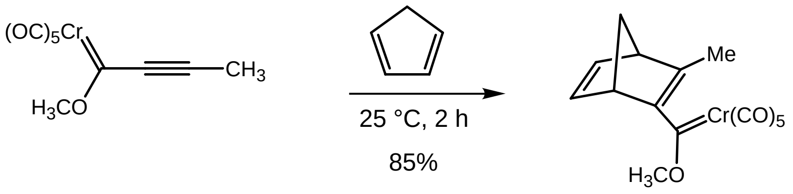
10^4 times faster than methyl acrylate

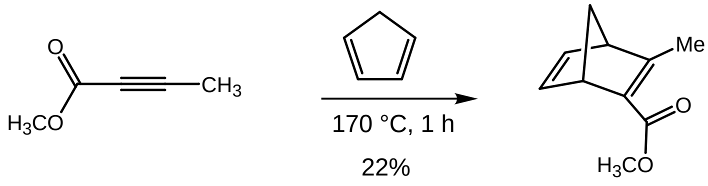


92:8
regioselectivity

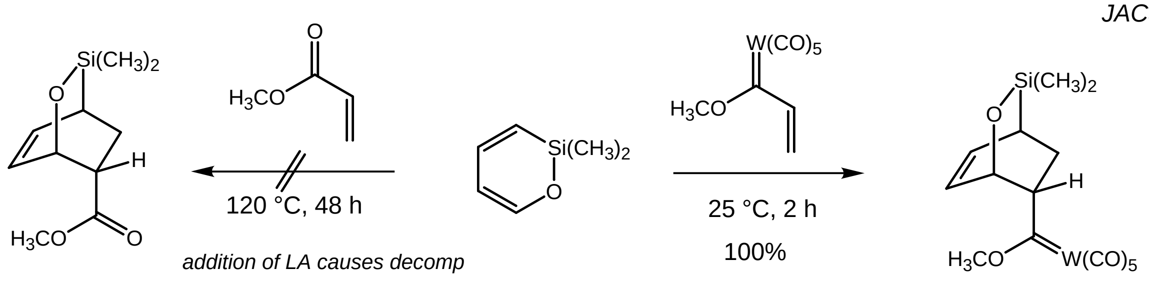
Wulff, *JACS*, **1990**, 4550.

Diels-Alder Cycloadditions

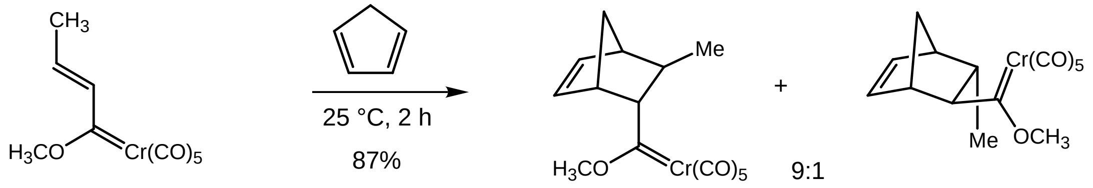


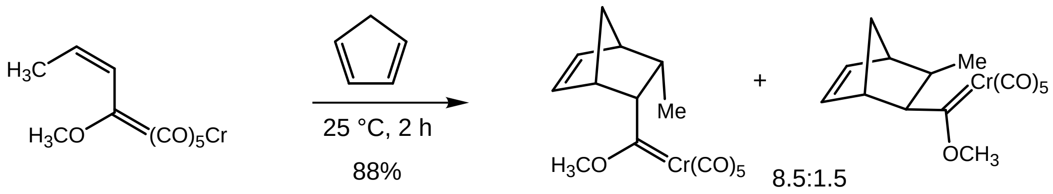


Wulff
JACS **1983**, 6726.
JACS **1990**, 3642.



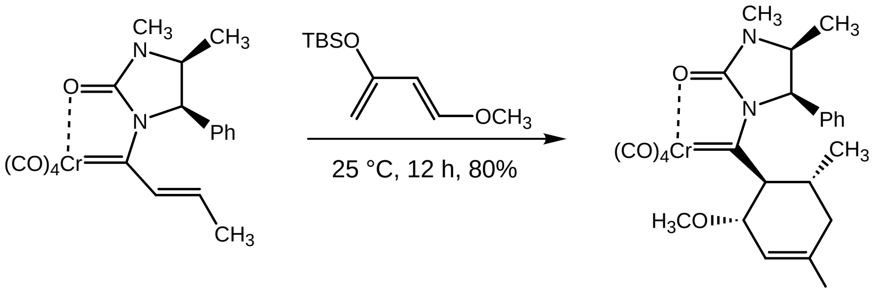
Diels-Alder Cycloadditions



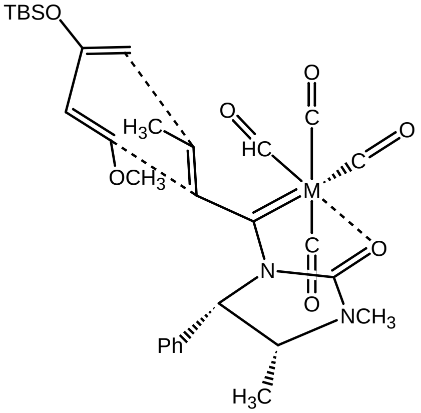


Wulff, *JACS*, **1990**, 3642.

Asymmetric Exo-Selective Diels-Alder Reaction



exo:endo
>96:4

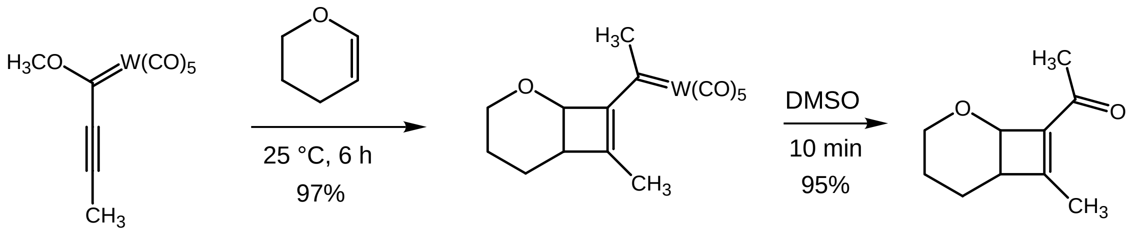


Proposed Transition State

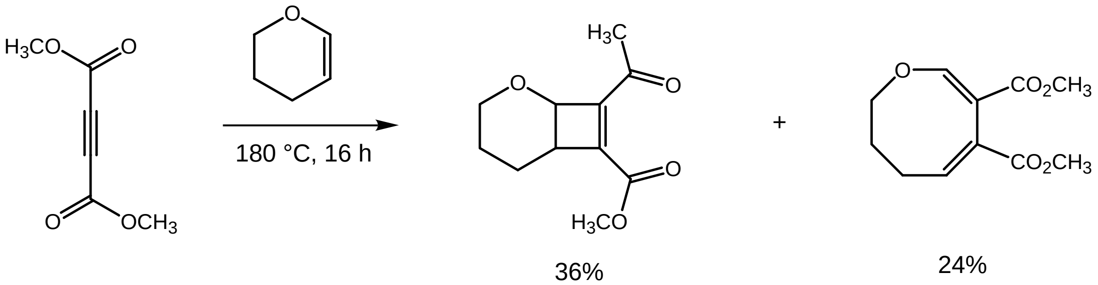
non-oxygenated dienes give ~85:15 exo:endo

Wulff, *JACS*, **1997**, 6438.

[2 + 2] Cycloaddition

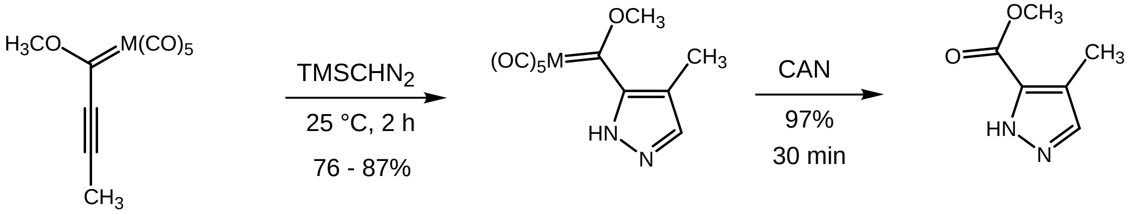


corresponding ester does not react

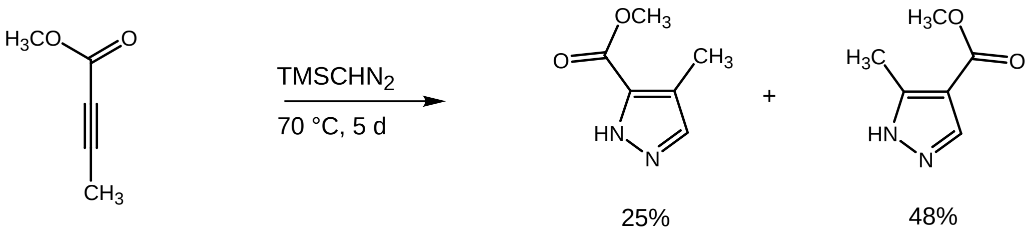


Wulff, *JACS*, **1988**, 8727.

[3 + 2] Cycloaddition



>300:1 regioselection

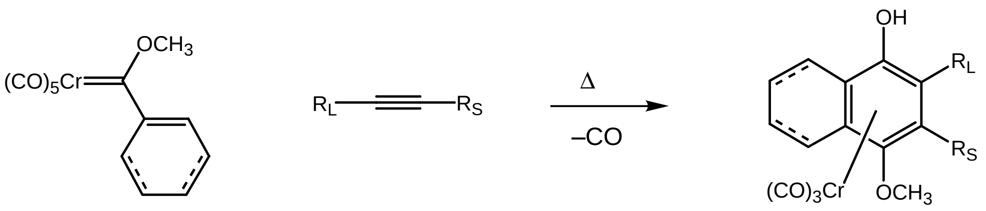


Wulff, *JACS*, **1986**, 6726.
Barluenga *TL*, **1998**, 4887.
Barluenga *JCS Perkin I*, **1997**, 2267.

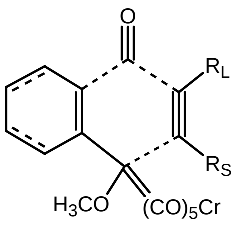
Dotz Reaction

Thermal Reaction of Unsaturated Carbene Complexes

"...one of the most utilized reactions in natural product synthesis involving an organometallic process."

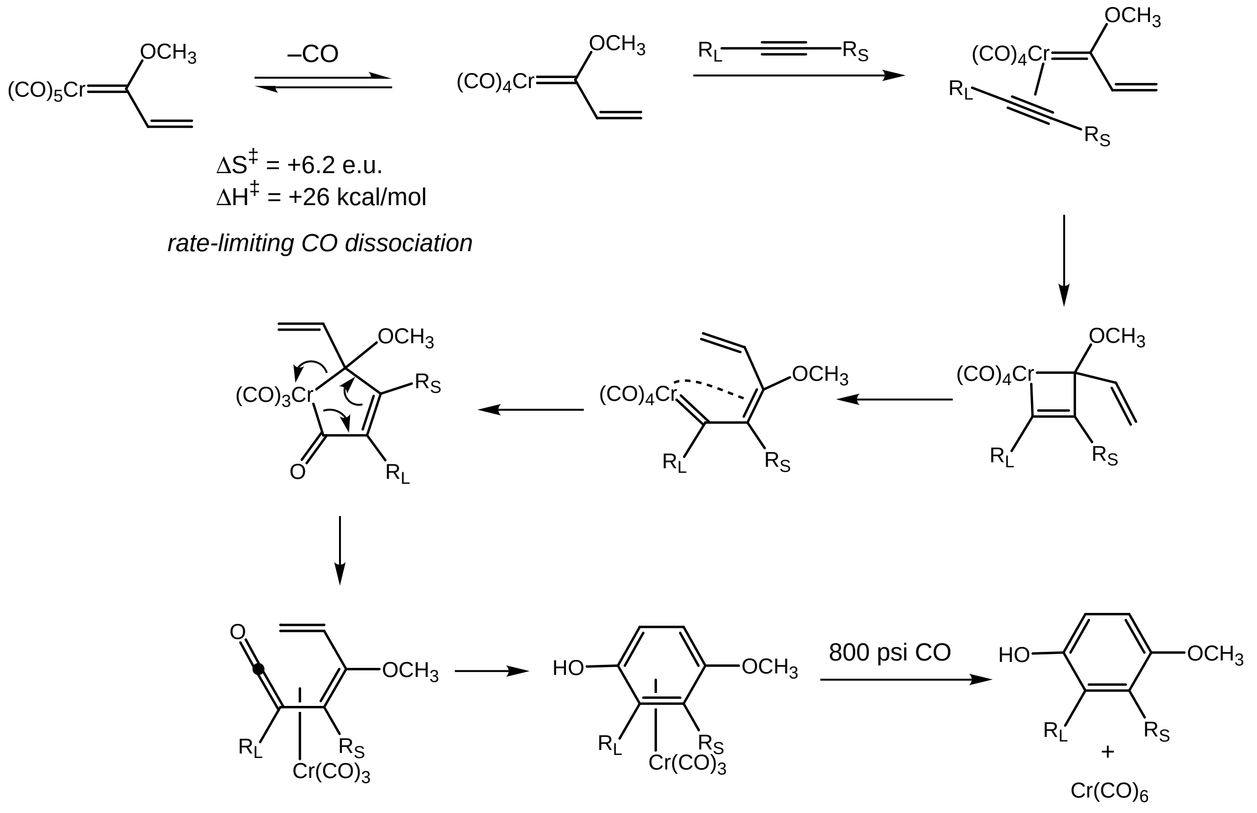


Observed Connectivity:



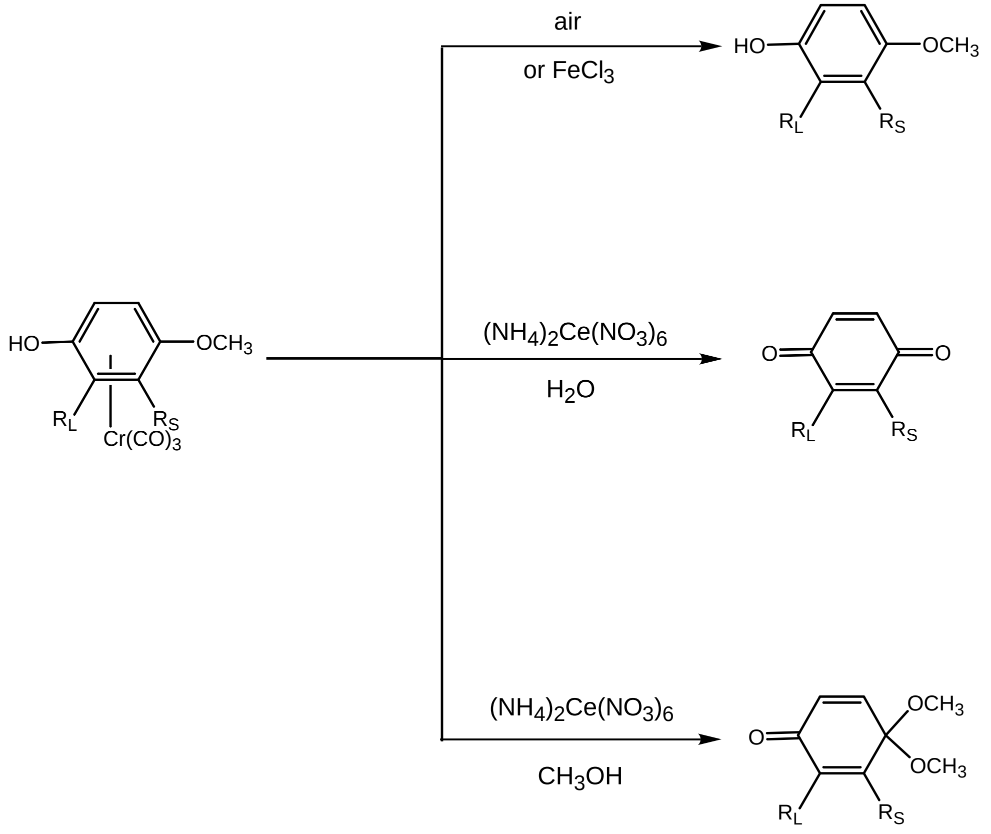
Dotz
ACIEE, **1975**, 644.
New J. Chem., **1990**, 433.
ACIEE, **1984**, 587.

Dotz Proposed Reaction Mechanism



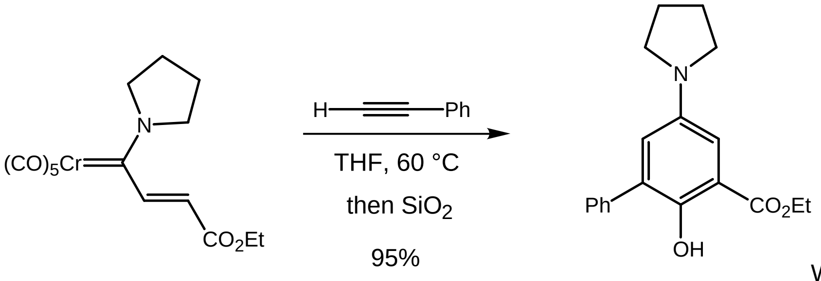
Barluenga, *JACS*, **1994**, 11191.

Dotz Alternative Workup Procedures



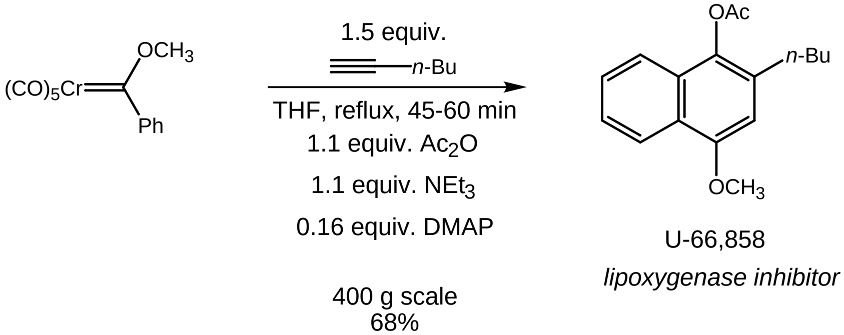
See Wulff, *JOC*, **1984**, 2293.

Dotz: Nitrogen Analog



Wulff, *JOC*, **1995**, 4566.
Barluenga, *JOC*, **1998**, 7588.

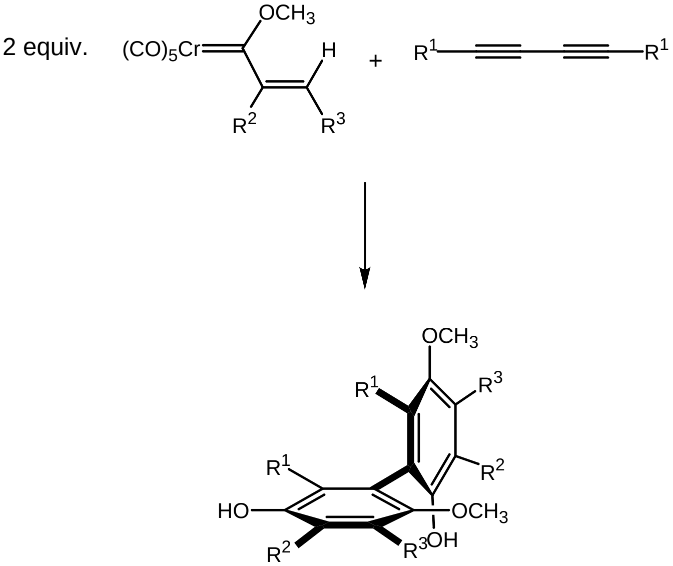
Dotz: Large Scale Applicability



U-66,858
lipoxygenase inhibitor

Timko
TL, **1988**, 2513.
Org. Synth., **1992**, 72.

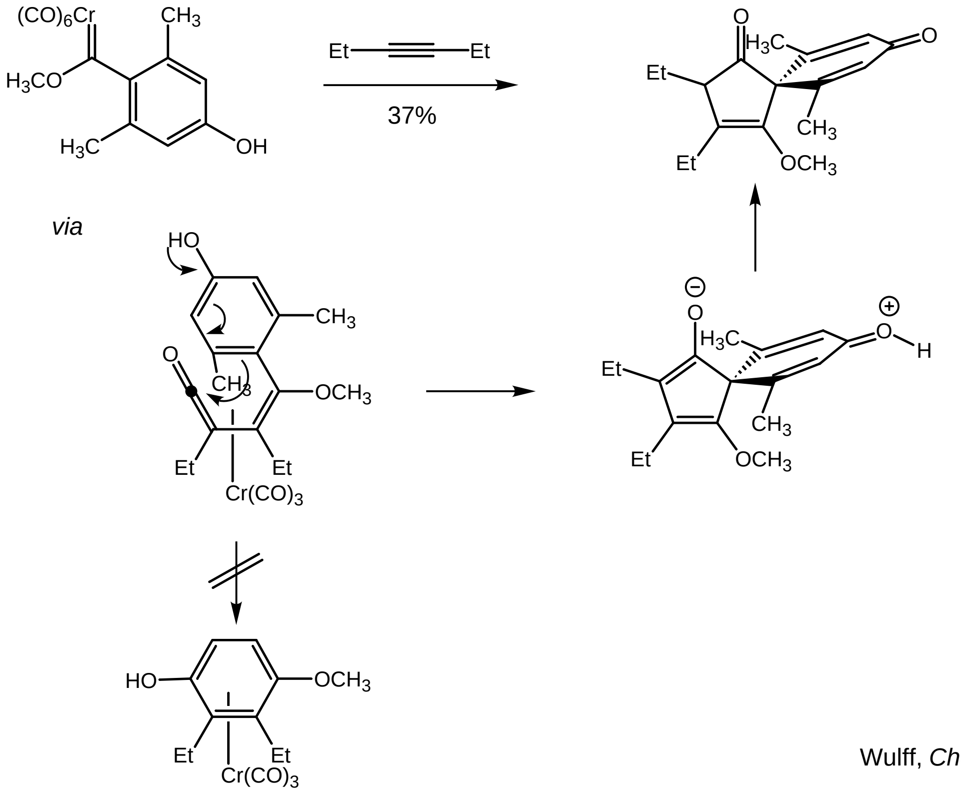
Biaryl Synthesis



The concept works, in moderate to low yield, but the reactions must be run stepwise.
Occasionally CO insertion is suppressed and five-membered rings are formed.

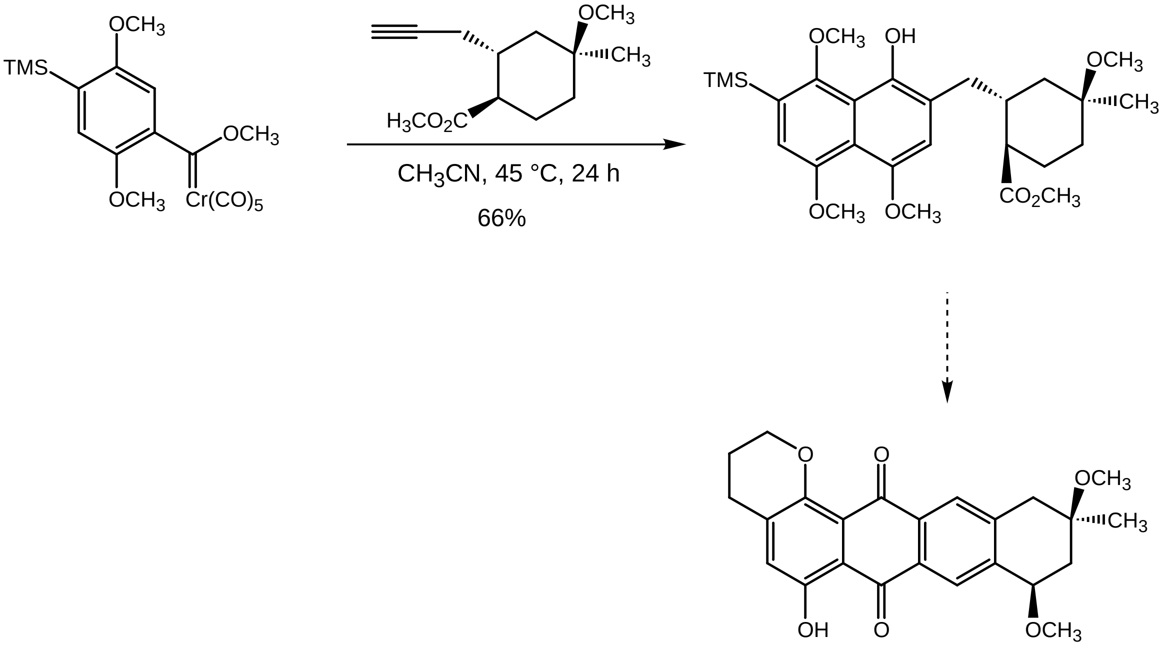
Wulff, *JACS*, **1996**, 2166.

Intercepted Intermediates



Wulff, *Chem. Commun.*, **1996**, 1863.

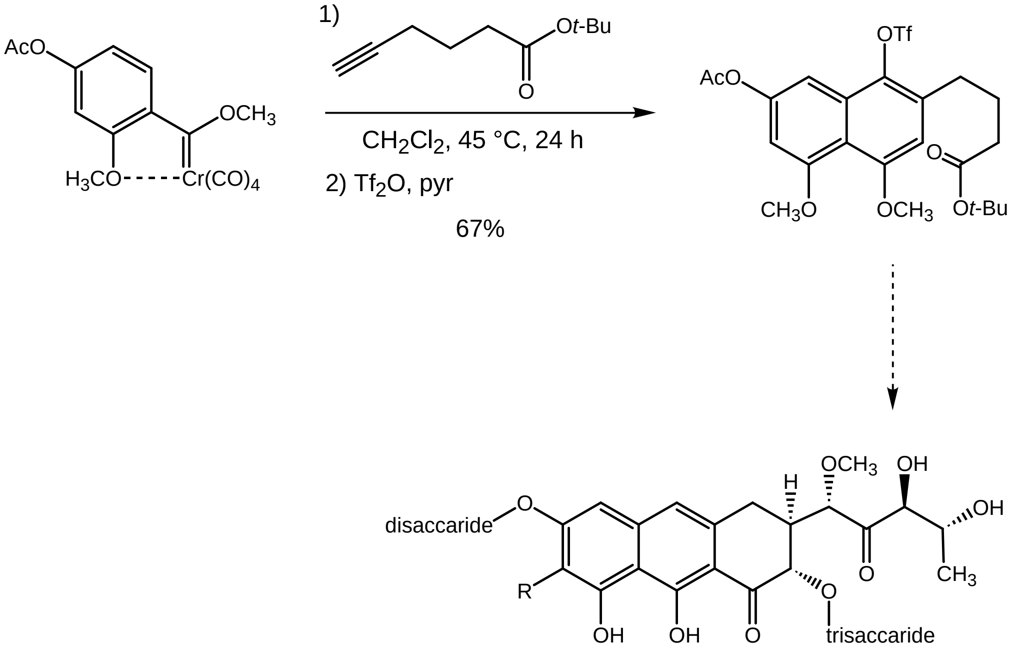
Synthetic Uses



menogaril
antitumor antibiotic

Wulff, *JOC*, **1998**, 840.

Synthetic Uses

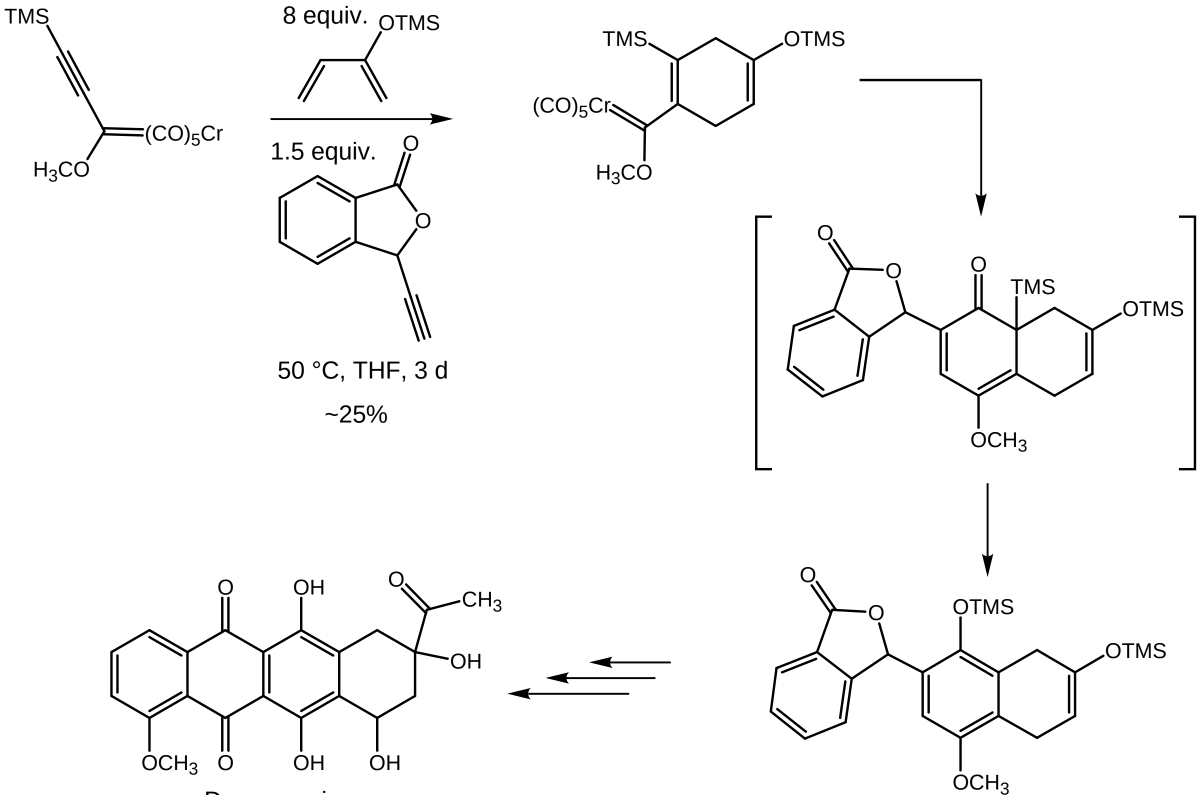


R = CH_3 Chromomycin
R = H, Olivomycin

antitumor antibiotics

Wulff, *Synthesis*, **1999**, 80.

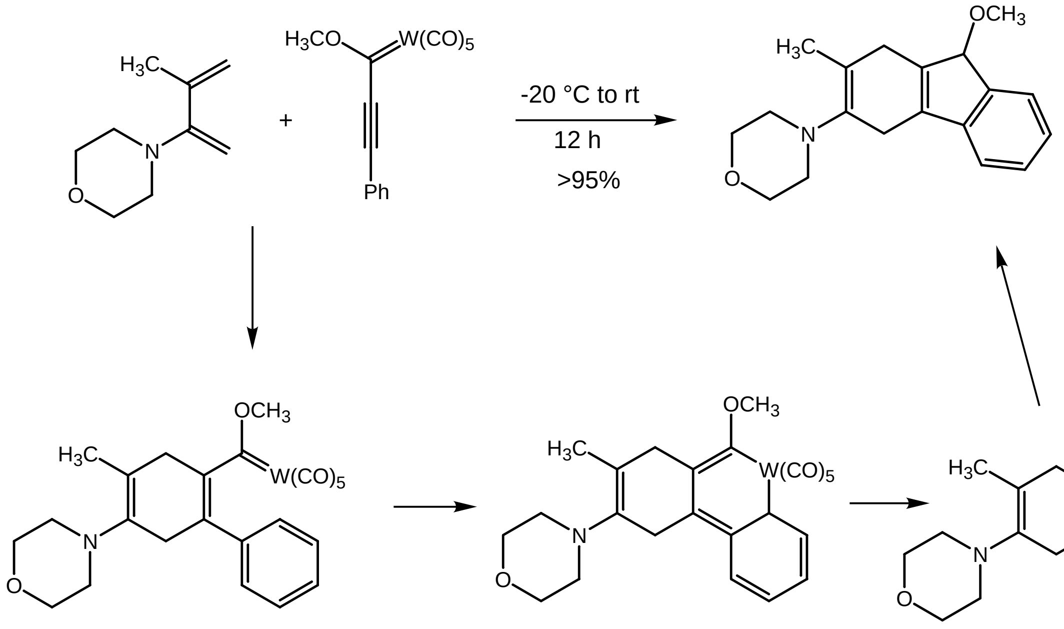
Application to Synthesis



Daunomycinone

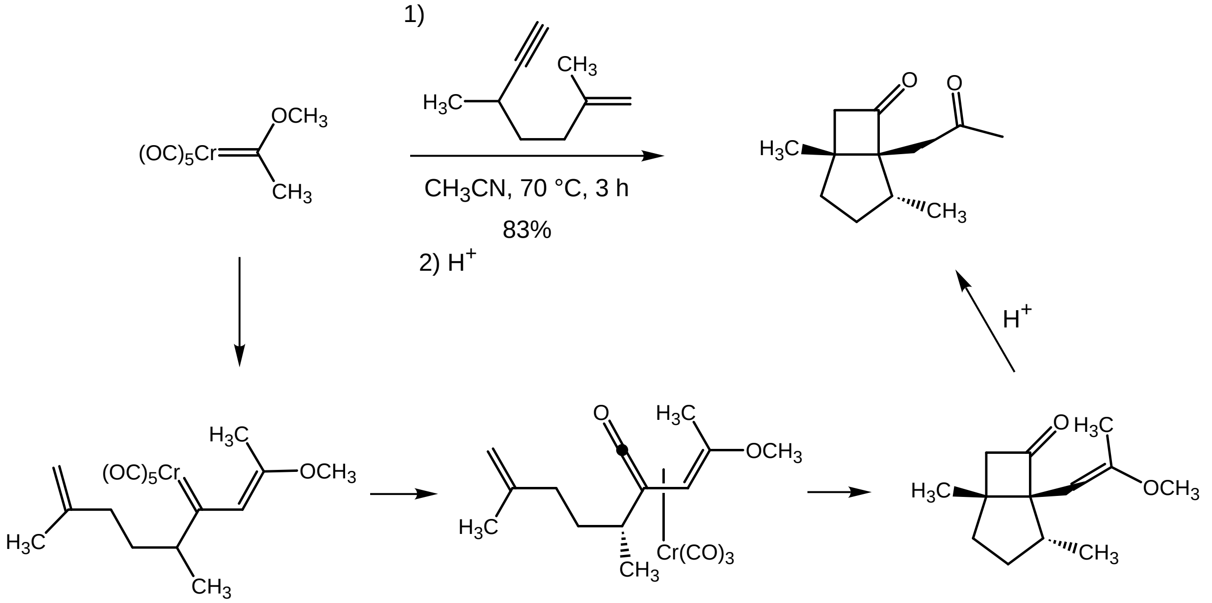
Wulff, *JACS*, **1984**, 434 & 7565.

Dihydrofluorene Synthesis



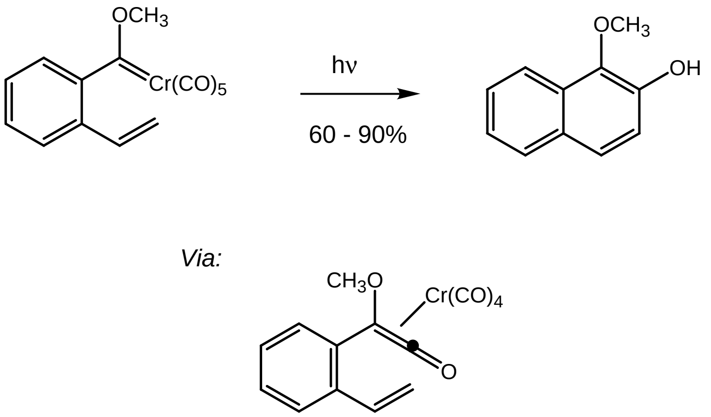
Barluenga, *Chem Commun.*, **1995**, 1973.

Alkyne-Alkene Reactions



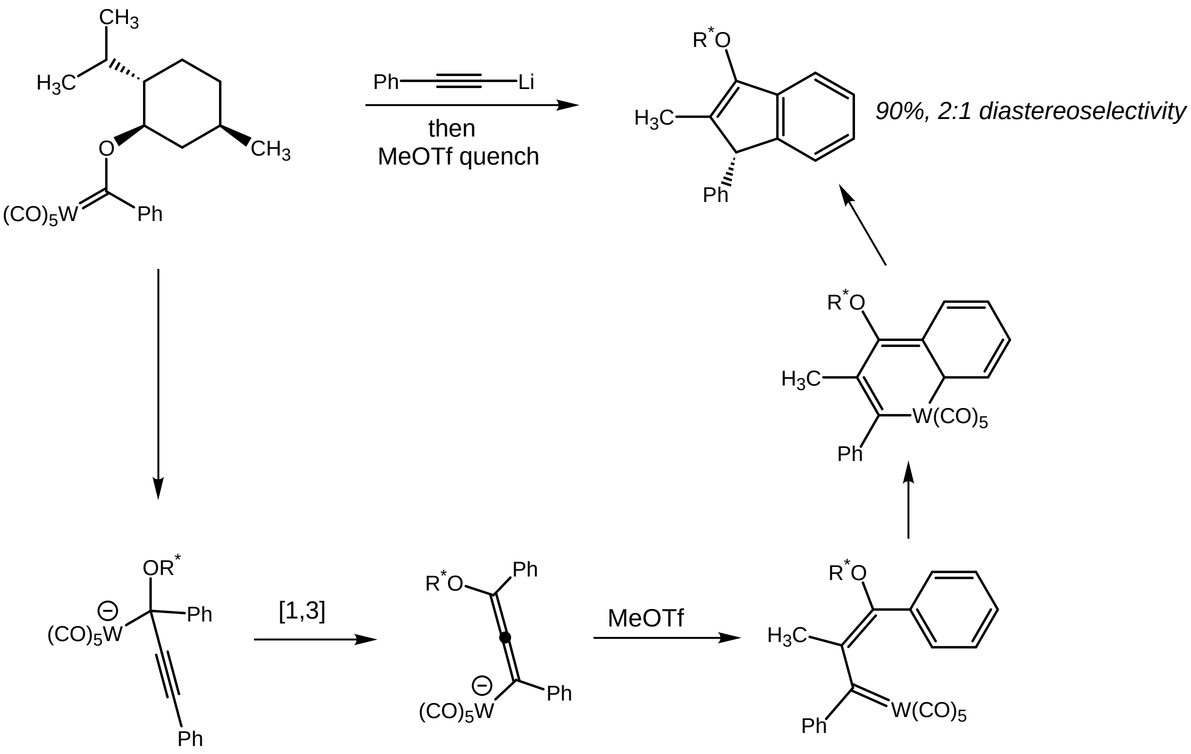
Wulff, *JOC*, **1993**, 5571.

Ketene Cyclizations



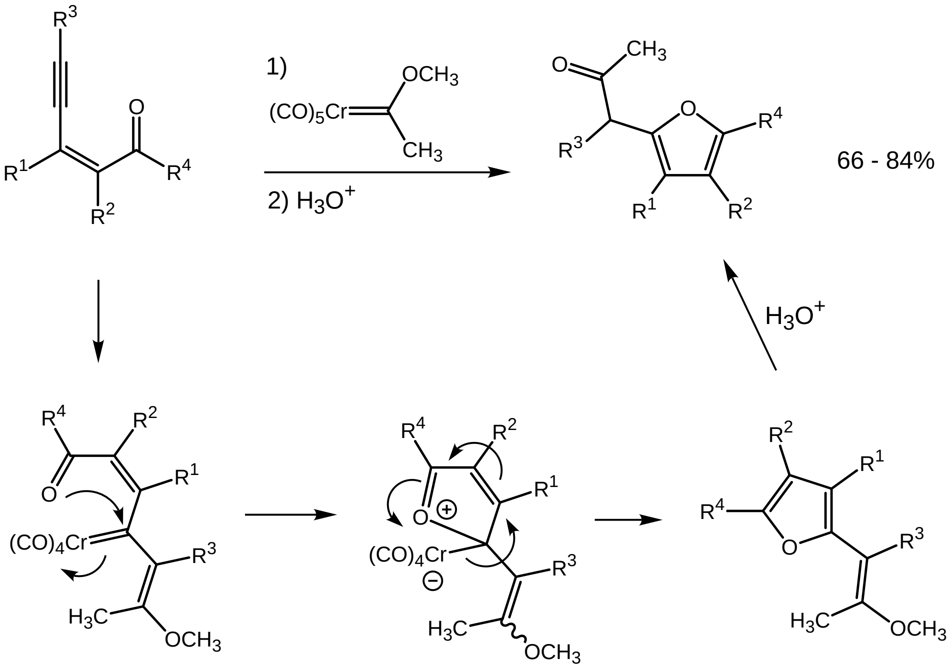
Merlic, *JACS*, **1992**, 5602.

"Asymmetric" Benzopentaannulation



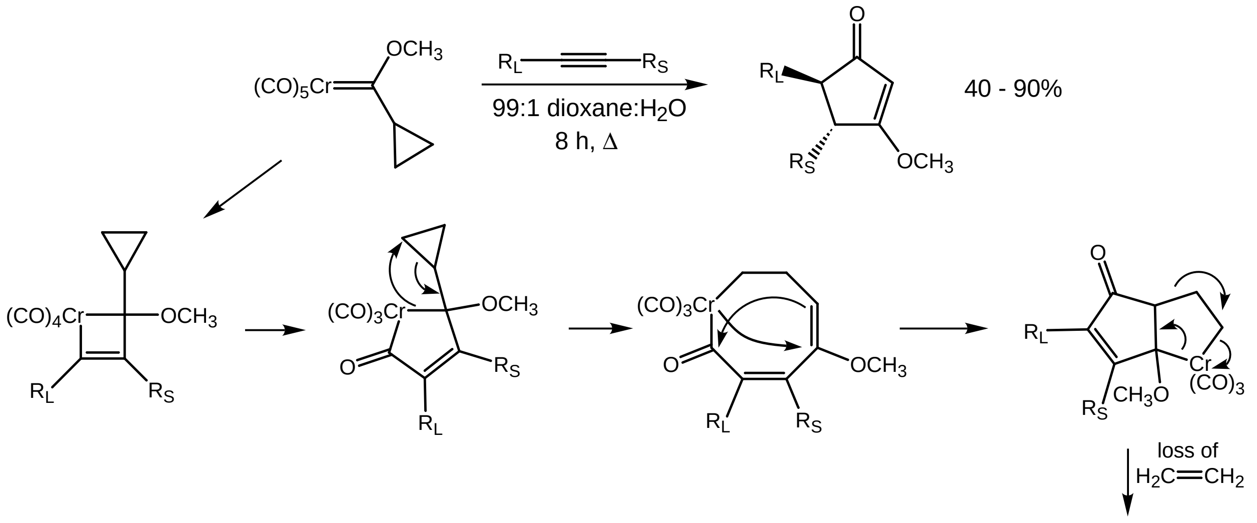
Barluenga, *JACS*, **1998**, 12129.

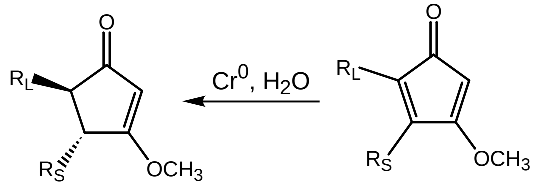
Furan Synthesis

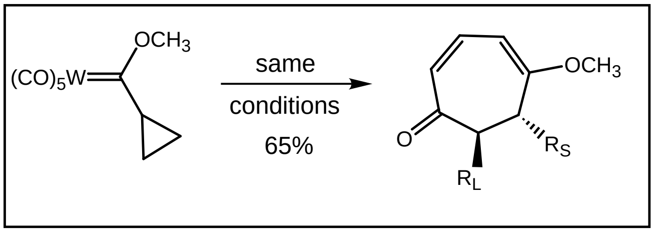


Herndon, *JOC*, **1998**, 4564.

"A Versatile [4 + 2 + 1 - 2] Cycloaddition"





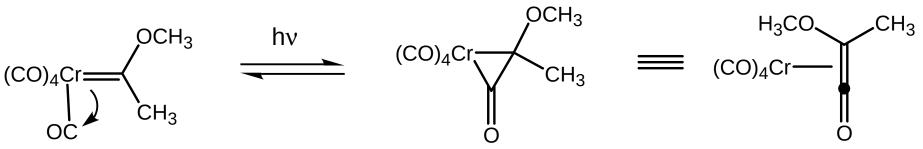


Herndon
JACS, **1988**, 3334.
TL, **1989**, 295.
JOC, **1990**, 786.
JACS, **1991**, 7808.
JACS, **1992**, 8394.

Photochemistry

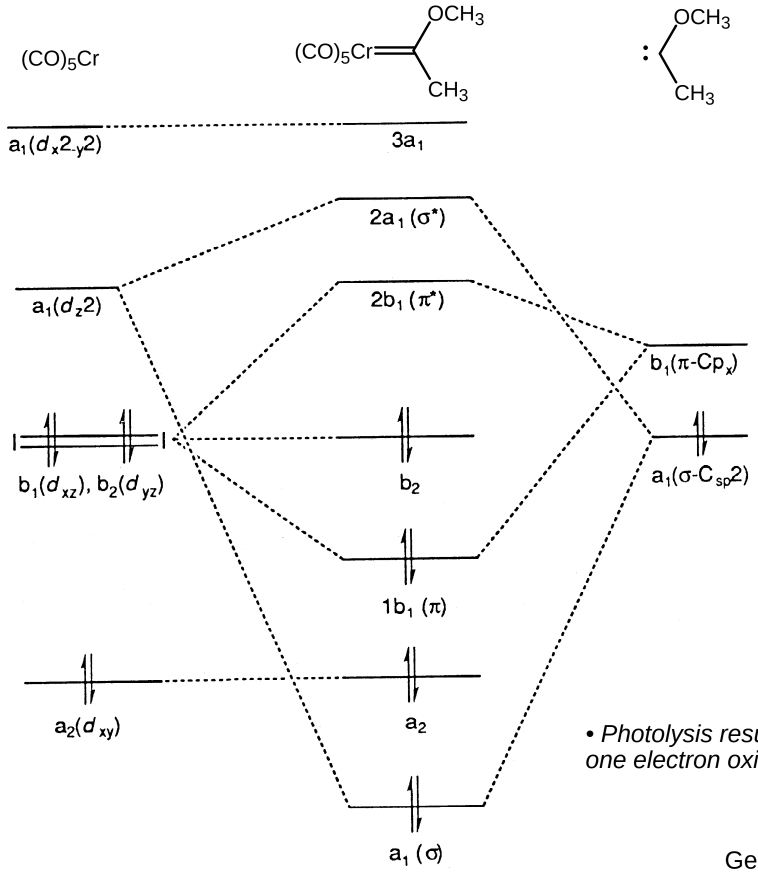
- Electronic absorption consists of three low-lying bands:
  - ~500 nm: spin-forbidden M → carbene π* charge transfer transition
  - 360-450 nm: spin allowed M → carbene π* charge transfer transition (visible)
  - 300-350 nm: ligand field transition
- In addition, all carbene complexes absorb strongly below 300 nm.

- Exposure to light leads to a *reversible* CO insertion:



Geoffroy, *JACS*, **1983**, 3064.

Molecular Orbital Diagram



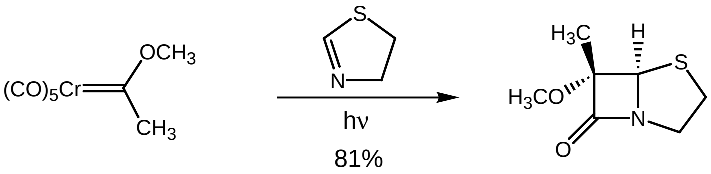
LUMO is carbene carbon p-orbital centered

HOMO is metal-d-orbital centered

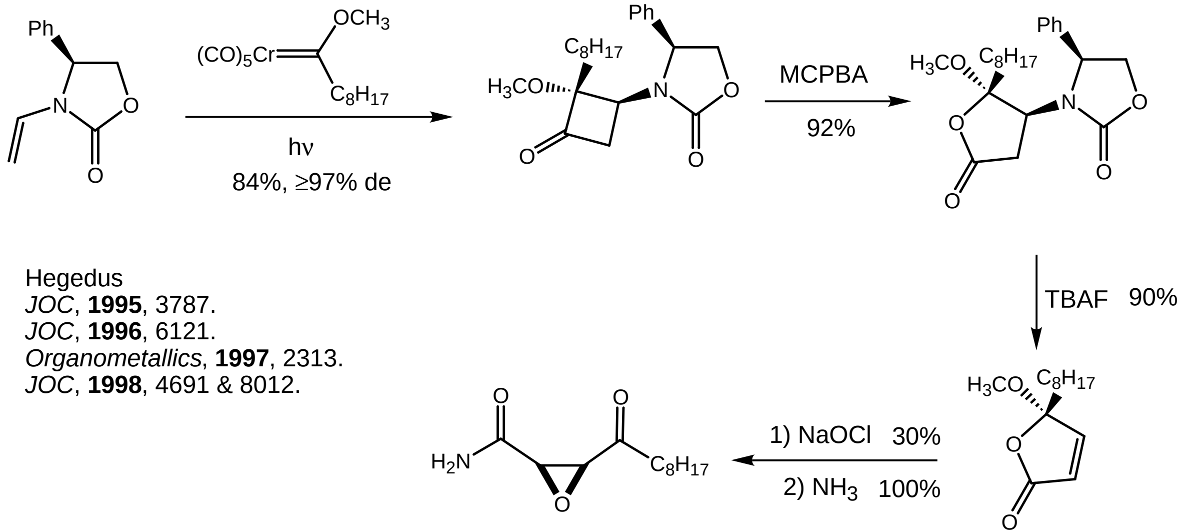
- *Photolysis results in a formal, reversible, one electron oxidation of the metal.*

Geoffroy, *JACS*, **1983**, 3064.

Ketene [2 + 2]



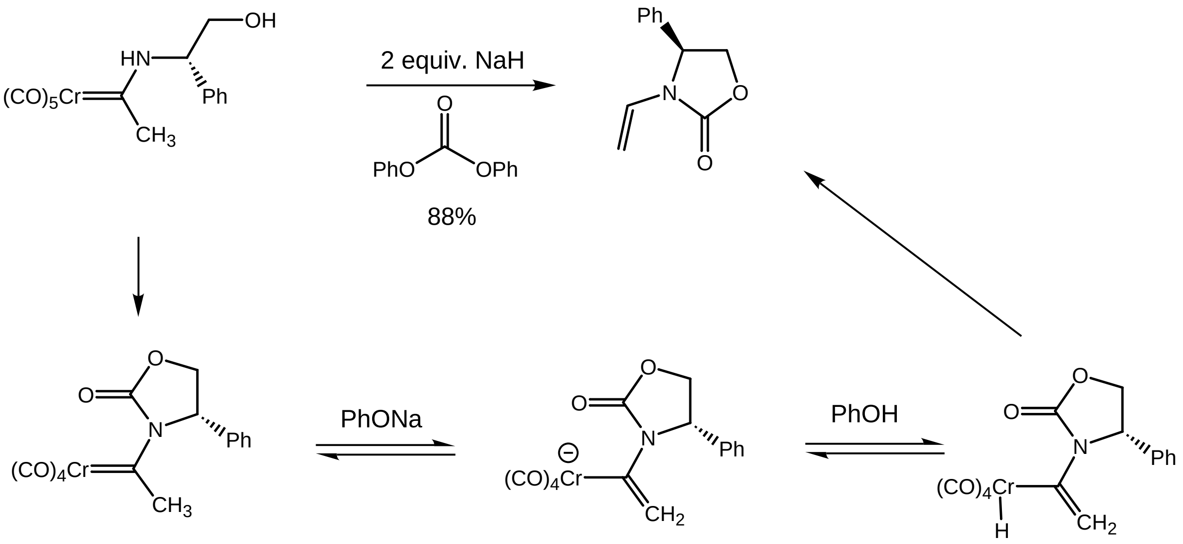
Hegedus
Tetrahedron, **1985**, 5833.
JOC, **1997**, 3586.



(+)-Cerulenin

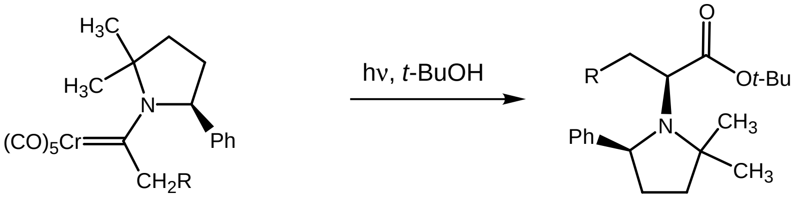
Hegedus
JOC, **1995**, 3787.
JOC, **1996**, 6121.
Organometallics, **1997**, 2313.
JOC, **1998**, 4691 & 8012.

Ene Carbamate Synthesis



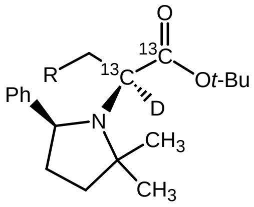
Hegedus, *JACS*, **1990**, 6255.

Amino Acid Synthesis



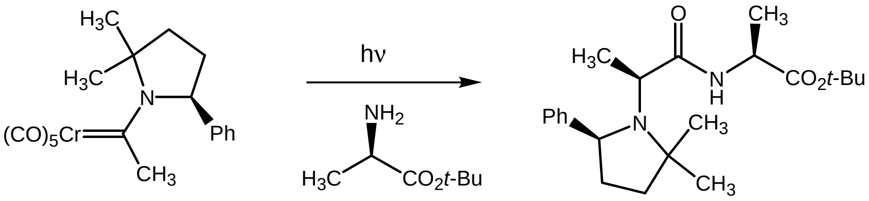
60-80%
≥97% de

- Mutiply-labeled amino acids are readily prepared from $(^{13}CO)_6CO$ and CH_3OD:



Hegedus
JACS, **1990**, 2264.
JACS, **1992**, 5602.
JACS, **1993**, 87.
Acc. Chem. Res., **1995**, 299.
JOC **1995**, 5831.
JACS, **1995**, 3697.
JOC **1997**, 7704.

Peptide Synthesis



68 - 88% yield
80-96% de

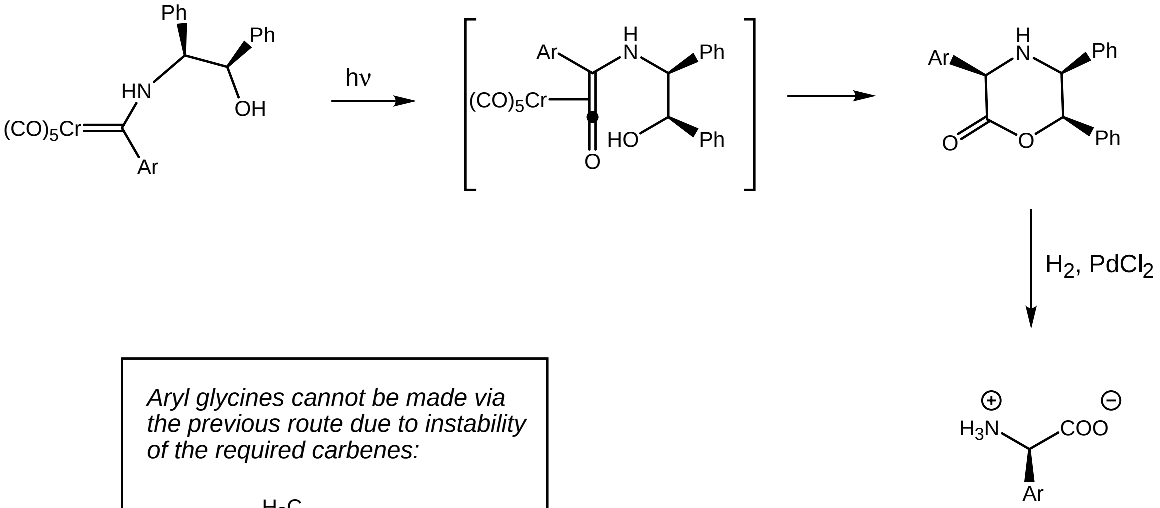
Solid Support

Merrifield Resin: *Acc. Chem. Res.*, **1995**, 299.
PEG: *JOC* **1995**, 5831; *JOC* **1997**, 7704.

- Reactions have been performed and do work, but are not as practical because the failure to achieve 100% yields and high diastereoselectivity limit this method.
- hard to work with because the polymer "sticks to everything, making quantitative transfer difficult".

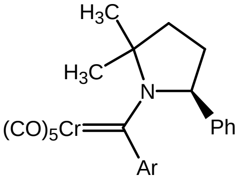
Acc. Chem. Res., **1995**, 299.

Aryl Glycines



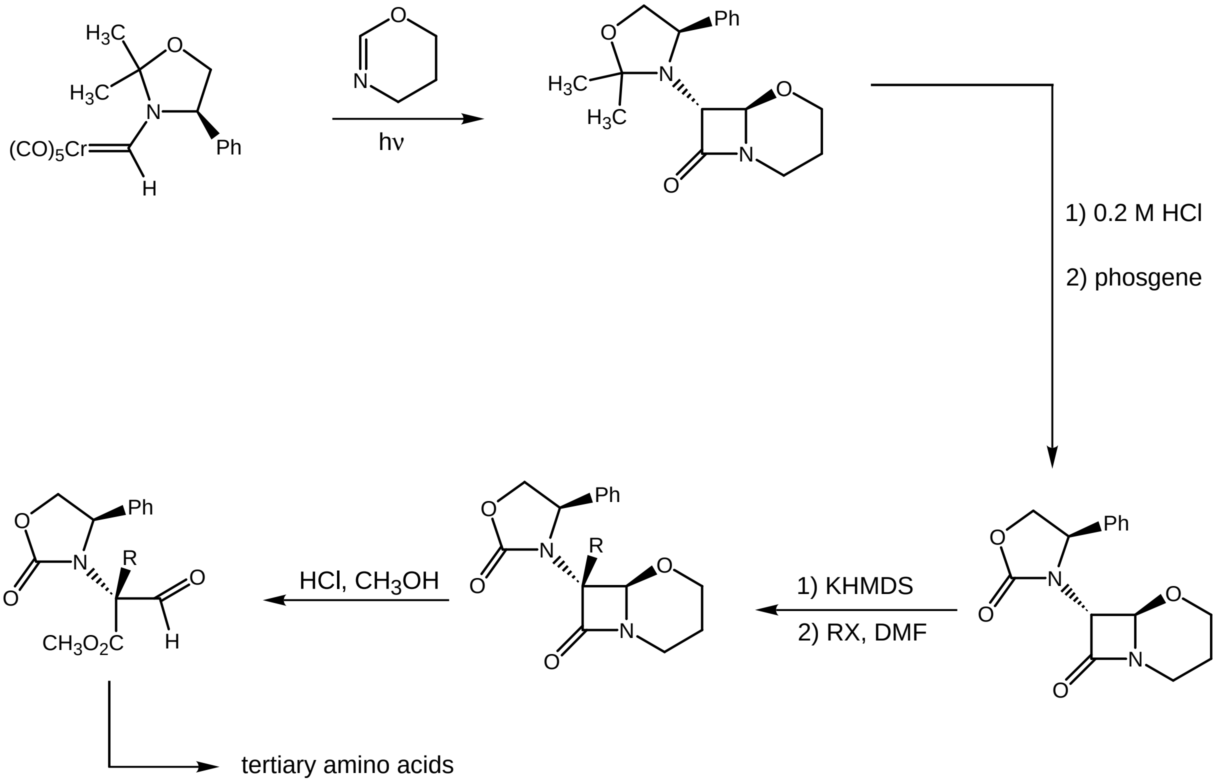
40 - 95% yield
56 - 98% ee

Aryl glycines cannot be made via the previous route due to instability of the required carbenes:



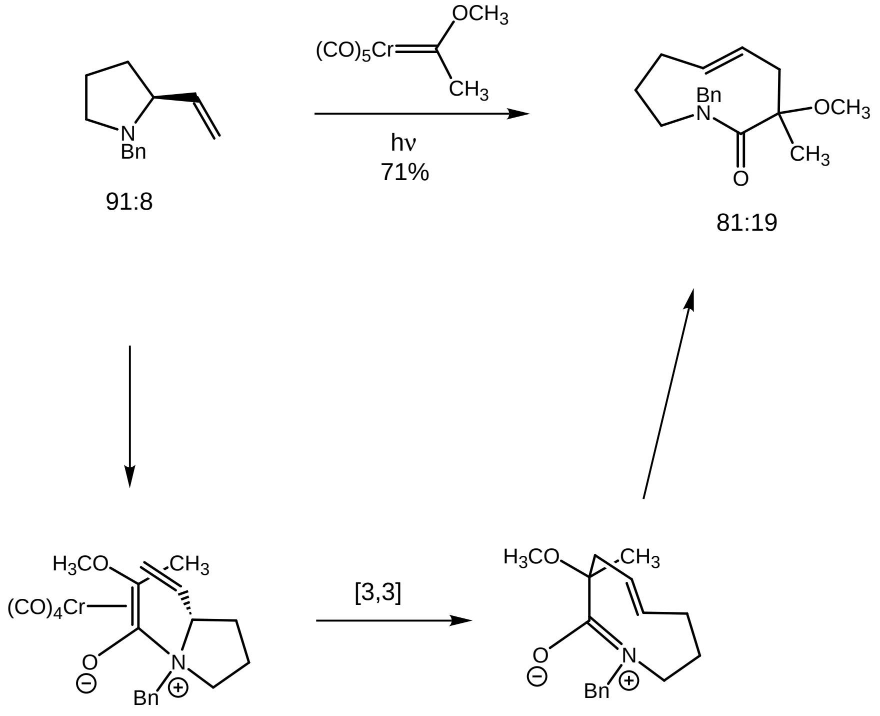
Hegedus, *JOC*, **1992**, 6914.

Tertiary Amino Acids



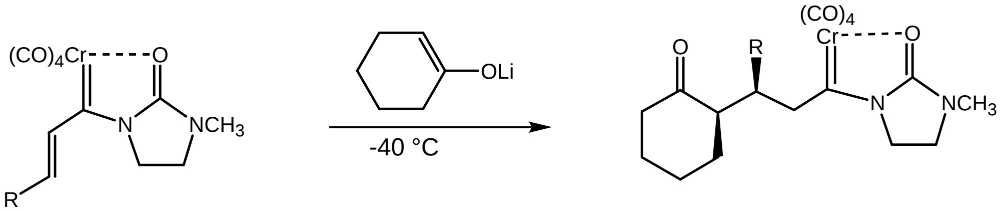
Hegedus, *JOC*, **1993**, 5918.

Zwitterionic Aza Cope Rearrangement



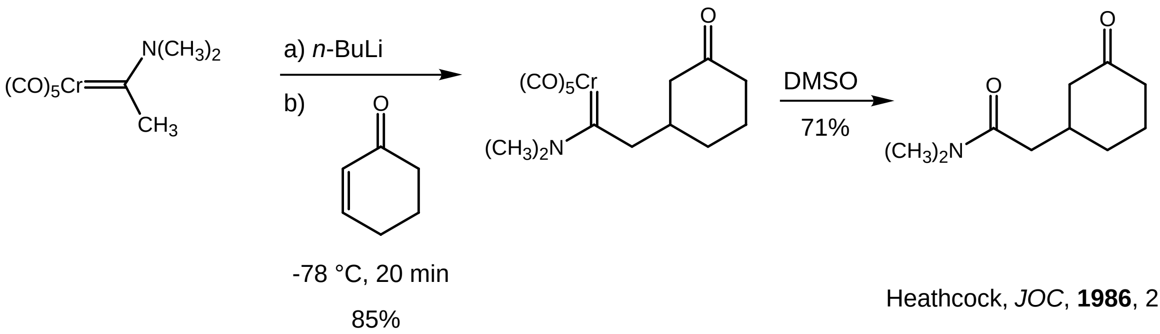
Hegedus, *JOC*, **1996**, 2871.

Michael Reaction



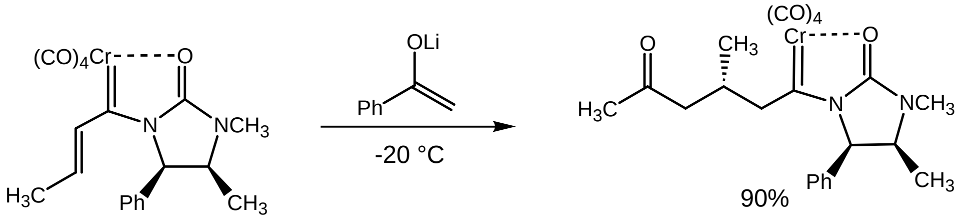
R	Yield	*syn:anti*
Ph	81%	99.5:0.5
CH_3	92%	98.3:1.7

Wulff, *JACS*, **1993**, 4602.

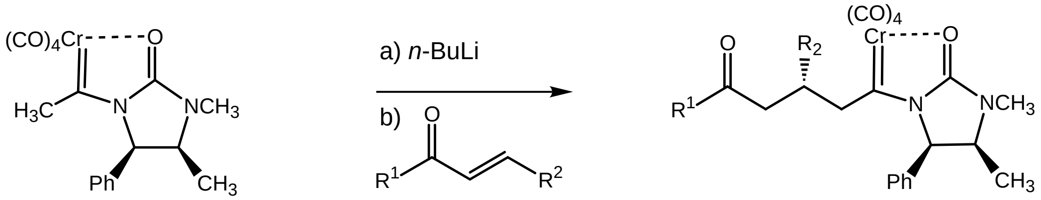


Heathcock, *JOC*, **1986**, 279.

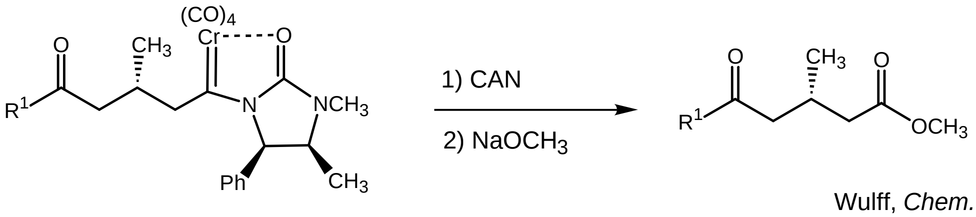
Asymmetric Michael Addition



90%
3:1diastereoselection

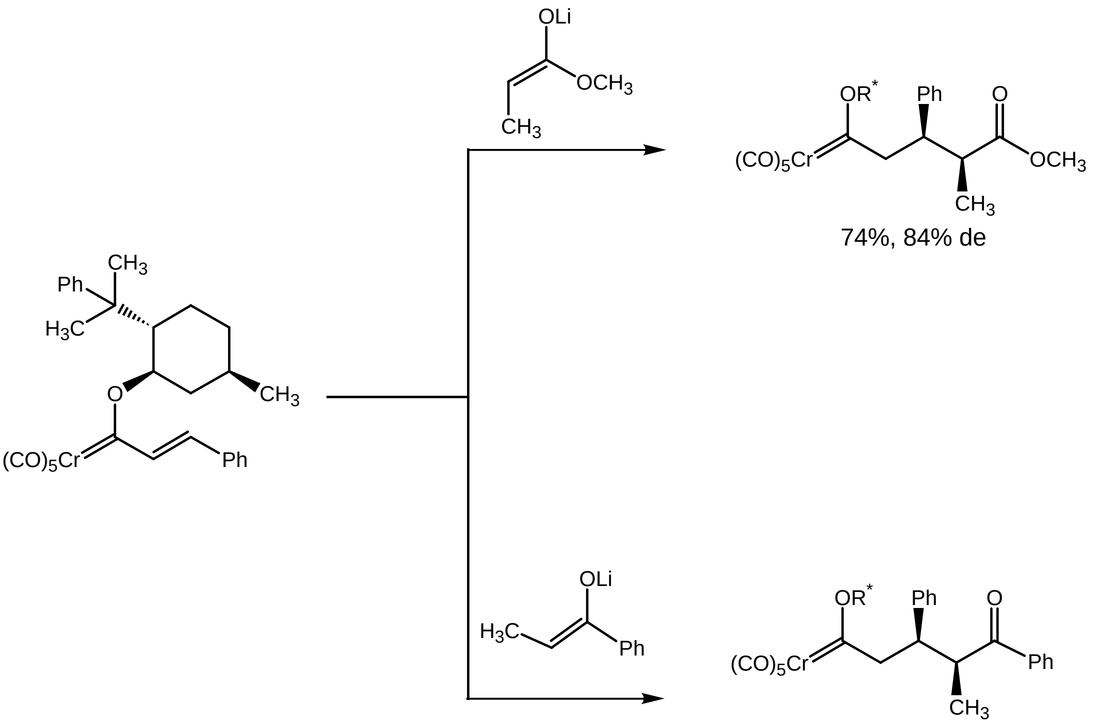


80%
>96:4 diastereoselection



Wulff, *Chem. Commun.*, **1996**, 2601.

Asymmetric Michael Reaction

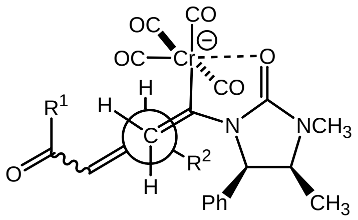


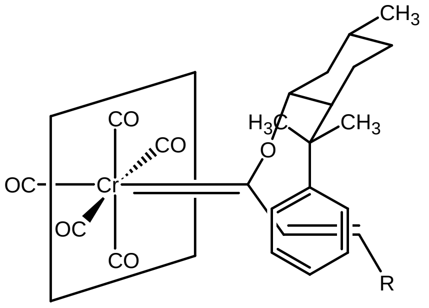
74%, 84% de

89%, 99% de

Barluenga, *Chem. Eur. J.*, **1995**, 236.

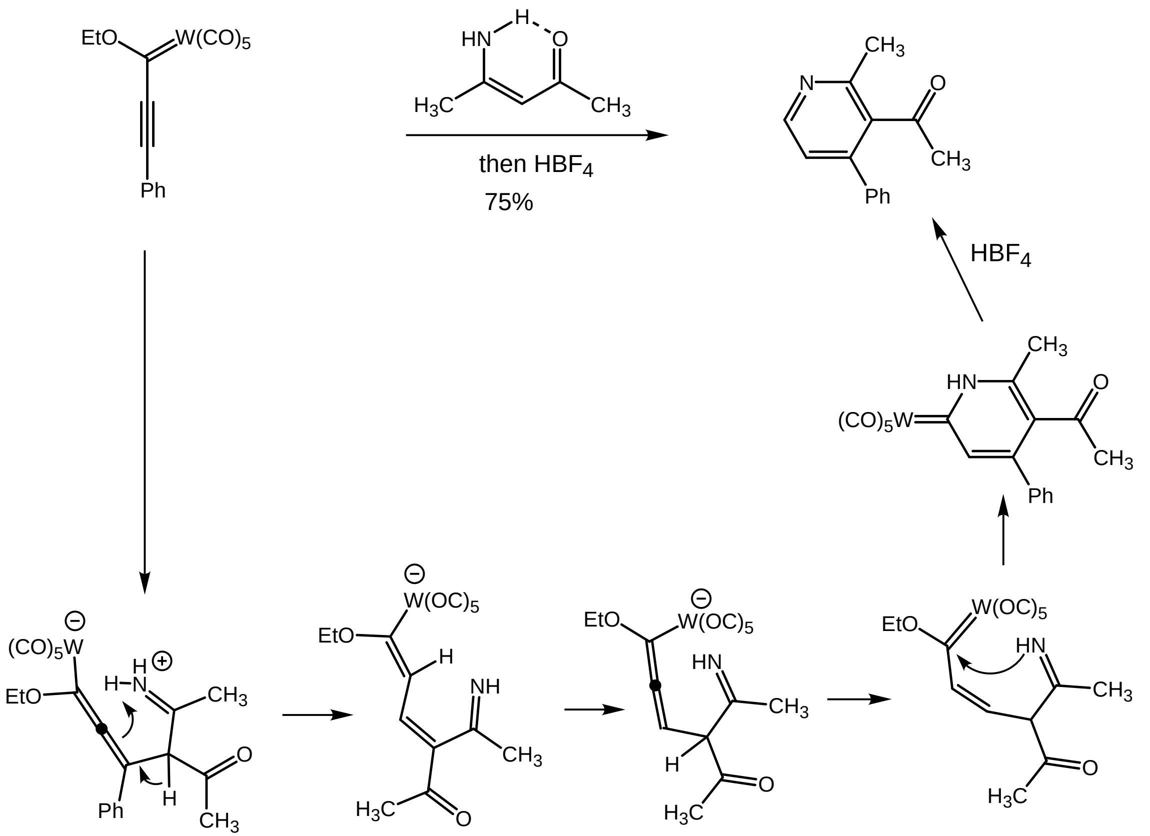
Michael Reactions: Selectivity





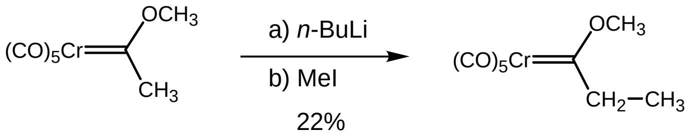
Open Transition States are Postulated

Pyridine Synthesis

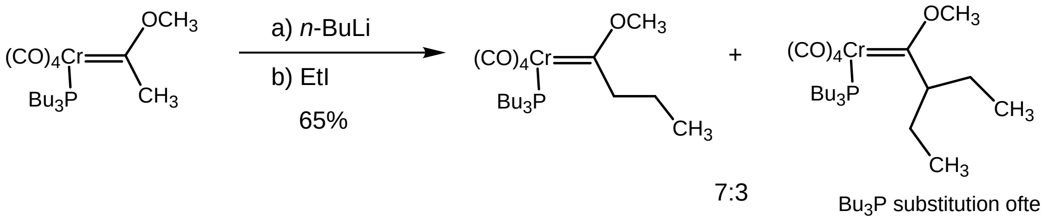


Aumann, *Synlett*, **1993**, 669.

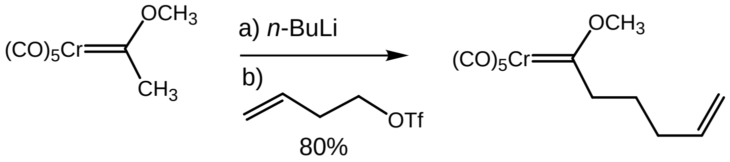
Alkylation



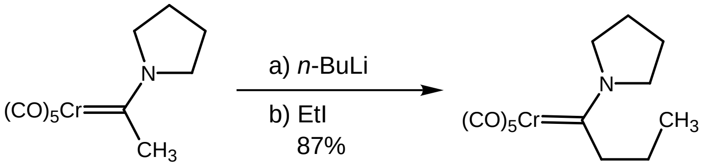
Hegedus *Org. Synth.*, **1987**, 140.



Bu_3P substitution often leads to different reactivity:
TL, **1995**, 8159.

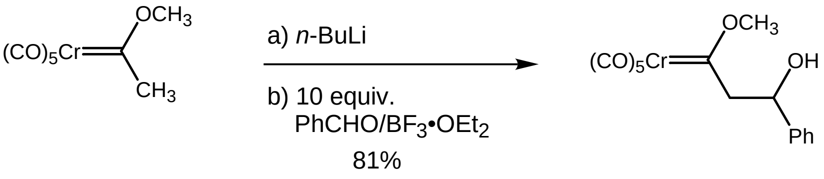


Wulff, *JOC*, **1987**, 3263.

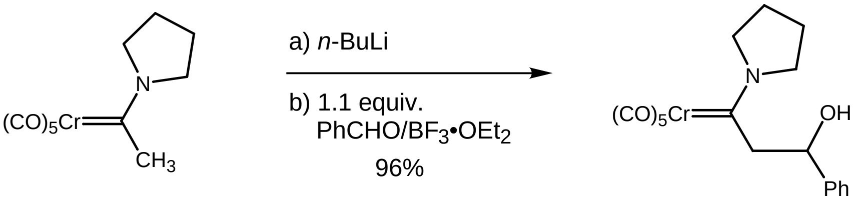


Wulff, *TL*, **1989**, 4061.

"Aldol" Reaction

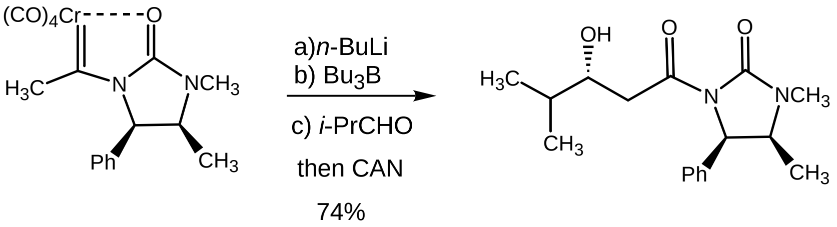


Wulff, *JACS*, **1985**, 503.



Wulff, *JACS*, **1989**, 5485.

Ketones work as well.



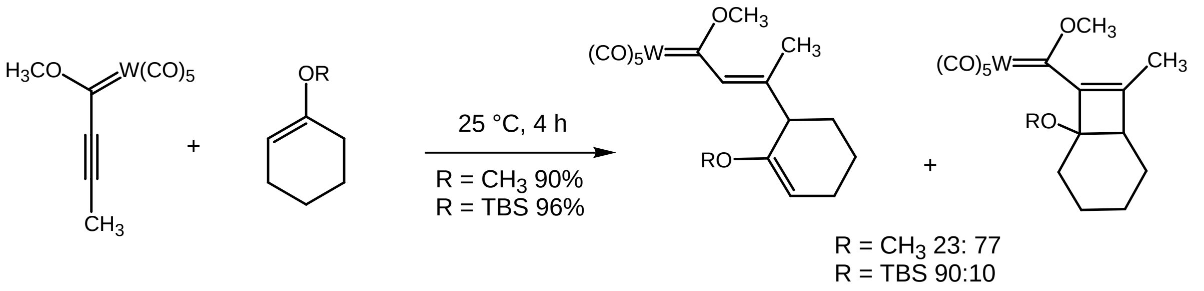
Wulff, *JOC*, **1994**, 6882.

ds: 98.6: 1.4

in absense of Bu_3B, ds: 91:9

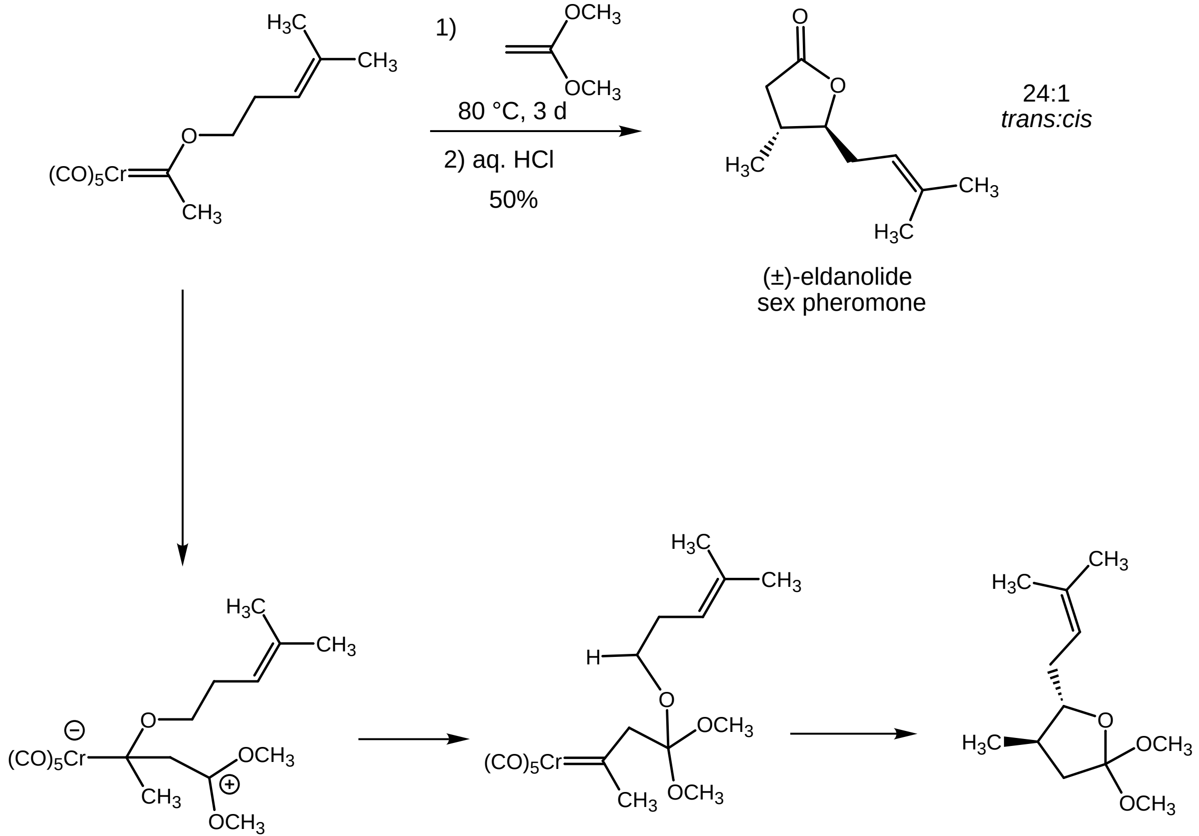
oxazolidinone complexes were unstable:
Hegedus, *JACS*, **1990**, 6255.

Ene Reaction



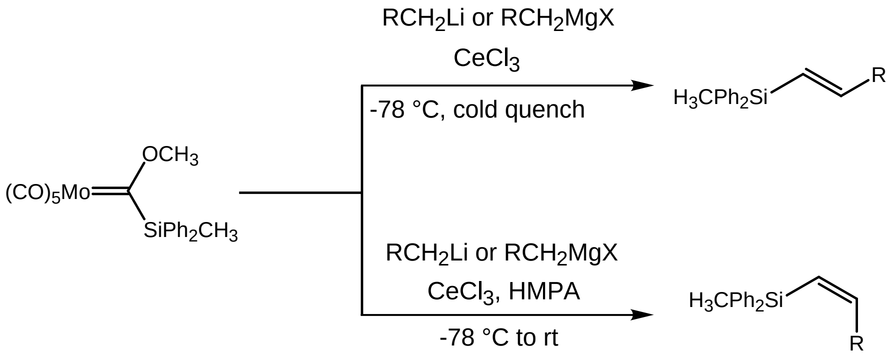
Wulff, *JACS*, **1990**, 6419.

Reaction of Ketene Acetals



Wulff, *JACS*, **1992**, 10665.

Vinylsilane Synthesis

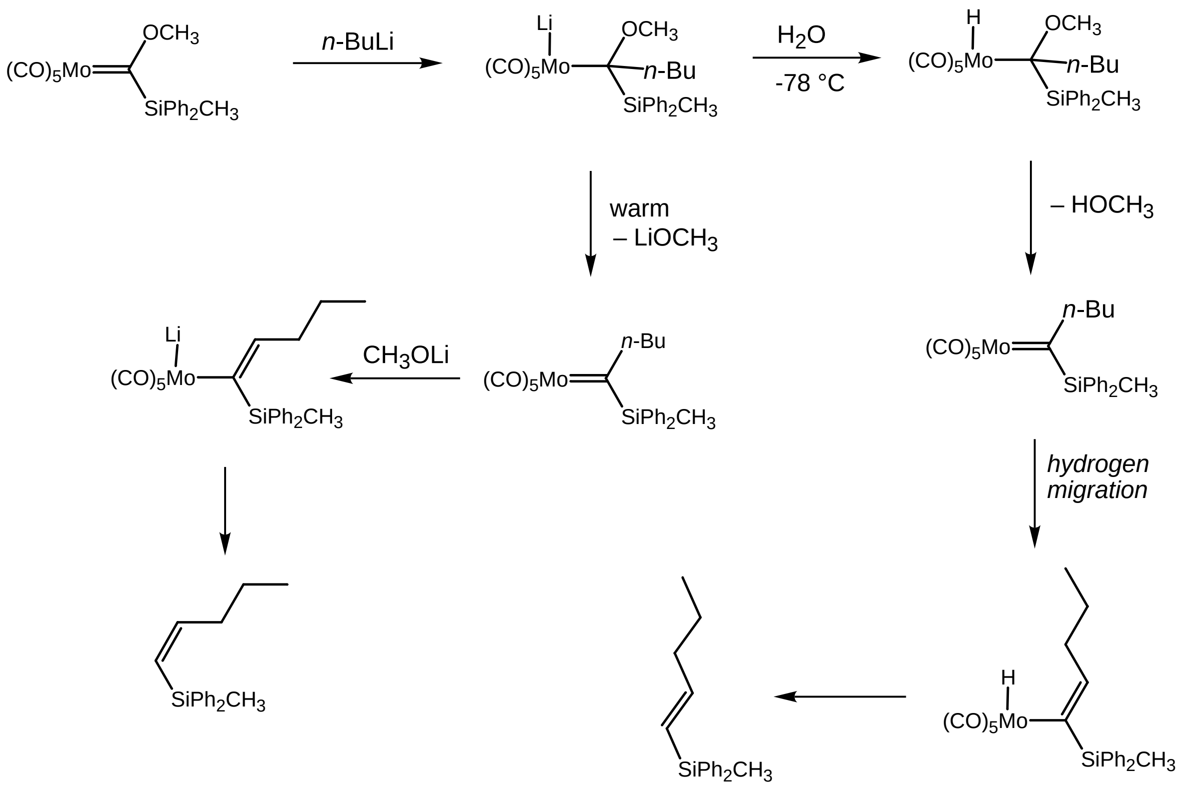


R = *i*-Pr, 94%, 96:4 E:Z
R = Bu, 86%, 96:4 E:Z
R = *i*-Bu, 85%, 97:3 E:Z

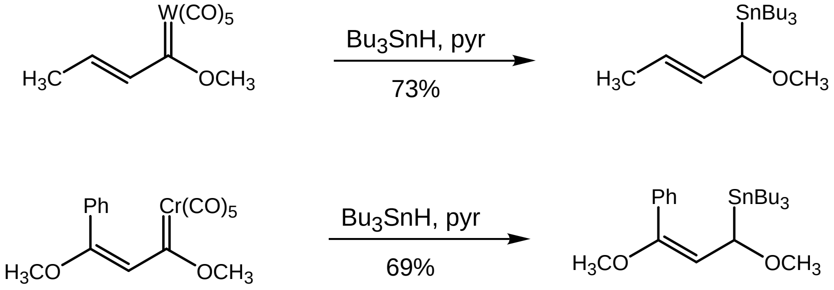
R = *i*-Pr, 76%, 92:8 Z:E
R = Bu, 79%, 97:3 Z:E
R = *i*-Bu, 61%, 97:3 Z:E

Iwasawa, *Chem. Lett.*, **1994**, 231.

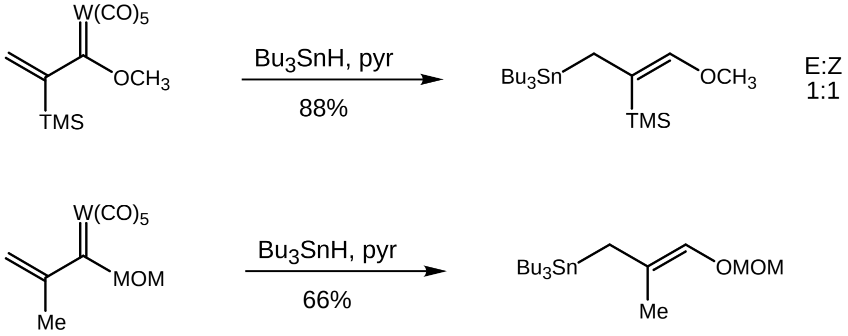
Vinylsilane Synthesis
Proposed Mechanism



Allyl Stannane Synthesis

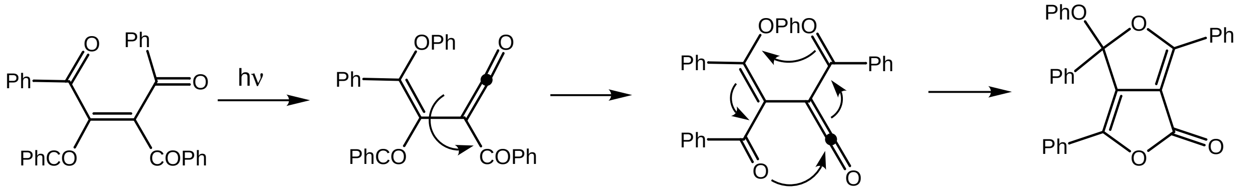


1,1 addition is usually observed, however 1,3 addition is possible:

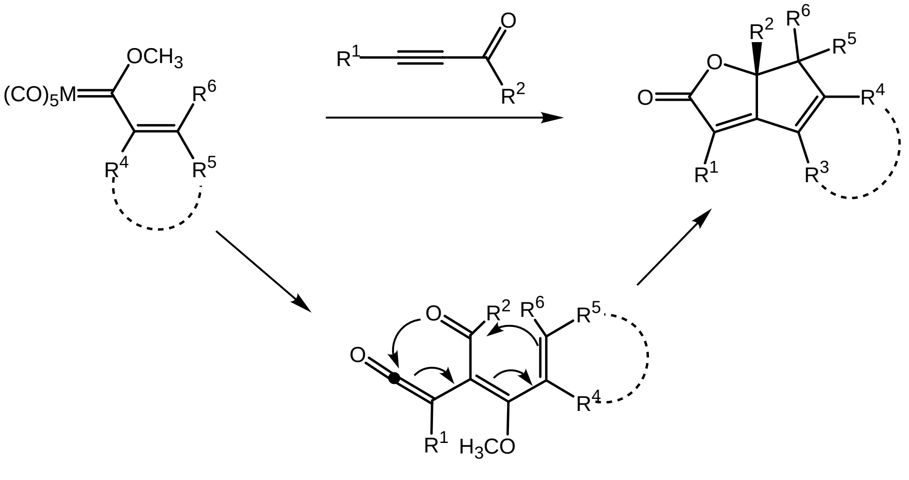


Merlic, *TL*, **1995**, 1007.

Halban-White Cyclizations



Andres, A. Dissertation, Strasbourg, 1911.
van Halban, *Helv. Chim. Acta*, **1948**, 1899.



yields 30-70%
Dotz byproduct

Wulff
JACS, **1990**, 1645.
JACS, **1991**, 5459.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 36

Introduction to Organosilicon Chemistry

- Silicon Bonding Considerations
- The Silicon–Proton Analogy
- C=O Addition of Organosilanes
- Sigmatropic Rearrangements of Organosilanes
- Anionic (Brook) Rearrangements
- Peterson Olefination Reaction
- Survey of Silicon (and related) Protecting Groups

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 9, " C–C Bond Forming Rxns of Boron, Silicon & Tin", 595–680.

Fleming, I.; Barbero, A.; Walter, D. "Stereochemical control in organic synthesis using silicon-containing compounds." *Chem. Rev*. **1997**, *97*, 2063-2192. (**Web**)

Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084 (**handout**)

Masse, C. E.; Panek, J. S. "Diastereoselective reactions of chiral allyl- and allenylsilanes with activated C-X pi-bonds." *Chem. Rev.* **1995**, *95*, 1293-1316.

Ager, D. J. "The Peterson olefination reaction." *Org. Reactions* **1990**, *38*, 1-224

Colvin, E. "Silicon in Organic Synthesis," *Butterworths,* **1981**

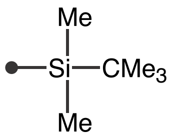
Bois, et al. "SiliconTethered Reactions" *Chem. Rev*. **1995**, *95*, 1253-1277. (**Handout**)

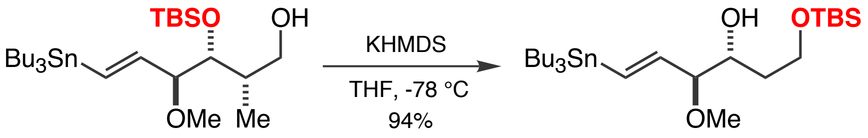
D. A. Evans Monday,
December 15, 2003

Problems to Contemplate

Explain what drives this rearrangement.

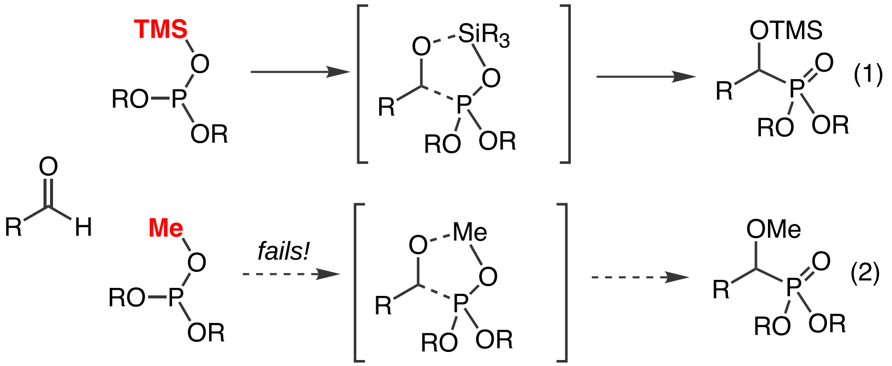
TBS =



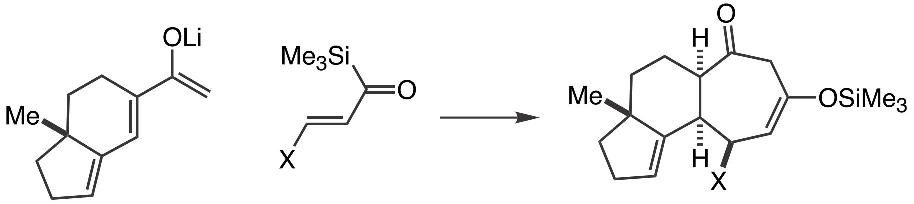


Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

The C=O addition illustrated in eq 1 proceeds while the carbon analogue (eq 2) does not. Explain



Provide a mechanism for the indicated transformation



Takeda, *Org. Lett*, **2000**, *2*, 903-1905

Bonding Considerations: Carbon vs Silicon

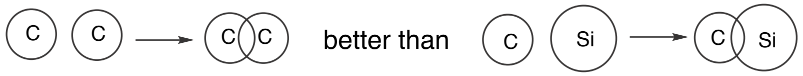
Average Bond dissociation eneregies (Kcal/mol)

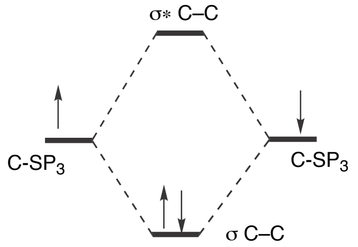
C–C	C–Si	Si–Si	C–F	Si–F	C–O	Si–O
83	76	53	116	135	86	108

C–H	Si–H
83	76

Average Bond Lengths (Å)

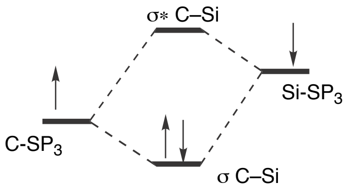
C–C	C–Si	C–O	Si–O
1.54	1.87	1.43	1.66





$H_3C–CH_3$ BDE = 83 kcal/mol

Bond length = 1.534 Å



$H_3C–SiH_3$ BDE ~ 76 kcal/mol

Bond length = 1.87 Å

This trend is even more dramatic with pi-bonds:

π C–C = 65 kcal/mol π C–Si = 36 kcal/mol π Si–Si = 23 kcal/mol

$$\boxed{\overset{\delta-}{\mathrm{C}}\text{——}\overset{\delta+}{\mathrm{Si}}}$$

Group IV Electronegativities (Pauling)

Carbon	Silicon	Germanium	Tin	Lead
2.55	1.90	2.01	1.96	2.33

+2 Oxidation state becones increasingly more stable →

Hypervalent 5-Coordinate Silicon Compounds

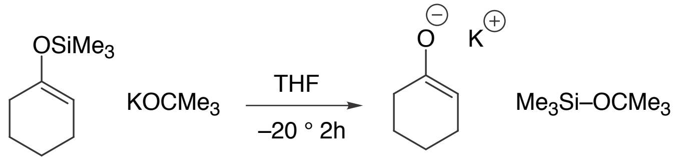
Akiba, "Chemistry of hypervalent Compounds" Wiley-VCH, Chapters 4-5, 1999

Penta-coordinate silicates are commonly observed

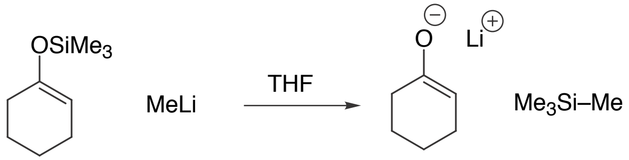
$\overset{\ominus}{\mathrm{MeSiF_4}}\ \overset{\oplus}{\mathrm{NEt_4}}$ $\overset{\ominus}{\mathrm{Ph_3SiF_2}}\ \overset{\oplus}{\mathrm{NR_4}}$

Nucleophilic substitution at Silicon

$$\mathrm{RO{-}SiMe_3} \xrightarrow{F^{\ominus}} \mathrm{RO^{\ominus}} + \mathrm{F{-}SiMe_3}$$

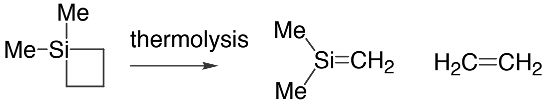


Duhamel et al. *J. Org. Chem.* **1996**, *61*, 2232

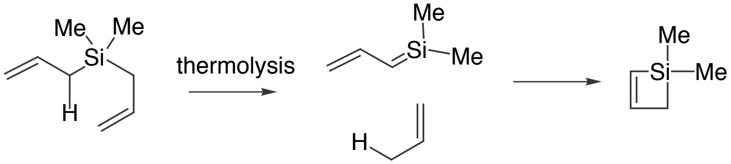


Stork et al. *JACS.* **1968**, *90*, 4462, 4464

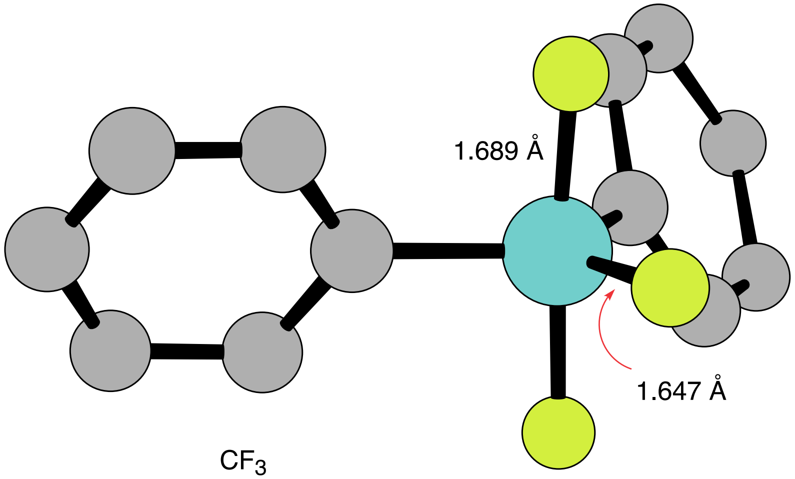
Thermal Rearrangements One may readily access divalent intermediates

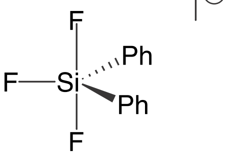


Colvin, pp 7-9

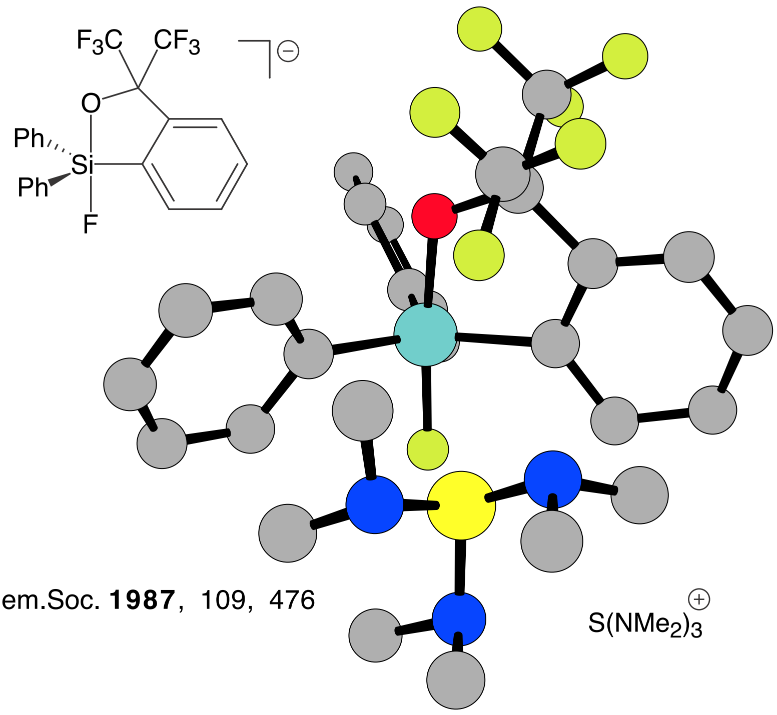


Hypervalent Silicon Ate-Complexes

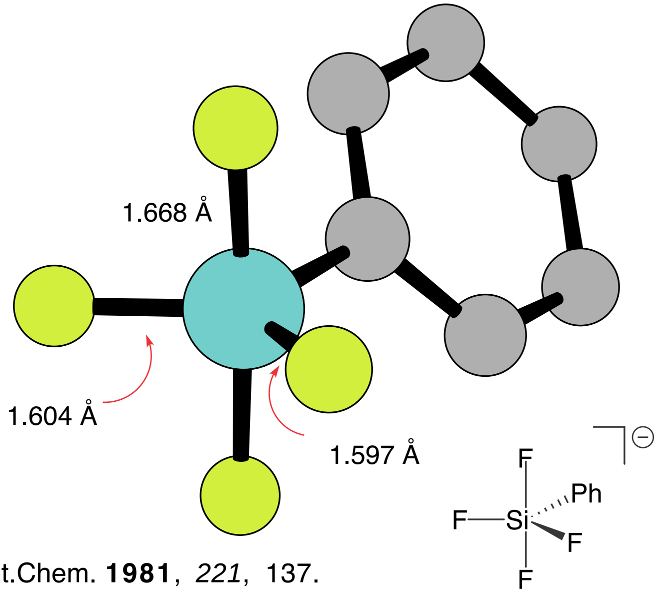




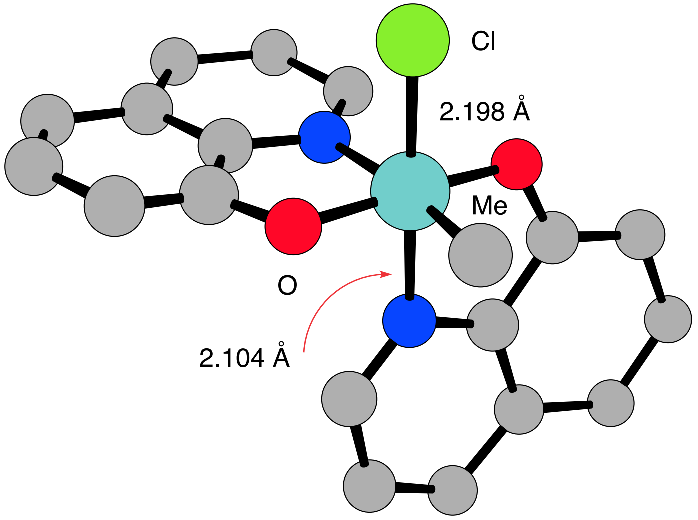
Inorg. Chem. **1984**, *23*, 1378



J. Am. Chem.Soc. **1987**, 109, 476



J. Organomet.Chem. **1981**, *221*, 137.

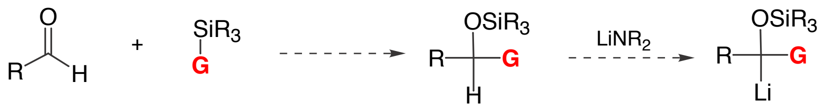


Acta Crystallogr. Sect. C **1984**, *40*, 476

Bonding Considerations: Carbon vs Silicon

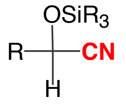
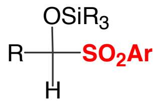
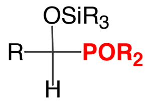
Carbonyl addition Reactions

1970 DAE Objective: *Develop a reagent that will transform aldehydes into protected cyanohydrins in one step*

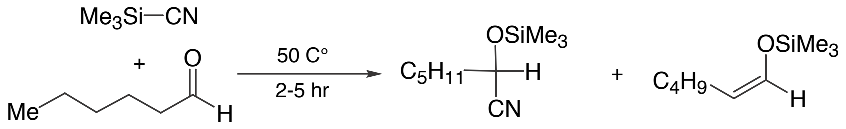


G = carbanion-stabilizing FG

Carbonyl Anion Equivalent

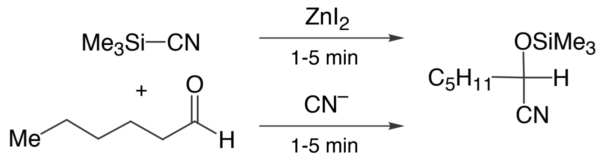
$R_3Si—G$ Candidates	Carbonyl Adducts
$R_3Si—CN$	
$R_3Si—OSO_2Ar$	
$R_3Si—OPR_2$	

Thermal C=O addition of TMSCN is not a clean reaction



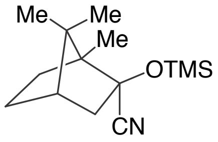
ratio: 65:35

The prospect of catalysis was investigated

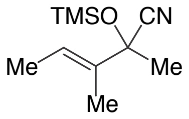


reaction was instaneous and quantiltative

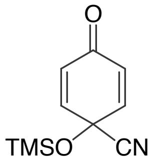
Principle established that normally inaccessible cyanohydrin derivatives may now be accessed



>95% yield
(ZnI_2 catalysis)



92% yield
only 1,2-addition
(ZnI_2 catalysis)

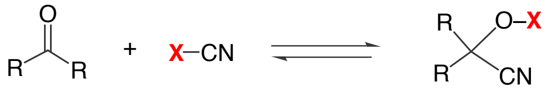


>95% yield
only 1,2-addition
(CN^- catalysis)

with Truesdale, Carroll, *Chem Commun.* **1973**, 55; *J. Org. Chem.*. **1974**, *39*, 914
Tetrahedron Lett **1973**, 4929 (first discussion of Nu catalysis)

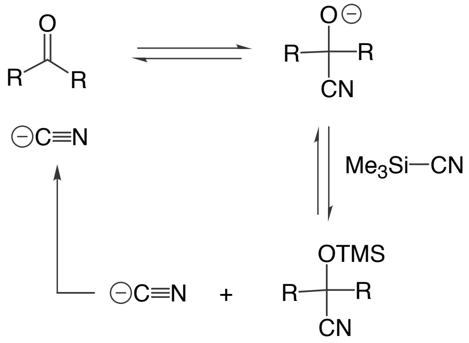
"The Silicon Advantage"

From the preceding case, it is clear that ΔH_{Si} is more exothermic than ΔH_H

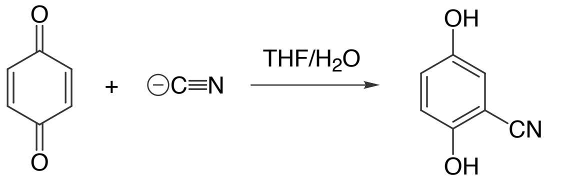


$\Delta H_{Si} > \Delta H_H$

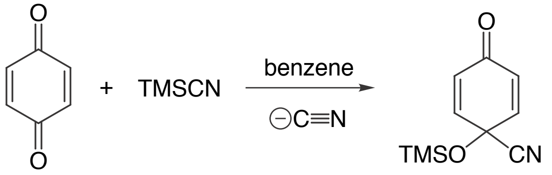
Nucleophilic Catalysis



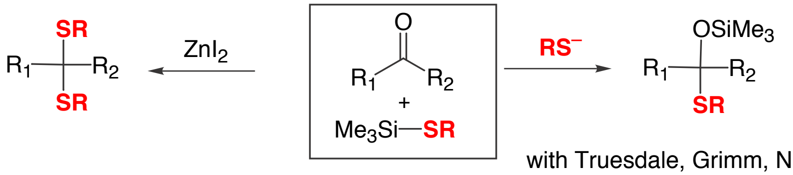
Explain the following observations



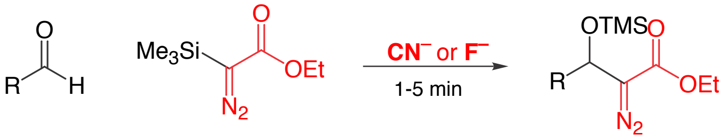
1-4 addition



1-2 addition

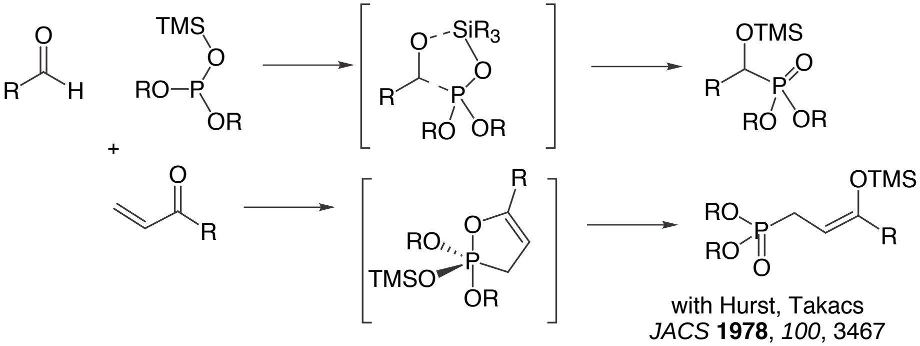


with Truesdale, Grimm, Nesbitt,
JACS **1975**, *97*, 3229
JACS **1977**, *99*, 5009



Non-catalyzed processes may also occur if a proper geometry for atom transfer can be achieved

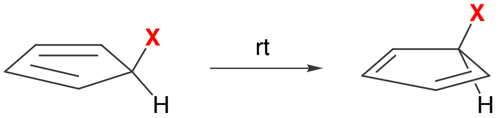
with Truesdale, Grimm
JOC **1976**, *41*, 3335



with Hurst, Takacs
JACS **1978**, *100*, 3467

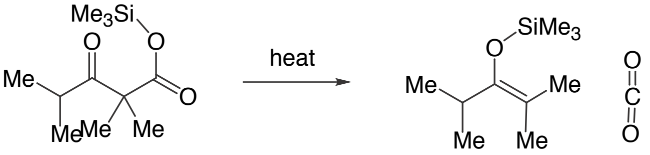
"The Proton–Silicon Correlation"

- 🟥 Organosilanes undergo carbonyl addition processes in direct analogy with their proton counterparts but with an attendant greater exothermicity.
- 🟥 Organosilanes undergo a range of thermal rearrangements processes in direct analogy with their proton counterparts.

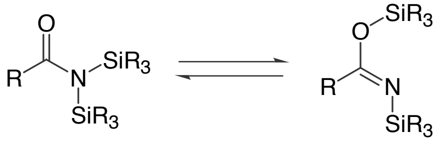


$k(Si) = 10^{+6}\ K(H)$

A. J. Ashe III, *JACS* **1970**. *92*, 1233



Colvin, pp 37-8



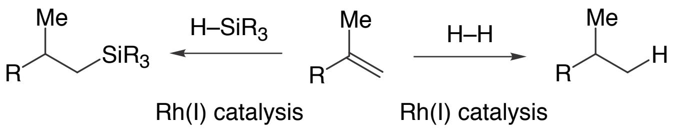
ΔG^* 15-22kcal/mol

Si transfer is intramolecular

Yoder et al., *JACS* **1974**. *96*, 4283

$Me_3Si{-}C{\equiv}N \rightleftharpoons C{\equiv}N{-}SiMe_3$

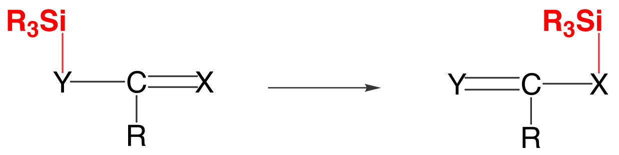
- 🟥 Organosilicon hydrides undergo transition metal catalyzed hydrosilylation processes in direct analogy with normal hydrogenation reactions



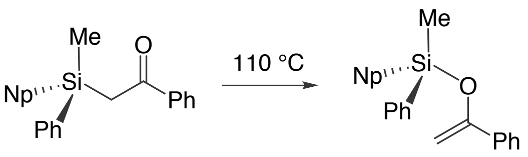
"Hydrosilylation of C–C Bonds". T. Hayashi In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol I, 319-332.

Carbonyl [1,2] & [1,3] Sigmatropic Rearrangements

[1,3]-Sigmatropic Rearrangements



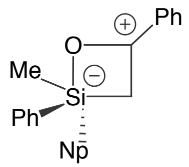
Y = C; X = O



Complete retention of Si stereochemistry was noted.

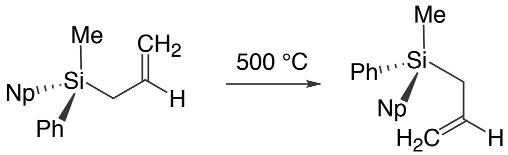
Ea = 28 kcal/mol

A. G. Brook *Accts. Chem. Research* **1974**, *7*, 77-84



Brook speculates that a hypervalent Si intermediate might be involved in the rearrangement.

Y = C; X = C



Inversion of Si stereochemistry was noted.

Ea = 48 kcal/mol

H. Kwart et al., *JACS* **1973**. *95*, 8678

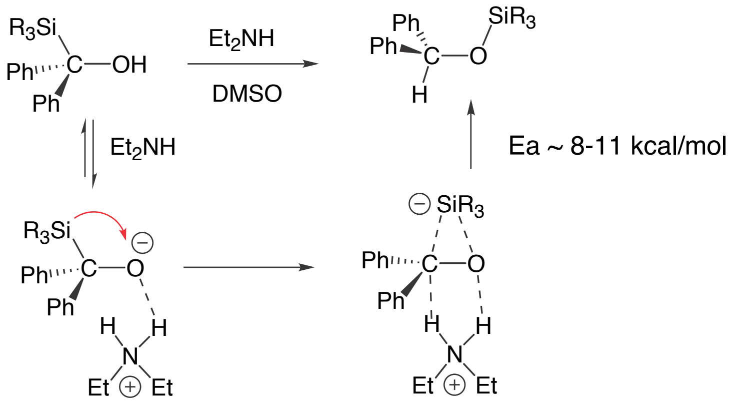
Theoretical calculations lead to the conclusion that the concerted [1,3] sigmatropic rearrangement with ***retention*** of Si-configuration should represent the lower energy pathway.

Yamabe, *JACS* **1997**, *119*, 808

At the present time these rearrangements are not well studied,

"The Brook Rearrangement(s)"

A. G. Brook *Accts. Chem. Research* **1974**, *7*, 77-84

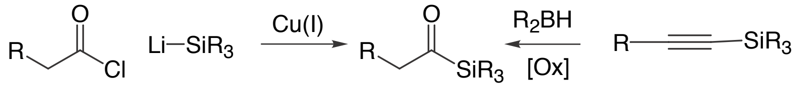


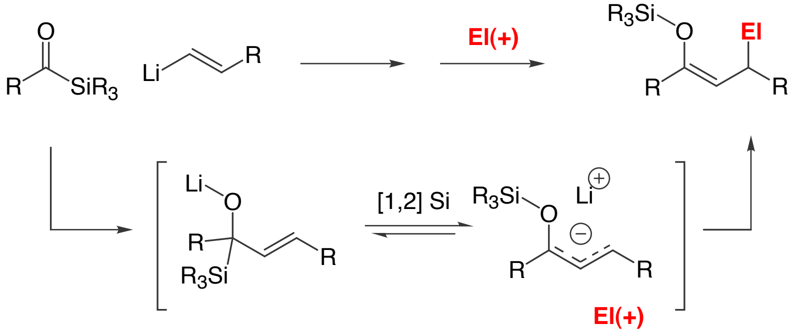
Brook has documented that **retention** at Silicon & **inversion** at Carbon occur.

Transformations Involving the Brook Rearrangement

Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084

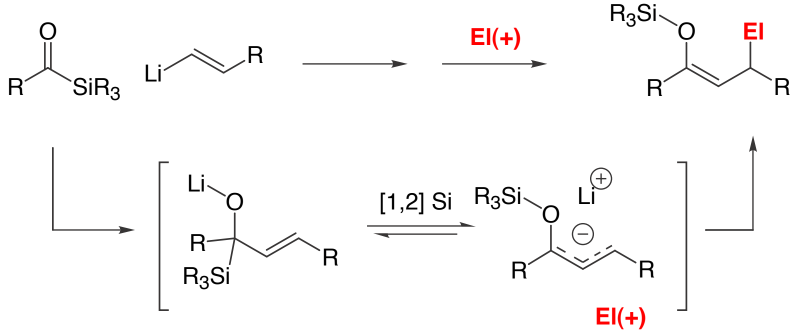
Acylsilanes

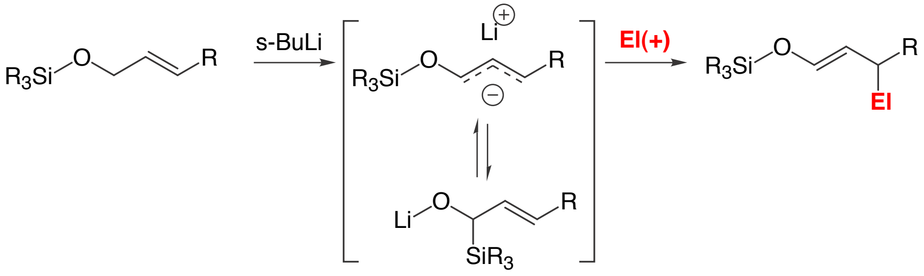


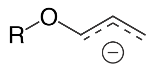


Transformations Involving the Brook Rearrangement

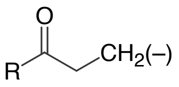
Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084





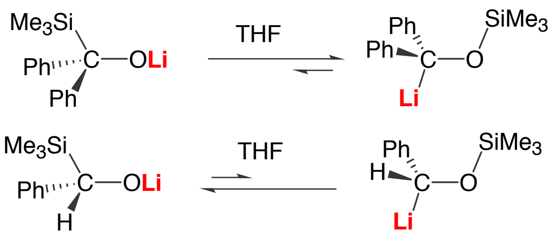


These reagents are useful homoenolate anion equivalents

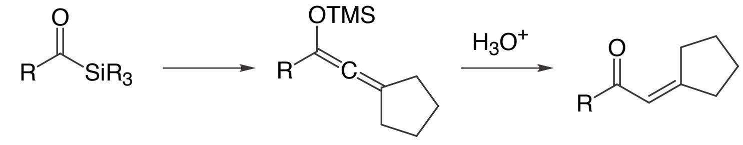


"Metalated Allylic Ethers as Homoenolate Anion Equivalents".
Evans, D. A.; Andrews, G. C.; Buckwalter, B. *JACS* **1974**, *96*, 5560.
Si–Variant: Still & MacDonald *JACS* **1974**, *96*, 5561

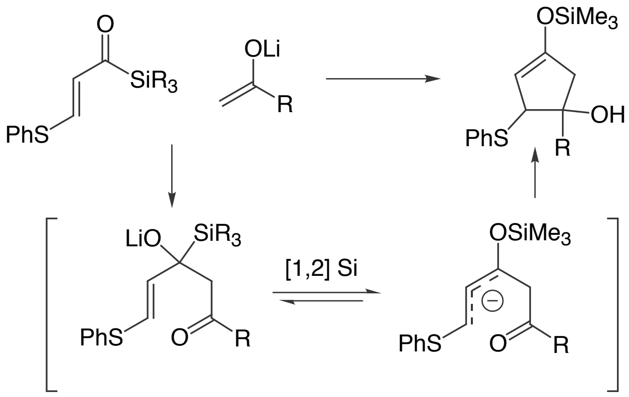
Brook Equilibrium Reich *JACS* **1980**, *102*, 1423 (see footnote 8)



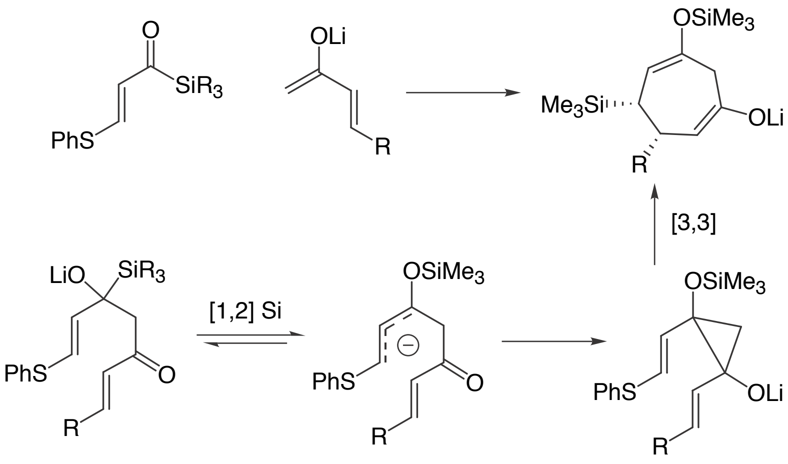
Intramolecular alkylations may be carried out:



Reich *JACS* **1980**, *102*, 1423



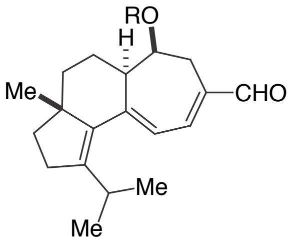
Takeda *JACS* **1993**, *115*, 9351; *Synlett* **1994**, 178; *SynLett* **1997**, 255



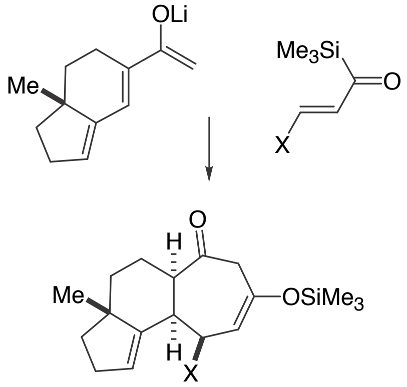
Tetrahedron **2001**, *57*, 2065-2084, footnote 16

Transformations Involving the Brook Rearrangements

The natural product target:



The key reaction



Takeda, *Org. Lett*, **2000**, *2*, 903-1905

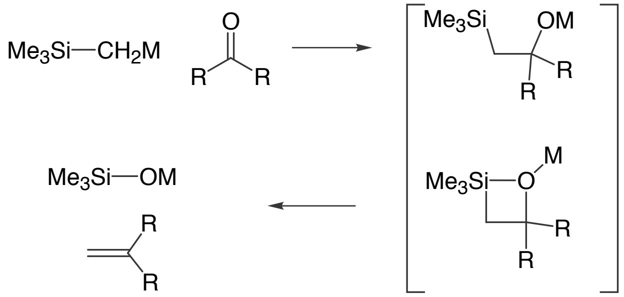
The Peterson Olefination Reaction

Ager, D. J. "The Peterson olefination reaction."
Org. Reactions **1990**, *38*, 1-224

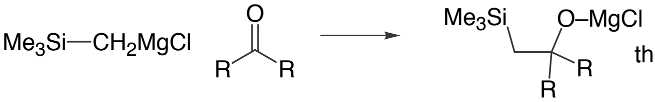
C	**N**
Si	**P**

The key paper: Peterson, *J. Org. Chem*. **1968**, *33*, 780-784

It was Peterson's intent to find a silicon analog to the Wittig rxn.
The reaction concept is outlined below:

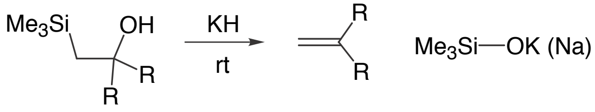


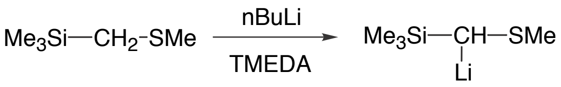
Magnesium alkoxides: Stable

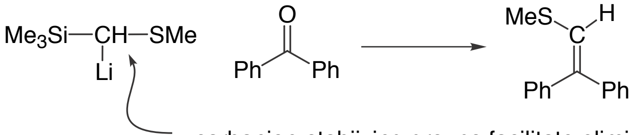


these adducts are
quite stable

Na & K alkoxides: Eliminate



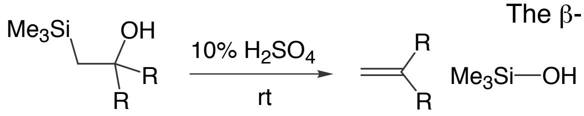




carbanion-stabiizing groups facilitate elimination

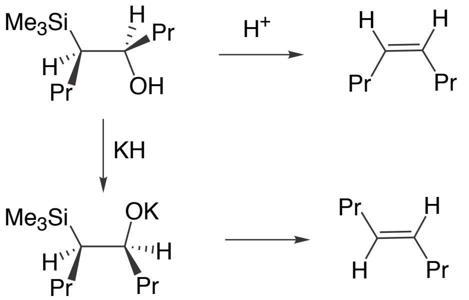
Elimination could also be effected with dilute acid

The β-Effect (lecture 32)



analogy provided by Whitmore et al. *JACS* **1947**, *69*, 1551

Mechanistic aspects of Beta-OH Elimination



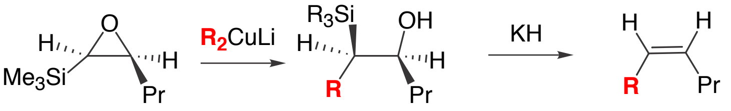
Anti Elimination

The β-Effect (lecture 32)

Syn Elimination

Hudrlik et al. *JACS* **1975**, *97*, 1464

Colvin chapter 12, pp 141

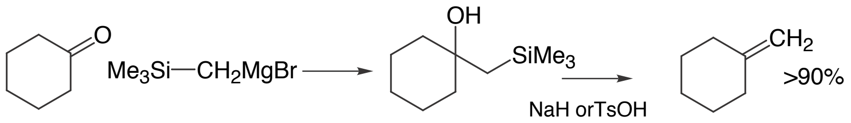


reaction is stereospecific

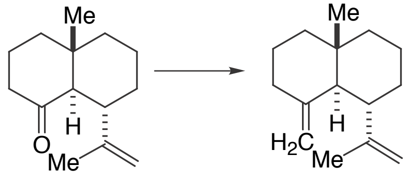
note site of nu attack. Why?

The Peterson Olefination Reaction

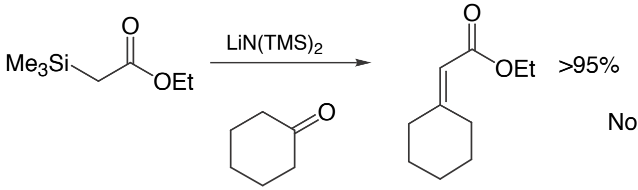
■ Simple Examples: Taken from Organic Rxns review



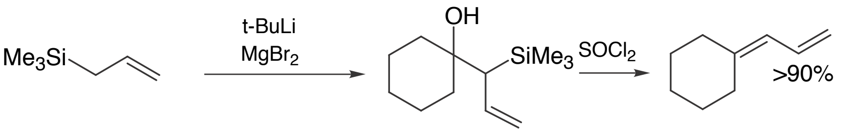
This reagent is better that $H_2C{=}PPh_3$ for hindered ketones



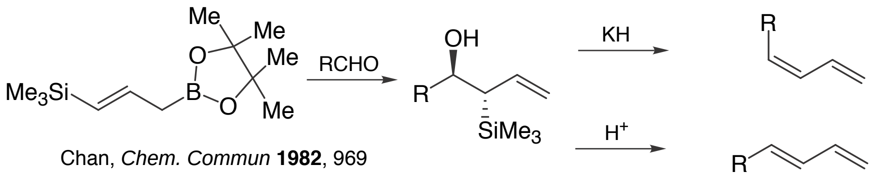
Boeckman, *Tet. Lett* **1973**, 3437



Nozaki, *JACS* **1974**, *96*, 1620



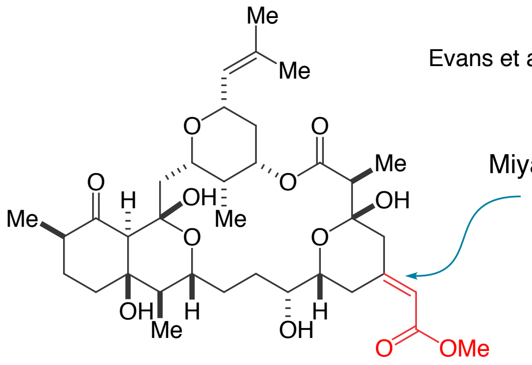
Chan, *Tet. Lett* **1978**, 2383



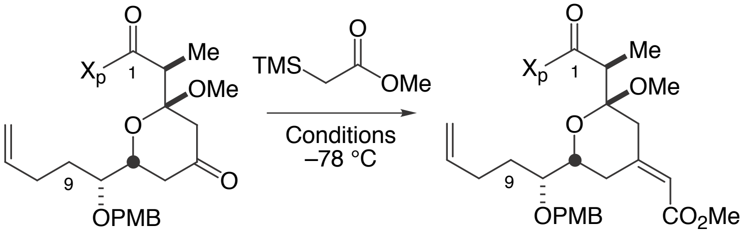
Chan, *Chem. Commun* **1982**, 969

Miyakolide (+)-1

Evans et al. *JACS* **1999**, *121*, 6816-6826.

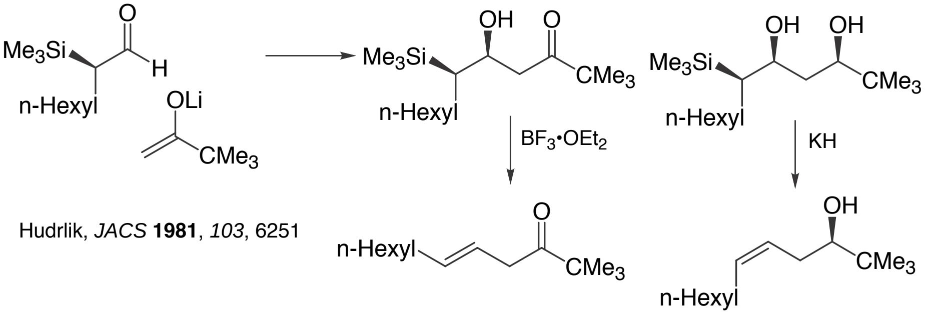


Miyakolide presents an interesting olefin geometry challenge



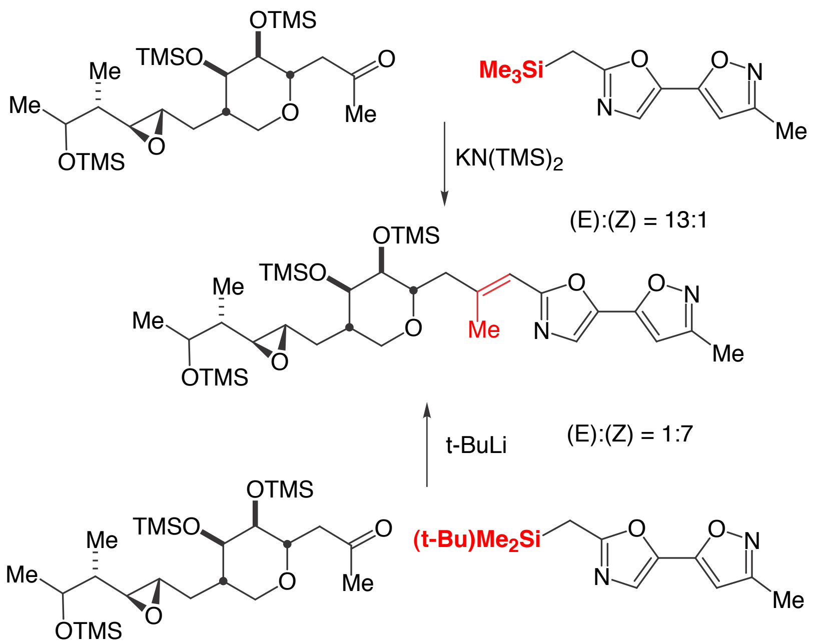
19-E

entry	base	solvent	*E* : *Z*
1	**LDA**	**THF**	**73 : 27**
2	NaHMDS	THF	18 : 82
3	LDA	Et_2O	66 : 33
4	LDA	PhMe	66 : 33



Hudrlik, *JACS* **1981**, *103*, 6251

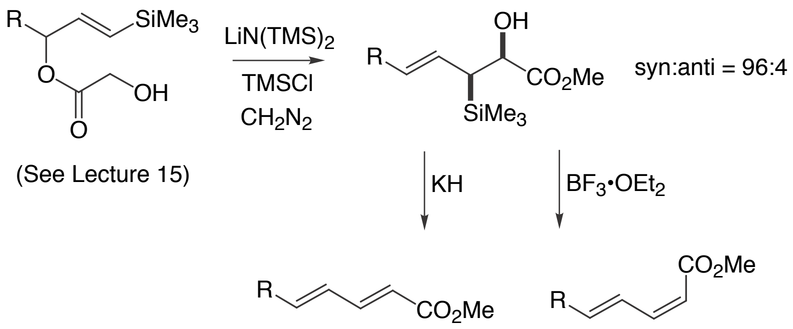
The Peterson Olefination Reaction



Bell et al. *Tetrahedron* **1994**, *50*, 6643

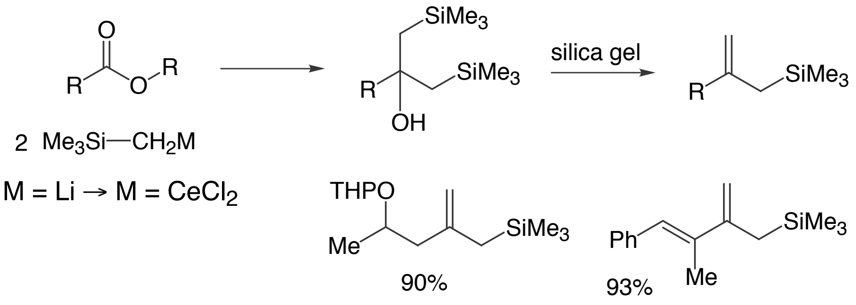
Reaction may be altered significantly with an attendant change in stereoselection

Ireland Enolate Claisen Coupled to Peterson Olefination

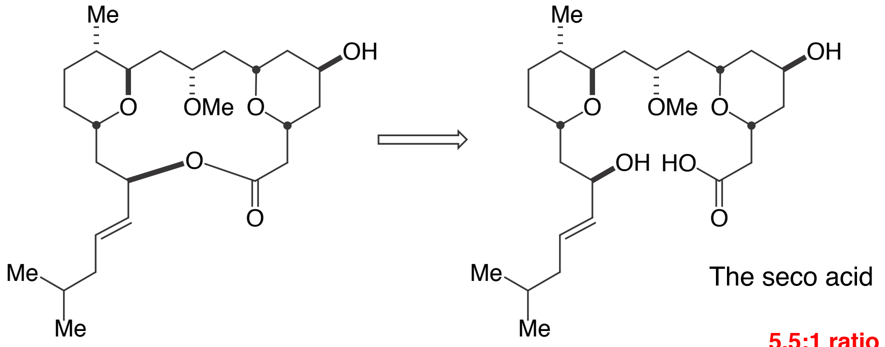


Sato et al. *Chem. Lett* **1986**, 1553

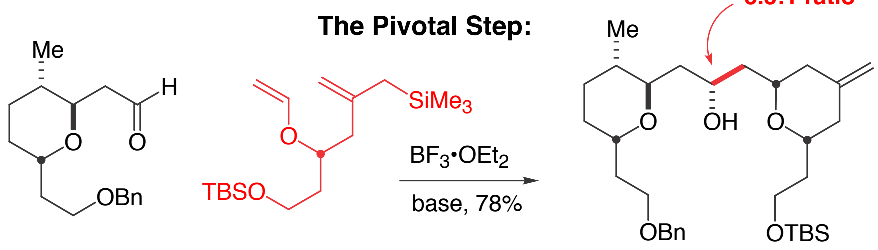
Bunnelle-Peterson Allylsilane Synthesis

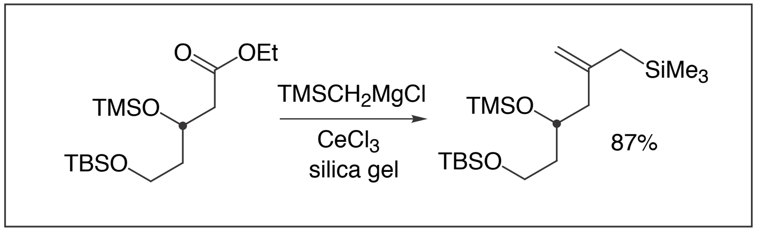


Application to Leucasandrolide: *Rychnovsky JACS*, **2001**, *123,* 8420



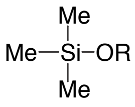
The Pivotal Step:





ROH Protecting Groups

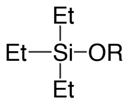
Silyl Ethers:



$Me_3Si{-}OR$

trimethylsilyl

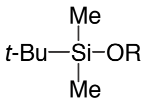
(TMS)



$Et_3Si{-}OR$

triethylsilyl

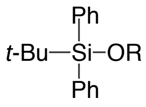
(TES)



$t\text{-}BuMe_2Si{-}OR$

tert-butyldimethylsilyl

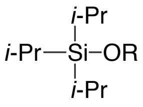
(TBS or TBDMS)



$t\text{-}BuPh_2Si{-}OR$

tert-butyldiphenylsilyl

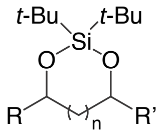
(TBDPS)



$(i\text{-}Pr)_3Si{-}OR$

triisopropylsilyl

(TIPS)



di-*tert*-butyldimethylsilylene

(DTBS)

Formation:

By far the two most common methods:

$$R{-}OH \xrightarrow[\text{DMF, R.T.}]{R_3Si\text{-}Cl,\ \text{imidazole}} R{-}OSiR_3$$

2 equiv of imidazole are required relative to R_3SiCl.

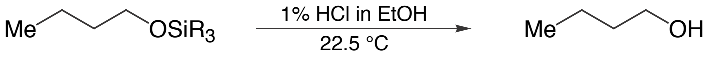
Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

$$R{-}OH \xrightarrow[CH_2Cl_2,\ 0\ °C]{R_3Si\text{-}OTf,\ 2,6\text{-lutidine}} R{-}OSiR_3$$

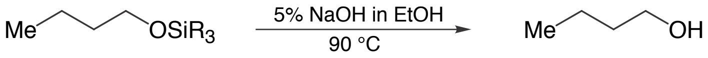
Corey, E. J. et al., *Tetrahedron Lett.* **1981**, *22*, 3455.

Relative stabilities:

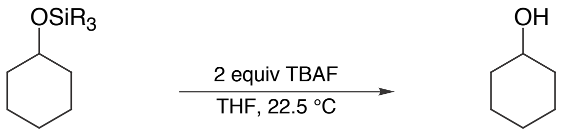
TES ~10^2 times more stable to acidic hydrolysis than TMS
TBS ~10^4 times more stable to acidic hydrolysis than TMS



SiR_3	Half-life
TBS	< 1 min
TIPS	18 min
TBDPS	244 min



SiR_3	Half-life
TBS	1 h
TIPS	14 h
TBDPS	< 4 h

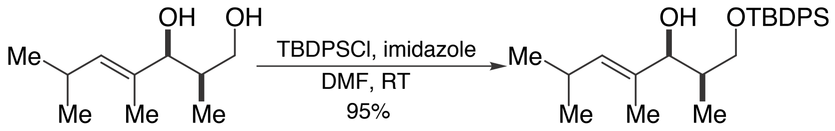


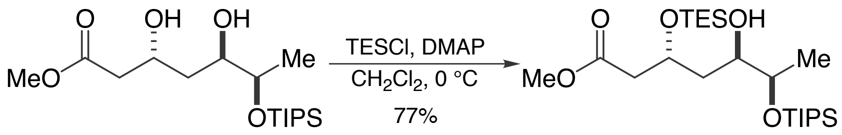
SiR_3	Half-life
TBS	76 min
TIPS	137 min

Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797-4798.

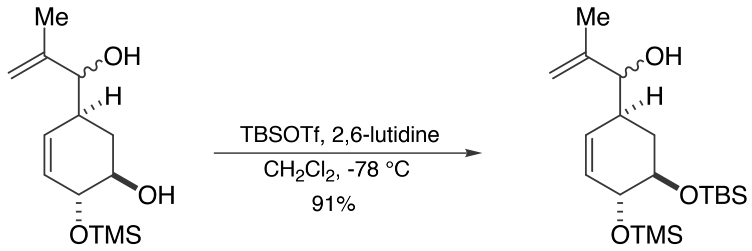
ROH Protecting Groups-2

Selective Protection:

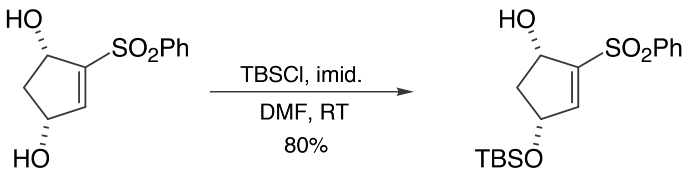




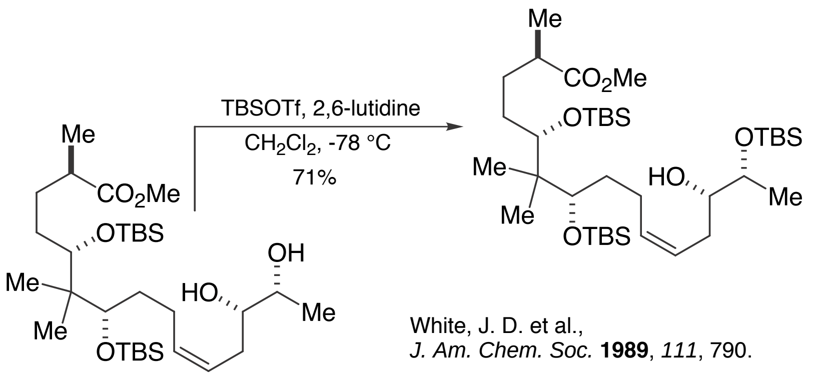
Evans et al.JACS **1999**, *121*, 7540-7552.



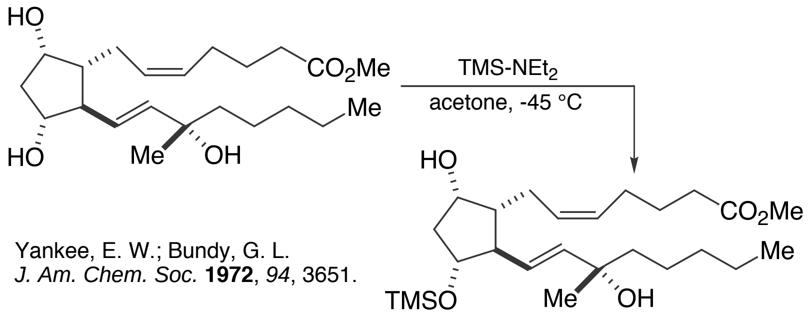
Askin, D.; Angst, D.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622.



Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2108.

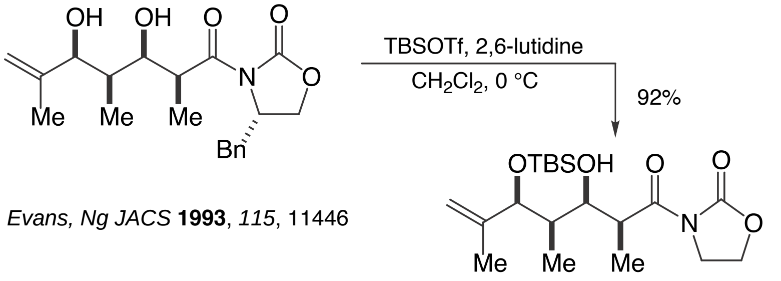


White, J. D. et al.,
J. Am. Chem. Soc. **1989**, *111*, 790.



Yankee, E. W.; Bundy, G. L.
J. Am. Chem. Soc. **1972**, *94*, 3651.

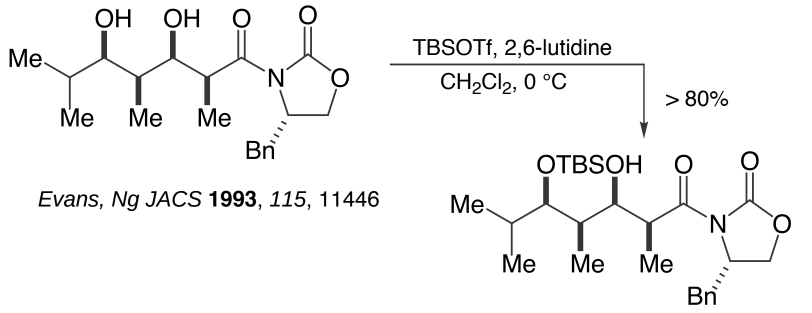
TMS-NEt_2 has been reported to selectively protect equatorial alcohols in the presence of axial alcohols:
Weisz, I. et al. *Acta. Chim. Acad. Sci. Hung.* **1968**, *58*, 189.



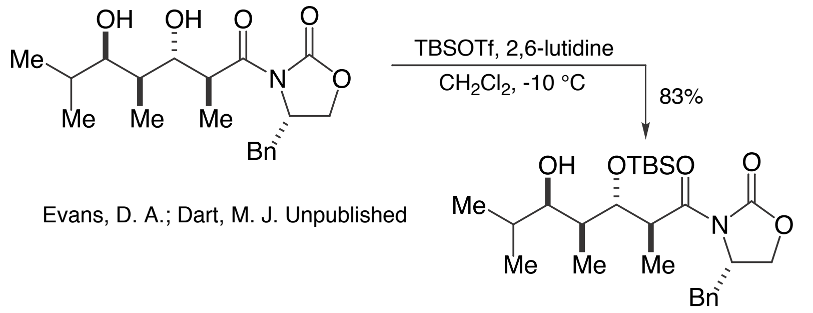
Evans, Ng JACS **1993**, *115*, 11446

ROH Protecting Groups-2

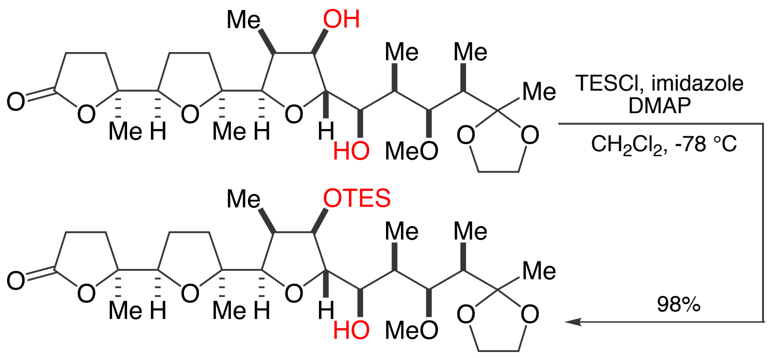
Selective Protection:



Evans, Ng JACS **1993**, *115*, 11446

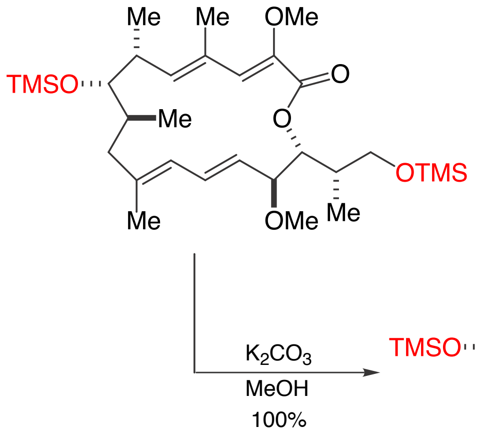


Evans, D. A.; Dart, M. J. Unpublished

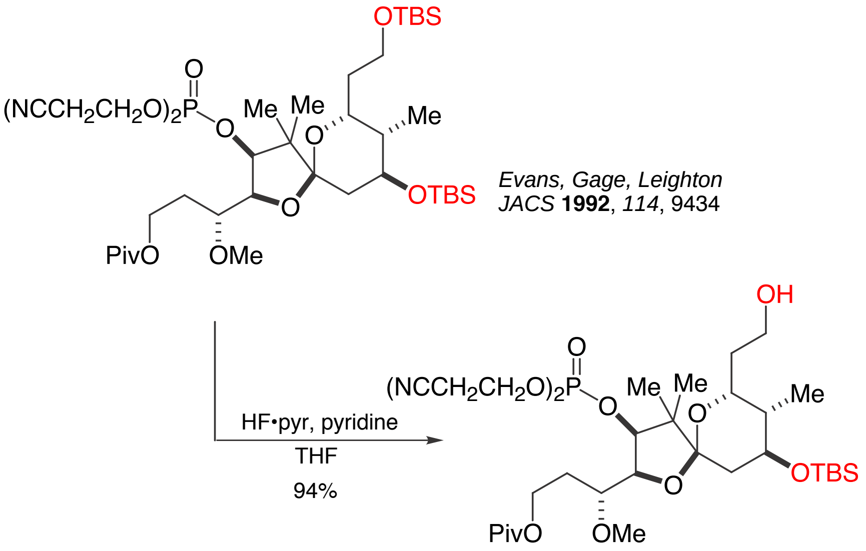


Evans, Ratz JACS **1995**, *117*, 3448

Selective Deprotection:



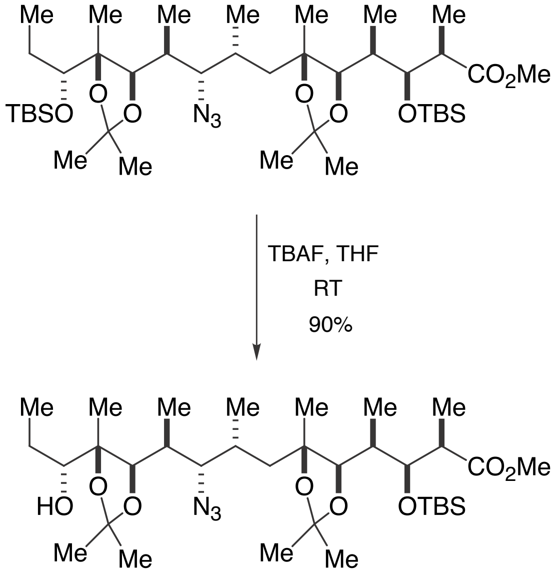
Calter, M. A. Ph. D. Thesis, Harvard University, 1993



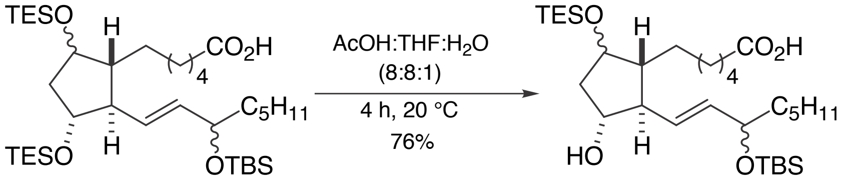
Evans, Gage, Leighton JACS **1992**, *114*, 9434

ROH Protecting Groups-2

Selective Deprotection:

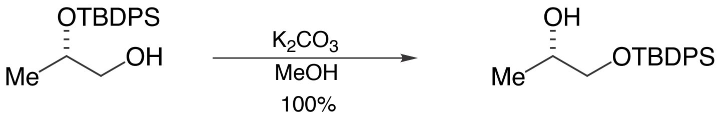


Nakaba, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219, 2223.



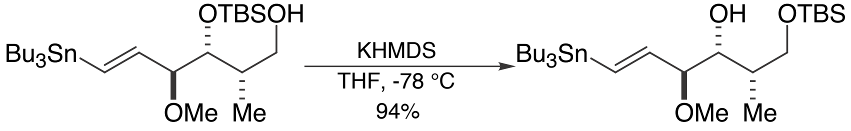
Hart, T. W.; Metcalfe, D. A.; Scheinmann, F.
J. Chem. Soc., Chem. ommun. **1979**, 156.

1,2-Migration:

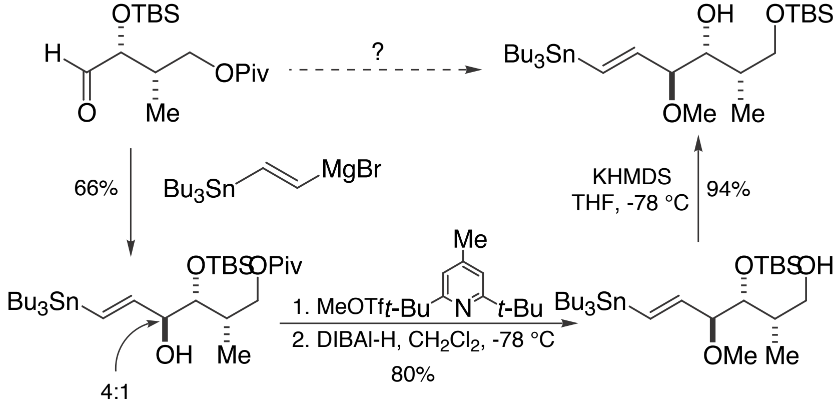


Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed. Eng.* **1990**, *29*, 431-432.

1,3-Migration:



Calter, M. A. Ph. D. Thesis, Harvard University, 1993.



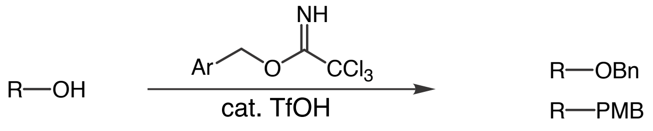
Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

Principle Methods for Benzylation of Alcohols:

1.

$$R{-}OH \xrightarrow[\text{2. BnBr/PMBBr}]{\text{1. NaH, DMF, 0 °C}} \begin{matrix} R{-}OBn \\ R{-}PMB \end{matrix}$$

2.



Ar = Ph: CH_2Cl_2

Ar = 4-MeO-Ph: Et_2O

Ar = Ph: Iversen, T.; Bundle, K. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

Ar = 4-MeO-Ph: Yonemitsu, O. et al., *Tetrahedron Lett.* **1988**, *29*, 4139.

3.

$$R{-}OH \xrightarrow[\text{2. BnBr, } N\text{-methylimidazole}]{\text{1. } (Bu_3Sn)_2O\text{, PhMe, } \uparrow\downarrow} R{-}OBn$$

Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, *54*, 465.

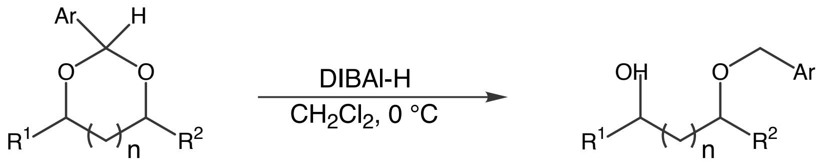
Review: David, S.; Hanessian, S. *Tetrahedron*, **1985**, *41*, 643-663.

4.

$$R{-}OH \xrightarrow[\text{DMF}]{Ag_2O\text{, BnBr}} R{-}OBn$$

Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3940.

Via Benzylidene Acetal:



Takano, S. et al., *Synthesis* **1986**, 811-817.

Priciple Methods for Deprotection:

1. Hydrogenation

$$R{-}OBn \xrightarrow[\text{EtOH/EtOAc/AcOH}]{\text{10\% Pd on C, } H_2} R{-}OH$$

See Greene, p. 49.

2. Transfer Hydrogenation

$$R{-}OBn \xrightarrow[\text{Hydrogen Source}]{\text{10\% Pd on C}} R{-}OH$$

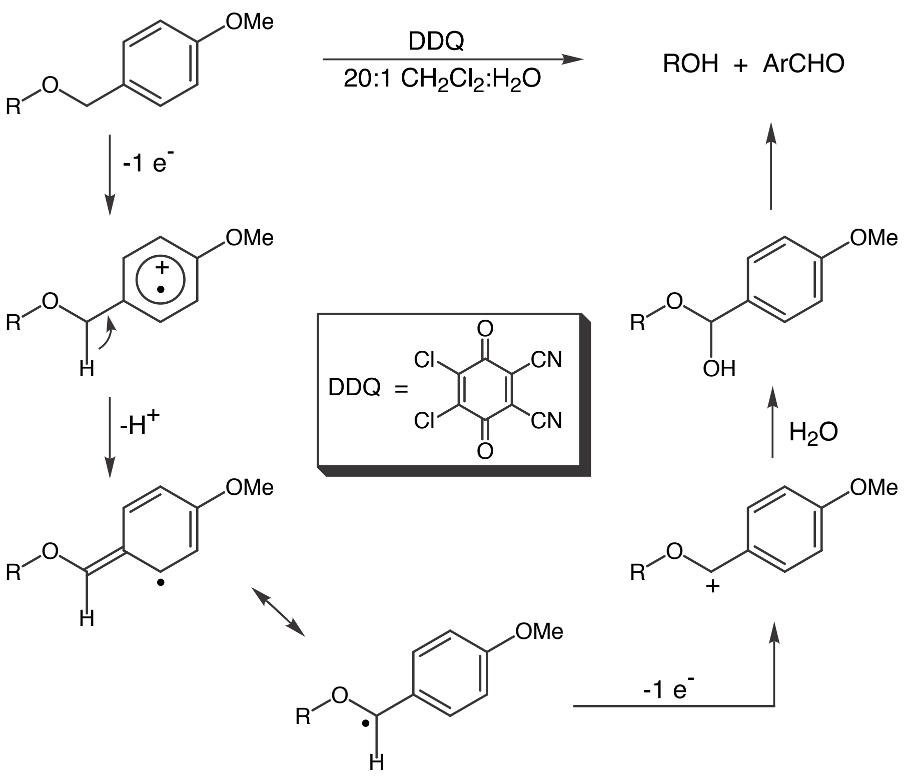
Hydrogen Source	Ref.
Cyclohexene	*Synthesis* **1981**, 396.
Cyclohexadiene	*J. Org. Chem.* **1978**, *43*, 4194.
HCO_2H	*J. Org. Chem.* **1979**, *44*, 3442.
i-PrOH	*Tetrahedron Lett.* **1986**, *27*, 2497

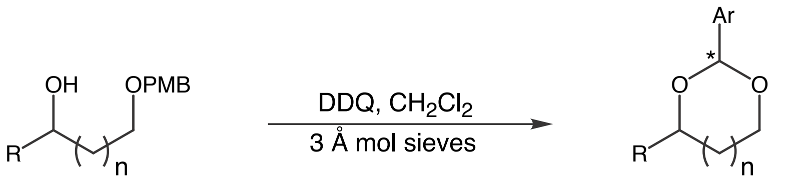
3. Lewis Acids

$$R{-}OBn \longrightarrow R{-}OH$$

Reagents	Ref.
$BF_3{\bullet}OEt_2$, EtSH	*Tetrahedron Lett.* **1989**, *30*, 5713.
1. BCl_3, -78 °C to 0 °C. 2. MeOH, -78 °C.	*J. Am. Chem. Soc.* **1989**, *111*, 1923.
TMSBr, C_6H_5SMe	*Chem. Pharm. Bull.* **1987**, *35*, 3880.

PMB Deprotection:



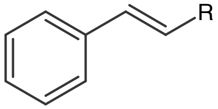


Yonemitsu, O. et al., *Tetrahedron* **1986**, *42*, 3021.

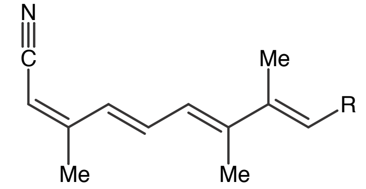
Other Oxidants: NBS, Br_2, CAN ($(NH_4)_2Ce(NO_3)_6$).

Acta Chem. Scand. Ser. B, **1984**, *B38*, 419.
J. Chem. Soc., Perkin Trans. I, **1984**, 2371.

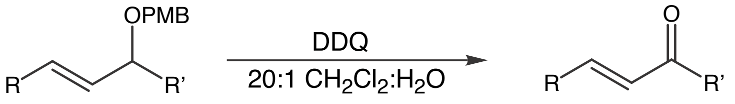
DDQ is incompatible with:



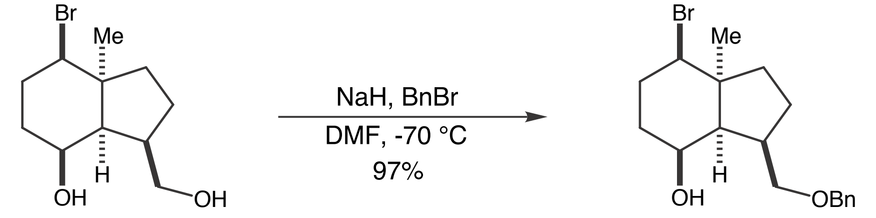
styryl



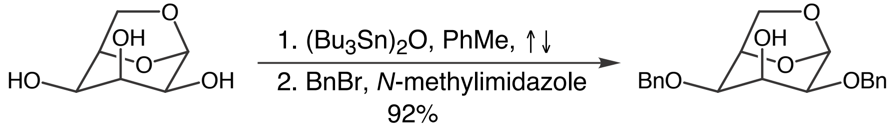
extended conjugated polyenes



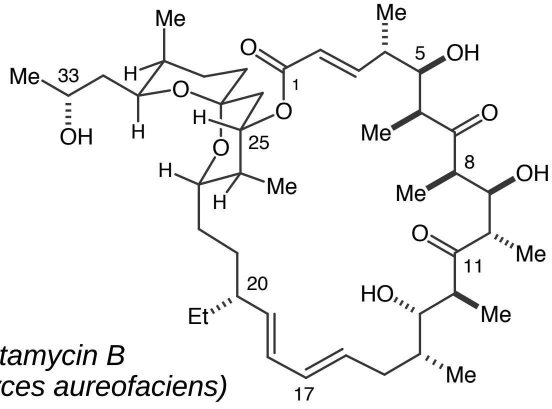
Selective Benzylation:



Fukuzawa, A. et al. *Tetrahedron Lett.* **1987**, *28*, 4303.

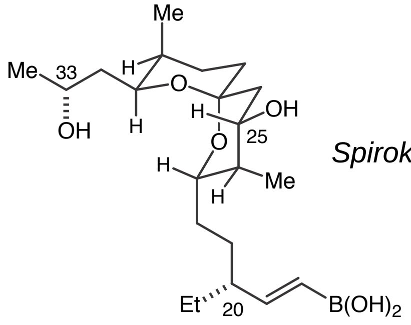


Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, *54*, 465.

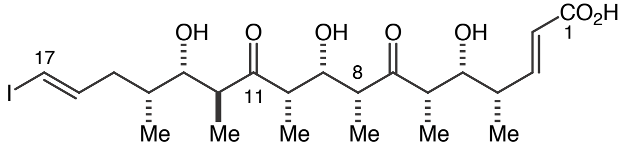


Rutamycin B
(Streptomyces aureofaciens)

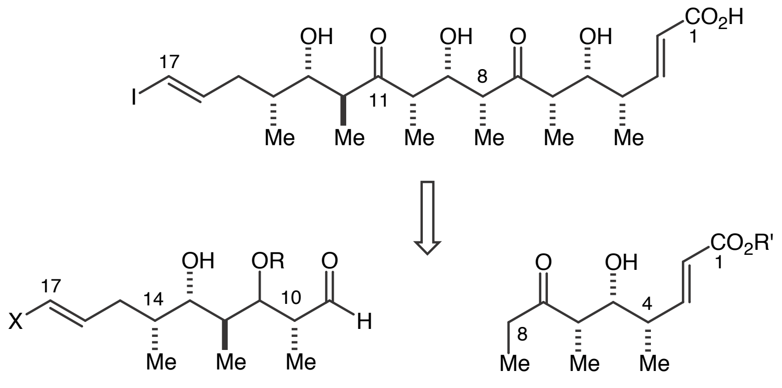
Ng, H. P. Ph. D. Thesis,
Harvard University, 1993



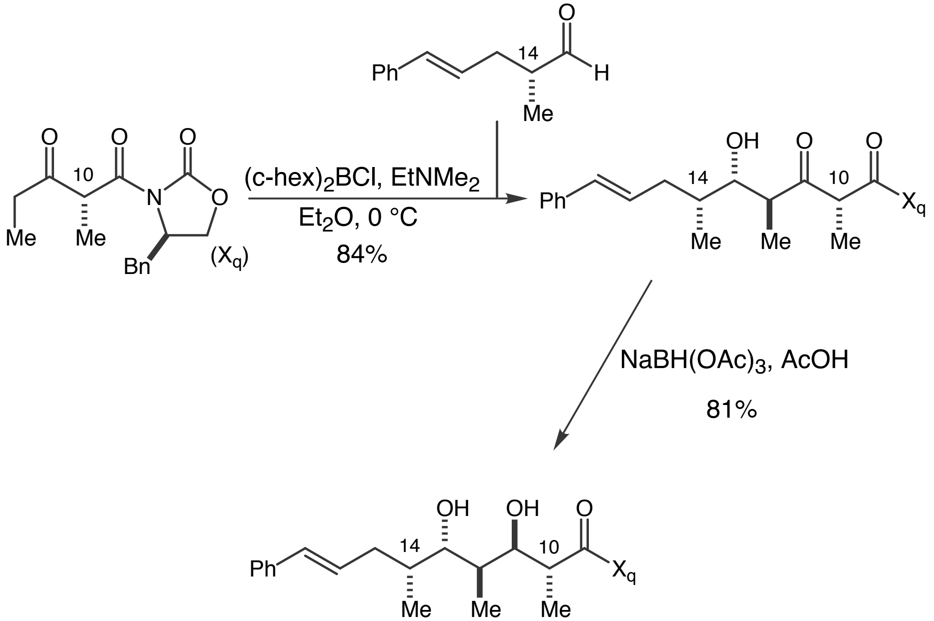
Spiroketal Fragment

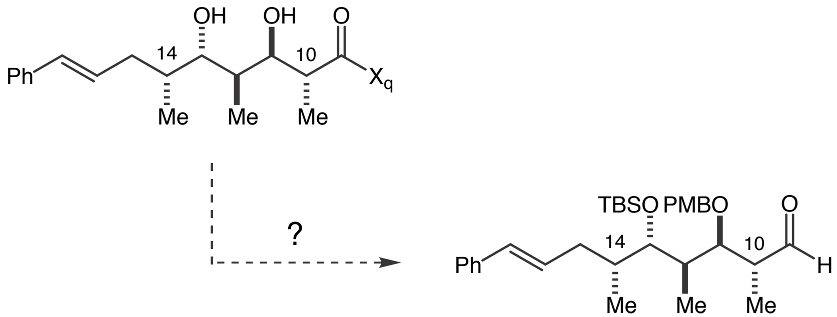


Polypropionate Fragment

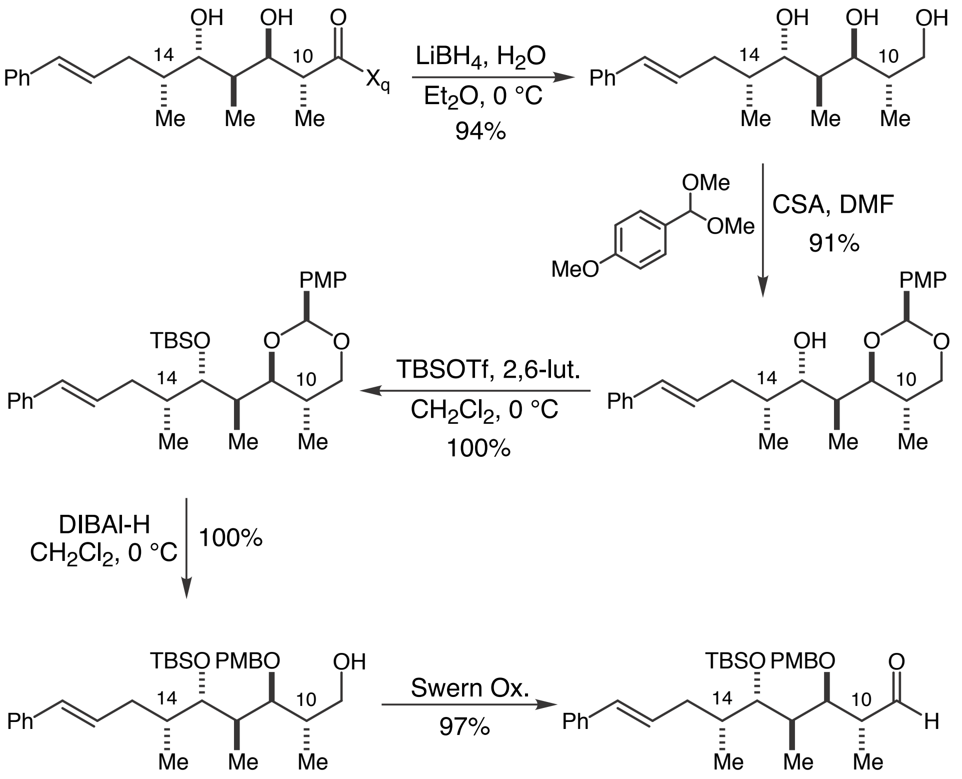


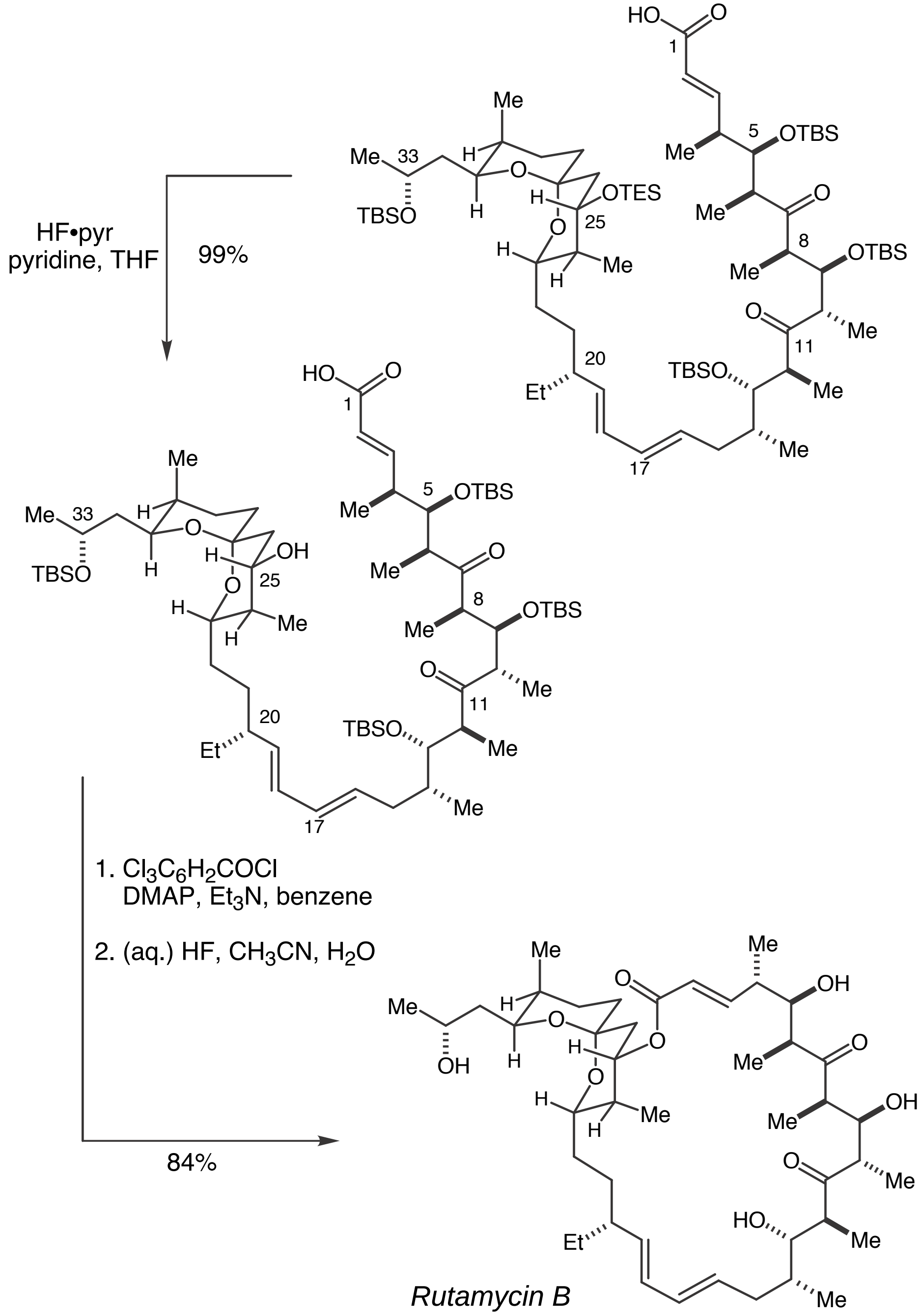
C_9-C_{17} Subunit *C_1-C_8 Subunit*



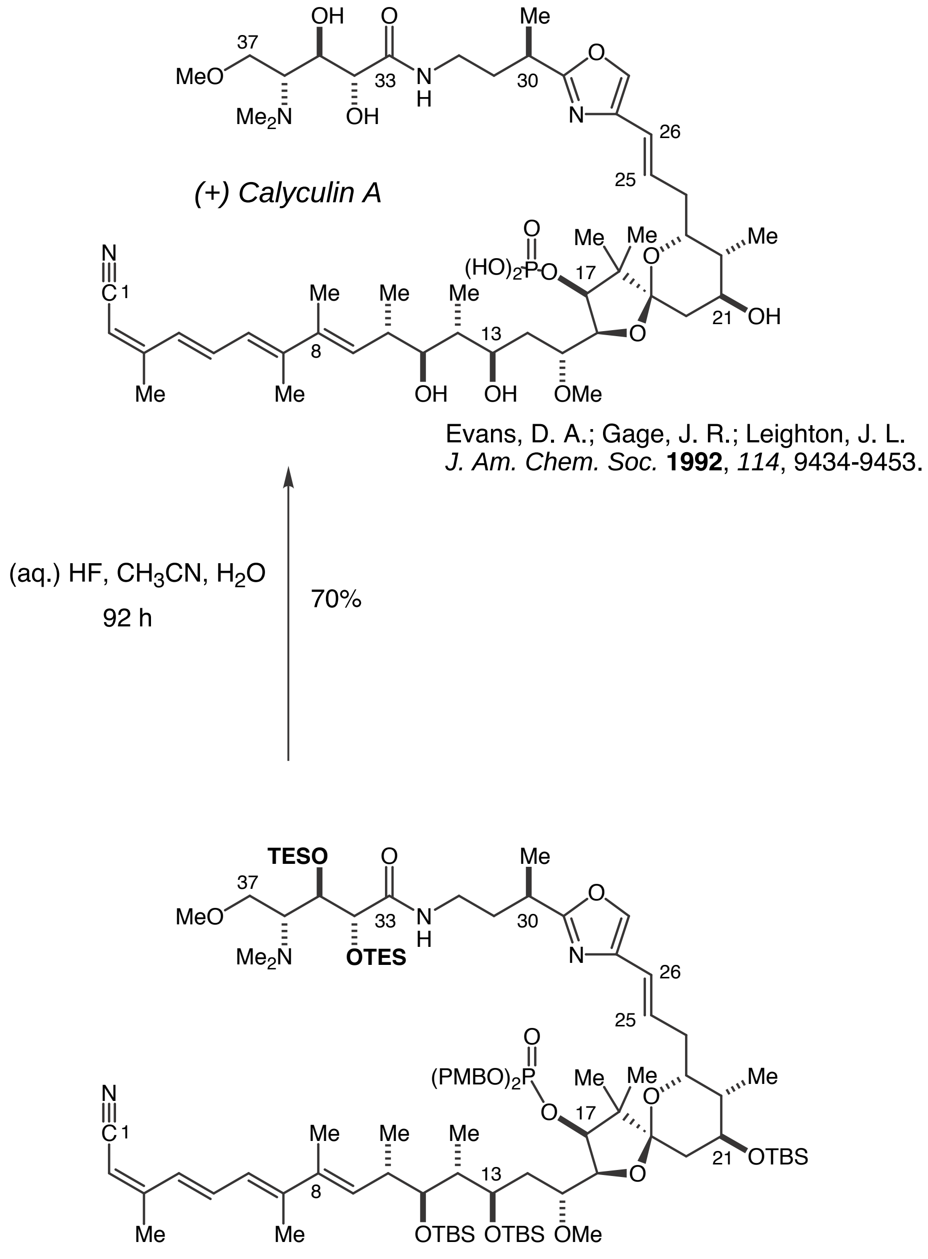


Selective silylation was unsuccessful.

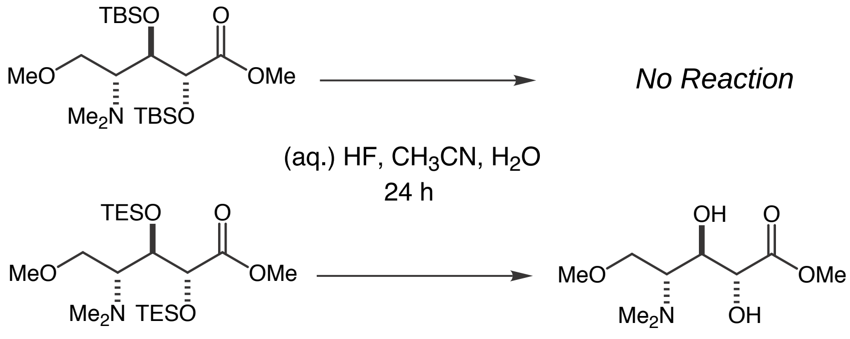




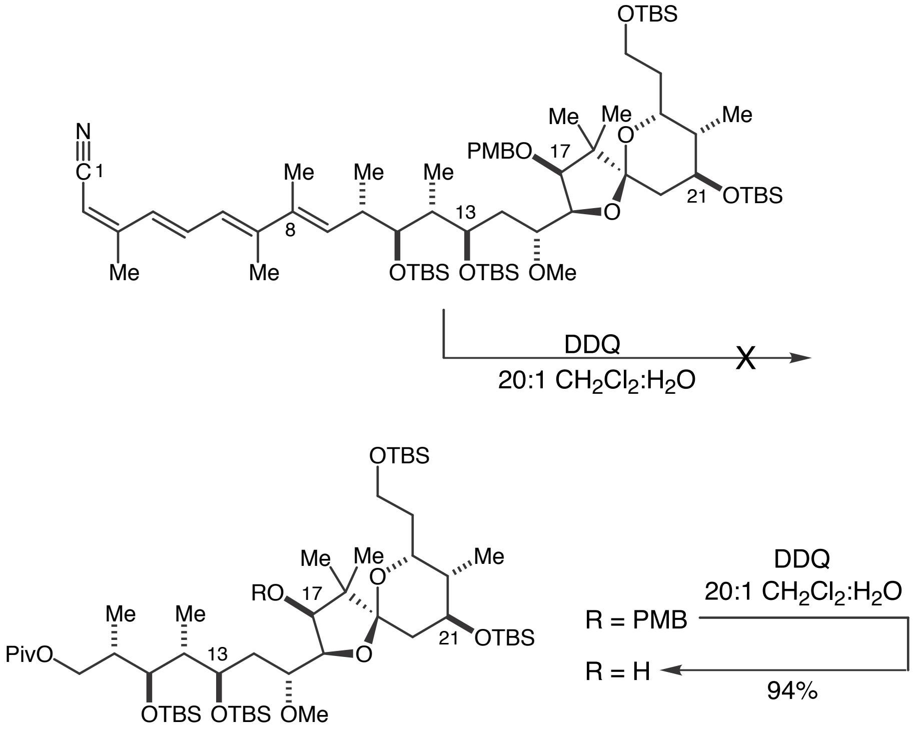
Rutamycin B



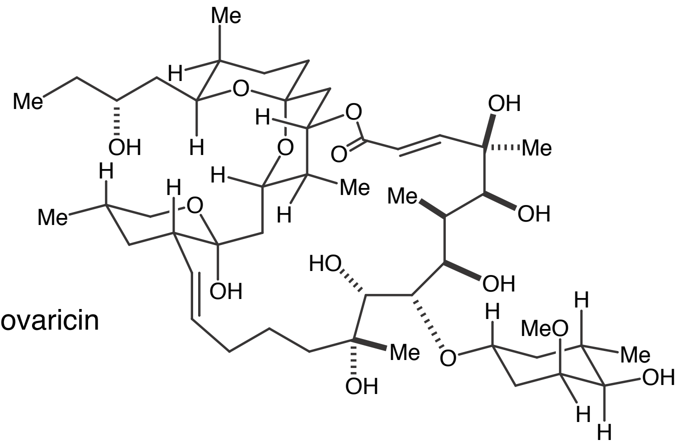
Evans, D. A.; Gage, J. R.; Leighton, J. L.
J. Am. Chem. Soc. **1992**, *114*, 9434-9453.



After protonation of the amine, coulombic repulsion insulates against formation of another cationic site in the vicinity.



ROH Protecting Groups

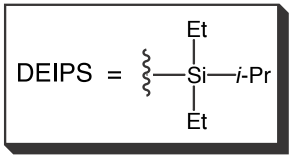


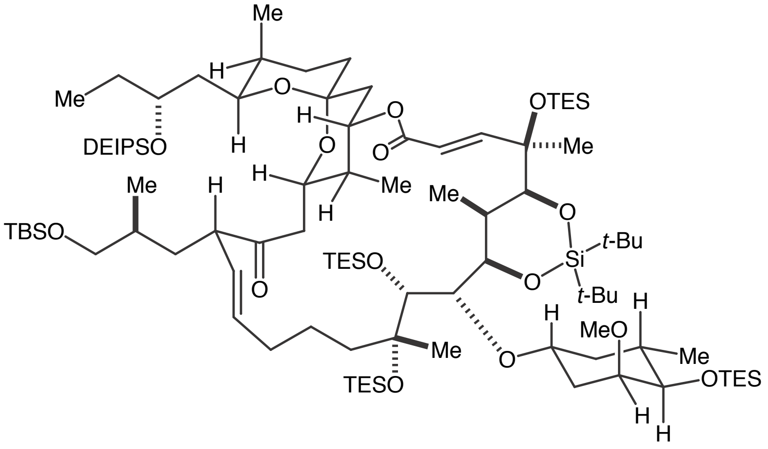
Cytovaricin

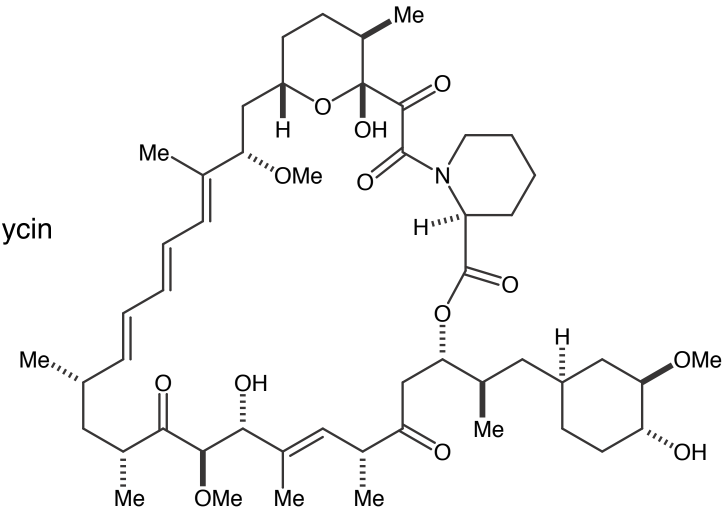
Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J.
J. Am. Chem. Soc. **1990**, *112*, 7001-7031.

HF•pyr, pyridine
THF, RT

74%







Rapamycin

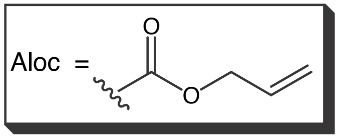
Romo, D.; Meyer, S. D.;
Johnson, D. D.; Schreiber, S. L.
J. Am. Chem. Soc. **1993**, *115*, 7906-7907.

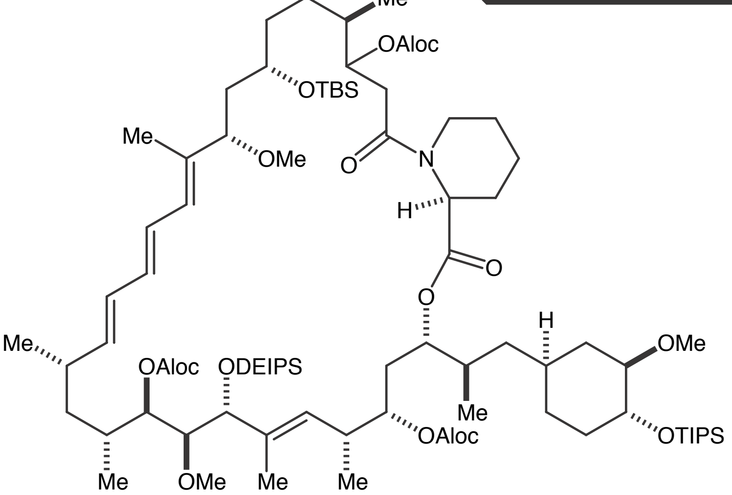
1. Pd$(Ph_3P)_4$, HCO_2NH_4, THF

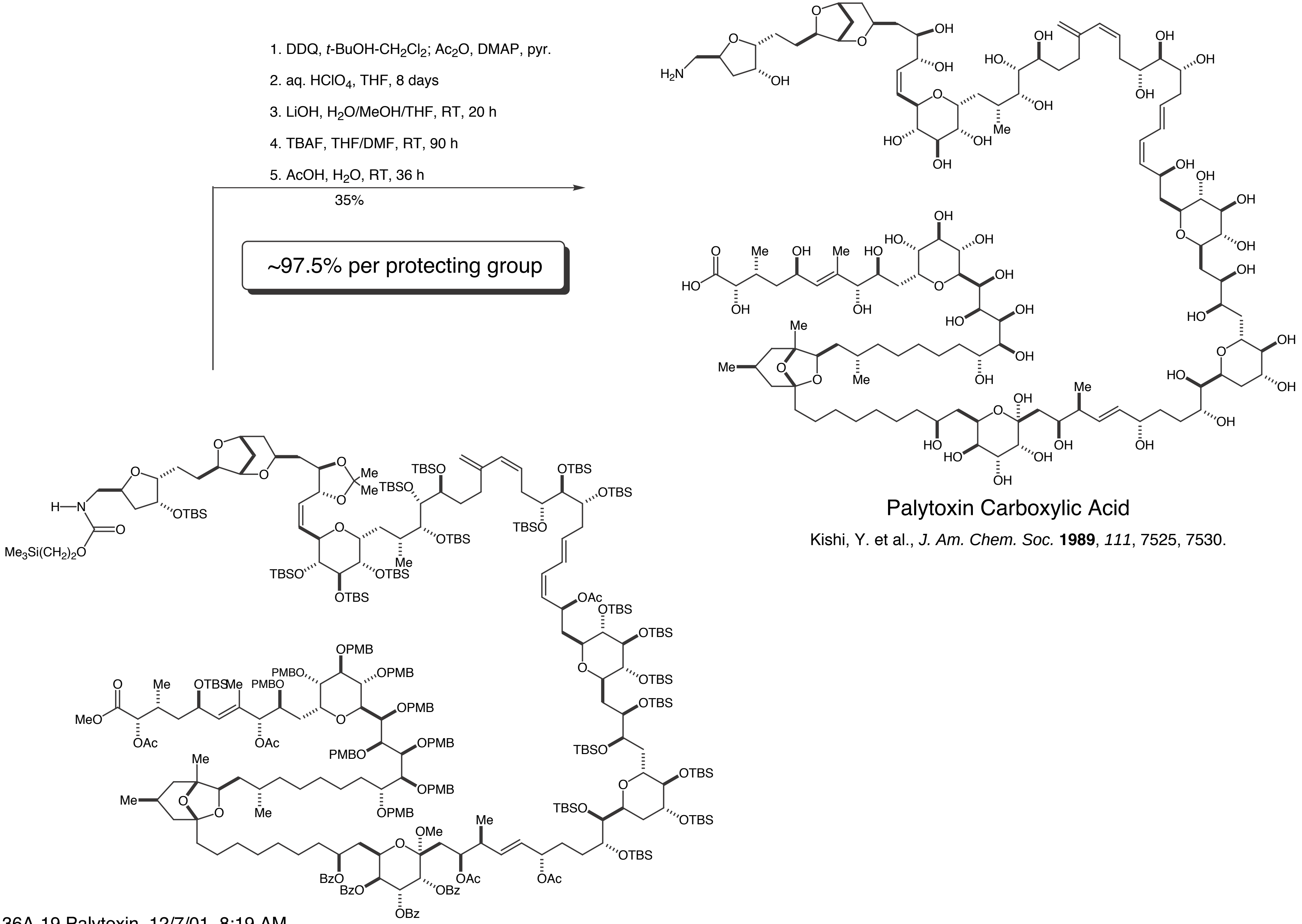
2. Dess-Martin Periodinane

3. HF•pyr, pyridine, THF

30% overall







1. DDQ, *t*-BuOH-CH_2Cl_2; Ac_2O, DMAP, pyr.
2. aq. $HClO_4$, THF, 8 days
3. LiOH, H_2O/MeOH/THF, RT, 20 h
4. TBAF, THF/DMF, RT, 90 h
5. AcOH, H_2O, RT, 36 h

35%

~97.5% per protecting group

Palytoxin Carboxylic Acid

Kishi, Y. et al., *J. Am. Chem. Soc.* **1989**, *111*, 7525, 7530.

General References

Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part B*, Plenum Press: New York, **1990**, p. 615-664.

Hudlicky, M. In *Reductions in Organic Chemistry 2nd Ed.*, American Chemical Society Monograph 188: Washington DC, **1996**, p. 19-30.

Brown, H. C.; Ramachandran, P. V. In *Reductions in Organic Synthesis: Recent Advances and Practical Applications*, Abdel-Magid, A. F. Ed.; American Chemical Society: Washington DC, **1996**, p. 1-30.

Seyden-Penne, J. In *Reductions by the Alumino- and Borohydrides in Organic Synthesis, 2nd Ed.*, Wiley-VCH: New York, **1997**, p. 1-36.

Reactivity Trends

- Following are general guidelines concerning the reactivities of various reducing agents.

Substrates, Reduction Products

Hydride Donors	Iminium Ion	Acid Halide	Aldehyde	Ester	Amide	Carboxylate Salt
$LiAlH_4$	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
DIBAL	–	Alcohol	Alcohol	Alcohol or Aldehyde	Amine or Aldehyde	Alcohol
$NaAlH(O\text{-}t\text{-}Bu)_3$	–	Aldehyde	Alcohol	Alcohol (slow)	Amine (slow)	–
AlH_3	–	Alcohol	Alcohol	Alcohol	Amine	Alcohol
$NaBH_4$	Amine	–	Alcohol	–**	–	–
$NaCNBH_3$	Amine	–	Alcohol (slow)	–	–	–
$Na(AcO)_3BH$	Amine	–	Alcohol (slow)	Alcohol (slow)	Amine (slow)	–
B_2H_6	–	–	Alcohol	Alcohol (slow)	Amine (slow)	Alcohol
$Li(Et)_3BH$	–	Alcohol	Alcohol	Alcohol	Alcohol (tertiary amide)	–
H_2 (catalyst)	Amine	Alcohol	Alcohol	Alcohol	Amine	–

** α-alkoxy esters are reduced to the corresponding alcohols.

– indicates no reaction or no productive reaction (alcohols are deprotonated in many instances, e.g.)

- Catalytic hydrogenation is used for the reduction of many organic functional groups. The reaction can be modified with respect to catalyst, hydrogen pressure, solvent, and temperature in order to execute a desired reduction.
- A brief list of recommended reaction conditions for catalytic hydrogenations of selected functional groups is given below.

Substrate	Product	Catalyst	Catalyst/Compound Ratio (wt%)	Pressure (atm)
Alkene	Alkane	5% Pd/C	5-10%	1-3
Alkyne	Alkene	5% $Pd(BaSO_4)$	2% + 2% quinoline	1
Aldehyde (Ketone)	Alcohol	PtO_2	2-4%	1
Halide	Alkane	5% Pd/C	1-15%, KOH	1
Nitrile	Amine	Raney Ni	3-30%	35-70

Adapted from: Hudlicky, M. In *Reductions in Organic Chemistry 2nd Ed.*, American Chemical Society Monograph 188: Washington DC, **1996**, p. 8.

Summary of Reagents for Reductive Functional Group Interconversions:

Acid → **Alcohol**

Lithium Aluminum Hydride (LAH)
Lithium Borohydride
Borane Complexes

Ester → **Aldehyde**

Diisobutylaluminum Hydride (DIBAL)
Reduction of Acid Chlorides, Amides, and Nitriles
Lithium Triethoxyaluminohydride (LTEAH)

Aldehyde → **Alcohol**

Reductive Amination
Luche Reduction
Samarium Iodide
Sodium Borohydride
Ionic Hydrogenation

Aldehyde → **Alkane**

Deoxygenation of Tosylhydrazones
Desulfurization with Raney Nickel
Wolff–Kishner Reduction
Clemmensen Reduction

Alcohol → **Alkane**

Barton Deoxygenation
Diazene-Mediated Deoxygenation
Reduction of Alkyl Tosylates
Radical Dehalogenation

Acid → **Alkane**

Barton Decarboxylation

Mark G. Charest

Acid → Alcohol

Lithium Aluminum Hydride (LAH): $LiAlH_4$

- LAH is a powerful and rather nonselective hydride-transfer reagent that readily reduces carboxylic acids, esters, lactones, anhydrides, amides and nitriles to the corresponding alcohols or amines. In addition, aldehydes, ketones, epoxides, alkyl halides, and many other functional groups are reduced readily by LAH.

- LAH is commercially available as a dry, grey solid or as a solution in a variety of organic solvents, e.g., ethyl ether. Both the solid and solution forms of LAH are highly flammable and should be stored protected from moisture.

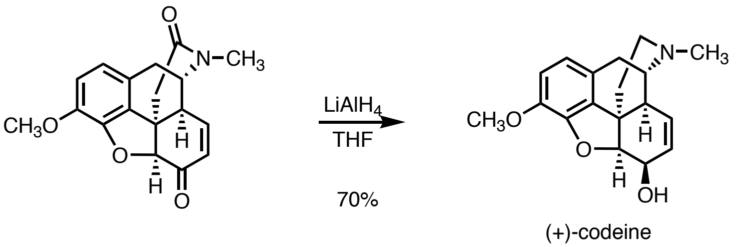
- Several work-up procedures for LAH reductions are available that avoid the difficulties of separating by-products of the reduction. In the Fieser work-up, following reduction with *n* grams of LAH, careful successive dropwise addition of *n* mL of water, *n* mL of 15% NaOH solution, and 3*n* mL of water provides a granular inorganic precipitate that is easy to rinse and filter. For moisture-sensitive substrates, ethyl acetate can be added to consume any excess LAH and the reduction product, ethanol, is unlikely to interfere with product isolation.

- Although, in theory, one equivalent of LAH provides four equivalents of hydride, an excess of the reagent is typically used.

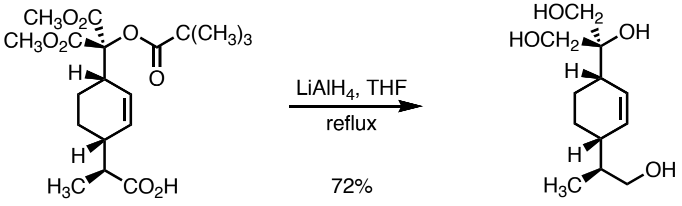
Paquette, L. A. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 199-204.

Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581-595.

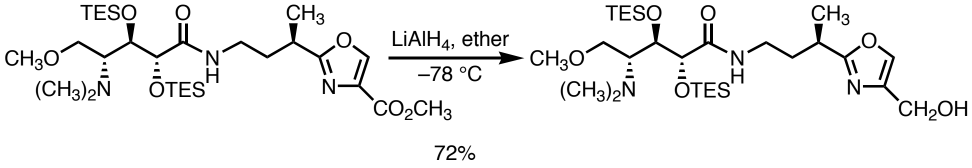
- Examples



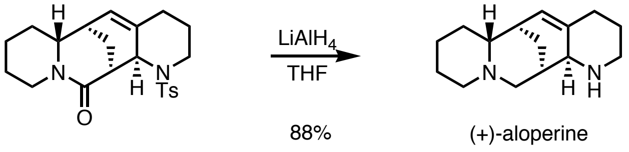
White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871-7884.



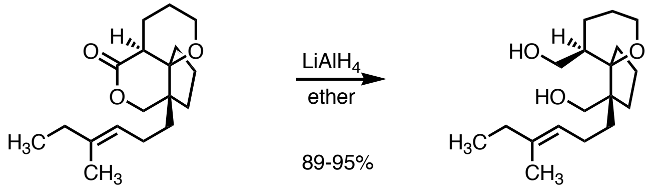
Bergner, E. J.; Helmchen, G. *J. Org. Chem.* **2000**, *65*, 5072-5074.



Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434-9453.

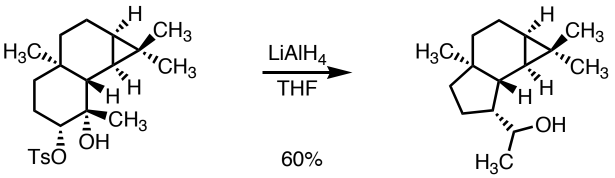


Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700-709.



Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585-2599.

- In the following example, rearrangement accompanied reduction.



Bates, R. B.; Büchi, G.; Matsuura, T.; Shaffer, R. R. *J. Am. Chem. Soc.* **1960**, *82*, 2327-2337.

Mark G. Charest

Lithium Borohydride: $LiBH_4$

- Lithium borohydride is commonly used for the selective reduction of esters and lactones to the corresponding alcohols in the presence of carboxylic acids, tertiary amides, and nitriles. Aldehydes, ketones, epoxides, and several other functional groups can also be reduced by lithium borohydride.

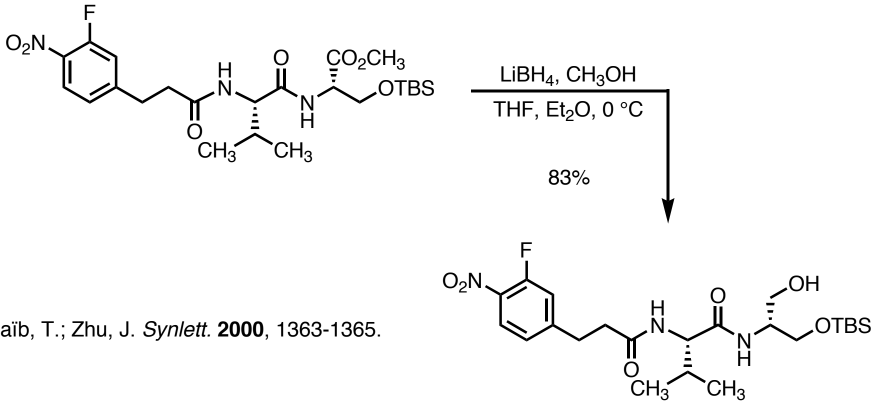
- The reactivity of lithium borohydride is dependent on the reaction medium and follows the order: ether > THF > 2-propanol. This is attributed to the availability of the lithium counterion for coordination to the substrate, promoting reduction.

- Lithium borohydride is commercially available in solid form and as solutions in many organic solvents, e.g., THF. Both are inflammable and should be stored protected from moisture.

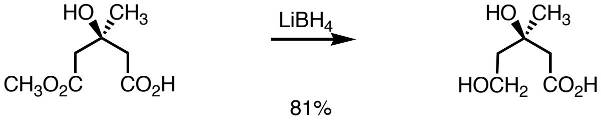
Nystrom, R. F.; Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 3245-3246.

Banfi, L.; Narisano, E.; Riva, R. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 209-212.

- Examples



Laïb, T.; Zhu, J. *Synlett.* **2000**, 1363-1365.



Huang, F.-C.; Lee, L. F.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J. *J. Am. Chem. Soc.* **1975**, *97*, 4144-4145.

Borane Complexes: BH_3•L

- Borane is commonly used for the reduction of carboxylic acids in the presence of esters, lactones, amides, halides and other functional groups. In addition, borane rapidly reduces aldehydes, ketones, and alkenes.

- Borane is commercially available as a neat complex with tetrahydrofuran (THF) or dimethysulfide or in solution. In addition, gaseous diborane (B_2H_6) is available.

- The borane-dimethylsulfide complex exhibits improved stability and solubility compared to the borane-THF complex.

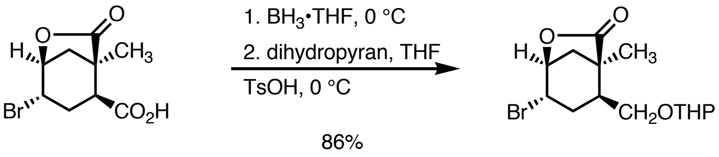
- Competing hydroboration of carbon-carbon double bonds can limit the usefulness of borane-THF as a reducing agent.

Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786-2792.

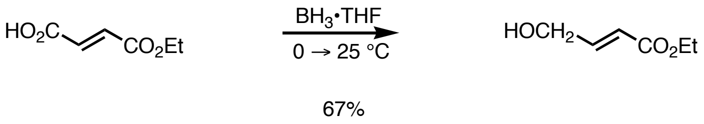
Lane, C. F. *Chem. Rev.* **1976**, *76*, 773-799.

Brown, H. C.; Stocky, T. P. *J. Am. Chem. Soc.* **1977**, *99*, 8218-8226.

- Examples

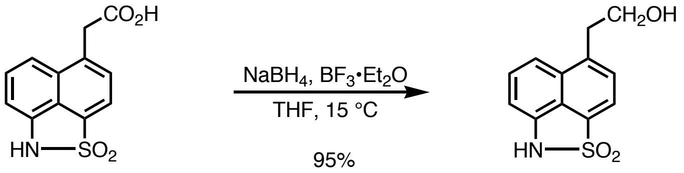


Corey, E. J.; Sachdev, H. S. *J. Org. Chem.* **1975**, *40*, 579-581.



Kende, A. S.; Fludzinski, P. *Org. Synth.* **1986**, *64*, 104-107.

- The combination of boron trifluoride etherate and sodium borohydride has been used to generate diborane in situ.



Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Ceglia, S. S.; Kennedy, D. J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 1399-1406.

Mark G. Charest

Ester → Aldehyde

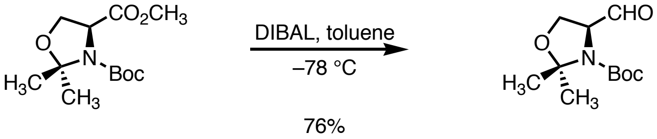
Diisobutylaluminum Hydride (DIBAL): *i*-Bu_2AlH

- At low temperatures, DIBAL reduces esters to the corresponding aldehydes, and lactones to lactols.
- Typically, toluene is used as the reaction solvent, but other solvents have also been employed, including dichloromethane.

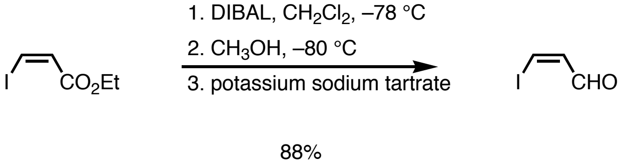
Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627-630.

Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, *3*, 619-620.

- Examples

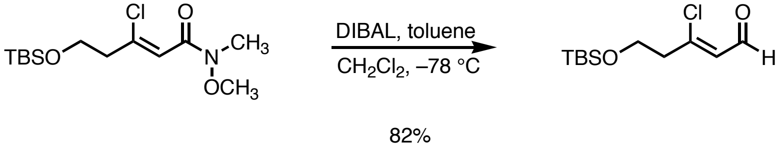


Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18-28.

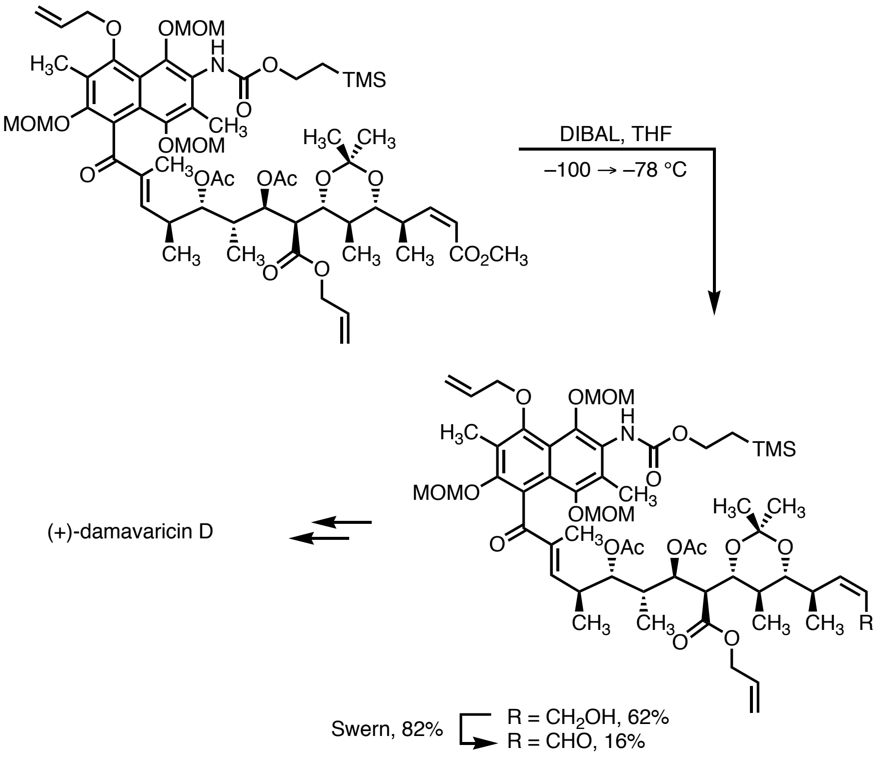


Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1996**, *74*, 194-204.

- Reduction of *N*-methoxy-*N*-methyl amides, also known as Weinreb amides, is one of the most frequent means of converting a carboxylic acid to an aldehyde.

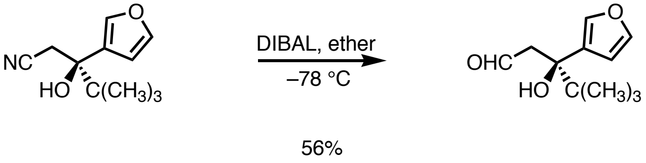


Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3542-3545.



Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331-11332.

- Nitriles are reduced to imines, which hydrolyze upon work-up to furnish aldehydes.



Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3146-3155.

Mark G. Charest

Lithium Triethoxyaluminohydride (LTEAH): $Li(EtO)_3AlH$

- LTEAH selectively reduces aromatic and aliphatic nitriles to the corresponding aldehydes (after aqueous workup) in yields of 70-90%.
- Tertiary amides are efficiently reduced to the corresponding aldehydes with LTEAH.
- LTEAH is formed by the reaction of 1 mole of LAH solution in ethyl ether with 3 moles of ethyl alcohol or 1.5 moles of ethyl acetate.

$$LiAlH_4 \quad + \quad 3\ EtOH \quad \xrightarrow[0\ °C]{Et_2O} \quad Li(EtO)_3AlH \quad + \quad 3H_2$$

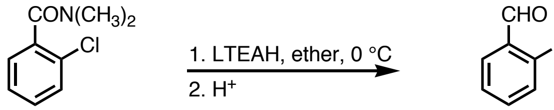
$$LiAlH_4 \quad + \quad 1.5\ CH_3CO_2Et \quad \xrightarrow[0\ °C]{Et_2O} \quad Li(EtO)_3AlH$$

Brown, H. C.; Shoaf, C. J. *J. Am. Chem. Soc.* **1964**, *86*, 1079-1085.

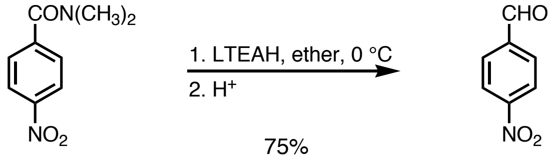
Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085-1089.

Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089-1095.

- Examples

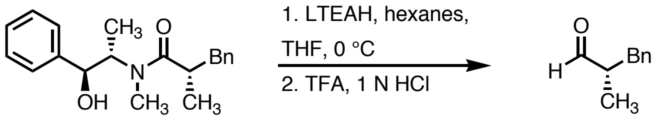


80%



75%

Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567-607.



>99% de

77% (94% ee)

Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

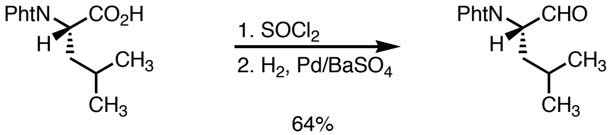
Reduction of Acid Chlorides

- The Rosemund reduction is a classic method for the preparation of aldehydes from carboxylic acids by the selective hydrogenation of the corresponding acid chloride.
- Over-reduction and decarbonylation of the aldehyde product can limit the usefulness of the Rosemund protocol.
- The reduction is carried out by bubbling hydrogen through a hot solution of the acid chloride in which the catalyst, usually palladium on barium sulfate, is suspended.

Rosemund, K. W.; Zetzsche, F. *Chem. Ber.* **1921**, *54*, 425-437.

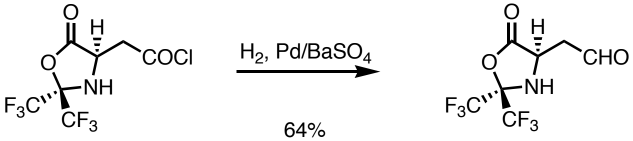
Mosetting, E.; Mozingo, R. *Org. React.* **1948**, *4*, 362-377.

- Examples



64%

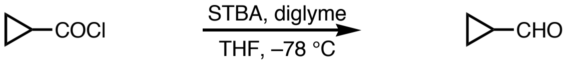
Johnson, R. L. *J. Med. Chem.* **1982**, *25*, 605-610.



64%

Winkler, D.; Burger, K. *Synthesis* **1996**, 1419-1421.

- Sodium tri-*tert*-butoxyaluminohydride (STBA), generated by the reaction of sodium aluminum hydride with 3 equivalents of *tert*-butyl alcohol, reduces aliphatic and aromatic acid chlorides to the corresponding aldehydes in high yields.



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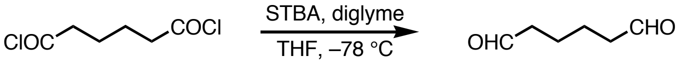


93%

diglyme = $(CH_3OCH_2CH_2)_2O$

Cha, J. S.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 4732-4734.

Mark G. Charest

Aldehyde or Ketone → Alkane

Deoxygenation of Tosylhydrazones

- Reduction of tosylhydrazones to hydrocarbons with hydride donors, such as sodium cyanoborohydride, sodium triacetoxyborohydride, or catecholborane, is a mild and selective method for carbonyl deoxygenation.

- Esters, amides, nitriles, nitro groups, and alkyl halides are compatible with the reaction conditions.

- Most hindered carbonyl groups are readily reduced to the corresponding hydrocarbon.

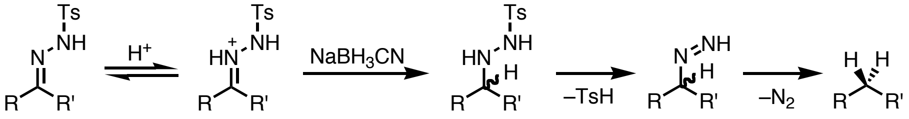
- However, electron-poor aryl carbonyls prove to be resistant to reduction.

Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662-3668.

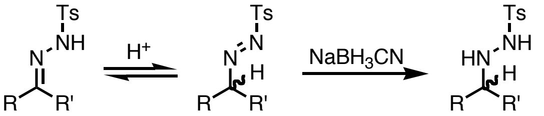
Kabalka, G. W.; Baker, J. D., Jr. *J. Org. Chem.* **1975**, *40*, 1834-1835.

Kabalka, G. W.; Chandler, J. H. *Synth. Commun.* **1979**, *9*, 275-279.

- Two possible mechanisms for reduction of tosylhydrazones by sodium cyanoborohydride have been suggested. Direct hydride attack by sodium cyanoborohydride on an iminium ion is proposed in most cases.



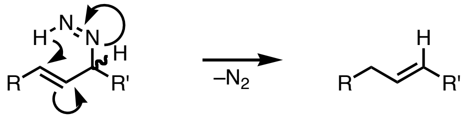
- However, reduction of an azohydrazine is proposed when inductive effects and/or conformational constraints favor tautomerization of the hydrazone to an azohydrazine.



Miller, V. P.; Yang, D.-y.; Weigel, T. M.; Han, O.; Liu, H.-w. *J. Org. Chem.* **1989**, *54*, 4175-4188.

- α,β-Unsaturated carbonyl compounds are reduced with concomitant migration of the conjugated alkene.

- The mechanism for this "alkene walk" reaction apparently proceeds through a diazene intermediate which transfers hydride by 1,5-sigmatropic rearrangement.

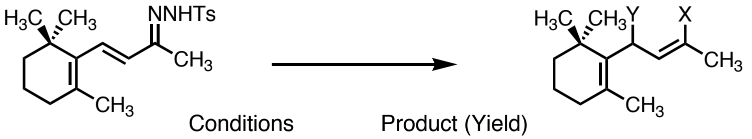


Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923-926.

Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574-575.

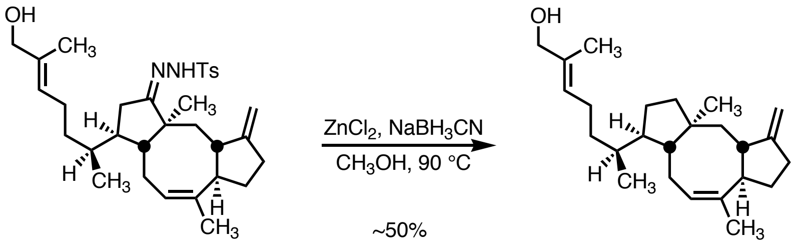
- Examples

- In the following example, exchange of the tosylhydrazone N-H proton is evidently faster than reduction and hydride transfer.



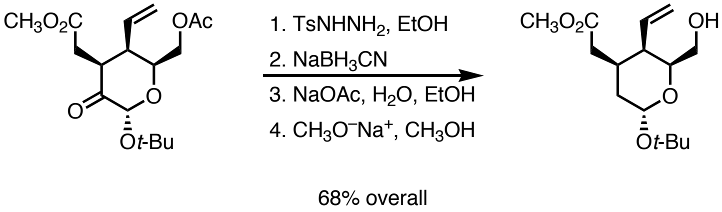
Conditions	Product (Yield)
$NaBD_4$, AcOH	X = D, Y = H (75%)
$NaBH_4$, AcOD	X = H, Y = D (72%)
$NaBD_4$, AcOD	X = Y = D (81%)

Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299-2301.



(±)-ceroplastol I

Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737-2739.



Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947-2949.

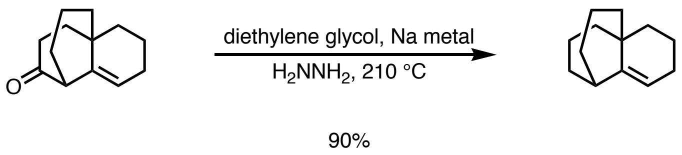
Wolff–Kishner Reduction

- The Wolff–Kishner reduction is a classic method for the conversion of the carbonyl group in aldehydes or ketones to a methylene group. It is conducted by heating the corresponding hydrazone (or semicarbazone) derivative in the presence of an alkaline catalyst.
- Numerous modified procedures to the classic Wolff–Kishner reduction have been reported. In general, the improvements have focused on driving hydrazone formation to completion by removal of water, and by the use of high concentrations of hydrazine.
- The two principal side reactions associated with the Wolff–Kishner reduction are azine formation and alcohol formation.

Todd, D. *Org. React.* **1948**, *4*, 378-423.

Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 8, p. 327-362.

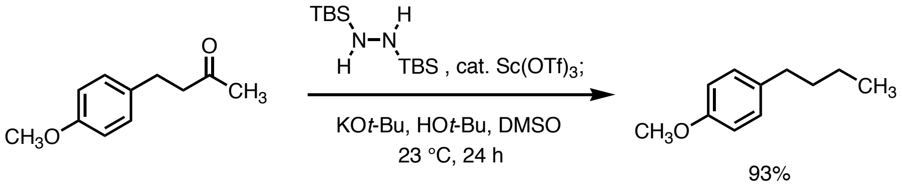
- Examples

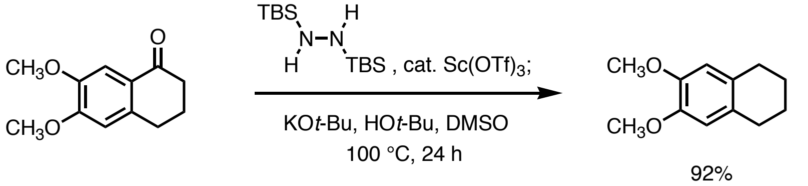


Piers, E.; Zbozny, M. *Can. J. Chem.* **1979**, *57*, 1064-1074.

Reduced-Temperature Wolff-Kisher-Type Reduction

- *N*-*tert*-butyldimethylsilylhydrazone (TBSH) derivatives serve as superior alternatives to hydrazones.
- TBSH derivatives of aliphatic carbonyl compounds undergo Wolff-Kishner-type reduction at 23 °C; derivatives of aromatic carbonyl undergo reduction at 100 °C.





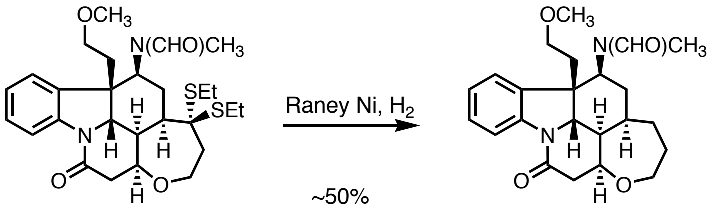
Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436.

Desulfurization With Raney Nickel

- Thioacetal (or thioketal) reduction with Raney nickel and hydrogen is a classic method to prepare a methylene group from a carbonyl compound.
- The most common limitation of the desulfurization method is the competitive hydrogenation of alkenes.

Pettit, G. R.; Tamelen, E. E. *Org. React.* **1962**, *12*, 356-521.

- Example



Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107-2115.

Clemmensen Reduction

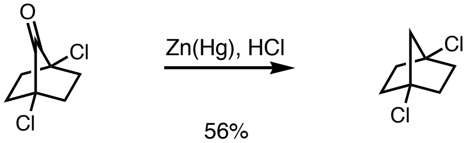
- The Clemmensen reduction of ketones and aldehydes using zinc and hydrochloric acid is a classic method for converting a carbonyl group into a methylene group.
- Typically, the classic Clemmensen reduction involves refluxing a carbonyl substrate with 40% aqueous hydrochloric acid, amalgamated zinc, and an organic solvent such as toluene. This reduction is rarely performed on polyfunctional molecules due to the harsh conditions employed.
- Anhydrous hydrogen chloride and zinc dust in organic solvents has been used as a milder alternative to the classic Clemmensen reduction conditions.

Vedejs, E. *Org. React.* **1975**, *22*, 401-415.

Yamamura, S.; Ueda, S.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1967**, 1049-1050.

Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 264-266.

- Example



Marchand, A. P.; Weimer, W. R., Jr. *J. Org. Chem.* **1969**, *34*, 1109-1112.

Aldehyde or Ketone → Alcohol

Sodium Borohydride: $NaBH_4$

- Sodium borohydride reduces aldehydes and ketones to the corresponding alcohols at or near 25 °C. Under these conditions, esters, epoxides, lactones, carboxylic acids, nitro groups, and nitriles are not reduced.

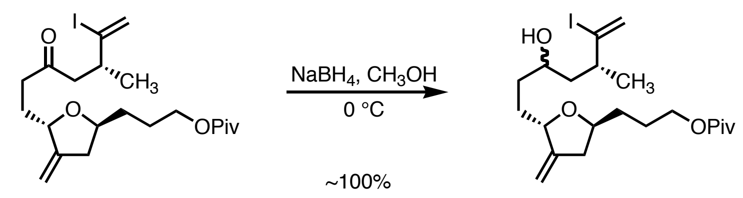
- Sodium borohydride is commercially available as a solid, in powder or pellets, or as a solution in various solvents.

- Typically, sodium borohydride reductions are performed in ethanol or methanol, often with an excess of reagent (to counter the consumption of the reagent by its reaction with the solvent).

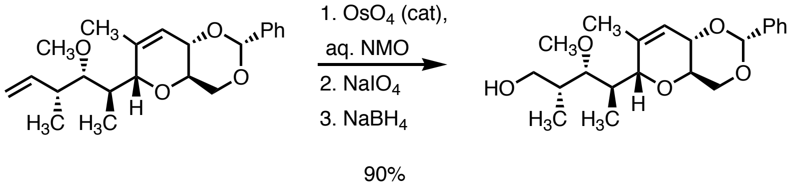
Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122-125.

Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567-607.

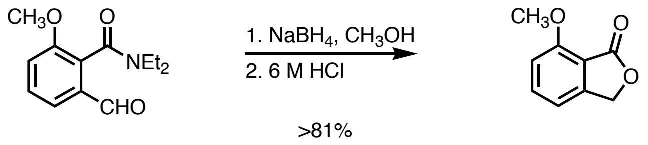
- Examples



Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162-3164.



Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152-7165.



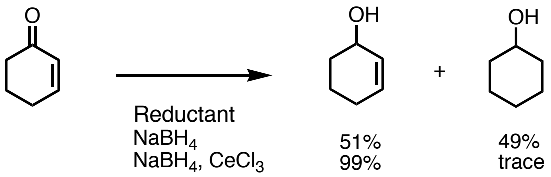
Wang, X.; de Silva, S. O.; Reed, J. N.; Billadeau, R.; Griffen, E. J.; Chan, A.; Snieckus, V. *Org. Synth.* **1993**, *72*, 163-172.

Luche Reduction

- Sodium borohydride in combination with cerium (III) chloride ($CeCl_3$) selectively reduces α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols.

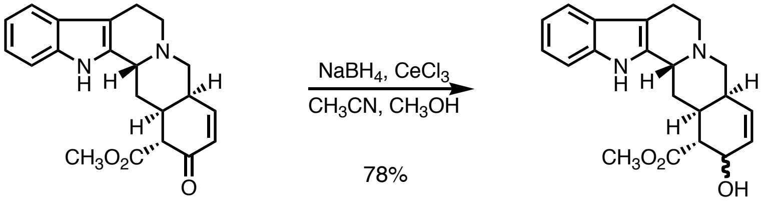
- Typically, a stoichiometric quantity of cerium (III) chloride and sodium borohydride is added to an α,β-unsaturated carbonyl substrate in methanol at 0 °C.

- Control experiments reveal the dramatic influence of the lanthanide on the regiochemistry of the reduction.

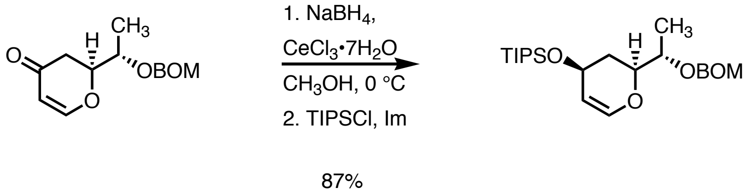


Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

- Examples



Binns, F.; Brown, R. T.; Dauda, B. E. N. *Tetrahedron Lett.* **2000**, *41*, 5631-5635.



Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073-10092.

Ionic Hydrogenation

- Ionic hydrogenation refers to the general class of reactions involving the reduction of a carbonium ion intermediate, often generated by protonation of a ketone, alkene, or a lactol, with a hydride donor.

- Generally, ionic hydrogenations are conducted with a proton donor in combination with a hydride donor. These components must react with the substrate faster than with each other.

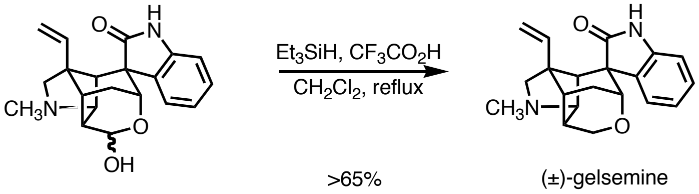
- Organosilanes and trifluoroacetic acid have proven to be one of the most useful reagent combinations for the ionic hydrogenation reaction.

- Carboxylic acids, esters, amides, and nitriles do not react with organosilanes and trifluoroacetic acid. Alcohols, ethers, alkyl halides, and olefins are sometimes reduced.

Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633-651.

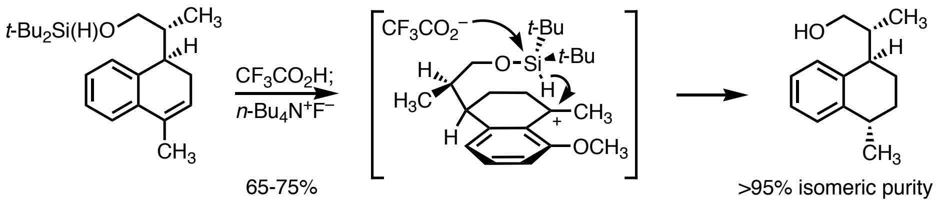
- Examples

- The ionic hydrogenation has been used to prepare ethers from the corresponding lactols.



Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2934-2936.

- Intramolecular ionic hydrogenation reactions have been used in stereoselective reductions.



McCombie, S. W.; Cox, B.; Lin, S.-I.; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 2083-2086.

Samarium Iodide: SmI_2

- Samarium iodide effectively reduces aldehydes, ketones, and alkyl halides in the presence of carboxylic acids and esters.

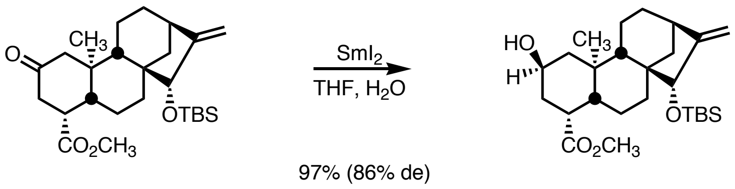
- Aldehydes are often reduced much more rapidly than ketones.

Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.

Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68.

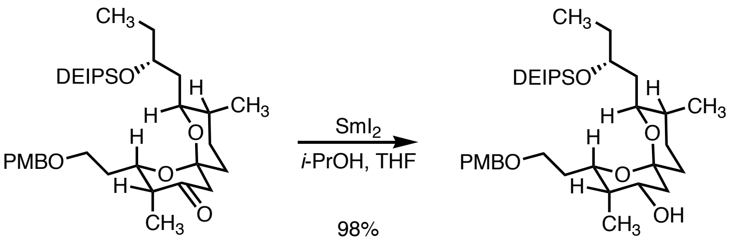
Soderquist, J. A. *Aldrichimica Acta.* **1991**, *24*, 15-23.

- Examples



Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187-6189.

- In the following example, a samarium-catalyzed Meerwein–Ponndorf–Verley reduction successfully reduced the ketone to the alcohol where many other reductants failed.



Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

Mark G. Charest

Reductive Amination

- The reductive amination of aldehydes and ketones is an important method for the synthesis of primary, secondary, and tertiary amines.

- Iminium ions can be reduced selectively in the presence of their carbonyl precursors. Reductive aminations are often conducted by in situ generation of the imine (iminium ion) intermediate in the presence of a mild acid.

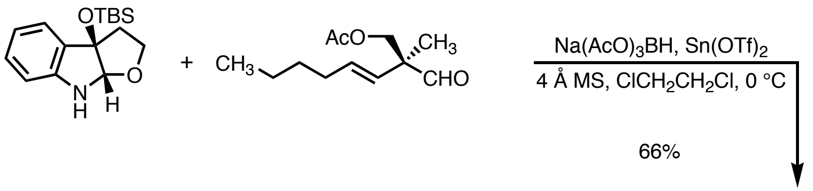
- Reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride react selectively with iminium ions and are frequently used for reductive aminations.

Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897-2904.

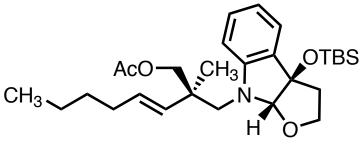
Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron* **1990**, *31*, 5595-5598.

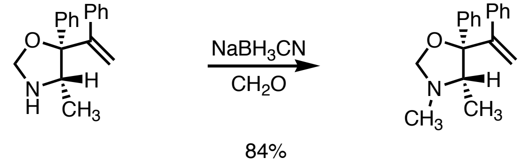
Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.

- Examples

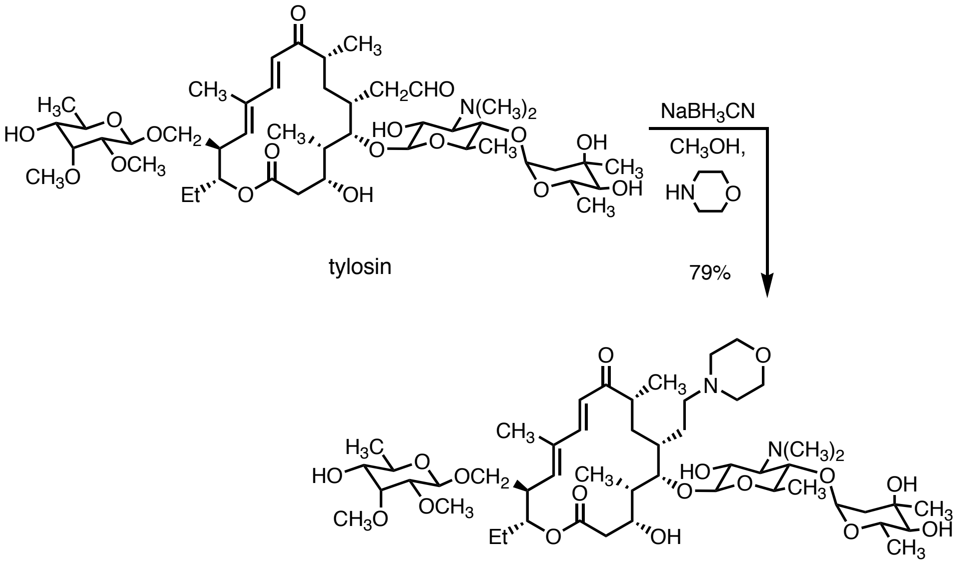


Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435-6439.

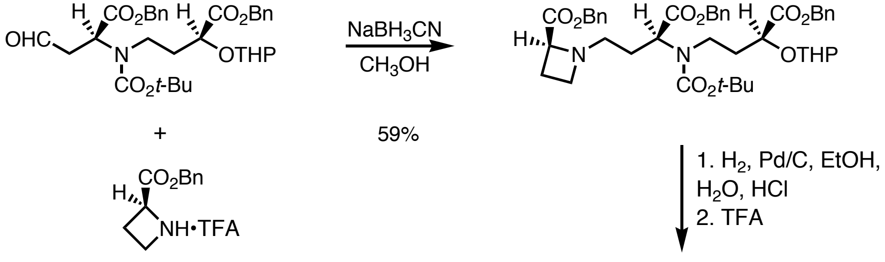




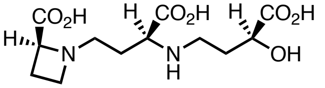
Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329-4336.



Matsubara, H.; Inokoshi, J.; Nakagawa, A.; Tanaka, H.; Omura, S. *J. Antibiotics* **1983**, *36*, 1713-1721.



Ohfune, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409-2410.



2'-deoxymugineic acid

Mark G. Charest

Alcohol → Alkane

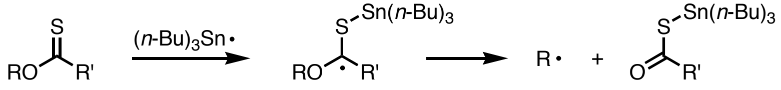
Barton Deoxygenation

- Radical-induced deoxygenation of *O*-thiocarbonate derivatives of alcohols in the presence of hydrogen-atom donors is a versatile and widely-used method for the preparation of an alkane from the corresponding alcohol.

- The Barton deoxygenation is a two-step process. In the initial step, the alcohol is acylated to generate an *O*-thiocarbonate derivative, which is then typically reduced by heating in an aprotic solvent in the presence of a hydrogen-atom donor.

- The method has been adapted for the deoxygenation of primary, secondary, and tertiary alcohols. In addition, monodeoxygenation of 1,2- and 1,3-diols has been achieved.

- The accepted mechanism of reduction proceeds by attack of a tin radical on the thiocarbonyl sulfur atom. Subsequent fragmentation of this intermediate generates an alkyl radical which propagates the chain.


S
RO
R'
$(n\text{-Bu})_3\text{Sn}\bullet$
$\text{Sn}(n\text{-Bu})_3$
S
RO
R'
R•
+
S
$\text{Sn}(n\text{-Bu})_3$
O
R'

Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574-1585.

Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743-745.

Barton, D. H. R.; Hartwig, W.; Hay-Motherwell, R. S.; Motherwell, W. B.; Stange, A. *Tetrahedron Lett.* **1982**, *23*, 2019-2022.

Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675-684.

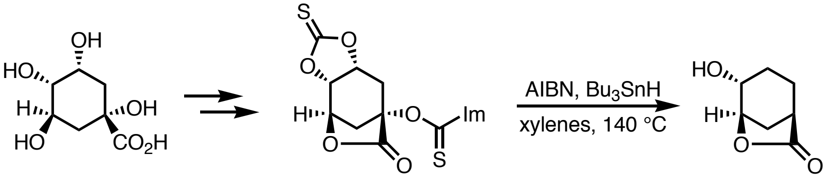
Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619-2622.

Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 3991-3994.

Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 4681-4684.

Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *47*, 8969-8984.

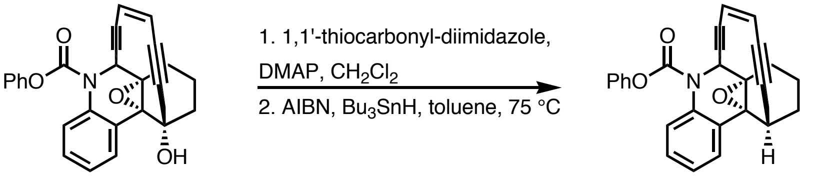
- Examples



quinic acid

40%

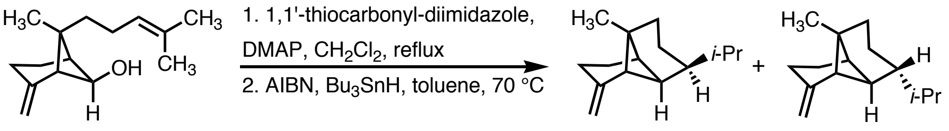
Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281-284.


O
PhO
N
O
OH
1. 1,1'-thiocarbonyl-diimidazole,
DMAP, CH_2Cl_2
2. AIBN, Bu_3SnH, toluene, 75 °C
O
PhO
N
O
H

75%

Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416-7418.

- In the following example, the radical generated during the deoxygenation reaction undergoes 6-exo-trig radical cyclization.


H_3C
CH_3
CH_3
OH
H
1. 1,1'-thiocarbonyl-diimidazole,
DMAP, CH_2Cl_2, reflux
2. AIBN, Bu_3SnH, toluene, 70 °C
H_3C
i-Pr
H
H
+
H_3C
H
i-Pr
H

46% (1 : 1 mixture)

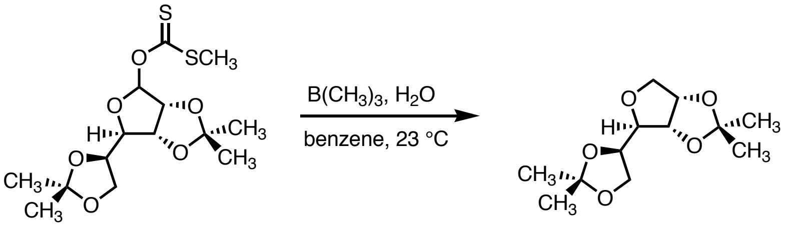
β-ylangene

β-copaene

Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568-1576.

Tin-Free Barton-Type Reduction Employing Water as a Hydrogen Atom Source:

- Trialkylborane acts as both the radical initiator and an activator of water prior to hydrogen atom abstraction.
- Simple concentration of the reaction mixture provides products in high purity.



91%

Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, ASAP.

Mark G. Charest, Jason Brubaker

Diazene-Mediated Deoxygenation

- Deoxygenation proceeds by Mitsunobu displacement of the alcohol with *o*-nitrobenzenesulfonylhydrazine (NBSH) followed by in situ elimination of *o*-nitrobenzene sulfinic acid. The resulting monoalkyl diazene is proposed to decompose by a free-radical mechanism to form deoxygenated products.

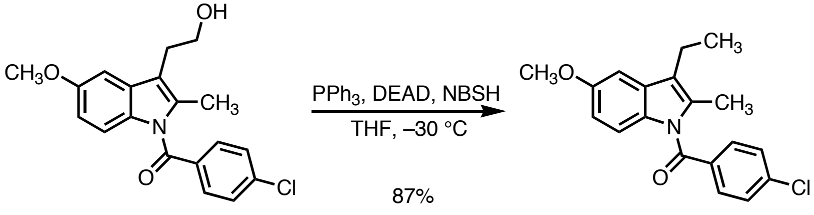
- The deoxygenation is carried out in a single step without using metal hydride reagents.

- The method is found to work well for unhindered alcohols, but sterically encumbered and β-oxygenated alcohols fail to undergo the Mitsunobu displacement and are recovered unchanged from the reaction mixture.

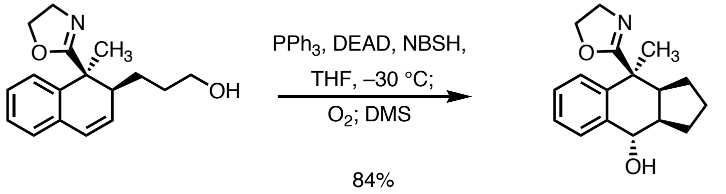
$$RCH_2OH \xrightarrow[\text{THF, –30 °C}]{\text{PPh}_3\text{, DEAD, NBSH}} RCH_2N(NH_2)SO_2Ar \xrightarrow{\geq 0\ °C} [\ RCH_2N{=}NH\ ] \xrightarrow[-N_2]{} RCH_3$$

Ar = 2-$O_2NC_6H_4$

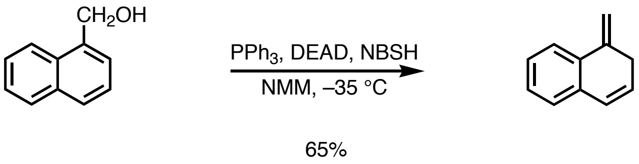
- Examples



- In the following example, the radical generated from decomposition of the diazene intermediate underwent a rapid 5-exo-trig radical cyclization. This generated a second radical that was trapped with oxygen to provide the cyclic carbinol shown after work-up with methyl sulfide.

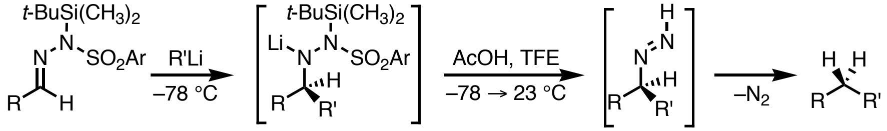


- Monoalkyl diazenes will undergo concerted sigmatropic elimination of dinitrogen in preference to radical decomposition where this is possible.



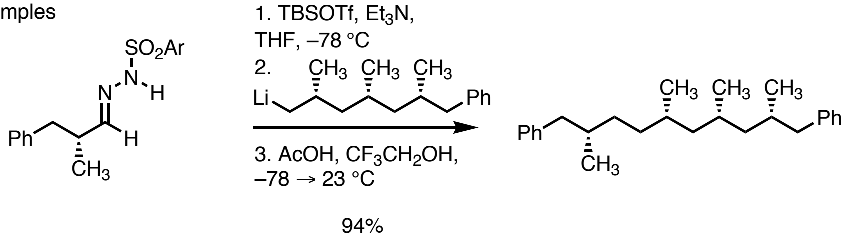
Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572-8573.

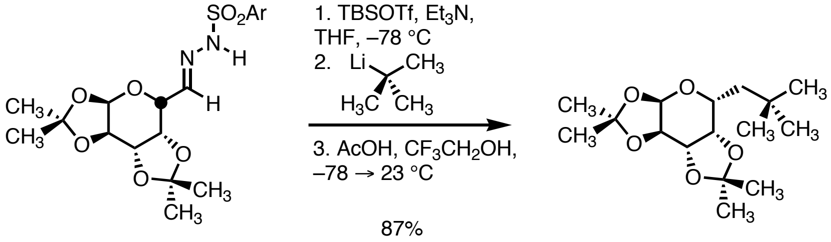
- In related studies, it was shown that alkyllithium reagents add to *N-tert*-butyldimethylsilyl aldehyde tosylhydrazones at –78 °C and that the resulting adducts can be made to extrude dinitrogen in a free-radical process.



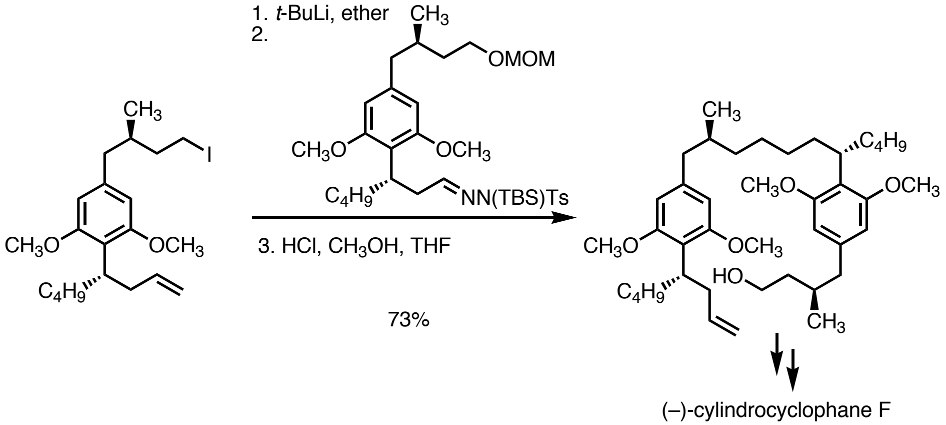
Ar = 2,4,6-triisopropylbenzene

- Examples





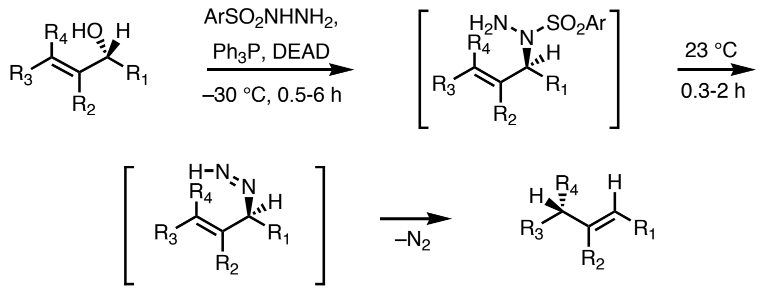
Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.



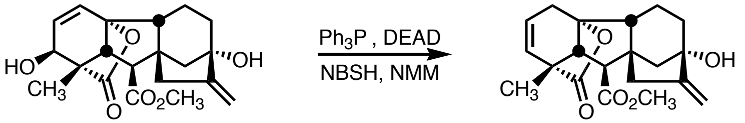
Smith, A. B., III; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423-7424.

Mark G. Charest

- Reductive 1,3-transposition of allylic alcohols proceeds with excellent regio- and stereochemical control.



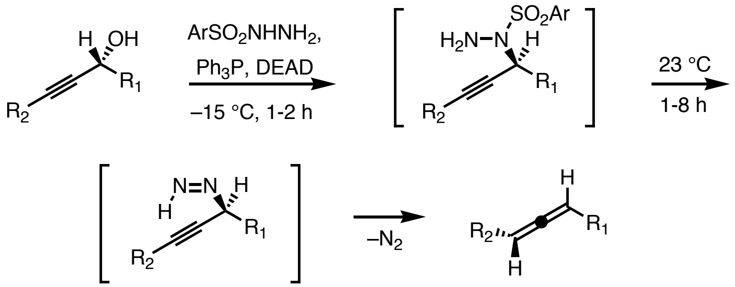
- Example



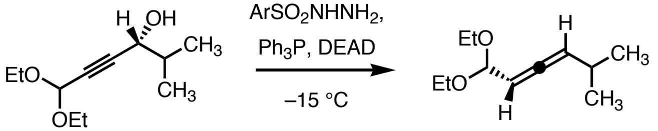
66%

Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841-4844.

- In addition, allenes can be prepared stereospecifically from propargylic alcohols.



- Example



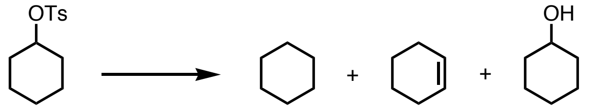
74%

Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.

Reduction of Alkyl Tosylates

- *p*-Toluenesulfonate ester derivatives of alcohols are reduced to the corresponding alkanes with certain powerful metal hydrides.

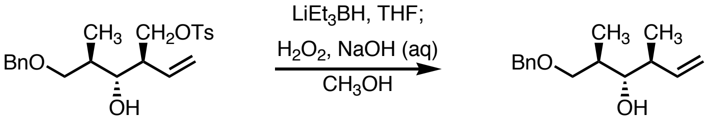
- Among hydride sources, lithium triethylborohydride (Super Hydride, $LiEt_3BH$) has been shown to rapidly reduce alkyl tosylates efficiently, even thoes derived from hindered alcohols.



Reductant			
LAH	54%	25%	19%
$LiEt_3BH$	80%	20%	0%

Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064-3066.

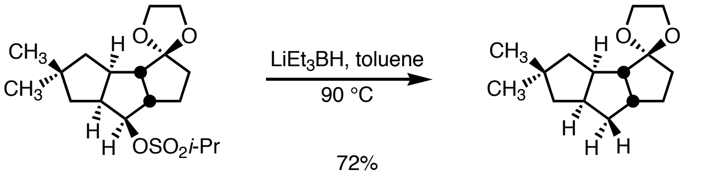
- Examples



92%

Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

- In the following example, selective C-O bond cleavage by $LiEt_3BH$ could only be achieved with a 2-propanesulfonate ester. The corresponding mesylate and tosylate underwent S-O bond cleavage when treated with $LiEt_3BH$.



72%

Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507-515.

Mark G. Charest

Radical Dehalogenation

- Alkyl bromides and iodides are reduced efficiently to the corresponding alkanes in a free-radical chain mechanism with tri-*n*-butyltin hydride.

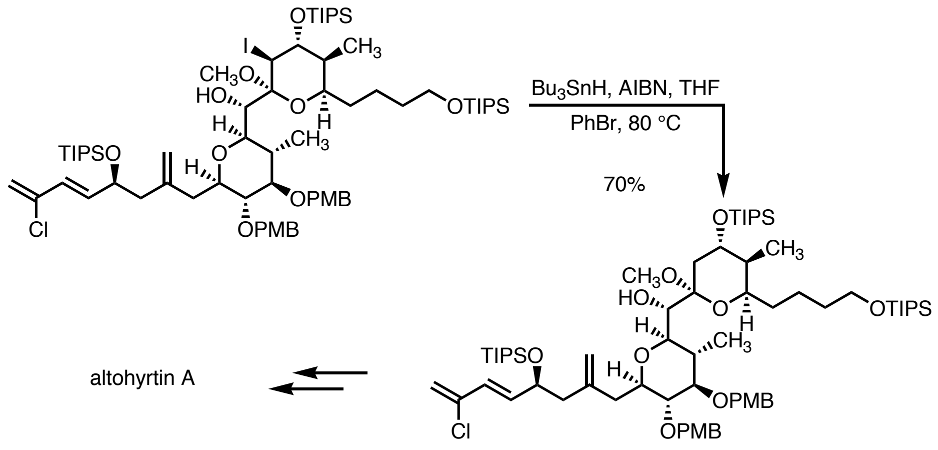
- The reduction of chlorides usually requires more forcing reaction conditions and alkyl fluorides are practically unreactive.

- The reactivity of alkyl halides parallels the thermodynamic stability of the radical produced and follows the order: tertiary > secondary > primary.

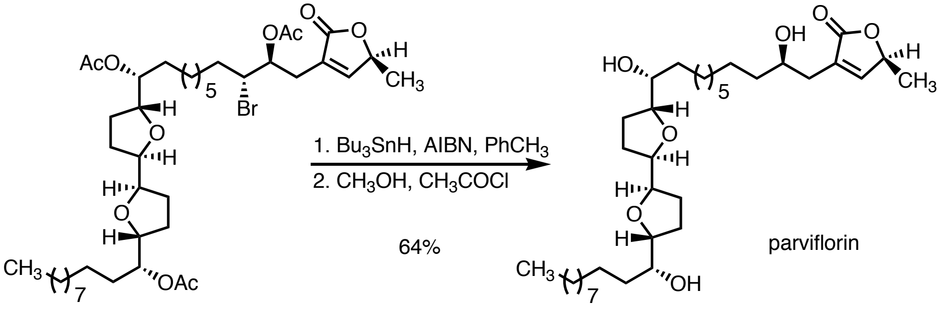
- Triethylboron-oxygen is a highly effective free-radical initiator. Reduction of bromides and iodides can occur at –78 °C with this initiator.

Neumann, W. P. *Synthesis* **1987**, 665-683.

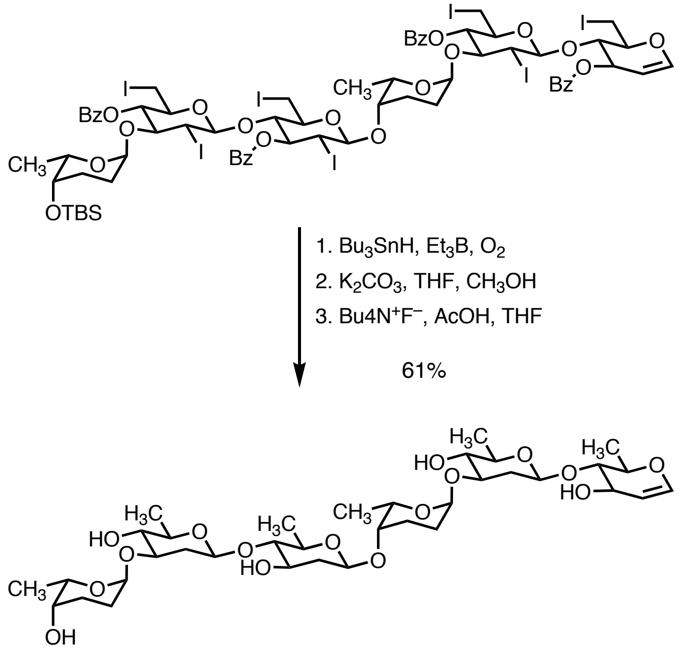
Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143-147.



Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187-196.

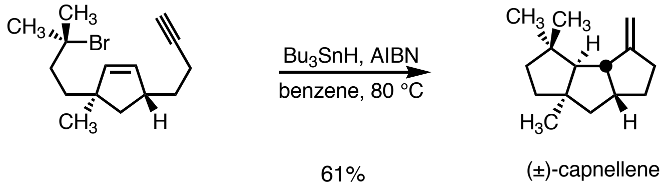


Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632-2635.


I
BzO
O
O
I
Bz
O
CH_3
O
OTBS
1. Bu_3SnH, Et_3B, O_2
2. K_2CO_3, THF, CH_3OH
3. $Bu4N^+F^-$, AcOH, THF
61%
H_3C
HO
O
OH

Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124-6125.

- In the following example, the radical generated during the dehalogenation reaction undergoes a tandem radical cyclization.



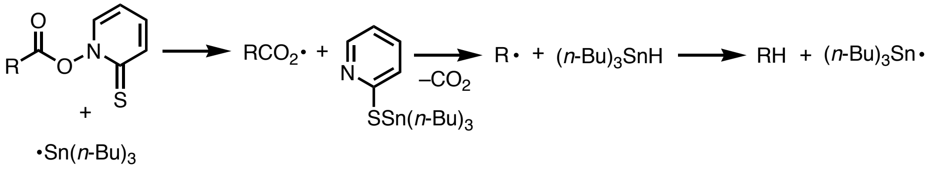
Curran, D. E.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991-4994.

Mark G. Charest

Acid → Alkane

Barton Decarboxylation

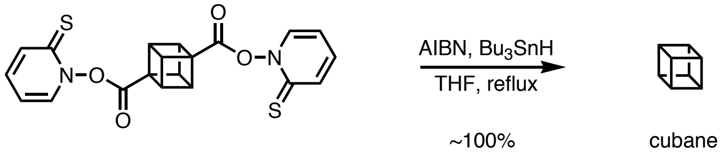
- *O*-Esters of thiohydroxamic acids are reduced in a radical chain reaction by tin hydride reagents.
- These are typically prepared by the reaction of commercial *N*-hydroxypyridine-2-thione with activated carboxylic esters.



Barton, D. H. R.; Circh, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941.

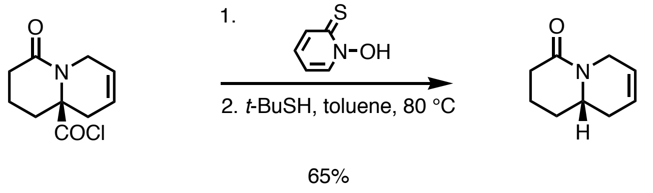
Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733-2740.

- Examples

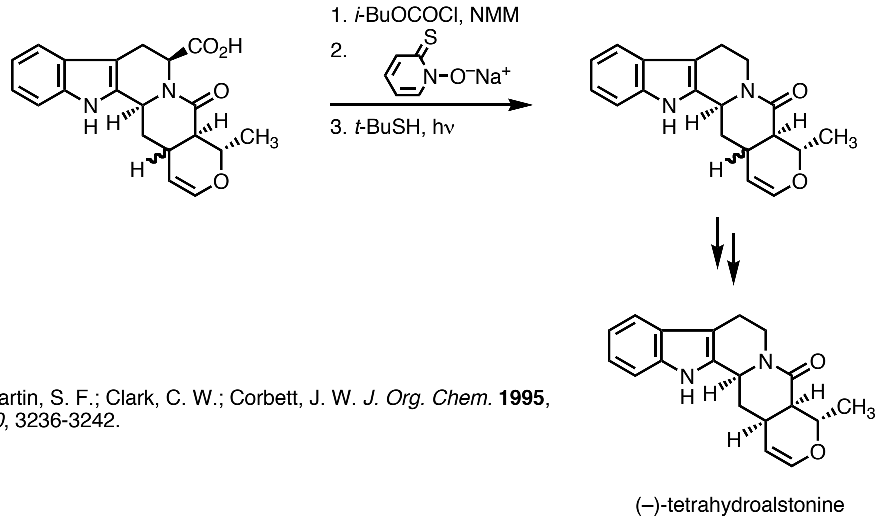


Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1421-1436.

- The Barton decarboxylation is known to be stereoselective in rigid bicycles.

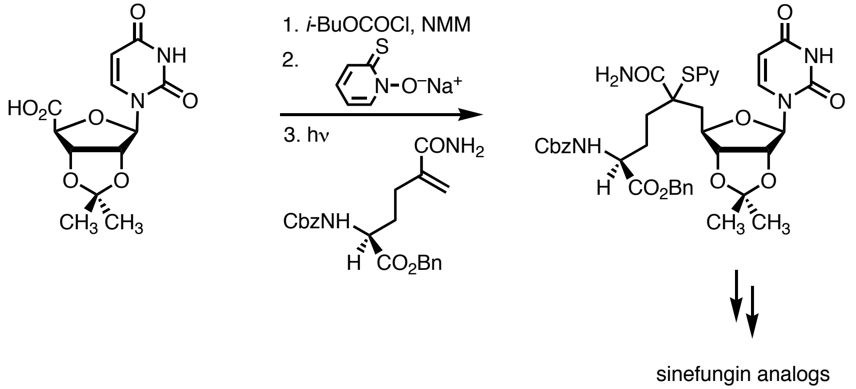


Diedrichs, N.; Westermann, B. *Synlett.* **1999**, 1127-1129.



Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236-3242.

- In the following example, the alkyl radical generated from the decarboxylation reaction was trapped with an electron-deficient olefin. This produced a second radical intermediate that continued the chain to give the stereoisomeric mixture of products shown.



Barton, D. H. R.; Géro, S. D.; Lawrence, F.; Robert-Gero, M.; Quiclet-Sire, B.; Samadi, M. *J. Med. Chem.* **1992**, *35*, 63-67.

Mark G. Charest

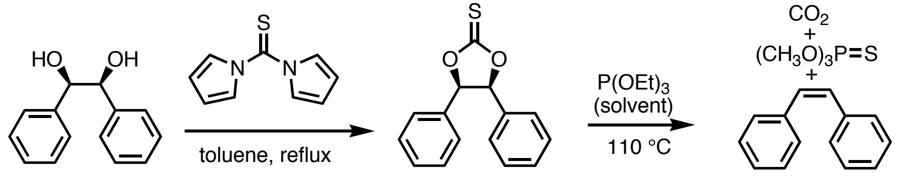
Diol → Olefin

General Reference:

Block, E. *Org. React.* **1984**, *30*, 457.

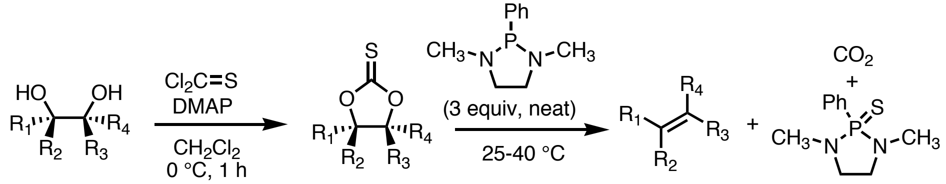
Corey-Winter Olefination:

- This is a two-step procedure. The diol is converted to a thionocarbonate by addition of thiocarbonyldiimidazole in refluxing toluene. The intermediate thionocarbonate is then desulfurized (with concomitant loss of carbon dioxide) upon heating in the presence of a trialkylphophite.
- The elimination is stereospecific.
- Original report:

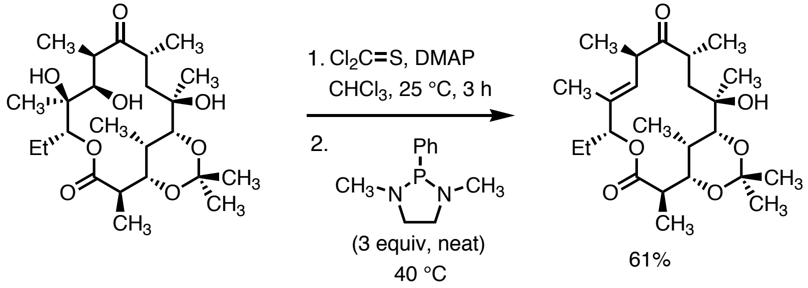


Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.

- Milder conditions have been reported for both the formation of the thiocarbonate intermediate and the subsequent decomposition to the desired olefin.

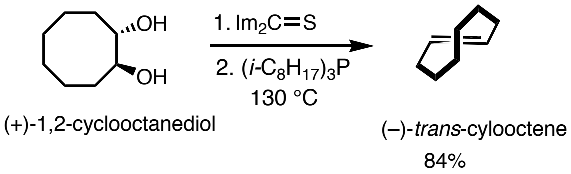


- These milder conditions have been used effectively for the olefination of highly functionalized diols:



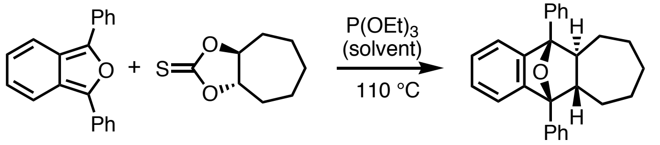
Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979.

- This method has been useful in the preparation of highly strained *trans*-cycloalkenes:



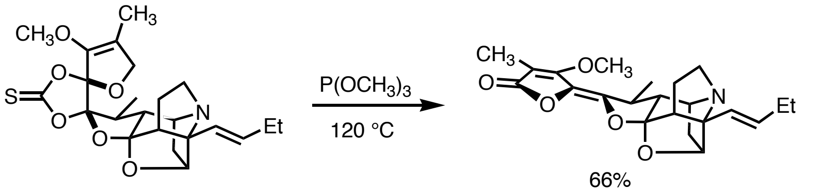
Corey, E. J.; Shulman, J. I. *Tetrahedron Lett.* **1968**, *8*, 3655.

- In an initial attempt to prepare *trans*-cycloheptene, the only product observed was the *cis*-isomer. Performing the olefination reaction in the presence of 2,5-diphenyl-3,4-isobenzofuran traps the highly strained olefin before isomerization to the *cis*-isomer can occur:



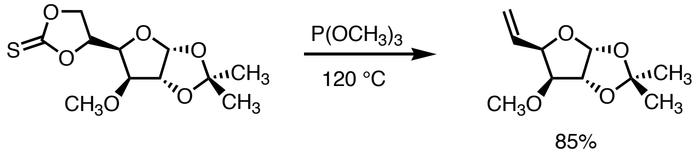
Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, *87*, 934.

- Synthesis examples:



Bruggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284.

- Preparation of Unsaturated Sugars:



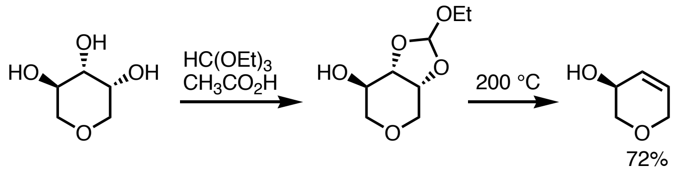
Barton, D. H. R.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1,* **1975**, 1773.

Jason Brubaker

Eastwood Deoxygenation:

Crank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1385.

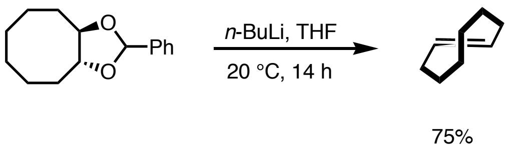
- A vicinal diol is treated with ethyl orthoformate at high temperature (140-180 °C), followed by pyrolysis of the resulting cyclic orthoformate (160-220 °C) in the presence of a carboxylic acid (typically acetic acid).
- The elimination is stereospecific.
- Not suitable for functionalized substrates.



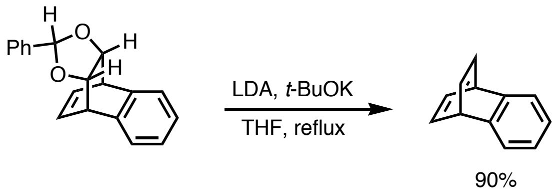
Fleet, G. W. J.; Gough, M. J. *Tetrahedron Lett.* **1982**, *23*, 4509.

Base Induced Decomposition of Benzylidene Acetals:

- The elimination is stereospecific.
- Long reaction times and high temperatures under extremely basic conditions make this an unsuitable method for functionalized substrates.



Hines, J. N.; Peagram, M. J.; Whitham, G. H.; Wright, M. *J. Chem. Soc., Chem. Commun.* **1968**, 1593.



Pu, L.; Grubbs, R. H.; *J. Org. Chem.* **1994**, *59*, 1351.

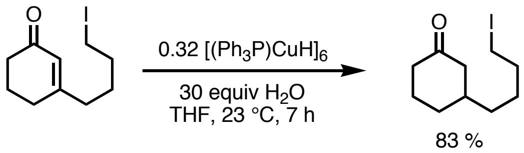
α,β-Unsaturated Carbonyl ⟶ Carbonyl

Catalytic Hydrogenation:

- The carbon-carbon double bond of α,β-unsaturated carbonyl compounds can be reduced selectively by catalytic hydrogenation, affording the corresponding carbonyl compounds.
- This method is not compatible with olefins, alkynes, and halides.

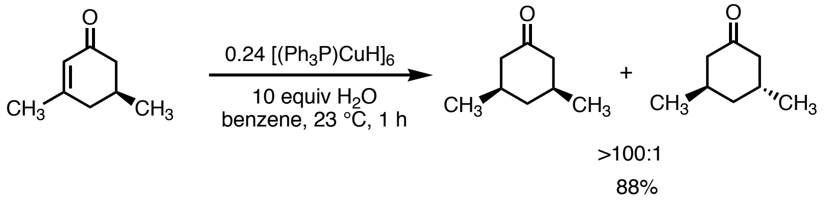
Stryker Reduction:

- α,β-Unsaturated carbonyl compounds undergo selective 1,4-reduction with $[(Ph_3P)CuH]_6$.
- $[(Ph_3P)CuH]_6$ is stable indefinitely, provided that the reagent is stored under an inert atmosphere. The reagent can be weighed quickly in the air, but the reaction solutions must be deoxygenated. The reaction is unaffected by the presence of water (in fact, deoxygenated water is often added as a proton source).
- α,β-Unsaturated ketones, esters, aldehydes, nitriles, sulfones, and sulfonates are all suitable substrates.
- This method is compatible with isolated olefins, halides, and carbonyl groups (in contrast to reduction by catalytic hydrogenation).
- Each of the six hydrides of the copper cluster can be transferred.
- TBS-Cl is often added during the reduction of α,β-unsaturated aldehydes to suppress side reactions arising from aldol condensation of the copper enolate intermediates.



Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237.

- The reduction is highly steroselective, with addition occuring to the less hindered face of the olefin:



Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

Jason Brubaker

General Introductory References

March, J. In *Advanced Organic Chemistry*, John Wiley and Sons: New York, **1992**, p. 1158-1238.

Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part B*, Plenum Press: New York, **1990**, p. 615-664.

Carruthers, W. In *Some Modern Methods of Organic Synthesis 3rd Ed.*, Cambridge University Press: Cambridge, UK, **1987**, p. 344-410.

Oxidation States of Organic Functional Groups

The notion of oxidation state is useful in categorizing many organic transformations. This is illustrated by the progression of a methyl group to a carboxylic acid in a series of 2-electron oxidations, as shown at right. Included are several functional group equivalents considered to be at the same oxidation state.

Summary of Reagents for Oxidative Functional Group Interconversions:

Alcohol → Aldehyde or Ketone

Dimethylsulfoxide-Mediated Oxidations
Dess-Martin Periodinane (DMP)
o-Iodoxybenzoic Acid (IBX)
tetra-*n*-Propylammonium Perruthenate (TPAP)
N-Oxoammonium-Mediated Oxidation
Manganese Dioxide
Barium Manganate
Oppenauer Oxidation
Chromium (VI) Oxidants
Sodium Hypochlorite
N-Bromosuccinimide (NBS)
Bromine
Cerium (IV) Oxidants

Aldehyde → Acid

Sodium Chlorite
Potassium Permanganate
Silver Oxide
Pyridinium Dichromate (PDC)

Aldehyde → Ester

Corey-Gilman-Ganem Oxidation
Bromine

Ketone → Ester

Baeyer-Villiger Oxidation

Alcohol → Acid

Ruthenium Tetroxide
O_2/Pt
Jones Oxidation

Ketone → α-Hydroxy Ketone

Davis Oxaziridine
MoOPH
Rubottom Oxidation

Diol → Lactone

Fetizon's Reagent
O_2/Pt
N-Oxoammonium-Mediated Oxidation

Alkane $R\text{-}CH_3$

organoboranes RCH_2BR_2'
organosilanes RCH_2SiR_3'
organometallics in general RCH_2M (M = Li, MgX, ZnX...)

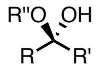
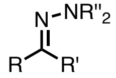
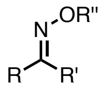
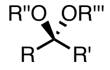
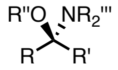
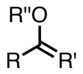
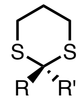
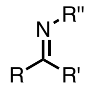
↓

Alcohol $R\text{-}CH_2OH$ ($R\text{-}CH_2X$)

alkyl halide X = halide
alkylamine $X = NR'_2$
alkane sulfonate $X = OSO_2R'$
alkylthio ether X = SR'
alkyl azide $X = N_3$
alkyl ether X = OR'

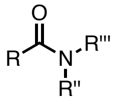
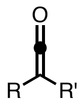
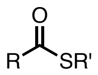
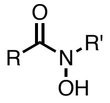
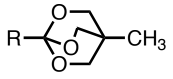
↓

Aldehyde (Ketone) R-CHO (RCOR')

hemiketal (hemiacetal)

hydrazone

oxime

ketal (acetal)

geminal dihalide RCX_2R'
aminal

enol ether (enamine)

dithiane

imine


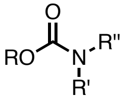
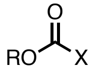
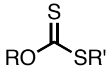
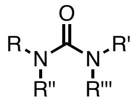
↓

Carboxylic Acid $R\text{-}CO_2H$

ester RCO_2R'
amide

ketene

thioester

trihalomethyl RCX_3
nitrile R−C≡N
hydroxamic acid

orthoester

(OBO ester shown)

↓

Carbonic Acid Ester $ROH + CO_2$ ($ROCO_2H$)

carbamate

alkyl haloformate

xanthate

isocyanate R−N=C=O
carbodiimide R−N=C=N−R'
urea


Mark G. Charest

Alcohol $\longrightarrow$ Aldehyde or Ketone

Dimethylsulfoxide-Mediated Oxidations

- Reviews

Lee, T. V. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 291-303.

Tidwell, T. T. *Synthesis* **1990**, 857-870.

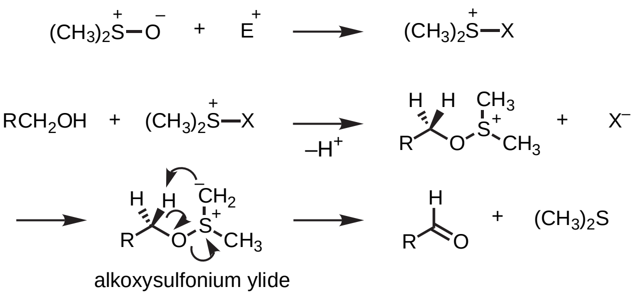
Tidwell, T. T. *Organic Reactions* **1990**, *39*, 297-557.

General Mechanism

- Dimethylsulfoxide (DMSO) can be activated by reaction with a variety of electrophilic reagents, including oxalyl chloride, dicyclohexylcarbodiimide, sulfur trioxide, acetic anhydride, and *N*-chlorosuccinimide.

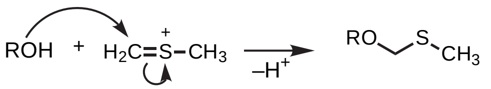
- The mechanism can be considered generally as shown, where the initial step involves electrophilic (E^+) attack on the sulfoxide oxygen atom.

- Subsequent nucleophilic attack of an alcohol substrate on the activated sulfoxonium intermediate leads to alkoxysulfonium salt formation. This intermediate breaks down under basic conditions to furnish the carbonyl compound and dimethyl sulfide.



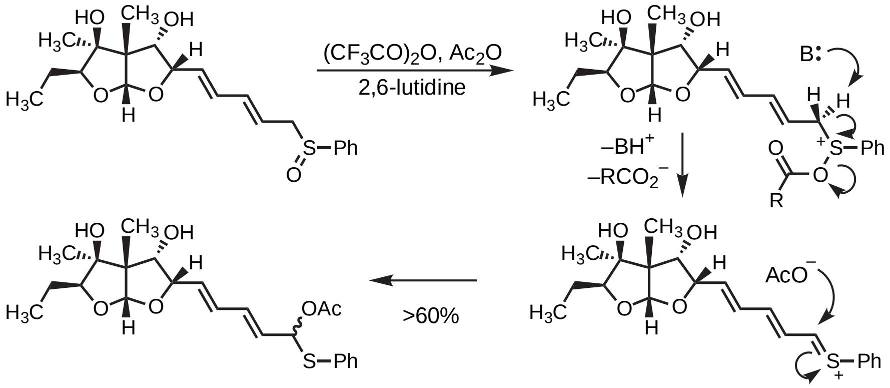
$(CH_3)_2\overset{+}{S}-\overset{-}{O}$ + E^+ → $(CH_3)_2\overset{+}{S}-X$
RCH_2OH + $(CH_3)_2\overset{+}{S}-X$ → (–H^+) + X^-
alkoxysulfonium ylide
$(CH_3)_2S$

- Methylthiomethyl (MTM) ether formation can occur as a side reaction, by nucleophilic attack of an alcohol on methyl(methylene)sulfonium cations generated from the dissociation of sulfonium ylide intermediates present in the reaction mixture. This type of transformation is related to the Pummerer Rearrangement.



Fenselau, A. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1762-1765.

- Pummerer Rearrangement



Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186-4188.

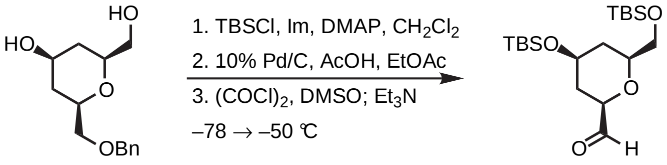
Swern Procedure

- Typically, 2 equivalents of DMSO are activated with oxalyl chloride in dichloromethane at or below –60 ℃.

- Subsequent addition of the alcohol substrate and triethylamine leads to carbonyl formation.

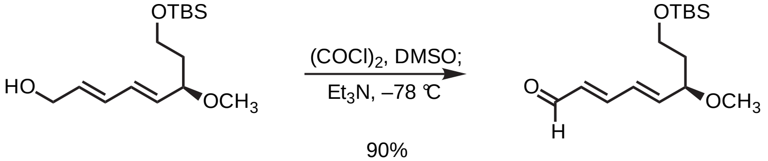
- The mild reaction conditions have been exploited to prepare many sensitive aldehydes. Careful optimization of the reaction temperature is often necessary.

Huang, S. L.; Mancuso, A. J.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.



66%

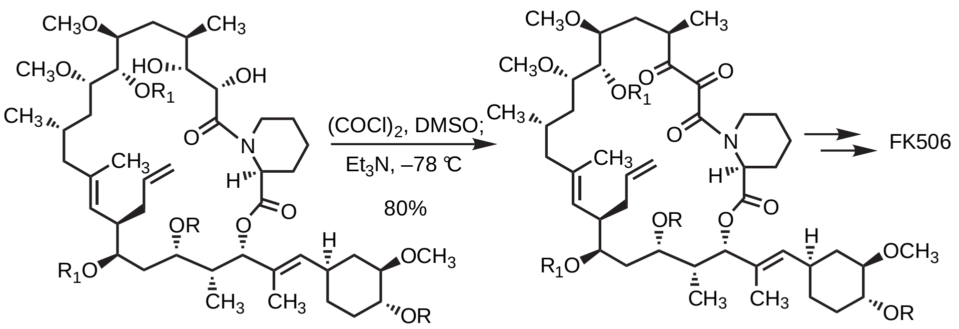
Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2354-2359.



90%

Smith, A. B., III; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738-3753.

Mark G. Charest

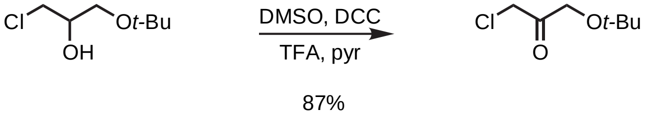


R = TIPS, R$_1$ = TBS

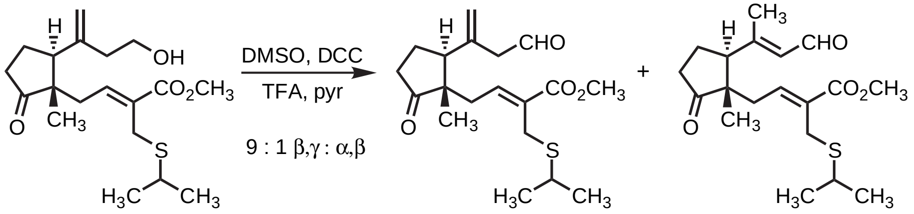
Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998-3017.

Pfitzner-Moffatt Procedure

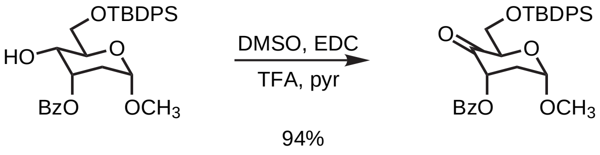
- The first reported DMSO-based oxidation procedure.
- Dicyclohexylcarbodiimide (DCC) functions as the electrophilic activating agent in conjunction with a Brønsted acid promoter.
- Typically, oxidations are carried out with an excess of DCC at or near 23 ℃.
- Separation of the by-product dicyclohexylurea and MTM ether formation can limit usefulness.
- Alternative carbodiimides that yield water-soluble by-products (e.g., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)) can simplify workup procedures.



Corey, E. J.; Kim, C. U.; Misco, P. F. *Org. Synth. Coll. Vol. VI* **1988**, 220-222.



Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* **1978**, *100*, 5565-5576.



$EDC = (CH_3)_2N{-}(CH_2)_3{-}N{=}C{=}N{-}CH_2CH_3 \cdot HCl$

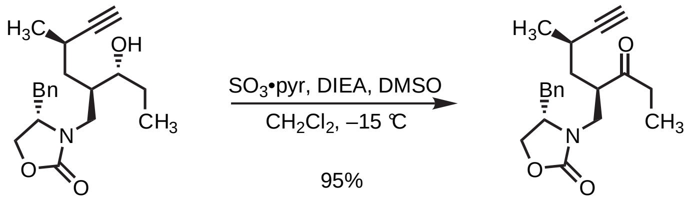
Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1981**, *59*, 870-877.

Parikh-Doering Procedure

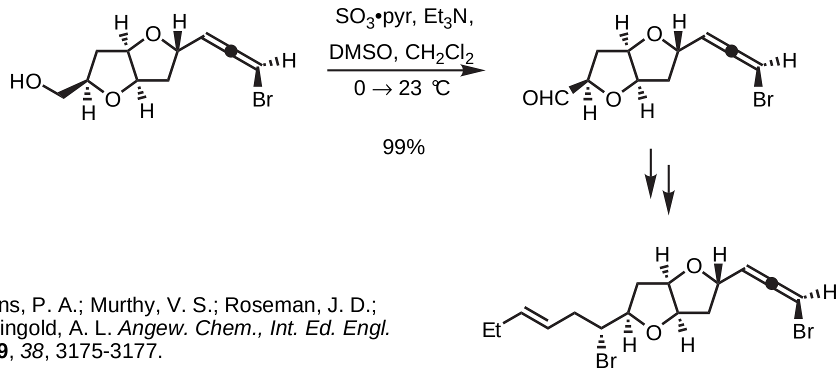
- Sulfur trioxide-pyridine is used to activate DMSO.
- Ease of workup and at-or-near ambient reaction temperatures make the method attractive for large-scale reactions.

Parihk, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

- Examples



Evans, D. A.; Ripin, D. H.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816-6826.



Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3175-3177.

(–)-kumausallene

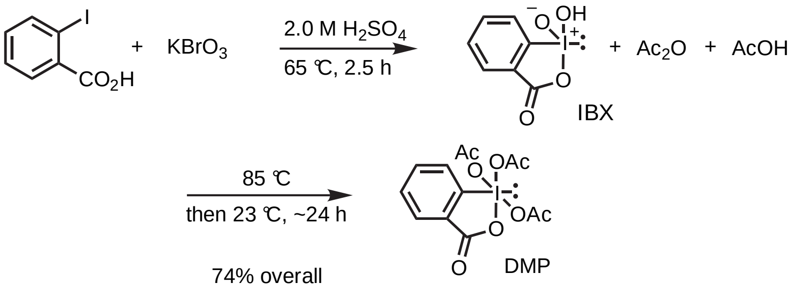
Dess-Martin Periodinane (DMP)

- DMP has found wide utility in the preparation of sensitive, highly functionalized molecules.
- DMP oxidations are characterized by short reaction times, use of a single equivalent of oxidant, and can be moderated with regard to acidity by the incorporation of additives such as pyridine.
- DMP and its precurser *o*-iodoxybenzoic acid (IBX) are potentially heat and shock sensitive and should be handled with appropriate care.

Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *48*, 4155-4156.

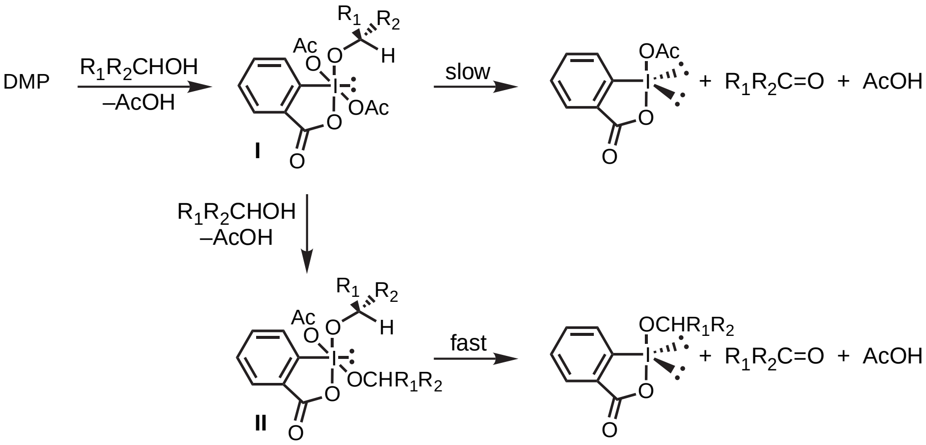
Boeckman, R. K.; Shao, P.; Mulins, J. J. *Org. Synth.* **1999**, *77*, 141-152.

Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, July 16, 3.



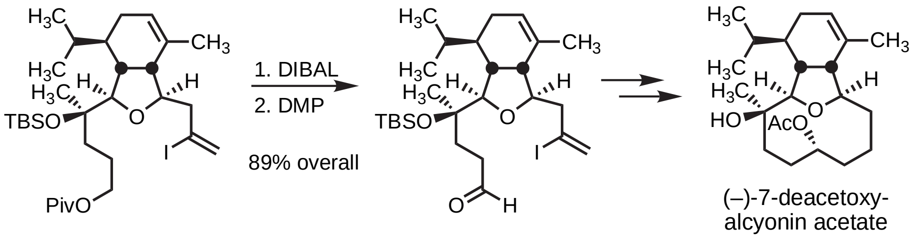
- Addition of one equivalent of water has been found to accelerate the reaction, perhaps due to the formation of an intermediate analogous to **II**. It is proposed that the decomposition of **II** is more rapid than the initially formed intermediate **I**.

Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549-7552.



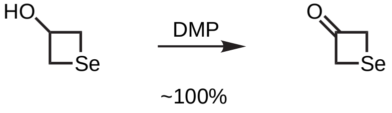
Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

- Examples

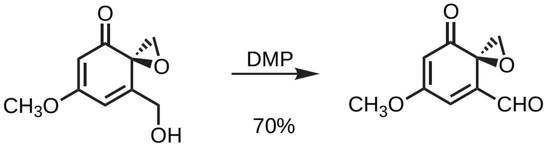


(–)-7-deacetoxy-alcyonin acetate

Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683-2686.

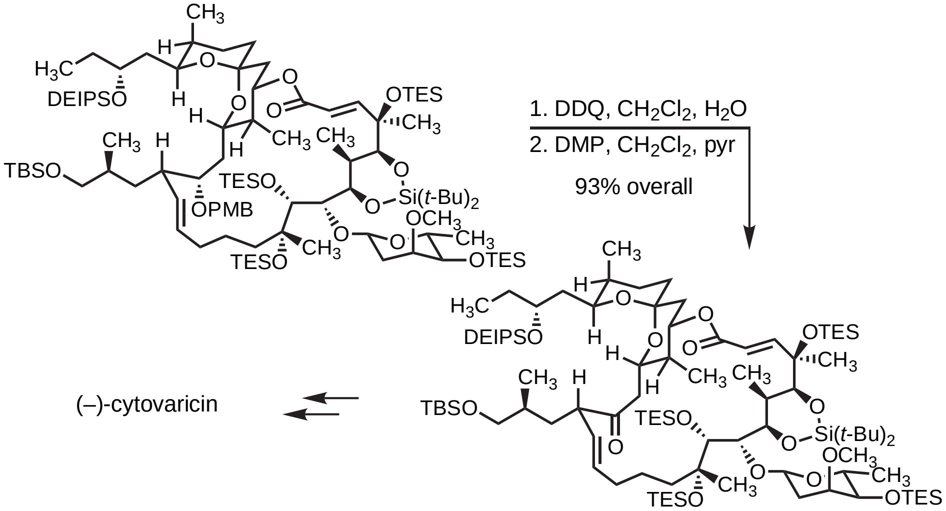


Polson, G.; Dittmer, D. C. *J. Org. Chem.* **1988**, *53*, 791-794.



Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Schulte, G. K. *J. Am. Chem. Soc.* **1988**, *110*, 6890-6891.

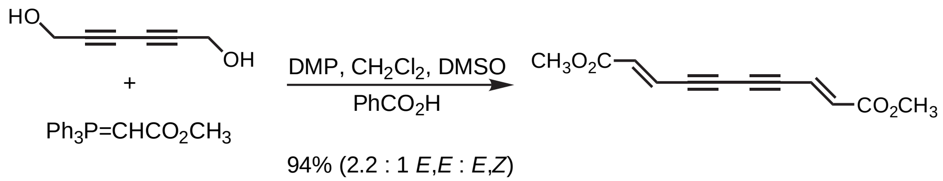
- Use of other oxidants in the following example led to conjugation of the β,γ-unsaturated ketone, which did not occur when DMP was used.



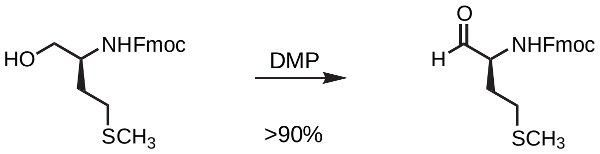
Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

Mark G. Charest

- DMP oxidation in the presence of phosphorous ylides allows for the trapping of sensitive aldehydes.



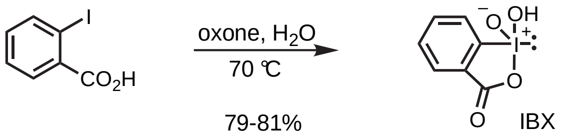
Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376-9378.



Myers, A. G.; Zhong, B.; Kung, D. W.; Movassaghi, M.; Lanman, B. A.; Kwon, S. *Org. Lett.*, in press.

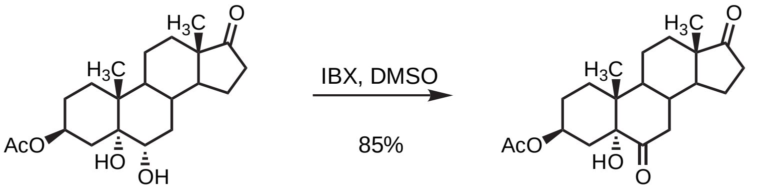
o-Iodoxybenzoic Acid (IBX)

- The DMP precursor IBX is gaining use as a mild reagent for the oxidation of alcohols.
- A simpler preparation of IBX has recently been reported.



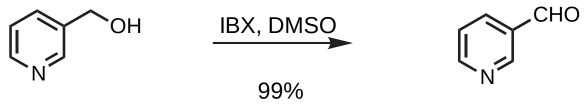
Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.

- IBX is used as a mild reagent for the oxidation of 1,2-diols without C-C bond cleavage.



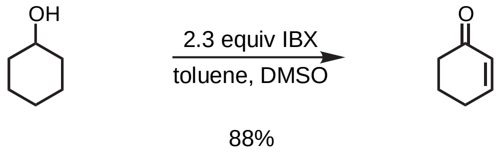
Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019-8022.

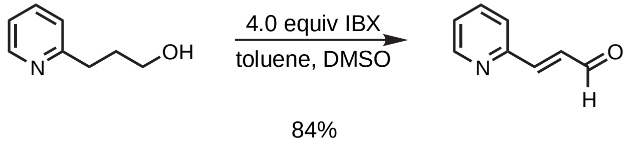
- Pyridines are not oxidized at a rate competitive with the oxidation of a primary alcohol.

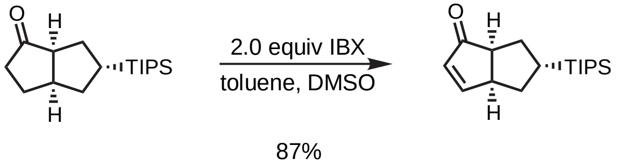


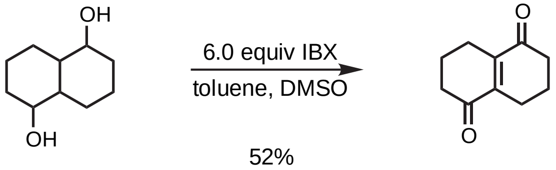
Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019-8022.

- IBX has been shown to form α,β-unsaturated carbonyl compounds from the corresponding saturated alcohol or carbonyl compound.









Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596-7597.

tetra-*n*-Propylammonium Perruthenate (TPAP): $Pr_4N^+RuO_4^-$

- Reviews

Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.

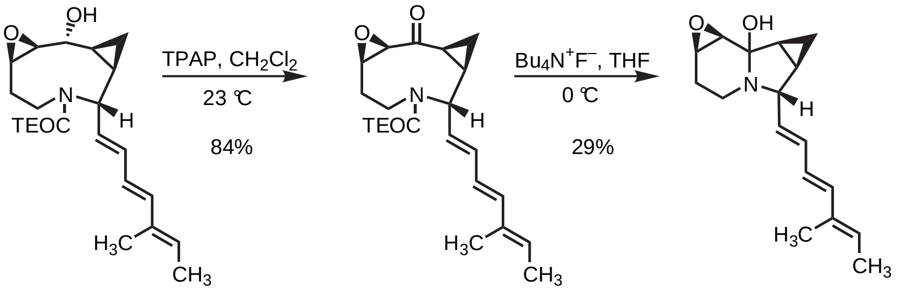
Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13-19.

- Ruthenium tetroxide (RuO_4, Ru(VIII)) and, to a lesser extent, the perruthenate ion (RuO_4^-, Ru(VII)) are powerful and rather nonselective oxidants.
- However, perruthenate salts with large organic counterions prove to be mild and selective oxidants in a variety of organic solvents.
- In conjunction with a stoichiometric oxidant such as *N*-methylmorpholine-*N*-oxide (NMO), TPAP oxidations are catalytic in ruthenium, and operate at room temperature. The reagents are relatively non-toxic and non-hazardous.
- To achieve high catalytic turnovers, the addition of powdered molecular sieves (to remove both the water of crystallization of NMO and the water formed during the reaction) is essential.
- The following oxidation state changes have been proposed to occur during the reaction:

$$\begin{aligned} \mathrm{Ru(VII)} + 2e^- &\rightarrow \mathrm{Ru(V)} \\ 2\mathrm{Ru(V)} &\rightarrow \mathrm{Ru(VI)} + \mathrm{Ru(IV)} \\ \mathrm{Ru(VI)} + 2e^- &\rightarrow \mathrm{Ru(IV)} \end{aligned}$$

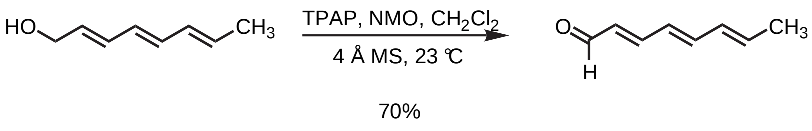
Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.

- Examples

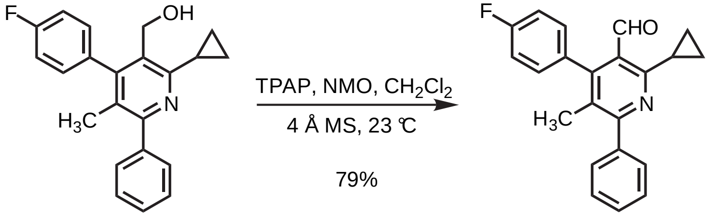


(±)-indolizomycin

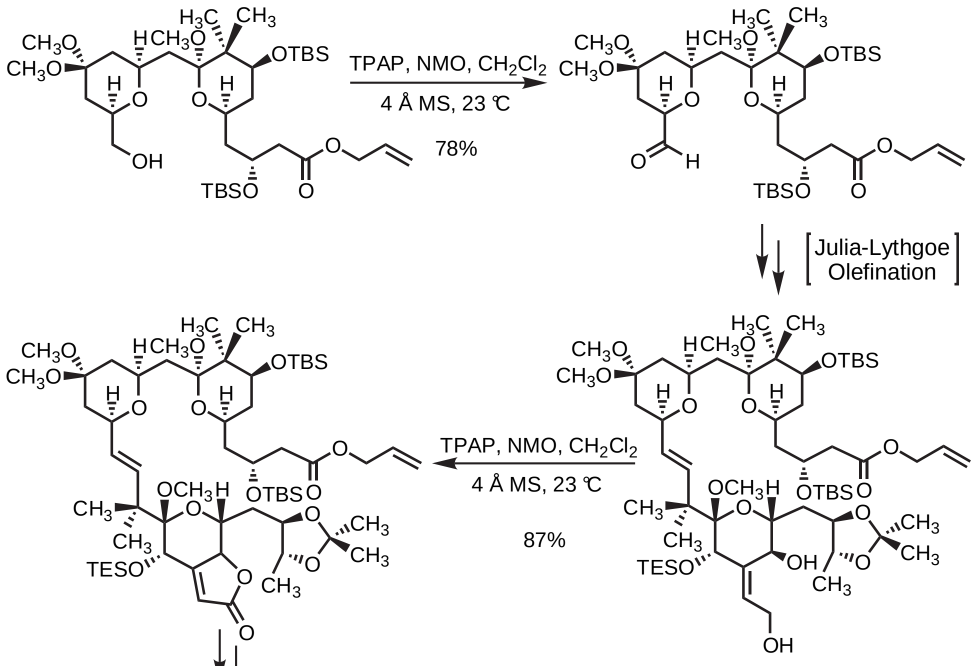
Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30-39.

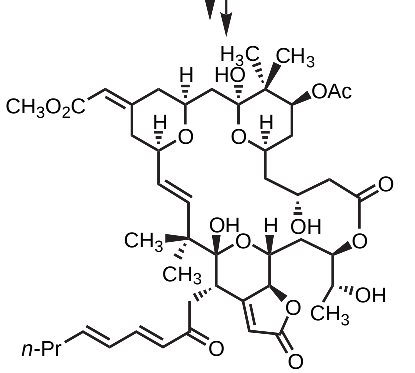


Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145-1174.



Robol, J. A.; Duncan, L. A.; Pluscec, J.; Karanewsky, D. S.; Gordon, E. M.; Ciosek, C. P.; Rich, L. C.; Dehmel, V. C.; Slusarchyk, D. A.; Harrity, T. W.; Obrien, K. A. *J. Med. Chem.* **1991**, *34*, 2804-2815.





bryostatin 3

Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2290-2294.

Mark G. Charest

***N*-Oxoammonium-Mediated Oxidation**

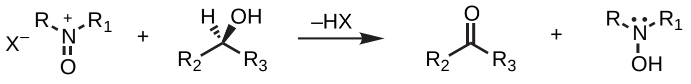
- Reviews

de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153-1174.

Bobbitt, J. M.; Flores, C. L. *Heterocycles* **1988**, *24*, 509-533.

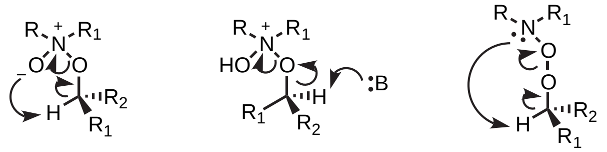
Rozantsev, E. G.; Sholle, V. D. *Synthesis* **1971**, 401-414.

- *N*-Oxoammonium salts are mild and selective oxidants for the conversion of primary and secondary alcohols to the corresponding carbonyl compounds. These oxidants are unstable and are invariably generated in situ in a catalytic cycle using a stable, stoichiometric oxidant.



N-oxoammonium salt

- Three possible transition states have been proposed:

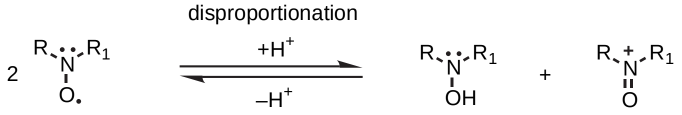


Ganem, B. *J. Org. Chem.* **1975**, *40*, 1998-2000.

Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A. *Tetrahedron Lett.* **1986**, *27*, 1119-1122.

Bobbitt, J. M.; Ma, Z. *J. Org. Chem.* **1991**, *56*, 6110-6114.

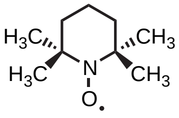
- *N*-Oxoammonium salts may be formed in situ by the acid-promoted disproportionation of nitroxyl radicals. Alternatively, oxidation of a nitroxyl radical or hydroxyl amine can generate the corresponding *N*-oxoammonium salt.



nitroxyl radical

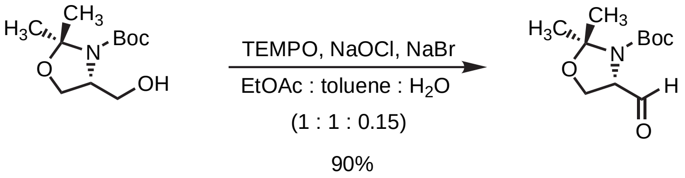
Golubev, V. A.; Sen', V. D.; Kulyk, I. V.; Aleksandrov, A. L. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1975**, 2119-2126.

- 2,2,6,6-Tetramethyl-1-piperidinyloxyl (TEMPO) catalyzes the oxidation of alcohols to aldehydes and ketones in the presence of a variety of stoichiometric oxidants, including *m*-chloroperoxybenzoic acid (*m*-CPBA), sodium hypochlorite (NaOCl), [bis(acetoxy)-iodo]benzene (BAIB), sodium bromite ($NaBrO_2$), and Oxone ($2KHSO_5•KHSO_4•K_2SO_4$).

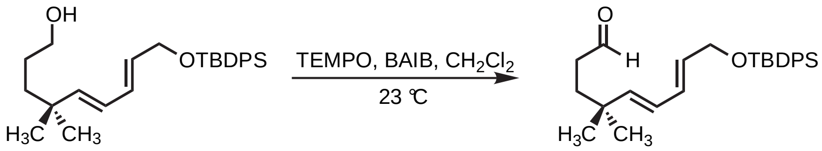


TEMPO

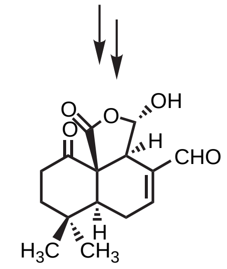
- Examples



Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gryza, H.; Prokopoxicz, P. *Tetrahedron* **1998**, *54*, 6051-6064.

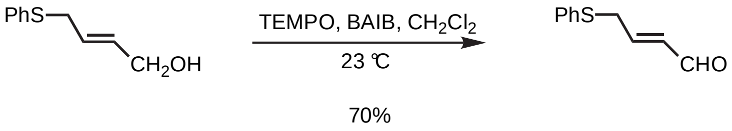


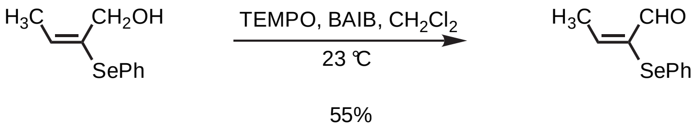
Jauch, J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2764-2765.



kuehneromycin A

- Selective oxidation of allylic alcohols in the presence of sulfur and selenium has been demonstrated.





De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974-6977.

Mark G. Charest

Manganese Dioxide: MnO_2

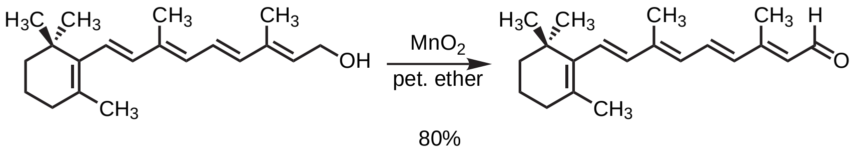
- Reviews

Cahiez, G.; Alami, M. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 231-236.

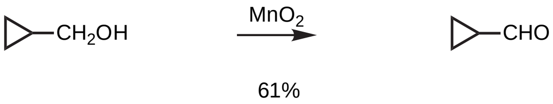
Fatiadi, A. J. *Synthesis* **1976**, 65-104.

Fatiadi, A. J. *Synthesis* **1976**, 133-167.

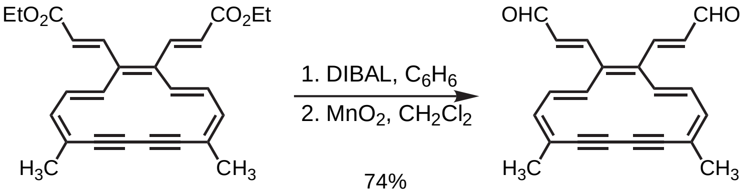
- A heterogenous suspension of active manganese dioxide in a neutral medium can selectively oxidize allylic, benzylic and other activated alcohols to the corresponding aldehyde or ketone.
- The structure and reactivity of active manganese dioxide depends on the method of preparation.
- Active manganese oxides are nonstoichiometric materials (in general MnO_x, $1.93 < x < 2$) consisting of Mn (II) and Mn (III) oxides and hydroxides, as well as hydrated MnO_2.
- Hydrogen-bond donor solvents and, to a lesser extent, polar solvents have been shown to exhibit a strong deactivating effect, perhaps due to competition with the substrate for the active MnO_2 surface.
- Examples



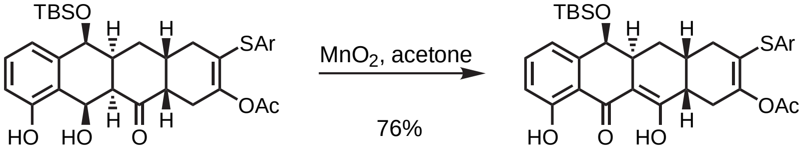
Ball, S.; Goodwin, T. W.; Morton, R. A. *Biochem. J.* **1948**, *42*, 516-523.



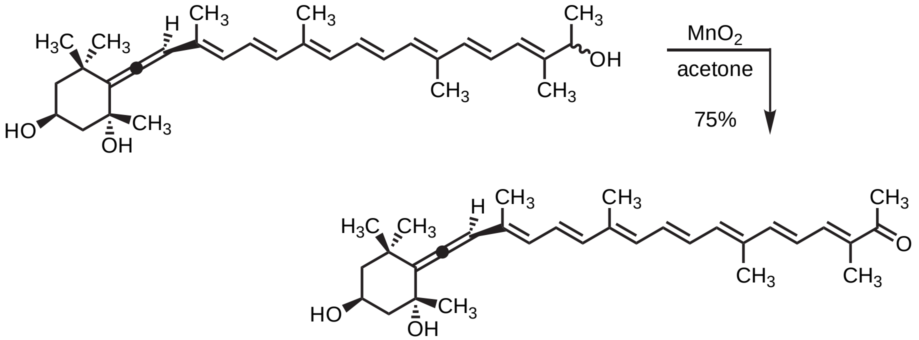
Crombie, L.; Crossley, J. *J. Chem. Soc.* **1963**, 4983-4984.



Cresp, T. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1975**, 97, 4412-4413.



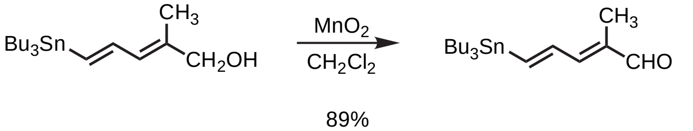
Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252-3265.



paracentrone

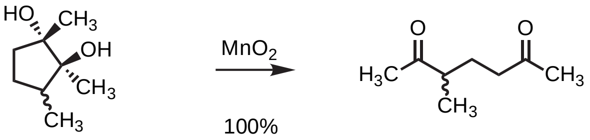
Haugan, J. A. *Tetrahedron Lett.* **1996**, *37*, 3887-3890.

- Vinyl stannanes are tolerated.



Alvarez, R.; Iglesias, B.; Lopez, S.; de Lera, A. R. *Tetrahedron Lett.* **1998**, *39*, 5659-5662.

- Syn or anti vicinal diols are cleaved by MnO_2.



Ohloff, G.; Giersch, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 401-402.

Mark G. Charest

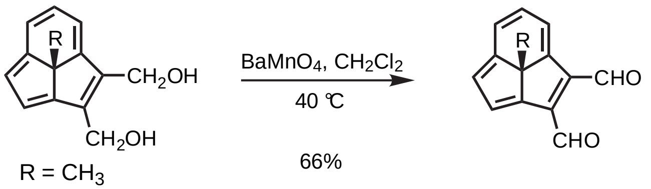
Barium Manganate: $BaMnO_4$

- Review

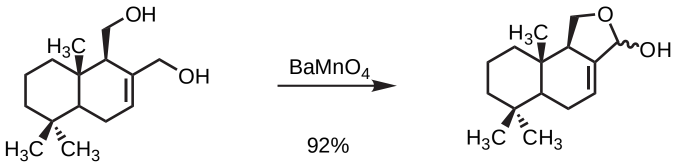
Fatiadi, A. J. *Synthesis* **1987**, 85-127.

- Barium manganate and potassium manganate are deep green salts that can be used without prior activation for the oxidation of primary and secondary allylic and benzylic alcohols.

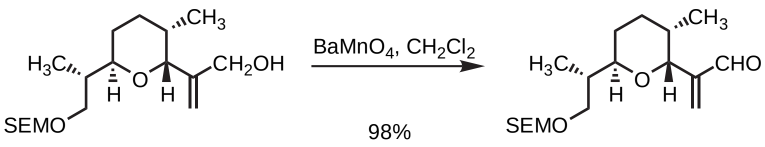
- Examples



Gilchrist, T. L.; Tuddenham, D. *J. Chem. Soc., Chem. Commun.* **1981**, 657-658.



Howell, S. C.; Ley, S. V.; Mahon, M. *J. Chem. Soc., Chem. Commun.* **1981**, 507-508.



Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332-347.

Oppenauer Oxidation

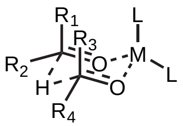
- Review

de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007-1017.

- A classic oxidation method achieved by heating the alcohol to be oxidized with a metal alkoxide in the presence of a carbonyl compound as a hydride acceptor.

- Effectively the reverse of the Meerwein-Pondorff-Verley Reduction.

- The reaction is an equilibrium process and is believed to proceed through a cyclic transition state. The use of easily reduced carbonyl compounds, such as quinone, helps drive the reaction in the desired direction.

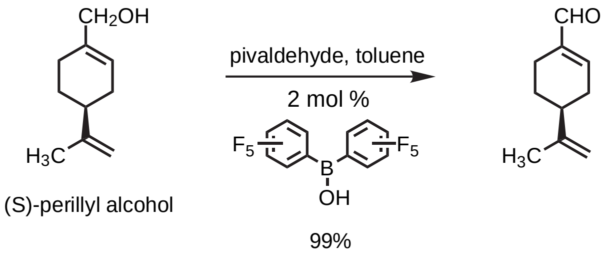


Proposed Transition State

Djerassi, C. *Org. React.* **1951**, *6*, 207.

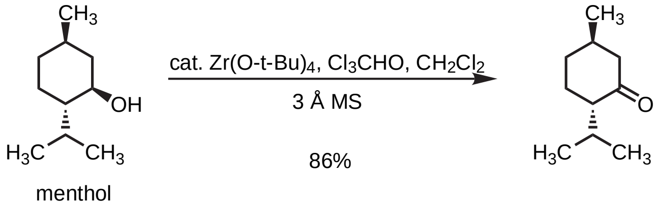
Oppenauer, R. V. *Rec. Trav. Chim. Pays-Bas* **1937**, *56*, 137-144.

- Examples



Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5664-5665.

- Highly reactive zirconium alkoxide catalysts undergo rapid ligand exchange and can be used in substoichiometric quantities.



Krohn, K.; Knauer, B.; Kupke, J.; Seebach, D.; Beck, A. K.; Hayakawa, M. *Synthesis* **1996**, 1341-1344.

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Chromium (VI) Oxidants

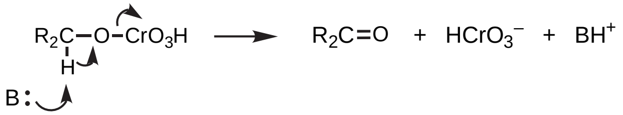
- Reviews

Ley, S. V.; Madin, A. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 251-289.

Luzzio, F. A. *Organic Reactions* **1998**, *53*, 1-122.

- The mechanism of chromic acid-mediated oxidation has been extensively studied and is commonly used as a model for other chromium-mediated oxidations.

$$R_2CHOH + HCrO_4^- + H^+ \longrightarrow R_2CHOCrO_3H + H_2O$$



Holloway, F.; Cohen, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1951**, *73*, 65-68.

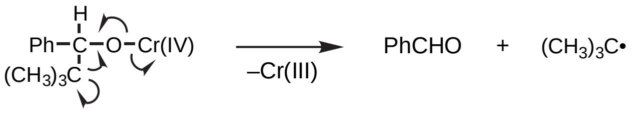
- A competing pathway involving free-radical intermediates has been identified.

$$R_2CHOH + Cr(IV) \longrightarrow R_2\dot{C}OH + Cr(III) + H^+$$
$$R_2\dot{C}OH + Cr(VI) \longrightarrow R_2C{=}O + Cr(V) + H^+$$
$$R_2CHOH + Cr(V) \longrightarrow R_2C{=}O + Cr(III) + 2H^+$$

Wiberg, K. B.; Mukherjee, S. K. *J. Am. Chem. Soc.* **1973**, *96*, 1884-1888.

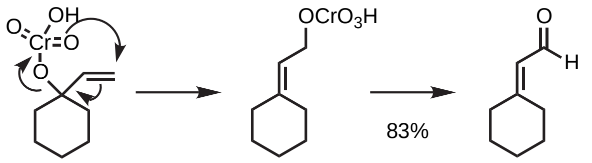
Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1973**, *96*, 1889-1892.

- Fragmentation has been observed with substrates that can form stabilized radicals.



Doyle, M.; Swedo, R. J.; Rocek, J. *J. Am. Chem. Soc.* **1973**, *95*, 8352-8357.

- Tertiary allylic alcohols are known to undergo oxidative transposition.



Collins Reagent: CrO_3•pyr_2

- CrO_3•pyr_2 is a hygroscopic red solid which is easily hydrolyzed to the yellow dipyridinium dichromate ($[Cr_2O_7]^{-2}(pyrH^+)_2$).

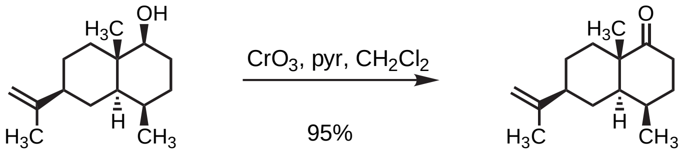
- Typically, 6 equiv of oxidant in a chlorinated solvent leads to rapid and clean oxidation of alcohols.

- Caution: Collins reagent should be prepared by the portionwise addition of solid CrO_3 to pyridine. Addition of pyridine to solid CrO_3 can lead to a violent reaction.

Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *30*, 3363-3366.

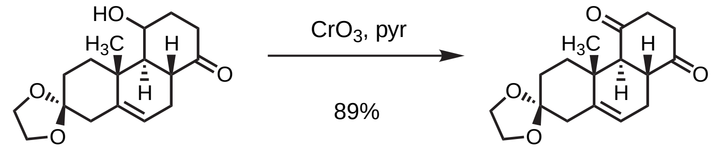
Collins, J. C.; Hess, W. W.; *Org. Synth.* **1972**, *52*, 5-9.

- In situ preparation of the reagent circumvents the difficulty and danger of preparing the pure complex.

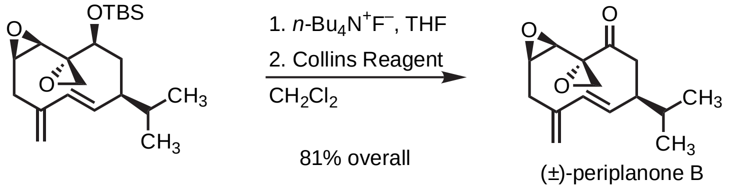


Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4003.

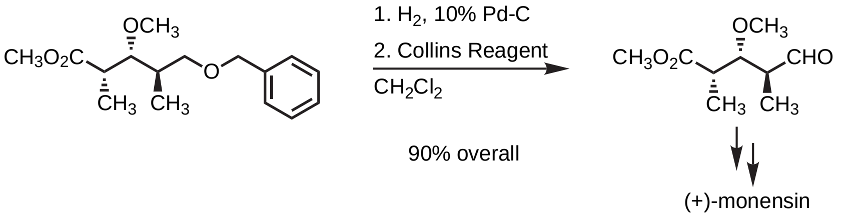
- Examples



Poos, G. I.; Arth, G. E.; Beyler, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 422-428.



Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493-2495.



Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117-2120.

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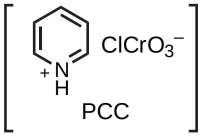
Pyridinium Chlorochromate (PCC, Corey's Reagent)



- PCC is an air-stable yellow solid which is not very hygroscopic.

- Typically, alcohols are oxidized rapidly and cleanly by 1.5 equivalents of PCC as a solution in *N*,*N*-dimethylformamide (DMF) or a suspension in chlorinated solvents.

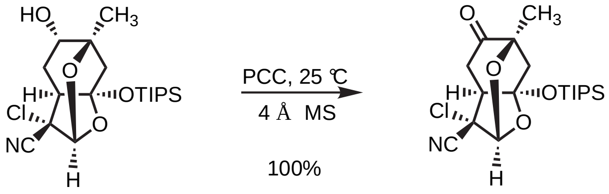
- The slightly acidic character of the reagent can be moderated by buffering the reaction mixture with powdered sodium acetate.

Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *26*, 2647-2650.

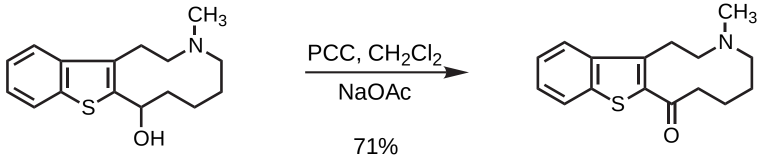
- Addition of molecular sieves can accelerate the rate of reaction.

Antonakis, K.; Egron, M. J.; Herscovici, J. *J. Chem. Soc., Perkin Trans. I* **1982**, 1967-1973.

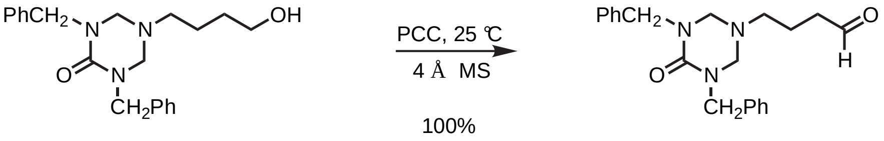
- Examples



Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871-8872.



Browne, E. J. *Aust. J. Chem.* **1985**, *38*, 756-776.



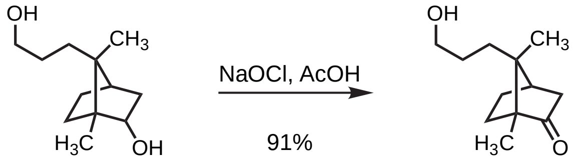
Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109-2112.

Sodium Hypochlorite: NaOCl

- Sodium hypochlorite in acetic acid solution selectively oxidizes secondary alcohols to ketones in the presence of primary alcohols.

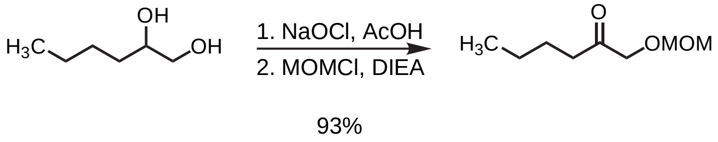
- A modified procedure employs calcium hypochlorite, a stable and easily handled solid hypochlorite oxidant.

- Examples

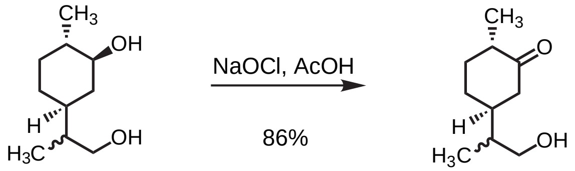


Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647-4650.

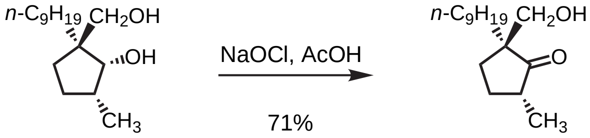
Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 35-38.



Kende, A. S.; Smalley, T. L., Jr.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431-7432.



Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777-12782.



Winter, E.; Hoppe, D. *Tetrahedron* **1998**, *54*, 10329-10338.

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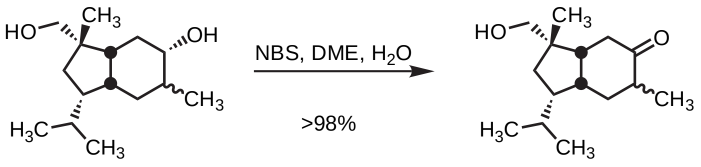
Selective Oxidations Using *N*-Bromosuccinimide (NBS) or Bromine

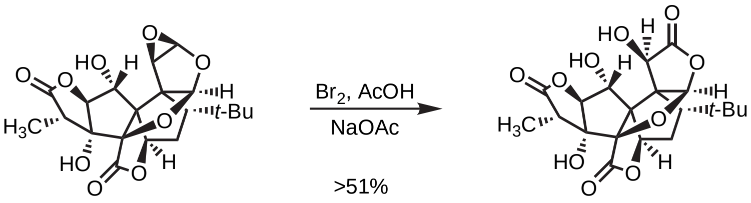
- NBS in aqueous dimethoxyethane selectively oxidizes secondary alcohols in the presence of primary alcohols.

- Examples



Corey, E. J.; Ishiguro, M. *Tetrahedron Lett.* **1979**, *20*, 2745-2748.

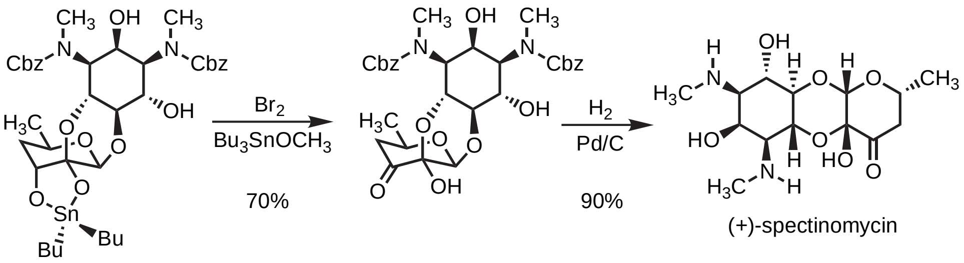
- Bromine has been employed for the selective oxidation of activated alcohols. In the following example, a lactol is oxidized selectively in the presence of two secondary alcohols.



(±)-ginkgolide B

Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453-8463.

- Stannylene acetals are oxidized in preference to alcohols in the presence of bromine.



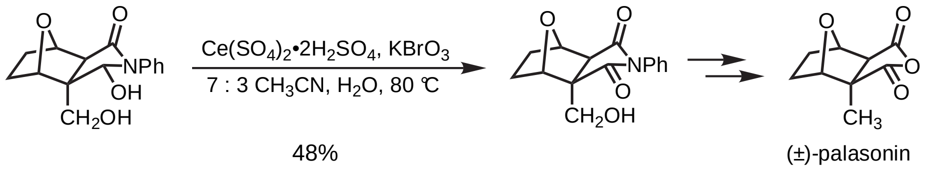
Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, *101*, 5839-5841.

Selective Oxidations using Other Methods

- Cerium (IV) complexes catalyze the selective oxidation of secondary alcohols in the presence of primary alcohols and a stoichiometric oxidant such as sodium bromate ($NaBrO_3$).

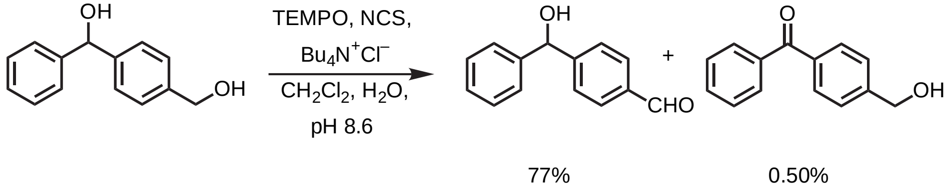
Tomioka, H.; Oshima, K.; Noxaki, H. *Tetrahedron Lett.* **1982**, *23*, 539-542.

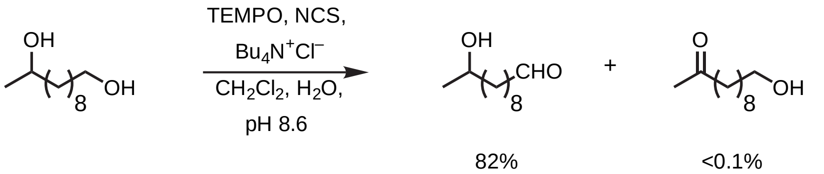
- In the following example, catalytic tetrahydrogen cerium (IV) tetrakissulfate and stoichiometric potassium bromate in aqueous acetonitrile was found to selectively oxidize the secondary alcohol in the substrate whereas NaOCl with acetic acid and NBS failed to give the desired imide.



Rydberg, D. B.; Meinwald, J. *Tetrahedron Lett.* **1996**, *37*, 1129-1132.

- TEMPO catalyzes the selective oxidation of primary alcohols to aldehydes in a biphasic mixture of dichloromethane and aqueous buffer (pH = 8.6) in the presence of *N*-chlorosuccinimide (NCS) as a stoichiometric oxidant and tetrabutylammonium chloride ($Bu_4N^+Cl^–$).





Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452-7454.

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Aldehyde → Acid

Sodium Chlorite: $NaClO_2$

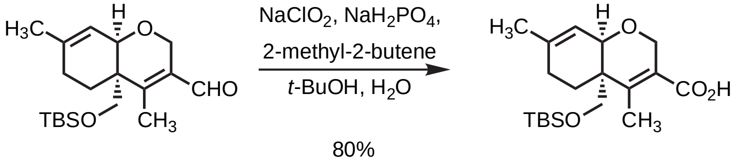
- Sodium chlorite is a mild, inexpensive, and selective reagent for the oxidation of aldehydes to the corresponding carboxylic acids under ambient reaction conditions.

- 2-methyl-2-butene is often incorporated as an additive and has been proposed to function as a scavenger of any electrophilic chlorine species generated in the reaction.

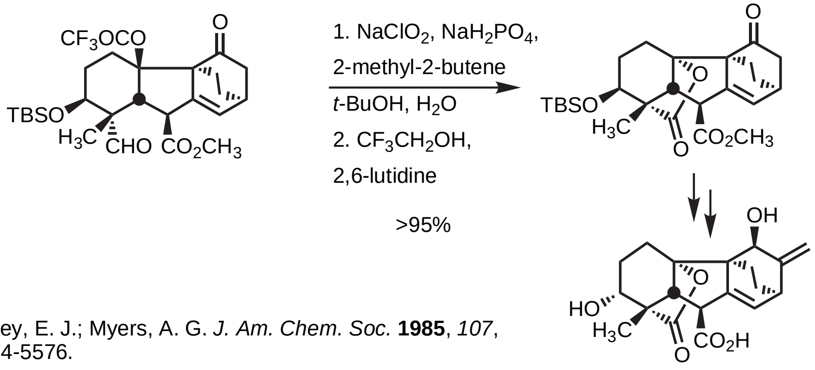
Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888-890.

Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825-4830.

- Examples

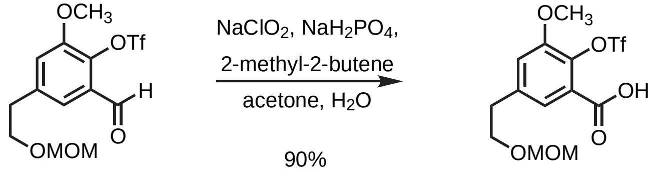


Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825-4830.

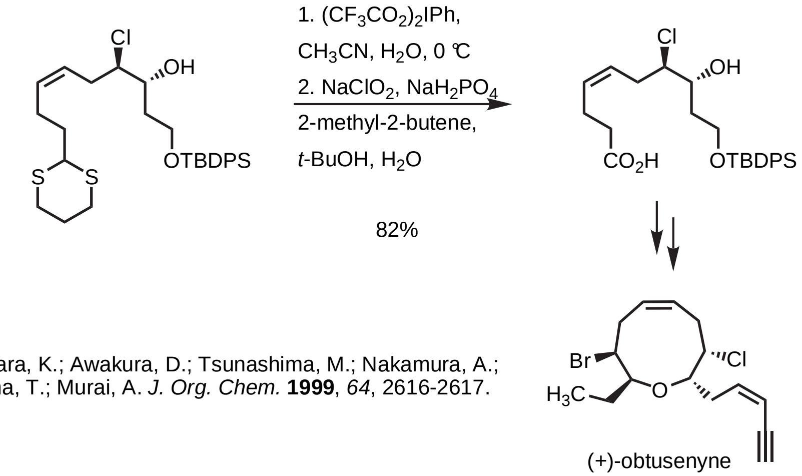


(±)-antheridic acid

Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574-5576.



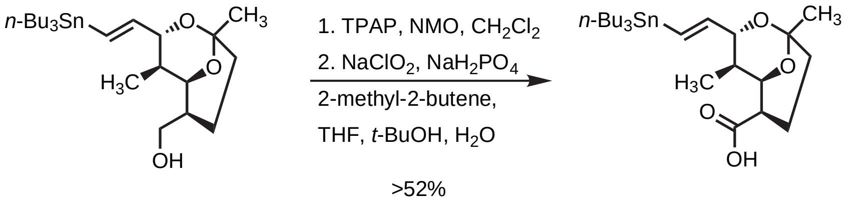
Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004-1015.



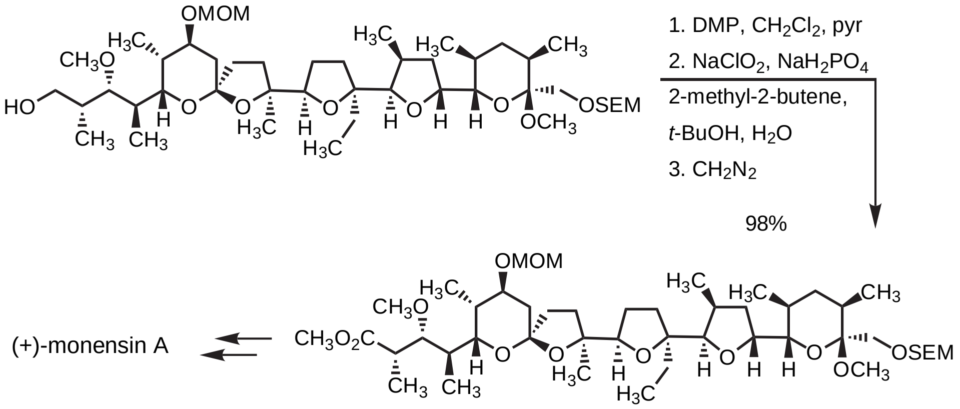
Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616-2617.

(+)-obtusenyne

- The two-step oxidation of an alcohol to the corresponding carboxylic acid is most common.



Nicolaou, K. C.; Ohshima, T.; Murphy, F.; Barluenga, S.; Xu, J.; Winssinger, N. *J. Chem. Soc., Chem. Commun.* **1999**, 809-810.



Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166-7172.

Potassium Permanganate: $KMnO_4$

- Review

Fatiadi, A. J. *Synthesis* **1987**, 85-127.

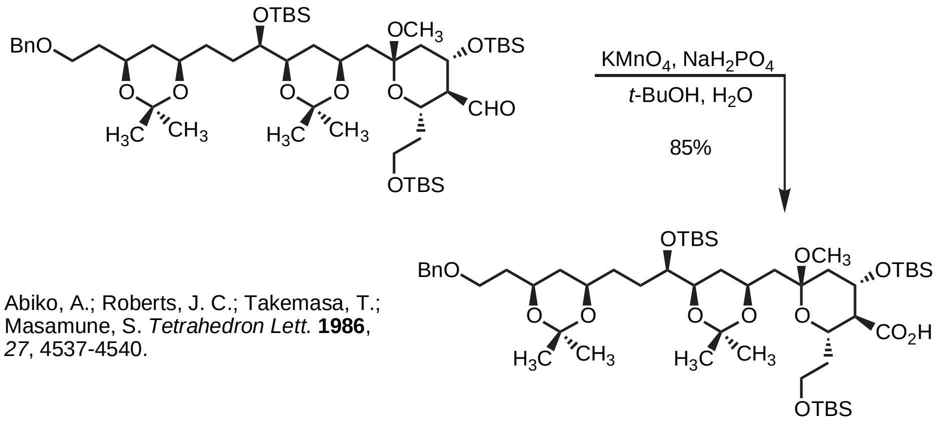
- Potassium permanganate is a mild reagent for the oxidation of aldehydes to the corresponding carboxylic acids over a relatively large pH range. Alcohols, alkenes, and other functional groups are also oxidized by potassium permanganate.

- Oxidation occurs through a coordinated permanganate intermediate by hydrogen atom-abstraction or hydride transfer.

Freeman, F.; Lin, D. K.; Moore, G. R. *J. Org. Chem.* **1982**, *47*, 56-59.

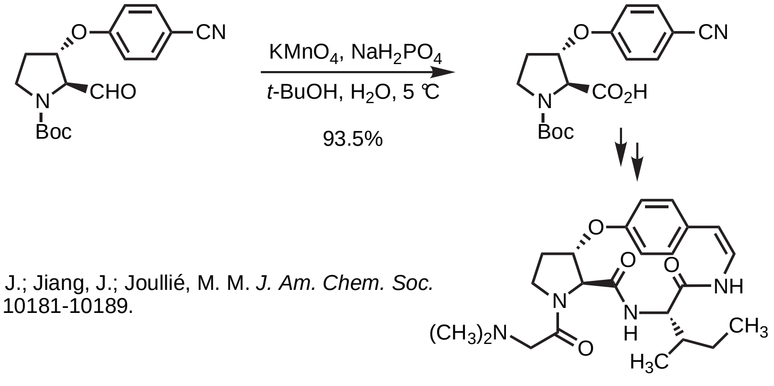
Rankin, K. N.; Liu, Q.; Henrdy, J.; Yee, H.; Noureldin, N. A.; Lee, D. G. *Tetrahedron Lett.* **1998**, *39*, 1095-1098.

- Potassium permanganate in the presence of *tert*-butyl alcohol and aqueous NaH_2PO_4 was shown to effectively oxidize the aldehyde in the following polyoxygenated substrate to the corresponding carboxylic acid whereas Jones reagent, $RuCl_3(H_2O)_n$-$NaIO_4$, and silver oxide failed.



Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537-4540.

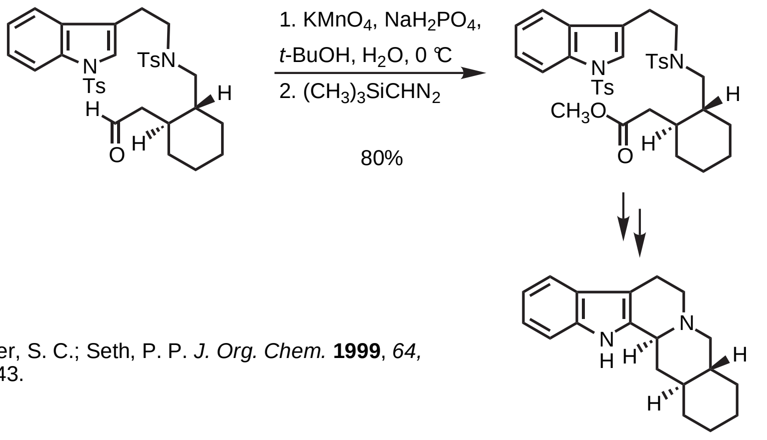
- Examples



(–)-nummularine F

Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114,* 10181-10189.

- In the following example, a number of other oxidants (including Jones reagent, NaOCl, and RuO_2) failed.



Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.* **1999**, *64,* 3237-3243.

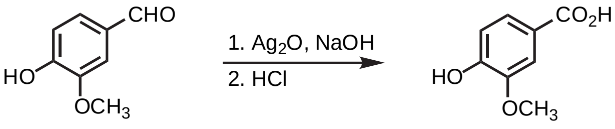
(–)-yohimbane

Silver Oxide: Ag_2O

- A classic method used to oxidize aldehydes to carboxylic acids.

- Cis/trans isomerization can be a problem with unsaturated systems under the strongly basic reaction conditions employed.

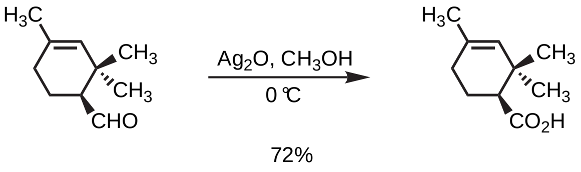
- Examples



90-97%

vanillic acid

Pearl, I. A. *Org. Synth. IV* **1963**, 972-978.



Sonawane, H. R.; Sudrik, S. G.; Jakkam, M. M.; Ramani, A.; Chanda, B. *Synlett.* **1996**, 175-176.

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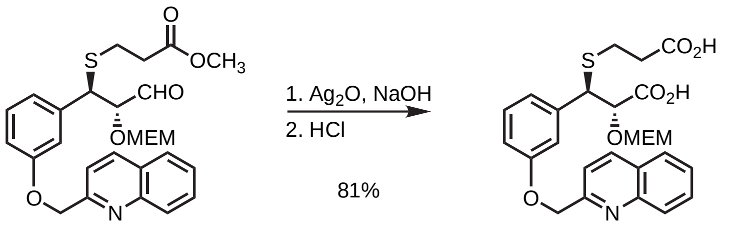
- In the following example, all chromium-based oxidants failed to give the desired acid.



Ovaska, T. V.; Voynov, G. H.; McNeil, N.; Hokkanen, J. A. *Chem. Lett.* **1997**, 15-16.

Pyridinium Dichromate: $(pyrH^+)_2Cr_2O_7$

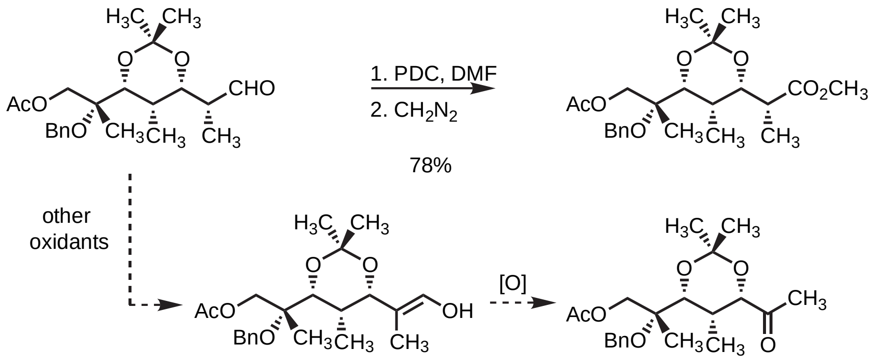
- Review

Ley, S. V.; Madin, A. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 251-289.

- PDC is a stable, bright orange solid prepared by dissolving CrO_3 in a minimun volume of water, adding pyridine and collecting the precipitated product.
- Non-conjugated aldehydes are readily oxidized to the corresponding carboxylic acids in good yields in DMF as solvent.
- Primary alcohols are oxidized to the corresponding carboxylic acids in good yields.

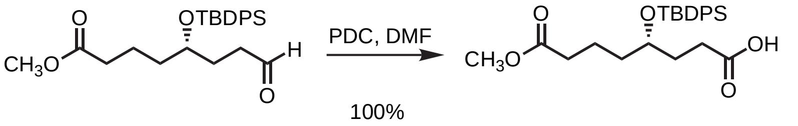
Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399-402.

- In the following example, PDC was found to be effective while many other reagents led to oxidative C-C bond cleavage.



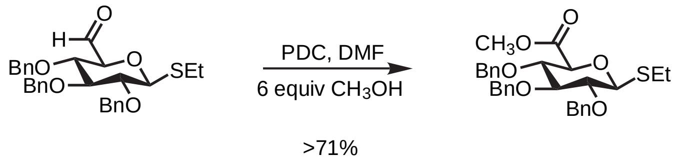
Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095-2105.

- Additional Examples



Mazur, P.; Nakanishi, K. *J. Org. Chem.* **1992**, *57*, 1047-1051.

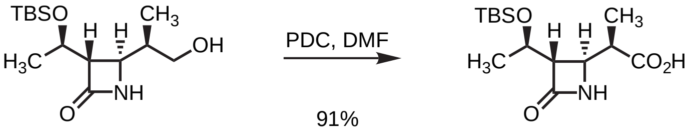
- PDC can oxidize aldehydes to the corresponding methyl esters in the presence of methanol. It appears that in certain cases, the oxidation of methanol by PDC is slow in comparison to the oxidation of the methyl hemiacetal.
- Attempts to form the ethyl and isopropyl esters were less successful.
- Note that in the following example sulfide oxidation did not occur.



O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235-3236.

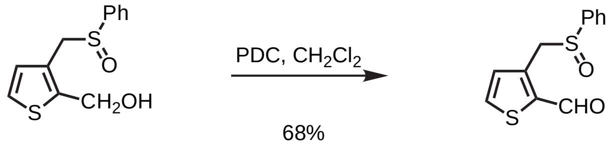
Garegg, P. J.; Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200-2204.

- PDC has also been used to oxidize alcohols to the corresponding carboxylic acids.



Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron* **1988**, *44*, 2149-2165.

- However, a suspension of PDC in dichloromethane oxidizes alcohols to the corresponding aldehyde.

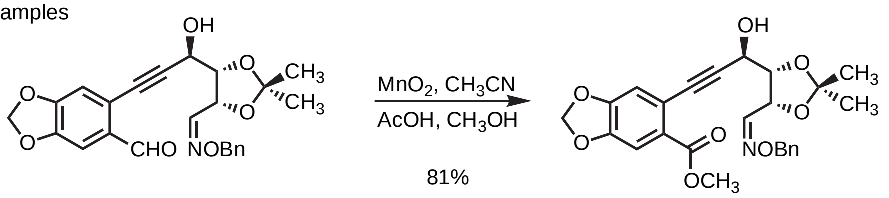


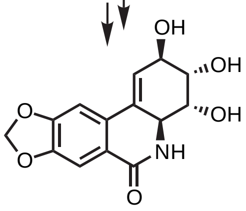
Terpstra, J. W.; van Leusen, A. M. *J. Org. Chem.* **1986**, *51*, 230-238.

Aldehyde → Ester

Corey-Gilman-Ganem Oxidation

- A convenient method to convert unsaturated aldehydes directly to the corresponding methyl esters.
- Cis/trans isomerization, a problem when other reagents such as basic silver oxide are employed, is avoided.
- The aldehyde substrate is initially transformed into a cyanohydrin intermediate. Subsequent oxidation of the cyanohydrin furnishes an acyl cyanide which is then trapped with methanol to give the desired methyl ester.
- Conjugate addition of cyanide ion can be problematic.
- Examples

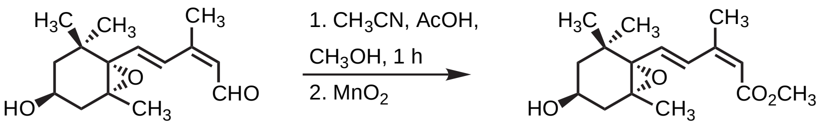




(–)-lycoricidine

Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121,* 5176-5190.

- In the following example, stepwise addition of reagents proved to be essential to achieve high yields.



97%

(2Z, 4E)-xanthoxin

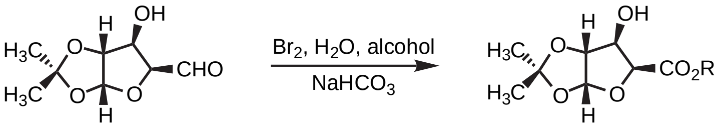
Yamamoto, H.; Oritani, T. *Tetrahedron Lett.* **1995**, *36,* 5797-5800.

Bromine

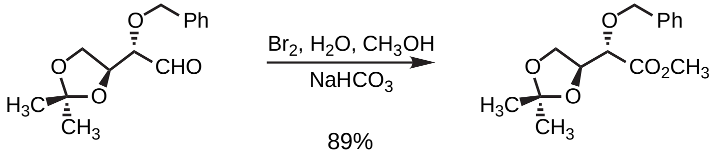
- Review

Palou, J. *Chem. Soc. Rev.* **1994**, 357-361.

- Bromine in alcoholic solvents is a convenient and inexpensive method for the direct conversion of aldehydes into ester derivatives.
- Under the reaction conditions employed, secondary alcohols are not oxidized to the corresponding ketones.
- Oxidation of a hemiacetal intermediate is proposed.
- Olefins, benzylidine acetals and thioketals are incompatiable with the reaction conditions.
- A variety of esters can be prepared.
- Examples



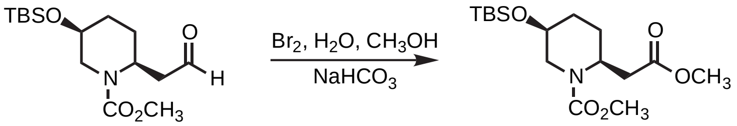
R = Me, 94%
R = Et, 91%
R = *i*-Pr, 80%



89%

Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29,* 5087-5090.

Lichtenthaler, F. W.; Jargils, P.; Lorenz, K. *Synthesis* **1988**, 790-792.



78%

Herdeis, C.; Held, W. A.; Kirfel, A.; Schwabenländer, F. *Tetrahedron* **1996**, *52,* 6409-6420.

Mark G. Charest

Ketone → Ester

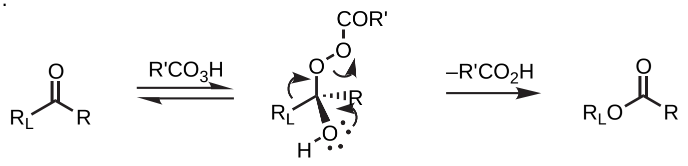
Bayer-Villiger Oxidation

- Reviews

Krow, G. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 671-688.

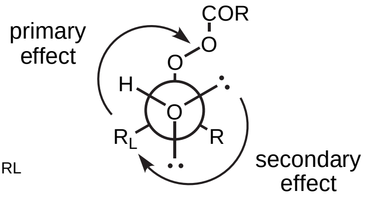
Krow, G. R. In *Organic Reactions*, Paquette, L. A., Ed., John Wiley and Sons: New York, **1993**, *Vol.* 43, p. 251-296.

- A classic method for the oxidative conversion of ketones into the corresponding esters or lactones by oxygen insertion into an acyl C-C bond.
- The migratory preference of alkyl groups has been suggested to reflect their electron-releasing ability and steric bulk.
- Typically, the order of migratory preference is tertiary > secondary > allyl > primary > methyl.
- The reactivity order of Bayer-Villiger oxidants parallels the acidity of the corresponding carboxylic acid (or alcohol): CF_3CO_3H > *p*-nitroperbenzoic acid > *m*-CPBA = HCO_3H > CH_3CO_3H > HOOH > *t*-BuOOH.



R_L = Large Group   Criegee Intermediate

- Primary and secondary stereoelectronic effects in the Bayer-Villiger reaction have been demonstrated.

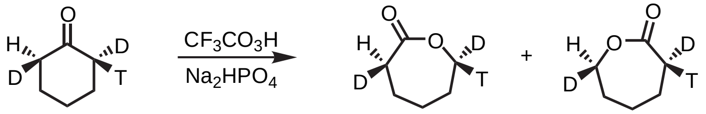


- Primary effect: antiperiplanar alignment of R_L and $\sigma_{O\text{-}O}$
- Secondary effect: antiperiplanar alignment of O_{lp} and $\sigma^*_{C\text{-}RL}$

Proposed TS‡

Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2852-2855.

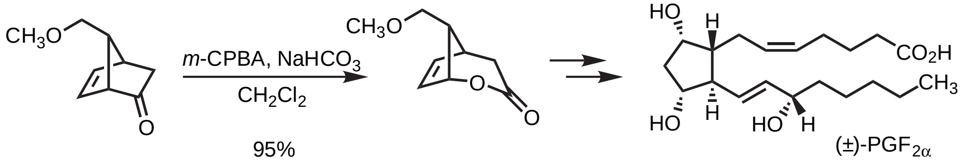
- The Bayer-Villiger reaction occurs with retention of stereochemistry at the migrating center.



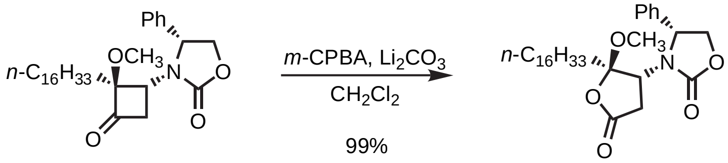
Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 878-882.

Gallagher, T. F.; Kritchevsky, T. H. *J. Am. Chem. Soc.* **1950**, *72*, 882-885.

- Examples

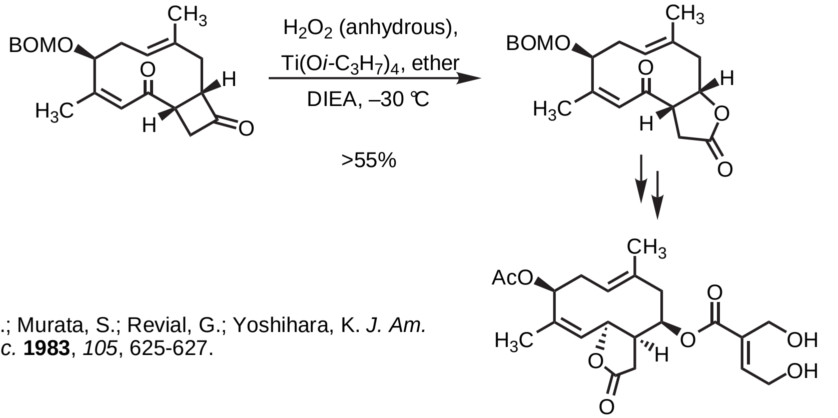


Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677.



Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779-6785.

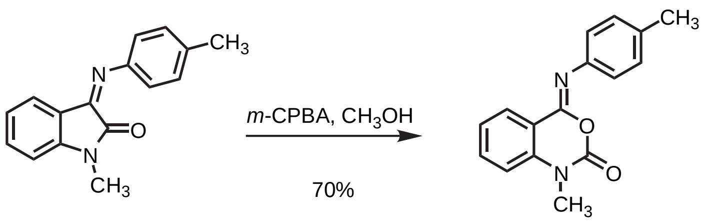
- Selective Bayer-Villiger oxidation in the presence of unsaturated ketones and isolated olefins has been achieved.



eucannabinolide

Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625-627.

- Carbamates have been prepared in some cases.



Azizian, J.; Mehrdad, M.; Jadid, K.; Sarrafi, Y. *Tetrahedron Lett.* **2000**, *41*, 5265-5268.

Alcohol → Acid

Ruthenium Tetroxide: RuO_4

- RuO_4 is used to oxidize alcohols to the corresponding carboxylic acid. It is a powerful oxidant that also attacks aromatic rings, olefins, diols, ethers, and many other functional groups.

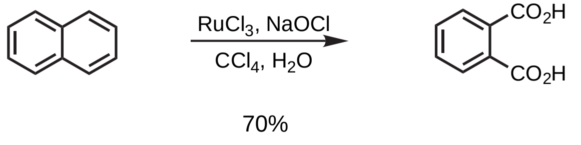
- Catalytic procedures employ 1-5% of ruthenium metal and a stoichiometric oxidant, such as sodium periodate ($NaIO_4$).

- Sharpless has introduced the use of acetonitrile as solvent to improve catalyst turnover. It is proposed to avoid the formation of insoluble Ru-carboxylate complexes and return the metal to the catalytic cycle.

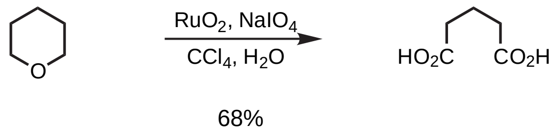
Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838-3840.

Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.

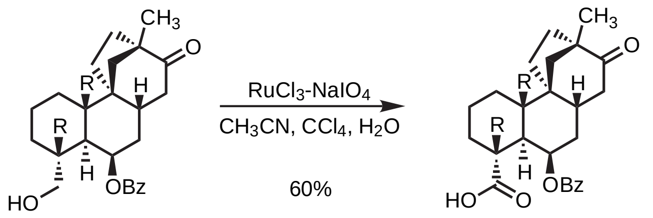
- Examples



Sptzer, U. A.; Lee, D. G. *J. Org. Chem.* **1974**, *39*, 2468-2469.



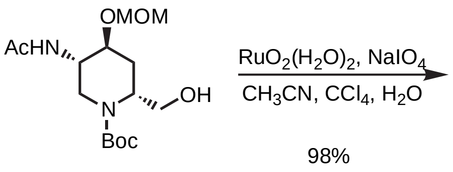
Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *10*, 205-211.



R = CH_3

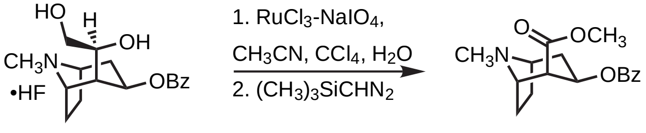
(±)-scopadulcic acid B

Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031-12040.



Clinch, K.; Vasella, A.; Schauer, R. *Tetrahedron Lett.* **1987**, *28*, 6425-6428.

- In the following example, sodium periodate cleaves the 1,2-diol to an aldehyde, which is further oxidized to the corresponding carboxylic acid by RuO_4. The amine is protonated and thereby protected from oxidation.



78% overall

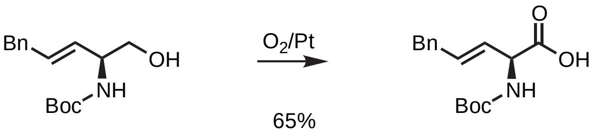
(*S*)-(+)-cocaine

Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773-4775.

Molecular Oxygen

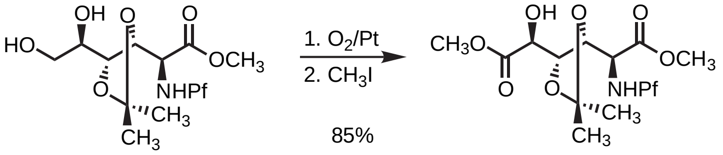
- Molecular oxygen in the presence of a platinum catalyst is a classic method for the oxidation of primary alcohols to the corresponding carboxylic acids.

- Examples



Mehmandoust, M.; Petit, Y.; Larcheveque, M. *Tetrahedron Lett.* **1992**, *33*, 4313-4316.

- Primary alcohols are oxidized selectively in the presence of secondary alcohols.

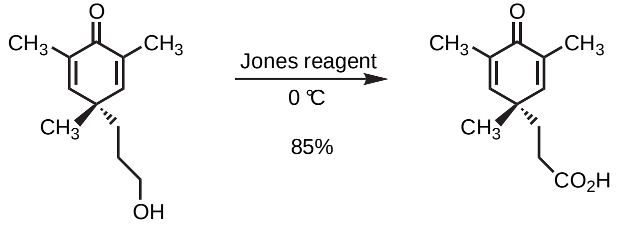


Pf = 9-phenylfluorenyl

Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394-399.

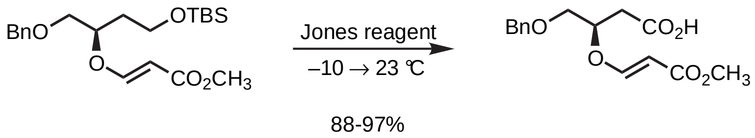
Jones Oxidation

- Jones reagent is a standard solution of chromic acid in aqueous sulfuric acid.
- Acetone is often benefical as a solvent and may function by reacting with any excess oxidant.
- Isolated olefins usually do not react, but some olefin isomerization may occur with unsaturated carbonyl compounds.
- 1,2-diols and α-hydroxy ketones are susceptible to cleavage under the reaction conditions.
- Examples



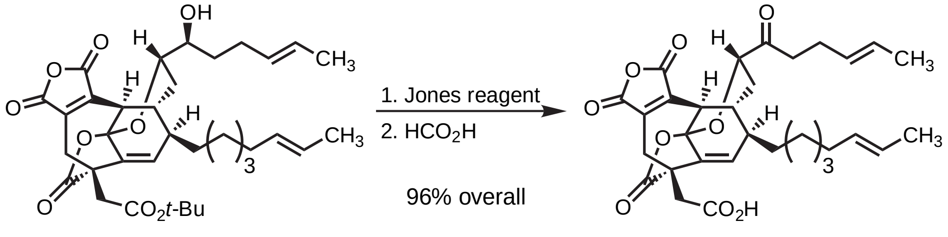
Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Flack, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618-4620.

- Silyl ethers can be cleaved under the acidic conditions of the Jones oxidation.



Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3175-3177.

- Ketones have been prepared efficiently by oxidation of the corresponding secondary alcohol.

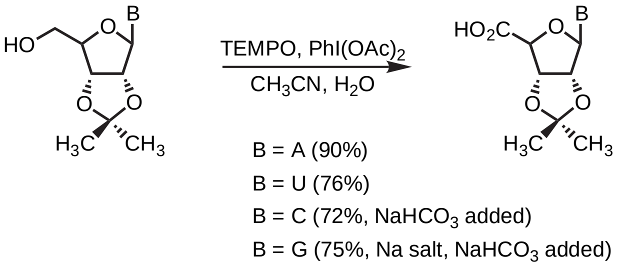


(–)-CP-263,114

Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825-7826.

N-Oxoammonium-Mediated Oxidation of Alcohols to Carboxylic Acids

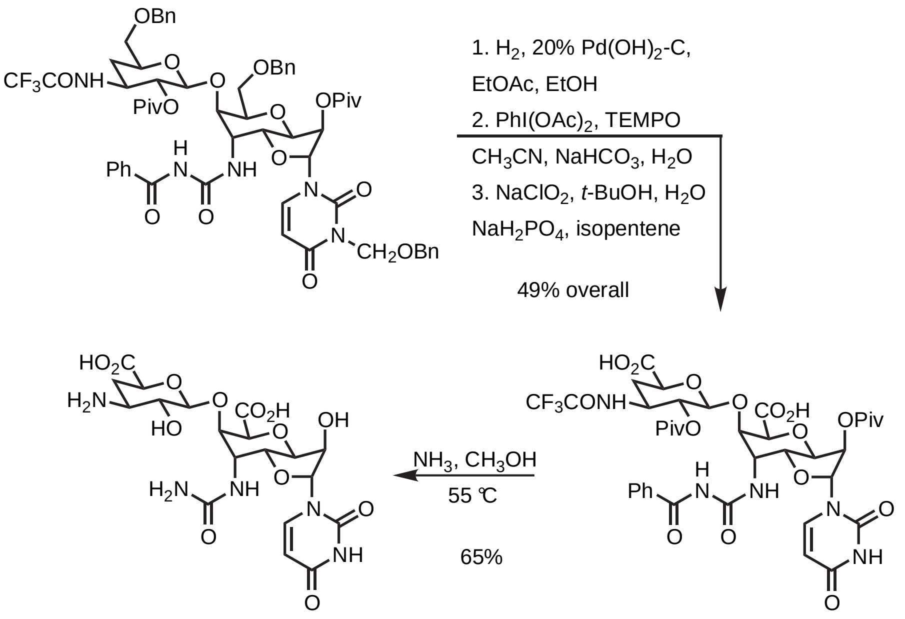
- A general method for the preparation of nucleoside 5'-carboxylates:



B = A (90%)
B = U (76%)
B = C (72%, NaHCO$_3$ added)
B = G (75%, Na salt, NaHCO$_3$ added)

Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293-295.

- A brief follow-up treatment with sodium chlorite was necessary to obtain complete oxidation to the bis-carboxylic acid in the following example.



4-desamino-4-oxo-ezomycin A$_2$

Knapp, S. K.; Gore, V. K. *Org. Lett.* **2000**, *2*, 1391-1393.

Mark G. Charest

Ketone → α-Hydroxy Ketone

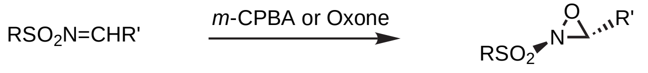
Davis Oxaziridine

- Reviews

Davis, F. A.; Chen, B. *Chem. Rev.* **1992**, *92*, 919-934.

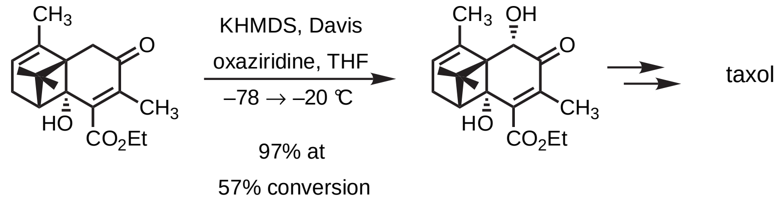
Jones, A. B. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 151-191.

- *N*-Sulfonyloxaziridines are prepared by the biphasic oxidation of the corresponding sulfonimine with *m*-CPBA or Oxone.

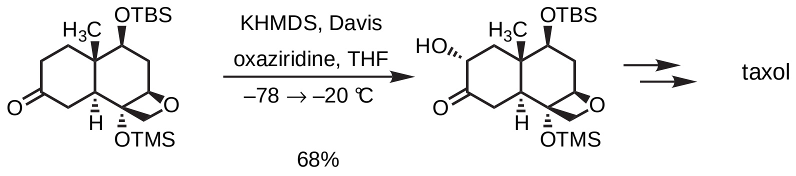


Davis oxaziridine: R = R' = Ph

- Nucleophilic attack by enolates on the electrophilic oxaziridine oxygen furnishes α-hydroxy ketones.
- Potassium enolates are generally the most successful.
- Examples

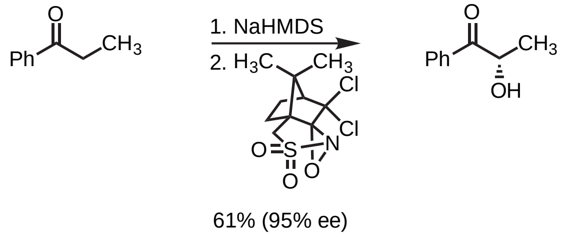


Wender, P. A.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758.

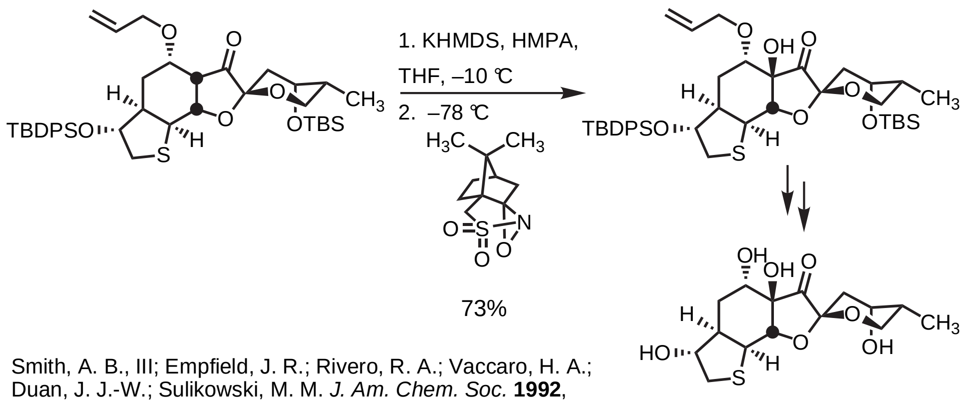


Grandi, M. J. D.; Coburn, C. A.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58* 7728-7731.

- Enantioselective hydroxylation of prochiral ketones has been demonstrated.

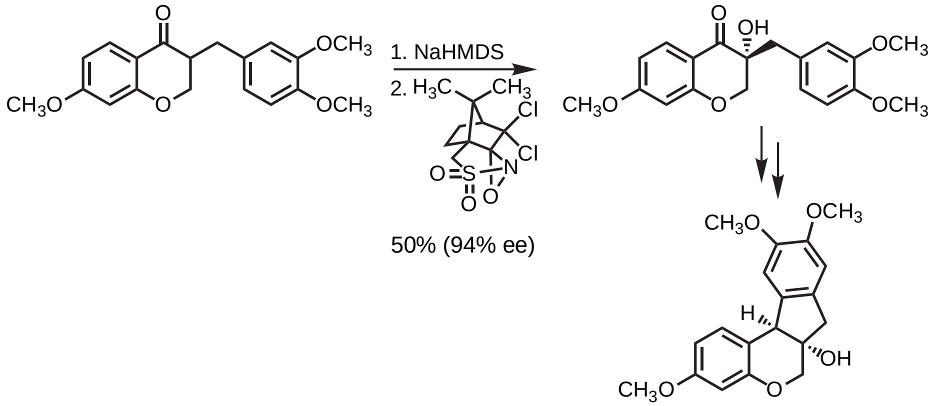


Davis, F. A.; Chen, B. *Chem. Rev.* **1992**, *92*, 919-934.



(±)-breynolide

Smith, A. B., III; Empfield, J. R.; Rivero, R. A.; Vaccaro, H. A.; Duan, J. J.-W.; Sulikowski, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 9419-9434.

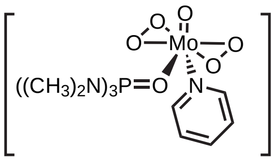


Davis, F. A.; Chen, B. *J. Org. Chem.* **1993**, *58*, 1751-1753.

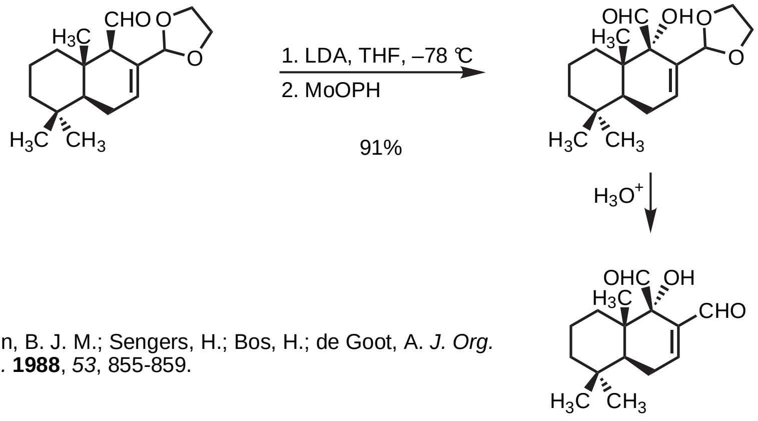
(+)-*O*-trimethylbrazilin

Mark G. Charest

Molybdenum peroxy compounds: MoO_5•pyr•HMPA

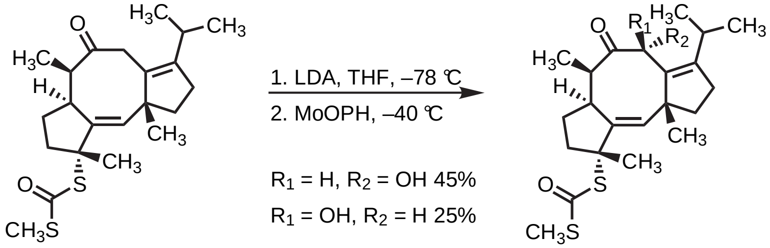


- Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) is commonly used to oxidize enolates to the corresponding hydroxylated compound.
- It is proposed that nucleophilic attack of the enolate occurs at a peroxyl oxygen atom, leading to O-O bond cleavage.
- β-Dicarbonyl compounds are not hydroxylated.
- Examples



(±)-warburganal

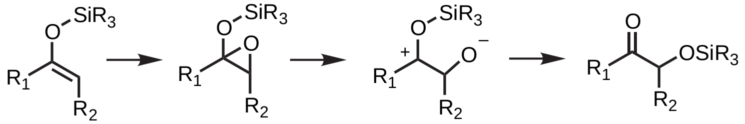
Jansen, B. J. M.; Sengers, H.; Bos, H.; de Goot, A. *J. Org. Chem.* **1988**, *53*, 855-859.



Kato, N.; Okamoto, H.; Arita, H.; Imaoka, T.; Miyagawa, H.; Takeshita, H. *Synlett.* **1994**, 337-339.

Rubottom Oxidation

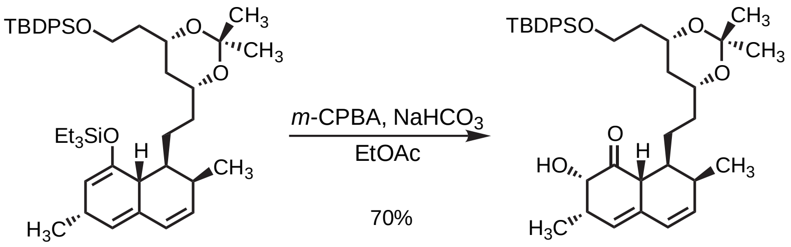
- Epoxidation of a silyl enol ether and subsequent silyl migration furnishes α-hydroxylated ketones.
- Silyl migration via an oxacarbenium ion has been postulated.



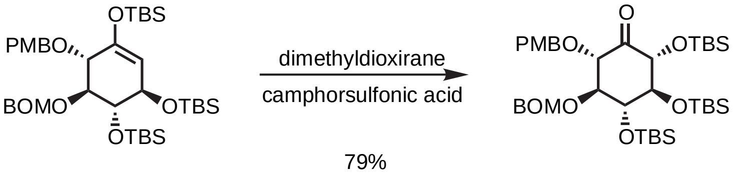
Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319-4322.

Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19-C21.

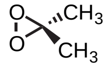
Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427-3429.



Clive, D. L. J.; Zhang, C. *J. Org. Chem.* **1995**, *60*, 1413-1427.



dimethyldioxirane =



Reddy, K. K.; Saady, M.; Falck, J. R. *J. Org. Chem.* **1995**, *60*, 3385-3390.

Mark G. Charest

Diol → Lactone

- Review

Procter, G. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 312-318.

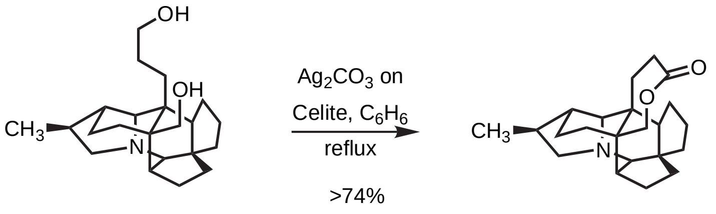
Fetizon's Reagent

- Silver carbonate absorbed on Celite has been found to selectively oxidize primary diols to lactones.

Fetizon, M.; Golfier, M.; Louis, J.-M. *J. Chem. Soc., Chem. Commun.* **1969**, 1102-1118.

Fetizon, M.; Golfier, M.; Mourgues, P. *Tetrahedron Lett.* **1972**, *13*, 4445-4448.

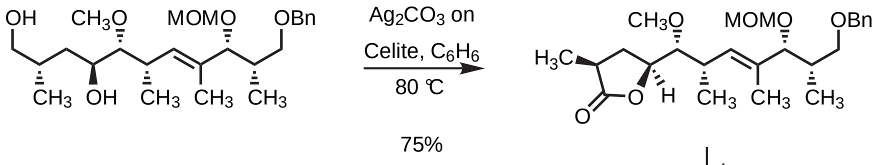
Kakis, F. J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. *J. Org. Chem.* **1974**, *39*, 523-533.



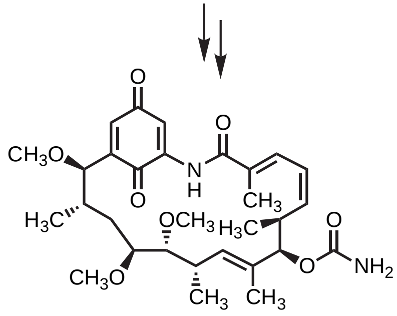
(±)-bukittinggine

Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575-2585.

- Epimerizable lactones have been prepared.

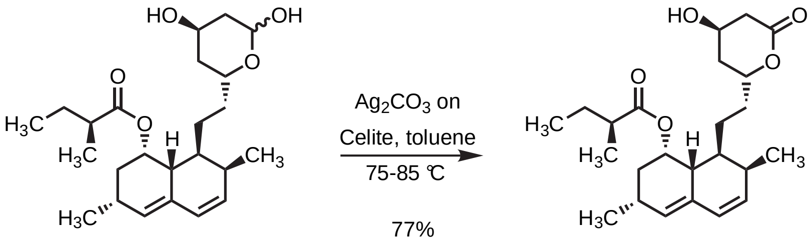


Coutts, S. J.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4305-4308.



(±)-macbecin I

- Lactols are oxidized selectively.

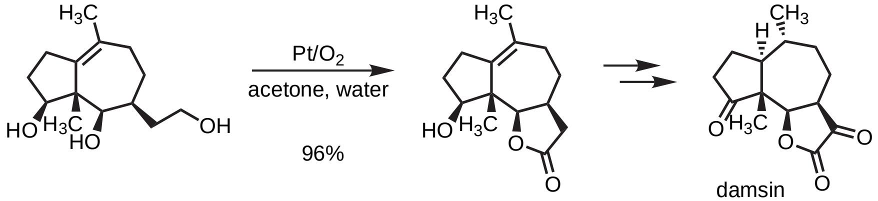


(+)-mevinolin

Clive, D. L. J.; et al. *J. Am. Chem. Soc.* **1990**, *112*, 3018-3028.

Other Methods

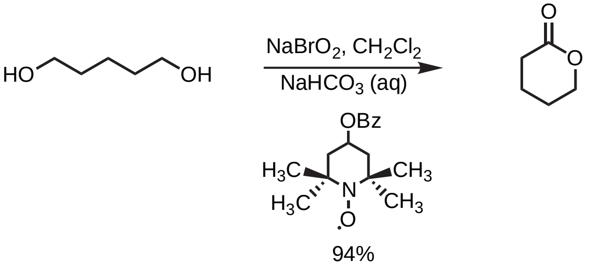
- Platinum and oxygen have been used for the selective oxidation of primary alcohols to lactones.



damsin

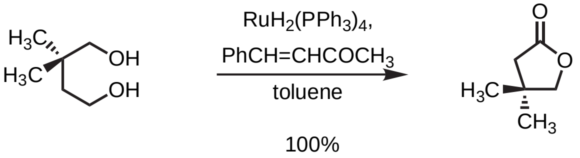
Kretchmer, R. A.; Thompson, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 3379-3380.

- TEMPO derivatives have been employed in the preparation of lactones.



Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462-466.

- Ru complexes have also been employed.



Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034-2039.

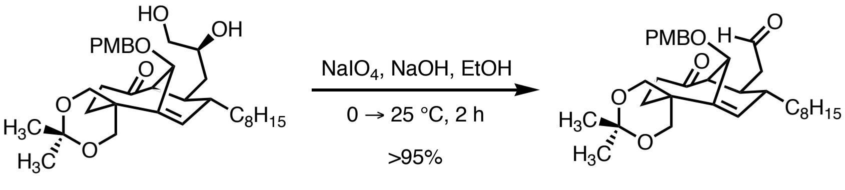
Oxidative Cleavage of Diols

Sodium periodate ($NaIO_4$)

- Reviews:

Wee, A. G.; Slobodian, J. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 420–423.

- One of the most common reagents for cleaving 1,2-diols.



Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202–2211.

Lead Tetraacetate ($Pb(OAc)_4$)

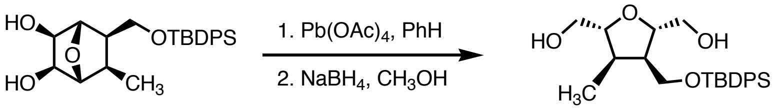
- Reviews:

Mihailovic, M. L.; Cekovic, Z. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 190–195.

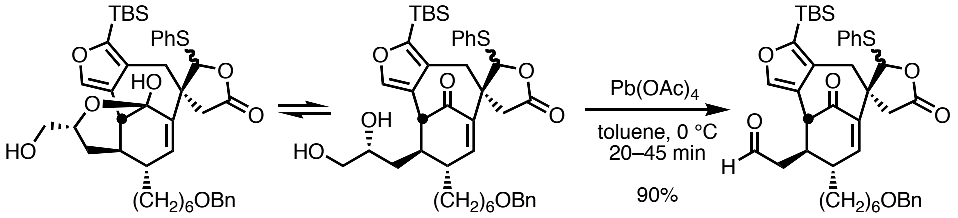
Butler, R. N. In *Synthetic Reagents*, Pizey, J. S., Ed., **1977**, Vol 3, p. 277–419.

Rubottom, G. M. In *Oxidation in Organic Chemistry*, Trahanovsky, W. S., Ed.; Organic Chemistry, A Series of Monographs, Vol 5, **1982**, Part D, p. 1–145.

- A common reagent for the cleavage of diols. However, $Pb(OAc)_4$ is a strong oxidant and can react with a variety of functional groups.
- Examples:

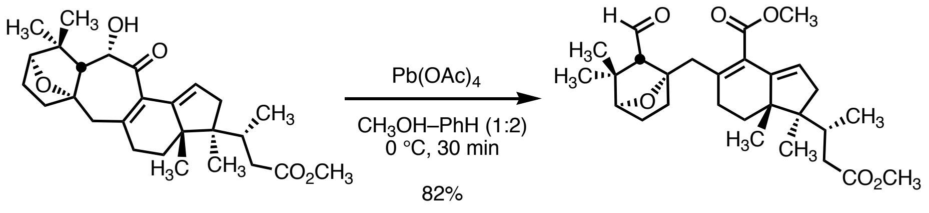


Takao, K.; Watanabe, G.; Yasui, H.; Tadano, K. *Org. Lett.* **2002**, *4*, 2941–2943.



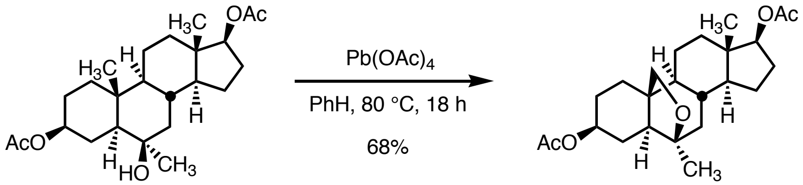
Tan, Q.; Danishefsky, S. J. *Angew. Chem. Int. Ed., Eng.* **2000**, *39*, 4509–4511.

- α-Hydroxyketones can be cleaved as well:



Corey, E. J.; Hong, B. *J. Am. Chem. Soc.* **1994**, *116*, 3149–3150.

- Oxidative cyclizations sometimes occur. This process likely proceeds by a free-radical mechanism involving homolytic cleavage of an RO–Pb bond.



Bowers, A.; Denot, E.; Ibáñez, L. C.; Cabezas, M. A.; Ringold, H. J. *J. Org. Chem.* **1962**, *27*, 1862–1867.

Mihailovic, M. L.; Cekovic, Z. *Synthesis* **1970**, *5*, 209–224.

- In addition, $Pb(OAc)_4$ can oxygenate alkenes, oxidize allylic or benzylic C–H bonds, and has been used to introduce an acetate group α to a ketone.

Landy Blasdel

Oxidative Cleavage of Alkenes

Ozone

- Reviews:

Berglund, R. A. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 270–275.

Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol 7, p. 543–558, 574–578.

Murray, R. W. In *Techniques and Methods of Organic and Organometallic Chemistry* , Denny, D. B., Ed., Marcel Dekker: New York, **1969**, Vol 1, p. 1–32.

Murray, R. W. *Acc. Chem. Res.* **1968**, *1*, 313–320.

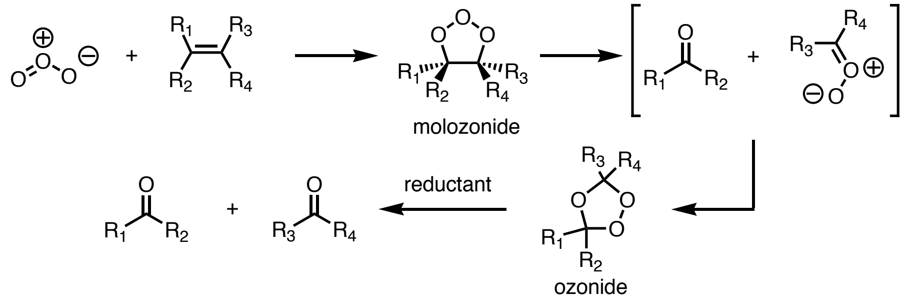
- Ozone is the most common reagent for the oxidative cleavage of olefins.

- The reaction is carried out in two steps:

(1) a stream of O_3 in air or O_2 is passed through the reaction solution at low temperature (0 °C to –78 °C) until excess O_3 in solution is evident from its blue color.

(2) reductive or oxidative work-up.

- Mechanism:



- Considered to be a concerted 3 + 2 cycloaddition of O_3 onto the alkene.

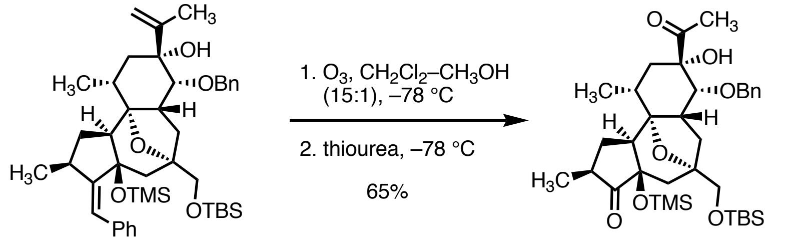
- Because ozonides are known to be explosive, they are rarely isolated and typically are transformed directly to the desired carbonyl compounds.

- Dimethyl sulfide is the most commonly used reducing agent. Others include I_2, phosphine, thiourea, catalytic hydrogenation, tetracyanoethylene, Zn–HOAc, $LiAlH_4$, and $NaBH_4$. The latter two reductants afford alcohols as products.

- Oxidative workup provides either ketone or carboxylic acid products. The most common oxidants are H_2O_2, AgO_2, CrO_3, $KMnO_4$, or O_2.

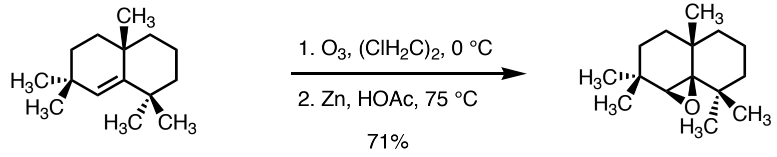
- Alkenes with electron-donating substituents are cleaved more readily than those with electron-withdrawing substituents, see: Pryor, W. A.; Giamalva, D.; Church, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 2793–2797.

- Examples



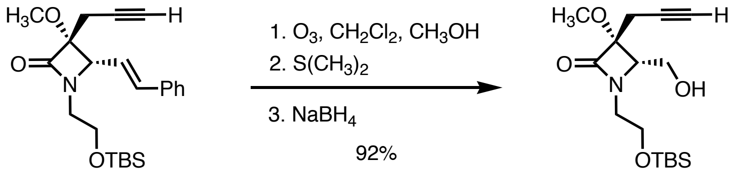
Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977.

- Forming the primary ozonide with sterically hindered olefins is difficult, and epoxides can be formed instead:



Hochstetler, A. R. *J. Org. Chem.* **1975**, *40*, 1536–1541.

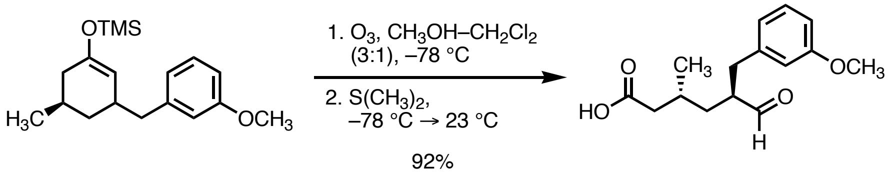
- Alkenes are ozonized more readily than alkynes:



- When a TMS-protected alkyne was used in the example above, the authors observed products arising from ozonolysis of the alkyne as well.

Banfi, L.; Guanti, G. *Tetrahedron Lett.* **2000**, *41*, 6523–6526.

- Ozonolysis of silyl enol ethers can afford carboxylic acids as products:



Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87.

Landy Blasdel

Oxidative Cleavage of Alkenes

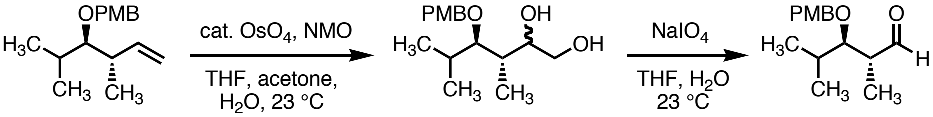
OsO_4, $NaIO_4$

Wee, A. G.; Liu, B. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 423–426.

Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p.564.

VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

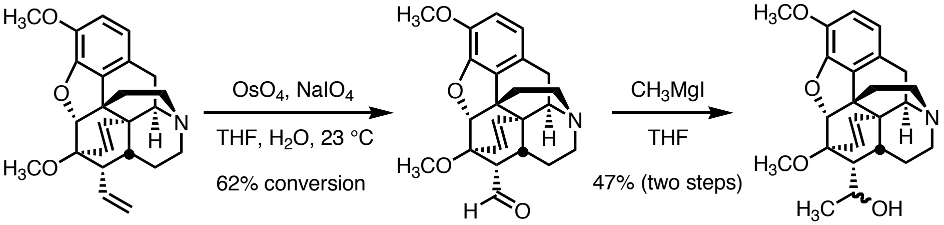
- A two-step procedure involving initial dihydroxylation with OsO_4 to form 1,2-diols, followed by cleavage with periodate.
- This procedure offers an alternative to ozonolysis, where it can be difficult to achieve selectivity for one olefin over another due to difficulties in adding precise quantities of ozone.
- Sharpless dihydroxylation conditions (AD-Mix α/β) can lead to enhanced selectivities.



93% (two steps)

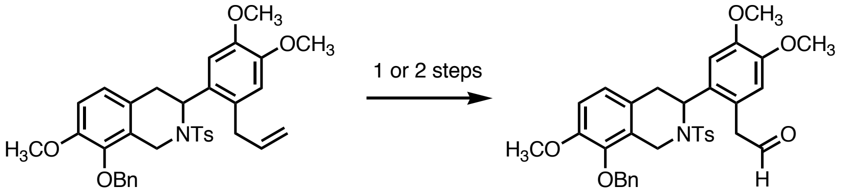
Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Sheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275–4283.

- The procedure is most often performed in two steps, but the transformation is sometimes accomplished in one:



- Notice that in the example above, the less-hindered olefin was cleaved selectively.

Maurer, P. J.; Rapoport, H. *J. Med. Chem.* **1987**, *30*, 2016–2026.



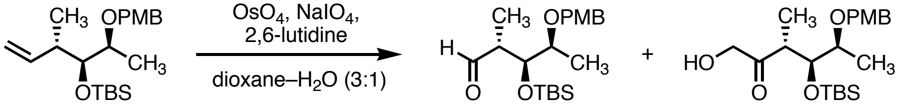
OsO_4 (cat.), $NaIO_4$, THF–H_2O (3:1)..................................77%

1. OsO_4 (cat.), NMO, acetone–H_2O–*t*-BuOH (4:2:1);
2. $NaIO_4$, THF–H_2O (3:1)..89%

- Frequently the two-step protocol is found to be superior to the one-pot procedure. In the example shown, over-oxidation of the aldehyde was observed in the one-pot reaction.

Bianchi, D. A.; Kaufman, T. S. *Can. J. Chem.* **2000**, *78*, 1165–1169.

- An improved one-pot procedure uses 2,6-lutidine as a buffering agent:



90%

6%

- Ozonolysis of this substrate resulted in PMB removal.
- The authors found that without base, the α-hydroxyketone was formed in ~30% yield. Using pyridine as base, epimerization of the aldehyde product was observed.

Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

Landy Blasdel

Oxidative Cleavage of Alkenes

RuO_4

- References:

Martín, V. S.; Palazón, J. M.; Rodríguez, C. M. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 346–353.

Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol 7, p.564–571, 587.

Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838–3840.

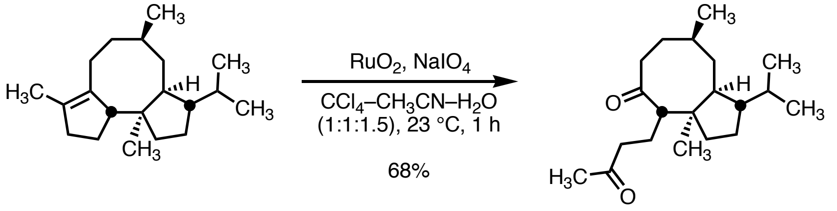
- RuO_4 is a powerful oxidant that is nevertheless useful in many synthetic transformations.

- RuO_4 has been used to cleave alkenes where other oxidation methods (e.g., O_3, $OsO_4/NaIO_4$) have failed.

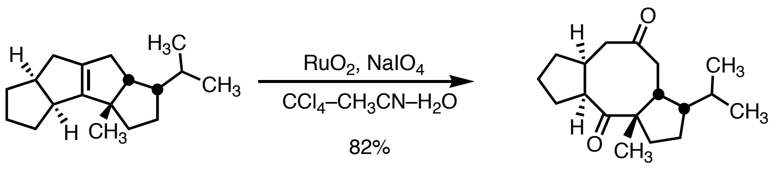
- Reaction conditions are relatively mild and usual involving generation of RuO_4 in situ from $RuO_2 \cdot 2H_2O$ or $RuCl_3 \cdot H_2O$ and an oxidant, such as $NaIO_4$.

- Solvent mixtures of CCl_4, H_2O and CH_3CN have been determined to be optimal. CH_3CN is a good ligand for low valent Ru, and it prevents formation of stable Ru(II/III)–carboxylate complexes which remove Ru from the catalytic cycle. See: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

- RuO_4 will also oxidize alcohols (to ketones), ethers (to lactones or to two carboxylic acids), diols (to two carboxylic acids), alkynes (to 1,2-diketones), and aryl rings (to carboxylic acid products). It will also remove aryl and alkyne groups, leaving carboxylic acids.



Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057–3083.



Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319–1321.

Ketone → α,β-Unsaturated Ketone

See also: *o*-Iodobenzoic Acid (IBX) earlier in handout

General Reference:

Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 7*, p. 119–149.

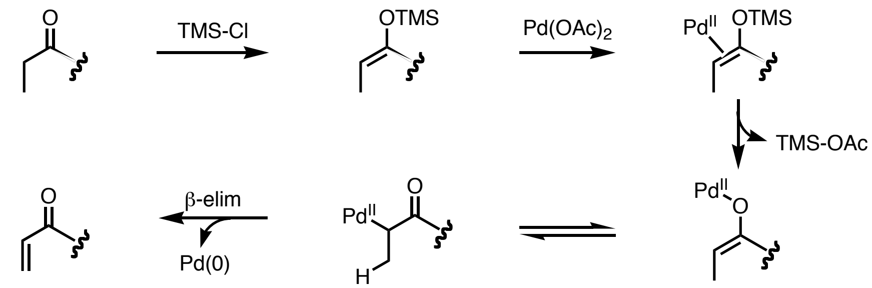
Saegusa Oxidation

Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

- A two-step procedure involving silyl enol ether formation, followed by treatment with Pd(II).

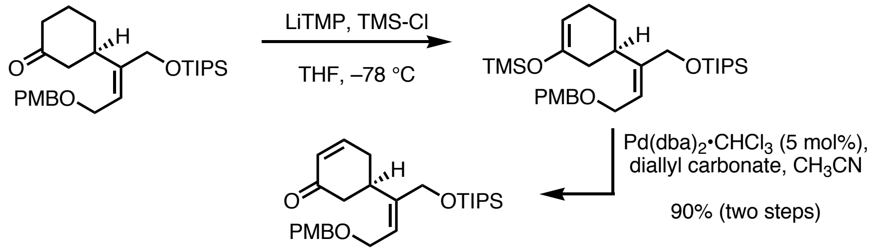
- The reaction can be performed with stoichiometric Pd(II), or can be rendered catalytic if a terminal oxidant, such as O_2 or *p*-benzoquinone, is used.

- Mechanism:



Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

Porth, S.; Bats, J. W.; Trauner, D.; Giester, G.; Mulzer, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2015–2016



- In this case, diallyl carbonate is used as a terminal oxidant.

Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546–14547.

Ketone ⟶ α,β-Unsaturated Ketone

Selenation/Oxidation/Elimination

Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 7, p. 128–135.

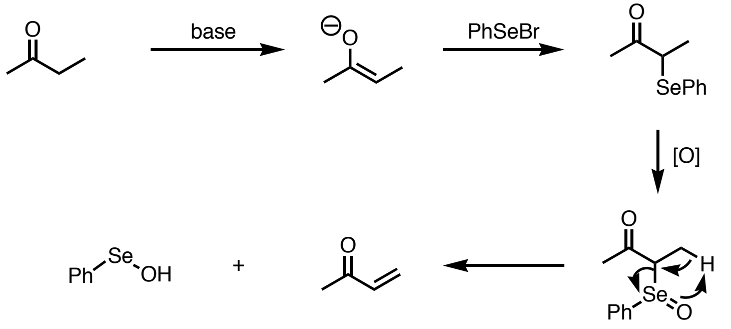
Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979–1982.

Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139.

Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813–5815.

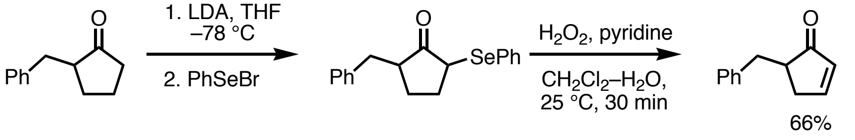
Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

- PhSeBr and PhSeCl can be used to selenate enolates of ketones, esters, lactones and lactams.
- PhSeSePh can be used as well, but ketone enolates are unreactive
- Aldehydes can be selenated via:
  - enol ethers: Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J. *Synthesis* **1979**, 982–984.
  - enamines: Williams, D. R.; Nishitani, K. *Tetrahedron Lett.* **1980**, *21*, 4417–4420.
  - one-step procedure with PhSeSePh, SeO_2, and a catalytic amount of H_2SO_4: Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1982**, *23*, 4813–4816.
- Mechanism:



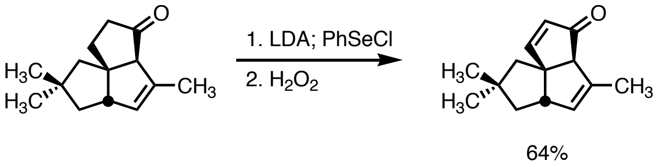
- Common oxidants include H_2O_2, O_3, and $NaIO_4$.
- Elimination is *syn*-specific, see: Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86–87.
- Electron withdrawing groups on the phenyl ring facilitate the elimination step, which can be difficult with primary or β- or γ-branched selenoxides: Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947–948.

- Examples:

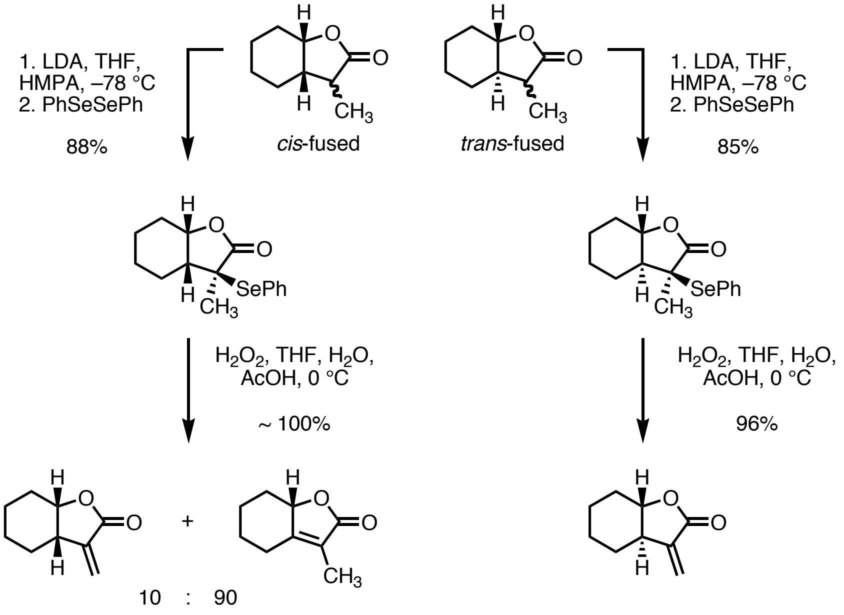


- Generating the enolate under kinetic conditions can allow for formation of the less-substituted double bond.

Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.



Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504–4506.



- The example above illustrates how the stereospecificity (*syn*) of the elimination can be used to achieve selectivity in olefin formation.

Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120–122.

Landy Blasdel

Alkene → Allylic alcohol

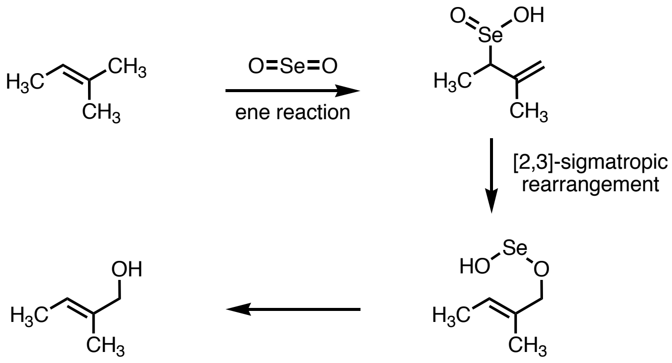
SeO_2

- References

Bulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, Vol. 7, p. 84–91, 108–110.

Rabjohn, N. In *Organic Reactions*, **1976**,Vol 24, p. 261–415.

- General method for oxidizing alkenes to allylic alcohols.
- Although the reaction can be performed with stoichiometric SeO_2, catalytic methods employing a stoichiometric oxidant (e.g., *t*-BuOOH) are more frequently used.
- Mechanism:



Singleton, D. A.; Hang, C. *J. Org. Chem.* **2000**, *65*, 7554–7560.

Selectivity:

(a) oxidation typically occurs at the more highly substituted terminus of the alkene

(b) the order of reactivity of C–H bonds is $CH_2 > CH_3 > CH$
[rule (a) takes precedence over rule (b)]

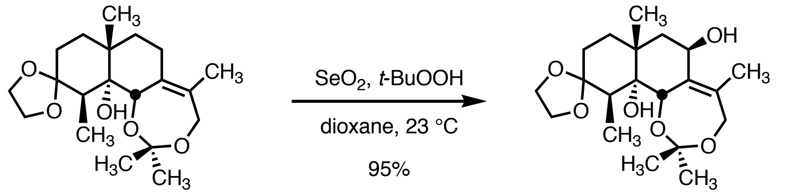
(c) when the double bond is within a ring, oxidation occurs within the ring

(4) *gem*-dimethyl trisubstituted alkenes form (*E*)-α-hydroxy alkenes stereoselectively

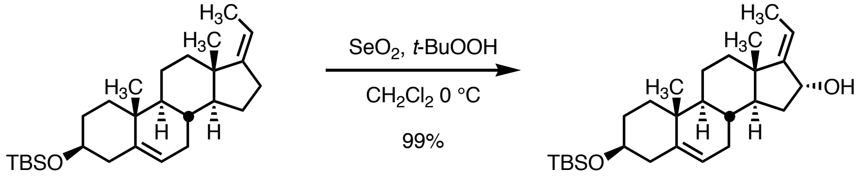
Hoekstra, W. J. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 358–359.

Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835–4840.

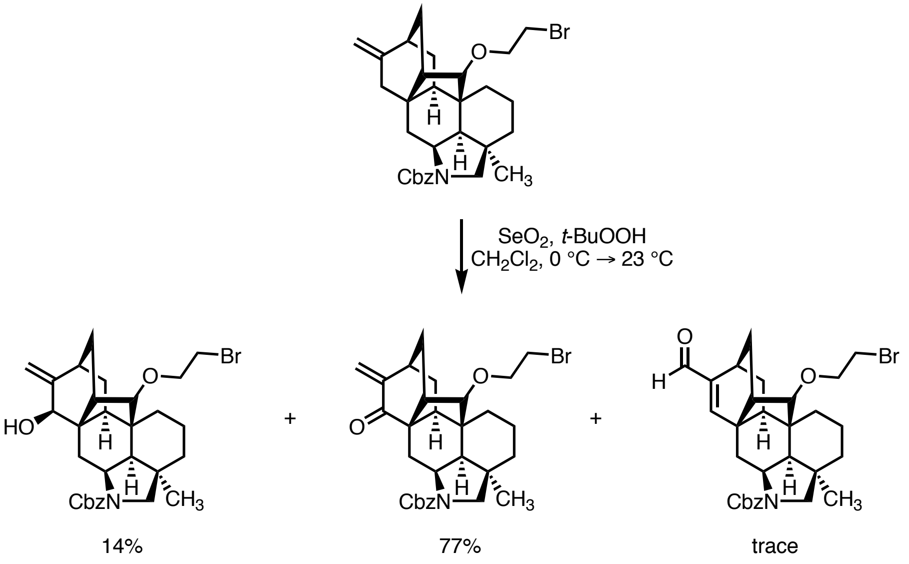
- Examples:



Xia, W. J.; Li, D. R.; Shi, L.; Tu, Y. Q. *Tetrahedron Lett.* **2002**, *43*, 627–630.



Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369–3370.



Muratake, H.; Natsume, M. *Angew. Chem. Int. Ed., Eng.* **2004**, *43*, 4646–4649.

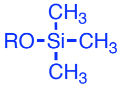
Landy Blasdel

General References:

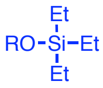
Kocienski, P. J. *Protecting Groups, 3rd ed.*; Georg Thieme Verlag: New York, **2005**.

Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis, 3rd ed.*; John Wiley & Sons: New York, **1991**.

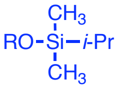
Important Silyl Ether Protective Groups:


$RO-\overset{CH_3}{\underset{CH_3}{Si}}-CH_3$

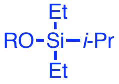
Trimethylsilyl (TMS)


$RO-\overset{Et}{\underset{Et}{Si}}-Et$

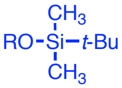
Triethylsilyl (TES)


$RO-\overset{CH_3}{\underset{CH_3}{Si}}-i\text{-}Pr$

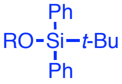
Dimethylisopropylsilyl (IPDMS)


$RO-\overset{Et}{\underset{Et}{Si}}-i\text{-}Pr$

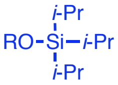
Diethylisopropylsilyl (DEIPS)


$RO-\overset{CH_3}{\underset{CH_3}{Si}}-t\text{-}Bu$

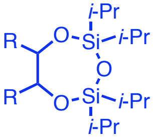
t-Butyldimethylsilyl (TBS)


$RO-\overset{Ph}{\underset{Ph}{Si}}-t\text{-}Bu$

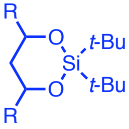
t-Butyldiphenylsilyl (TBDPS)


$RO-\overset{i\text{-}Pr}{\underset{i\text{-}Pr}{Si}}-i\text{-}Pr$

Triisopropylsilyl (TIPS)



Tetraisopropyldisilylene (TIPDS)



Di-*t*-butyldimethylsilylene (DTBS)

General methods for the formation of silyl ethers:

$$ROH \xrightarrow[\text{imidazole, DMF}]{R'_3SiCl} ROSiR'_3$$

Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

$$ROH \xrightarrow[\text{2,6 lutidine, } CH_2Cl_2]{R'_3SiOTf} ROSiR'_3$$

Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

- In general, the stability of silyl ethers towards acidic media increases as indicated:

  TMS (1) $<$ TES (64) $<$ TBS (20,000) $<$ TIPS (700,000) $<$ TBDPS (5,000,000)

- In general, stability towards basic media increases in the following order:

  TMS (1) $<$ TES (10-100) $<$ TBS ~ TBDPS (20,000) $<$ TIPS (100,000)

Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis, 3rd ed.;* John Wiley & Sons: New York, **1991**.

Silyl Ether	Half Life (5% NaOH–95% MeOH)	Half Life (1% HCl–MeOH, 25 °C)
n-C_6H_{13}OTMS	≤1 min	≤1 min
n-C_6H_{13}OSi-i-Bu$(CH_3)_2$	2.5 min	≤1 min
n-C_6H_{13}OTBS	Stable for 24 h	≤1 min
n-$C_6H_{13}OSiCH_3Ph_2$	≤1 min	14 min
n-C_6H_{13}OTIPS	Stable for 24 h	55 min
n-C_6H_{13}OTBDPS	Stable for 24 h	225 min

Davies, J. S.; Higginbotham, L. C. L.; Tremeer, E. J.; Brown, C.; Treadgold, *J. Chem. Soc., Perkin Trans . 1* **1992**, 3043.

- A study comparing alkoxysilyl vs. trialkylsilyl groups has also been done:

Silyl Ether	Half Life $Bu_4N^+F^-$ (0.06 M, 6 equiv)	Half Life $HClO_4$ (0.01 M)
n-$C_{12}H_{25}$OTBS	140 h	1.4 h
n-$C_{12}H_{25}$OTBDPS	375 h	> 200 h
n-$C_{12}H_{25}OSiPh_2$(Oi-Pr)	<0.03 h	0.7 h
n-$C_{12}H_{25}OSiPh_2$(Ot-Bu)	5.8 h	17.5 h
n-$C_{12}H_{25}$OPh(t-Bu)(OCH_3)	22 h	200h

Gillard, J.W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnell, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602.

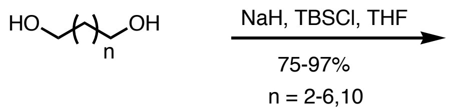
- Silyl groups are typically deprotected with a source of fluoride ion. The Si–F bond stength is about 30 kcal/mol stronger than the Si–O bond.

Fluoride sources:

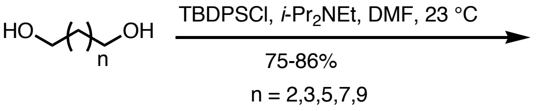
Tetrabutylammonium fluoride, $Bu_4N^+F^-$ (TBAF)
Pyridine•$(HF)_x$
Triethylamine trihydrofluoride, Et_3N•3HF
Hydrofluoric acid
Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)
Ammonium fluoride, $H_4N^+F^-$

P. Hogan

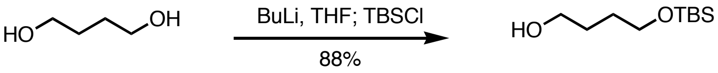
- Monosilylation of symmetrical diols is possible, and useful.



McDougal, P.G.; Rico, J.G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

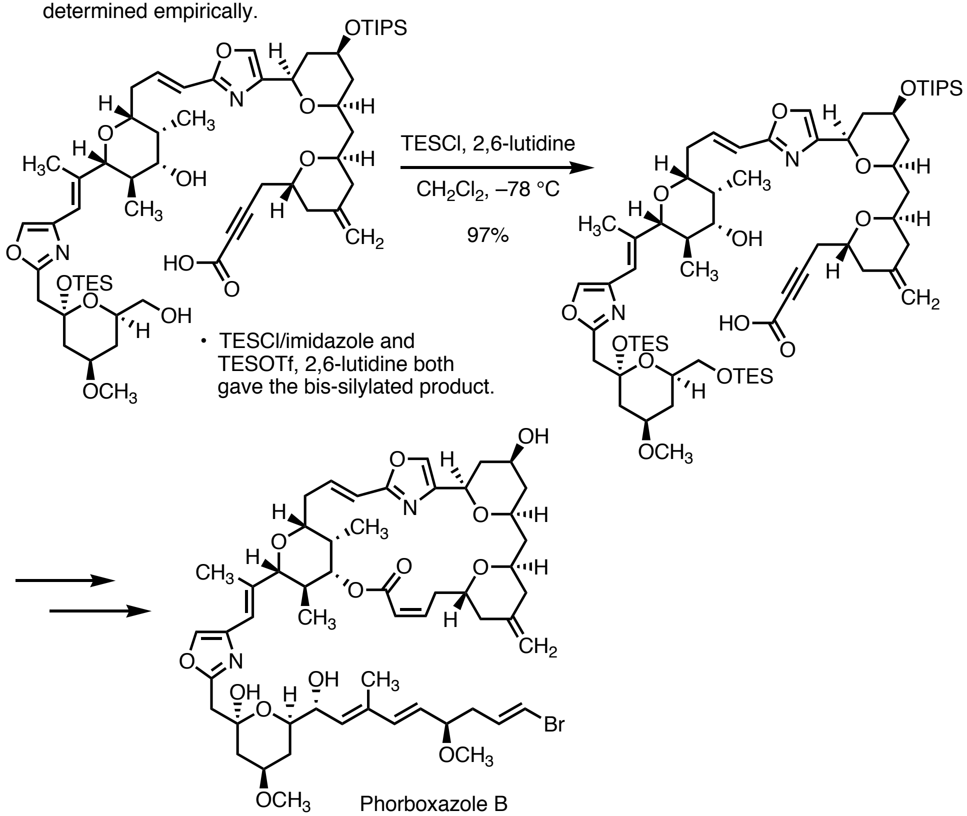


Hu, L.; Liu, B.; Yu, C. *Tetrahedron Lett.* **2000**, *41*, 4281.



Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1983**, *49*, 4674.

- Selective protection of alcohols is of great importance in synthesis. Conditions often must be determined empirically.

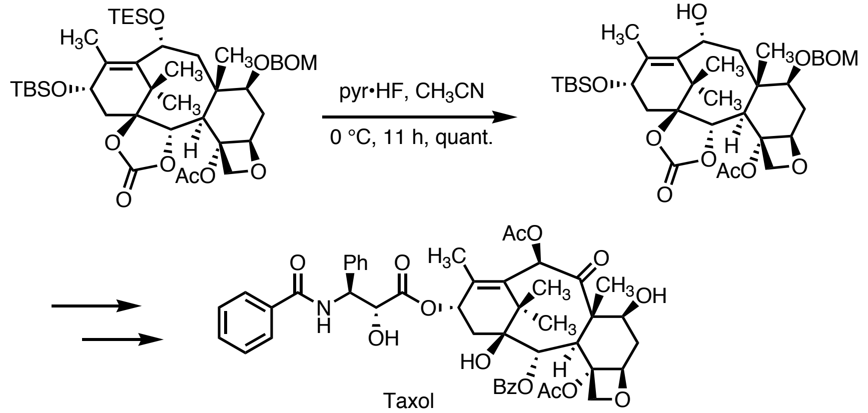


- TESCl/imidazole and TESOTf, 2,6-lutidine both gave the bis-silylated product.

Phorboxazole B

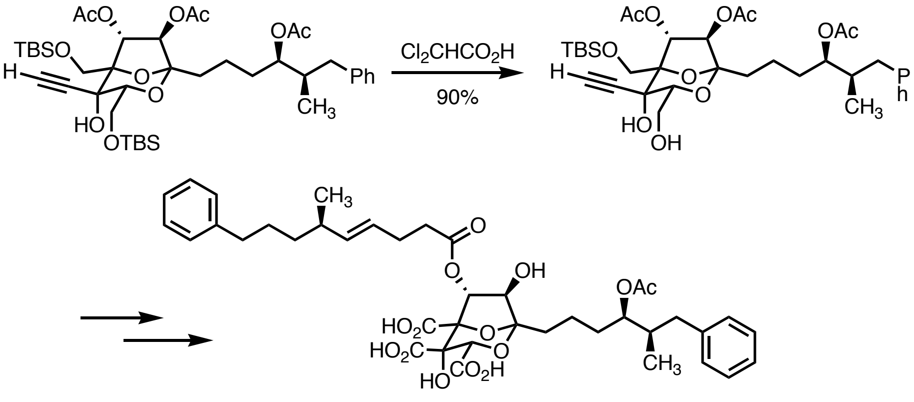
Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2536.

- Selective deprotection of silyl ethers is also important, and is also subject to empirical determination.



Taxol

Holton, R. A., et al. *J. Am. Chem. Soc.*, **1994**, *116*, 1599.



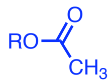
Zaragozic acid

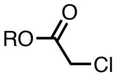
Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

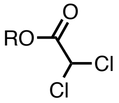
- Selective deprotections in organic synthesis have been reviewed: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1065.

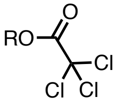
P. Hogan

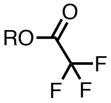
Esters and Carbonates:

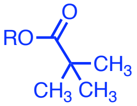

Acetate (Ac)

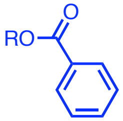

Chloroacetate

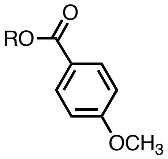

Dichloroacetate

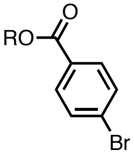

Trichloroacetate

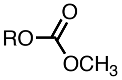

Trifluoroacetate (TFA)

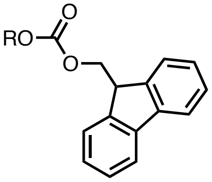

Pivaloate (Pv)

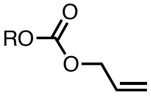

Benzoate (Bz)

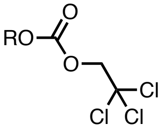

p-Methoxybenzoate

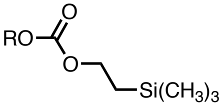

p-Bromobenzoate

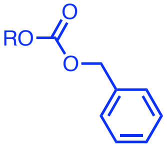

Methyl Carbonate

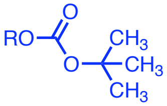

9-(Fluorenylmethyl) Carbonate (Fmoc)

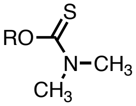

Allyl Carbonate (Alloc)


2,2,2-Trichloroethyl Carbonate (Troc)

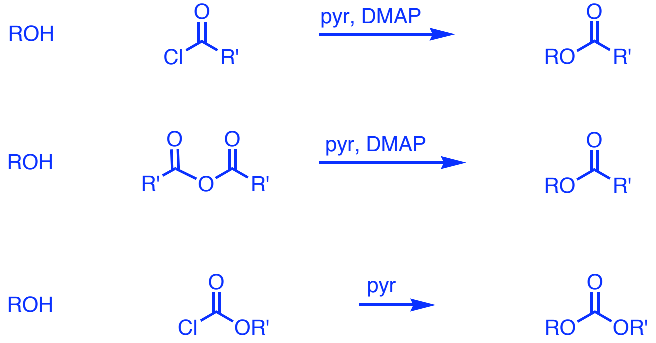

2-(Trimethylsilyl)ethyl Carbonate (Teoc)


Benzyl Carbonate (Cbz)

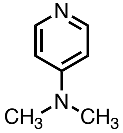

t-Butyl Carbonate (Boc)

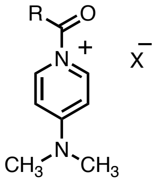

Dimethylthiocarbamate (DMTC)

General methods used to form esters and carbonates:



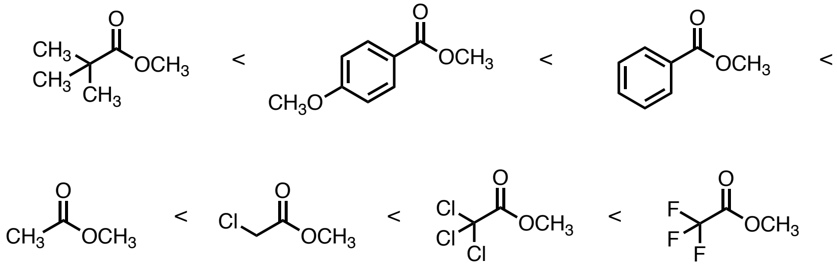
DMAP = 4-Dimethylaminopyridine:




- Proposed intermediate

DMAP is used to accelerate reactions between nucleophiles and activated esters.
Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

- In general, the susceptibility of esters to base catalyzed hydrolysis increases with the acidity of the product acid.



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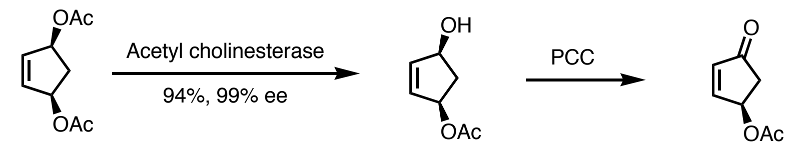
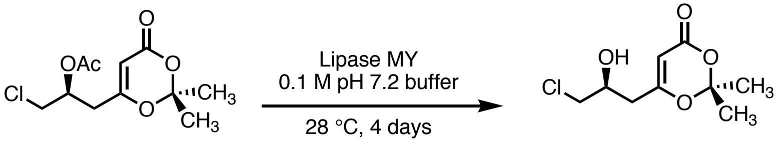
Acetate Esters:

- Several methods for forming and cleaving acetate esters have been developed. Lipases can often be used for the enantioselective hydrolysis of acetate esters. The enantioselective hydrolysis of meso diesters is an important synthetic transformation and racemic esters have been kinetically resolved using lipases.



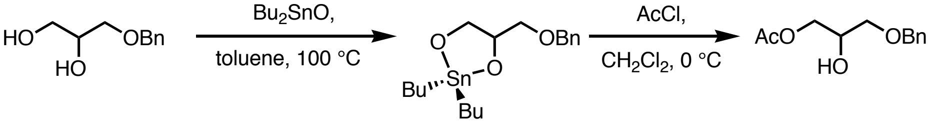
Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.

- Lipases can also be effective for deprotection under very mild conditions, as in the case shown below, where conventional methods were unsuccessful.



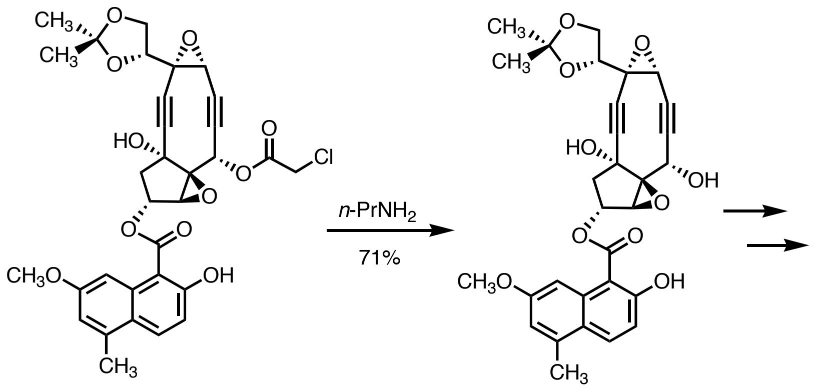
Sakaki, J.; Sakoda, H.; Sugita, Y.; Sato, M.; Kaneto, C. *Tetrahedron: Asymmetry*, **1991**, *2*, 343.

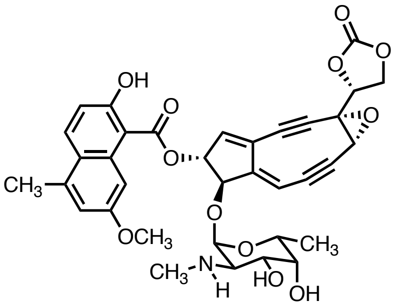
- A potentially general method for selectively acylating the primary hydroxyl group of a 1,2-diol makes use of stannylene acetals as intermediates:



Review: Hannessian, S.; David, S. *Tetrahedron*, **1985**, *41*, 643.

- Good selectivity can often be achieved in the selective deprotection of different esters.





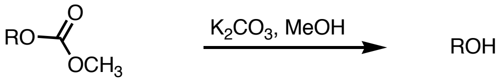
Neocarzinostatin Chromophore

Myers, A. G.; Liang, J.; Hammond, M.; Wu, Y.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319.

- When one protective group is stable to conditions that cleave another and the converse is also true, these groups are often said to be to bear an **orthogonal** relationship. This concept is illustrated well in the context of carbonates (and carbamates).

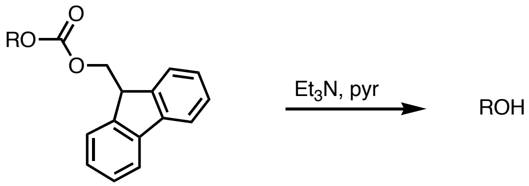
Summary of methods for deprotecting carbonates:

Methyl Carbonate:



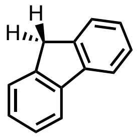
Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D. *Tetrahedron Lett.* **1978**, *19*, 1375.

9-Fuorenylmethyl Carbonate:



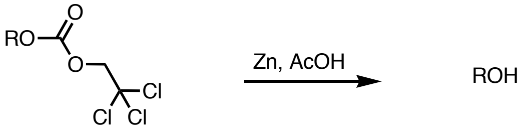
- The pK_a of fluorene is ≈ 10.3

fluorene =



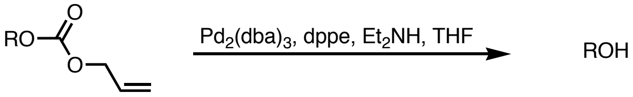
Chattopadhyaya, J. B.; Gioeli, C. *J. Chem. Soc., Chem. Comm.* **1982**, 672.

Trichloroethyl Carbonate:



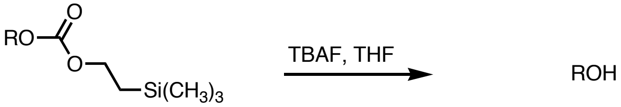
Windholz, T.B.; Johnston, D. B. R. *Tetrahedron Lett.* **1988**, *29*, 2227.

Allyl Carbonate:



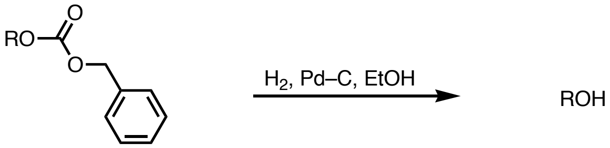
Genet, J.P.; Blart E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. *Synlett* **1993**, 680.

2-(Trimethylsilyl)ethyl Carbonate:



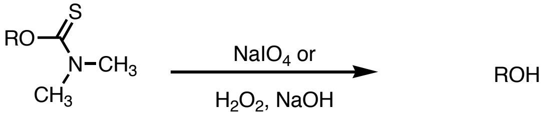
Gioeli, C.; Balgobin, S.; Josephson, S.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 969.

Benzyl Carbonate:



Daubert, B. F.; King, G. C. *J. Am. Chem. Soc.* **1939**, *61*, 3328.

Dimethylthiocarbamate (DMTC) Carbamate:



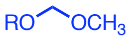
- The DMTC group is stable to a variety of reagents and reaction conditions (PCC oxidations, Swern oxidations, chromium reagents, Grignard and alkyllithium reagents, phosphorous ylides, LAH, HF, TBAF, and borane).

- The protecting group is introduced using imid$_2$CS followed by treatment with dimethylamine, or by reaction with commercially available $ClCSN(CH_3)_2$.

Barma, D. K.; Bandyopadhyay, A.; Capdevilla, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755.

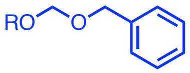
P. Hogan/Seth B. Herzon

Acetals as Protective Groups:



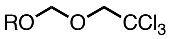
Methoxymethyl Ether

(MOM)

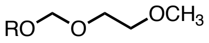


Benzyloxymethyl Ether

(BOM)

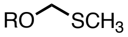


2,2,2-Trichloroethoxymethyl Ether



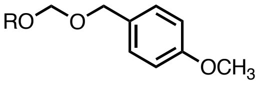
2-Methoxyethoxymethyl Ether

(MEM)



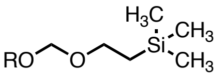
Methylthiomethyl Ether

(MTM)



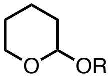
p-Methoxybenzyl Ether

(PMBM)



2-(Trimethylsilyl)ethoxymethyl Ether

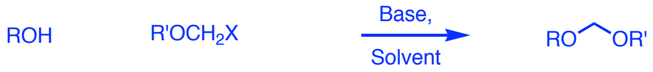
(SEM)



Tetrahydropyranyl Ether

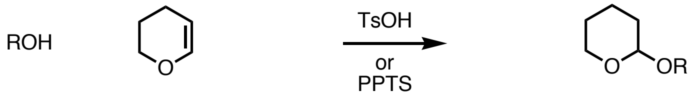
(THP)

General methods for forming acyclic, mixed acetals:



Base-solvent combinations are often diisopropylethylamine-CH_2Cl_2, NaH-THF, or NaH-DMF. Sometimes a source of iodide ion is added to enhance the reactivity of the alkylating reagent. Typical sources include $Bu_4N^+I^-$, LiI, or NaI.

General methods for introducing 2-tetrahydropyranyl ethers:

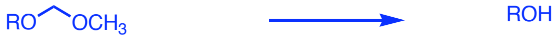


PPTS = Pyridinium *p*-toluenesulfonate

Grieco, P. A.; Yoshikoshi, A.; Miyashita, M. *J. Org. Chem.* **1977**, *42*, 3772, and references cited therein.

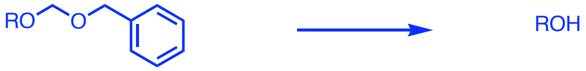
Cleavage of acetal protective groups:

Methoxymethyl Ethers:



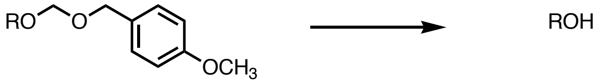
1. Conc. HCl, MeOH. Weinreb, S.; Auerbach, J. *J. Chem. Soc., Chem. Comm.* **1974**, 889.
2. Bromocatechol borane. This reagent cleaves a number of protective groups in approximately the following order: MOMOR ≈ MEMOR > *t*-BuO_2CNHR > BnO_2CNHR ≈ *t*-BuOR > BnOR > allylOR > *t*-BuO_2CR ≈ 2° alkylOR > BnO_2CR > 1° alkylOR >> alkylO_2CR. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.
3. $LiBF_4$, CH_3CN, H_2O. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.

Benzyloxymethyl Ethers:



1. Na, NH_3. Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.
2. H_2, Pd–C. D. Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395.
3. Dowex 50W–X8, acidic ion exchange resin. Roush, W. R.; Michaelidies, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575.

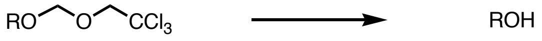
4-Methoxybenzyloxymethyl Ether:



1. DDQ, H_2O. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125.

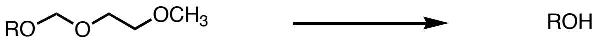
P. Hogan

2,2,2-Trichloroethoxymethyl Ether:



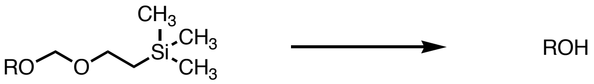
1. Zn–Cu or Zn–Ag, MeOH. Jacobson, R. M.; Clader, J. W. *Synth. Commun.* **1979**, *9*, 57.
2. 6% Na(Hg), MeOH, THF. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

2-Methoxyethoxymethyl Ether:



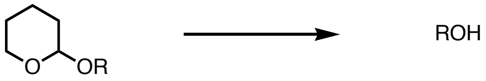
1. $ZnBr_2$, CH_2Cl_2. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
2. Bromocatechol borane. Refer to the section on MOM ethers.
3. PPTS, *t*-BuOH, heat. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Comm.* **1983**, *13*, 1021.

2-(Trimethylsilyl)ethoxymethyl Ether:



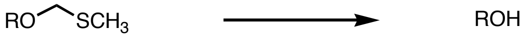
1. n-$Bu_4N^+F^-$, THF. Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
2. TFA, CH_2Cl_2. Jansson, K.; Frejd, J.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1988**, *29*, 361.

Tetrahydropyranyl Ether:



1. PPTS, EtOH, 55 °C. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.*, **1977**, *44*, 1438.
2. TsOH, MeOH, 25 °C. Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.

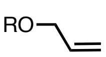
Methylthiomethyl Ether:



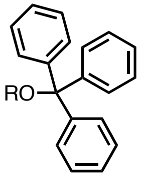
1. $HgCl_2$, CH_3CN, H_2O. Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 3269.
2. $AgNO_3$, THF, H_2O, 2,6-lutidine. Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 3269.
3. $MgBr_2$, n-BuSH, Et_2O. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett*, **1992**, 183.

P.Hogan

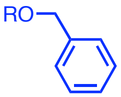
Ethers as Protective Groups:



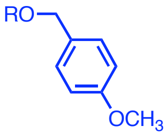
Allyl Ether



Trityl Ether

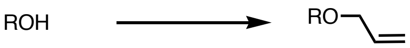


Benzyl Ether



p-Methoxybenzyl Ether

Allyl ether formation:



1. NaH, allyl bromide, benzene. Corey, E. J.; Suggs, W. J.; *J. Org. Chem.* **1973**, *38*, 3224.

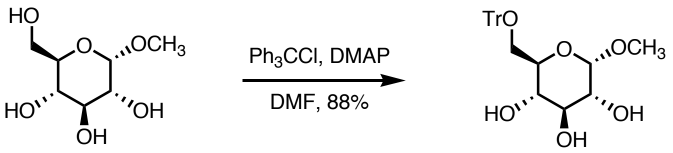
2. CH_2=$CHCH_2OC$(=NH)CCl_3, H^+. This procedure is useful for base-sensitive substrates. Wessel, H.-P.; Iverson, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

Allyl ether cleavage:

1. The use of allyl ether protective groups in synthesis has been reviewed: Guibe, F. *Tetrahedron* **1998**, *54*, 2967.

2. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.

Formation of trityl ethers:



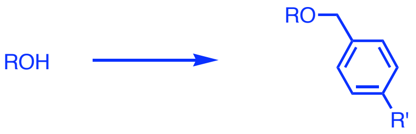
Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *19*, 95. In general, selective protection of primary alcohols can be achieved.

Cleavage of trityl ethers:

1. Amberlyst 15-H, MeOH. Malanga, C. *Chem. Ind.* **1987**, 856.

2. CF_3CO_2H, *t*-BuOH. MacCross, M.; Cameron, D. J. *Carbohydr. Res.* **1978**, *60*, 206.

Formation of benzyl ethers:



R' = H or OCH_3

1. NaH, benzyl bromide, THF. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535.

2. *p*-$CH_3OC_6H_4CH_2OC$(=NH)CCl_3, H^+. These are useful conditions for base-sensitive substrates. Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139. Similar conditions have been developed for benzyl ethers: White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624.

3. *p*-$CH_3OC_6H_4CH_2Cl$, NaH, THF. Marco, J. L.; Hueso-Rodriguez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459.

Cleavage of benzyl ethers:

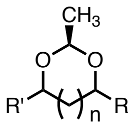
1. H_2/ Pd-C, EtOH. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746. Ammonium formate is often used as a source of H_2: Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

Cleavage of 4-methoxybenzyl ethers:

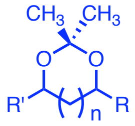
1. DDQ, CH_2Cl_2. Benzyl ethers are stable to these conditions. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y. Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

P. Hogan

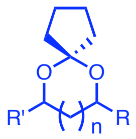
Protection of 1,2- and 1,3- Diols:



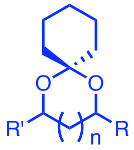
Ethylidene Acetal



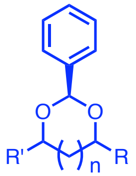
Acetonide



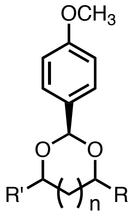
Cyclopentylidene Ketal



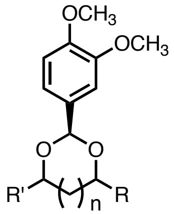
Cyclohexylidene Ketal



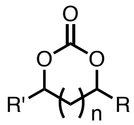
Benzylidene Acetal



4-Methoxybenzylidene Acetal



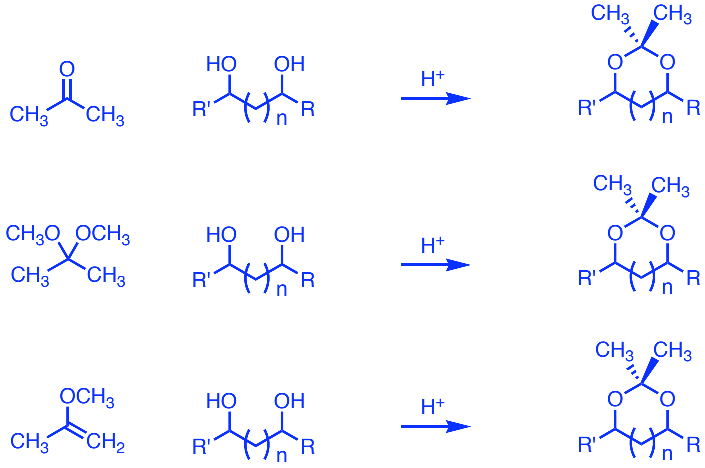
3,4-Dimethoxybenzylidene Acetal



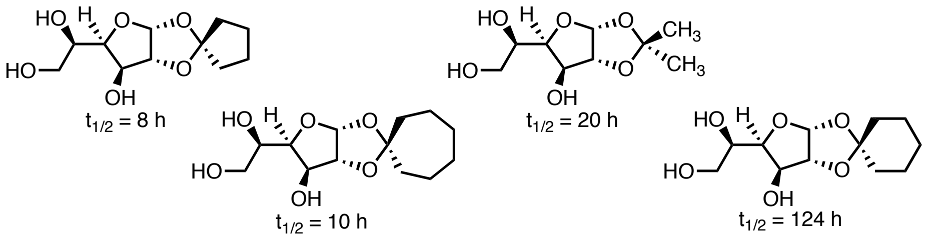
Cyclic Carbonate

- Generally, n = 0 or 1.

General methods used to form acetals and ketals (illustrated for acetonides):

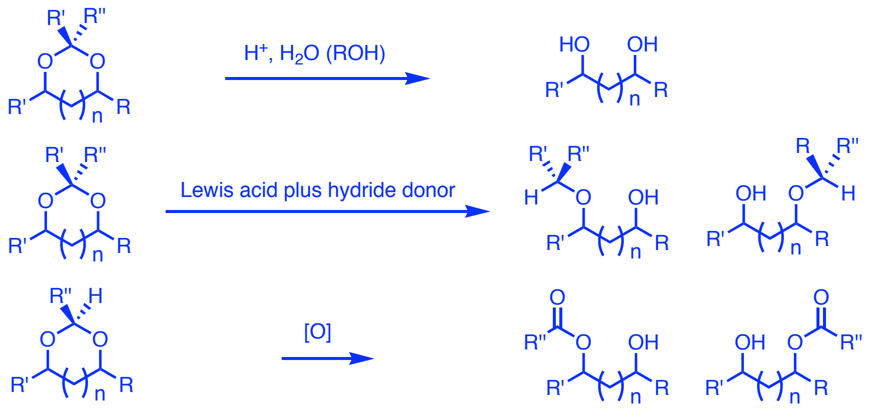


The relative rates of hydrolysis of 1,2-*O*-alkylidene-a-glucofuranoses have been studied.



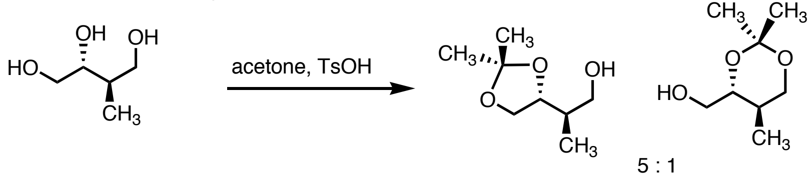
Van Heeswijk, W. A. R.; Goedhart, J. B.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1977**, *58*, 337.

General methods of cleavage:



Selective protection of polyols:

- In general, acetonide formation with 1,2-diols occurs in preference protection to 1,3-diols; benzylidene acetals display reversed selectivity. It is often possible to discriminate between 1,2- and 1,3-diols of a triol group.



Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *206*, 2949.

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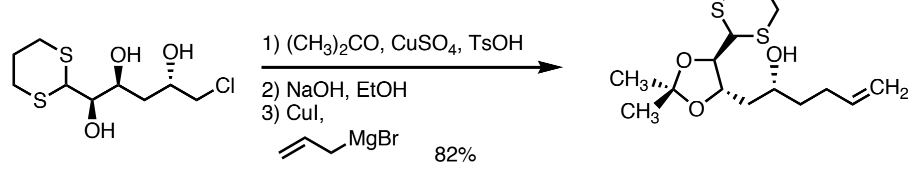
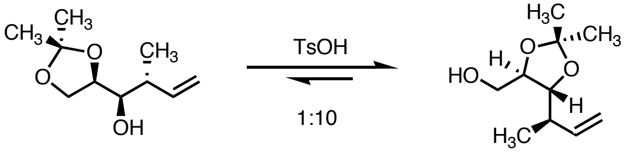
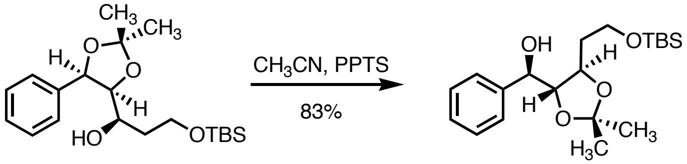


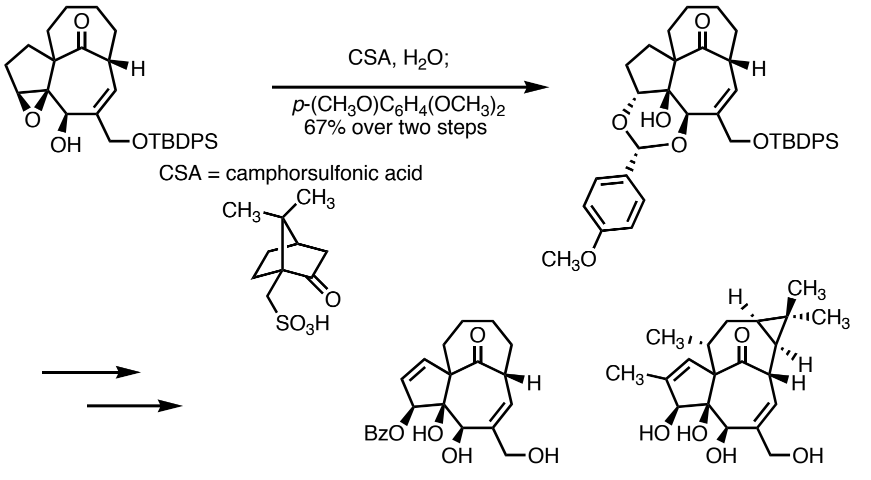
Mortlock, S. V.; Stacey, N. A.; Thomas, E. J. *J. Chem. Soc., Chem. Comm.* **1987**, 880.

- In the case of a 1,2,3-triol, careful analysis must be performed to accurately predict the site of acetonide formation. The more substituted acetonide will be favored in cases where the substiuents on the resultant five-membered ring will be trans. If the substituents on the five-membered ring would be oriented cis, then the alternative, less substituted acetonide may be favored.





Roush, W. R.; Coe, J. W. *J. Org. Chem.* **1989**, *54*, 915. See also, Mukai, C.; Miyakawa, M.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 913.

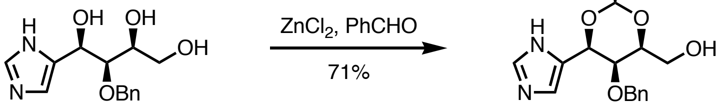


CSA = camphorsulfonic acid

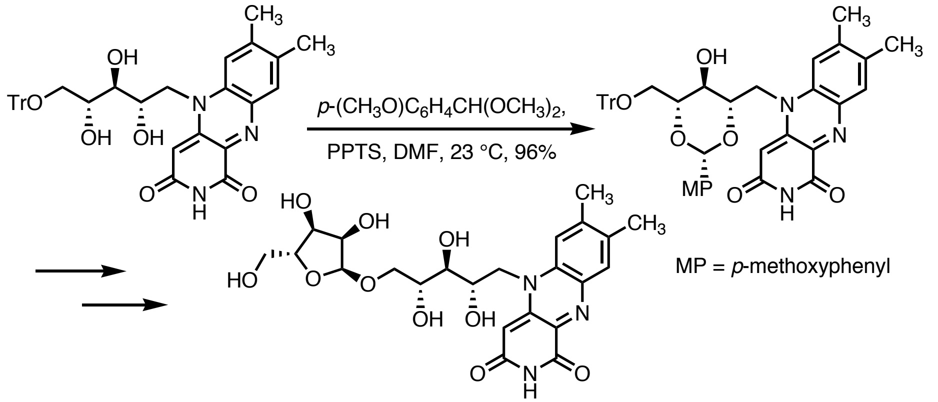
Ingenol analog

Ingenol

Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296.



Frankowski, A.; Deredas, D.; Le Noen, D.; Tschamber, T.; Strieth, J. *Helv. Chim. Acta.* **1995**, *78*, 1837.



MP = p-methoxyphenyl

Lampteroflavin, a source of bioluminescence.

Isobe, M.; Takahashi, H.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 717.

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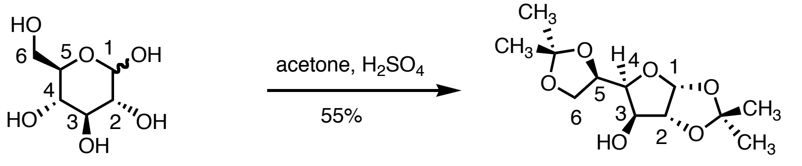
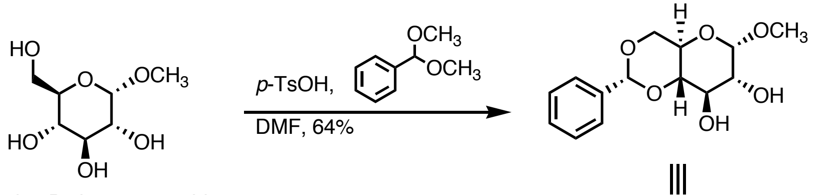
- Selective protection methods are central to carbohydrate chemistry. The most common protective groups in carbohydrate chemistry are acetonides, benzylidene acetals, and substituted benzylidene acetals. This subject has been reviewed: Calinaud, P.; Gelas, J. in *Preparative Carbohydrate Chemistry*. Hanessian, S. Ed. Marcel Dekker, Inc.: New York, **1997**.

Selective Protection: thermodynamic control

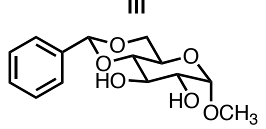


D-glucose 1,2:5,6-Di-O-isopropylidene-*D*-glucopyranose

Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318.



methyl-a-*D*-glucopyranoside

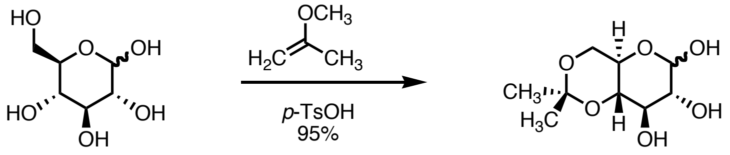


Evans, M. E. *Carbohydr. Res.* **1972**, *21*, 473.

methyl 4,6-benzylidene-a-*D*-glucopyranoside

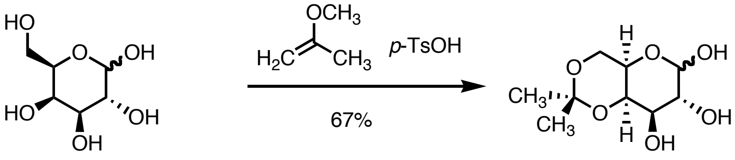
- Note the preference for 1,3-diol protection with the benzylidene acetal. The phenyl group is oriented exclusively as shown, in an equatorial orientation.

Selective Protection: kinetic control



D-glucose

Wolfrom, M. L.; Diwadkar, A. B.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1974**, *35*, 87.

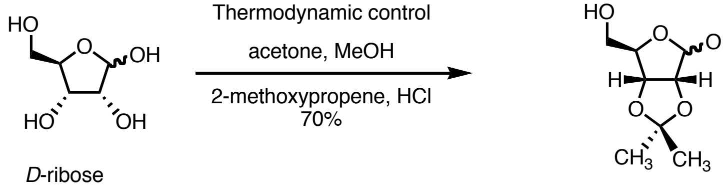


D-galactose

Gelas, J.; Horton, D. *Carbohydr. Res.* **1979**, *71*, 103.

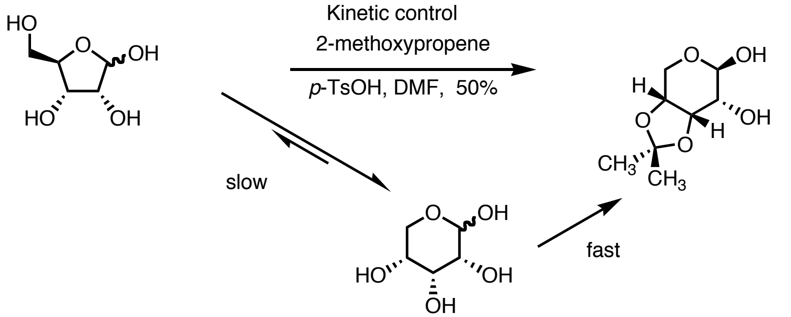
- Note that under kinetic control the most sterically accessible (primary) alcohol is preferentially attacked.
- This reaction can be applied to many hexoses, including mannose, allose, and tallose

Kinetic vs. thermodynamic control with a pentose

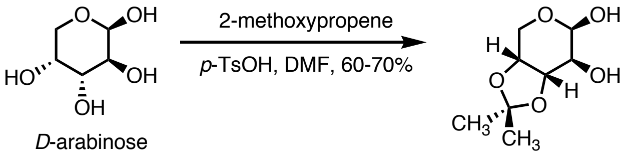


D-ribose

Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485.



The major isomer in solution is the pyranose form (≈ 80%). Under conditions that favor kinetic control, the least sterically encumbered alcohol in this form reacts preferentially. Isomerization is proposed to be slower than acetonide formation. This procedure also works well with arabinose:



D-arabinose

Gelas, J.; Horton, D. *Carbohydr. Res.* **1975**, *45*, 181.

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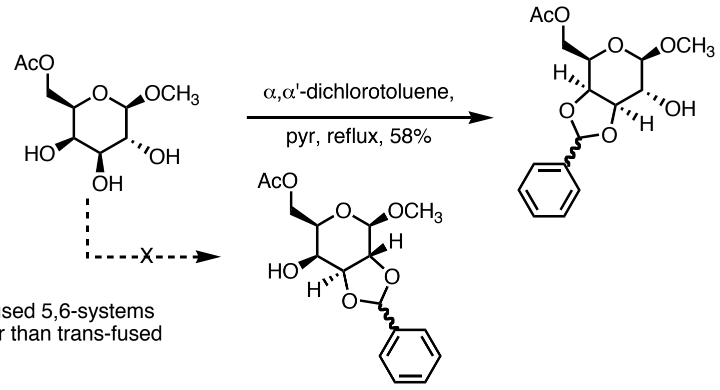
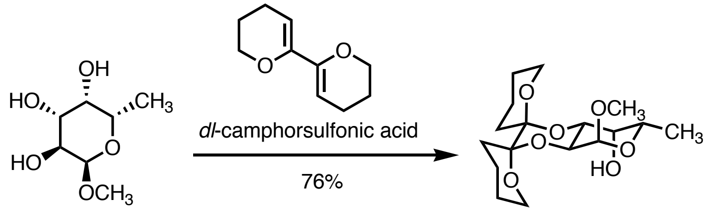
Protection of cis-vicinal diols:



- In general, cis-fused 5,6-systems are formed faster than trans-fused 5,6-systems.

Garegg, P. J.; Maron, L.; Swahn, C. G. *Acta. Chem. Scand.* **1972**, *26*, 518.

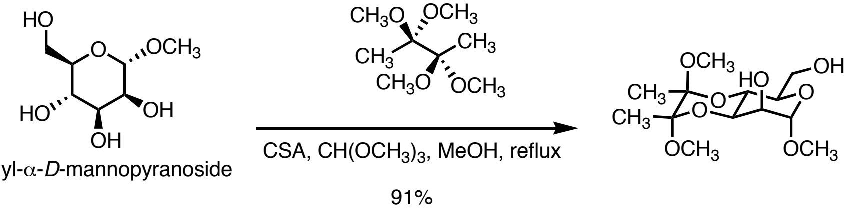
Formation of dispiroacetals as a protective group for vicinal trans diequatorial diols:



methyl-α-*L*-fucopyranoside
(derived from *L*-fucose)

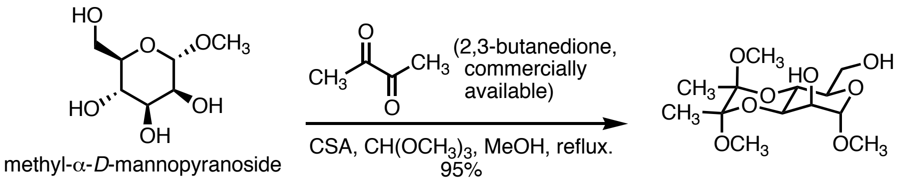
Ley, S. V.; Leslie, R.; Tiffin, P. D.; Woods, M. *Tetrahedron Lett.* **1992**, 4767.

A cheaper alternative has also been developed:



methyl-α-*D*-mannopyranoside

Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897.


(2,3-butanedione, commercially available)
CSA, CH(OCH3)3, MeOH, reflux.
95%

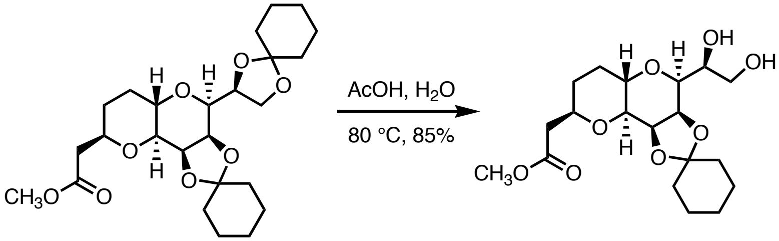
methyl-α-*D*-mannopyranoside

BF_3•OEt_2 is also an effective catalyst at 23 °C.

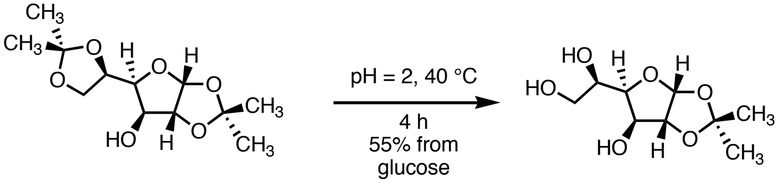
Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, R. D.; Poisson, J.-F.; Warriner, S. L.; Wesson., K. E. *J. Chem. Soc., Perkins Trans. 1* **1997**, 2023.

Generalities concerning the selective removal of acetals and ketals:

- Hydrolysis of the less substituted dioxane or dioxolane ring occurs preferentially in substrates bearing two such groups.

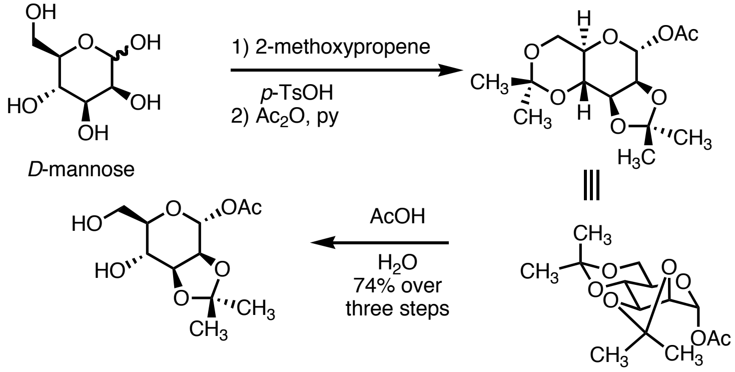


Kishi, Y.; Stamos, D.P. *Tetrahedron Lett.* **1996**, *37*, 8643



Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318.

- 2,2-disubstittued 1,3-dioxanes (6-membered rings) are generally hydrolyzed faster than the corresponding dioxolanes (5-membered rings).



Horton, D.; Gelas, J. *Carbohydr. Res.* **1978**, *45*, 181.

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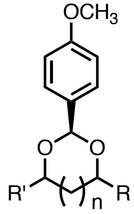
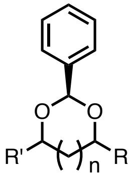
Special properties of benzylidene and substituted benzylidene acetals:

- In general, substitution of the ring of a benzylidene acetal with a *p*-methoxy substituent increases the rate of hydrolysis by about an order of magnitude.

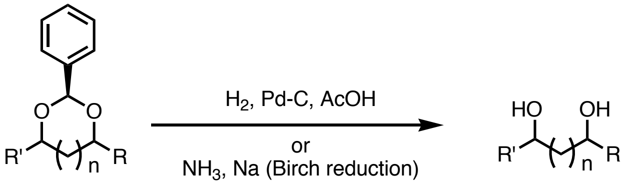


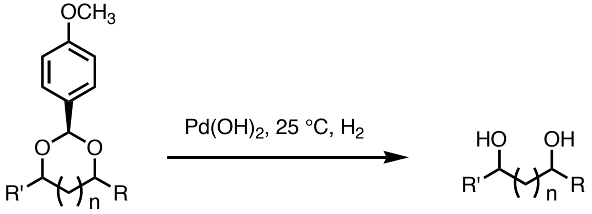
is more rapidly hyrolyzed than



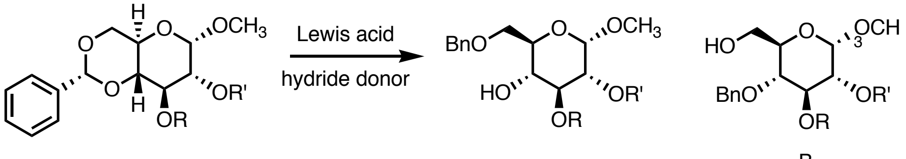
Smith, M.; Rammler, D. H.; Goldberg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430.

- Benzylidene acetals can can also be cleaved from the diol reductively.





- Methods have also been developed to cleave only one carbon-oxygen bond resulting in the formation of a benzyl ether. This reaction has been extensively studied in the context of carbohydrate chemistry.



A

B

R'	R'	Lewis acid	hydride donor	yield (regioisomer)
Ac	Ac	TFA	Et$_3$SiH	95% (A)
Bn	Bn	TFA	Et$_3$SiH	80% (A)
Bn	Bn	Bu$_2$BOTf	BH$_3$•THF	87% (B)
Bn	Bn	AlCl$_3$	BH$_3$•N(CH$_3$)$_3$	72% (A)
Bn	Bn	HCl, THF	NaBH$_3$CN	82% (A)

- The trifluroacetic acid/triethylsilane reagent was ineffective with a galactose derivative, however the others apperar to be general methods. Acetonides and other ketals and acetals can also be reduced, so care in synthetic planning must be exercised.

Trifluoroacetic acid, triethylsilane :
DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *5*, 669.

Dibutylboron triflate, borane:
Chan, T. H.; Lu, J. *Tetrahedron Lett.*, **1998**, *39*, 355.

Aluminum trichloride, borane trimethylamine complex;
Garegg, P. J. *Pure. Appl. Chem.* **1984**, *56*, 845.

HCl, sodium cyanoborohydride:
Qiao, L.; Vederas, J. C. *J. Org. Chem.* **1993**, *58*, 3480.

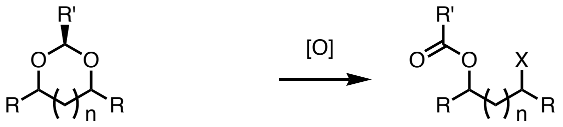
TfOH, sodium cyanoborohydride
Kiessling, L. L.; Pohl, N. L. *Tetrahedron Lett.* **1997**, *38*, 6985.

Diisobutyl aluminum hydride is also an effective reagent for regioselective reduction of benzylidene acetals. This reagent gives the more hindered ether.

Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

Oxidation of benzylidene and substituted benzylidene acetals:

- Acetals containing a methine group may be oxidized at that position resulting in the formation of a hydroxy esters.



- This transformation can be effected under a variety of condtions, and and some variants can be used to further functionalize a substrate.

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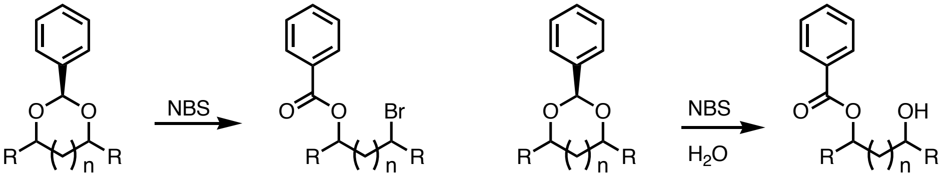
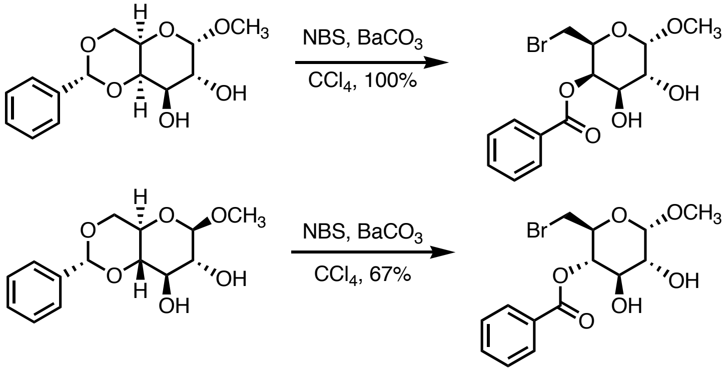
General Reactions:

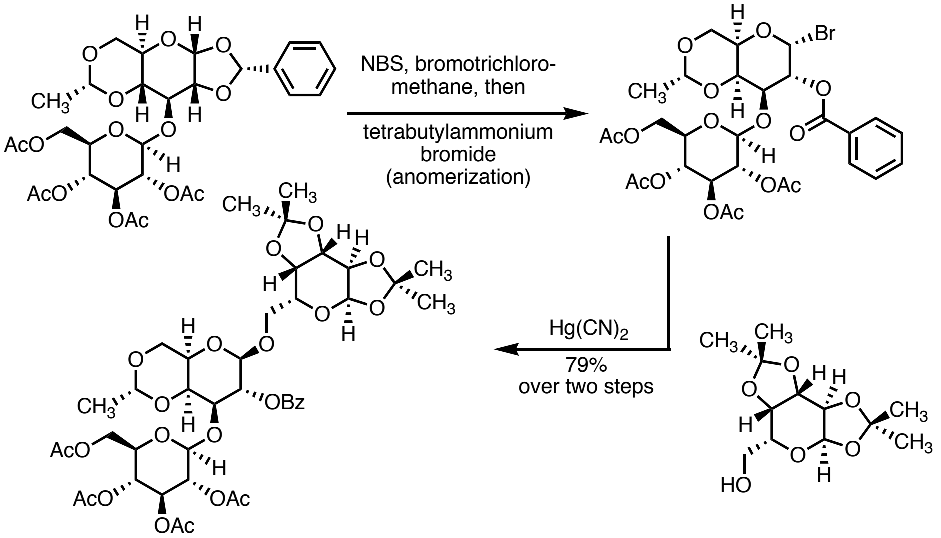


In the methyl 4,6-*O*-benzylidenehexopyranoside series, the oxidative formation of bromo benzoates is a general reaction:



Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035, 1045, and 1053.

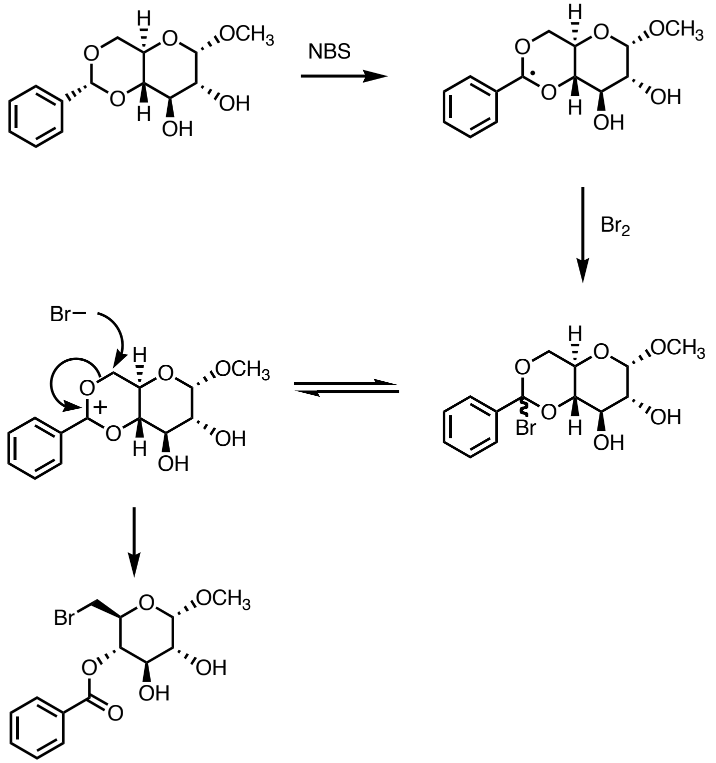
- This reaction has also been used to generate glycosylating reagents



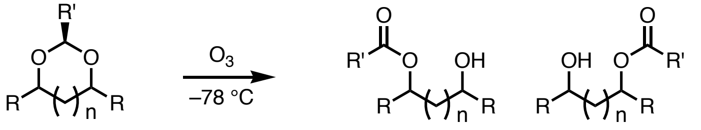
CH_3
AcO
OAc
NBS, bromotrichloro-methane, then
tetrabutylammonium bromide (anomerization)
Br
OBz
$Hg(CN)_2$
79%
over two steps
HO

Collins, J. M.; Manro, A.; Opara-Mottah, E. C.; Ali, M. H.
J. Chem. Soc., Chem. Comm. **1988**, 272.

Proposed Mechanism:



- Ozonolysis also cleaves acetals to hydroxy esters efficiently. This reaction has been reviewed: Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.



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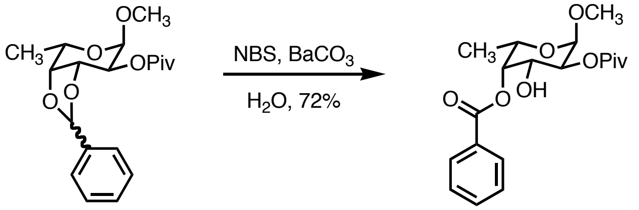
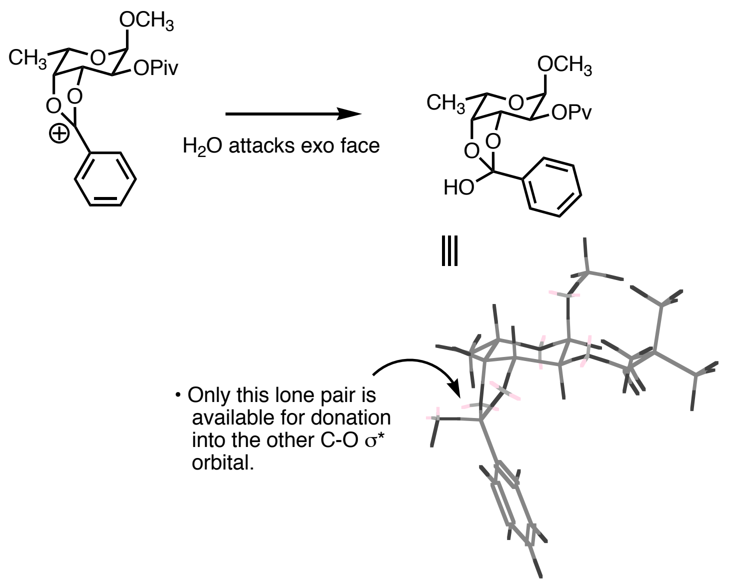
- Hydroxy benzoates are obtained in the presence of water.
- The axial benzoate is usually obtained.

Binkley, R. W.; Goewey, G. S.; Johnston, J. C. *J. Org. Chem.* **1984**, *49*, 992

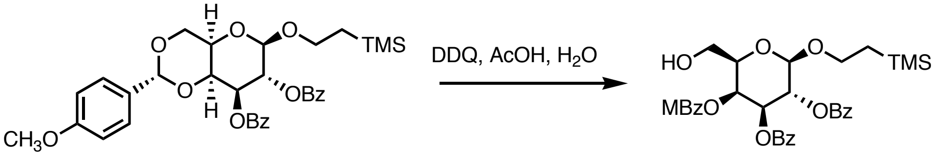




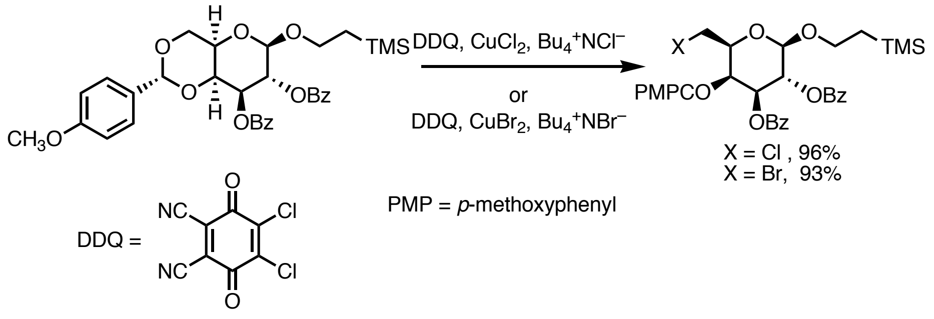
- Only this lone pair is available for donation into the other C-O σ* orbital.

King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754.

- Oxidation of 4-methoxybenzylidene acetals has also been studied:



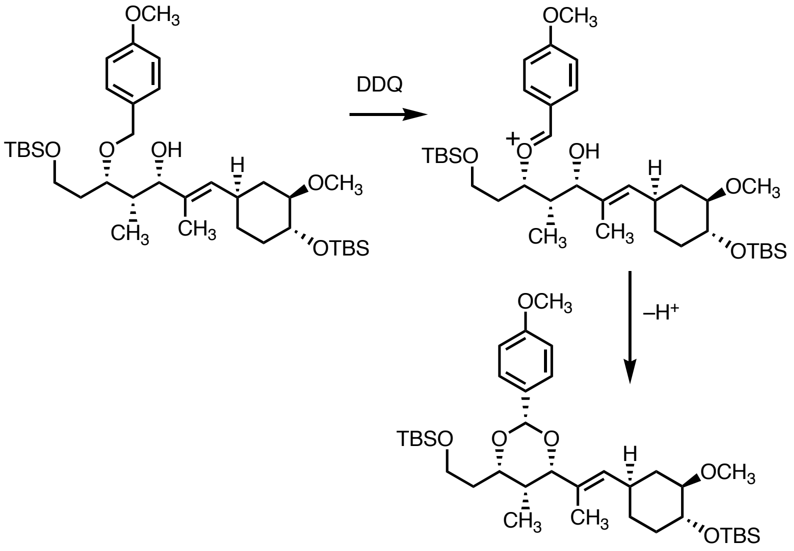
79% (19% of regioisomer)



PMP = *p*-methoxyphenyl

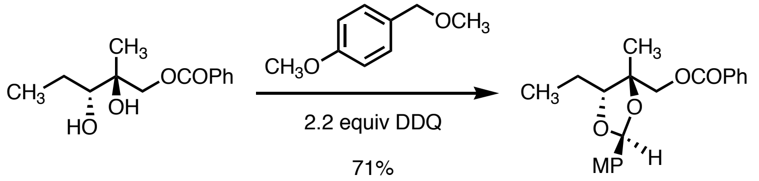
Zhang, Z.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 2394.

- 2- electron oxidation of 4-methoxybenzyl groups with DDQ is a general reaction.
- This has been used extensively to remove 4-methoxybenzyl ethers, and also to form 4-methoxybenzylidene acetals.



Jones, A. B.; Yamaguchi, M.; Patten, S.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17.

A useful extension of this reaction has been developed to protect diols directly:



Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037.

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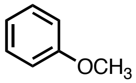
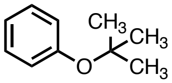
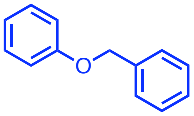
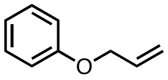
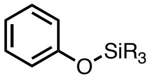
Phenolic Protective Groups:

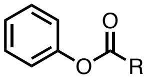

Methyl Ether

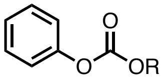

t-Butyl Ether

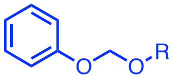

Benzyl Ether

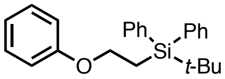

Allyl Ether


Silyl Ethers

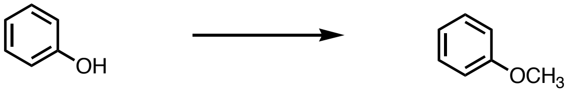

Phenyl Esters


Phenyl Carbonates


Acetals


t-Butyldiphenylsilylethyl Ether

Methyl ether formation:



1. MeI, K_2CO_3, acetone. Vyas, G. N.; Shah, N. M. *Org Synth., Collect. Vol. IV* **1963**, 836.

2. Diazomethane, Et_2O. Bracher, F.; Schulte, B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2619.

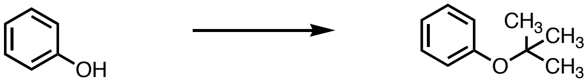
Methyl ether cleavage:

1. Me_3SiI, $CHCl_3$, 25-50 °C. This reagent also cleaves benzyl, trityl, and *t*-butyl ethers rapidly. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

2. EtSNa, DMF, reflux. Ahmad, R.; Saa, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228.

3. 9-Bromo-9-borabicyclo[3.3.0]nonane, CH_2Cl_2. Bhatt, M. V. *J. Organomet. Chem.* **1978**, *156*, 221.

t-Butyl ether formation:



1. Isobutylene, CF_3SO_3H, CH_2Cl_2, –78 °C. Holcombe, J. L.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 11.

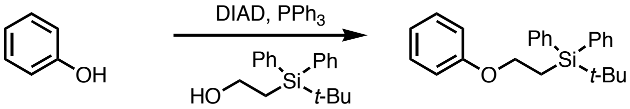
2. *t*-Butyl halide, pyr. Masada, H.; Oishi, Y. *Chem. Lett.* **1978**, 57.

t-Butyl Ether Cleavage:

1. CF_3CO_2H, 25 °C. Beyerman, H. C.; Bontekoe, J. S. *Recl. Trav. Chim. Pays-Bas.* **1962**, *81*, 691.

- For the other phenol protective groups, the sections describing these groups in the context of alcohols should be consulted. Most of the preparations are used for alcohols are applicable to phenols. Hydroxyl protective groups that are cleaved with base are generally more labile with phenols.

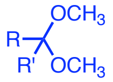
t-Butyldiphenylsilylethyl (TBDPSE) ether formation:

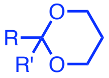


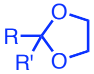
- The TBDPSE group is stable to 5% TFA–CH_2Cl_2, 20% piperidine–CH_2Cl_2, catalytic hydrogenation, *n*-BuLi, and lead tetraacetate.
- The TBDPSE group has been cleaved using TBAF (2.0 equiv, 40 °C, overnight) or 50% TFA–CH_2Cl_2.

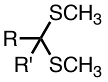
Gerstenberger, B. S.; Konopelski, J. P. *J. Org. Chem.* **2005**, *70*, 1467.

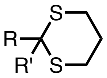
Carbonyl protective groups:

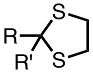

dimethyl acetal

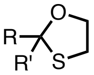

1,3-dioxane


1,3-dioxolane


S,S'-dimethylthioacetal


1,3-dithiane

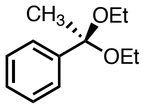

1,3-dithiolane

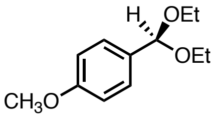

1,3-oxathiolane

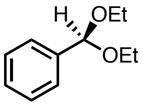
General order of reactivity of carbonyl groups towards nucleophiles:

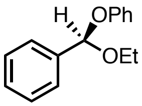
aldehydes (aliphatic > aromatic) > acylic ketones ≈ cyclohexanones > cyclopentanones > a,b-unsaturated ketones ≈ a,a disubstituted ketones >> aromatic ketones.

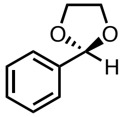
Approximate rates (L mol $^{-1}$s^{-1} at 25-30 °C) for proton-catalyzed (HCl, water or dioxane-water) cleavage of acetals and ketals.


6 X 10^3


5 X 10^3


160


41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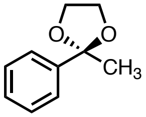
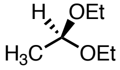
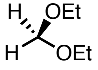
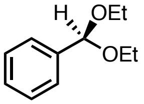

1.2

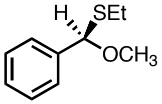

1.6


1.5 X 10^{-4}

- In general, cyclic acetals are cleaved more slowly than their open chain analogs
- In general, dithio acetals are not cleaved by Brønsted acids.

Rates of acid-catalyzed cleavage of mono thioacetals and acetals have been determined:


160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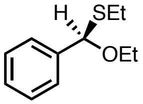
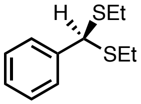
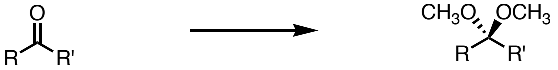

1.3


3.5 X 10^{-4}

Satchell, D. P. N.; Satchell, R. S. *Chem. Soc. Rev.* **1990**, *19*, 55.

Preparation of dimethyl acetals and ketals:

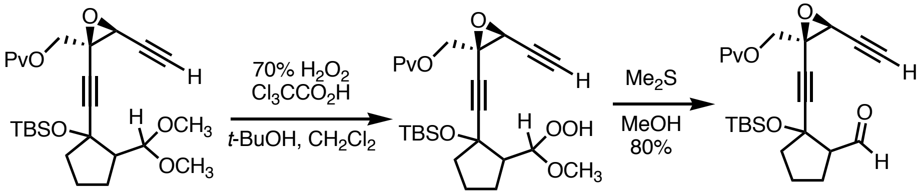


1. MeOH, dry HCl. Cameron, A. F. B.; Hunt, J. S.; Oughton, J. F.; Wilkinson, P. A.; Wilson, B. M. *J. Chem. Soc.* **1953**, 3864.
2. MeOH, $LaCl_3$, $(MeO)_3CH$. Acetals are formed efficiently, but ketalization is unpredictable. Gemal, A. L.; Luche, J.-L. *J. Org. Chem.* **1979**, *44*, 4187.
3. Me_3SiOCH_3, Me_3SiOTf, CH_2Cl_2, –78 °C. Lipshutz, B. H.; Burgess-Henry, J.; Roth, G. P. *Tetrahedron Lett.* **1993**, *34*, 995.
4. $Sc(OTf)_3$, $(MeO)_3CH$, toluene, 0 °C. Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839.

- Other dialkyl acetals are formed similarly.

Cleavage of dimethyl acetals and ketals:

1. TFA, $CHCl_3$, H_2O. These conditions cleaved a dimethyl acetal in the presence of a 1,3-dithiane and a dioxolane acetal. Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.
2. TsOH, acetone. Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1971**, 858.
3. 70% H_2O_2, Cl_3CCO_2H, CH_2Cl_2, *t*-BuOH; dimethyl sulfide. Myers, A. G.; Fundy, M. A. M.; Lindstrom, Jr. P. A. *Tetrahedron Lett.* **1988**, *29*, 5609.

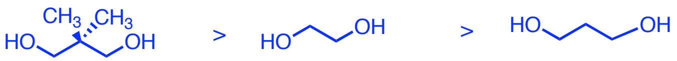


- Other methods resulted in cleavage of the epoxide.

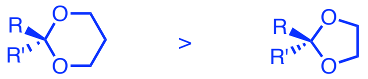
P. Hogan

Cyclic acetals and ketals:

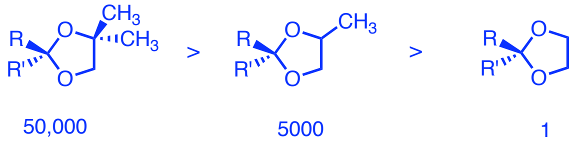
Relative rates of ketalization with common diols:



Cleavage of 1,3-dioxolanes vs. 1,3-dioxanes:

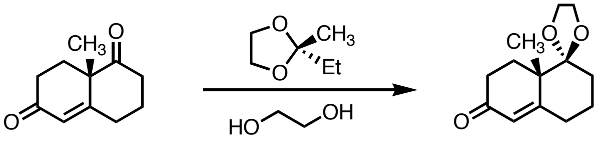


Relative rates of cleavage for 1,3-dioxolanes:



Okawara, H.; Nakai, H.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1087.

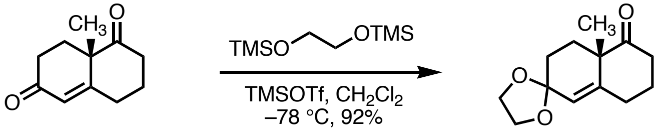
- In general, saturated ketones can be selectively protected in the presence of α,β-unsaturated ketones.



p-TsOH•H_2O, 95%

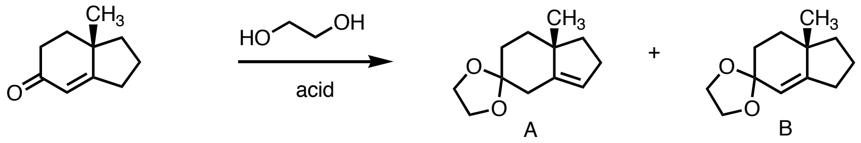
Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, T.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

- Conditions have been developed to protect α,β-unsaturated ketones selectively.



Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

- When protecting α,β-unsaturated ketones, olefin isomerization is common.



Strong acids ($pK_a \approx 1$) tend to favor isomerization, while weaker acids ($pK_a \geq 3$) favor isomerization much less so, or not at all.

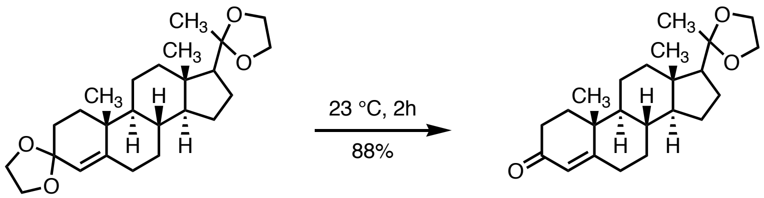
acid	pK_a	%A	%B	% conversion
fumaric acid	3.03	100	0	90
phthalic acid	2.89	70	30	90
oxalic acid	1.23	80	20	93
TsOH	< 1.0	0	100	100

De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas.* **1973**, *92*, 1047.

- Generally, methods used for formation of 1,3-dioxolanes are also useful for formation of 1,3-dioxanes.

Cleavage of 1,3-dioxanes and 1,3-dioxolanes:

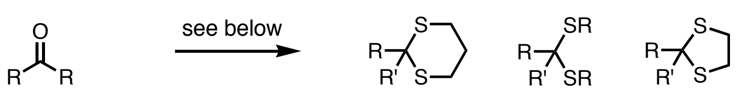
1. PPTS, acetone, H_2O, heat. Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1351.
2. 1M HCl, THF. Grieco, P. A.; Nishizawa, M.; Oguri, T. Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *43*, 4178.
3. Me_2BBr, CH_2Cl_2, –78 °C. This reagent also cleaves MEM and MOM ethers. Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969.
4. NaI, $CeCl_3$•$7H_2O$, CH_3CN. Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. This method is selective for cleavage of ketals in the presence of acetals. It is also selective for ketals of α,β-unsaturated ketones over ketals of saturated ketones.



P. Hogan

Dithioacetals:

General methods of formation of *S,S*"-dialkyl acetals:



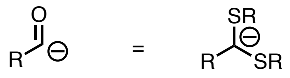
1. RSH, HCl, 20 °C. Zinner, H. *Chem. Ber.* **1950**, *83*, 275.
2. RSSi(CH_3)$_3$, ZnI_2, Et_2O. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.
3. RSH, $BF_3 \cdot Et_2O$, CH_2Cl_2. Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, 871. See also Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. α,β-Unsaturated ketones are reported not to isomerize under these conditions. However, with any of the above mentioned conditions conjugate addition is a concern.

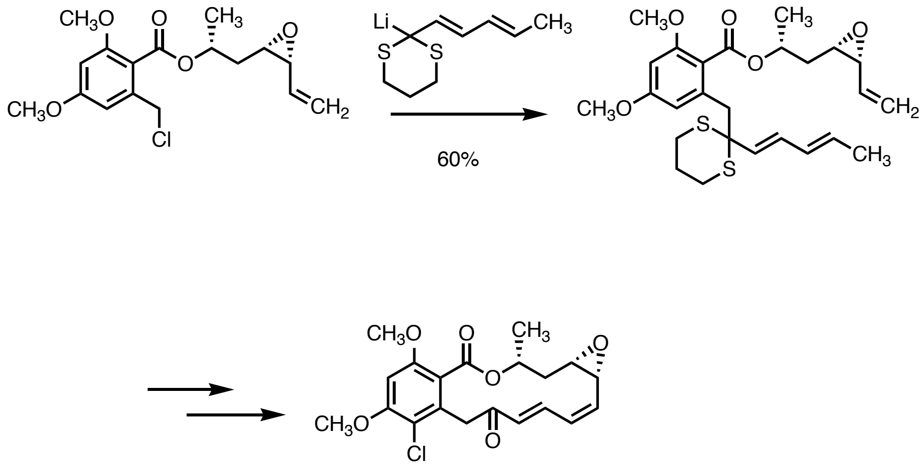
- A variety of methods has been developed for the cleavage of *S,S*"-dialkyl acetals, largely due to the fact that these functional groups *are often difficult to remove*.

General methods of cleavage of *S,S*"-dialkyl acetals:

1. Hg(ClO_4)$_2$, MeOH, $CHCl_3$. Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15, and references therein.
2. $CuCl_2$, CuO, acetone, reflux. Stutz, P.; Stadler, P. A. *Org. Synth. Collect. Vol.* **1988**, *6*, 109.
3. *m*-CPBA; Et_3N Ac_2O, H_2O. Kishi, Y.; Fukuyama, T.; Natatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490.
4. (CF_3CO_2)$_2$IPh, H_2O, CH_3CN. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

In addition to serving as a protective group, *S, S'*-dialkyl acetals serve as an umpolung synthon in the construction the of carbon-carbon bonds.

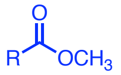




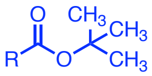
Radicicol dimethyl ether

Garbaccio, R. M.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3127.

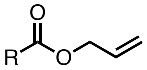
Carboxyl Protective Groups:



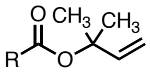
Methyl Ester



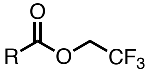
t-Butyl Ester



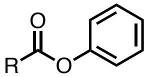
Allyl Ester



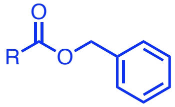
1,1-Dimethylallyl Ester



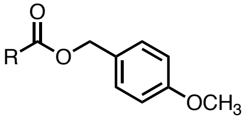
2,2,2-Trifluoroethyl Ester



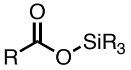
Phenyl Ester



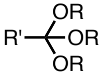
Benzyl Ester



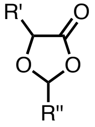
4-Methoxybenzyl Ester



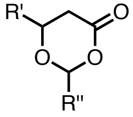
Silyl Ester



Ortho Ester



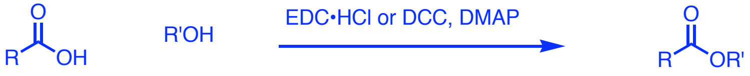
1,3-Dioxalone



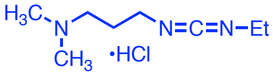
1,3-Dioxanone

Specific to a- and ß-hydroxy acids

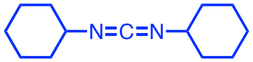
General preparations of esters:



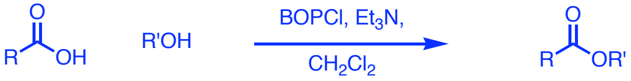
EDC = 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride

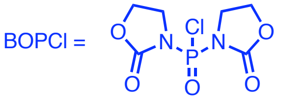


DCC = dicyclohexyldiimide



EDC •HCl is more expensive, but the urea by-product is water soluble and simplifies the purification of products.

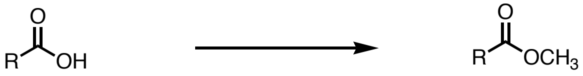




DIago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis*, **1980**, 547.

Methyl esters:

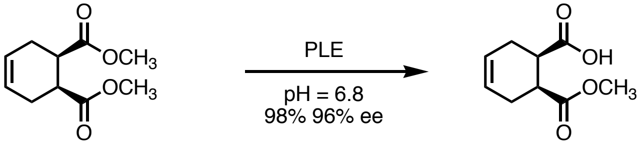
Formation:



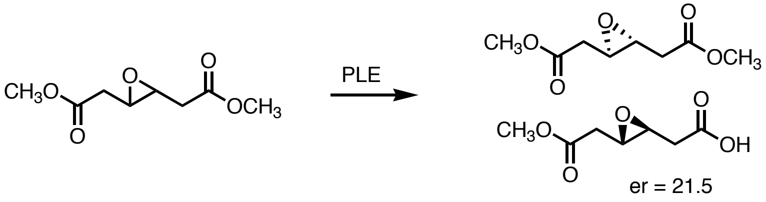
1. TMSCHN$_2$, MeOH, benzene. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. This is considered a safe alternative to using diazomethane.
2. MeOH, H$_2$SO$_4$. Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536.

Cleavage:

1. LiOH, MeOH, 5 °C. Corey, E. J.; Szekely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, 3529.
2. Pig liver esterase. This enzyme is often effective for the enantioselective cleavage of a meso diester.



Kobayashi, S.; Kamiyama, K.; Iimori, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 2557.

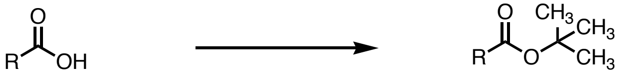


Mohr, P.; Rosslein, L.; Tamm, C. *Tetrahedron Lett.* **1989**, *30*, 2513.

P. Hogan/Seth B. Herzon

t-Butyl esters

Formation:



1. Isobutylene, H_2SO_4, Et_2O, 25 °C. McCloskey, A. L.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. *Org. Synth., Collect. Vol. IV.* **1963**, 261.

2. 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; *t*-BuOH, DMAP, benzene, 20 °C. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

3. *t*-BuOH, EDC•HCl, DMAP, CH_2Cl_2. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

4. *i*-PrN=C(O-*t*Bu)NH-*i*-Pr, toluene, 60 °C. Burk, R. M.; Berger, G. D.; Bugianesi, R. L.; Girotra, N. N.; Parsons, W. H.; Ponpipom, M. M. *Tetrahedron Lett.* **1993**, *34*, 975.

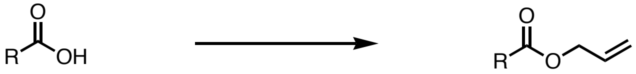
Cleavage:

1. CF_3CO_2H, CH_2Cl_2. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.

2. Bromocatechol borane. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

Allyl esters

Formation:



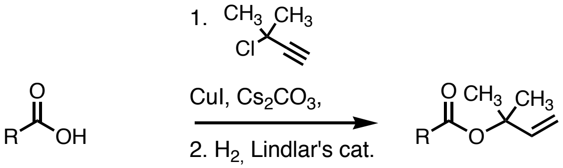
1. Allyl bromide, Cs_2CO_3, DMF. Kunz, H.; Waldmann, H.; Unverzagt, C. *Int. J. Pept. Protein Res.* **1985**, *26*, 493.
2. Allyl alcohol, TsOH, benzene, ($–H_2O$). Wladmann, H.; Kunz, H. *Liebigs Ann. Chem.*, **1983**, 1712.

Cleavage:

1. The use of allyl esters in synthesis has been reviewed. Guibe, F.: *Tetrahedron*, **1998**, *54*, 2967.
2. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.

1,1-Dimethylallyl esters

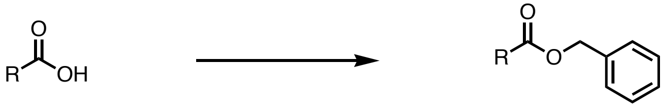
Formation:



- The 1,1-dimethylallyl ester is removed under the same conditions as an allyl ester, but is less susceptible to nucleophilic attack at the acyl carbon.

Sedighi, M.; Lipton, M. A. *Org. Lett.* **2005**, *7*, 1473.

Benzyl ester.



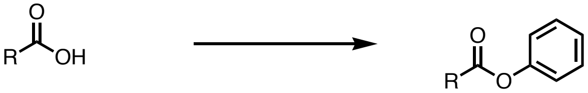
Benzyl esters are typically prepared by the methods outlined in the general methods section.

cleavage:

1. H_2, Pd–C. Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263.
2. BCl_3, CH_2Cl_2. Schmidt, U.; Kroner, M.; Griesser, H. *Synthesis*. **1991**, 294.

Phenyl esters

Formation:



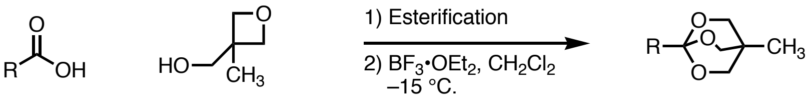
Phenyl esters typically prepared by the methods outlined in the general methods section. They have have the advantage of being cleaved under mild, basic conditions.

1. H_2O_2, H_2O, DMF, pH = 10.5. Kenner, G. W.; Seely, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3259.

P. Hogan/ Seth B. Herzon

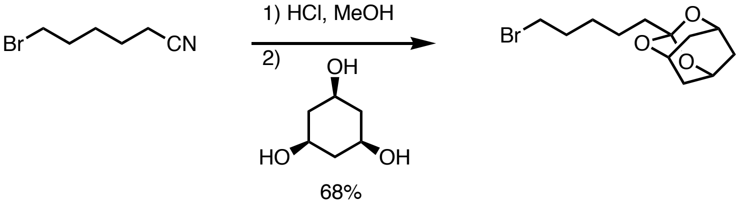
Ortho Esters:
The synthesis of simple ortho esters has been reviewed: Dewolfe, R. H. *Synthesis*, **1974**, 153.

OBO ester



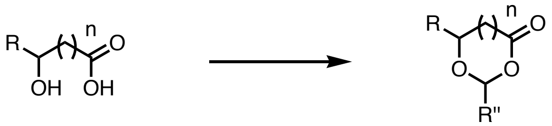
Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.

Alternatively, ortho esters can be prepared from a nitrile:



Voss, G.; Gerlach, H. *Helv. Chim. Acta.* **1983**, *66*, 2294.

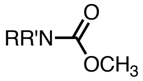
Special Carboxylates, α-Hydroxy and ß-Hydroxy:

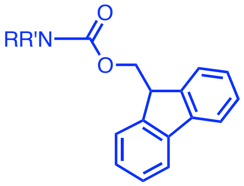


Formation:

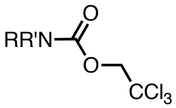
1. Ketone or aldehyde, $Sc(NTf_2)_3$, CH_2Cl_2, $MgSO_4$. Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839.
2. Pivaldehyde, acid catalyst. Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta.* **1986**, *70*, 448, and references cited therein.

Protection of amines:

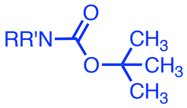

Methyl Carbamate


9-Fluorenylmethyl Carbamate

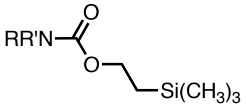
(Fmoc)


2,2,2-Trichloroethyl Carbamate

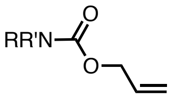
(Troc)


t-Butyl Carbamate

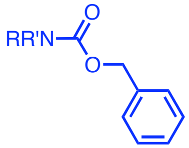
(Boc)


2-(Trimethylsilyl)ethyl Carbamate

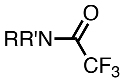
(Teoc)

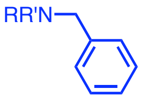

Allyl Carbamate

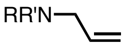
(Alloc)

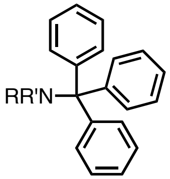

Benzyl carbamate

(Cbz)

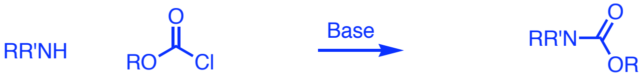

Trifluoroacetamide

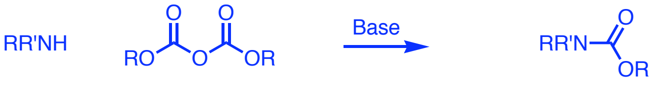

Benzylamine

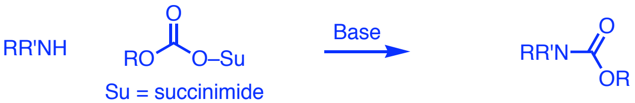

Allylamine


Tritylamine

General preparation of carbamates:



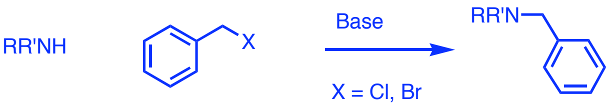




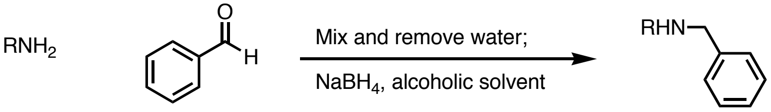
Su = succinimide

Bases that are typically employed are tertiary amines or aqueous hydroxide.

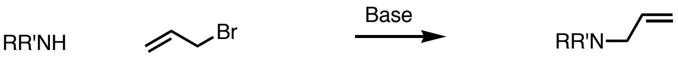
Formation of benzylamines:



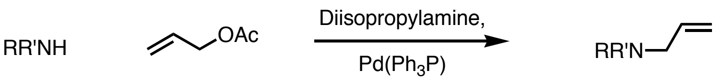
If primary amines are the starting materials, dibenzylamines are the products.



Formation of allylamines:

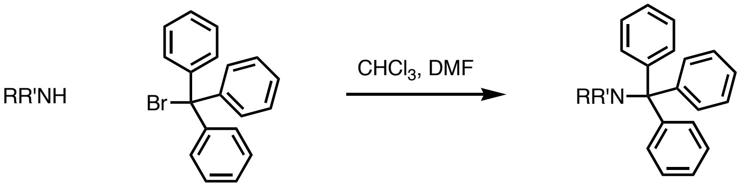


If primary amines are the starting materials, diallylamines are the products.



Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.

Formation of tritylamines:

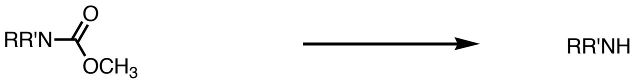


Mutter, M.; Hersperger, R. *Synthesis* **1989**, 198.

P. Hogan

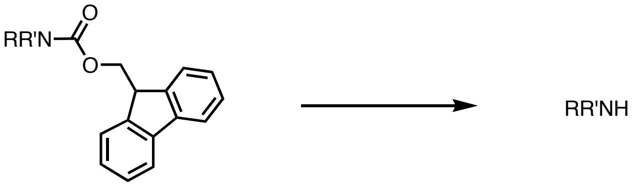
Cleavage of carbamates:

Methyl Carbamate:



1. TMSI, CH_2Cl_2. Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442.
2. MeLi, THF. Tius, M.; Keer, M. A. *J. Am. Chem. Soc.* **1992**, *114* , 5959.

9-Fluorenylmethyl Carbamate:

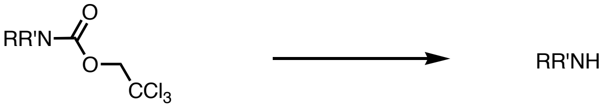


1. Amine base. The half-lives for the deprotection of Fmoc-ValOH have been studied Atherton, E.; Sheppard R. C. in *The Peptides*, Udenfriend, S. and Meienhefer Eds., Academic Press: New York, **1987**, Vol. 9, p. 1.

Amine base in DMF	Half-Life
20% piperidine	6 s
5% piperidine	20 s
50% morpholine	1 min
50% dicyclohexylamine	35 min
10% *p*-dimethylaminopyridine	85 min
50% diisopropylethylamine	10.1 h

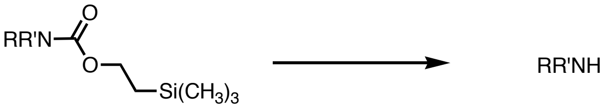
2. $Bu_4^+F^-$, DMF. Ueki, M.; Amemiya, M. *Tetrahedron Lett.* **1987**, *28*, 6617.
3. $Bu_4^+F^-$, *n*-$C_8H_{17}SH$. Thiols can be used to scavenge liberated fulvene. Ueki, M.; Nishigaki, N.; Aoki, H.; Tsurusaki, T.; Katoh, T. *Chem. Lett.* **1993**, 721.

2,2,2-Trichloroethyl Carbamate:



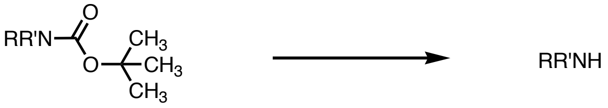
1. Zn, H_2O, THF, pH = 4.2. Just. G.; Grozinger, K. *Synthesis*, **1976**, 457.
2. Cd, AcOH. Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249.

2-Trimethylsilylethyl Carbamate:



1. $Bu_4N^+F^-$, $KF{\bullet}H_2O$, CH_3CN, 50 °C. Carpino, L. A.; Sau A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.
2. CF_3COOH, 0 °C. Carpino, L. A.; Tsao, J. H,; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358.
3. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), DMF. Roush, W. R.; Coffey, D.S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *49*, 2325.

t-Butyl carbamate:



1. CF_3COOH, PhSH. Thiophenol is used to scavenge *t*-butyl cations. TBS and TBDMS ethers are reported to be stable under these conditions. Jacobi, P, A.; Murphree, F.; Rupprecht, F.; Zheng, W. *J . Org. Chem.* **1996**, *61*, 2413.
2. Bromocatecholborane. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

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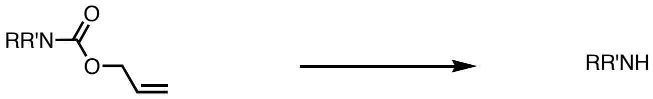
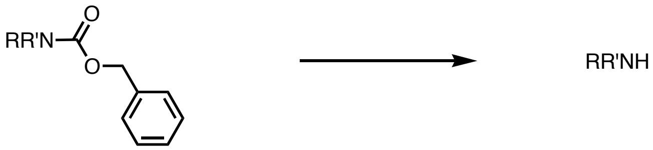
Allyl Carbamate:



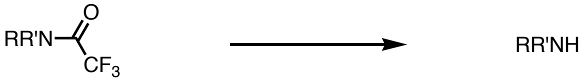
1. $Pd(Ph_3P)_4$, Bu_3SnH, AcOH, 70 – 100% yield. Dangles, O.; Guibe, F.; Balavoin, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.
2. $Pd(Ph_3P)_4$, $(CH_3)_2NTMS$, 89 – 100% yield. Merzouk A.; Guibe, F. *Tetrahedron Lett.* **1992**, *33*, 477.

Benzyl Carbamate:



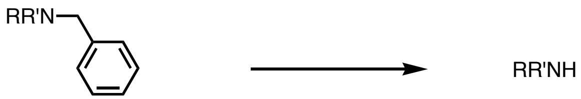
1. H_2/Pd–C. Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.
2. H_2/Pd–C, NH_3. These conditions cleave the benzyl carbamate in the presence of a benzyl ether. Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465.
3. BBr_3, CH_2Cl_2. Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427.
4. Bromocatecholborane. This reagent is reported to cleave benzyl carbamates in the presence of benzyl ethers and TBS ethers. Boeckman Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

Trifluoroacetamide:



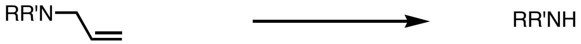
1. K_2CO_3, MeOH. Bergeron, R. J.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108.

Benzylamine:



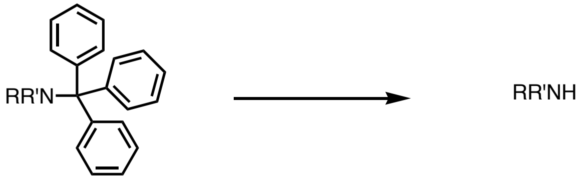
1. Pd–C, ROH, HCO_2NH_4. Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.
2. Na, NH_3. Bernotas, R. C.; Cube, R. V. *Synth. Comm.* **1990**, *20*, 1209.

Allylamine:



1. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2. Most allyl groups are cleaved by this method, including allyl ethers and esters. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.

Tritylamine:



1. 0.2% TFA, 1% H_2O, CH_2Cl_2. Alsina, J.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1996**, *37*, 4195.

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Alkyne protecting groups:

$$\mathrm{R{-}C{\equiv}C{-}SiR'_3}$$

trialkylsilylalkyne

- Typical silyl groups include TMS, TES, TBS, TIPS, and TBDMS. Many silyl acetylenes are commercially available, and are useful acetylene equivalents.

General preparation of silyl acetylenes:

$$\mathrm{R{-}C{\equiv}C{-}M} \xrightarrow[\text{X= Cl, OTf}]{\mathrm{R'_3SiX}} \mathrm{R{-}C{\equiv}C{-}SiR'_3}$$

M = Li, Mg

- Silyl chorides are suitable for smaller silyl groups, but the preparation of more hindered silyl acetylenes may require the use of the more reactive silyl triflate.

- In general, a strong fluoride source such as TBAF is used to cleave silylalkynes. In the case of trimethylsilylalkynes, milder conditions can be used.

$$\mathrm{R{-}C{\equiv}C{-}SiR'_3} \xrightarrow{\text{TBAF, THF}} \mathrm{R{-}C{\equiv}C{-}H}$$

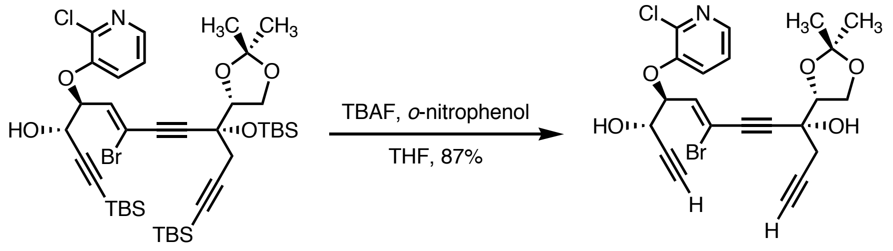
Cleavage of trimethysilylalkynes:

1. KF, MeOH, 50 °C. Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.

2. $AgNO_3$ 2,6-lutidine. Carreira, E. M.; Du Bois, J. *J. Am. Chem Soc.* **1995**, *117*, 8106.

3. K_2CO_3, MeOH. Cai, C.; Vasella, A. *Helv. Chim. Acta.* **1995**, *78*, 732.

- Buffered TBAF was used to deprotect the silyalkynes in the example shown below to prevent elimination of the sensitive vinyl bromide.



Myers, A.G.; Goldberg, S. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *15*, 2732.

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Reviews:

Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1-334.

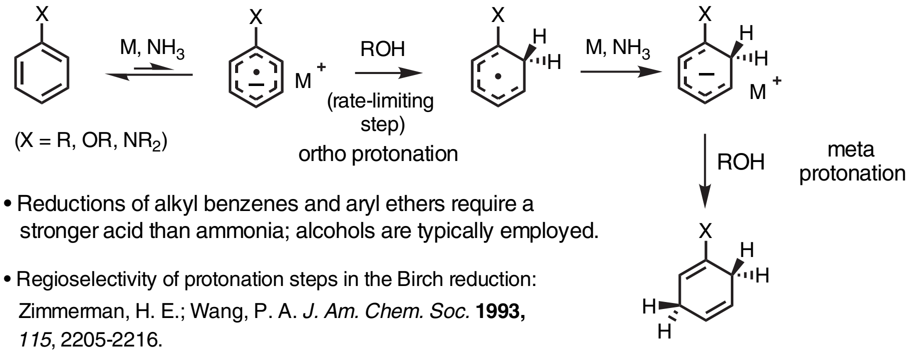
Mander, L. N. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Ed.; Pergamon: Oxford, **1991**, Vol. 8, pp. 489-521.

Hook, J. M.; Mander, L. N. *Natural Prod. Rep.* **1986**, *3*, 35-85.

Propects for Stereocontrol in the Reduction of Aromatic Compounds: Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron: Asymmetry* **1996**, *7*, 317-344.

Mechanism:

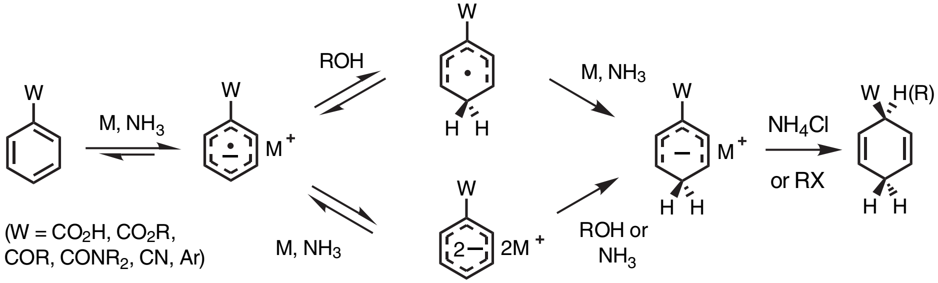
Electron-Donor Substituents (X):



- Reductions of alkyl benzenes and aryl ethers require a stronger acid than ammonia; alcohols are typically employed.
- Regioselectivity of protonation steps in the Birch reduction: Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993,** *115*, 2205-2216.

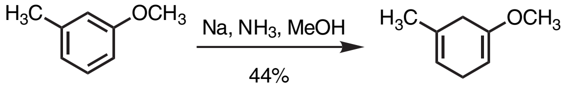
- Protonation of cyclohexadienyl anions is kinetically controlled and occurs at the central carbon.

Electron-Withdrawing Substituents (W):

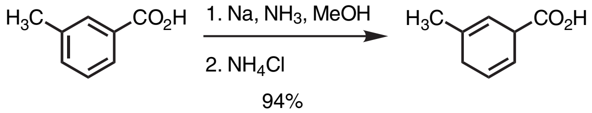


- Aromatic carboxylic acids and carboxylates are readily reduced with Li/NH_3 in the absence of alcohol additives.

Additivity of Substituent Effects:



Birch, A. J. *J. Chem. Soc.* **1944**, 430-436.



Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41-47.

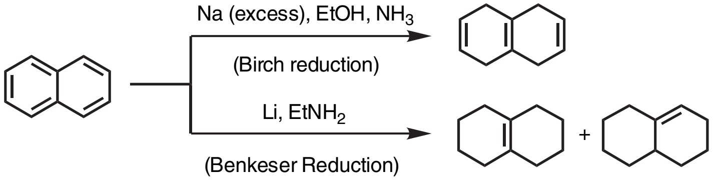
Conditions:

- Metals: Li, K, Na, occasionally Ca or Mg.
- Co-solvents: diethyl ether, THF, glymes.
- Proton sources (where appropriate): *t*-BuOH and EtOH are most common, also MeOH, NH_4Cl, and water.

Metal	Solubility in NH_3 at –33 °C (g-atom M/mol NH_3)	Normal reduction potential at –50 °C in NH_3 (V)
Li	0.26	–2.99
Na	0.18	–2.59
K	0.21	–2.73

From: Briner, K. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed.; John Wiley and Sons: New York, **1995**, Vol. 5, pp. 3003-3007.

- Reduction in low molecular weight amines (Benkeser reduction):



- Reduction in low molecular weight amines (in the absence of alcohol additives) furnishes more extensively reduced products than are obtained under Birch conditions (M, NH_3, ROH).

A Comparison of Methods Using Lithium/Amine and Birch Reduction Systems: Kaiser, E. M. *Synthesis* **1972**, 391-415.

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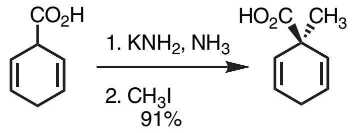
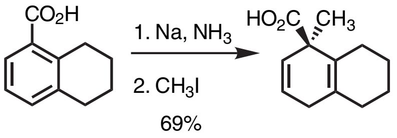
Reductive alkylation:

- Enolates derived from 1,4-dihydrobenzoic acids are selectively alkylated at the α-carbon.



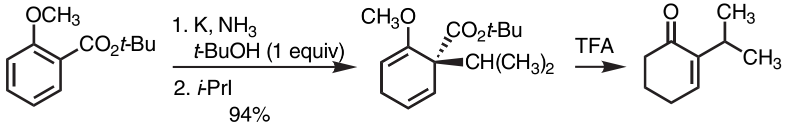
Nelson, N. A.; Fassnacht, J. H.; Piper, J. U. *J. Am. Chem. Soc.* **1961**, *83*, 206-213.
See also: Birch, A. J. *J. Chem. Soc.* **1950**, 1551-1556.

- Loewenthal and co-workers first demonstrated single step reductive alkylation of aromatic compounds:

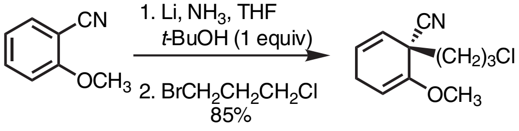


Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *J. Org. Chem.* **1969**, *34*, 126-135.

- Reductive alkylations of aromatic esters, amides, ketones, and nitriles typically are conducted in the presence of one equivalent of an alcohol:



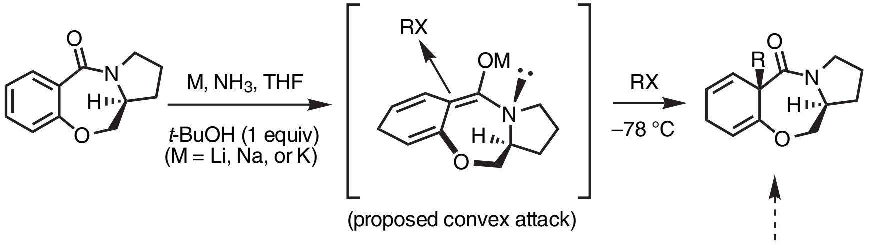
Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095-1098.



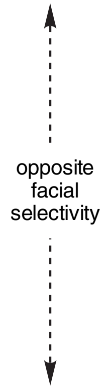
Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983-4987.

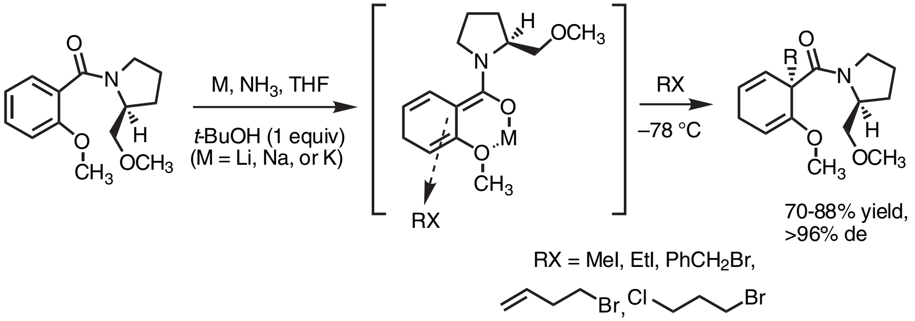
Asymmetric Birch Reduction:

Reviews: Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207-213; Schultz, A. G. *Chem. Commun.* **1999**, 1263–1271.



RX	yield (%)	de (%)
MeI	67	60
EtI	82	>98
CH_2=CH_2CH_2Br	75	>96
$PhCH_2Br$	73	>96
CH_2=$CH_2CH_2CH_2Br$	89	96
$ClCH_2CH_2CH_2Br$	91	(n.d.)

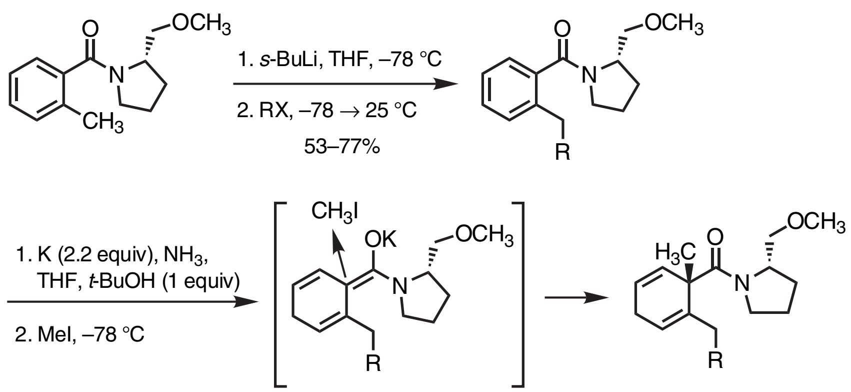




- Transition state may be complex, viz., enolate aggregation and nitrogen pyramidalization.
- Schultz proposes that Birch reduction results in kinetically controlled formation of a dimeric enolate aggregate wherein the metal is chelated by the aryl ether; the side chain of the chiral auxiliary is proposed to block the β-face of the enolate.

Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828-7841.

- 1,6-Dialkyl-1,4-cyclohexadienes are accessible by asymmetric Birch alkylation:

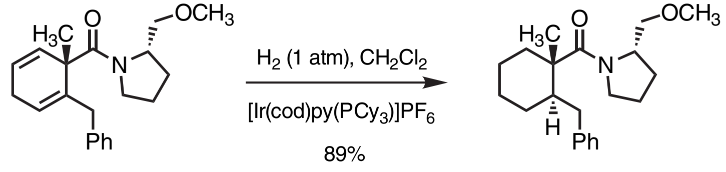


R	yield (%)	de (%)
H	90	> 98
Me	66	93
Et	79	90
$CH_2CH{=}CH_2$	76	93
$CH_2CH_2CH{=}CH_2$	69	90
CH_2Ph	62	95
CH_2CH_2Ph	77	93
$CH_2OCH_2CH_2SiMe_3$	71	94
CH_2CH_2OTBS	88	96
CH_2CH_2OMe	79	95
Ph	69	96

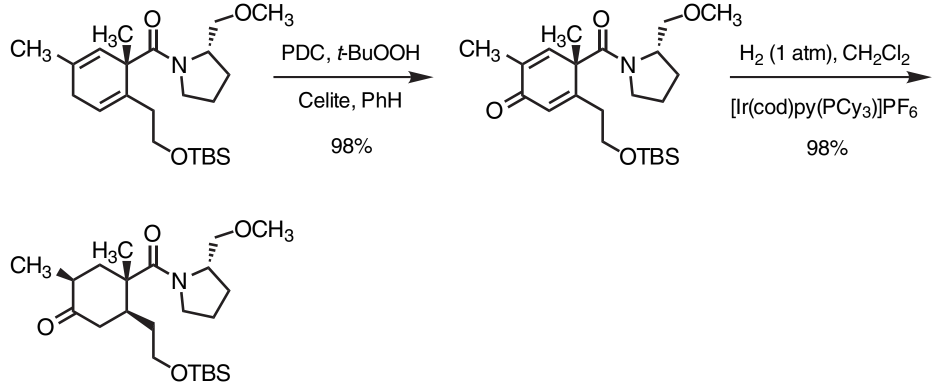
Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.

Transformations of asymmetric Birch alkylation products:

- Amide-directed hydrogenation with Crabtree's catalyst:

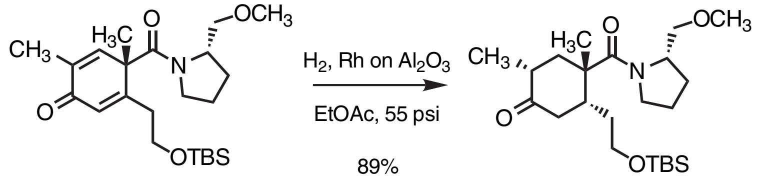


Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.



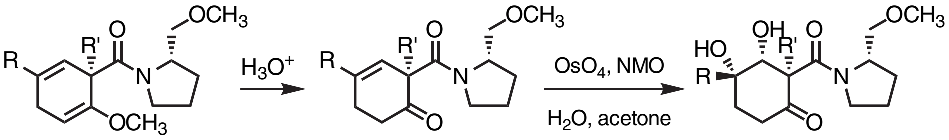
Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611–6614.

- Heterogenous hydrogenation with rhodium on alumina occurs *anti* to the bulky amide, presumably due to steric factors.



Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611–6614.

- Dihydroxylation of 3-cyclohexen-1-ones obtained by Schultz's asymmetric Birch alkylation occurs exclusively *anti* to the amido substiuent:



R	R'	yield (%)
H	Me	91
H	CH_2Ph	86
H	$(CH_2)_3N_3$	88
H	$(CH_2)_3Cl$	94
CH_2Ph	Et	73
Me	Et	76

Schultz, A. G.; Dai, M.; Tham, F. S.; Zhang, X. *Tetrahedron Lett.* **1998**, *39*, 6663–6666.

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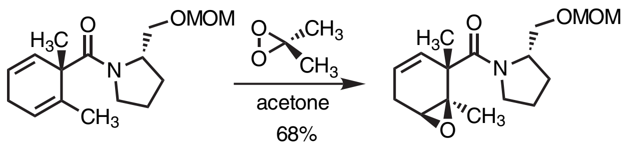
- Regio- and stereo-selective epoxidation has been demonstrated:

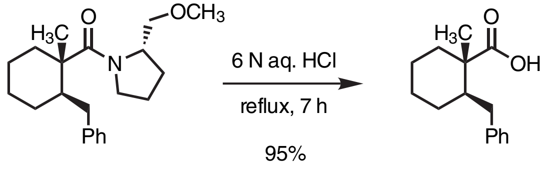


>13 : 1 diastereoselectivity

Schultz, A. G.; Harrington, R. E.; Tham, F. S. *Tetrahedron Lett.* **1992**, *33*, 6097–6100.

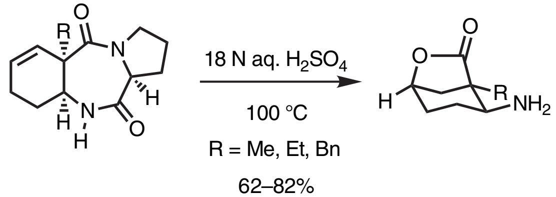
Methods of cleavage of Schultz's chiral auxiliaries:

- Acid catalyzed cleavage of the alkylation products requires harsh conditions:



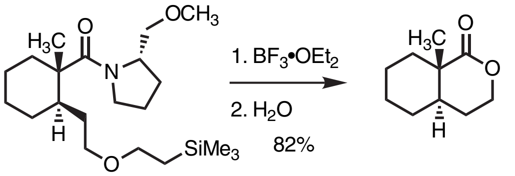
Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.

- Olefinic substrates undergo protiolactonization under the conditions of acidic hydrolysis:

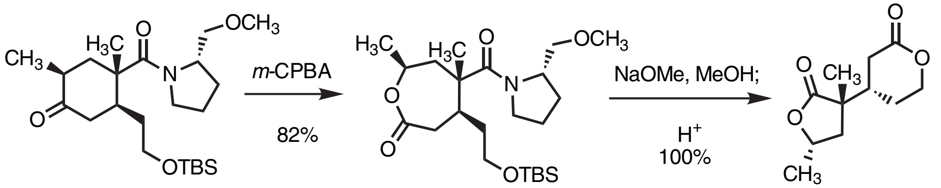


Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, 109, 6493–6502.

- Lactonization can be effectively employed for amide cleavage:

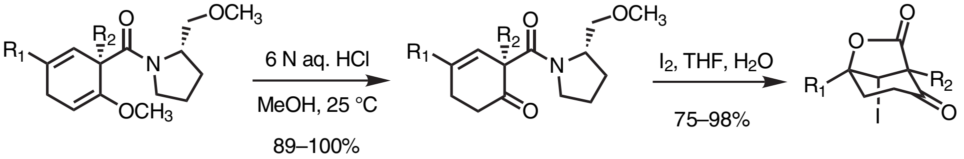


Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.



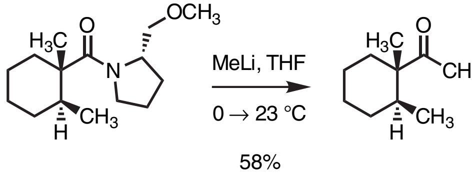
Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611–6614.

- Iodolactonization:



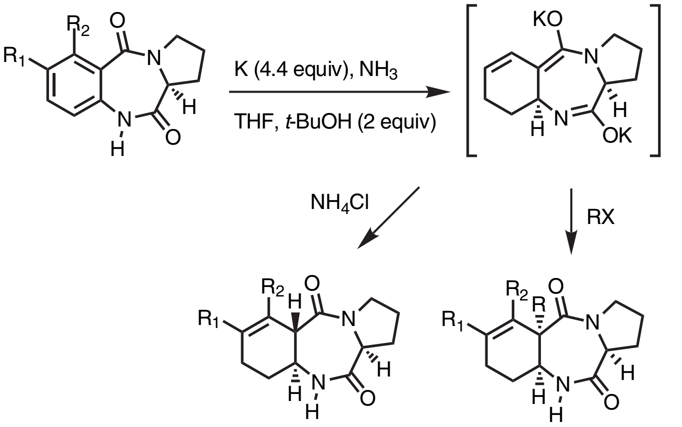
Schultz, A. G.; Dai, M.; Khim, S.-K.; Pettus, L.; Thakkar, K. *Tetrahedron Lett.* **1998**, *39*, 4203–4206.

- Addition of alkyllithium reagents:



Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828-7841.

Asymmetric synthesis of amino-substituted cyclohexenes:



R_1		RX	yield (%)	de (%)
H	H	MeI	54	70
H	H	EtI	68	82
H	H	NH_4Cl	73	not reported
H	Me	MeI	53	> 88
Me	H	NH_4Cl	84	one diastereomer
Me	H	MeI	78	52
Me	H	EtI	87	78
Me	H	CH_2=$CHCH_2Br$	68	> 95 : 5
Me	H	BnBr	78	> 95 : 5

Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, 109, 6493–6502.

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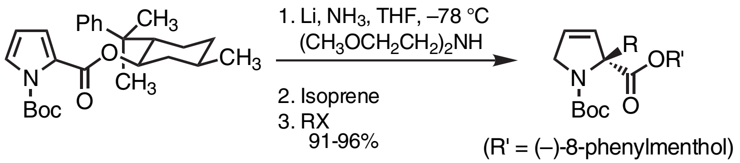
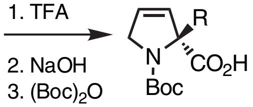
Asymmetric Birch Reduction of heterocycles:

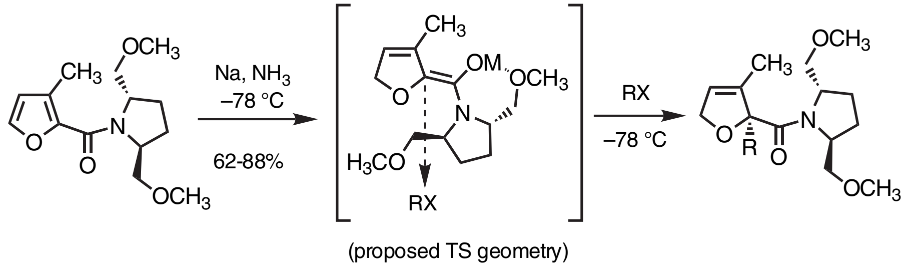


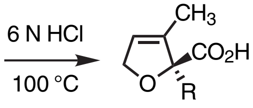


R	yield(%)	ee(%)
Me	79	78
Et	71	86
i-Bu	70	90
CH_2Ph	67	90

- Addition of the chelating amine $(CH_3OCH_2CH_2)_2NH$ was found to increase yields; the anion derived from this amine is less basic and less nucleophilic than $LiNH_2$, supressing byproduct formation.

Donohoe, T. J.; Guyo, P. M.; Helliwell, M. *Tetrahedron Lett.* **1999**, *40*, 435-438.

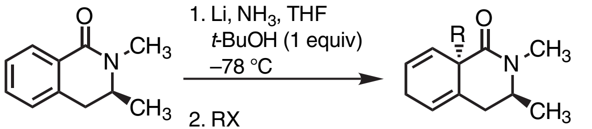




R	yield(%)	ee(%)
Me	86	>94
Et	74	>94
i-Bu	68	>94

Donohoe, T. J.; Helliwell, M.; Stevenson, C. A.*Tetrahedron Lett.* **1998**, *39*, 3071-3074.

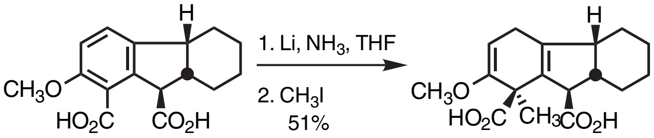
Chiral substrates:



>90% de

R = CH_3	72%
R = $CH_2CH{=}CH_2$	66%
R = CH_2Ph	68%

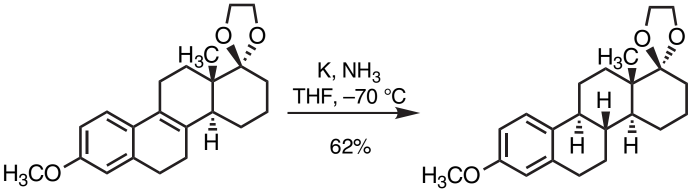
Schultz, A. G.; Kirinich, S. J.; Rahm, R. *Tetrahedron Lett.* **1995**, *36*, 4551-4554.



House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.* **1976**, *41*, 2401-2408.

Dissolving metal reductions of conjugated alkenes:

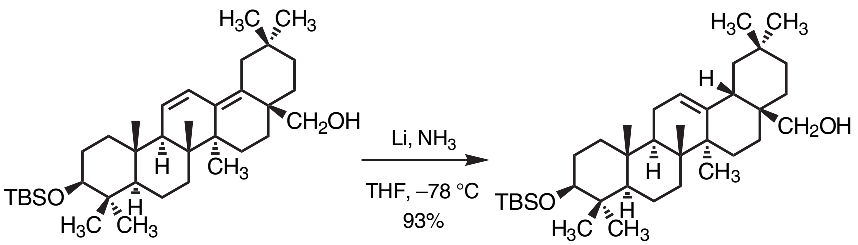
- Styrenes, conjugated dienes, and enones are more readily reduced under dissolving metal conditions than are aromatics; reduction occurs at low temperature without alcohol additives.



Ananchenko, S. N.; Limanov, V. Y.; Leonov, V. N.; Rzheznikov, V. N.; Torgov, I. V. *Tetrahedron* **1962**, *18*, 1355-1367.

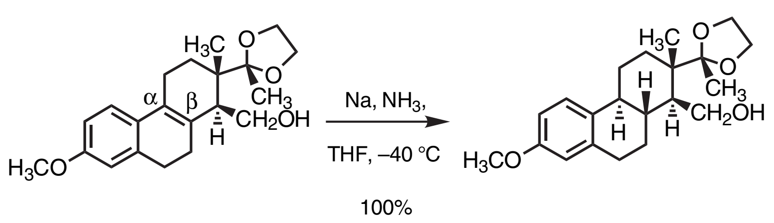
- Trans-fused products are favored, carbon proposed pyramidalized in the transition state.

Stereochemical and/or regiochemical control by intramolecular protonation:

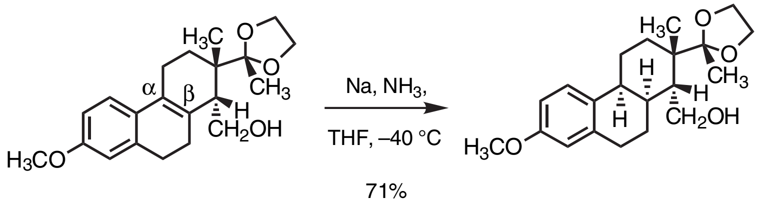


- It is proposed that the stereochemical outcome is the result of intramolecular protonation of the radical anion.

Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873-8874.

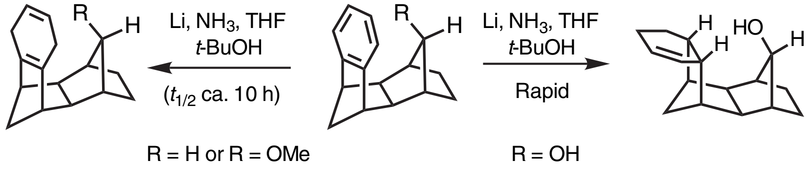


whereas:



- Initial intramolecular protonation at the β-position is proposed.

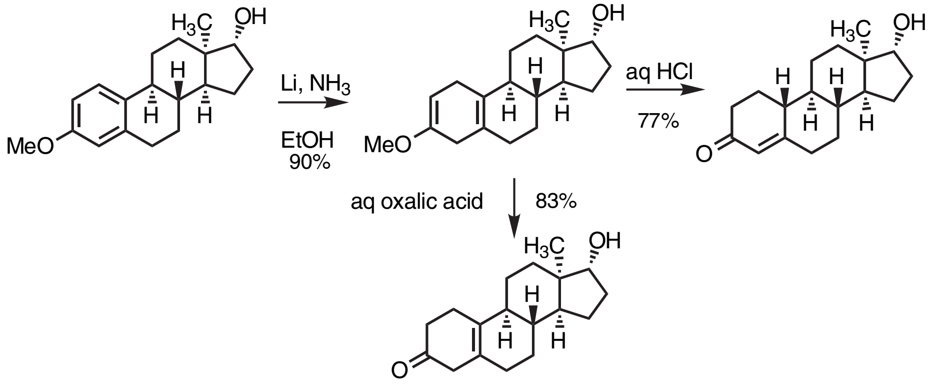
Lin, Z.; Chen, J.; Valenta, Z. *Tetrahedron Lett.* **1997**, *38*, 3863-3866.



Cotsaris, E.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1982**, 1206-1208.

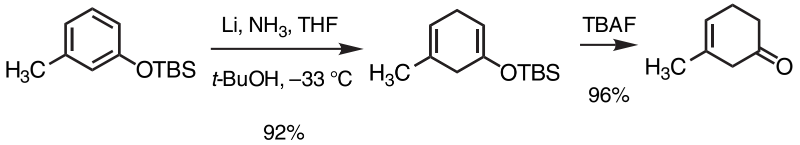
Transformations of Birch Reduction products:

- Synthesis of α,β or β,γ-unsaturated cyclohexanones



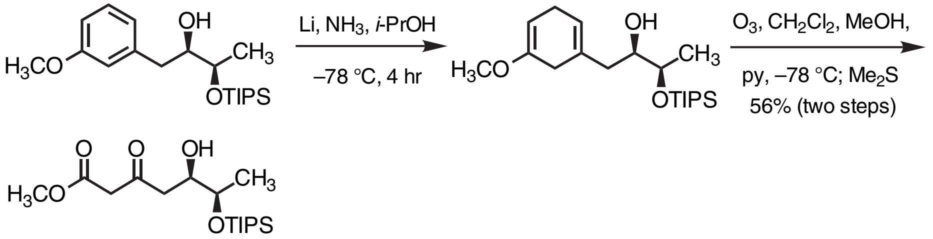
Nelson, N. A.; Wilds, A. L. *J. Am. Chem. Soc.* **1953**, *75*, 5366-5369.

- Reduction of aryl silyl ethers and synthesis of β,γ-unsaturated cyclohexanones:



Fuchs, P. L.; Donaldson, R. E. *J. Org. Chem.* **1977**, *42*, 2032-2034.

- Ozonolysis of Birch reduction products:



Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741-750.

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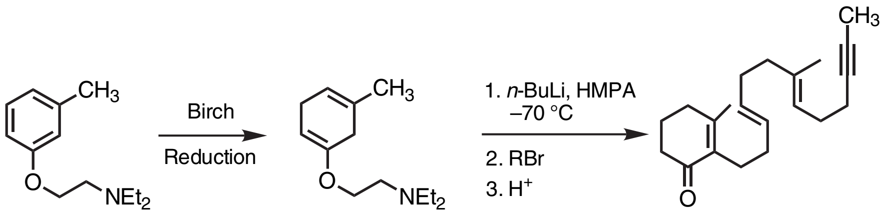
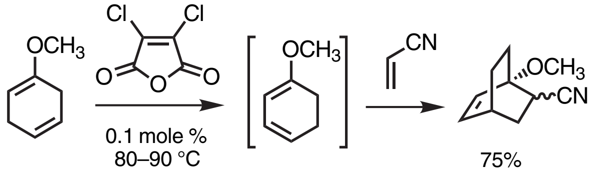
- Reductive alkylation of aromatics without electron-withdrawing groups is unsuccessful.
- Directed metalation of Birch products is possible:



Amupitan, J.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1978**, 852-853.
Bishop, P. M.; Pearson, J. R.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1983**, 123-124.

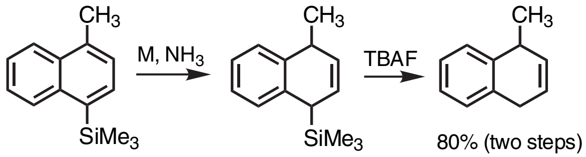
- Diels-Alder cycloaddition by isomerization of 1,3-dienes in situ:



- Isomerization is proposed to occur through a charge transfer complex.

Birch, A. J.; Dastur, K. P. *Tetrahedron Lett.* **1972**, *41*,4195-4196.

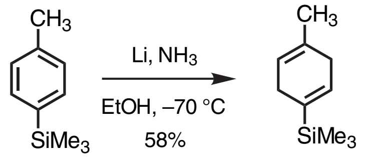
- Silyl substituents can be used to modify the regiochemistry of Birch reduction:



Rabideau, P. W.; Karrick, G. L. *Tetrahedron Lett.* **1987**, *28*, 2481-2484.

- In the absence of competing factors, allylic silanes are generally produced from Birch reduction of aryl silanes; this is attributed to stabilization of negative charge at the α-carbon by silicon.

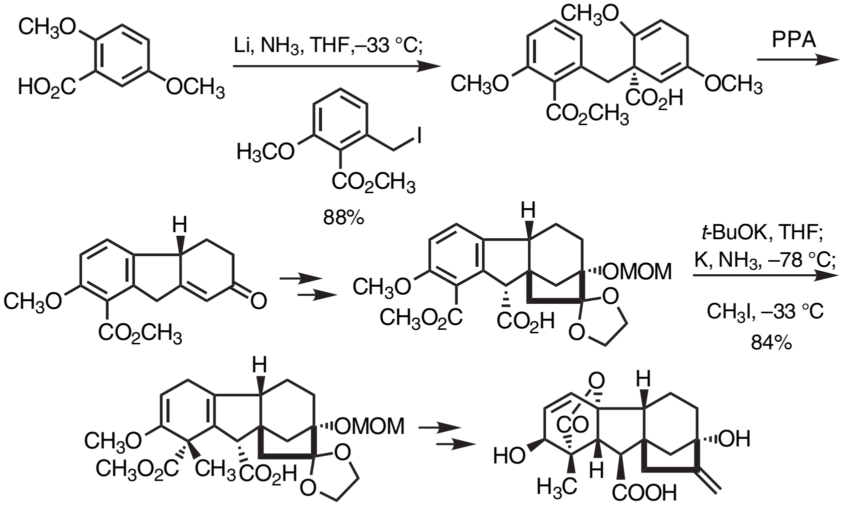
But:



Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans. I* **1975**, 470-474.

Birch Reduction – Application in Synthesis:

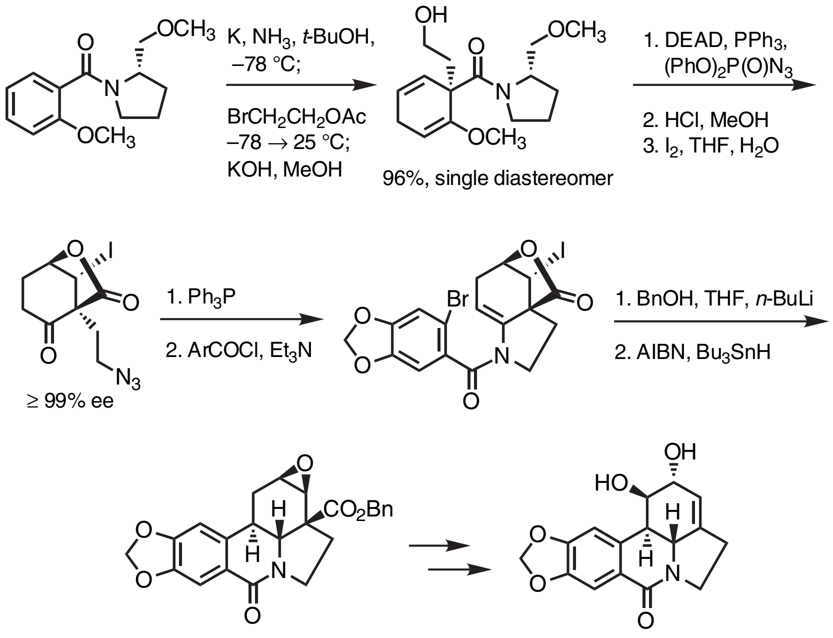
(±)-Gibberellic Acid:



(±)-Gibberellic Acid

Hook, J. M.; Mander, L. N.; Urech, R. *J. Org. Chem.* **1984**, *49*, 3250-3260.

(+)-Lycorine:

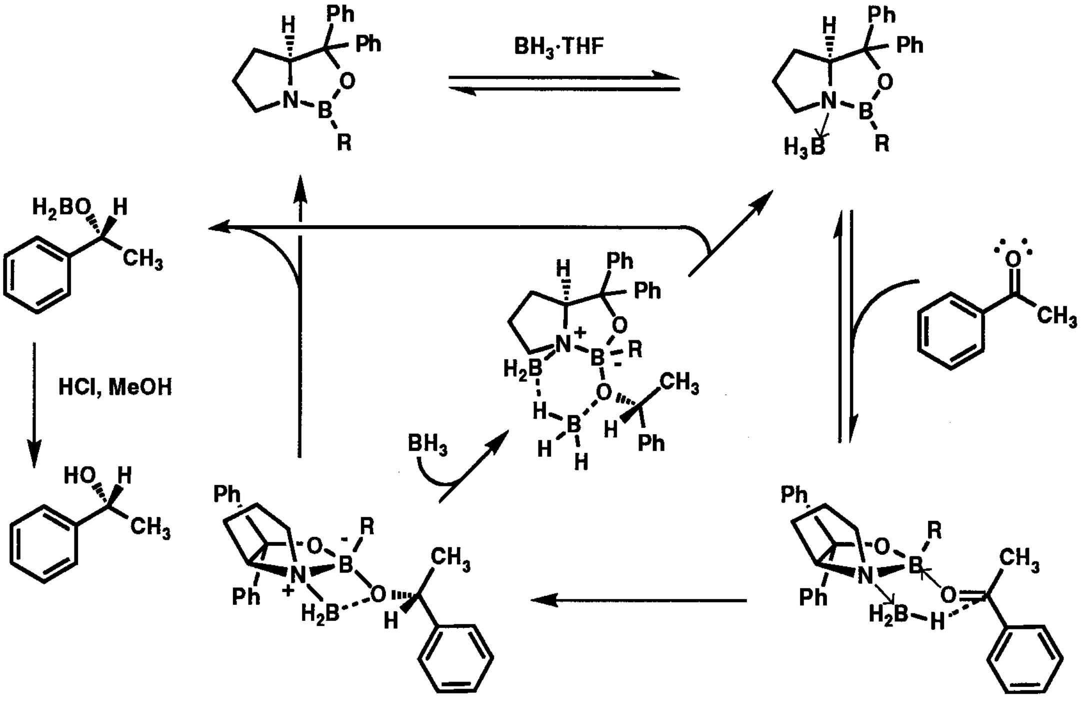


(single diastereomer)

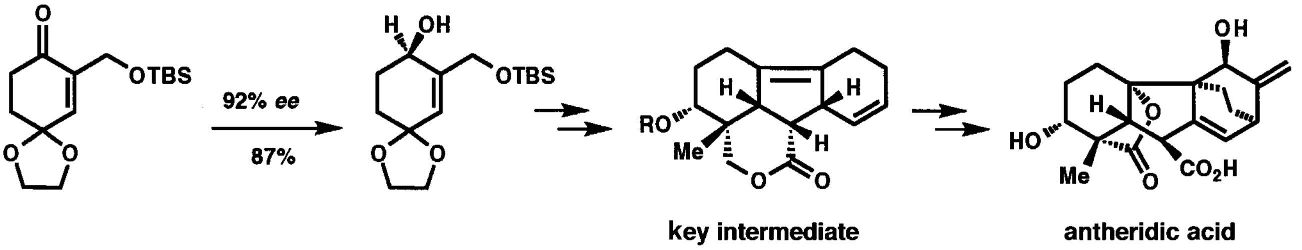
(+)-Lycorine

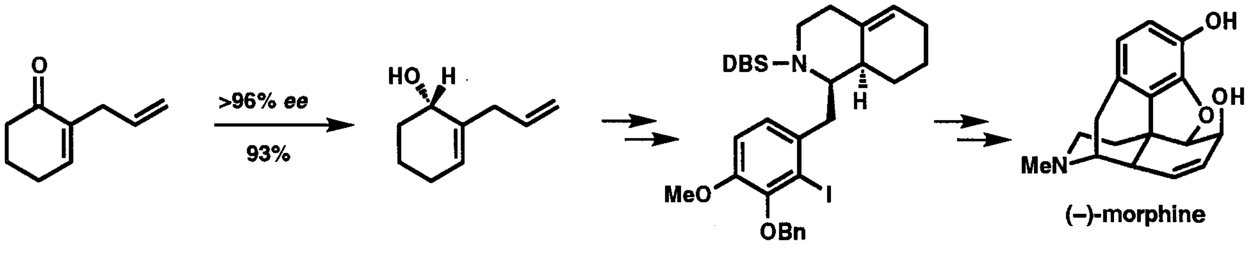
Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210-6219.

Kent Barbay



Remarkable advances in catalytic methods for enantioselective synthesis of chiral organic molecules have made the past decade truly momentous for organic chemistry. Great progress has been made not only in the discovery of useful new reactions, but also in our understanding of the fundamental mechanistic principles underlying enantioselective catalysis.





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Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method**

Elias J. Corey* and Christopher J. Helal

The introduction of complex metal hydrides such as lithium aluminum hydride and sodium borohydride into synthetic organic chemistry half a century ago greatly accelerated progress in this field. For many years, efforts to combine these reducing agents with various chiral ligands for the purpose of achieving efficient asymmetric synthesis proved disappointing. However, promising results obtained by Itsuno and his collaborators in the 1980s with mixtures of chiral 1,2-amino alcohols and borane paved the way for the discovery of oxazaborolidines as chiral catalysts for the borane-mediated enantioselective reduction of a wide variety of achiral ketones (CBS reduction). The well-defined structure of the catalyst and the straightforward reaction pathway have allowed the rapid expansion of the scope of the CBS reduction and the rational modification of catalyst structure to achieve optimal enantioselectivity for a particular type of substrate. This enantioselective catalytic reduction is now established as a major synthetic method for the asymmetric synthesis of chiral medicinals, catalytic ligands, complex natural products, and synthetic intermediates.

Keywords: asymmetric catalysis · boron · ketones · reductions · total synthesis

1. Introduction

The introduction of aluminum and boron hydrides for the reduction of carbonyl groups half a century ago had an enormous impact on the field of synthetic chemistry, and helped to usher in a golden age for the rationally planned multistep construction of complex organic molecules.[1] These reagents not only provided predictable site selectivity in multifunctional substrates, but often predictable diastereoselectivity as well. The versatile parent compounds $LiAlH_4$,[2] AlH_3,[3] $NaBH_4$,[4] and $BH_3 \cdot THF$[5] have been modified in almost every conceivable way to generate a large collection of derivatives, each of which has a special reactivity and utility, for example $NaBH(OMe)_3$, $NaBH(OAc)_3$, $NaBH_3CN$, $LiBH(sBu)_3$, Cl_2BH, $(cyclohexyl)_2BH$, catecholborane, $(RS)_2BH$, $NaBH_4 \cdot CeCl_3$, $LiAlH(OtBu)_3$, $LiAlH(OMe)_3$, $NaAlH_2(OR)_2$, and iBu_2AlH.[6] The literature on carbonyl reduction by this extensive family of hydride/hydrogen donors is so vast that a comprehensive review would require several large volumes. However, despite five decades of research and countless thousands of applications of hydride donors, much remains to be learned regarding detailed reaction mechanisms and transition-state structures.[6, 7] One consequence of this primitive understanding of transition-state structure is that it is difficult to predict how a new reagent will behave.

In view of the enormous utility of Al–H and B–H reagents for the reduction of carbonyl groups, it is natural that the modification of these structures by the emplacement of chiral ligands would be investigated for the purpose of achieving absolute stereochemical control (*re-* or *si*-face selectivity) in the synthesis of chiral alcohols. For more than thirty years there have been numerous studies of mixtures of $LiAlH_4$, $NaBH_4$, or $BH_3 \cdot THF$ with chiral 1,2-diols, 1,2-amino alcohols, or 1,2-diamines as reagents for enantioselective carbonyl reduction.[8] Specific examples of such "mixture reagents" include *cis*-2,3-pinanediol and $LiAlH_4$;[9a] (2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (Darvon alcohol) and $LiAlH_4$;[9b, c, d] (−)-*N*-methyl-*N*-(1-phenylethyl)amine · HCl and $LiAlH_4$;[9e] hydroxymethyl oxazolines and $LiAlH_4$;[9f] (−)-*N*-methylephedrine, various phenols, and $LiAlH_4$;[9g, h, i] (*S*)-leucine methyl ester · BH_3 and BF_3;[9j] 2,2′-dihydroxy-1,1′-binaphthol, ethanol, and $LiAlH_4$ (BINAL-H);[9k, l] (*S*)-2-(*N*-arylaminomethyl)pyrrolidines and $LiAlH_4$;[9m] (*S*)-4-anilinyl-3-methylamino-1-butanol and $LiAlH_4$;[9n, o] 2,2′-dihydroxy-6,6′-dimethylbiphenyl, $BH_3 \cdot THF$, and various amines;[9p] (−)-*N*-methylephedrine, 2-alkylaminopyridines, and $LiAlH_4$;[9q] *N*-

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[**] A list of abbreviations used is provided in the Appendix.

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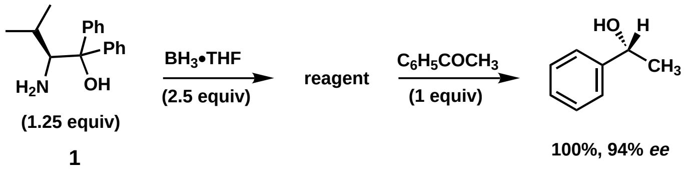
benzoylcysteine, $LiBH_4$, and *tert*-butyl alcohol;[9r] and (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol and $BH_3 \cdot Me_2S$.[9s]

While good levels of enantioselectivity have been reported for some of these early empirical studies, these reducing systems have seen very limited use in synthesis. In addition, because the reactive species are generally unknown, and in many cases insoluble as well, there has been no reliable information on the mechanistic basis for enantioselectivity. This is the situation for the Darvon alcohol – $LiAlH_4$ complex, introduced by Mosher and Yamaguchi,[9b] and used with some success by others.[9c, d] It is probably the best known of these mixture reagents. The Noyori reagent BINAL-H[9k, l]—which is made from (*S*)- or (*R*)-BINOL, $LiAlH_4$, and ethanol, and seems to be structurally better defined—also has seen very little use although it reacts with very high enantioselectivity with certain substrates; clearly high cost and marginal practicality are factors which detract from the usefullness of this reducing system.

After a survey of the extensive literature of these mixture reagents for hydride reduction and in an attempt to rationalize the basis for the observed enantioselectivities, we became very interested in a system introduced by Itsuno et al. in 1981.[10] In this initial work, the authors reported the novel finding that mixtures of chiral amino alcohols such as (*S*)-valinol and $BH_3 \cdot THF$ in a ratio of 1:2 in THF at 30 °C effected the enantioselective reduction of a number of achiral ketones to chiral secondary alcohols in nearly 100 % yield with enantiomeric excesses in the range of 10 – 73 % *ee*.[11] The most thoroughly studied substrate, butyrophenone, was reduced by this reagent to (*R*)-1-phenylbutan-1-ol with 69 % enantiomeric purity. Upon screening numerous amino alcohols, it was discovered that the tertiary amino alcohol **1** derived from (*S*)-valine together with two equivalents of $BH_3 \cdot THF$ at -78 to 0 °C over several hours converted acetophenone into (*R*)-1-phenylethanol with a much improved enantiomeric excess (94 %, Scheme 1).[12] The dependence of the enantioselectivity of this process on the ratio of BH_3 to amino alcohol, the quantity of hydride present in the reagent, and the steric bulk of the ketone substituents was studied. However, no mechanistic rationale was proposed by Itsuno et al. for either the sense or magnitude of this surprisingly good enantioselectivity. No applications were reported by other groups. Studies of this intriguing reaction were initiated by our group on the basis of mechanistic insights which were subsequently confirmed and which led to a new and powerful catalytic version of the original stoichiometric Itsuno reduction.



Scheme 1. Highly enantioselective ketone reduction reported by Itsuno.

2. Development of the CBS Catalytic Enantioselective Reduction[13]

From the outset it appeared reasonable that the primary reaction product of the tertiary amino alcohol **1** would be an oxazaborolidine of structure **2**. This was confirmed in 1986 – 1987 by Bakshi and Shibata of our laboratories. They found that the reaction of amino alcohol **1** with two equivalents of BH_3 in THF at 35 °C produced two equivalents of hydrogen gas and the oxazaborolidine **2**, which was obtained in pure form upon sublimation (105 – 130 °C, 0.05 Torr) after removal of the solvent and excess BH_3 in vacuo (see Scheme 2). Its structure was demonstrated by FT-IR and ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI). Although solutions of **2** in THF did not reduce acetophenone after several hours at 23 °C, mixtures of **2** and $BH_3 \cdot THF$ (0.6 equiv) effected the rapid reduction of acetophenone in less than one minute at 23 °C to afford (*R*)-1-phenylethanol in 94.7 % *ee*, which is

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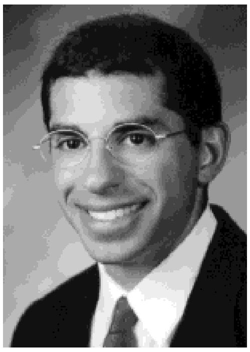
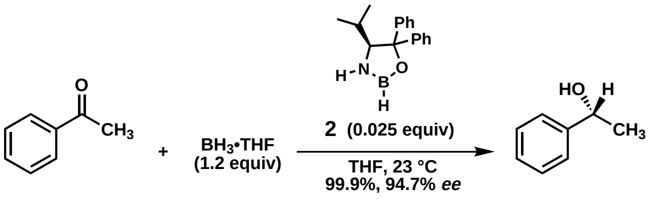
Christopher J. Helal, born in 1969 in Columbus, OH, received his Bachelor of Science degree in chemistry in 1991 from the Ohio State University. He enrolled in the graduate program at Harvard University, where he was a National Science Foundation Graduate Fellowship recipient. He earned his doctorate in 1997 under the direction of Professor E. J. Corey on the investigation of novel electronic and steric effects in the enantioselective oxazaborolidine-catalyzed reduction of ketones, and is currently employed at Pfizer Central Research, Groton, CT, where he is involved in drug discovery.

E. J. Corey



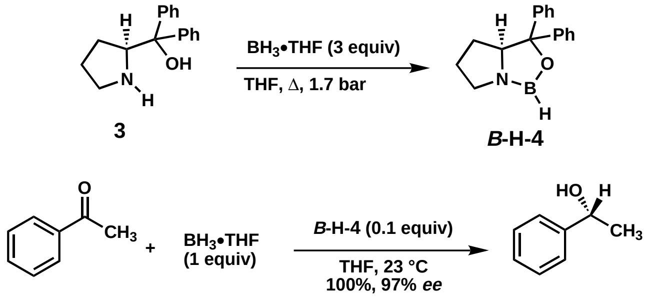
C. J. Helal

comparable to the results reported by Itsuno.[12] In the absence of **2**, acetophenone was reduced relatively slowly with $BH_3 \cdot THF$ at 23 °C. The rate acceleration with **2** immediately suggested that substoichiometric quantities of **2** could effect an asymmetric reduction of a ketone. This was readily verified by an experiment with 2.5–5 mol% of **2** and 1.2 equivalents of $BH_3 \cdot THF$, which produced (*R*)-1-phenylethanol with 94.7% *ee* (Scheme 2). Thus, the careful investigation of an impressive yet, in the original report, poorly understood reaction led to the discovery of a highly enantioselective *catalytic* reduction of ketones mediated by an *isolable* and *structurally defined* catalyst.



Scheme 2. Oxazaborolidine-catalyzed reduction with borane.

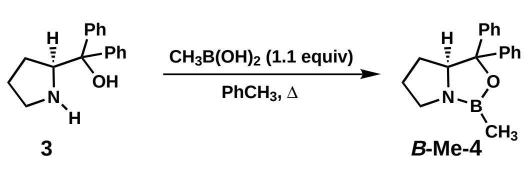
The demonstration of the catalytic activity of oxazaborolidine **2** and mechanistic considerations (see Section 3) led to the expectation that oxazaborolidine **4** should be a superior reagent (Scheme 3). Treatment of amino alcohol **3**[14a, b] with $BH_3 \cdot THF$ gave oxazaborolidine *B*-H-**4** (CBS catalyst named after *C*orey, *B*akshi, and *S*hibata), which was characterized by ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI).



Scheme 3. A superior oxazaborolidine catalyst for the enantioselective reduction of ketones.

Oxazaborolidine **4** was indeed found to be generally superior to **2** as an enantioselective reduction catalyst. For example, the reduction of acetophenone with 1.2 equivalents of $BH_3 \cdot THF$ and 0.1 equivalents of *B*-H-**4** in THF at 25 °C gave (*R*)-1-phenylethanol with 97% *ee* and in quantitative yield.

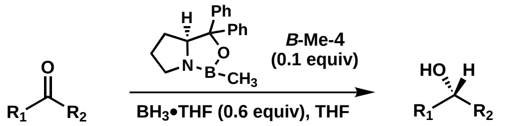
The methyl-substituted oxazaborolidine *B*-Me-**4** was prepared as shown in Scheme 4 and characterized by ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI). An improvement in the selectivity and practicality of the CBS reduction was realized with this catalyst relative to the *B*-H analogue. The reduction of ketones with *B*-Me-**4** as the catalyst frequently resulted in appreciably higher enantioselectivity than with *B*-H-**4**. Additionally, *B*-H-**4** is extremely air- and moisture-sensitive, and its formation requires extended heating with BH_3 under increased pressure. On the other hand, *B*-Me-**4** is less sensitive and can be stored in closed containers, weighed or transferred in air, and is readily formed by heating **3** and methaneboronic acid at reflux in toluene for 4 h with removal of water.

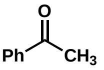
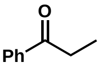
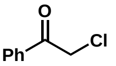
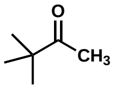
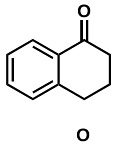
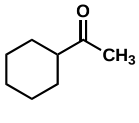
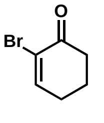
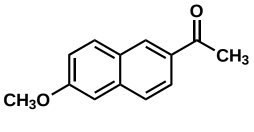
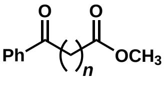


Scheme 4. A more stable and enantioselective catalyst.

Table 1 summarizes the results for the reduction of a variety of different ketones with *B*-Me-**4** as the catalyst.[13b] These data show that the CBS reduction process results in excellent enantioselectivities, near quantitative yields, and short reaction times, and leads to a product whose absolute configuration can be predicted from the relative effective steric bulk of the two carbonyl appendages. Another notable attribute of

Table 1. CBS reduction of ketones catalyzed by *B*-Me-**4**.[13b]



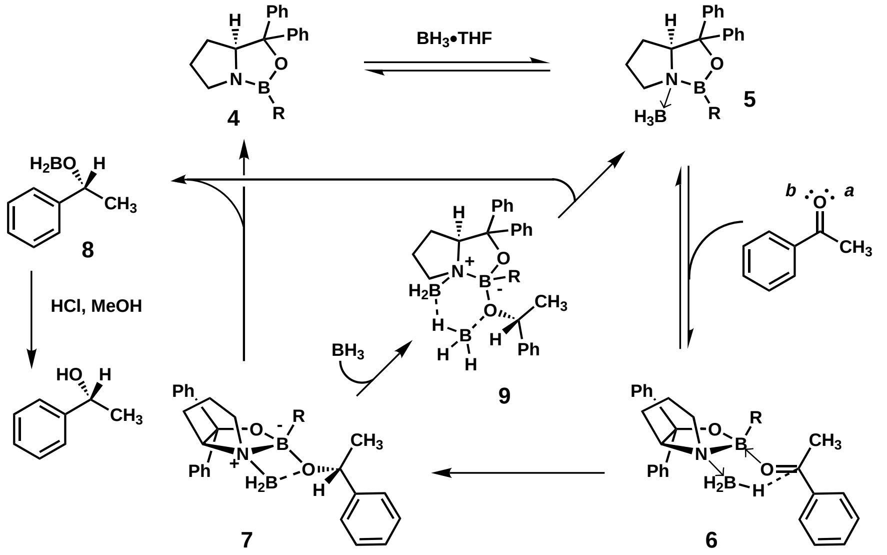
Ketone	Config. (*ee* [%])	*T* [°C]
	*R* (96.5)	2
	*R* (96.7)	– 10
	*S* (95.3)	32
	*R* (97.3)	– 10
	*R* (86)[a]	– 15
	*R* (84)	– 10
	*R* (91)	23
	*R* (97.6)	23
 *n* = 2	*R* (94)	0[b]
n = 3	*R* (96.7)	0[b]

[a] 0.25 equiv of *B*-Me-**4**. [b] The reaction time was 25 min.

this methodology is the easy recovery of the catalyst precursor **3** by precipitation from organic solvent as the hydrochloride salt and efficient recycling.[14c]

3. Mechanistic Rationale[13, 15]

The general mechanistic model which was developed for reduction of ketones with oxazaborolidine catalyst **4** (and analogous catalysts such as **2**) is outlined in Scheme 5. The mechanistic model explains 1) the absolute stereochemistry of the reduction, 2) the outstanding enantioselectivity obtained for the reduction, 3) the exceptional rate enhancement of the reduction, and 4) the turnover of the catalyst.

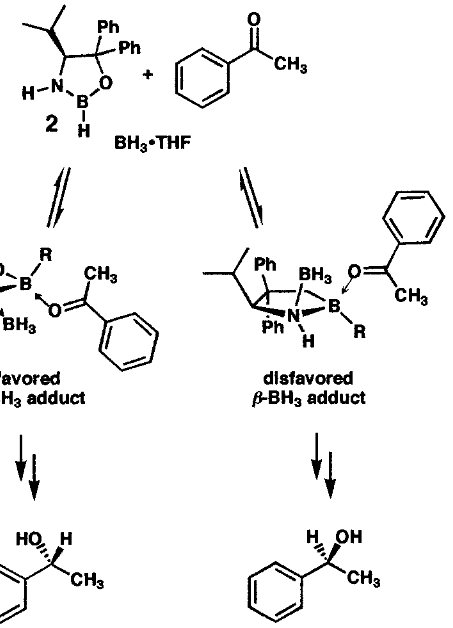


Scheme 5. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines **4**.

The initial step in the pathway is the rapid (and probably reversible) coordination of BH_3 to the Lewis basic nitrogen atom on the *α* face of oxazaborolidine **4** to form the *cis*-fused oxazaborolidine · BH_3 complex **5**. Unambiguous support for the initial step comes from the observation by ^{11}B NMR spectroscopy[16] that **4** and BH_3 · THF form the 1:1 complex *B*-H-**5** and the fact that crystalline *B*-Me-**5** (**5**, R = Me) can be isolated and structurally defined by single-crystal X-ray diffraction analysis.[17] The coordination of the electrophilic BH_3 to the nitrogen atom of **4** serves to activate BH_3 as a hydride donor and also to increase strongly the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex **5** then readily binds to the ketonic substrate, for example acetophenone, at the more sterically accessible electron lone pair (*a* in the case of acetophenone) and *cis* to the vicinal BH_3 group (→**6**). This manner of binding minimizes unfavorable steric interactions between the oxazaborolidine and the ketone, and aligns the electronically deficient carbonyl carbon atom and the coordinated BH_3 for stereoelectronically favorable, face-selective hydride transfer via a six-membered transition state to form the reduction product **7**. Thus, the rate enhancement for the oxazaborolidine-catalyzed reduction is due to the activation of the stoichiometric reducing agent BH_3 by coordination with the Lewis basic nitrogen atom of **4** with simultaneous intensification of the Lewis acidity of the boron atom in the heterocycle for coordination to the ketone. This leads to subsequent enthalpically and entropically favorable face-selective intramolecular hydride transfer.[18]

Dissociation of the reduction product from **7** to regenerate the oxazaborolidine catalyst may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocyclic boron atom with the adjacent boron atom of **7** to regenerate **4** and form the borinate **8** by cycloelimination;[13d, 15] or 2) by the addition of BH_3 to **7** to form a six-membered BH_3-bridged species **9**, which decomposes to produce the catalyst – BH_3 complex **5** and borinate **8**.[19, 20] The facile disproportionation of **8** to afford dialkoxyborane $(RO)_2BH$ and BH_3 allows the efficient use of the three hydrogen atoms of the stoichiometric reductant.[21]

The mechanism proposed in Scheme 5 provides a simple explanation for the superior effectiveness of oxazaborolidine **4** relative to **2**. As shown in Scheme 6, the selective binding of BH_3 to one face of **2** is the result of a steric preference for a *trans* relationship between the isopropyl substituent and BH_3. Competing formation of the *cis* adduct leads to lower enantioselectivity of the reduction. The rigid [3.3.0] ring system of **4**, however, strictly requires the *α* coordination



Scheme 6. A possible reduction pathway for catalyst **2** with low enantioselectivity.

of BH_3 to the Lewis basic nitrogen atom (see **6**); β coordination would result in a very strained (by ca. 10 kcal mol^{-1}) *trans*-fused [3.3.0]pentalane. Thus, production of the undesired alcohol enantiomer through a diastereomeric BH_3 coordination mode is energetically precluded with CBS catalyst **4**.

A final issue posed by the mechanistic model in Scheme 5 is whether the complexation of the ketone by **5** or the subsequent hydride transfer to form **7** is the rate-limiting step of the reduction. To answer this question, the rates of reduction of acetophenone and the *p*-NO_2 and *p*-MeO derivatives catalyzed by *B*-Me-**4** were measured.[22a] The relative rates of reduction were 3.4 (*p*-NO_2), 1.8 (*p*-MeO), and 1.0 (*p*-H).[22b] This implies that the coordination of the ketone to **5** is not strictly rate-limiting for these substrates. Additional information was obtained from the $^1H-^2H$ kinetic isotope effect (k_H/k_D) for hydride transfer, which was measured with an excess of a 1:1 mixture of B^1H_3 and B^2H_3 (6 equiv of each) in THF with two equivalents of oxazaborolidine B-Me-**4** and one equivalent of acetophenone. The ratio of ^1H to ^2H in the reduction product 1-phenylethanol at low conversion was determined by mass spectrometry to be 1.7, which is then the approximate value of k_H/k_D.[22a] This low value is indicative of an early transition state for highly exothermic transfer of hydride from the boron atom to the carbonyl group. Thus, both association to the carbonyl comound and hydride transfer are probably fast and comparably rate-limiting. In agreement with these experimental results, semiempirical molecular orbital calculations with the AM1 Hamiltonian provided similar transition state enthalpies for ketone complexation and hydride transfer.[18c] The calculated kinetic isotope effect for the oxazaborolidine-catalyzed reduction of 2-propanone was 1.8 at 23 °C, which is in agreement with the experimentally determined value of 1.7.[23]

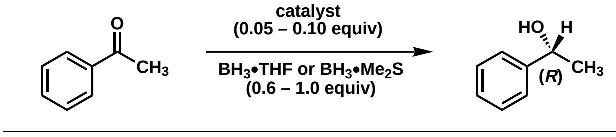
4. Further Studies in the Optimization of the CBS Reduction

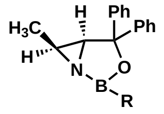
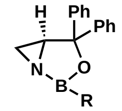
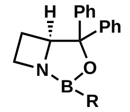
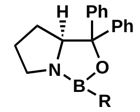
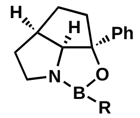
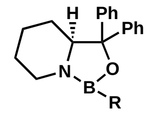
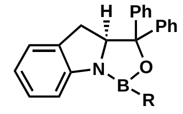
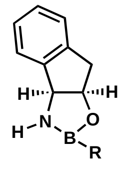
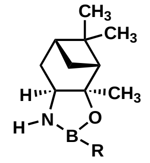
The high enantioselectivity, generality, and profound mechanistic understanding of the CBS reduction have led to a number of other studies aimed at further elucidating in ever increasing detail the effect of five variations in the structure of the oxazaborolidine catalyst on enantioselectivity over a wide range of substrates. Described in the following are results from investigations of varying 1) the oxazaborolidine ring system, 2) the *gem*-diphenyl substituents, 3) the group on the endocyclic boron atom, 4) the stoichiometric reducing agent, and 5) the mode of catalyst preparation.

4.1. Variations in the Oxazaborolidine Ring System

Subsequent to the discovery of the high enantioselectivity imparted by the proline-derived oxazaborolidine catalyst **4** in the reduction of ketones with BH_3, many other fused bicyclic oxazaborolidines have been prepared by other research groups and by our own to demonstrate the relationship between catalyst structure and enantioselectivity. The effectiveness of the various oxazaborolidine catalysts for the enantioselective reduction of acetophenone is summarized in Table 2. For example, the aziridine (entries 1 and 2),[24] azetidine (entry 3),[25] and pyrrolidine catalysts (entry 4, **4**)[13] afford (*R*)-1-phenylethanol in very high enantiomeric excess (94–97%). The structurally constrained tricyclic oxazaborolidine in entry 5 is among the most effective of all the oxazaborolidines synthesized, as it has demonstrated exceptional enantioselectivity for the reduction of acetophenone (98% *ee*) as well as numerous other substrates.[26] The use of a catalyst with a more flexible [4.3.0] ring system (entry 6) resulted in lower enantioselectivity.[27] Entry 7 reveals that the

Table 2. Fused bicyclic oxazaborolidine catalysts for the enantioselective reduction of acetophenone.



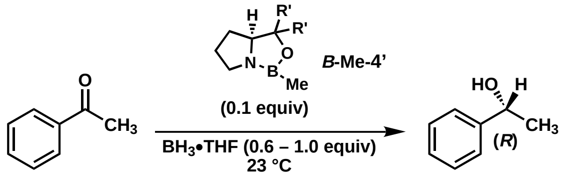
Entry	Catalyst	R	*ee* [%]	Solvent, *T* [°C]
1		H	94	THF, 23
2		H	94	$PhCH_3$, 23
3		H Me	97 75	THF, 23 $PhCH_3$, 23
4		H Me	97 97	THF, 23 THF, 23
5		Me	98	THF, 0
6		H	87	THF, 0
7		H Me	96 92	THF, 23 $PhCH_3$, 27
8		Me	86	THF, 0
9		H Me	94 93	THF, 25–30 THF, 0–5

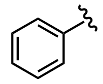
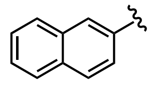
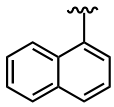
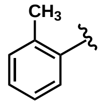
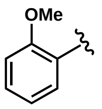
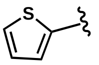
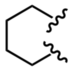
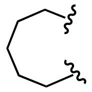
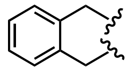
enantioselectivity of the reduction is not strongly affected by decreased Lewis basicity of the endocyclic nitrogen atom of the catalyst owing to conjugation with the fused aromatic ring (up to 96% *ee* for the reduction of acetophenone).[28] Industrial interest in the large-scale application of CBS reductions has led to the search for other inexpensive and readily available enantiopure amino alcohols as precursors to chiral oxazaborolidines. Towards this end, enantiopure *cis*-1-amino-2-indanol (entry 8, prepared in four steps from indene)[29] and an amino alcohol derived from α-pinene (entry 9, prepared from α-pinene)[30] have been used to generate bicyclic oxazaborolidine catalysts which mediate the reduction of acetophenone with high enantioselectivity (86 and 94% *ee*, respectively).

4.2. Variation of the Carbinol Substituents

The effects of the *gem*-diphenyl substituents of the carbinol center (R′) on the enantioselectivity of acetophenone reduction are summarized in Table 3. Replacing the phenyl group (entry 1, *B*-Me-**4**) by the somewhat bulkier β-naphthyl group (entry 2) leads to a slight increase in enantioselectivity (98% *ee*) in this and some other cases.[31] The use of still bulkier *ortho*-substituted aromatic groups such as α-naphthyl (entry 3),[25c] *ortho*-tolyl (entry 4),[32] or *ortho*-anisyl (entry 5),[32] however, results in considerably lower enantioselectivity, as does the use of the smaller 2-thienyl group (entry 6).[32] Substitution with straight-chain alkyl (*n*-butyl, entry 7)[25c] and spiroalkyl groups (entries 8 and 9),[33] did not provide useful catalysts. However, a catalyst containing the rigid spiro-2-indanyl substituent (entry 10) afforded the reduction product with high enantioselectivity (96% *ee*).[34] Emplacement of two strongly electron-withdrawing trifluoromethyl groups on the oxazaborolidine ring system (entry 11), which should inductively increase the Lewis acidity of the heterocyclic boron atom, led to a catalyst which provided relatively poor enantioselectivity.[35, 36]

Table 3. Influence of the substituents R′ at the carbinol center.



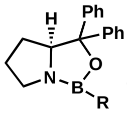
Entry	R′	*ee* [%]
1		97
2		98
3		62
4		76
5		28
6		82
7	$CH_3CH_2CH_2CH_2$	55
8[a]		67
9[a]		71
10[a]		96
11[b]	CF_3	60

[a] The oxazaborolidine (0.15 equiv) was formed from the corresponding precursor by reaction with $BH_3 \cdot THF$ and contains a hydrogen atom on boron instead of the methyl group. The reduction was carried out at 0 °C. [b] The group on the oxazaborolidine boron atom was *n*-pentyl.

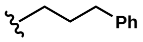
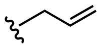
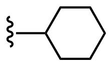
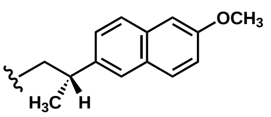
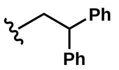
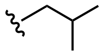
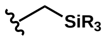
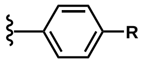
4.3. Variation of the Substituent on the Heterocyclic Boron Atom

The group R on the heterocyclic boron atom can play an important role in determining the selectivity of complexation by the catalyst to the two possible ketone electron lone pairs. Because of differential steric interactions between R and the carbonyl substituents (see **6**, Scheme 5), a discrimination is crucial to the enantioselectivity of the reduction. Table 4 lists several groups which have been studied as boron substituents in our laboratory[37] for the CBS reduction of a range of ketonic substrates. Besides the compounds *B*-H-**4** (entry 1) and *B*-Me-**4** (entry 2) previously discussed, a variety of other catalysts containing *n*-alkyl (entries 3,[38] 4,[39] 5[35]), 3-phenylpropyl (entry 6),[40] allyl (entry 7),[37] *s*-alkyl (entry 8),[40] and β-branched attachments both with chiral centers (entry 9)[41] and without (entries 10[40] and 11[42]) have been synthesized and tested in the enantioselective reduction. In general, the R group exerts a steric effect in proximity to the boron atom to which it is attached that can influence the selectivity of binding at one of the oxygen lone pairs. In addition, it has been possible to design substituents, such as trialkylsilylmethyl (entry 12)[43] and *p*-substituted aryl groups (entry 13),[44] which interact sterically with more remote sites on the coordinated ketone and thus influence dramatically the enantioselectivity of reduction (see Sections 5, 6.3, and 6.4). The optimal R group for enantioselective reduction can be expected to depend on the structure of the substrate, as discussed in Section 5.

Table 4. Boron substituents in CBS catalysts.



4

Entry	R
1	H
2	CH_3
3	CH_2CH_3
4	$CH_2CH_2CH_2CH_3$
5	$CH_2CH_2CH_2CH_2CH_3$
6	
7	
8	
9	
10	
11	
12	
13	

4.4. Variation of the Stoichiometric Reducing Agent

Since the initial use of $BH_3 \cdot THF$ as the stoichiometric reductant in the CBS reduction, a number of other BH_3 complexes have been employed—including $BH_3 \cdot Me_2S$,[44b] $BH_3 \cdot$ 1,4-thioxane,[45] and $BH_3 \cdot$ diethylaniline[46]—all of which lead to comparable enantioselectivity. An advantage of these reagents over $BH_3 \cdot THF$ is lower sensitivity to moisture and oxygen. The coordination of Me_2S, THF, etc. to BH_3 generally does not effect the level of enantioselection except at temperatures below −30 °C.[47] At this temperature the equilibria between BH_3, the coordinated ligand, the oxazaborolidine catalyst, and the ketone are sufficiently altered to allow the intervention of competing reduction pathways; this then results in diminished enantioselectivity. The use of catecholborane,[48] a less reactive monohydridic reagent that requires no ancillary ligand for stabilization, permits CBS reductions to occur at temperatures as low as −126 °C in noncoordinating solvents (CH_2Cl_2 or toluene) with excellent enantioselectivity.[31, 47] Furthermore, the decreased reactivity of catecholborane as compared to BH_3, especially at lower temperatures, minimizes both uncatalyzed ketone reduction and hydroboration of sensitive functional groups (e.g., C=C, C≡C, C=O) within the ketonic substrate.

4.5. Variations in Oxazaborolidine Formation

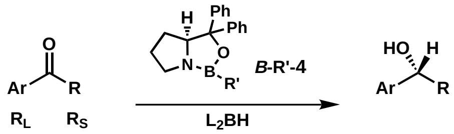
The preparation of chiral oxazaborolidines in pure form was vital to the discovery of the CBS catalyst *B*-H-**4** and the demonstration of the mechanism outlined in Scheme 5. Catalyst purity is essential for the attainment of high enantioselectivity and reproducibility in the reduction of ketones. As a result, considerable effort has been extended towards the development of effective procedures for the generation of pure oxazaborolidines without the need for a purification step. The first-generation CBS catalyst *B*-H-**4** was originally prepared by the extended heating of amino alcohol **3** with three equivalents of $BH_3 \cdot THF$ under argon (1.7 bar) followed by sublimation.[13a] Subsequently, a more convenient procedure was developed for the synthesis of *B*-H-**4** that consists of heating **3** and $BH_3 \cdot Me_2S$ in toluene at reflux for 17 h and then removing solvent in vacuo without further purification.[49, 50] The alkyl- and aryl-substituted oxazaborolidines (Section 4.3) are easily prepared by heating a solution of **3** and the corresponding boronic acid $RB(OH)_2$ or boroxine $(RBO)_3$ at reflux in toluene for 12–24 h with removal of water with molecular sieves.[51] To shorten the time required for complete catalyst formation, the more reactive boronic acid equivalents bis(trifluoroethyl)alkyl boronates ($RB(OCH_2CF_3)_2$) have been developed; they allow for quantitative oxazaborolidine formation in less than one hour.[52]

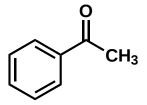
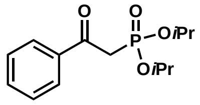
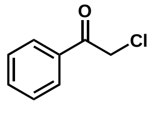
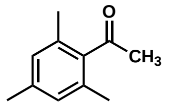
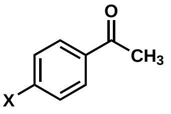
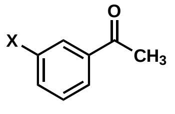
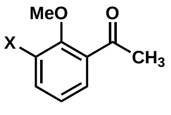
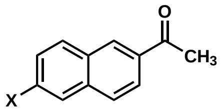
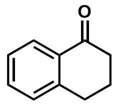
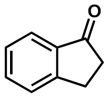
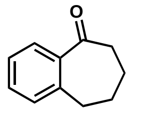
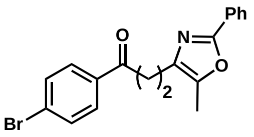
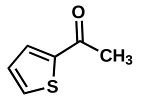
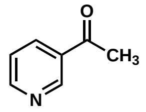
5. Scope of Oxazaborolidine-Catalyzed Reductions

The well-defined mechanistic pathway of the enantioselective reduction of ketones mediated by chiral oxazaborolidine **4** greatly simplified application of this reaction to the enantioselective reduction of many different types of ketones and to the expansion of its scope and generality. As shown in Table 5, many conjugated aryl ketones of varying structure undergo highly enantioselective reduction with BH_3 or catecholborane in the presence of the proline-derived oxazaborolidine **4**. For example, acetophenone[46] and derivatives with functional groups on the alkyl side chain such as $P(O)(O\mathit{i}Pr)_2$[53] or Cl[44a] are reduced with high enantioselectivity, as are the *para*-,[17b] *meta*-,[13b, 54] and *ortho*-substituted[55] aryl ketones and the cyclic aryl ketones 1-tetralone,[46] 1-indanone,[17b] and 1-benzosuberone.[17b] The presence of nitrogen and other heteroatoms in the ketonic substrate is tolerated in the oxazaborolidine-catalyzed reduction, but often requires the use of an additional equivalent of the stoichiometric reductant L_2BH to coordinate to the Lewis basic site.[50a, 56] Representative procedures for the CBS reduction of acetophenone and α-chloroacetophenone are detailed in reference [57].

Recently, the oxazaborolidine-catalyzed reduction of essentially isosteric electronically biased benzophenones[58, 59] as well as *ortho*-substituted benzophenones[59] and 2-benzoyl pyridinium triflates[59] has been shown to be strikingly selective as a result of gearing effects between the aromatic rings. This reaction provides an efficient route to optically active benzhydrols (Table 6).[60] The presence of an *ortho*-substituent on the aromatic ring also proved to be very

Table 5. Oxazaborolidine-catalyzed reduction of aryl ketones.



Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]	Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	99[46]	*B*-Me-**4**	BDEA	30		91[53]	*B*-*n*Bu-**4**	CB	−20
	98[44a]	*B*-Me-**4**	BDEA	31		99.7[55a]	*B*-*n*Bu-**4**	CB	−78
	97 (X = F)[17b] 99 (X = OMe)[17b]	*B*-Me-**4** $\cdot BH_3$	BMS	−20		96 (X = Br)[54] 97 (X = OMe)[54]	*B*-Me-**4**	BTHF	23
	97 (X = OMe)[55b] 94 (X = H)[55b]	*B*-Me-**4**	BMS	23		96 (X = H)[54] 98 (X = OMe)[13b]	*B*-Me-**4**	BTHF	23
	≥ 99[46]	*B*-Me-**4**	BDEA	20		98[17b]	*B*-Me-**4** $\cdot BH_3$	BMS	−20
	99[17b]	*B*-Me-**4** $\cdot BH_3$	BMS	−20		94[56]	*B*-Me-**4**	BMS	25
	94[56]	*B*-Me-**4**	BMS	25		99[50a]	**3** + $(MeO)_3B$	BMS	23

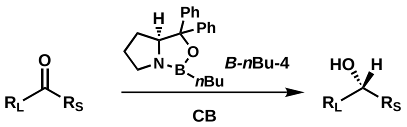
important for the enantioselective reduction of aryl diisopropylphosphono ketones.[53]

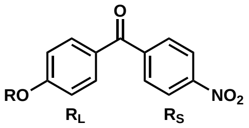
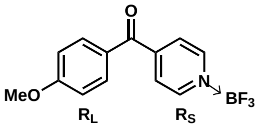
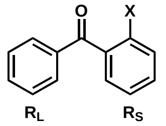
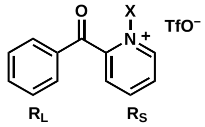
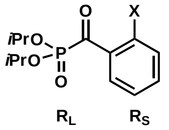
α,β-Enones have been extensively investigated as CBS reduction substrates since enantiopure allyl alcohols are extremely versatile intermediates which can participate in many useful synthetic elaborations, for example the Claisen rearrangement or S_N2' displacement reactions with organometallic reagents that allow transfer of chirality by cleavage of C–O bonds and formation of C–C bonds to new chiral centers. It is interesting to note that in the case of acyclic enones (Table 7) the olefinic portion generally behaves as the large group R_L, especially in the presence of a β substituent such as aryl,[58] trimethylsilyl, tri-*n*-butylstannyl,[61] or alkyl groups.[62b–f]. Even an α substituent[62a, f] (see below) can serve to reinforce the intrinsic preference for lone pair coordination. For cyclic α,β-enones with endocyclic unsaturation, α substitution of the C–C double bond with alkyl[47, 63] or halogen[64] is crucial for effective steric differentiation of the carbonyl oxygen electron lone pairs (Table 8). The reduction of cyclic α,β-enones with an exocyclic double bond has not been extensively studied. However, it can be expected that β substitution is not crucial for high enantioselectivity, but helps to minimize reduction of the conjugated double bond.[65, 66]

The oxazaborolidine-catalyzed reduction of α,β-ynones to afford propargyl alcohols of high optical purity has recently been accomplished by two different reaction protocols (Table 9). The use of (*S*)-*B*-Me-**4** as catalystand $BH_3 \cdot Me_2S$ as reductant in THF leads to (*S*)-alcohols, with ethynyl behaving as the small group R_S.[67] In contrast, the use of (*S*)-*B*-CH_2SiMe_3-**4**[43] or (*S*)-*B*-*p*-*t*BuC_6H_4-**4**[44a] and catecholborane in CH_2Cl_2 for the reduction of triisopropylsilyl or trimethylsilylacetylene ketones furnishes (*R*)-propargyl alcohols, with ethynyl behaving as the large group R_L.[68] This intriguing reversal in the enantioselectivity of the reduction is the consequence of repulsive interactions between the remotely situated bulky substituents on the triple bond and the heterocyclic boron atom of the catalyst.[43]

Ketones with two sp^3-hydridized carbon atoms attached to the carbonyl center can also be reduced with high enantio-

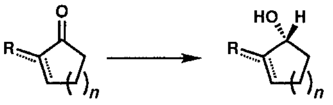
Table 6. Oxazaborolidine-catalyzed reduction of diaryl- and aryl diisopropylphosphono ketones.[a]



Ketone	*ee* [%]	*T* [°C]
	95[58]	−78
	93[59]	−78
	97 (X = Br,Me)[59]	−40
	> 90 (X = Me)[59] 99 (X = allyl)[59]	−40
	91–97 (X = F,Cl,Br,I,Me)[53]	−20

[a] A procedure for the CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)-pyridinium triflate is provided in reference [60].

Table 8. Oxazaborolidine-catalyzed reduction of cyclic α,β-enones.



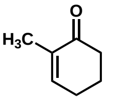
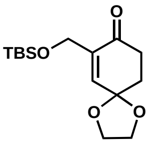
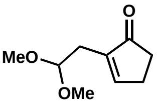
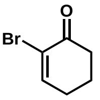
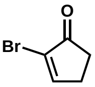
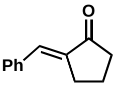
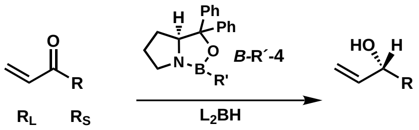
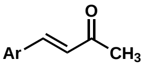
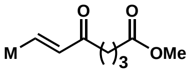
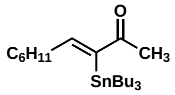
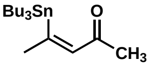
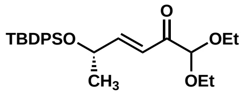
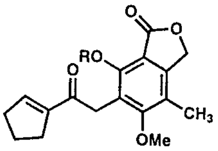
Enone	*ee* [%]	Catalyst	L$_2$BH	*T* [°C]
	93[47]	*B*-*n*Bu-**4**	CB	−78
	92[63a]	*B*-*n*Bu-**4**	BTHF	37
	93[63b]	*B*-Me-**4**	BTHF	10
	96[64a]	*B*-Me-**4**	BMS	−15
	90[64b]	*B*-Me-**4**	BTHF	23
	96[65]	*B*-Me-**4**·BH$_3$	BMS	−20

Table 7. Oxazaborolidine-catalyzed reduction of acyclic α,β-enones.[a]

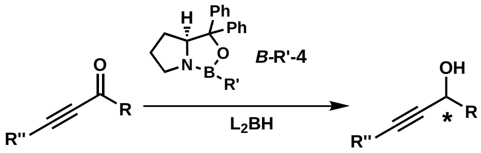


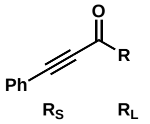
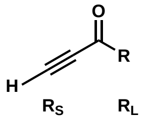
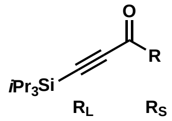
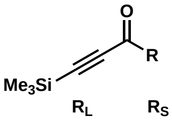
Enone	*ee* [%]	Catalyst	L$_2$BH	*T* [°C]
	97 (Ar = Ph)[58] 95 (Ar = 4-MeOC$_4$H$_4$)[58]	*B*-*n*Bu-**4**	CB	−78
	94 (M = SiMe$_3$)[61] 88 (M = SnBu$_3$)[61]	*B*-CH$_2$SiMe$_3$-**4**	CB	−78 −60
	94[62a]	*B*-*n*Bu-**4**	CB	−78
	85[62b,c]	*B*-Me-**4**	CB	−30
	95[62d,e]	*B*-*n*Bu-**4**	BMS	23
	92–97[62f]	*B*-Me-**4**	BMS	−30

[a] A procedure for the CBS reduction of (*E*)-4-(4′-methoxyphenyl)-3-buten-2-one is provided in reference [66].

selectivity whenever there are substantial differences in the accessibility of the two oxygen electron lone pairs for coordination (Table 10). For example, ketones having a *tert*-alkyl group and a primary or *n*-alkyl-type group as carbonyl appendages can be reduced with high enantioselectivity.[44a, 46] The reduction of some ketones, especially those in which the carbonyl group is quite hindered, often proceeds with better stereoselectivity at higher temperatures (30–120 °C), possibly due to accelerated removal of the bulky boronate product from the oxazaborolidine.[55a, 69a, b] The highly enantioselective reduction of *s*-alkyl ketones such as cyclohexyl methyl ketone and isopropyl methyl ketone was recently accomplished by the use of $BH_3 \cdot$diethylaniline as stoichiometric reductant.[46] In the CBS reduction of cyclopropyl isopropyl ketone, the strong influence of electronic factors is clearly evidenced, as the π electron rich cyclopropyl group behaves as R_L in comparison to the sterically similar isopropyl group.[58] Methyl *n*-alkyl ketones are reduced with modest selectivity with *n*-alkyl as R_L,[70] but the factors responsible for enantiodifferentiation of di-*n*-alkyl ketones can be quite subtle;[71] further study of the reduction of such challenging substrates represents an attractive area for future research.

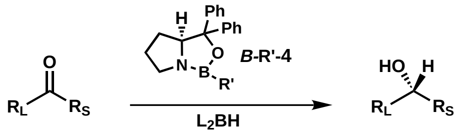
Table 9. Oxazaborolidine-catalyzed reduction of α,β-ynones.

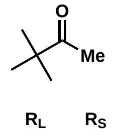
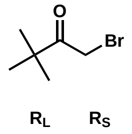
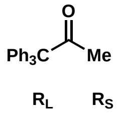
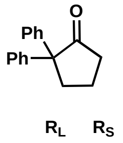
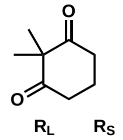
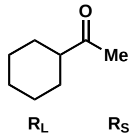
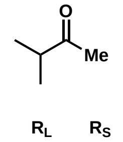
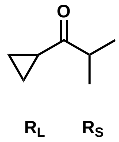
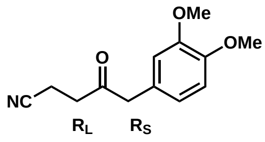
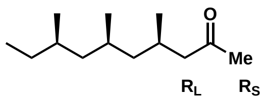


Ynone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	71–88 (R = *n*-alkyl)[67] 94–96 (R = *s*-alkyl)[67]	*B*-Me-**4**[a]	BMS	–30
	95 (R = *n*-alkyl)[67] 98 (R = *c*-Hexyl)[67]	*B*-Me-**4**[a]	BMS	–30
	90–97 (R = *n*-, *s*-alkyl)[43]	*B*-CH_2SiMe_3-**4**	CB	–78
	91–97 (R = CH_3, *n*-alkyl)[44a]	*B*-*p*-*t*BuC_6H_4-**4**	CB	–40

[a] 2 equiv of *B*-Me-**4**.

Table 10. Oxazaborolidine-catalyzed reduction of dialkyl ketones.



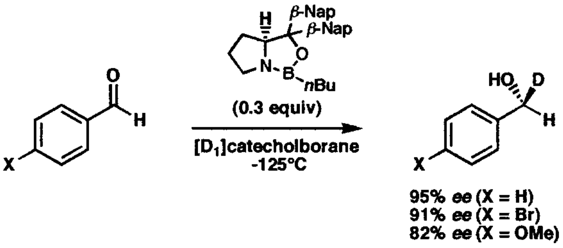
Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]	Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	97.4[46]	*B*-Me-**4**	BDEA	20		97[44a]	*B*-*n*Bu-**4**	BMS	23
	97[55a]	*B*-Me-**4**	BTHF	120		92[69a]	*B*-Me-**4**	BMS	40
	93[70]	*B*-*n*Bu-**4**	CB	25		≥ 99[46]	*B*-Me-**4**	BDEA	20
	91[46]	*B*-Me-**4**	BDEA	20		91[58]	*B*-*n*Bu-**4**	CB	–78
	82[71]	*B*-Me-**4**	BMS	–15		–[a]	*B*-Me-**4**	BTHF	23

[a] 70 % *de*.[70]

Transition metal π complexes of achiral ketones can often be reduced with high enantioselectivity. Thus, the CBS reduction of a variety of ketones π-complexed with chromium,[72] cobalt,[58] iron,[73] or ruthenium[73b] has been investigated with outstanding results (Table 11). The resulting optically active products are useful for the synthesis of pharmaceutically important compounds[72] and chiral ligands for asymmetric catalysis.[73]

The study of trihalomethyl ketones has provided deep insights into the connection between ketone conformation and reactivity.[22, 74] The electron-withdrawing nature of the trihalomethyl group results in a stereoelectronically favorable deformation of the carbonyl group towards CX_3. Together with the steric bulk of the trihalomethyl group, this leads to highly selective catalyst binding *anti* to CX_3 and subsequent fast hydride transfer[22] to furnish trihalomethyl carbinols of high enantiopurity across a wide range of ketonic structures (Table 12).[75]

Primary alcohols deuterated in the 1-position have been prepared by the reduction of the corresponding aldehydes with [D_1]catecholborane at low temperature (Scheme 7).[31] 1-Octanal (90% *ee*) and cyclohexanecarbaldehyde (92% *ee*) also undergo highly selective reduction under these conditions.

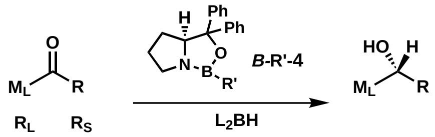


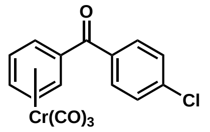
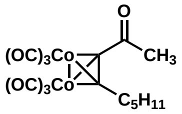
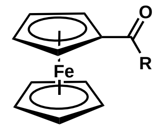
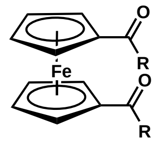
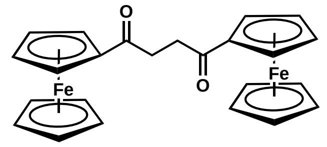
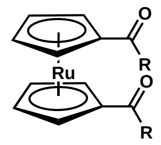
Scheme 7. Preparation of primary alcohols deuterated in the 1-position.

6. Applications of the Oxazaborolidine-Catalyzed Reduction of Ketones

The ever-increasing need for absolute stereochemical control in the construction of organic molecules has resulted

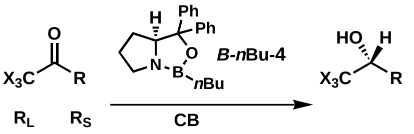
Table 11. Oxazaborolidine-catalyzed reduction of ketones in ligands of metal complexes.

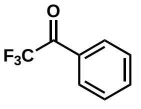
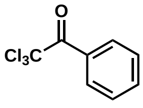
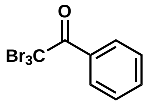
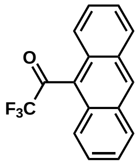
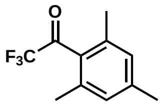
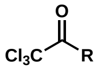


Complex	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	98[72]	*B*-*n*Bu-**4**	CB	−40
	97[58]	*B*-CH_2SiMe_3-**4**	CB	−78
	> 95 (R = Me, Et, Ph, *i*Pr)[73a]	*B*-Me-**4**	BTHF	0
	> 99 (R = *n*-, *s*-alkyl, Ph)[a][73b]	*B*-Me-**4**	BTHF	0
	> 98[b][73c]	*B*-Me-**4**	BTHF	0
	> 99 (R = Me, *n*-pentyl)[c][73b]	*B*-Me-**4**	BTHF	0

[a] 74–94% *de*. [b] 74% *de*. [c] 68–78% *de*.

Table 12. Oxazaborolidine-catalyzed reduction of trihalomethyl ketones.

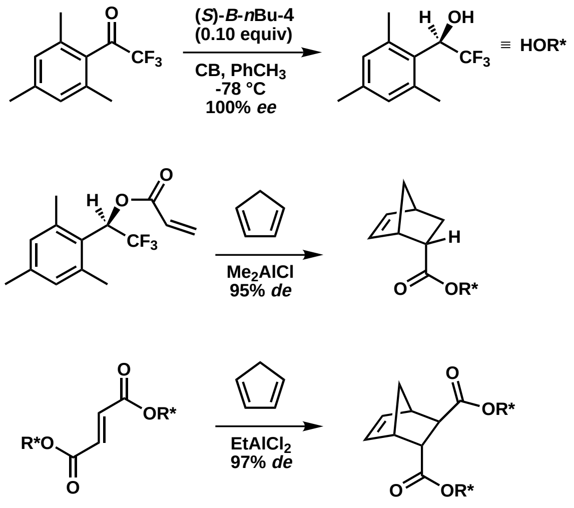


Ketone	*ee* [%]	*T* [°C]
	90[47]	– 78
	96[22]	– 23
	98[22]	– 23
	94[47]	– 78
	100[55a]	– 78
	92–98 (R = *n*-, *s*-, *t*-alkyl)[75]	– 23 bis – 78

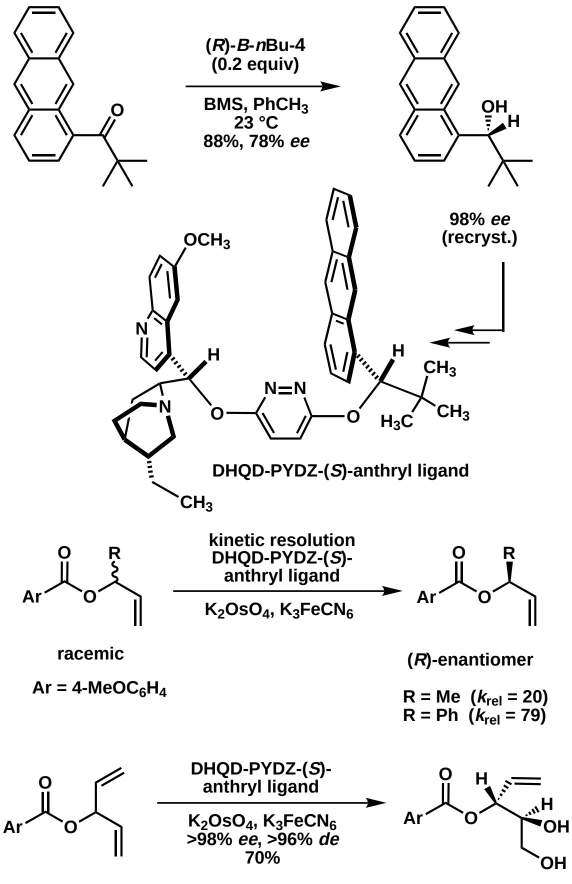
in a large number of applications of the CBS reduction to asymmetric synthesis. These applications include the preparation of 1) chiral ligands for enantioselective synthesis, 2) highly useful chiral intermediates, 3) synthetic bioactive compounds, and 4) natural products.

6.1. Preparation of Enantiopure Ligands for Asymmetric Synthesis

The CBS reduction of 1-mesityl trifluoromethyl ketone provided the corresponding (*R*)-alcohol with greater than 99.8% *ee* (Scheme 8).[55a] This product served as a useful chiral controller in Lewis acid catalyzed Diels–Alder reactions. The corresponding acrylate and fumarate esters react with cyclopentadiene to form Diels–Alder adducts with excellent diastereoselectivity.[76]



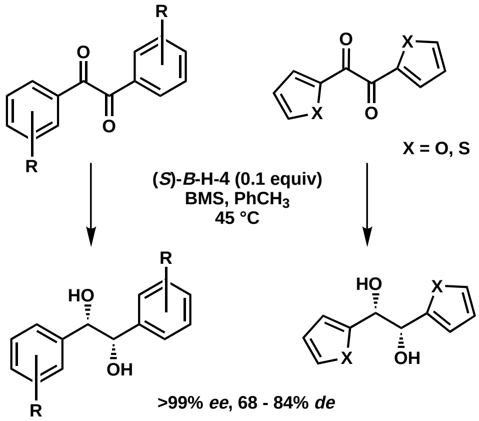
Scheme 8. Synthesis of (*R*)-(–)-mesityl-2,2,2-trifluoroethanol, an outstanding chiral auxiliary for the Lewis acid catalyzed Diels–Alder reaction.



Scheme 9. Highly selective kinetic resolution of allyl alcohol derivatives with a catalyst for asymmetric dihydroxylation.

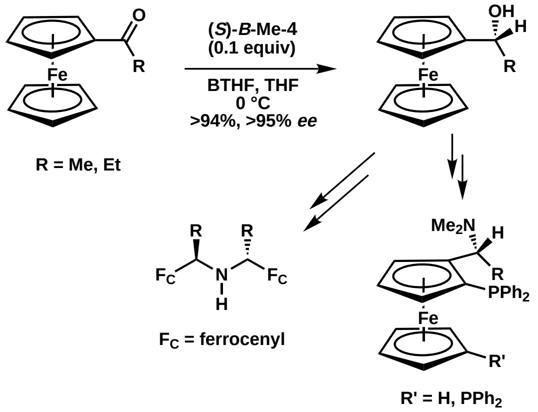
The Sharpless asymmetric dihydroxylation (AD) of olefins is broadly useful in organic synthesis. To increase the scope of this reaction, the DHQD-PYDZ-(*S*)-anthryl ligand (designed under guidance from the dihydroxylation mechanism) was prepared from enantioenriched *tert*-butyl anthryl alcohol (Scheme 9).[77] This catalyst has a deep binding pocket that can accommodate olefinic substrates with remote binding groups, such as allyl 4-methoxybenzoates.[78] It is highly effective for kinetic resolution of racemic allyl 4-methoxybenzoate (Scheme 9).

Chiral 1,2-diols have been extensively utilized as ligands and chiral controllers for the asymmetric preparation of C–X and C–C stereocenters. The CBS reduction of 1,2-diketones, in particular benzil derivatives and heterocyclic analogues, with $BH_3 \cdot Me_2S$ in the presence of (*S*)-*B*-H-**4** furnishes the optically active (*S,S*)-hydrobenzoins with outstanding enantiomeric excess and good diastereomeric excess (Scheme 10).[79]



Scheme 10. Enantioselective reduction of 1,2-diketones to valuable chiral 1,2-diols.

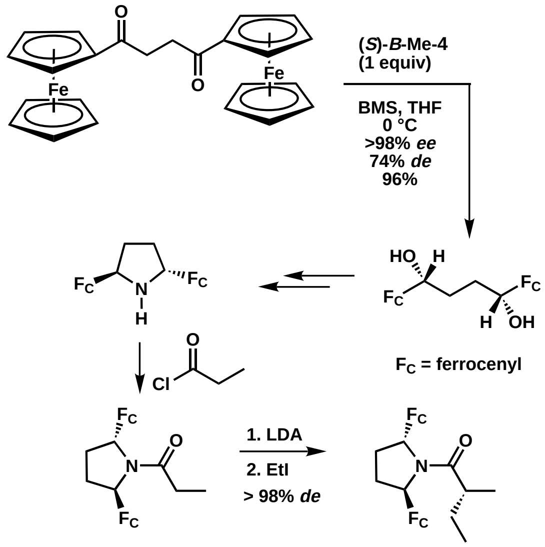
The oxazaborolidine-catalyzed reduction of ferrocenyl ketones, F_CCOR, proceeds with excellent enantioselectivity (>95% *ee*, Scheme 11 and Table 11).[76] The resultant optically active ferrocenyl carbinols can be converted into chiral ferrocenylamines with complete retention of configuration. This affords useful chiral bases for asymmetric deprotonation or chiral ligands for transition metal catalyzed reactions.



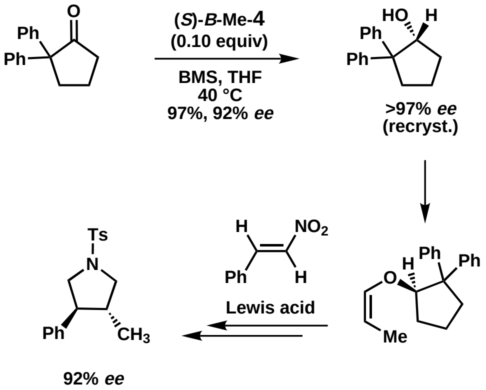
Scheme 11. CBS reduction of acylferrocenes to useful chiral ligands.

The asymmetric reduction of 1,2-bis(ferrocenoyl)ethane occurs with high enantioselectivity (>98% *ee*) and diastereoselectivity (74% *de*) to form a diol which was converted into a chiral C_2-symmetric pyrrolidine. This is a useful chiral auxiliary for diastereoselective alkylation (Scheme 12).[73c]

(*R*)-2,2-Diphenylcyclopentanol was obtained by oxazaborolidine-catalyzed reduction (92% *ee*) and converted into vinyl ethers for Lewis acid promoted [4+2] cycloaddition with 2-substituted 1-nitroalkenes. Hydrogenation of the resulting cycloadducts affords a route to chiral 3,4-disubstituted pyrrolidines (Scheme 13).[69a, 80]



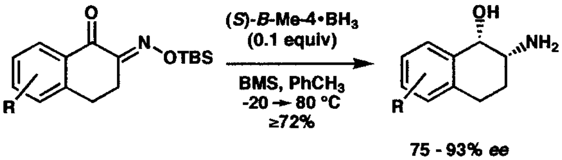
Scheme 12. A C_2-symmetric ferrocenylpyrrolidine is an effective chiral auxiliary.



Scheme 13. Preparation of a useful auxiliary for nitroalkene–vinyl ether cycloadditions.

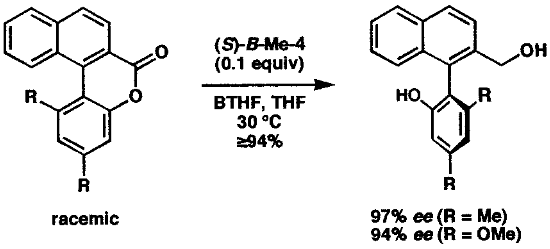
6.2. Preparation of Useful Chiral Building Blocks

Enantiopure amino alcohols are of interest because of their biological activity and value as chiral ligands in metal-catalyzed organic reactions. The catalytic oxazaborolidine-mediated reduction of α-keto oximes results in reduction of C=O followed by C=N to give primarily the *cis*-amino alcohol (Scheme 14).[81]



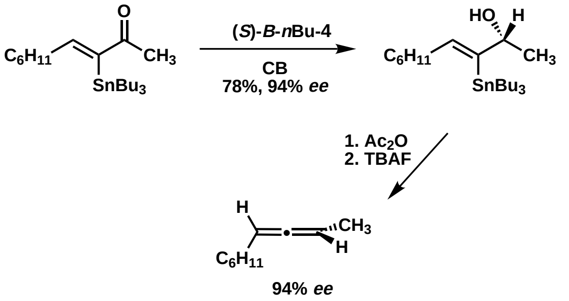
Scheme 14. One-step synthesis of optically active *cis*-amino alcohols.

In a particularly striking example of the broad applicability of the CBS methodology, the enantioselective reduction of axially prostereogenic biaryl lactones affords one atropisomer in a ratio of 97:3 or higher (Scheme 15).[82] It was proposed that the product-determining step is the selective reduction of an equilibrating mixture of enantiomeric hydroxy aldehydes.



Scheme 15. Selective ring opening to an atropisomer of axially chiral biaryl compounds.

The chiral stannylated allyl alcohol shown in Scheme 16 was readily obtained by CBS reduction and transformed into a chiral allene by fluoride-catalyzed elimination.[62a]

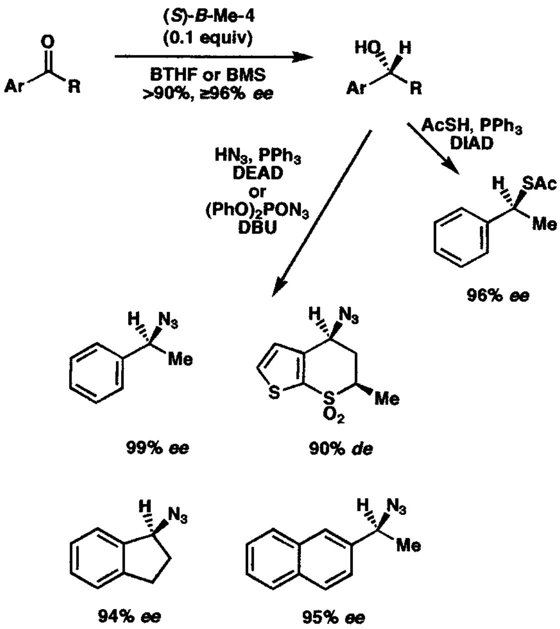


Scheme 16. A different route to optically active allenes.

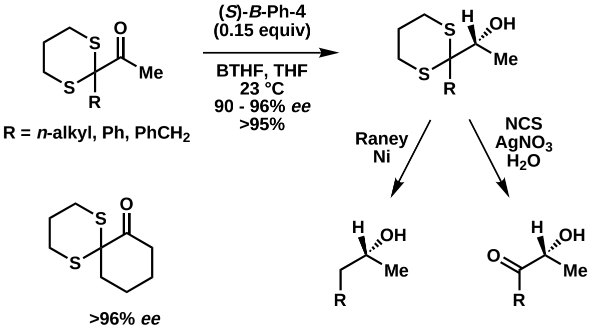
Whereas chiral C–O stereocenters can be readily accessed by oxazaborolidine-catalyzed reduction of ketones, the asymmetric reductions of other heteroatom–carbon double bonds are not as efficient. To overcome these limitations, the displacement of the hydroxyl group of chiral secondary alcohols from the CBS reduction with either nitrogen or sulfur nucleophiles under Mitsunobu-type conditions has been investigated and found to occur by S_N2 inversion; this yields optically active nitrogen[54, 83] and sulfur compounds[86] (Scheme 17). These results are especially noteworthy considering the tendency of benzyl substrates to undergo S_N1 displacement with loss of configuration.

The dithiane protecting group for ketones has been utilized as a steric control element in the CBS reduction to differentiate the carbonyl oxygen electron lone pairs (Scheme 18).[85] The reductions were highly enantioselective for both acyclic and cyclic compounds. Subsequent desulfurization (with Raney Ni) gave aliphatic carbinols, whereas hydrolysis gave α-hydroxy ketones.

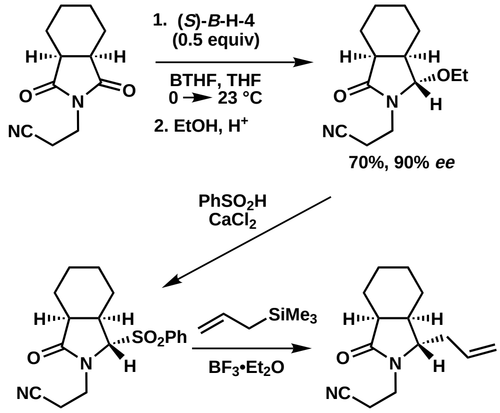
The desymmetrization of a *meso*-imide by the selective reaction of one of the two prochiral carbonyl groups is extremely powerful as three new chiral centers result. As shown in Scheme 19, oxazaborolidine-catalyzed reduction accomplishes this transformation with good enantiomeric excess (90% *ee*). This provides a route to enantioenriched starting materials for *N*-acyliminium ion chemistry.[86]



Scheme 17. The Mitsunobu route to chiral nitrogen and sulfur compounds.

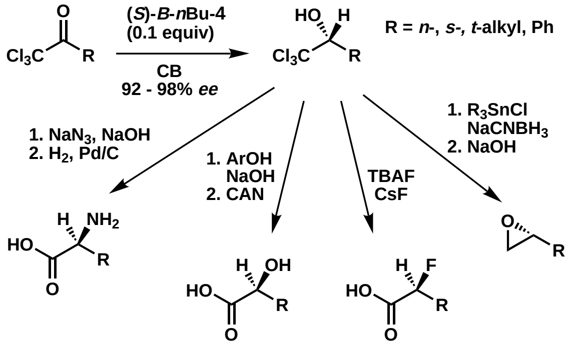


Scheme 18. Dithiane as the large group R_L in the CBS reduction.



Scheme 19. CBS reduction of *meso*-imides yields chiral pyrrolidinones.

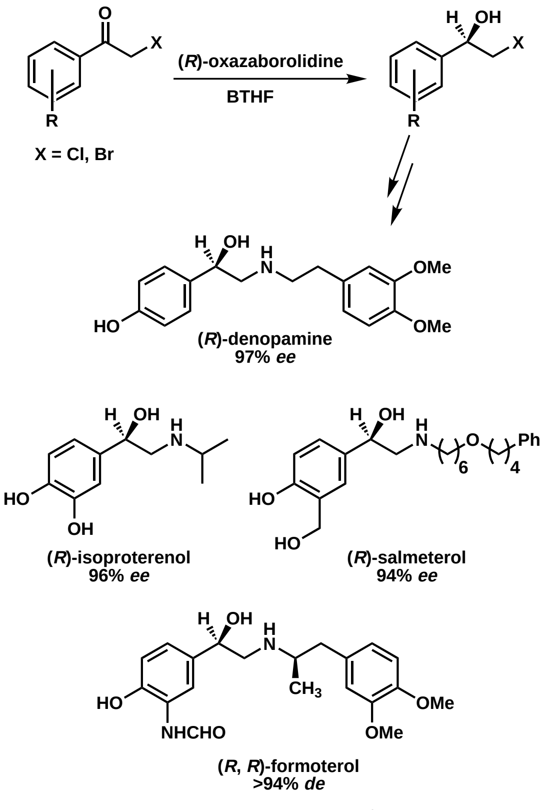
Trichloromethyl carbinols, which are available with very high levels of enantioselectivity by the asymmetric reduction of achiral trichloromethyl ketones,[87] are readily converted into α-amino,[75] α-hydroxy,[88] and α-fluoro acids[89] under basic conditions via a highly reactive 1,1-dichloro epoxide (Scheme 20). The selective dechlorination of trichloromethyl carbinols to chlorohydrins followed by ring closure provides a straightforward route to optically active terminal oxiranes.[90]



Scheme 20. Trichloromethyl alcohols give access to many useful chiral intermediates.

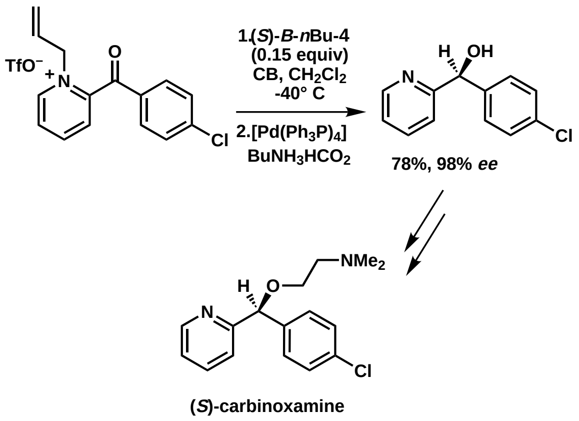
6.3. Synthesis of Bioactive Compounds

Many β-agonists, which are useful in the treatment of asthma and bronchitis, are currently sold as racemates despite the demonstration of enhanced efficacy of the *R* isomers. The oxazaborolidine-catalyzed reduction of α-haloacetophenones has permitted the highly efficient preparation of a number of β-agonists in enantiomerically pure form by amination of the corresponding optically active styrene oxide or O-silyl halohydrin (Scheme 21).[91]



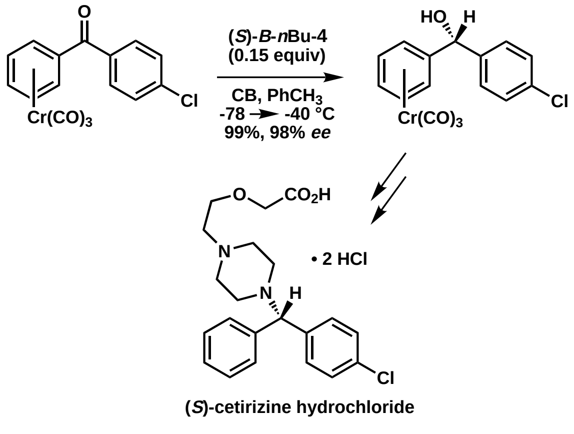
Scheme 21. Enantioselective synthesis of β-agonists.

The commercial histamine antagonist carbinoxamine has been prepared as essentially a single enantiomer (98% *ee*); the key steps are a CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate followed by in situ deallylation (Scheme 22).[59, 60] The allyl group serves both to prevent coordination of the pyridine nitrogen atom to the stoichiometric reductant catecholborane and/or the oxazaborolidine catalyst, and to provide the necessary steric bias for the selective binding of one of the carbonyl oxygen electron lone pairs to the catalyst.



Scheme 22. Enantioselective synthesis of (*S*)-carbinoxamine.

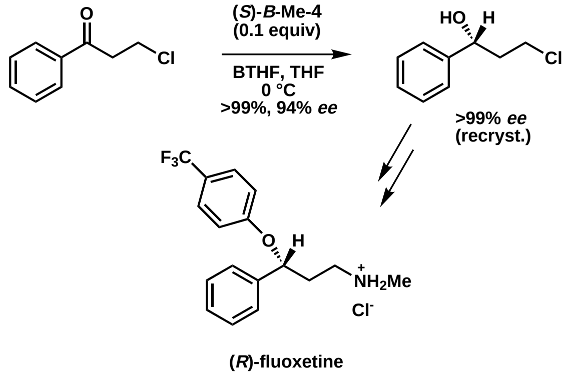
Cetirizine hydrochloride (zyrtec), an antihistamine that is notable for its nonsedating properties and potency, contains an amino-substituted benzhydril stereocenter. This stereocenter has been established by a highly selective CBS reduction of a benzophenone–$Cr(CO)_3$ π complex (Scheme 23).[75] The complexed $Cr(CO)_3$ group behaves as R_L both for steric and electronic reasons, and functions as a controller for the enantiospecific displacement of the hydroxyl group by amine with retention of configuration.



Scheme 23. Enantioselective synthesis of (*S*)-cetirizine hydrochloride.

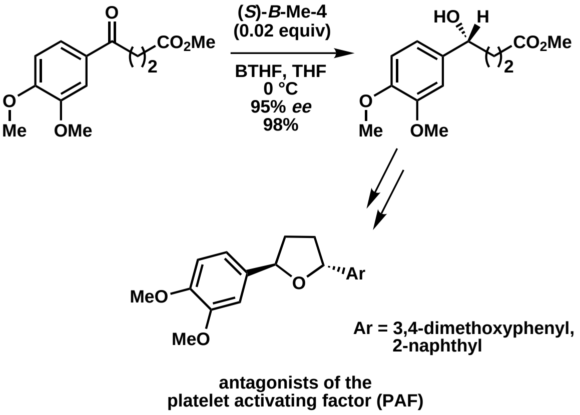
The antidepressant fluoxetine hydrochloride (prozac, Eli Lilly) has been synthesized in enantiomerically pure form by the oxazaborolidine-catalyzed reduction of β-chloropropiophenone as a key step (Scheme 24).[92] This four-step synthesis proceeds in high overall yield (77–82%) and does not require chromatographic purification.

Chiral *trans*-2,5-diaryltetrahydrofurans, inhibitors of the platelet activating factor, have been prepared by CBS



Scheme 24. Enantioselective synthesis of (*R*)-fluoxetine.

reduction of a γ-ketoester followed by lactonization, reduction, and stereoselective arylation (Scheme 25).[93]



Scheme 25. Enantioselective synthesis of antagonists of the platelet activating factor (PAF).

The chiral thioether L-691,698, an antagonist of leukotriene D_4, has also been synthesized by the oxazaborolidine-catalyzed reduction (Scheme 26).[94]

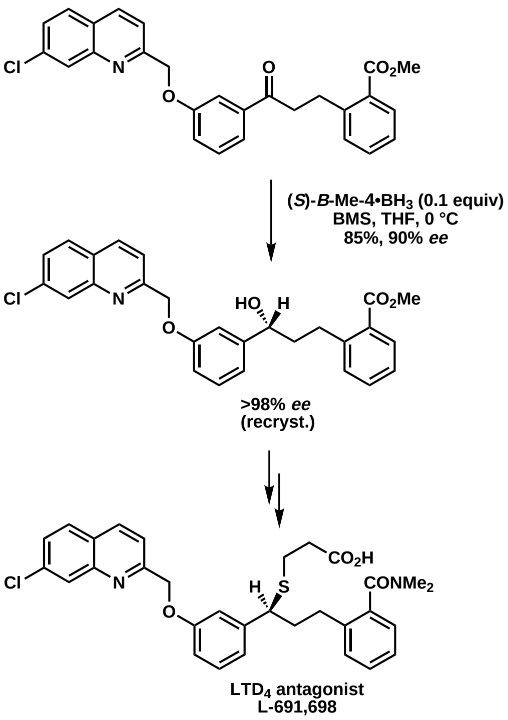
The carbonic anhydrase inhibitor MK-0417 has been prepared on a large scale by the oxazaborolidine-catalyzed reduction of the heterocyclic ketone shown in Scheme 27.[44b]

The synthesis of the potassium channel blocker MK-0499 utilized a variant of the CBS reduction in which one equivalent of 2-propanol was added prior to $BH_3 \cdot SMe_2$ (Scheme 28).[21] The use of 2-propanol as additive increased the diastereoselectivity from 93 to 98%.

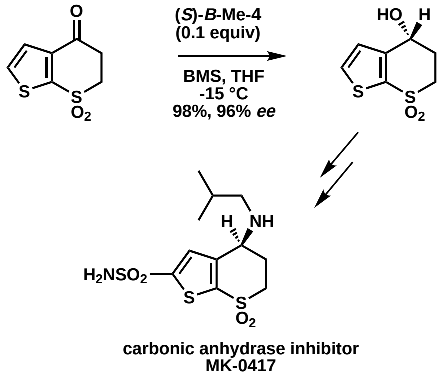
The CBS reduction of the acyclic α,β-enone shown in Scheme 29 proceeded diastereoselectively to form the corresponding allyl alcohol, which was used for the synthesis of an isomer of colletallol.[62d, e]

Oxazaborolidine-catalyzed reduction of the α,β-enone in Scheme 30 to the optically pure allyl alcohol provided the first chiral center in the synthesis of the antiinflammatory and immunosuppressive agent RS-97613.[62f] Subsequent stereoselective orthoester Johnson–Claisen rearrangement, diastereoselective α-methylation, and hydrolysis completed the synthesis of this analogue of mycophenolic acid.

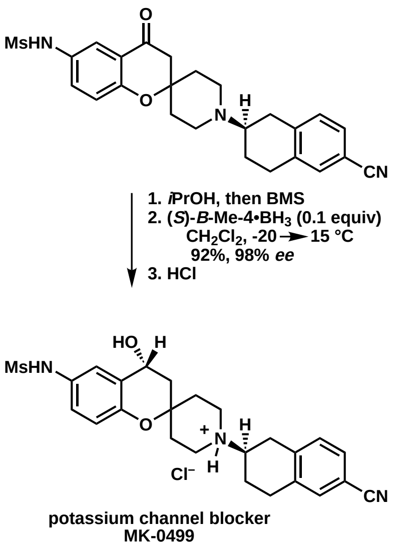
The 3-deoxy-3-thia analogue of vitamin D was synthesized by CBS reduction of the cyclic α,β-enone shown in Scheme 31.



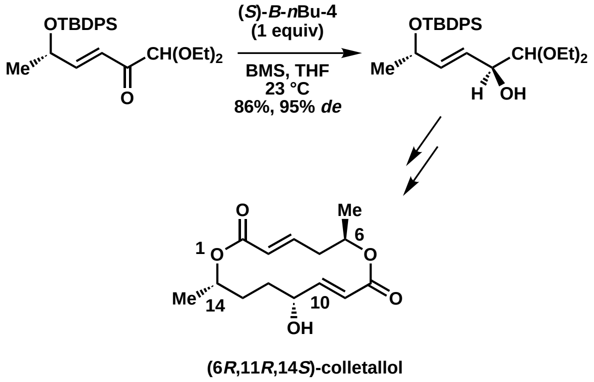
Scheme 26. Enantioselective synthesis of a leukotriene D_4 antagonist.



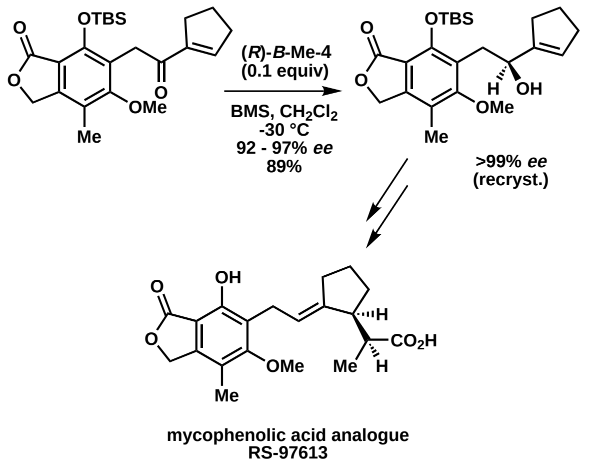
Scheme 27. Enantioselective synthesis of a carbonic anhydrase inhibitor.



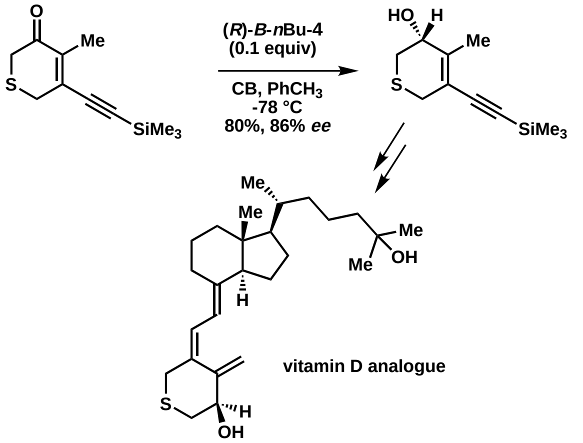
Scheme 28. Enantioselective synthesis of a potassium channel blocker.



Scheme 29. Asymmetric synthesis of (6*R*,11*R*,14*S*)-colletallol.



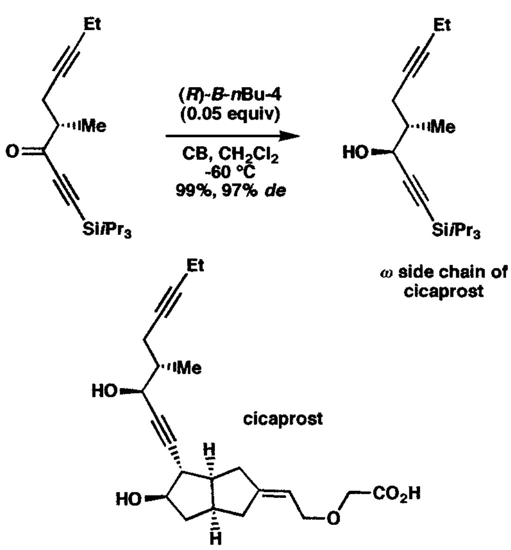
Scheme 30. Enantioselective synthesis of an immunosuppressive and antiinflammatory agent.



Scheme 31. Asymmetric synthesis of a vitamin D analogue.

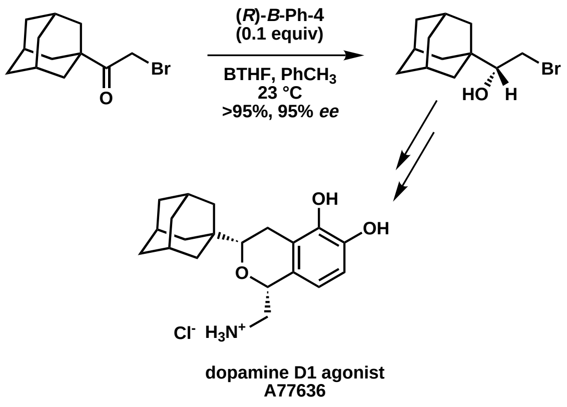
This provided a chiral allyl alcohol corresponding to the A ring.[95]

Cicaprost, an orally active, metabolically stable prostaglandin I_2 (PGI_2) analogue, contains a complex side chain which was constructed by oxazaborolidine-catalyzed reduction (Scheme 32).[96] Long-range steric interactions between *n*-butyl group on the boron atom of the catalyst and the triisopropylsilyl group of the ketonic substrate cause ethynyl to behave as the large group R_L. The chirality of the starting ketone does not affect the selectivity of the reduction since the use of the enantiomeric (*S*)-oxazaborolidine catalyst gave the other diastereomer with high diastereomeric excess (96%).



Scheme 32. Asymmetric synthesis of the *ω* side chain of cicaprost.

The dopamine D1 agonist A77636 was recently prepared in optically pure form by oxazaborolidine-catalyzed reduction of adamantyl bromomethyl ketone (Scheme 33).[97] Conversion of the chiral bromohydrin into the corresponding epoxide, ring opening with an aryllithium reagent, intramolecular acetal cyclization, and deprotection gave the desired product in very good yield.

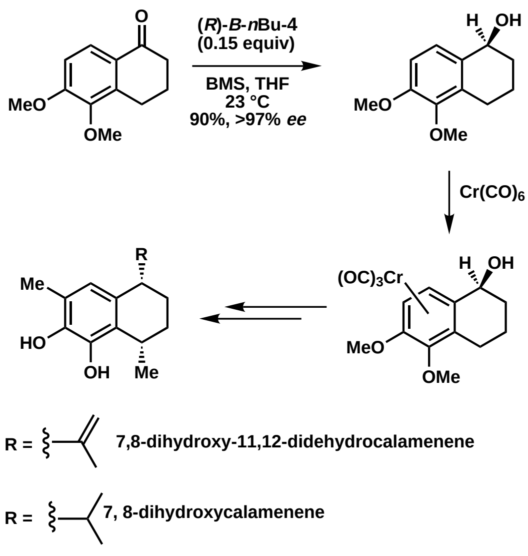


Scheme 33. Asymmetric synthesis of A77636.

6.4. Synthesis of Natural Products

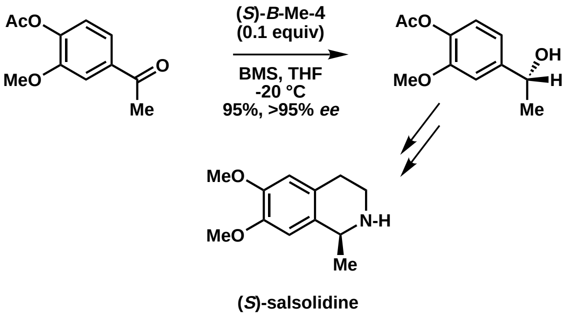
The antiinfective compounds 7,8-dihydroxycalamenene and 7,8-dihydroxy-11,12-didehydrocalamenene were synthesized by CBS reduction of 5,6-dimethoxy-1-tetralone, hydroxyl-directed face-selective complexation of a $Cr(CO)_3$ moiety, and subsequent hydrogenolysis, metalation/alkylation, and decomplexation (Scheme 34).[98]

The tetrahydroisoquinoline (*S*)-salsolidine was prepared efficiently by oxazaborolidine-catalyzed reduction of a substituted acetophenone followed by Mitsunobu displacement



Scheme 34. Enantio- and stereocontrolled synthesis of chiralen antiinfective tetralins.

of the hydroxyl group with a sulfonamide and intramolecular cyclization (Scheme 35).[99] This approach should be applicable to the synthesis of a number of enantiopure tetrahydroisoquinoline derivatives.

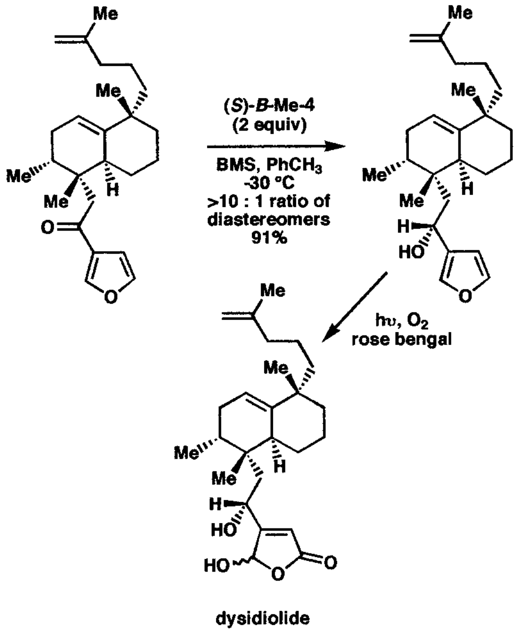


Scheme 35. Enantioselective synthesis of (*S*)-salsolidine.

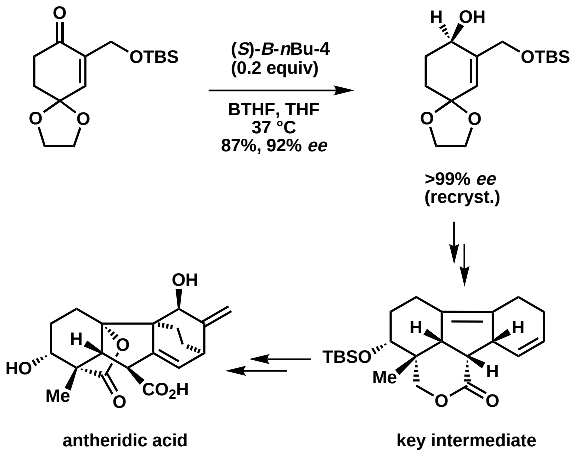
In a recent total synthesis of the sesterterpene dysidiolide, a marine sponge metabolite that has been shown to exhibit antitumor activity, oxazaborolidine-catalyzed reduction afforded greater than 10:1 selectivity for the required alcohol; the 3-furyl group acted effectively as R_L, and the bicyclic ring system as R_S (Scheme 36).[100] Importantly, this route permitted conversion of the *S* diastereomer into the desired *R* isomer by oxidation and subsequent asymmetric reduction. Mitsunobu displacement of the hydroxyl group of the *S* diastereomer was nonstereoselective.

The fern hormone antheridic acid was initially synthesized in racemic form. An enantioselective synthesis of a key intermediate was achieved by the oxazaborolidine-catalyzed reduction and subsequent conversions depicted in Scheme 37.[63a]

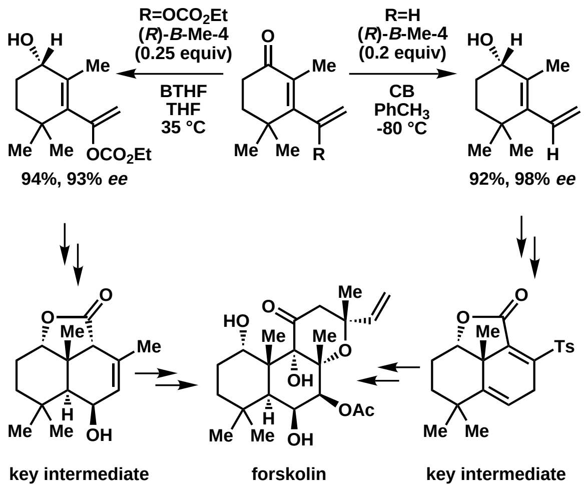
Two different routes to optically active intermediates for the synthesis of forskolin, a potent activator of adenylate cyclase, have been devised utilizing CBS reduction of the dieneones shown in Scheme 38.[101, 102]



Scheme 36. Enantioselective synthesis of dysidiolide.

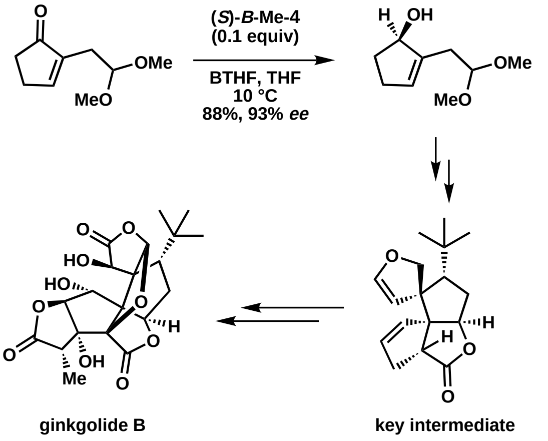


Scheme 37. Enantioselective synthesis of antheridic acid.

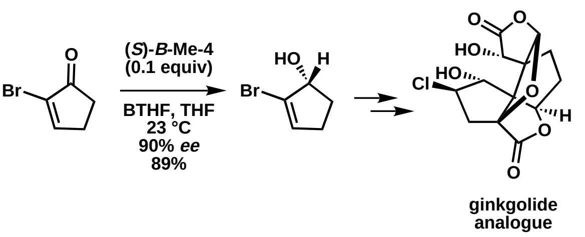


Scheme 38. Enantioselective synthesis of forskolin.

Ginkgolide B, a potent antagonist of the platelet activating factor, has been synthesized enantioselectively by CBS reduction of a α-functionalized cyclopentenone to introduce chirality (Scheme 39).[63b] The resulting optically active allyl alcohol was then elaborated in a stereocontrolled fashion via a tetracyclic lactone to ginkgolide B. The CBS reduction of 2-bromo-2-cyclopentenone served as a key step in the synthesis of a truncated analogue of ginkgolide B (Scheme 40).[64b]

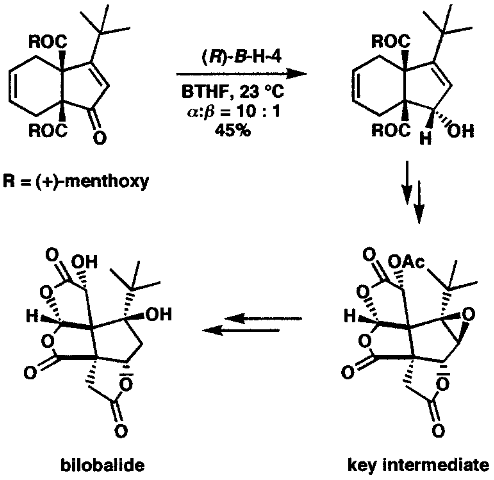


Scheme 39. Enantioselective synthesis of ginkgolide B.



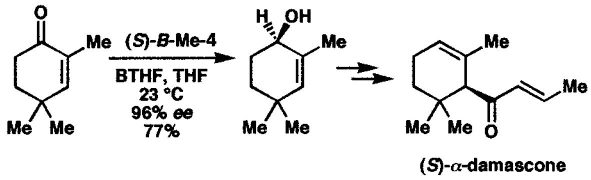
Scheme 40. Enantioselective synthesis of a ginkgolide analogue.

An asymmetric synthesis of bilobalide, an unusual substance produced by the gingko tree *Ginkgo biloba*, has been carried out starting from the bicyclic enone depicted in Scheme 41.[103] Attempts to reduce this chiral ketone to the α-epimer with a number of reagents ($NaBH_4$, $Zn(BH_4)_2$, SmI_2 in THF/MeOH, $BH_3 \cdot THF$, Na powder in 2-propanol/toluene) gave unsatisfactory results. The oxazaborolidine-mediated reduction of this substrate, however, provided greater than 10:1 selectivity for the α-epimer, which was then transformed into bilobalide via the tetracyclic trilactone shown.



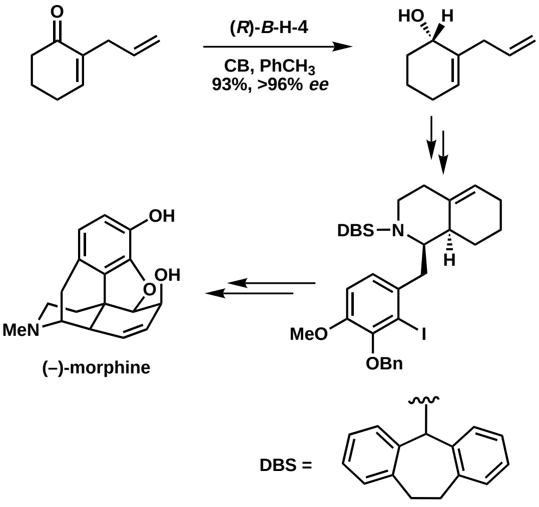
Scheme 41. Enantioselective synthesis of bilobalide.

The important fragrance (S)-α-damascone could be prepared by a sequence involving CBS reduction of the cyclic α-methyl-α,β-enone shown in Scheme 42, transfer of chirality from C–O to C–C by the Still variant of the [2,3] Wittig rearrangement to set the tertiary chiral center, oxidation, and introduction of the side chain.[104]



Scheme 42. Enantioselective synthesis of (S)-α-damascone.

A recent elegant synthesis of (−)-morphine also employed a highly enantioselective CBS reduction (Scheme 43).[105] Stereospecific conversion of the hydroxyl group into dimethylphenylsilyl and the terminal vinyl moiety into an amino substituent (N-DBS) set the stage for an intramolecular iminium ion–allylsilane cyclization to give the bicyclic system shown in Scheme 43. The bridgehead ring system was established by an intramolecular Heck reaction.

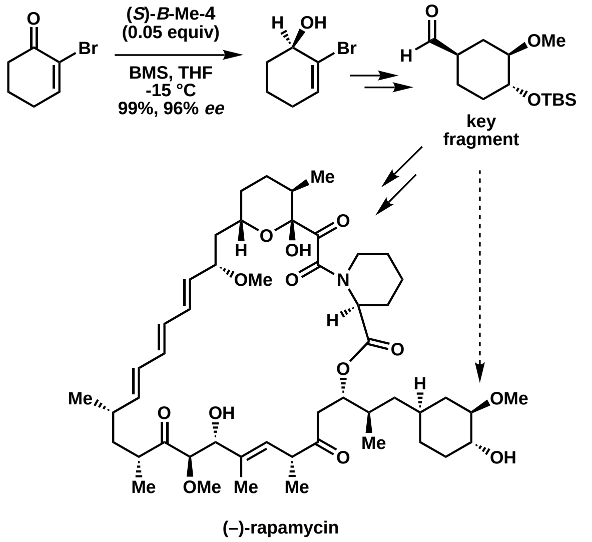


Scheme 43. Enantioselective synthesis of (−)-morphine.

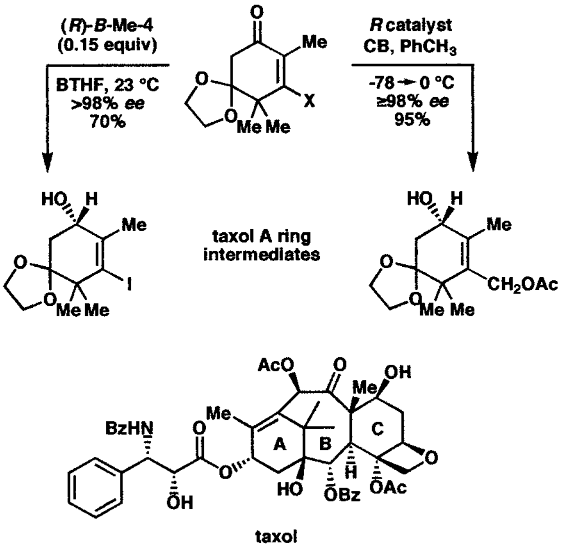
In the synthesis of the powerful immunosupressive agent (−)-rapamycin, oxazaborolidine-catalyzed reduction of 2-bromo-2-cyclohexen-1-one was used to generate the functionalized cyclohexyl subunit (Scheme 44).[64a, 106]

Two conceptually similar routes to the A ring of taxol have been developed by CBS reduction of functionalized cyclohexenones (Scheme 45).[107]

While many conjugated cyclic α,β-enones with *endocyclic* (*s-trans*) unsaturation have been reduced to allyl alcohols in



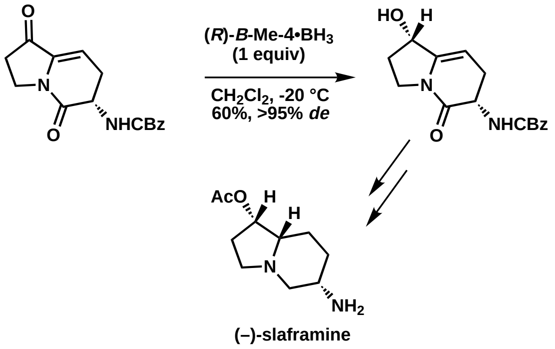
Scheme 44. Asymmetric synthesis of the cyclohexyl moiety of (−)-rapamycin.



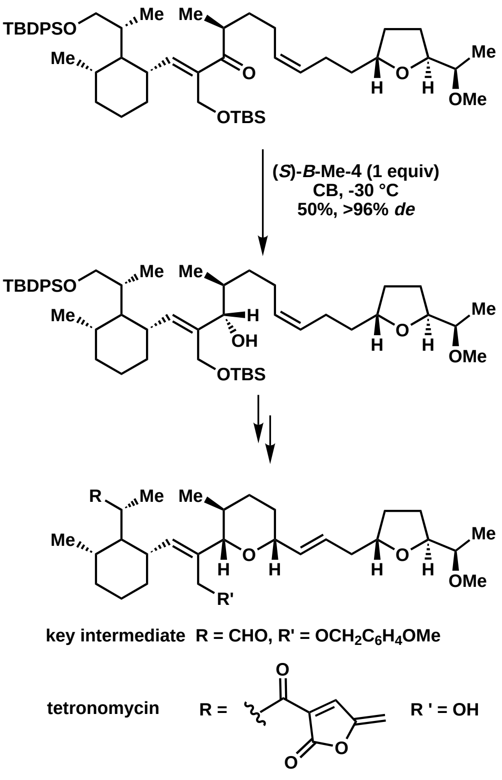
Scheme 45. Enantioselective synthesis of taxol A ring intermediates.

the presence of chiral oxazaborolidines, the reduction of such compounds with *exocyclic* (*s-cis*) double bonds has been reported only recently in connection with the synthesis of the alkaloid (−)-slaframine.[108] The chiral α,β-enone shown in Scheme 46 was reduced with one equivalent of the (*R*)-*B*-Me-**4** · BH_3 complex (*B*-Me-**5**) to provide the required allyl alcohol with excellent diastereomeric purity. In contrast, the use of the enantiomeric oxazaborolidine – BH_3 complex afforded the other diastereomer with high selectivity.

An approach to the synthesis of the ionophore antibiotic tetronomycin utilized the CBS reduction outlined in Scheme 47[109] (>96% *de*) followed by an intramolecular Pd^{II}-mediated cyclization to establish the central *cis*-substituted tetrahydropyran ring. Attempts to prepare the same allyl alcohol by addition of vinyllithium to an aldehyde yielded a 1:2 ratio of desired to undesired diastereomeric alcohols.



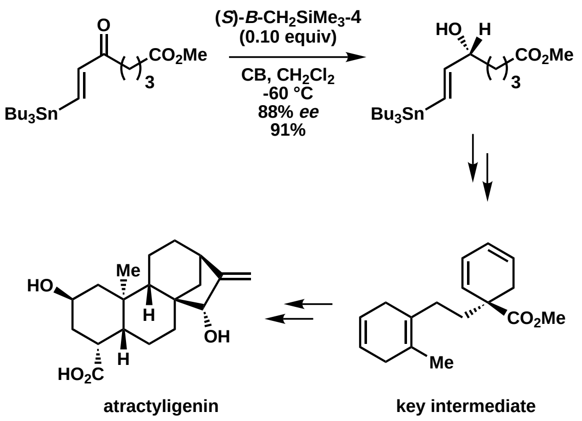
Scheme 46. Asymmetric synthesis of (−)-slaframine.



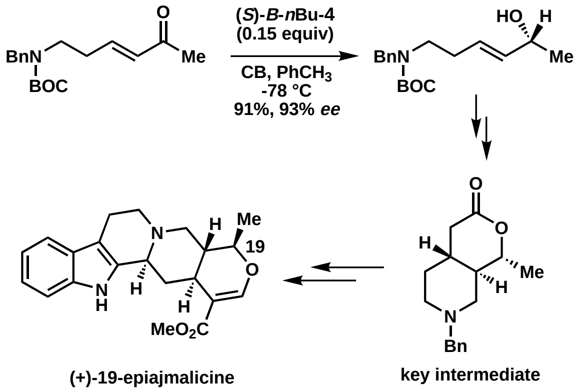
Scheme 47. Diastereoselective CBS reduction of a chiral ketone on the way to tetronomycin.

The naturally occurring adenosine diphosphate transport inhibitor atractilygenin was originally synthesized as the racemate; the first key chiral intermediate in the enantioselective CBS reduction is the substituted 1,3-cyclohexadiene shown in Scheme 48.[61] The use of the β-trialkylstannyl substituent on the enone to provide temporary steric bulk and the CH_2SiMe_3 group on the boron atom of the catalyst to maximize long-range steric interactions were crucial for high enantioselectivity in the oxazaborolidine-catalyzed reduction. Subsequent steps including a Claisen rearrangement effected the transfer of chirality from C–O to C–C to form the quaternary carbon stereocenter of the key intermediate.

A recent study on the synthesis of heteroyohimbine alkaloids utilized a CBS reduction of the acyclic α,β-enone shown in Scheme 49 to the allyl alcohol; the *B*-*n*Bu-oxazaborolidine catalyst (93% *ee*) was superior to the *B*-Me-oxazaborolidine catalyst (81% *ee*).[110] Orthoester Johnson–



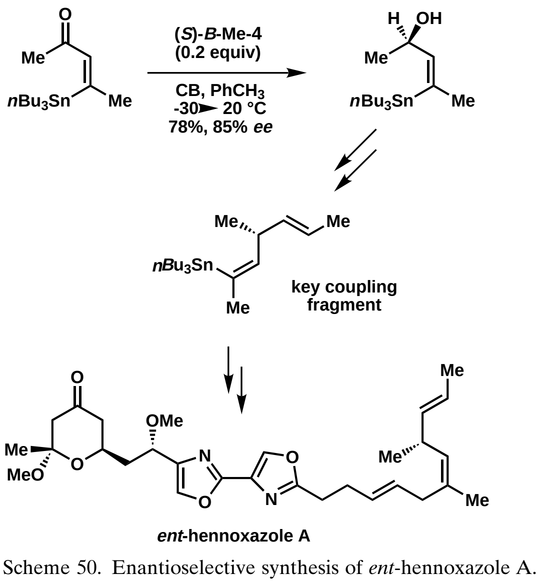
Scheme 48. Enantioselective synthesis of atractyligenin.



Scheme 49. Asymmetric synthesis of a key intermediate on the way to (+)-19-epiajmalicine.

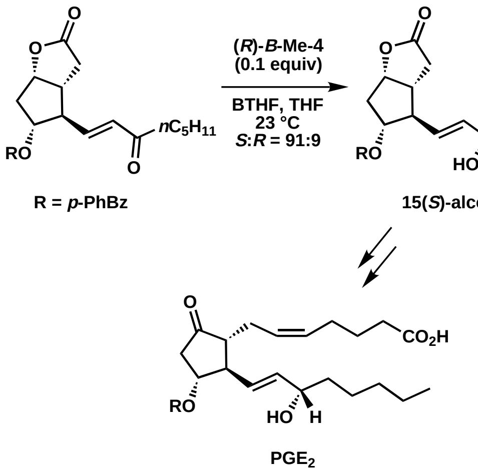
Claisen rearrangement and iminium ion biscyclization provided the bicyclic amino lactone.

The relative and absolute configurations of the marine alkaloid hennoxazole A, which actively inhibits the herpes simplex virus, were unambiguously determined by enantioselective total synthesis. CBS reduction of the *cis*-*β*-stannylenone as depicted in Scheme 50 followed by hydroxyl activation and stereospecific displacement with a propenyl cuprate gave the indicated chiral 1,4-diene fragment.[62b, c] Transmetalation of this key coupling fragment from the tin to the zinc derivative facilitated a palladium-mediated coupling with an allyl bromide to afford the carbon framework of the natural product.



Scheme 50. Enantioselective synthesis of *ent*-hennoxazole A.

A long-standing challenge in the synthesis of prostanoids has been the selective introduction of the C(15) hydroxyl-bearing stereocenter by reduction of the *α*,*β*-enone. While a number of reagents and reaction conditions have been designed to effect this transformation, the CBS reduction provides a pleasing catalytic solution, and furnishes a 10:1 ratio of the diastereomeric alcohols under exceedingly mild conditions (Scheme 51).[13b]

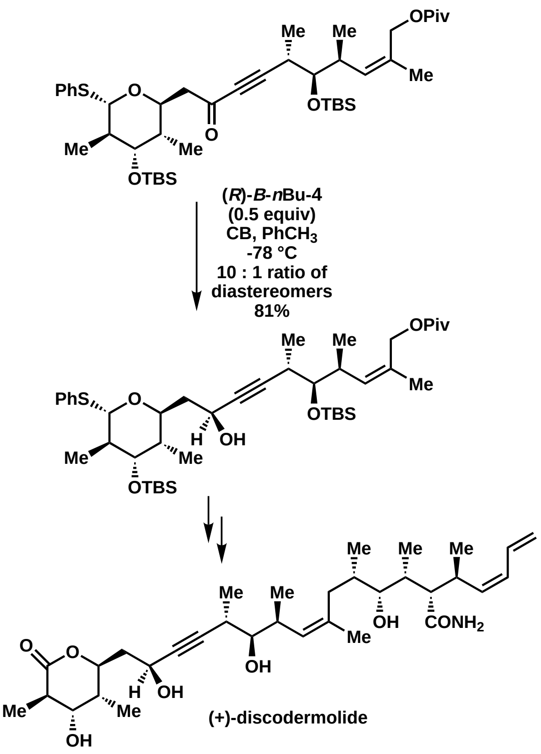


Scheme 51. Asymmetric synthesis of prostaglandins.

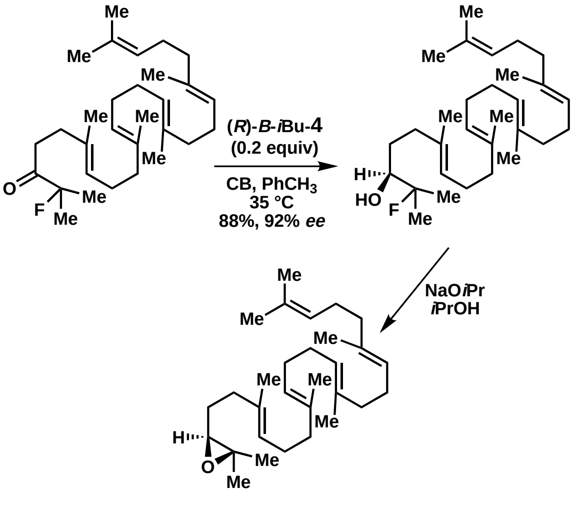
The scarce marine natural product (+)-discodermolide has been observed to possess impressive immunosuppressive activity and, as a result, has been the object of total synthesis. Oxazaborolidine-catalyzed reduction of the propargylic ketone shown in Scheme 52 gave a 10:1 mixture of isomers with the desired antipode predominating.[111] The alkynyl group behaved as R_L in this CBS reduction in a nonpolar solvent and with catecholborane as stoichiometric reductant, which is in agreement with other studies (see Table 9).[43]

(3*S*)-2,3-Oxidosqualene is the biosynthetic precursor to numerous steroids and polycyclic triterpenoids. Asymmetric reduction of the *α*-fluoro ketone shown in Scheme 53 followed by oxirane ring closure gave (3*S*)-2,3-oxidosqualene with 92 % *ee*.[42] The choice of *α*-fluoro ketone was crucial for high enantioselectivity in the reduction, since the use of the *α*-chloro or *β*-bromo ketone resulted in slow reaction rates and only modest enantioselectivities. The magnitude and sense of enantioselectivity were highly dependent on temperature: The enantiomeric ratio *S*:*R* is 96:4 at 35 °C, 93:7 at 23 °C, and 20:80 at −23 °C.

In a recent improved synthesis of the right half of halichondrin B, a potent antitumor agent, a Nozaki–Kishi coupling of vinyl iodide with aldehyde afforded a 4:1 ratio of diastereomers favoring the desired alcohol.[112] Dess–Martin oxidation of the mixture of alcohols to the *α*-substituted *α*,*β*-



Scheme 52. Enantioselective synthesis of discodermolide.



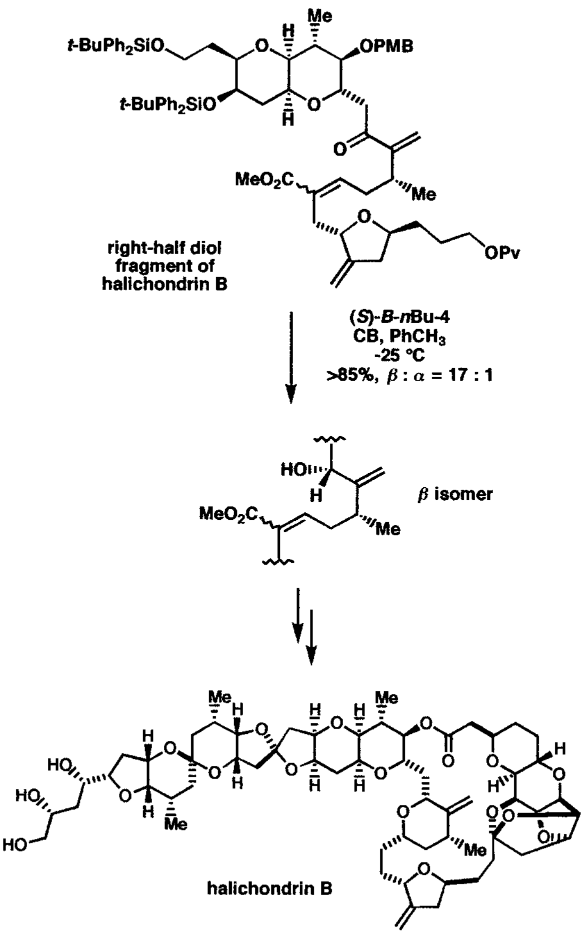
(3S)-2,3-oxidosqualene

Scheme 53. Enantioselective synthesis of (3*S*)-2,3-oxidosqualene.

enone followed by CBS reduction gave a much improved 17:1 ratio of diastereomers at the carbinol center and permitted the efficient stereoselective construction of the central pyran unit of the right-half diol fragment (Scheme 54).

7. Summary and Outlook

Chiral oxazaborolidine-catalyzed reduction of ketones with coordinated borane or catecholborane as stoichiometric reductant provides access to a broad range of chiral secondary alcohols. These products, in turn, can serve as key intermediates for the synthesis of an enormous range of compounds with regard to functionality, size, and topological complexity. Thus, many types of chiral natural products and bioactive molecules can be synthesized efficiently without the need for optical resolution. The applications of this methodology continue to increase rapidly in number and could become commercially important.



Scheme 54. Asymmetric synthesis of halichondrin B.

Appendix: Abbreviations Used

BDEA = $BH_3 \cdot$ diethylaniline, BMS = $BH_3 \cdot Me_2S$, Bn = benzyl, BOC = *tert*-butoxycarbonyl, BTHF = $BH_3 \cdot THF$, Bz = benzoyl, CAN = cerammonium nitrate, CB = catecholborane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DEAD = diethyl azodicarboxylate, DIAD = iiisopropyl azodicarboxylate, Ms = methanesulfonyl, Nap = naphthyl, NCS = *N*-chlorosuccinimide, Piv = pivaloyl, PMB = *p*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

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[51] a) Preparation of (*S*)-*B*-*n*Bu-**4**: Toluene (15–20 mL) was added to amino alcohol **3** (253 mg, 1 mmol) and $nBuB(OH)_2 \cdot nH_2O$ (164 mg) in a 25-mL round-bottom flask fitted with a Dean–Stark apparatus (sidearm filled with 4-Å molecular sieves) and a reflux condenser. The mixture was vigorously heated at reflux for 12 h. The toluene was removed by distillation through the Dean–Stark sidearm until about 3 mL were left. After the reaction mixture was cooled to 23 °C, the Dean–Stark apparatus was replaced by a rubber septum and the remaining toluene was removed in vacuo at 40 °C. Toluene (5.0 mL) was added to provide a 0.20 M solution of (*S*)-*B*-*n*Bu-**4** (> 95% conversion as determined by ^1H NMR spectroscopy). Spectral data were indentical to that reported in the literature.[14a] The catalyst was stored by placing an additional rubber septum on the flask followed by cooling the solution to −78 °C under a positive pressure of nitrogen. The nitrogen source was removed, and the catalyst solution was stored in a jar containing Drierite at −20 °C. This precooling procedure prevents possible introduction of air into the flask due to a pressure difference. b) $nBuB(OH)_2$ was prepared by a known method (H. C. Brown, T. E. Cole, *Organometallics* **1983**, *2*, 1316–1319) except that aqueous 1 N HCl was used instead of anhydrous HCl in the workup. The amount of water in the $nBuB(OH)_2$ prepared by this method varies. Therefore, ^1H NMR analysis of the catalyst formation is required to ascertain the exact amount of the boronic acid necessary for complete catalyst formation. Once this is known for a specific batch of $nBuB(OH)_2$, however, the proper amount of boronic acid (1.05 equiv) can be added at the start of the reaction. c) Preparation of *B*-Me-**4**: The catalyst was prepared from amino alcohol **3** (253 mg, 1 mmol) and $MeB(OH)_2$ (72 mg, 1.2 mmol) as described above for (*S*)-*B*-*n*Bu-**4**, except that 1) the reaction mixture was heated at 60 °C for 1 h before heating at reflux temperature and 2) heating at reflux was maintained for 5 h. The material so obtained showed identical spectral properties with those reported.[14a]

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[57] a) Reduction of acetophenone with *B*-Me-**4** as catalyst and $BH_3 \cdot$ diethylaniline (BDEA) as stoichiometric reductant (from reference [46]): A dry 100-mL two-necked flask equipped with an addition funnel, magnetic stirring bar, thermocouple, and septum inlet was charged with a solution of (*R*)-*B*-Me-**4** (0.84 mmol, 0.084 M in toluene, 10 mL) followed by BDEA (2.74 g, 16.8 mmol). The reaction vessel was immersed in a water bath, and acetophenone (2.0 mL, 16.6 mmol) in toluene (5 mL) was added through the addition funnel over 1–1.5 h. After ketone addition was complete, the reaction mixture was stirred for an additional hour. MeOH (5 mL) was then slowly added (hydrogen evolution) followed by aqueous 1 N HCl (10 mL). After 15–20 min the organic and aqueous layers were separated, and the aqueous layer was extracted with toluene or Et_2O (3 × 10 mL). The combined organic layers were washed with aqueous 1 N HCl (2 × 10 mL), water, and brine, and then dried ($MgSO_4$). Analysis of the organic layer by gas chromatography (CDX-B column, 30 m × 0.25 mm, J&W Scientific) showed the product to be (*S*)-1-phenylethanol with 94.7% *ee*. Removal of the solvent in vacuo followed by distillation gave (*S*)-1-phenylethanol that was spectroscopically identical with an authentic sample. b) Reduction of α-chloroacetophenone with *B*-*n*Bu-**4** as catalyst and $BH_3 \cdot Me_2S$ (BMS) as stoichiometric reductant: This protocol requires the *simultaneous* addition of ketone and BMS to a solution of the catalyst (0.01 equiv) in order to suppress uncatalyzed reduction pathways and is practical on multigram scale. Dry THF (10 mL) was added to (*S*)-*B*-*n*Bu-**4** (0.647 mmol, 0.2 M in toluene, 3.2 mL) and BMS (65 µL, 0.65 mmol, 10 M (neat)) under nitrogen. Separate solutions of α-chloroacetophenone (10 g, 64.7 mmol, azeotropically dried with benzene) in dry THF (40 mL) and BMS (4.5 mL, 45 mmol, 10 M (neat)) in dry THF (40 mL) were then added simultaneously to the solution of the oxazaborolidine catalyst over 1 h. After addition of ketone and BMS was complete no starting material remained, as determined by thin-layer chromatography. A solution of HCl in MeOH (0.5 M, 1.5 mL, 1.2 equiv; prepared by adding acetyl chloride to MeOH at 0 °C) was then slowly added (hydrogen evolution), and the solution was stirred for 30 min. THF was removed in vacuo, Et_2O (75 mL) added, and the HCl salt of the amino alcohol that precipitated as a white solid removed by filtration. The Et_2O layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. HPLC analysis (Chiralcel OD, 2-propanol/hexane 2.5/97.5, 1 mL min^{-1}, $\lambda = 254$ nm) showed the product to be of 98.5% *ee*; t_R: 17.2 min, major; 22.5 min, minor isomer. Purification by filtration through a small plug of silica gel with hexanes/EtOAc (4/1) afforded 10 g (99%) of (*S*)-2-chloro-1-phenylethanol. See reference [13c] for the first report of this procedure with (*S*)-*B*-Me-**4** as catalyst and $BH_3 \cdot THF$ (BTHF).

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[60] CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate and in situ deallylation: A flame-dried flask was charged with a solution of (*S*)-*B*-*n*Bu-**4** (370 µL, 0.074 mmol, 0.20 M in toluene), and the toluene was removed in vacuo. CH_2Cl_2 (370 µL) was added followed by catecholborane (104 µL, 0.98 mmol). The solution was cooled to −78 °C, and *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate (200 mg, 0.49 mmol, azeotropically dried with CH_2Cl_2) in CH_2Cl_2 (2 mL) was added. After 5 min the heterogeneous mixture was warmed to −40 °C and vigorously stirred for 36 h, over which period the mixture became homogeneous. MeOH (300 µL) was added, the solution was warmed to 23 °C, and $[Pd(PPh_3)_4]$ (30 mg, 0.025 mmol) and *n*-butylammonium

formate (300 µL) were added. The solution was stirred for 3 h at 23 °C, and Et_2O (60 mL) was then added. The organic layer was washed with buffer (pH = 13) until the aqueous washings were colorless. The solution was then washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by chromatography (silica gel, hexane/EtOAc 4/1 →2/1) provided 84 mg (78 %) of (*S*)-(4-chlorophenyl)-2-pyridylmethanol as a colorless oil. $[\alpha]_D^{23} = +119$ ($c = 0.50$ in $CHCl_3$, literature value for the *R* isomer: $[\alpha]_D^{16} = -132.5$ ($c = 0.7$ in $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.55$ (d, $J = 4.8$ Hz, 1 H), 7.63 (td, $J = 1.7, 7.7$ Hz, 1 H), 7.33–7.28 (m, 4 H), 7.20 (dd, $J = 5.0, 7.5$ Hz, 1 H), 7.12 (dd, $J = 0.4, 7.9$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.426$, 147.987, 141.789, 137.023, 133.666, 128.774, 128.457, 122.678, 121.283, 74.338. HPLC analysis (Chiralpak AD, 2-propanol/hexane 5/95, 1 mL min^{-1}, $\lambda = 254$ nm) showed the product to be of 98 % *ee*; t_R: 17.7 min, major; 23 min, minor isomer.

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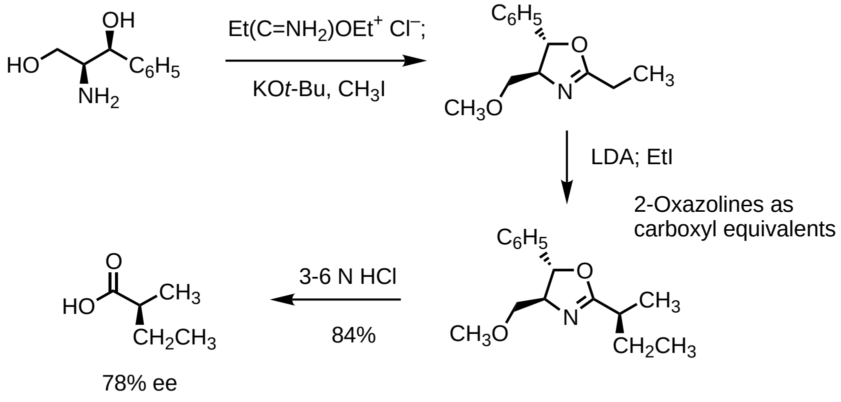
- An early milestone in the use of a chiral auxiliary for asymmetric alkylation:

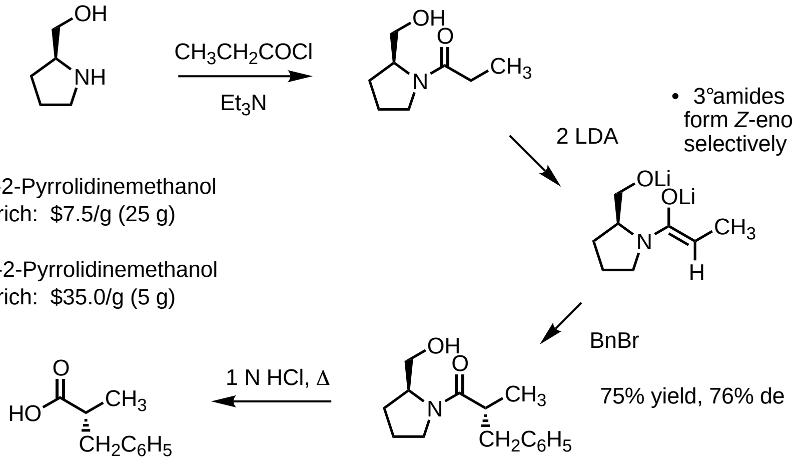


2-Oxazolines as carboxyl equivalents

78% ee

Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc*. **1976**, *98*, 567-576.

- Prolinol amide enolates provided an important advance:



- 3°amides form *Z*-enolates selectively

(*S*)-2-Pyrrolidinemethanol
Aldrich: $7.5/g (25 g)

(*R*)-2-Pyrrolidinemethanol
Aldrich: $35.0/g (5 g)

75% yield, 76% de

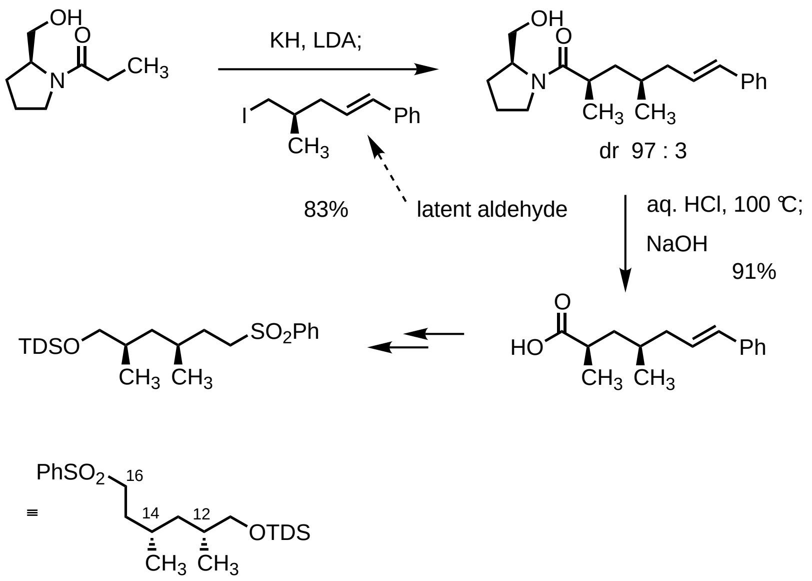
92% yield, $[\alpha]_D$: –18.89 °, Lit. –25.4 °

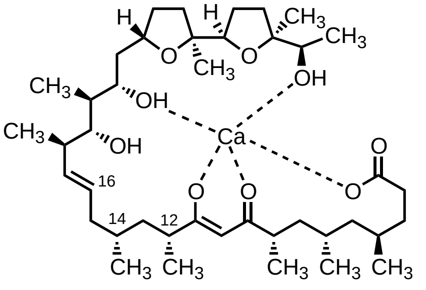
Evans, D.A.; Takacs, J.M.; *Tetrahedron Lett*. **1980**, *21*, 4233.

Sonnet, P.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

- Strongly nucleophilic prolinol amide enolates react with β-branched alkyl halides.

- proposal and application to iterative assembly of 1,3,n-substituted carbon chains by Evans et al. in synthesis of ionomycin:



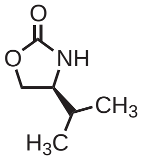


Ionomycin Calcium Complex

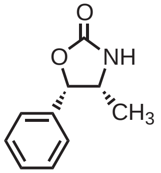
Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

Evans Oxazolidinone Auxiliaries in Asymmetric Synthesis: Alkylations

As Originally Introduced, Two Enantio-complimentary Reagents:



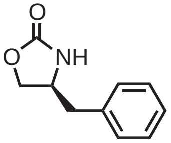
(*S*)-(–)-4-Isopropyl-2-oxazolidiinone 5 g $135



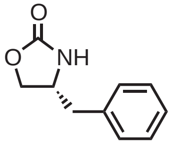
(4*R*, 5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone 5 g $167

Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.

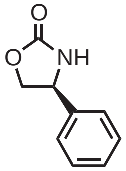
Now, several oxazolidinones are commercially available, in both enantiomeric forms:



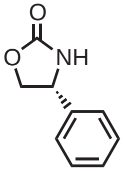
(*S*)-(–)-4-Benzyl-2-oxazolidiinone 25 g $185



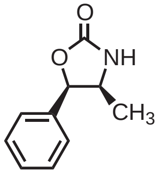
(*R*)-(+)-4-Benzyl-2-oxazolidiinone 25 g $240



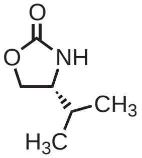
(*S*)-(–)-4-Phenyl-2-oxazolidiinone 5 g $134



(*R*)-(+)-4-Phenyl-2-oxazolidiinone 5 g $133



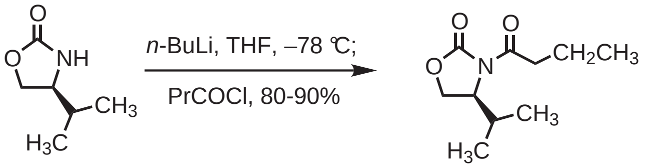
(4*S*, 5*R*)-(–)-4-Methyl-5-phenyl-2-oxazolidinone 5 g $156



(*R*)-(+)-4-Isopropyl-2-oxazolidiinone 2.5 g $102

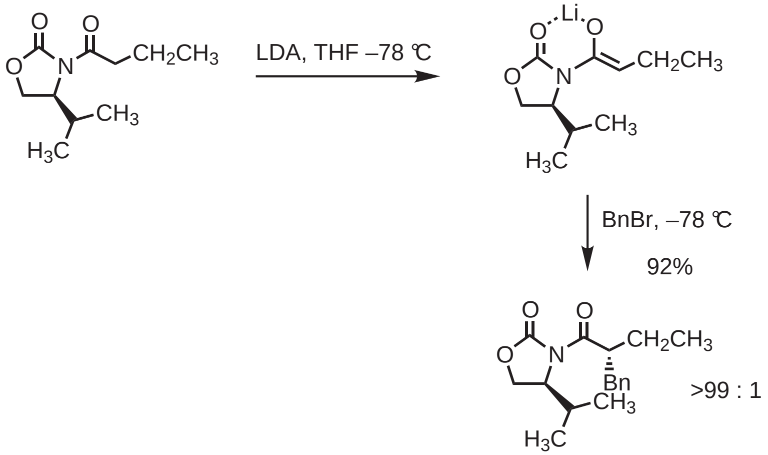
*1999 Aldrich Prices, can be dramatically lower from bulk suppliers.

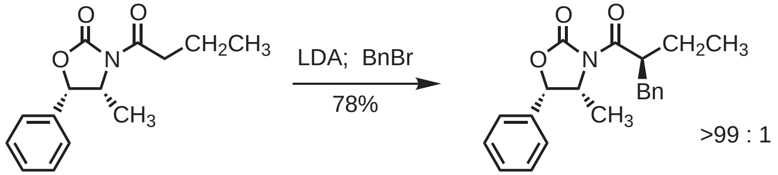
Acylation provides **Imides**, closer to esters than amides in terms of acidity, enolate nucleophilicity and cleavage chemistry.



Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

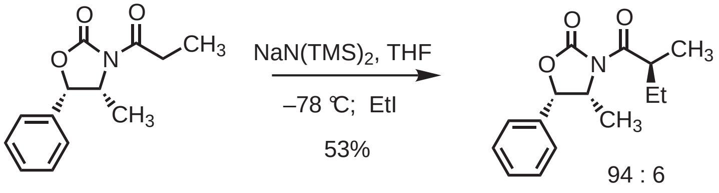
Z-Enolates are formed with very high selectivity. Chelated geometry presumed in ground and transition states.



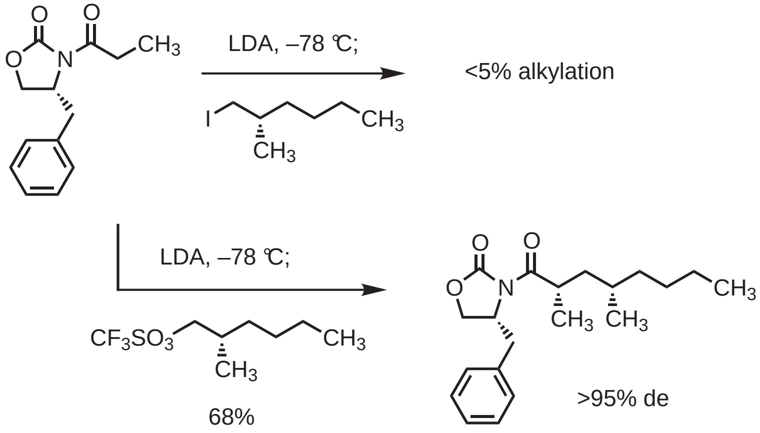


Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739

- Less reactive (non-allylic/benzylic) electrophiles require the use of sodium enolates or triflate as leaving group:



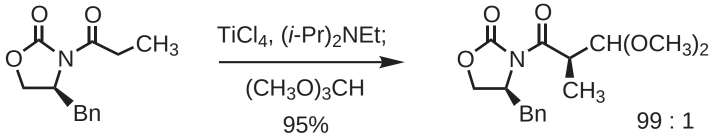
Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.



Decicco, C. P.; Grover, P. *J. Am. Chem. Soc.* **1996**, *61*, 3534-3541.

see also: Williams, D. R.; McGill, J. M. *J. Org. Chem.* **1990**, *55*, 3457-3459.

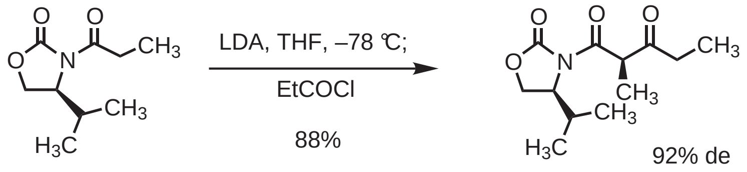
- Titanium enolates provide a route for diastereoselective S_N1-like coupling reactions:



Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T.
J. Am. Chem. Soc. **1990**, *112*, 8215-8216.

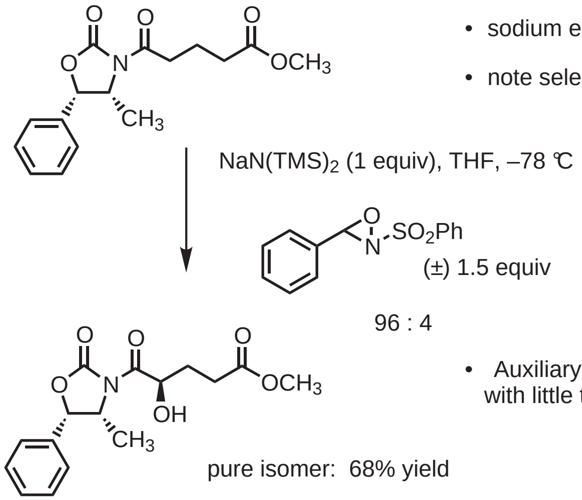
- Highly diastereoselective acylation of imide enolates is possible:

Exercise: Why are the products configurationally stable?



Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154-1156.

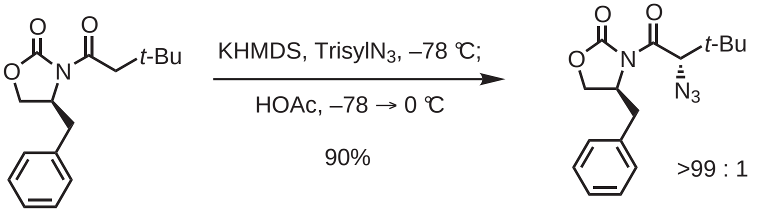
- Diastereoselective hydroxylation has been demonstrated:



- sodium enolate required
- note selective enolization of imide
- Auxiliary cleaved with $Mg(OMe)_2$ with little to no epimerization

Evans, D. A.; Morissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346-4348.

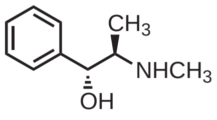
- Asymmetric azidation provides an important route to amino acid derivatives:



Trisyl = 2,4,6-triisopropylbenzenesulfonyl

Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.

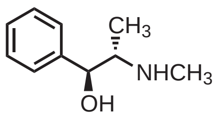
Pseudoephedrine as a Chiral Auxiliary in Asymmetric Alkylations



(*R, R*)-(–)-Pseudoephedrine

cost ~ \$150 / kilo

mp 118-120 ℃



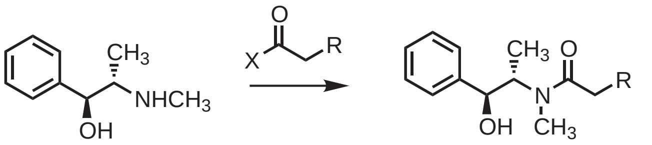
(*S,S*)-(+)-Pseudoephedrine

cost ~ \$65 / kilo

mp 118-120 ℃

- Pseudoephedrine is a commodity chemical, manufactured on multi-ton scale/annum

Preparation of Pseudoephedrine Amides:



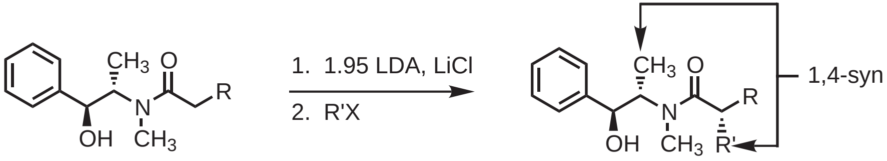
R	X	Yield (%)	mp
CH_3	O_2CCH_2R	95	114-115
CH_3	* OCH_3	89	114-115
n-Bu	O_2CCH_2R	91	62-63
Bn	Cl	83	102-104
Ph	Cl	88	145-146
Cl	Cl	90	79-81
i-Pr	Cl	92	73-74
t-Bu	Cl	88	68-69
CH_2Bn	Cl	81	100-102
2-thiophene	Cl	87	110-111
3-pyridyl	$O_2CC(CH_3)_3$	97	117.5-118.5

*Even unactivated esters react, under basic catalysis, presumably by transesterification followed by intramolecular *N*→*O* Acyl Transfer

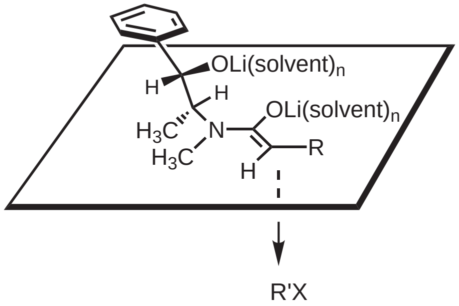
Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

- Enolates are formed using 1.95 equiv LDA
- Alkylations are highly diastereoselective
- LiCl (~6 equiv) promotes rapid, clean reaction

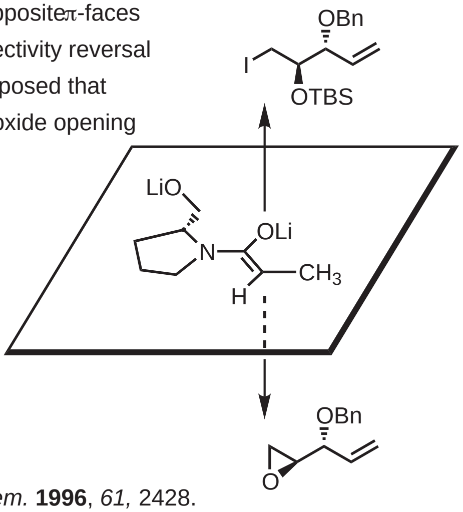
Mnemonic:



- Electrophile enters from same face as methyl group, when drawn in extended (zig-zag or all-anti) conformation
- A model is proposed to explain diastereoselectivity that invokes blocking of one enolate π-face by solvent:



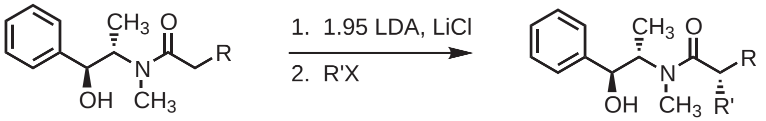
- Epoxides and alkyl halides attack opposite π-faces
- Askin et al. reported this type of selectivity reversal with prolinol amide enolates and proposed that Li cation coordinates, directs the epoxide opening



Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61,* 2428.

Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245.

Diastereoselective Alkylation Reactions

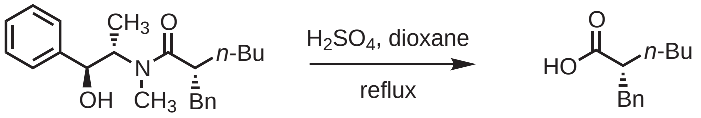


R	R'X	temp (℃)	crude (isol) de (%)	isol yield (%)
CH_3	BnBr	0	94 (≥99)	90
CH_3	*n*-BuI	0	98 (≥99)	80
CH_3	$BrCH_2CO_2$*t*-Bu	–78	94 (96)	78
Bn	CH_3I	0	94 (94)	99
n-Bu	CH_3I	0	94 (94)	94
n-Bu	BnBr	0	98 (≥99)	87
Ph	EtI	0	96 (≥99)	92
i-Pr	BnBr	0	98 (≥99)	83
t-Bu	BnBr	0	98 (≥99)	84
Cl	BnBr	–45	90 (≥99)	88

Hydrolysis of Alkylation Products

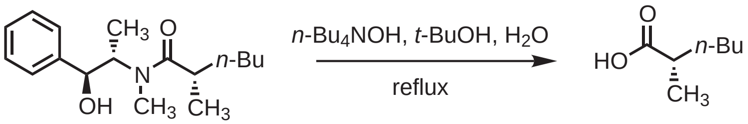
- Occurs under acidic or basic conditions. Both methods likely involve initial N→O acyl transfer.

- Strongly acidic conditions are required, but are well tolerated by many simple substrates.



≥99% de 94% 96% ee

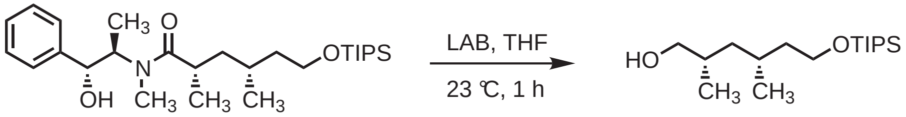
- Alkaline conditions work well with many substrates, but not those susceptible to facile epimerization (α-aryl).



≥99% de 93% 97% ee

Reduction of Pseudoephedrine Amides

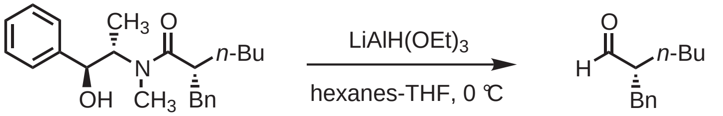
- Lithium Amidotrihydroborate (LiH_2NBH_3, LAB), prepared by deprotonation (LDA) of commercial, crystalline ammonia-borane complex, provides primary alcohols.



98% de 98% 97% ee

Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.
Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, *5*, 457.

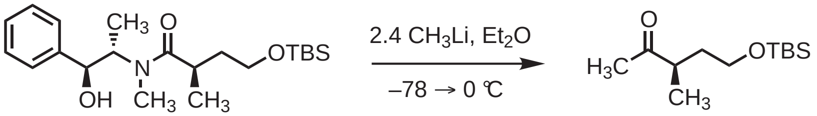
- Semi-reduction with Brown's lithium triethoxyborohydride provides aldehydes directly.



≥99% de 82% 97% ee

Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

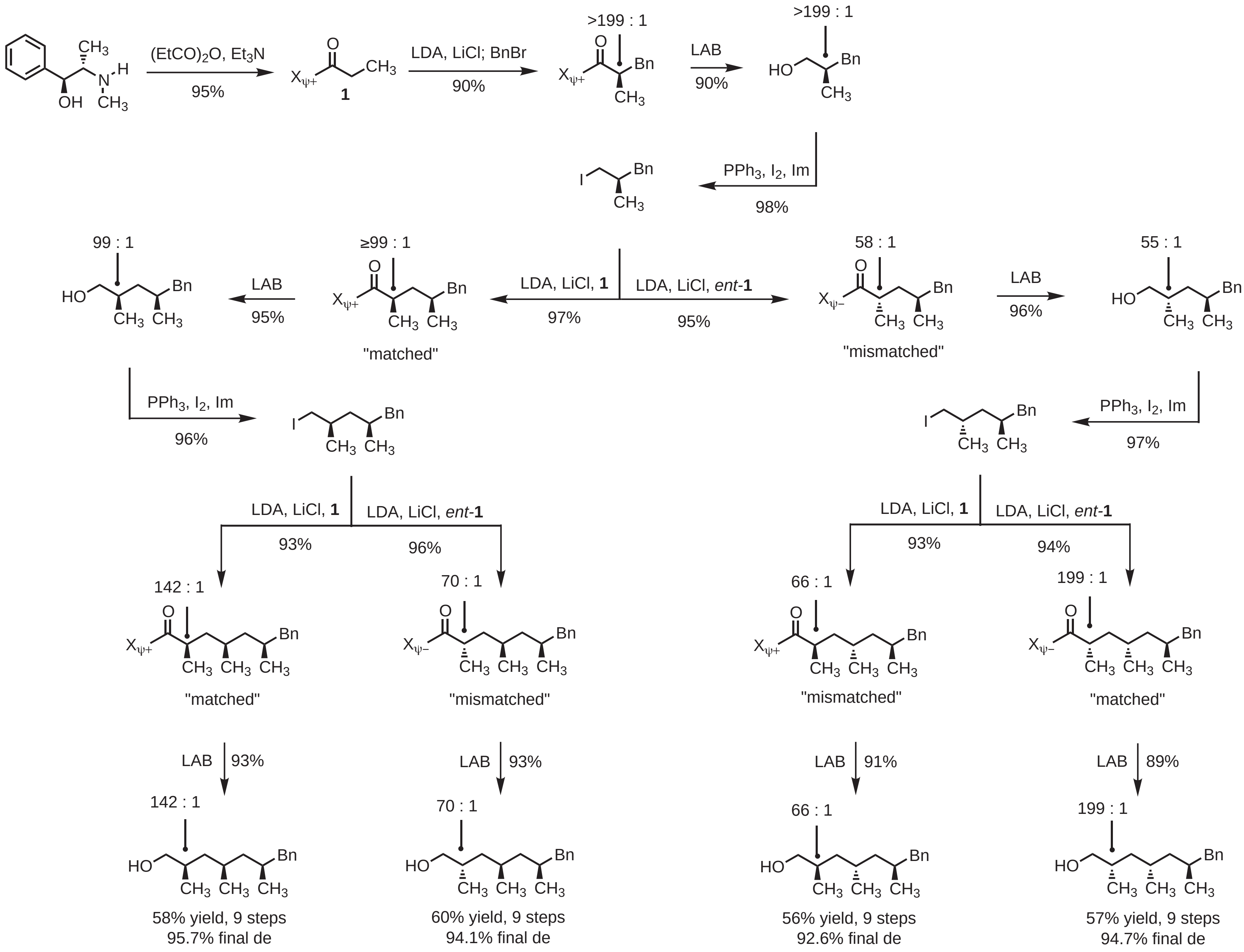
Addition of Alkyllithium Reagents to form Ketones



97% de 89% ≥95% ee

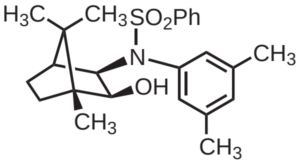
Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am Chem. Soc.* **1997**, *119*, 6496-6511.

Application to the Synthesis of 1,3,n-Substituted Carbon Chains by Iteration:

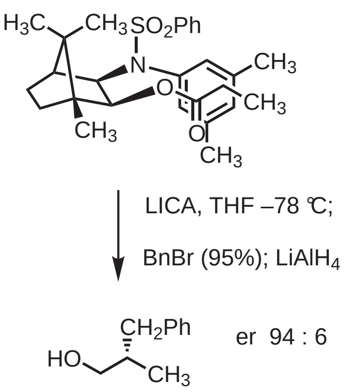


Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, *5*, 457-459.

- Helmchen camphor-derived auxiliaries



Aldrich: $65.4/g (1 g)



LICA, THF –78 ℃;

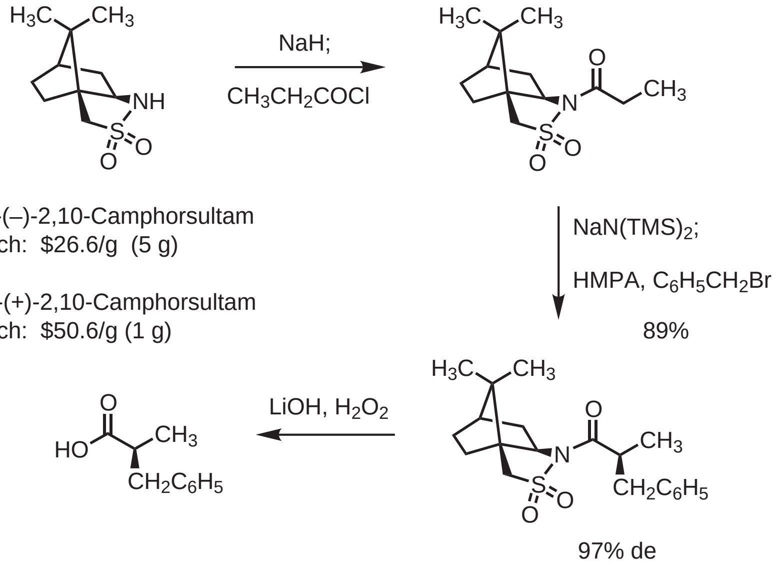
BnBr (95%); $LiAlH_4$

er 94 : 6

Exercise: use of HMPA in the enolization gives alkylated product of inverted configuration (dr 30 : 70). Rationalize these findings.

Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207-208.

- Oppolzer camphorsultam auxiliaries in asymmetric alkylation



NaH;

CH_3CH_2COCl

NaN(TMS)$_2$;

HMPA, $C_6H_5CH_2Br$

89%

LiOH, H_2O_2

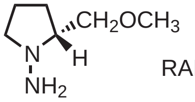
97% de

(1*S*)-(–)-2,10-Camphorsultam
Aldrich: $26.6/g (5 g)

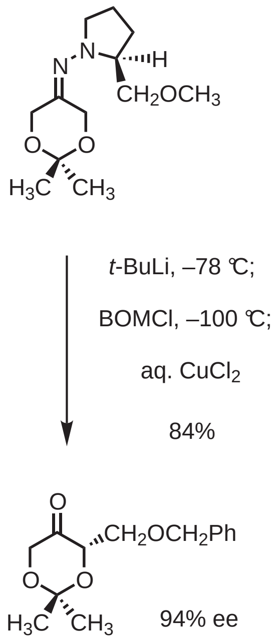
(1*R*)-(+)-2,10-Camphorsultam
Aldrich: $50.6/g (1 g)

Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett*. **1989**, *41*, 5603-5606

- Enders chiral hydrazone methodology



RAMP-Hydrazone



t-BuLi, –78 ℃;

BOMCl, –100 ℃;

aq. $CuCl_2$

84%

94% ee

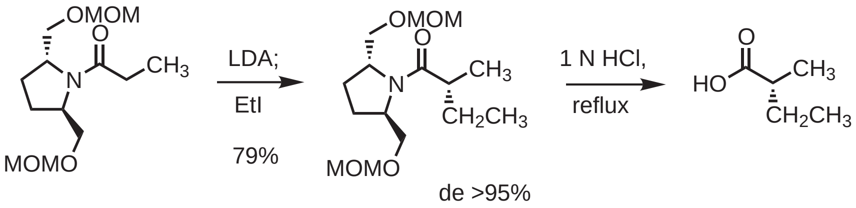
(*R*)-(+)-1-Amino-2-(methoxymethyl)
pyrrolidine [RAMP-Hydrazone]
$97.9/g (1 g)

(*S*)-(+)-1-Amino-2-(methoxymethyl)
pyrrolidine [SAMP-Hydrazone]
$46.1/g (1 g)

Enders, D. In *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 4.

Enders, D.; Hundertmark, T.; Lazny, R. *Syn. Comm.* **1999**, *29*, 27-33.

- Yamaguchi C_2-symmetric amine - auxiliary for asymmetric alkylation



LDA;

EtI

79%

1 N HCl,

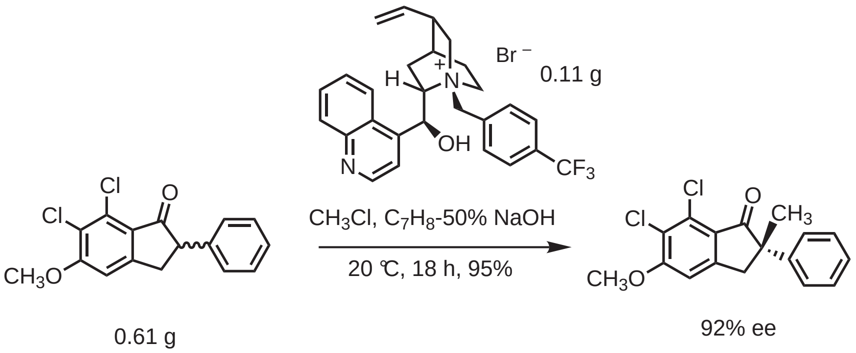
reflux

de >95%

- Highly diastereoselective.
- Auxiliary is not yet available for practical use; its removal is difficult.

Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857-860.

- An early, remarkable result from the Merck Process group:


0.11 g

CH_3Cl, C_7H_8-50% NaOH

20 °C, 18 h, 95%

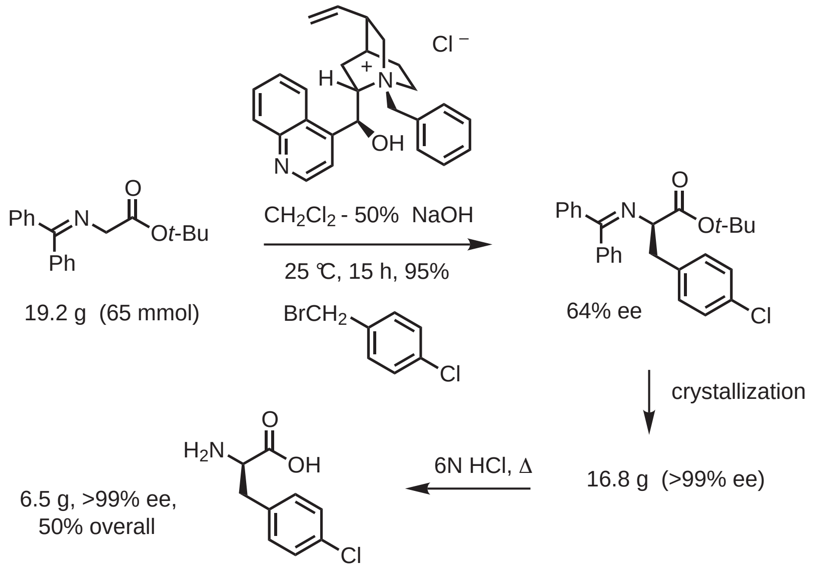
0.61 g

92% ee

- although narrow in scope, this provided a dramatic illustration of the potential of chiral phase-transfer catalysis for C-C bond formation.

Dolling, U.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

- The method was adapted by O'Donnell, who had earlier developed a PT method for the synthesis of racemic α-amino acids:


CH_2Cl_2 - 50% NaOH

25 °C, 15 h, 95%

19.2 g (65 mmol)

64% ee

crystallization

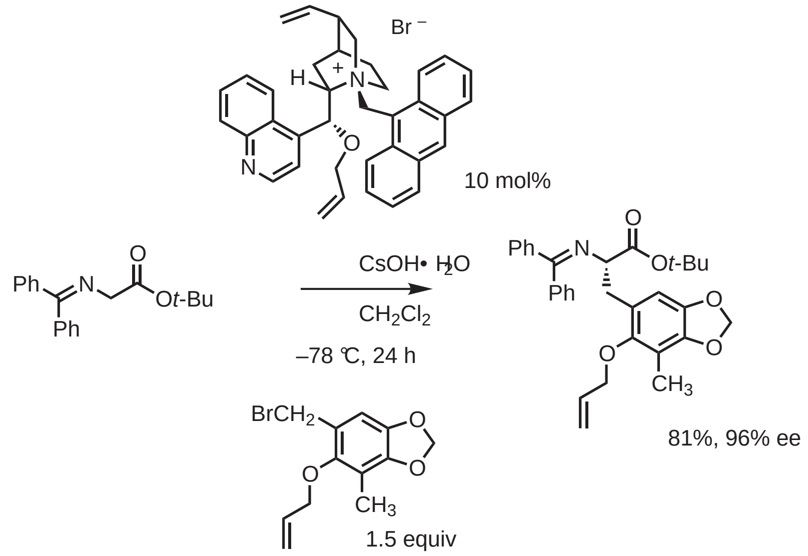
16.8 g (>99% ee)

6N HCl, Δ

6.5 g, >99% ee, 50% overall

O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355.

- Corey and co--workers have developed catalysts that are highly enantioselective:


10 mol%

$CsOH \cdot H_2O$

CH_2Cl_2

–78 °C, 24 h

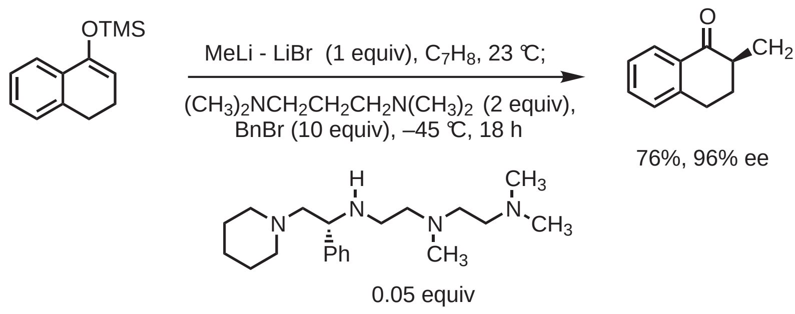
1.5 equiv

81%, 96% ee

Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.

Phosphazene bases can be used with the above catalyst, see: O'Donnell, M. F.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775-8778.

- Koga has developed chiral additives for the asymmetric alkylation of lithium enolates. The work has recently been extended to include examples of catalysis:


MeLi - LiBr (1 equiv), C_7H_8, 23 °C;

$(CH_3)_2NCH_2CH_2CH_2N(CH_3)_2$ (2 equiv), BnBr (10 equiv), –45 °C, 18 h

76%, 96% ee

0.05 equiv

Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K . *J. Am. Chem. Soc.* **1994**, *116*, 8829-8830.

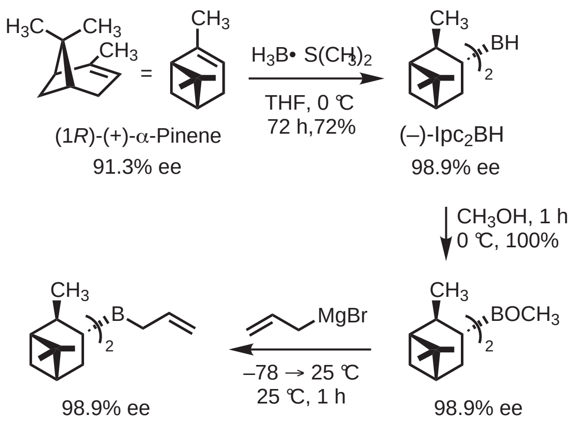
Brown Allylation and Crotylation Reactions

Reviews:

Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9.

Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 1-53.

Synthesis of *B*-Allyldiisopinocampheylborane



- Prolonged incubation at 0 °C affords enantiomerically enriched Ipc_2BH. This is due to equilibration of tetraisopinocampheyldiborane with α-pinene and triisopinocampheyldiborane; the symmetrical dimer crystallizes preferentially.

- Both enantiomers of α-pinene are commercially available and inexpensive (Aldrich: (1*R*)-(+)-α-pinene, 91% ee, \$100/500mL; (1*S*)-(–)-α-pinene, 87% ee, \$42/100mL).

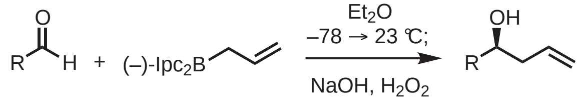
- *B*-Allyldiisopinocampheylborane can be prepared and used in situ after filtration of the magnesium salts produced during its formation.

Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065-5069.

Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945-947.

Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439.

Enantioselective Allylboration



R	yield (%)	ee (%)[a]	ee (%)[b]
CH_3	74	93	≥99
n-C_3H_7	71	86	-
n-C_4H_9	72	87	96
t-C_4H_9	88	83	≥99
C_6H_5	81	96	96

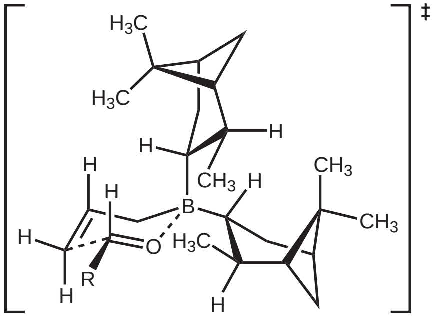
[a] Allylboration carried out without filtration of Mg salts. [b] Allylboration carried out at –100 °C under Mg-salt free conditions.

- The reaction is quite general; the stereochemistry of the addition is the same in all cases examined.

- Lower reaction temperatures (0 → –78 → –100 °C) lead to increased enantioselectivity.

- Only Mg-salt free reagent can be used at –100 °C because the reactive borane is sequestered by ate complex formation with CH_3OMgBr at this temperature.

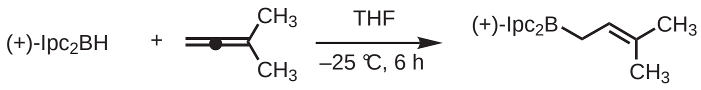
- Allylboration of aldehydes is essentially instantaneous at –78 or –100 °C in the absence of Mg salts.



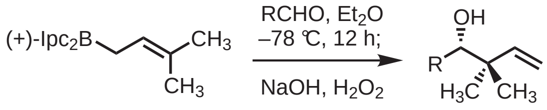
- Allylation of aldehydes proceeds through a chair-like TS where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial Ipc ligand and the allyl group.

Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093.
Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.
Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404.

Asymmetric Isoprenylation of Aldehydes



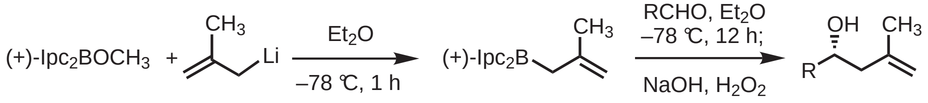
- Hydroboration of allenes is an efficient method for preparing *B*-allyldiisopinocamphenylboranes



R	yield (%)	ee (%)
CH_3	73	91
n-C_4H_9	79	92
CH_2=CH	70	95
$(CH_3)_2C$=CH	85	96

Brown, H. C.; Jadhav, P. K. *Tetrahedron Lett.* **1984**, *25*, 1215-1218.
Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439.

Methallylation of Aldehydes



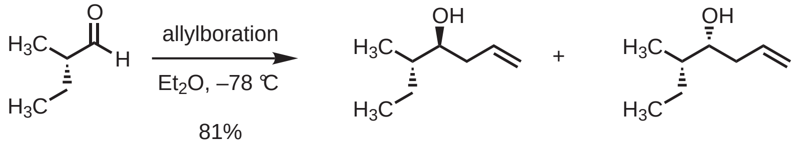
R	yield (%)	ee (%)
CH_3	56	90
n-C_3H_7	54	90
n-C_4H_9	56	91
t-C_4H_9	55	90
CH_2=CH	57	92

- The yields for methallylation of aldehydes are generally lower than in simple allylation reactions.

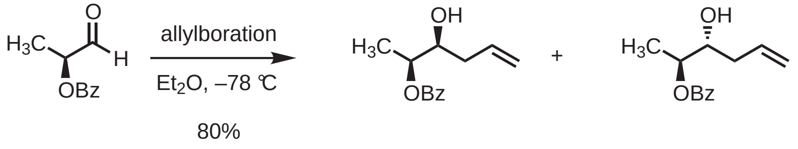
Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *Tetrahedron Lett.* **1984**, *25*, 5111-5114.
Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439.

Diastereoselective Allylboration of Chiral, α-Substituted Aldehydes

- The diastereofacial selectivity of the *B*-allyldiisopinocampheylborane reagent typically overrides any facial preference of the aldehyde for nucleophilic attack.

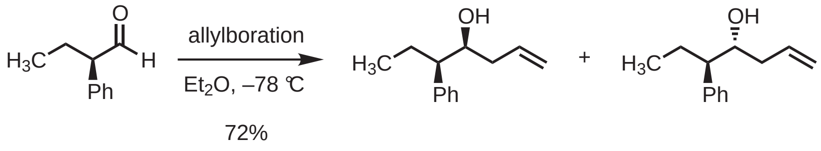


MATCHED:	(–)-$Ipc_2BCH_2CH=CH_2$	96	:	4	(92% de)
MISMATCHED:	(+)-$Ipc_2BCH_2CH=CH_2$	5	:	95	(90% de)



MISMATCHED:	(–)-$Ipc_2BCH_2CH=CH_2$	94	:	6	(88% de)
MATCHED:	(+)-$Ipc_2BCH_2CH=CH_2$	4	:	96	(92% de)

- Although the stereochemical outcome of the allylboration of aldehydes using *B*-allyldiisopino-campheylborane is typically reagent controlled, this selectivity may be challenged with certain substrates:

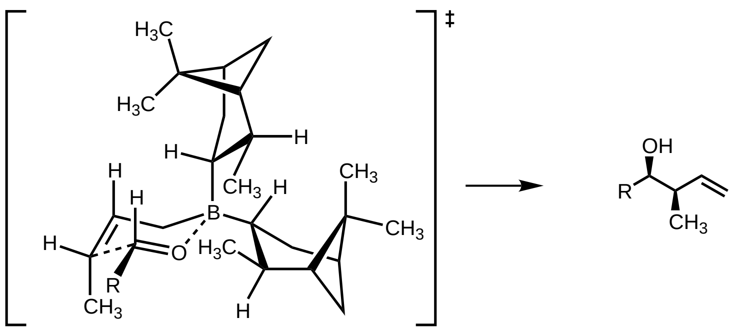


MISMATCHED:	(–)-$Ipc_2BCH_2CH=CH_2$	67	:	33	(34% de)
MATCHED:	(+)-$Ipc_2BCH_2CH=CH_2$	2	:	98	(96% de)

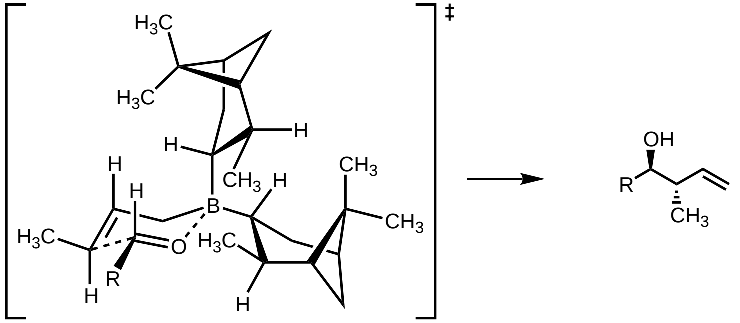
Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319-320.
Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570-1576.

M. Movassaghi

Chair TS's Produce syn Adducts from (*Z*)-Crotylboranes and anti Adducts from (*E*)-Crotylboranes.



"(*Z*)-crotylborane" "syn adduct"

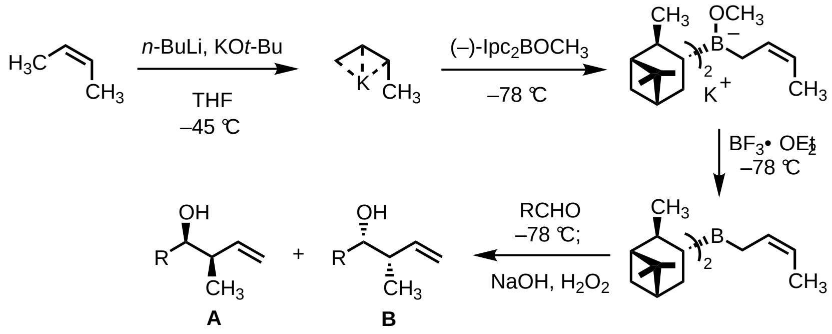


"(*E*)-crotylborane" "anti adduct"

- These adducts can be viewed as protected aldol products; "deprotection" is brought about by dihydroxylation/periodate cleavage or by ozonolysis.

Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294.
Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.
Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 1-53.

(*Z*)-Crotylboranes

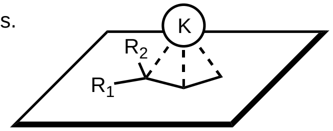


Ipc	aldehyde	yield (%)	**A**:**B**	ee (%)
–	CH_3CHO	75	95:5	90
+	CH_3CHO	72	4:96	92
–	C_2H_5CHO	70	95:5	90
+	C_2H_5CHO	78	4:96	92
–	CH_2=CHCHO	63	95:5	90
–	C_6H_5CHO	72	94:6	88

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by $BF_3 \cdot OEt_2$ at –78 ℃ to avoid crotyl isomerization.

"Superbases" for Organic Synthesis

- The "superbase" prepared by mixing *n*-butyllithium and potassium *t*-butoxide (1:1) can metalate hydrocarbons of low acidity–in particular–olefins.
- Allylic methyl groups are much more readily metalated than allylic methylene or methine centers.
- *cis*-2-alkenes generally react faster than their *trans*-isomers.
- The large atomic radius of potassium favors η^3-bonding in allyl, crotyl and prenyl derivatives:

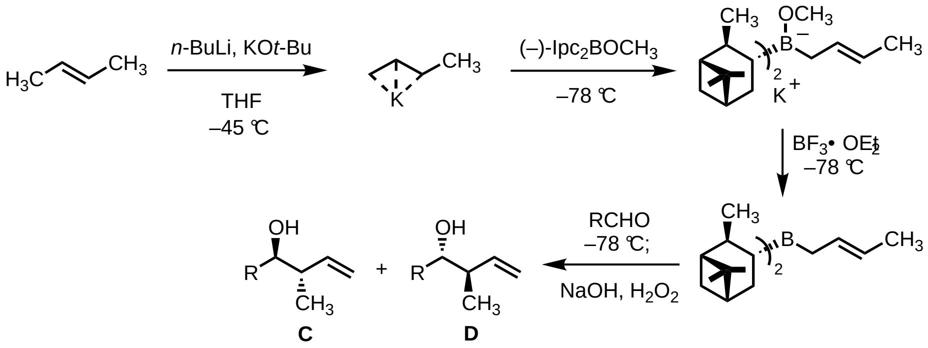


R_1, R_2 = H, CH_3

Schlosser, M. *Pure & Appl. Chem.* **1988**, *60*, 1627-1634.
Schlosser, M.; Stahle, M. *Angew. Chem.*, *Int. Ed. Engl.* **1980**, *19*, 487-489.

M. Movassaghi

(*E*)-Crotylboranes

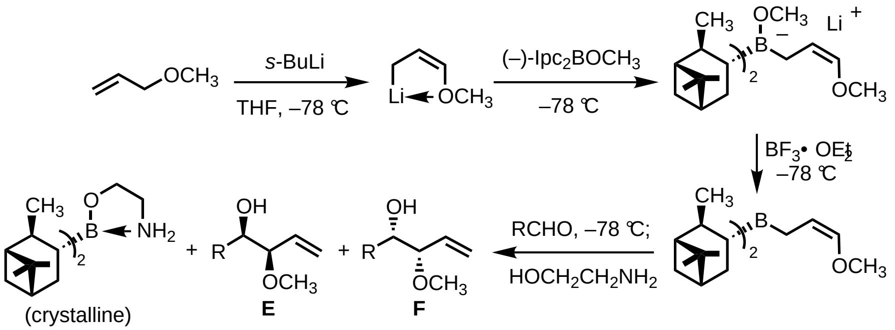


Ipc	aldehyde	yield (%)	**C**:**D**	ee (%)
–	CH_3CHO	78	95:5	90
+	CH_3CHO	76	4:96	92
–	C_2H_5CHO	70	95:5	90
+	C_2H_5CHO	69	4:96	92
–	CH_2=CHCHO	65	95:5	90
–	C_6H_5CHO	79	94:6	88

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by $BF_3\cdot OEt_2$ at –78 °C to avoid crotyl isomerization.

Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294.
Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.

Diastereo- and Enantioselective *vic*-Diol Synthesis



- Treatment of the crude product mixture withethanolamine allows for easy removal of the reagent by-product as a crystalline adduct; this is an alternative to oxidative work-up.

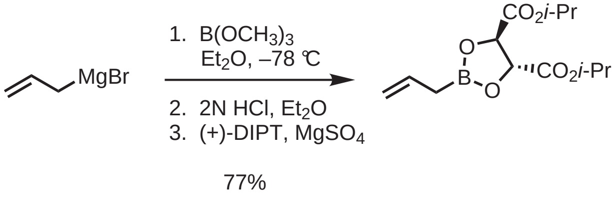
Ipc	aldehyde	yield (%)	**E**:**F**	ee (%)
–	CH_3CHO	57	95:5	90
+	CH_3CHO	59	4:96	92
–	C_2H_5CHO	65	96:4	92
+	C_2H_5CHO	68	5:95	90
–	CH_2=CHCHO	63	94:6	88
–	C_6H_5CHO	72	95:5	90

- Other vinyl ethers may be used, such asmethoxymethyl vinyl ether (affording the MOM-protected *vic*-diol).

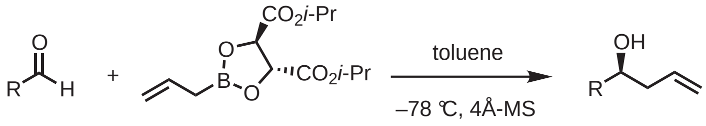
Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538.

Roush Allylation and Crotylation Reactions

Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 1-53.
Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359.
Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294-296.



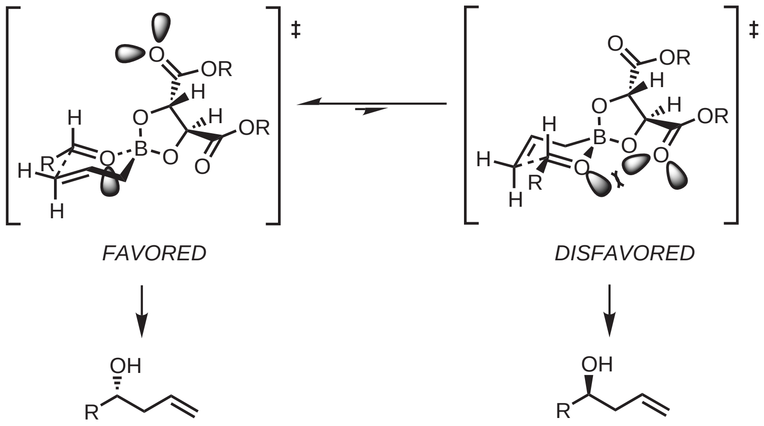
- The stability of allylboronate reagents permits their purification by distillation. Allyl diisopinocamphenyl reagents cannot be distilled.



aldehyde	yield (%)	ee (%)
n-$C_9H_{19}CHO$	86	79
c-$C_6H_{11}CHO$	77	78
C_6H_5CHO	78	71

- Enantioselectivities are typically moderate.
- 4Å-MS are necessary to achieve the highest levels of selectivity.

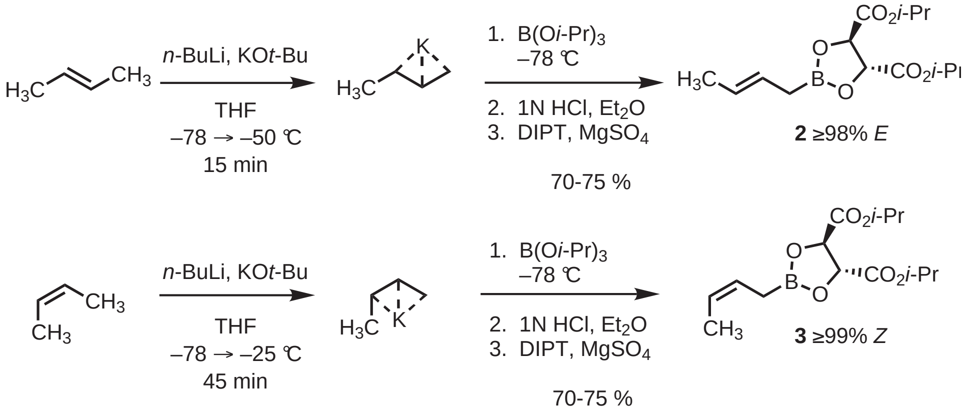
Proposed Origin of Selectivity in Tartarate Derived Allylboronate Additions



- The favored transition state is believed to minimize unfavorable lone-pair lone-pair interactions.

Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.

Preparation of (*E*)- and (*Z*)-Crotylboronate Reagents

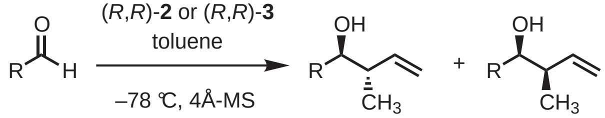


- Crotylboronates are configurationally stable at or slightly above room temperature.

- Tartrate modified (*E*)- and (*Z*)-Crotylboronates can be stored for several months at –20 °C in neat form or in solution with little noticeable deterioration.

- Competition experiments have shown that (*E*)-crotylboronates react faster with aldehydes than the corresponding (*Z*)-isomers.

- Essentially identical results are obtained with a range of commercially available tartrate esters (CH_3, Et, *i*-Pr).



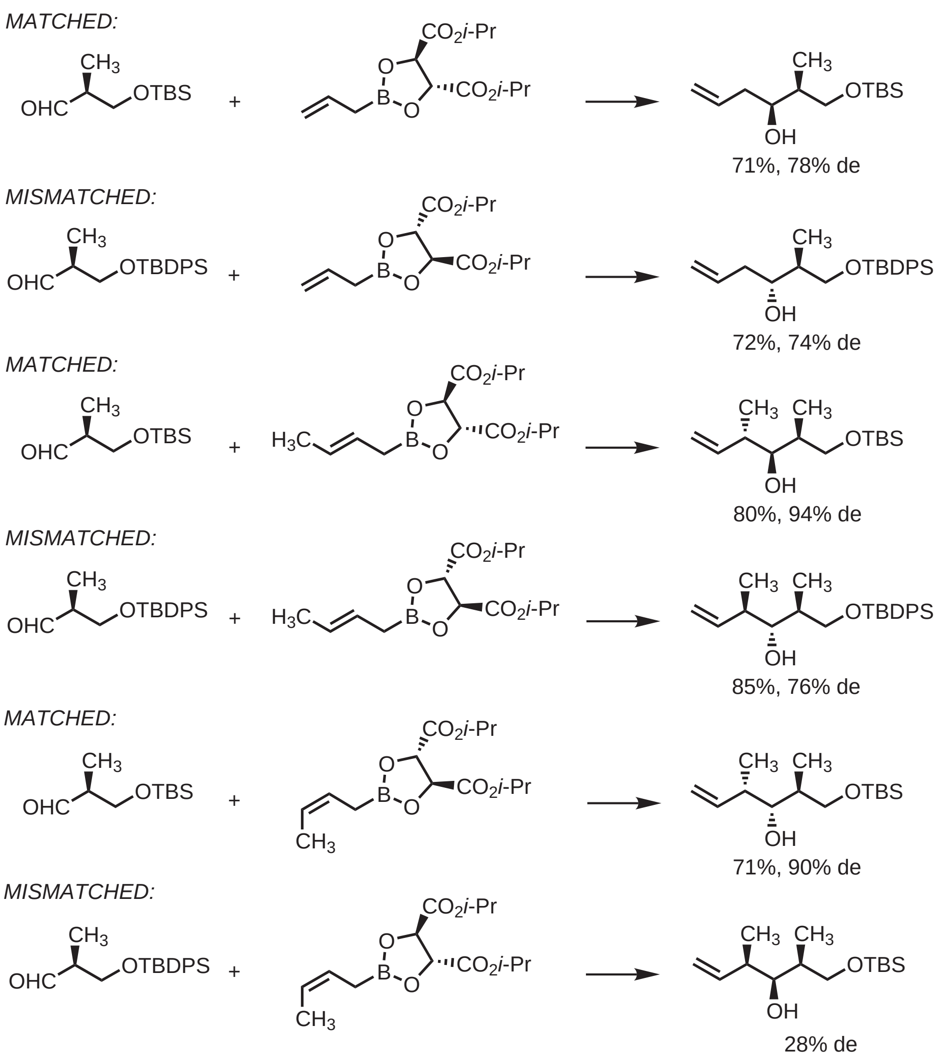
R	reagent	yield (%)	anti:syn	ee (%)^a
n-C_9H_{19}	**2**	90	95:5	86
n-C_9H_{19}	**3**	70	1:>99	77
c-C_6H_{11}	**2**	94	>99:1	86
c-C_6H_{11}	**3**	90	2:98	83
$TBSOCH_2CH_2$	**2**	71	≥98:2	85
$TBSOCH_2CH_2$	**3**	68	2:≥98	72

[a] ee of major diastereomer.

Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.
Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316-318.

M. Movassaghi

Reaction of Tartrate-Derived Allyl- or Crotylboronates with Chiral Aldehydes

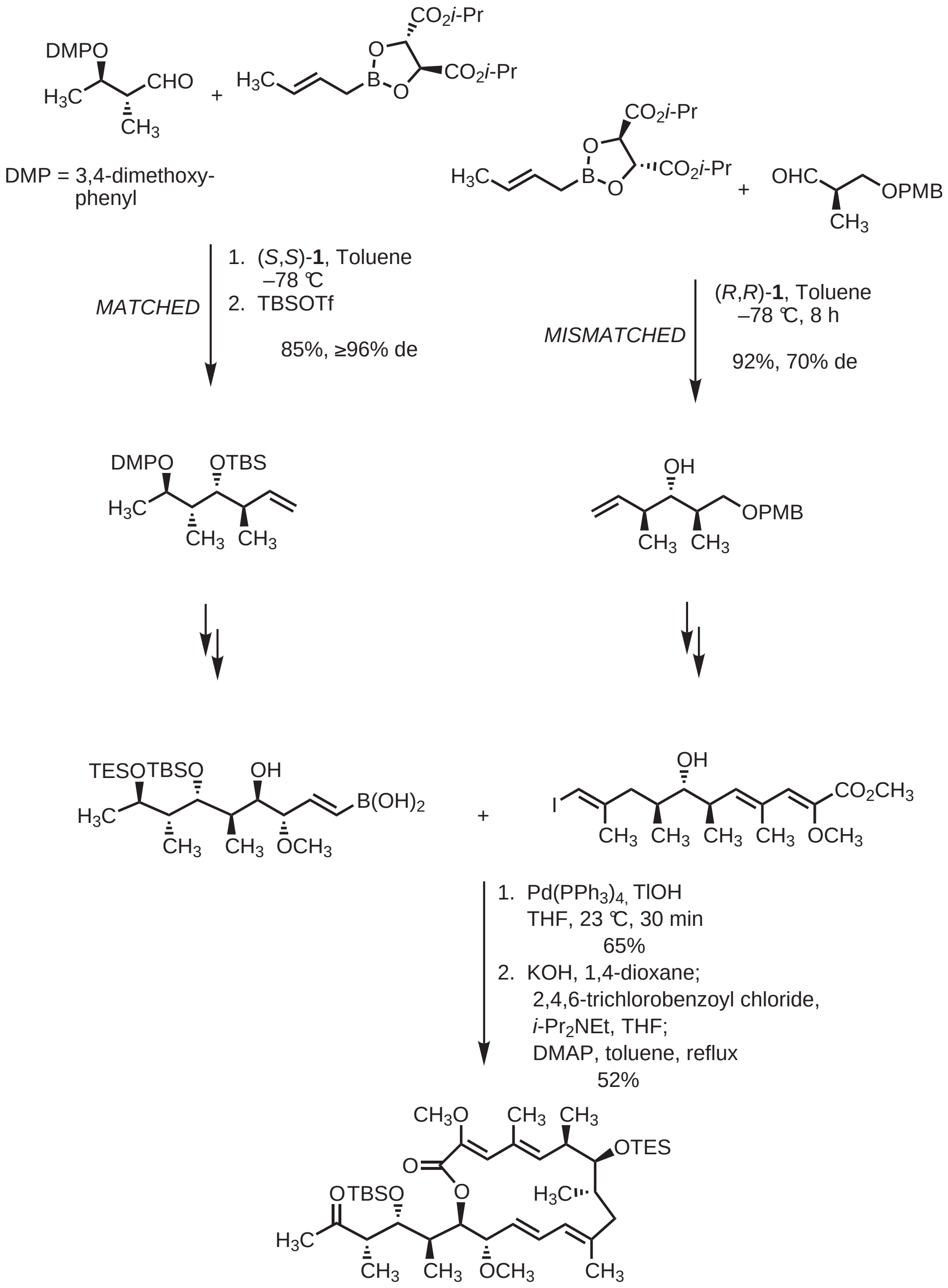


- All reactions were performed in toluene at –78 ℃ in the presence of 4Å-MS.

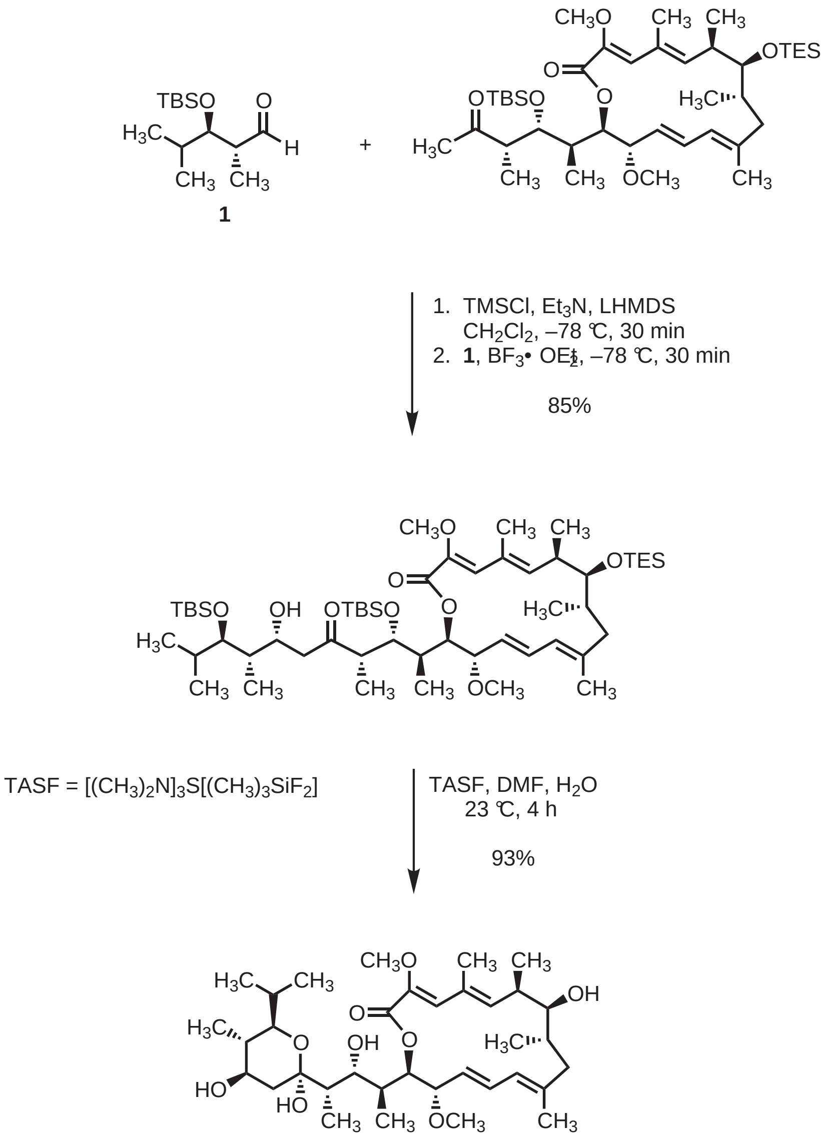
Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.

Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316-318.

(–)-Bafilomycin A_1:


DMP = 3,4-dimethoxy-phenyl
1. (S,S)-1, Toluene –78 ℃
2. TBSOTf
MATCHED
85%, ≥96% de
(R,R)-1, Toluene –78 ℃, 8 h
MISMATCHED
92%, 70% de
1. Pd(PPh3)4, TlOH THF, 23 ℃, 30 min
65%
2. KOH, 1,4-dioxane; 2,4,6-trichlorobenzoyl chloride, i-Pr2NEt, THF; DMAP, toluene, reflux
52%

M. Movassaghi

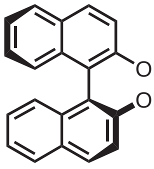


(–)-Bafilomycin A$_1$

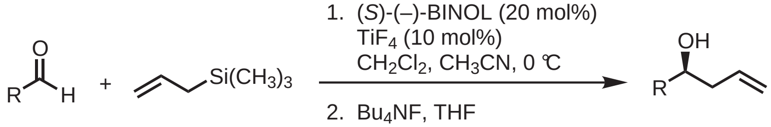
Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1652-1655.

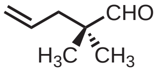
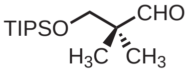
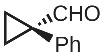
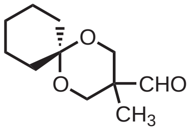
Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587-3590.

Catalytic, Enantioselective Addition of Allylsilanes to Aldehydes



(*S*)-(–)-BINOL



aldehyde	time (h)	yield (%)	ee (%)
	4	90	94
	20	93	84
$(CH_3)_3CCHO$	4	91	94
	20	92	93
	20	81[a]	74
PhCHO	4	85	80
c-$C_6H_{11}CHO$	4	72	60
$PhCH_2CH_2CHO$	4	69	61

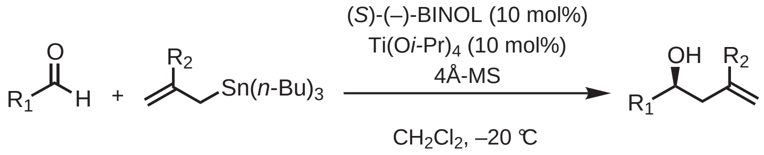
[a] Based on 25% recovered aldehyde.

- Allyltrimethylsilane initially reacts with the HF produced during catalyst preparation to give propene and $(CH_3)_3SiF$.
- It is important that the reaction be conducted in the presence of small amounts of CH_3CN to solubilize the polymeric TiF_4.
- α,α-Disubstituted aldehydes afford the highest enantioselectivities.

Gauthier, D. R. Jr.; Carreira, E. M. *Angew. Chem.*, *Int. Ed. Engl.* **1996**, *35*, 2363-2365.

M. Movassaghi

Catalytic, Enantioselective Addition of Allyltin Reagents to Aldehydes



R_1	R_2	time (h)	yield (%)	ee (%)
C_6H_5	H	70	88	95
C_6H_5	CH_3	60	75	91
c-C_6H_{11}	H	70	66	94
c-C_6H_{11}	CH_3	48	50	84
(E)-$C_6H_5CH{=}CH$	H	70	42	89
(E)-$C_6H_5CH{=}CH$	CH_3	12	68	87
$C_6H_5CH_2CH_2$	H	70	93	96
$C_6H_5CH_2CH_2$	CH_3	40	97	98
i-C_3H_7	H	70	89	96
furyl	H	70	73	96
furyl	CH_3	12	99	99
p-$CH_3OC_6H_4$	CH_3	48	61	93
p-$CH_3OC_6H_4CH_2OCH_2$	H	70	81	96
$BnOCH_2$	H	60	84	95

- Addition occurs to the *re* face of the aldehyde with the catalyst prepared from (*R*)-(+)-BINOL.

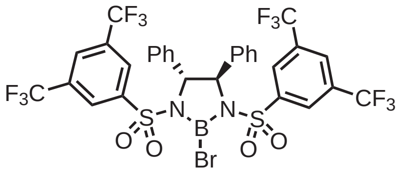
- This procedure allows for the efficient asymmetric methallylation of aldehydes, typically a difficult transformation.

Keck, G. E.; Krishnamurthy, D. *Org. Syn.* **1998**, *75*, 12-18.

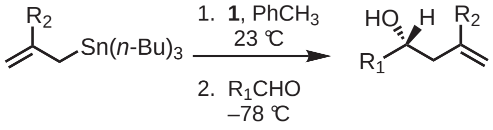
Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467-8468.

Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543-6544.

Enantioselective Allylation Using a Stoichiometric Chiral Controller Group



1



aldehyde	R_2	yield (%)	ee (%)
PhCHO	H	92	96
PhCHO	Cl	80	90
c-$C_6H_{11}CHO$	H	84	92
c-$C_6H_{11}CHO$	Cl	76	88

- Reagent **1** is produced from the corresponding (*R*,*R*)-bis-sulfonamide by reaction with BBr_3 in CH_2Cl_2.

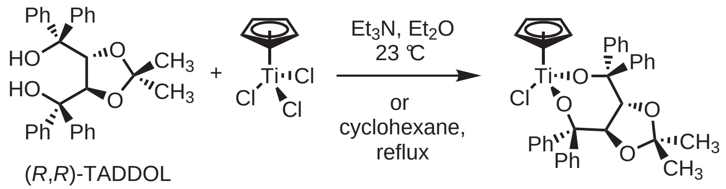
- Transmetallation of allyltin reagents with the chiral *B*-Bromoboron reagent **1** in toluene is complete in 3-20 h.

- The (*R*,*R*)-bis-sulfonamide can be recovered from the reaction mixture.

Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715-3718.

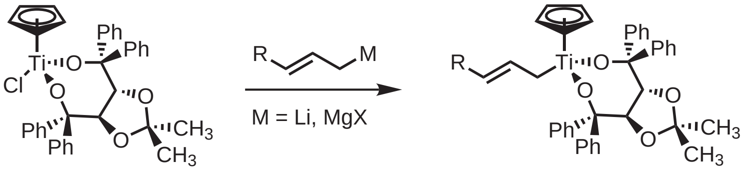
M. Movassaghi

Enantioselective Allyltitanation of Aldehydes

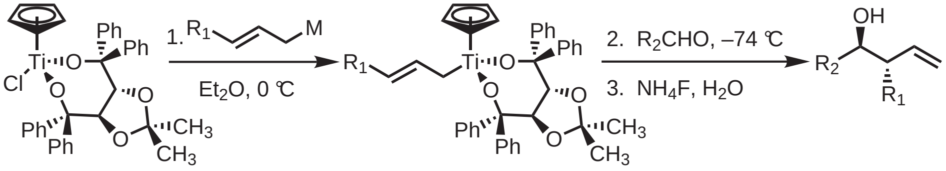


(*R*,*R*)-TADDOL

- The chiral diol is readily available in both enantiomeric forms from the corresponding tartrate esters.
- Complex formation is driven to completion by neutralization of HCl with Et_3N, or by removal of HCl by heating.
- The complex may be used in crude form, as prepared in solution, or the complex may be crystallized and isolated.



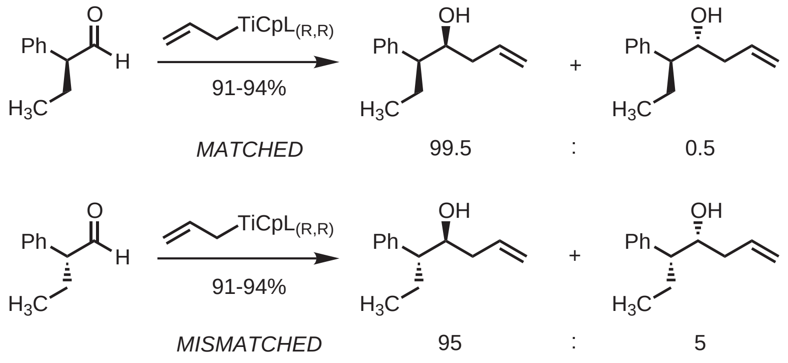
- (E)-Crotyltitanium reagents are produced from (*E*)- or (*Z*)-crotyl anion precursors.



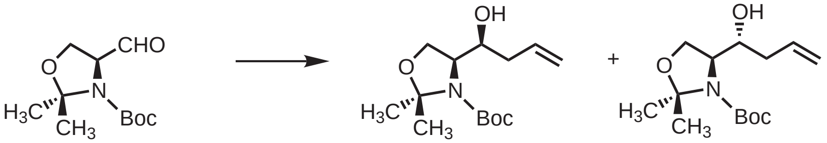
R_1	R_2	ee (%)	de (%)	yield (%)
H	Ph	95		93
H	$(CH_3)_2CH$	97		88
H	$CH_2=CH$	95		79
CH_3	Ph	98	97	89
Ph	Ph	97	≥98	54
$(CH_3)_3Si$	Ph	≥98	≥98	68
EtO	Ph	95	75	77
CH_3	$CH_3(CH_2)_8$	≥98	≥98	86
$(CH_3)_3Si$	$CH_3(CH_2)_8$	≥98	≥98	69

- (*E*)-Crotyltitanation of aldehydes affords anti products, presumably by a chair-like TS.

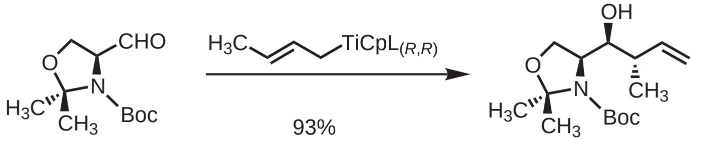
Diastereoselective Allyltitanation of Chiral Aldehydes



- Exceptionally high reagent selectivity is observed in the mismatched allylation of (*R*)-2-phenylbutyraldehyde (90% de) (cf., (–)-$Ipc_2BCH_2CH=CH_2$: 34% de).



reagent	yield		
$TiCpL_{(R,R)}$	93	98.1	1.9
$TiCpL_{(S,S)}$	95	0.5	99.5
$TiCp(Oi\text{-}Pr)_2$	89	37.3	62.7
MgCl	86	55.1	44.9



a single diastereomer

Hafner, A.; Duthaler, R. O; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336.

Duthaler, R. O.; Hafner, A.; Riediker, M. *Pure & Appl. Chem.* **1990**, *62*, 631-642.

M. Movassaghi

Chemical Reviews

Volume 88, Number 8 December 1988

The Thermal, Aliphatic Claisen Rearrangement

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Frederick E. Ziegler received his B.S. from Fairleigh Dickinson University in 1960 and Ph.D. in 1964 from Columbia University where he studied under Gilbert Stork. As an NSF postdoctoral student, he spent 1 year in the laboratory of George Büchi at The Massachusetts Institute of Technology. He joined the Yale University faculty in 1965 where he currently holds the rank of Professor of Chemistry. His research interests include the synthesis of physiologically active natural products, the study of the stereochemistry of organic reactions, and the development of new synthetic methods.

I. Introduction

This past year the diamond anniversary of the publication of Ludwig Claisen's paper "Über Umlagerung von Phenol-allyl-äthern in C-allyl-phenole" describing his now eponymous rearrangement[1] was observed. And what a gem it has proved to be! Ironically, the majority of the text of the paper and all the experimental details dealt with the substance of the title while the first paragraph mentioned, in almost parenthetical fashion, the rearrangement of the O-allylation product of acetoacetic ester **1** to its C-allylated isomer **2** upon distillation in the presence of ammonium chloride. Arguably, the aliphatic rearrangement has stimulated more interest in both its mechanistic and synthetic aspects than its aromatic counterpart. Today, the aliphatic Claisen rearrangement is but one member of the class of [3,3] sigmatropic rearrangements. The prototype for the rearrangement is the transformation of allyl vinyl ether **3** into 4-pentenal (**4**).

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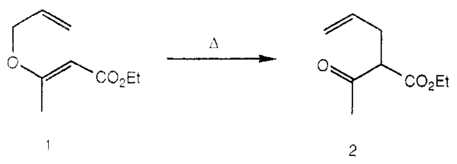

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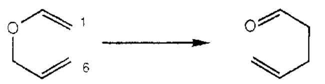
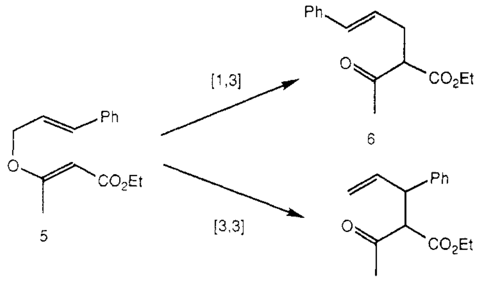


3 4

This review will deal with the history, mechanism, stereochemistry, and applications of the thermal, aliphatic rearrangement[2] over the past 75 years, as recent publications have provided excellent summaries of the effect of catalysts on the rearrangement.[3] While the contributions to this area are legion, an effort will be made to deal with both historical contributions and those reports that exemplify the scope of the reaction. Although heteroatom Claisen rearrangements will not be covered, examples will be provided as they apply to the discussions at hand.

II. Historical Overview

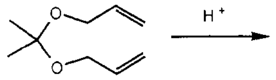
Bergmann and Corte (1935)[4] and Lauer and Kilburn (1937)[5] investigated the rearrangement of ethyl β-cinnamyloxycrotonate (**5**) in the presence of ammonium chloride to determine if "transposition" of the allyl unit occurs, as had been established in the aromatic series.[6] The former collaborators reported the formation of the "nontransposed" product **6** and "transposed" **7** while the latter investigators observed only the product of "transposition". The formation of β-keto ester **7** provided access to a product formally derived from the S_N2' C-alkylation of cinnamyl halides with acetoacetic ester anion.



5 6 7

Bergmann and Corte employed Claisen's method[7] of ammonium chloride catalyzed exchange of cinnamyl alcohol with ethyl 3-ethoxy-2-crotonate for the formation of **5** while Lauer and Kilburn used sodium cinnamylate and ethyl β-chlorocrotonate. The use of ammonium chloride in the rearrangement step soon disappeared, although it had been shown to have "a small, but significant, increase in rate" as a heterogeneous catalyst.[8]

While the β-keto esters provided access to γ,δ-unsaturated acids by Haller–Bauer cleavage (i.e., retro-Claisen condensation) and γ,δ-unsaturated ketones by acid hydrolysis, formation of γ,δ-unsaturated aldehydes had not been realized. In 1938, Hurd and Pollack[9a] subjected β-bromoethyl allyl ether to base-promoted dehydrohalogenation to form the archetypical allyl vinyl ether (**3**), which underwent successful rearrangement to aldehyde **4** at 255 °C. In addition, allyl isopropenyl ether (**9**) was prepared by acid-catalyzed elimination and was subjected to rearrangement to afford ketone **10**.



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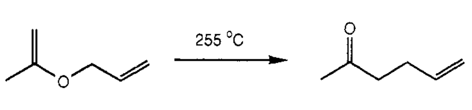
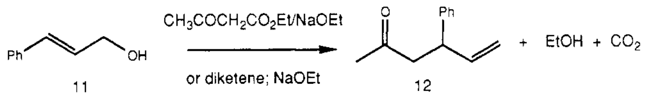


9 10

In the early 1940s, Carroll[10] investigated the base-catalyzed reaction of acetoacetic ester with allylic alcohols to produce olefinic ketones.[11] In particular, the stereospecificity of the reaction was demonstrated in the case of the structural isomers cinnamyl alcohol (**11**) and phenylvinylcarbinol (**13**), each giving a transposed product. Aware of the results of Bergmann and Lauer, Carroll proposed a mechanism that invoked S_N2' displacement of hydroxide by acetoacetate anion. Kimel and Cope[12] (1943) clarified the mechanism by demonstrating that acetoacetic acid esters derived from allylic alcohols undergo the rearrangement. Moreover, the use of diketene provided a reactive equivalent of acetoacetate that made the formation of substrates routine. Thus, this variation of the reaction provided nonacidic conditions, compared to those of Hurd, for the generation of γ,δ-butenyl methyl ketones.



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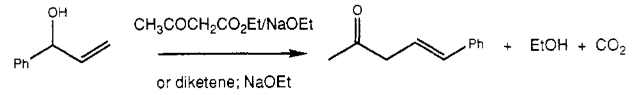
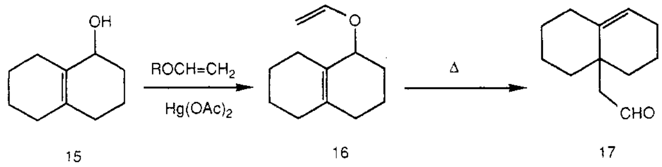


13 14

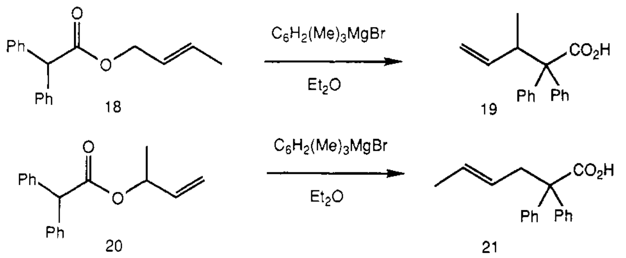
The generation of vinyl ethers by the dehydrohalogenation procedure of Hurd did not provide a general route for the derivatization of allylic alcohols. A solution to this problem was provided by Burgstahler and Nordin[13] who adapted the mercuric acetate catalyzed exchange of alcohols with alkyl vinyl ethers[14] to the formation of allyl vinyl ethers (**15** → **16**).[15] These investigators were able to demonstrate that the rearrangement was successful in systems wherein at least one of the double bonds is contained in a ring (**16** → **17**).



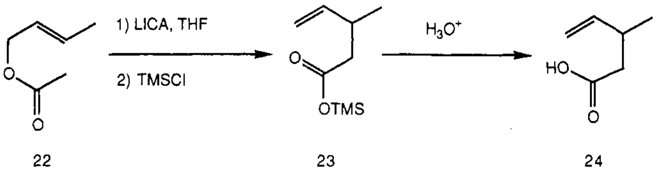
15 16 17

In 1967, Marbet and Saucy reported[16] the acid-catalyzed exchange and rearrangement of seemingly labile tertiary allylic alcohols with 2,2-dimethoxypropane or 2-methoxypropene that resulted in the formation of methyl ketones.[17] The conversion of linalool to geranylacetone laid the groundwork for a commercial synthesis of vitamin A alcohol.

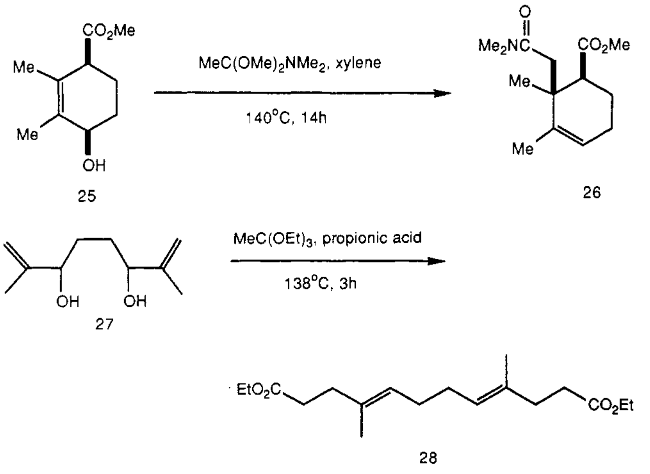
The first practical example of the preparation of γ,δ-unsaturated carboxylic acids via the aliphatic Claisen rearrangement was demonstrated by Arnold and co-workers[18] in 1949.[19] The allylic esters **18** and **20** of diphenylacetic acid underwent stereospecific rearrangement upon treatment with mesitylmagnesium bromide at ambient temperature.



Other variations employed sodium hydride as the base in refluxing toluene;[18a,20] however, a significant breakthrough was reported by Ireland[21] who, following Rathke's report[22] of the use of lithium dialkylamide bases for the generation of ester enolates, demonstrated that the method served as a means to achieve the Claisen rearrangement of acylated allylic alcohols at ambient temperature (**22** → **23**) and, as will be seen later, provided a method for the control of enolate geometry. Both the enolates and their *O*-silyl ketene acetals underwent facile rearrangement.[23]



Although Ireland's contribution improved the formation of γ,δ-unsaturated acids, it was preceded by two independent contributions that realized amides and esters via the Claisen rearrangement. In 1964 Eschenmoser[24a,b] adapted Meerwein's observations[24c] on the exchange of amide acetals with allylic alcohols, thereby facilitating the formation of γ,δ-unsaturated amides upon rearrangement (**25** → **26**). In a similar fashion, 1970 witnessed Johnson's report[25] of the acid-catalyzed exchange of ethyl orthoacetate with allylic alcohols and the subsequent formation of γ,δ-unsaturated esters upon rearrangement (**27** → **28**).



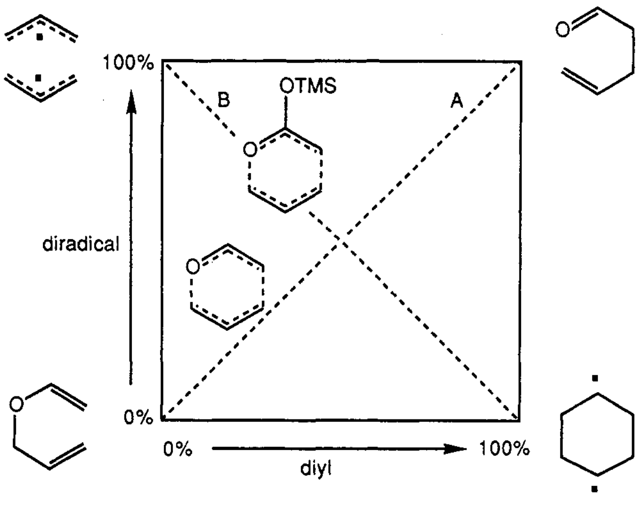


Figure 1. Transition-state profile of the aliphatic Claisen rearrangement.

III. Mechanistic Aspects

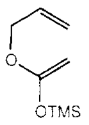
A. Kinetics

The ability of the Claisen rearrangement to give transposed structures led Hurd and Pollack[9b] to suggest a cyclic mechanism. The rearrangement of allyl vinyl ethers displays a negative entropy[26] and volume[27] of activation, both of which support a constrained transition state relative to ground-state geometries. First-order kinetics[8,26] and the lack of crossover products[8] argue for the intramolecularity of the reaction.

The overall exothermicity[26] of the rearrangement of allyl vinyl ethers indicates an early transition state.[28,29] Using secondary deuterium isotope effects as a mechanistic probe, Gajewski[29] has concluded that bond-breaking is more advanced than bond-making in the rearrangement of allyl vinyl ether itself. Thus, the transition state (TS) has been suggested to resemble more closely the diradical than the 1,4-diyl. Figure 1 (More O'Ferrall-Jencks diagram) locates the transition state for allyl vinyl ether above diagonal A (diradical > diyl) and below diagonal B (early, not late, TS). Dewar, using MINDO/3 calculations, has supported an early transition state for allyl vinyl ether with bond-making being more advanced than bond-breaking, thereby requiring diyl character in the transition state.[30]

Substituents play an important role in affecting the rate of the Claisen rearrangement. Burrows and Carpenter,[31] using phenyl anion as a transition-state model, have predicted that π-donor substituents at C_1, C_2, and C_4 of allyl vinyl ether should increase the rate of the rearrangement, while substitution at C_5 and C_6 should cause deceleration. However, Dewar[30] has argued that a C_5-methoxy substituent should have a greater accelerating effect than a C_2-methoxy group.

The presence of electron-donating groups, e.g., EtO–, R_3SiO–, and Me_2N–, at C_2 of the allyl vinyl ether causes a dramatic rate acceleration. Thus, the 2-(trimethylsilyl)oxy (**29**; $t_{1/2} = 210 \pm 30$ min at 32 °C)[21] and the 2-(*tert*-butyldimethylsilyl)oxy (**31a**; $t_{1/2} = 107$ min at 35 °C)[32] derivatives rearrange with facility under near ambient conditions, while allyl vinyl ether ($t_{1/2} = 1.7 \times 10^4$ min at 80 °C)[33] requires higher temperatures for rapid rearrangement. While both **29** and its 6-methyl congener **30a** ($t_{1/2} = 150 \pm 30$ min at 32 °C)[21] rearrange at nearly the same rate, the C_4-alkyl-substituted isomer **31b** rearranges an order of magnitude more rapidly than either.[34] This difference suggests a kinetic stabilization of the bond-breaking process by the alkyl group in **31b**.



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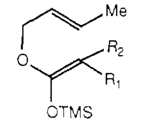
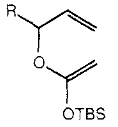
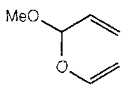


30a, $R_1=R_2=H$
b, $R_1=Me$, $R_2=H$
c, $R_1=R_2=Me$



31a, R=H
b, $R=C_5H_{11}$



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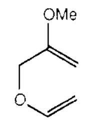

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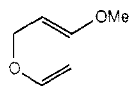
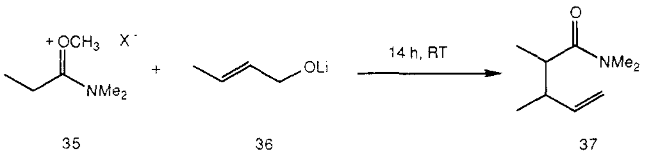


34

Coates and Curran[33] have measured the rates of rearrangement of the C_4-, C_5-, and C_6-methoxy-substituted allyl vinyl ethers at 80 °C in benzene. The 4-methoxy derivative **32** rearranges 100 times faster than the parent while the 6-methoxy isomer **34** is 10 times faster, thereby demonstrating a strong kinetic stabilization in the former case and a vinylogous, kinetic anomeric effect in the latter.[35] The observation of this effect is contrary to the Burrows–Carpenter model. In addition, the 5-methoxy isomer **33** is found to rearrange 40 times slower than the parent, in disagreement with the Dewar prediction. Coates and Curran have suggested a transition state for these systems with dipolar character (enolate–oxonium ion pair). When the solvent is changed from benzene to methanol, **32** and **34** show a 20- and 70-fold rate increase, respectively. In general, solvents have little effect on the rate of the rearrangement.

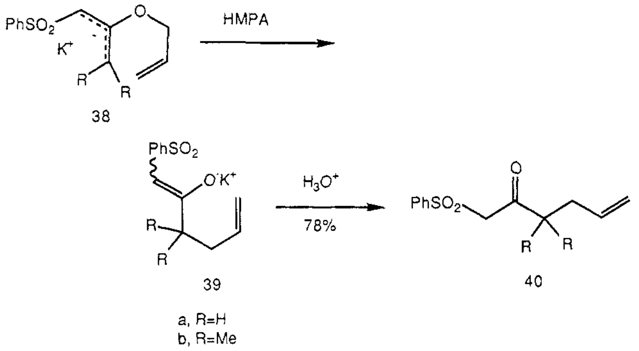
Gajewski[36] has attributed the rate enhancement and the greater degree of bond-breaking in the transition state of the Ireland–Claisen rearrangement to the greater stability of the 2-[(trimethylsilyl)oxy]-1-oxaallyl moiety over its oxaallyl counterpart (Figure 1). This conclusion derives from an examination of the heats of formation of the oxaallyl radicals and supports[21b] the finding that the relative rates of rearrangement of silyl ketene acetals **30** are **30c** > **30b** > **30a**.[37] The effect of the (trimethylsilyl)oxy group is not general to all [3,3] sigmatropic rearrangements as 2-[(trimethylsilyl)oxy]-3-methyl-1,5-hexadiene undergoes a Cope rearrangement with a half-life of 2 h at 210 °C.

Although the Johnson and the Eschenmoser variants are conducted at elevated temperature, these conditions are required for the alcohol exchange reaction, not necessarily for the rearrangement. This point is amply demonstrated in the latter instance when ketene *O,N*-acetals are generated by an alternative route (**35** + **36** → **37**).[38]



In an independent study, Carpenter and Burrows[39] have synthesized the five isomeric cyano-substituted derivatives of allyl vinyl ether and have measured their kinetic parameters. Rate accelerations are observed for the C_2-CN (k_{rel} = 111), C_3-CN (k_{rel} = 270), and C_4-CN (k_{rel} = 15.6) compounds while decelerations occur for the C_1-CN (k_{rel} = 0.90) and C_5-CN (k_{rel} = 0.11) isomers relative to allyl vinyl ether.

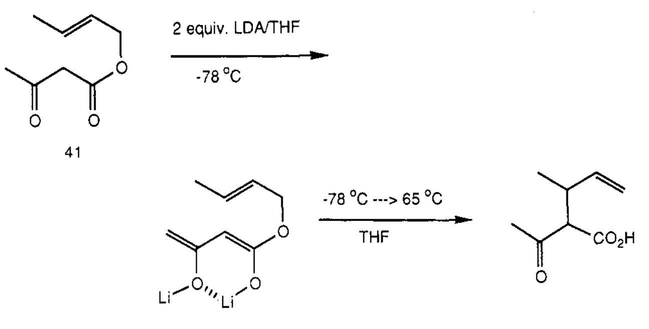
The formation of anionic species increases the rate of the rearrangement. The enolates of allyl esters should be considered as the prototypes of strong C_2 π-donors as they rearrange at ambient temperatures.[21] Denmark has reported[40] the first example of a carbanion-accelerated Claisen rearrangement.[41] The use of hexamethylphosphoramide (HMPA), as opposed to 18-crown-6/THF, accomplishes the conversion of **38a** → **39a** at a lower temperature (50 °C) and in a higher yield (78%). This solvent-induced rate enhancement has been interpreted as ion-pair dissociation. Disubstitution at C_1 (**38b** → **39b**) causes a greater rate enhancement (20 °C, 15 min),[42] similar to the silyl ketene acetal case.



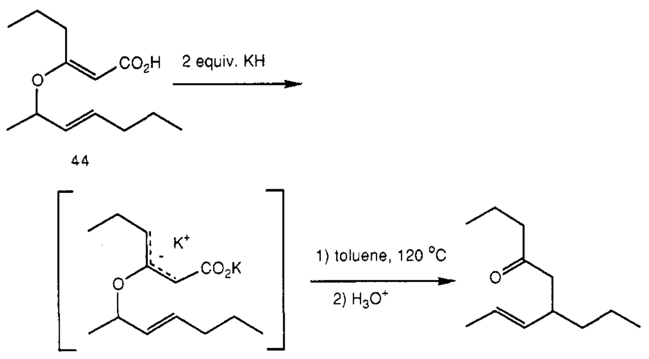
The Carroll rearrangement is accelerated by carbanion formation. Wilson[43] has demonstrated that β-keto ester **41**, formed by 4-(dimethylamino)pyridine (DMAP) catalyzed addition of (*E*)-2-buten-1-ol to diketene,[44] provides the β-keto acid **43** when treated with 2 equiv of lithium diisopropylamide (LDA) at −78 °C in THF followed by heating to reflux. Decarboxylation is readily accomplished in refluxing carbon tetrachloride to give the ketone in 95% yield. When 1 equiv of base is used, no reaction is observed. The thermal reaction in the absence of base requires heating at 200 °C, and the ketone is isolated in only 37% yield.

In a similar fashion, Büchi[45] has observed acceleration in the rearrangement of 3-(allyloxy)-2-butenoic acid **44** prepared by alkoxide addition to the 3-chloro-2-butenoate. When the acid is treated with 1 equiv of KH in refluxing toluene for 2–6 h, the potassium carboxylate is stable. However, the use of 2 equiv of KH effects rearrangement via dianion **45** under the same conditions, affording ketone **46** in 68% yield upon acidification and decarboxylation. The rate enhancement occurs for substrates derived from secondary allylic alcohols, but not for primary allylic alcohols. Silyl ketene acetals prepared from secondary alcohols have been observed to rearrange faster than those derived from primary allylic alcohols.[21b]

α-Allyloxy ketones have displayed remarkable rate accelerations. For example, Koreeda and Luengo[46a] have generated the enolate **48a** by conjugate addition of Me_2CuLi to 2-(allyloxy)-2-cyclohexenone (**47**); rearrangement to acyloin **49a** is complete in 15 min at 0 °C.[46b] The rate enhancement has been attributed to an allyl radical/oxyoxaallyl radical anion (semi-dione) pair. For comparison, the silyl enol ether **48b** is slower



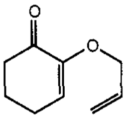
41 42 43



44 45 46

to rearrange, having $t_{1/2}$ = 1.6 h at 62.5 °C.

In a related study, Ponaras[47] has compared the relative rates of rearrangement of 2-(allyloxy)-3-methyl-2-cyclohexenone and its derivatives. In refluxing THF (65 °C), the parent ketone **50a** has $t_{1/2}$ = 340 h, affording the diosphenol **51**, while the rearrangement of carbomethoxyhydrazone **50b** to **52a** is appreciably faster ($t_{1/2}$ = 22 h). The sodium salt of the hydrazone (**50c**) is the fastest of the three, rearranging to give **52b** with $t_{1/2}$ = 1.5 h. This method has proved amenable to forming vicinal quaternary centers, and in the case of the carbomethoxyhydrazones **52**, a subsequent Wolff–Kishner reduction can be conducted to remove the accelerating functionality.[48]



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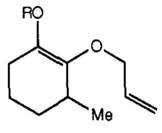
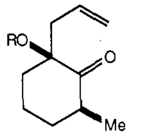
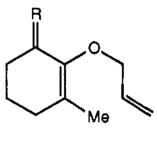


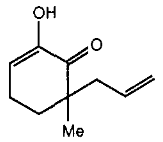
48a, R=MeCuLi
b, R=TMS



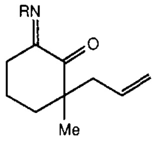
49a, R=H
b, R=TMS



50a, R=O
b, R=NN(H)CO2Me
c, R=NN(Na)CO2Me



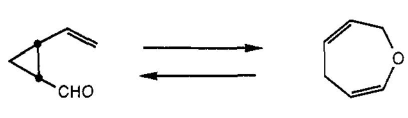
51



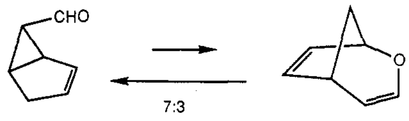
52a, R=NN(H)CO2Me
b, R=NN(Na)CO2Me

B. Retro-Claisen Rearrangement

The Claisen rearrangement, unlike its all carbon analogue the Cope rearrangement, is an irreversible reaction, except for several specially designed substrates. Vinylcyclopropanecarboxaldehyde (**53**) has been shown to be in rapid equilibrium with dihydrooxepine (**54**). Similarly, unsaturated aldehyde **55** forms a 7:3 equilibrium mixture with vinyl ether **56**. The equilibrium is shifted to the right by trapping the vinyl ether as its tetracyanoethylene derivative and to the left by formation of the bisulfite adduct of the aldehyde. Decomposition of the bisulfite adduct reestablishes the equilibrium. These equilibria are presumably driven by the strain of the cyclopropane ring.[49,50]

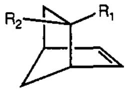


53 54

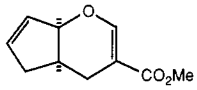


55 56

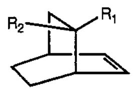
Oppolzer[51] has observed that silica gel chromatography of aldehyde ester **57a** provides recovered substrate (68%) in addition to unsaturated ester **58**. During the same period, Boeckman[52] observed that the rearrangement of **57a** to **58** occurs quantitatively at room temperature in 24 h. However, the less strained homologue **59a**, upon heating in refluxing toluene in the presence of a catalytic amount of HOAc, provides an equilibrium mixture of **59a** and **60** (89:11). Support for a sigmatropic rearrangement rather than a pathway invoking stepwise formation of carbocation intermediates follows from the observation that the stereoisomer **59b** does not undergo rearrangement under conditions that are successful with **59a**. However, $BF_3{\cdot}Et_2O$ at room temperature is able to convert stereoisomer **57b** into **58**, ostensibly through a carbocation intermediate that may only be required for the isomerization (**57b** → **57a**) and not necessarily for the rearrangement. These investigators have also observed acceleration in the $BF_3.Et_2O$-catalyzed rearrangement at −78 °C in alkyl-substituted congeners of **59a**. These observations have led Boeckman to suggest that the minor product, unsaturated ester **62**, formed in the $BF_3{\cdot}Et_2O$-catalyzed Diels–Alder reaction (−78 °C) between cyclopentadiene **61** and methyl 2-acetylacrylate, may well arise from the major product of the reaction, norbornene **63**, by way of the catalyzed retro-Claisen rearrangement.[53]



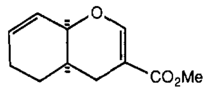
57a, R1=CHO, R2=CO2Me
b, R1=CO2Me, R2=CHO



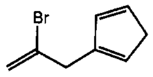
58



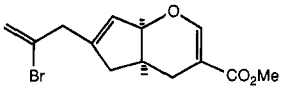
59a, R1=CHO, R2=CO2Me
b, R1=CO2Me, R2=CHO



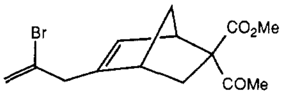
60



61



62

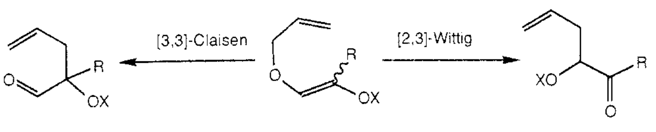


63

C. Competitive Rearrangements

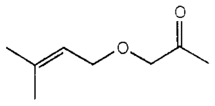
1. *[3,3] Claisen vs [2,3] Wittig Rearrangement*

Conceptually, α-allyloxy enolates of the type **65a** can undergo either [3,3] sigmatropic rearrangement (anionic oxy-Claisen rearrangement)[46] or [2,3] Wittig rearrangement.[54] Thomas[55] has observed that ketone **67**, upon exposure to *t*-BuOK/*t*-BuOH, undergoes a [2,3] Wittig rearrangement to "mainly" ketol **68**. In contrast, Koreeda[46a] has reported that the enolate of phenyl ketone **69** (from MH and MeOH) in toluene not only shows rate enhancement (M = K, −23 °C, $t_{1/2}$ = 3.3 h; M = Na, 0 °C, $t_{1/2}$ = 2.6 h; M = Li, 96.5 °C, $t_{1/2}$ = 1.1 h) but also gives a ratio of Claisen to Wittig product (**70**:**71**) of >98:<2 (M = K, Na) and a ratio of ~80:20 when M = Li. To ensure exclusive formation of the Claisen product, enolates need only be O-silylated (**65a** → **65b**) and rearranged to aldehydes (**64b**). Accordingly, the *O*-trimethylsilyl enol ether of ketone **69** affords the *O*-trimethylsilyl derivative of ketone **70** upon heating (71 °C, $t_{1/2}$ = 0.5 h). Earlier, Salomon[56] had demonstrated the utility of the transformation **65b** → **64b** by preparing the *O*-trimethylsilyl enol ethers with (TMS)Cl/Et_3N. The α-silyloxy aldehydes could be cleaved readily with methanolic periodic acid to afford β,γ-unsaturated ketones.

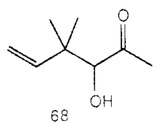


64 65 66

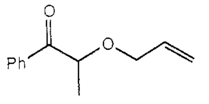
a, X=M, R=alkyl
b, X=TMS, R=alkyl
c, X=M, R=O-alkyl
d, X=M, R=OM
e, X=TMS, R=NR$_2$'
f, X=TMS, R=O-alkyl



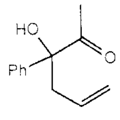
67



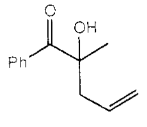
68



69



70

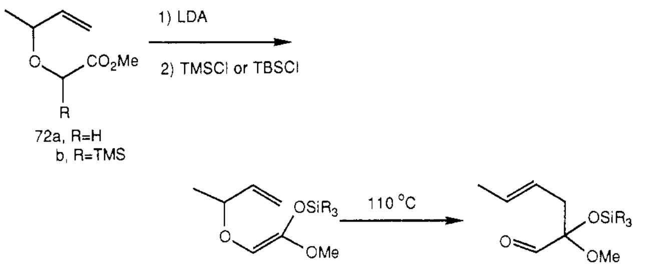


71

Surprisingly, the ester enolates of generic structure **65c** do not undergo a [2,3] Wittig rearrangement[57] while their carboxylate-derived dianions (**65d**) and dialkylamide anions (**65e**) do rearrange by this pathway.[58] Exclusive Claisen rearrangement of these substances can be accomplished via the trimethylsilyl ketene acetals (**65f** → **64f**). This procedure has been described independently by Nakai[57] and Raucher[59] in the transformation of ester **72a** to its (*Z*)-*O*-silyl ketene acetal **73** followed by Claisen rearrangement to the masked α-keto aldehyde **74**. Significantly, when the C-silylated ester **72b** is treated with tetra-*n*-butylammonium fluoride, formation of the [2,3] Wittig product occurs. On the other hand, the *O*-silyl derivative **73** gives the starting ester **72a**. This observation has led Nakai to suggest that a common "naked" anion is not involved in the two pathways but that separate C- and O-hypervalent silicon species are responsible for the dual reaction pathways.

2. Divinylcarbinol Derivatives

The competitive rearrangement of 4-vinylallyl vinyl ethers has provided information on the relative rates of substituted allyl residues. Scheme I illustrates such a study[60] wherein the β-substitution pattern of the allylic residue of allyl vinyl ether **75** is systematically altered. The vinyl residue reacts twice as fast as the (*E*)-β-vinyl group (**76a**:**77a**) and 19 times faster than the (*Z*)-β-vinyl (**76b**:**77b**). At first hand, these data suggest that, in a competition between the (*E*)- and (*Z*)-β-vinyl groups, the E isomer should react 9.5 times faster (**76b**:**77b** to **76a**:**77a**); the observed result is ~3:1 (**76c**:**77c**). As has been suggested,[61] each nonreacting group is a substitution for its reacting partner and need not offer additive substituent effects in each rearrangement. The presence of a 6-methyl substitution (*E* configuration) has a limited effect on the rate of rearrangement of vinyl ethers or silyl ketene acetals (cf., **29** vs **30a**). Terminal 6,6-substitution with two methyl substituents completely favors formation of **76d** over **77d**.

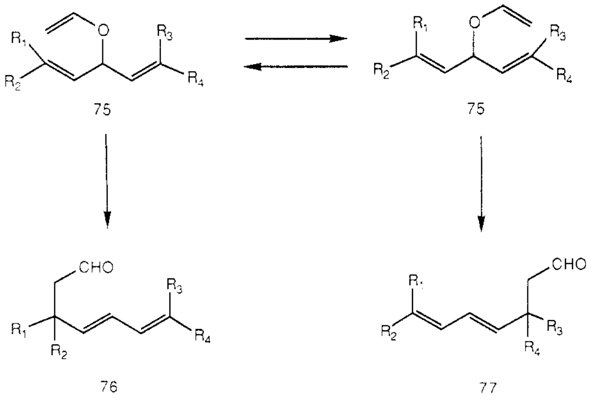


73 74

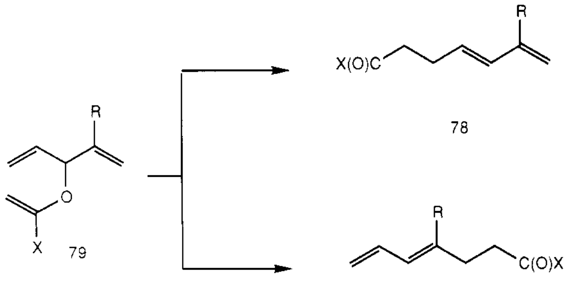
Parker and Farmar[62] have uncovered a subtle selectivity in the rearrangement of the series of divinylcarbinol derivatives **79**. The methyl substituent in **79a** and **79b** provides a small steric deceleration[63] while the less sterically demanding methoxyl group manifests itself as a decelerating C_5-donor group in both **79c** and **79d**. These observations lend additional support to the Burrows–Carpenter model for C_5-donors.[31]

For divinylcarbinols wherein one of the vinyl substituents is contained in a ring, rearrangement with the acyclic vinyl group is preferred when the acyclic unit is unsubstitued. Thus, vinyl ethers **82a** and **82b** give **81a** and **81b**, respectively, with high selectivity. The presence of an (*E*)-β-methylvinyl group retards acyclic rearrangement, but it still remains the major pathway for the rearrangement of **82d**.[64,65]

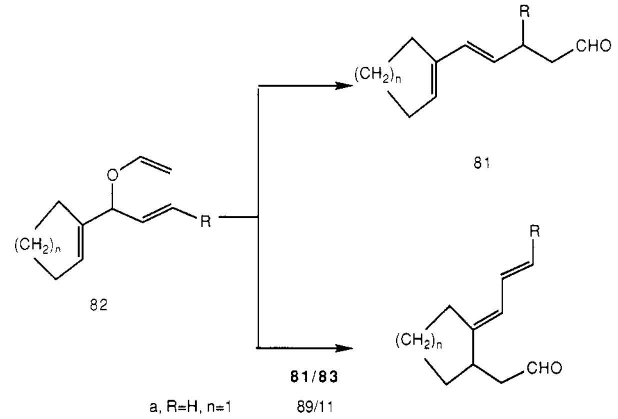
SCHEME I



	76/77
a, $R_1=R_2=R_3=H$; $R_4=Me$	2/1
b, $R_1=R_2=R_4=H$; $R_3=Me$	95/5
c, $R_1=R_4=H$; $R_2=R_3=Me$	78/22
d, $R_1=R_2=H$; $R_3=R_4=Me$	100/0



	78/80
a, R=Me, X=OEt	65/35
b, R=Me, X=NMe$_2$	74/26
c, R=OMe, X=OEt	95/5
d, R=OMe, X=NMe$_2$	97/3

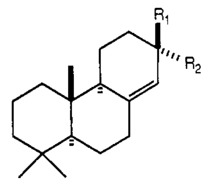


83

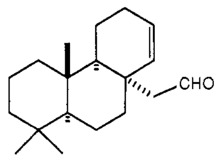
	81/83
a, R=H, n=1	89/11
b, R=H, n=2	88/12
c, R=Me, n=1	50/50
d, R=Me, n=2	65/35

3. Elimination

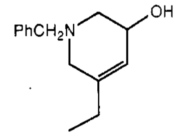
Alternative sigmatropic rearrangements are not the only irreversible processes that can compete with the Claisen rearrangement; elimination reactions are troublesome. This undesirable, competitive process is particularly acute when at least one olefin is contained in a ring. Cyclohex-2-en-1-ols have been particularly notorious in this regard. Ireland and co-workers[66] have prepared the isomeric allylic alcohols **84a** and **84b** by reduction of the corresponding enone. The minor axial alcohol **84a**, when subjected to mercuric ion catalyzed exchange with ethyl vinyl ether, undergoes elimination to dienic products. On the other hand, the major, equatorial allylic alcohol rearranges to aldehyde **85** without incident. An unfavorable transition state for the Claisen rearrangement in the former case may be the result of steric interactions between the angular methyl group and the forming C–C bond.



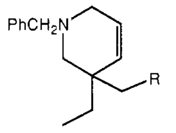
84a, R$_1$=OH, R$_2$=H
b, R$_1$=H, R$_2$=OH



85



86



87a, R=CONMe$_2$
b, R=CO$_2$Et

When confronted with the problem of elimination, the use of an alternative strategy is often beneficial. Thus, allylic alcohol **86**, when subjected to the Eschenmoser ketene *O,N*-acetal variant, provides only a 45% yield of the desired amide **87a** along with the products of disproportionation of the dihydropyridine, the immediate product of elimination. However, the Johnson orthoester route gives the ester **87b** in 74% yield.[67,68]

D. Stereochemistry

1. Transition State

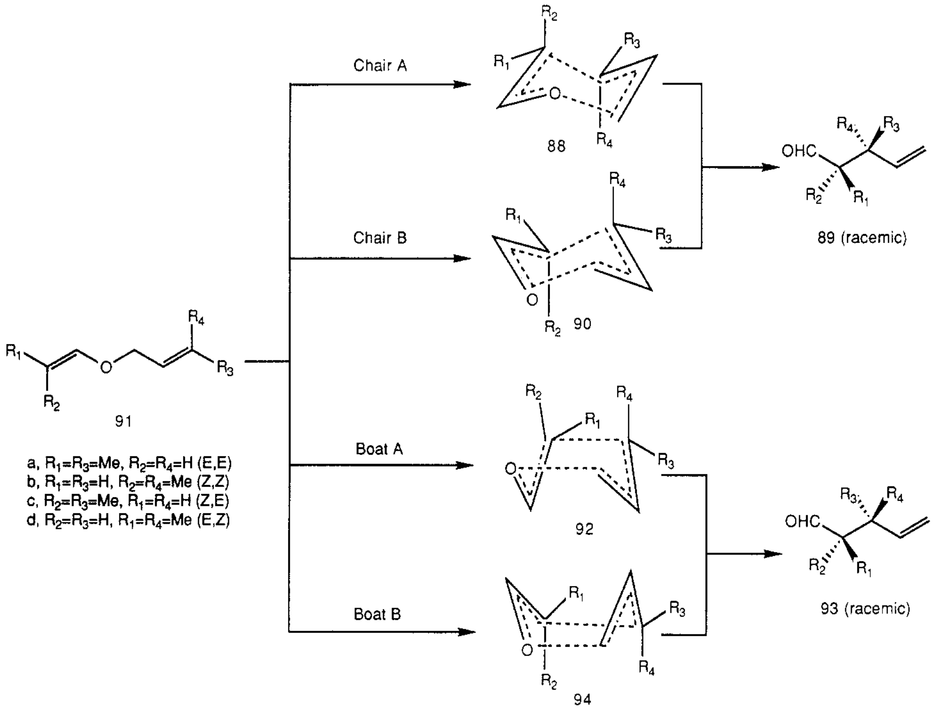
The Claisen rearrangement is a suprafacial, concerted, nonsynchronous pericyclic process that may be considered phenomenolologically as an intramolecular S_N2' alkylation. When the sp^2-hybridized C_1- and C_6-positions of allyl vinyl ether are substituted to provide enantiotopic faces at both termini, the rearrangement can proceed through two pairs of stochastically achiral transition states to provide two racemic diastereomers bearing newly created centers of asymmetry at C_2 and C_3 of the products (Scheme II). Thus, achiral allyl vinyl ether **91** can provide two enantiomeric chairlike transition states **88** and **90**, both of which lead to the racemic diastereomer **89**. Similarly, the enantiomeric boatlike transition states **92** and **94** provide racemic, diastereomeric aldehyde **93**. The two transition states are inherently unequal in energy and the ratio **89**:**93** reflects the transition-state geometry.

In a detailed study modeled after the Doering and Roth experiments that revealed the preferred chairlike transition state for the Cope rearrangement,[69] Schmid[26b,c] and his collaborators have examined the rate and stereochemistry of rearrangement of the four crotyl propenyl ethers **91a–d** in the gas phase at 160 °C. All isomers show the expected negative entropy of activation ($\Delta S^\ddagger = -10$ to -15 eu) with enthalpies of activation ranging from 25 to 27 kcal/mol. Each isomer shows a clear preference for the chairlike transition state (**91a**, 95.9:4.1; **91b**, 94.7:5.3; **91c**, 95.5:4.5; **91d**, 95.4:4.6). The *E* isomer **91a** is found to rearrange an order of magnitude faster than the *Z,Z* isomer **91b**, with the other two geometric isomers intermediate in rate. The *E,E* and *Z,Z* isomers rearrange through a chairlike transition state to give the threo isomer **89a** (**89b**) as the major product; likewise, the *Z,E* and *E,Z* isomers give the erythro isomer **89c** (**89d**) as the predominant stereoisomer. Since the four isomers **91** all proceed through the chairlike transition state, a change in the geometry of a single double bond exchanges the enantiotopicity of the faces of the double bond and leads to the opposite stereoisomer. Indeed, any pairwise change in olefin geometry for a given transition state, or single change of olefin geometry and change in transition state, results in the formation of the same diastereomer.[70]

2. Vinyl Double-Bond Geometry

Before proceeding to other substituent effects and how they control the transition state of the Claisen rearrangement, it is appropriate to consider the methods that are available to control the geometry of the vinyl double bond. Unfortunately, no convenient

SCHEME II


Chair A
Chair B
Boat A
Boat B
88
90
92
94
91
a, R1=R3=Me, R2=R4=H (E,E)
b, R1=R3=H, R2=R4=Me (Z,Z)
c, R2=R3=Me, R1=R4=H (Z,E)
d, R2=R3=H, R1=R4=Me (E,Z)
89 (racemic)
93 (racemic)
OHC
R1
R2
R3
R4

methods are available for the selective preparation of propenyl ethers. The same difficulty exists with the Johnson orthoester method. The use of orthoesters derived from propionic acid derivatives and their higher analogues fail to give stereochemically defined ketene acetals.[71] However, the ketene *O,N*-acetal rearrangement does provide for selectivity. Sucrow and Richter[72] have examined the Claisen rearrangement of the dimethyl acetal of *N,N*-dimethylpropionamide with (*E*)- and (*Z*)-crotyl alcohol (Scheme III). Although the intermediate ketene *O,N*-acetals are generated in situ and are not isolated, the assumption that a chairlike transition state is operable, coupled with a preferred axial orientation of the C_1-methyl group of the (*E*)-ketene *O,N*-acetal (**95**, **100**), correctly accounts for the stereochemistry of the products. The latter supposition is tenable as the dimethylamino group assists in delocalizing charge in the transition state and interacts with the C_1 substituent when it is equatorially disposed.[73]

An alternative approach to the use of the ketene *O,N*-acetals has been offered by the work of Ficini[74] who has employed 1-(*N,N*-diethylamino)-1-propyne (**101**) as the propionate source; however, no stereochemical study was conducted. Recognizing that the (*Z*)-ketene *O,N*-acetals of Scheme III are the products of thermodynamic control, Bartlett and Hahne[75] have prepared the less stable, kinetic (*E*)-ketene *O,N*-acetal by the stepwise, cis addition of the crotyl alcohols across the triple bond of the Ficini ynamine (Scheme IV). The slow addition of the crotyl alcohol to the ynamine at 140 °C serves to make rearrangement, a trap for the kinetic addition product, competitive with isomerization. Protonation of the ynamine provides the ketene immonium cation **102**, which adds alkoxide preferentially syn to the hydrogen atom via path A. In the case of the (*Z*)-alcohol, a 2.5:1 ratio of **108** to **107** is obtained; the (*E*)-alcohol also preferentially follows path A through **105** leading to a 2:1 ratio of **107** to **108**.

The Ireland variant[21] of the Claisen rearrangement has proved the most adaptable for the control of vinyl olefin geometry. The deprotonation of esters by lithium dialkylamide bases developed by Rathke[22,76] has proved amenable to the generation of specific enolates. Thus, treatment of butenyl propionates **110** and **114** (Scheme V) with lithium diisopropylamide (LDA) in THF under these kinetic conditions forms principally the (*Z*)-lithium enolates, which upon silylation (*tert*-butyldimethylsilyl (TBS) gives the (*E*)-*O*-silyl ketene acetal.[77,78] Rearrangement of silyl ketene acetal **109** provides an 87:13 mixture of acids **111** and **115** after desilylation while **116** gives an 89:11 ratio of **115** and **111**. These two products can also be obtained by using 23% HMPA–THF (HMPA = hexamethylphosphoramide)

SCHEME III

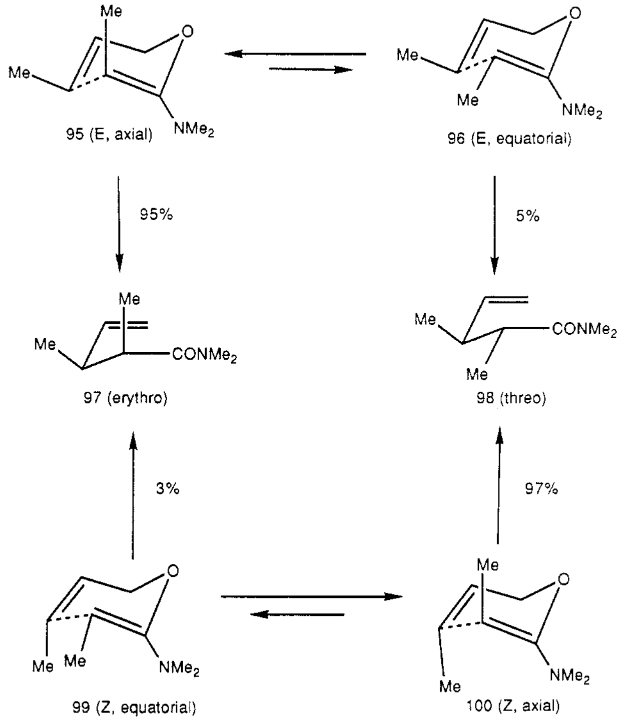
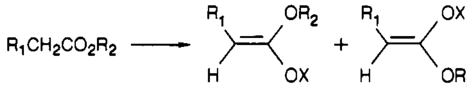


TABLE I. Geometry of Enolate Formation

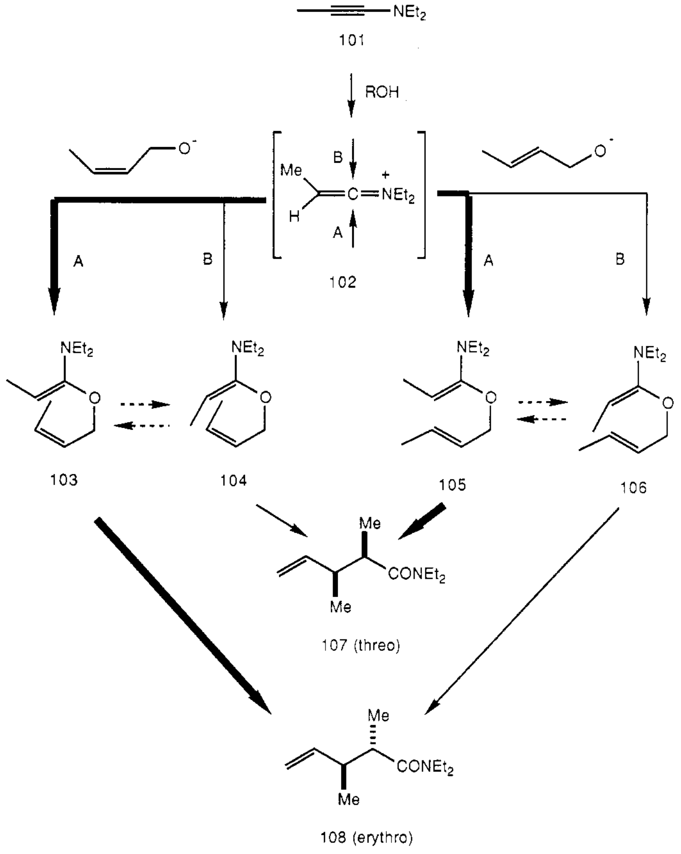


117 **118** **119**

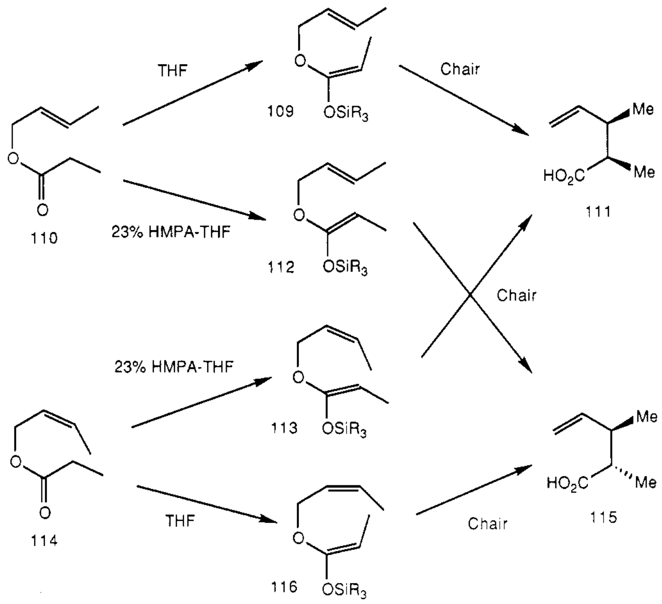
entry	ester	R_1	R_2	X^a	solvent^b	118/119
1	**117a**	C_2H_5	CH_3	TBS	THF	91/9[21b]
2	**117b**	$(CH_3)_3C$	CH_3	TBS	THF	97/3[21b]
3	**117c**	CH_3	C_2H_5	TMS	THF	85/15[80]
4	**117d**	C_2H_5	$(CH_3)_3C$	TBS	THF	95/5[21b]
5	**117e**	CH_3	CH_3	TES	23% HMPA-THF	9/91[81]
6	**117a**	C_2H_5	CH_3	TBS	23% HMPA-THF	16/84[21b]
7	**117b**	$(CH_3)_3C$	CH_3	TBS	23% HMPA-THF	9/91[21b]
8	**117c**	CH_3	C_2H_5	TMS	23% HMPA-THF	0/100[80]
9	**117c**	CH_3	C_2H_5	TES	23% HMPA-THF	13/87[81]
10	**117f**	CH_3	$(CH_3)_2CH$	TES	23% HMPA-THF	17/83[81]
11	**117d**	C_2H_5	$(CH_3)_3C$	TBS	23% HMPA-THF	23/77[21b]

[a] TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; TES = triethylsilyl. [b] Enolates were generated with LDA, −70 to −78 °C.

SCHEME IV



SCHEME V

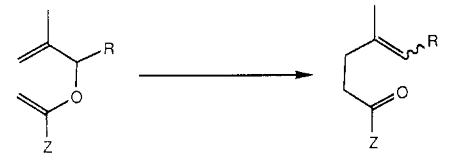


as an optimal solvent system for the generation of the thermodynamic[79] (*E*)-lithium enolates ((*Z*)-*O*-silyl ketene acetals **112** and **113**). *Z*-(*O*)-Silyl ketene acetal **112** provides an 81:19 mixture of **115** and **111** while **113** affords an 86:14 mixture of **111** and **115**. The major diastereomer in each rearrangement arises through the chairlike transition state, and once again, a single exchange of olefin geometry results in the other diastereomer becoming the major product. The erosion of diastereoselectivity can be attributed to two factors: the geometric integrity of the silyl ketene acetals and the selectivity of the chairlike vs boatlike transition state.

Table I provides examples for the selectivity of enolate formation by the LDA/silylation procedure.[82] The entries are listed in ascending bulk of the alcohol portion of the ester group for a given solvent. In general, enolate formation by the kinetic deprotonation procedure is somewhat more selective than the thermodynamic conditions. Because the silyl ketene acetal ratios are approximately equal to, or better than, the ratio of diastereomers **111** to **115**, the chairlike transition state is virtually the exclusive pathway for rearrangement.

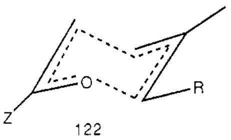
3. Secondary Allylic Alcohols

Although the aliphatic Claisen rearrangement of secondary allylic alcohols had been recognized to provide *E* double bonds,[83] Faulkner and Petersen[84] have examined the selectivity of olefin formation as a function of C_2 substituents. The vinyl ether rearrangement of vinyl ether **120a** provides a 90:10 ratio of (*E*)- to (*Z*)-unsaturated aldehydes **121a**. The congener **120b** bearing an isopropyl rather than an ethyl substituent is more selective affording a 93:7 ratio of (*E*)- to (*Z*)-olefinic aldehydes **121b**. An increase in the steric bulk of the C_2 substituent produces higher stereoselectivity. Thus, ketene *O*,*N*-acetal rearrangement of **120c** gives an *E*:*Z* ratio of 99.4:0.6 while the product from the 2-methoxypropene derivative of 2-methylpent-1-en-3-ol (**120d**) provides less than 1% of the (*Z*)-olefin. Similarly, Katzenellenbogen[85] has reported less than 1% of (*Z*)-olefin in the silyl ketene acetal rearrangement of **120e** and Johnson[86] has observed >98% *E* selectivity in the orthoester rearrangement of **120f**. This dramatic increase in selectivity observed in the C_2,C_4-substituted examples has been rationalized as the result of a pseudo-1,3-diaxial interaction in chairlike transition state **123** that leads to the (*Z*)-olefin as opposed to the less congested chairlike transition state **122** that gives the (*E*)-olefin.[84,87,88]

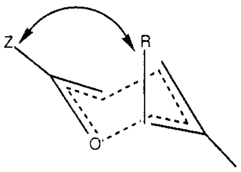


120 121

a, R=Et, Z=H
b, R=i-Pr, Z=H
c, R=Et, Z=NMe_2
d, R=Et, Z=Me
e, R=n-C_6H_{13}, Z=OTBS
f, R=$CH_2CH_2CH(Me){=}CH_2$



122



123

When the secondary allylic alcohol has a substituent at the terminus of the double bond (i.e., C_6), a center of asymmetry is destroyed during the rearrangement as a new one is created. This process has been often called "self-immolative"[89] and involves the "transfer of chirality".[2f] In the sense that racemic substances bearing centers of asymmetry are chiral, and recognizing the concerted, suprafacial nature of the rearrangement, the transformation of Scheme VI is, by necessity, chiral throughout. In more modern terms, that which is transferred is stereogenicity[90] (i.e., stereochemical information), and when practiced with enantiomerically pure allyl vinyl ethers (**124**), the rearrangement affords enantiomerically pure products (**126**).

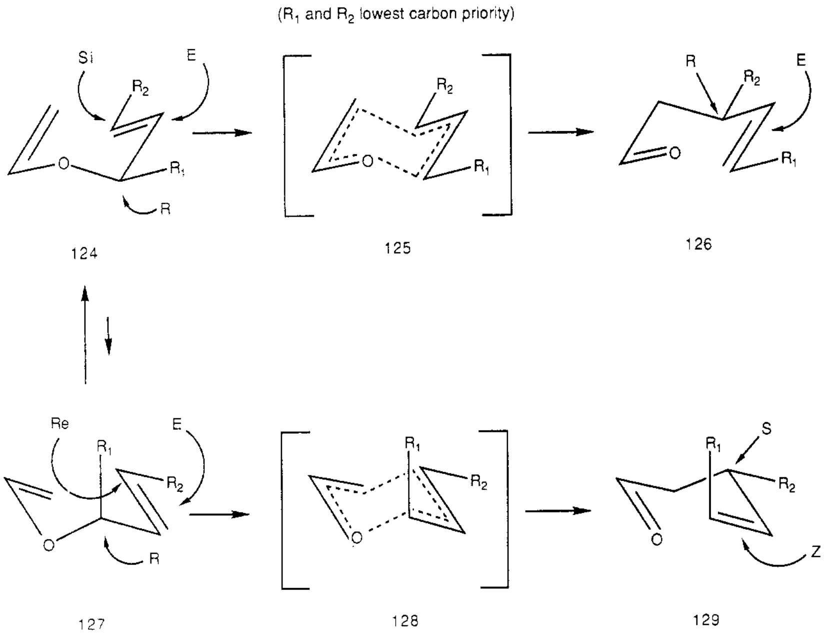
In the example of Scheme VI, the *R,E* enantiomer **124** bearing an equatorial R_1 substituent undergoes bond formation on the *si* face of the allylic double bond to produce the *R,E* enantiomer **126**. Conformational inversion of **124** leads to (*R,E*)-**127**. This conformation can undergo *re* bond formation through transition state **128** having the R_1 substituent axial, resulting in the formation of *S,Z* enantiomer **120**. Thus, the transition-state integrity may be monitored with enantiomerically pure reactants by measuring the enantiomeric excess of the dihydro aldehydes from reduction of **126** and **129**. In the racemic series, the value $(E - Z)/(E + Z)$ equals the enantiomeric excess that would be obtained using enantiomerically pure allylic alcohols. The chairlike vs boatlike transition state is not detectable in this case because there is no C_1 substituent.

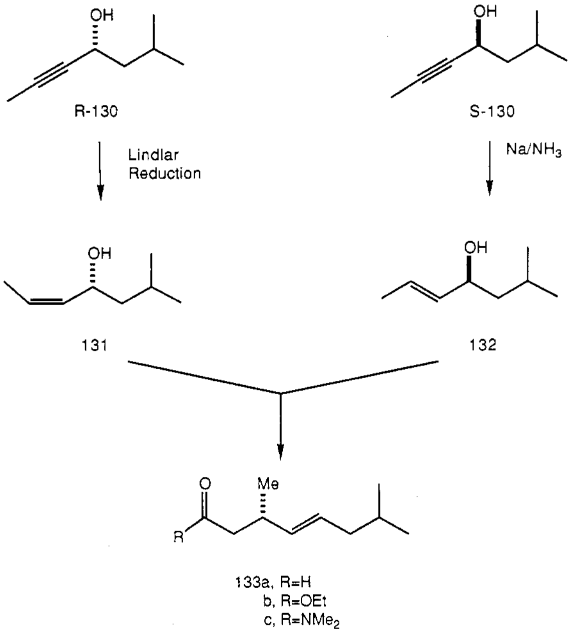
Hill has observed the "transfer of chirality" in the vinyl ether rearrangement of enantiomerically pure cyclopent-2-en-1-ol.[91a] The Eschenmoser and Johnson variants with enantiomerically pure (*E*)-pent-3-en-2-ol give products with 90% retention of enantiomeric purity as determined by optical rotation.[91b,c,92]

An ingenious, enantioconvergent variation on this theme has been executed by Chan.[93a] The enantiomers of propargyl alcohol **130** are prepared by resolution. The *R* enantiomer is reduced to the (*R,Z*)-allylic alcohol **131** while the *S* enantiomer is converted to the (*S,E*)-allylic alcohol **132**. Rearrangement to form the aldehyde, ester, or amide **133** occurs with "chirality transmission" of 94–99%. Thus, the (*R,Z*)-olefin exposes the *re* face while the (*S,E*)-olefin invokes the same *re* face, affording a single enantiomer, the (*S,E*)-olefin **133**. Clearly, the other enantiomer, (*R,E*)-**133**, is accessible by exchanging the reduction procedure for each enantiomer of **130**.[94]

The advent of the Sharpless kinetic resolution procedure[95] and the Midland asymmetric reduction of α,β-acetylenic ketones[96] has made a variety of secondary allylic alcohols readily available in both enantiomeric forms, thereby obviating the use of classical resolution.

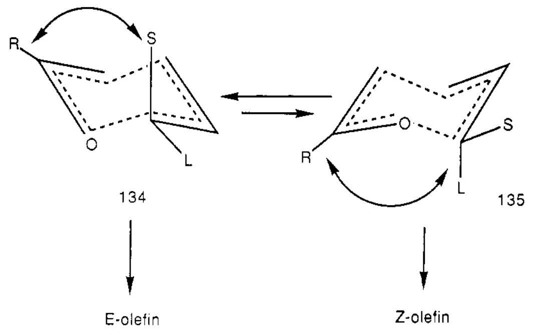
SCHEME VI

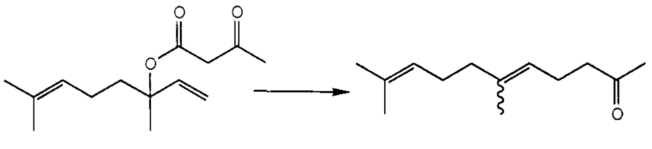




4. Tertiary Allylic Alcohols

Tertiary allylic alcohols fail to give trisubstituted olefins with high selectivity. The transition states **134** and **135** are nearly isoenergetic when the substituents S (small) and L (large) are not branched. The lack of selectivity is present even when C_2 is substituted.

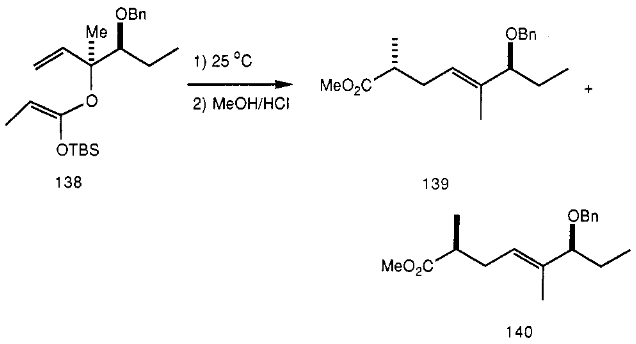




As an example, linalool acetoacetate (**136**), when subjected to the Carroll rearrangement, gives a 54:46 E:Z ratio of olefinic ketones **137**.[97] A similar ratio is realized with linalool using the Marbet–Saucy conditions (2-methoxypropene).[15a,16] Rearrangement of (Z)-silyl ketene acetal **138**, which is derived from a tertiary allylic alcohol bearing an α-branched "large" group and a methyl, provides a 7:1 ratio of esters **139** and **140**, respectively.[98] The olefin geometry is exclusively of the E geometry which requires the branched group to occupy an equatorial position in the transition state. The ratio of diastereomers is in accord with the enolization stereoselectivity.[99]

5. Ring-Bearing Substrates

Thus far the stereochemical discussions have focused upon rearrangements wherein neither olefin is contained in a ring, i.e., acyclic substrates. In ring-bearing allyl vinyl ethers, the boatlike transition state can be the major, if not exclusive, pathway for rearrangement.

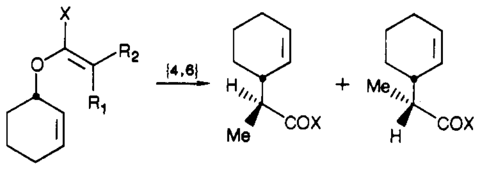


Before proceeding, it is worthwhile to consider a mnemonic device to describe various ring systems. The carbons (see structure **3**) to which the tether bridging the pericyclic array is attached are expressed in the form {m,n;o,p;...}. Thus, acyclic system **138** → **139** would be designated as a {0,0}, **86** → **87** a {4,6}, and **54** → **53** a {1,6}-rearrangement.

Bartlett and Pizzo[68d] have investigated the {4,6}-rearrangement illustrated in Table II with several propionate equivalents. Entries 1–4 involve routes that control C_1 stereochemistry; entry 5 does not. Entries 1 and 2 permutate two control elements, vinyl group geometry, and transition state, thereby providing the same major isomer. Entry 3, wherein the vinyl group has predictable Z geometry,[72] partitions equally between the chairlike and boatlike transition states. The ynamine experiment suggests high E selectivity in the formation of the vinyl group and a strong preference for the boatlike transition state as any (Z)-olefin would cause erosion of stereoselectivity.

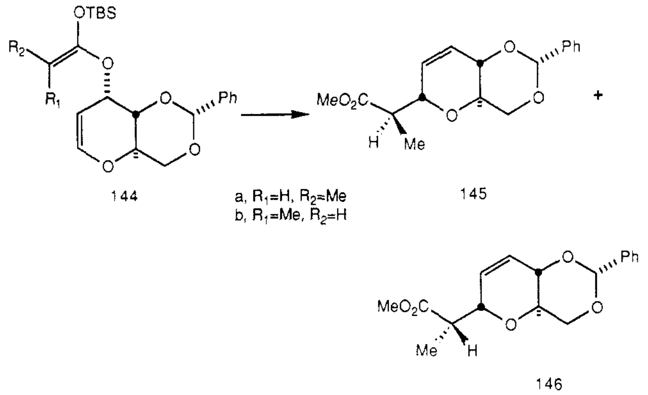
Ireland and his collaborators have examined the stereochemical course of the {4,6}-rearrangement of a number of carbohydrate-derived pyranoid and furanoid glycals as a prelude to the synthesis of complex natural products. (Z)-O-Silyl ketene acetal **144a**, derived by deprotonation of the propionate ester with lithium hexamethyldisilazide (LiHMDS, a reagent equivalent to 23% HMPA–THF for the generation of Z OLi enolates),[100] rearranges to provide ultimately a 90:10 mixture of esters **145** and **146**, respectively, wherein the boatlike transition state dominates. However, (E)-O-silyl ketene acetal **144b** gives a 65:35 ratio of the two diastereomers, with ester **145** still predominating, re-

TABLE II. Chair vs Boat Transition States in Cyclohexenol Derivatives



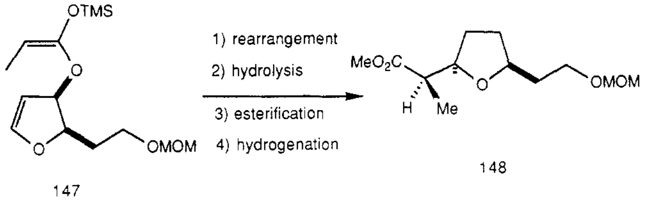
entry	method	X	R_1	R_2	142/143	favored TS
1	LDA/THF	OTBS	Me	H	85/15	chair
2	LDA/THF, 23% HMPA	OTBS	H	Me	75/25	boat
3	orthoamide	NEt_2	Me	H	50/50	neither
4	ynamine	NEt_2	H	Me	>90/10	boat
5	orthoester	OEt	(Me, H)		70/30	???

quiring the chairlike transition state to be slightly favored. In a related example, the (*E*)-*O*-silyl ketene acetal of the furanoid glycal **147** (from LDA deprotonation) gives principally (86–89% selectivity) stereoisomer **148** via a boatlike transition state.[101]



144 a, R_1=H, R_2=Me
b, R_1=Me, R_2=H
145

146

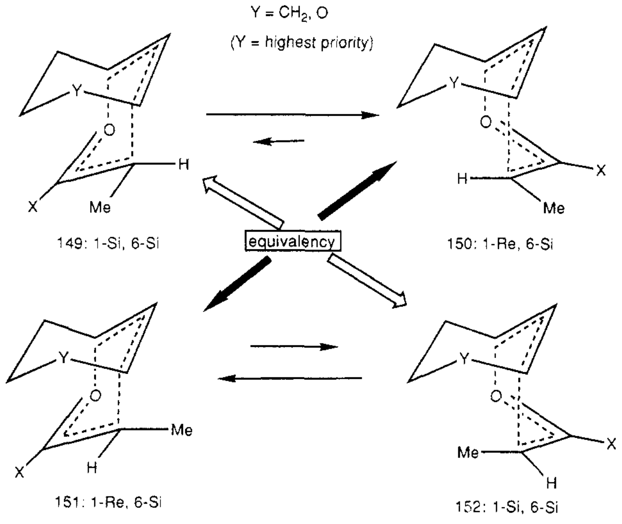


147 148

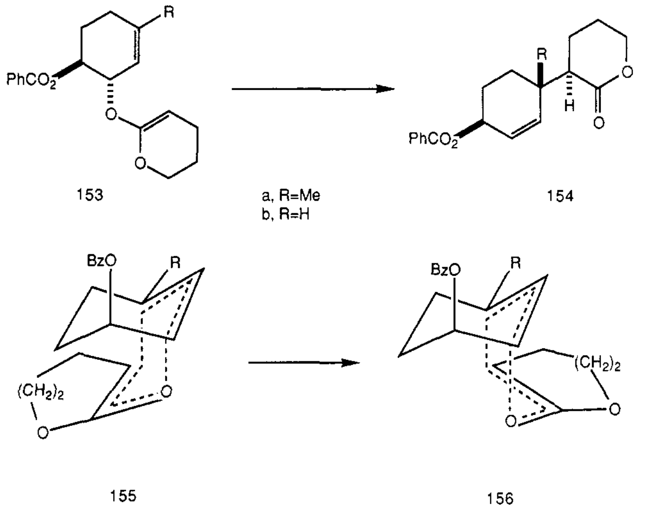
The Bartlett[68d] and Ireland[100,101] studies have been rationalized for the 6-membered ring case as is illustrated in Scheme VII. Chairlike transition state **149** is disfavored relative to the boat **150** as the methyl and X groups interact with ring substituents. The chairlike transition state **151** is slightly favored over the boat **152** as the steric interactions of the methyl group with the ring in **152** are seemingly greater than the interactions experienced by the X substituent in **151**. Once again, the change of two stereocontrol factors produces the same diastereomer.

Perhaps the most dramatic example of the intercedence of the boatlike transition state comes from Lythgoe's elegant application of the Claisen rearrangement to syntheses in the vitamin D field.[102] Ketene acetals **153a,b** of the {1,2;4,6}-type, whose vinyl olefins are perforce of the *E* geometry owing to the presence of the ring, rearrange exclusively through the boatlike transition state. The substituents of conformation **149**, having been transformed into the ring of **155**, exacerbate the steric interactions and allow only the boatlike transition state **156** to prevail.

SCHEME VII



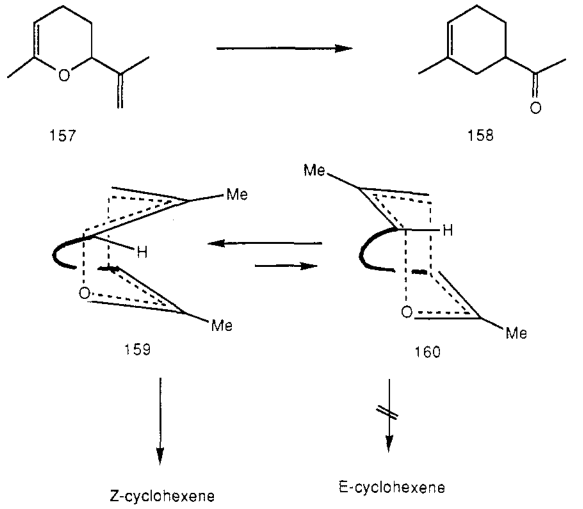
149: 1-Si, 6-Si
150: 1-Re, 6-Si
151: 1-Re, 6-Si
152: 1-Si, 6-Si



153 a, R=Me
b, R=H
154

155 156

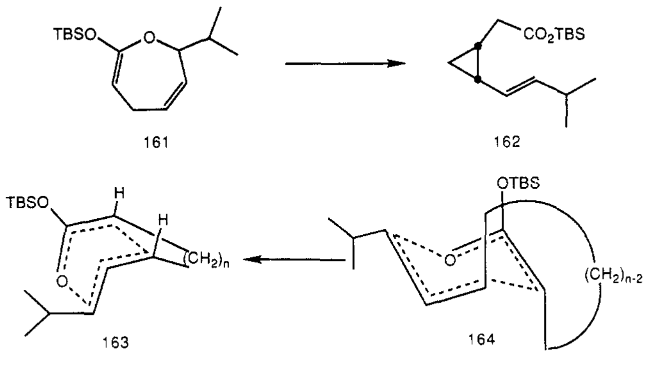
Conformational restraints on the transition state can be observed in both the {1,4}- and {1,6}-rearrangements. The former case, the operational equivalent of a "meta-Diels–Alder reaction" (**157** → **158**) when the tether is two carbons in length,[103] is constrained to proceed through boatlike transition state **159**, as the chairlike transition state **160** would lead to a strained (*E*)-cyclohexene.



157 158

159 160

The {1,6}-rearrangement, when constrained by a short tethered chain (**54** → **53**, **56** → **55**, or **161** → **162**), can proceed with greater facility through the boatlike transition state **163** rather than the more strained chairlike transition state **164**.[104]



161 162

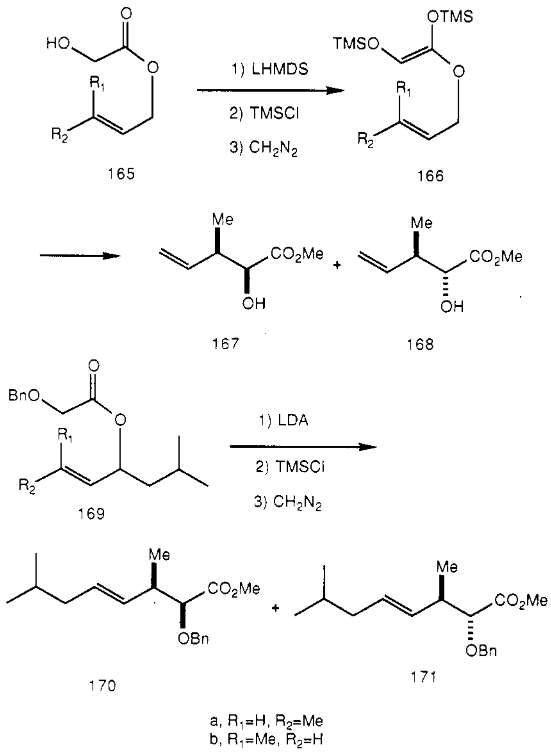
163 164

IV. Heteroatom Substituents

A. The Vinyl Group

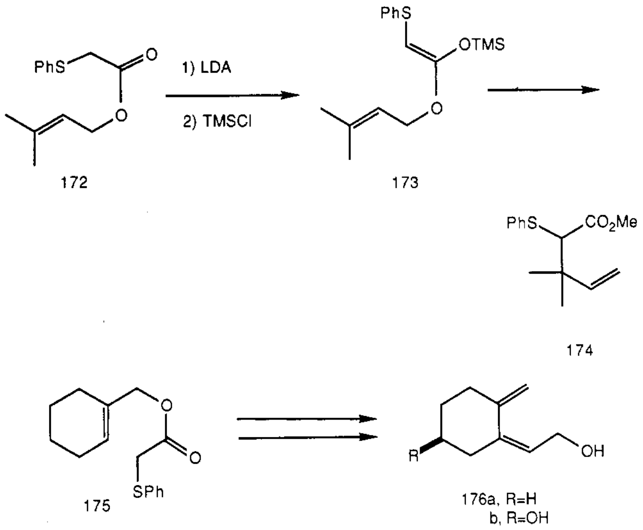
1. C$_1$ Hetero Substituents

The presence of a C$_1$-hydroxyl or -alkoxy group has been utilized to control enolate geometry. While early investigations exploited the reaction from the synthetic viewpoint,[105] a detailed analysis of the stereochemistry of the reaction awaited the studies of Bartlett[106a] on lactate and mandelate esters and, contemporaneously, Burke,[106b] Fujisawa,[106c,e,f] and Kallmerten[94a,106d] on glycolate esters. The hydroxyl or alkoxy group serves to form a chelated enolate. In the case of the α-hydroxy ester dianion, rearrangement does not proceed smoothly;[106c] but, it may be expedited by bis-O-silylation prior to rearrangement. The α-alkoxy ester enolates are also converted to their *O*-silyl ketene acetals prior to rearrangement. The (*E*)-butenyl glycolate ester **165a** affords a 98:2 ratio of esters **167** and **168**, respectively, after rearrangement, hydrolysis, and esterification. The reaction is stereospecific as the (*Z*)-butenoate gives a 2:98 ratio (**167** and **168**) of the two α-hydroxy esters.[106c] Similarly, allylic esters **169a** and **169b** rearrange with 100:1 diastereoselectivity; (*E*)-allylic ester gives principally α-benzyloxy ester **170** while **169b** provides mainly ester **171**.[94a] Worthy of note is the observation that an α-[(*tert*-butyldimethylsilyl)oxy]acetate ester forms the nonchelated *Z* lithium enolate.[94b,107]

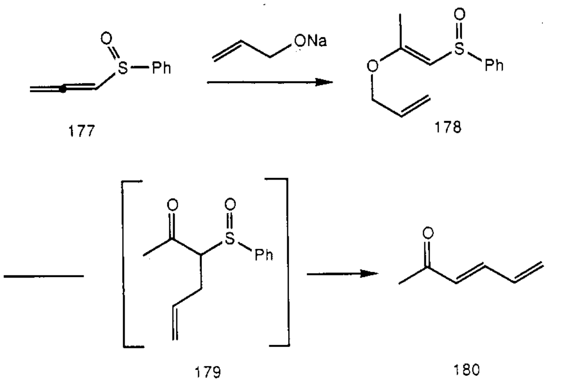


a, R$_1$=H, R$_2$=Me
b, R$_1$=Me, R$_2$=H

While the role of α-amino functionality has been explored, the reaction has been applied principally to the synthesis of unique amino acids.[108] On the other hand, α-thio substituents have proved useful as agents for the manipulation of functionality. The rearrangement of allyl α-(phenylthio)acetates, which can lead to a variety of sulfur-free products, has been reported by Lythgoe.[109] The α-phenylthio ester **174** can be oxidatively degraded to 2,2-dimethyl-3-butenal. The rearrangement of α-phenylthio ester **175** leads after several operations to (*Z*)-dienol **176a**, a model transformation for the preparation of diol **176b**, a degradation product of vitamin D$_2$.[106g]

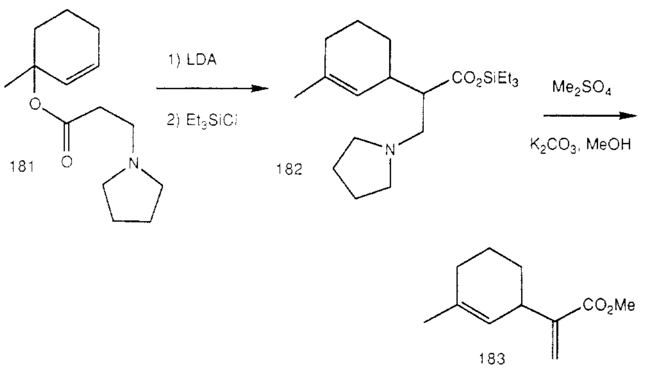


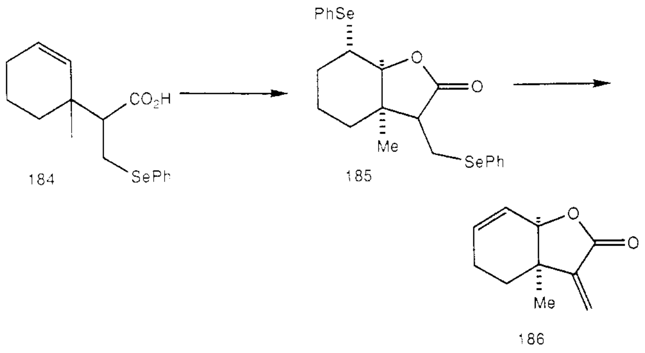
Cookson[110a] has examined the addition of allylic alkoxides to allenic sulfoxide **177**. When the isolated adduct **178** is subjected to rearrangement, subsequent sulfoxide elimination occurs, leading to dienone **180**. Similar processes have been initiated by the addition of allylic alcohols to (phenylthio)acetylene to form dienals[110b] and to phenylthio ynamines to produce α,β;β,γ-unsaturated amides.[110c]



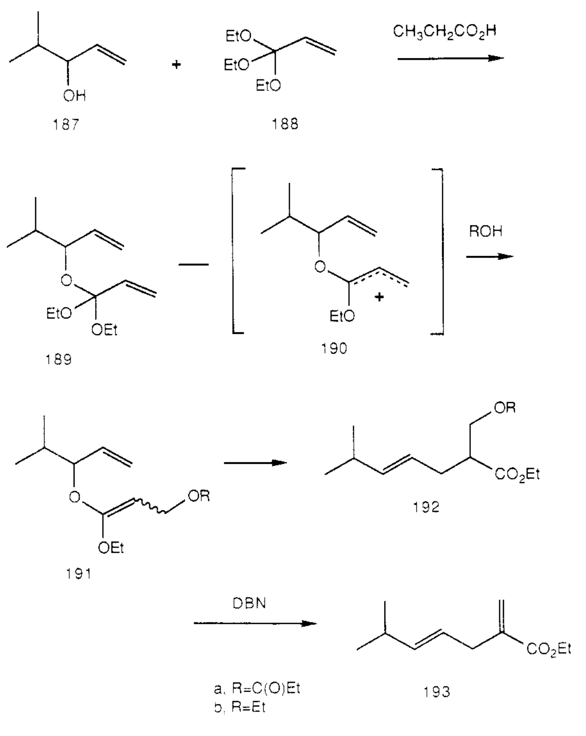
2. C$_1$ Carbon Hetero Substituents

An increase in the oxidation level at the β-position of propionate residues permits the formation of α-methylene esters and α-methylene γ-butyrolactones, the latter functionality arising through halo- and selenolactonization techniques. Still[111] has demonstrated that allyl 3-pyrrolidinopropionate **181** can be deprotonated without elimination and the resultant triethylsilyl ketene acetal rearranges to ester **182**. The silyl ester is transformed into the methyl acrylate in a single operation. Similarly, Raucher[112] has used 3-methylcyclohex-2-en-1-ol in conjunction with trimethyl 3-(phenylseleno)orthopropionate to produce acid **184**. Selenolactonization and subsequent double selenoxide elimination leads to the α-methylene γ-butyrolactones **186**. Owing to the thermal instability of the selenium-based reagent, trimethyl β-methoxyorthopropionate is a suitable substitute. The resultant β-methoxy esters undergo facile elimination to the acrylates with potassium *tert*-butoxide.[113]

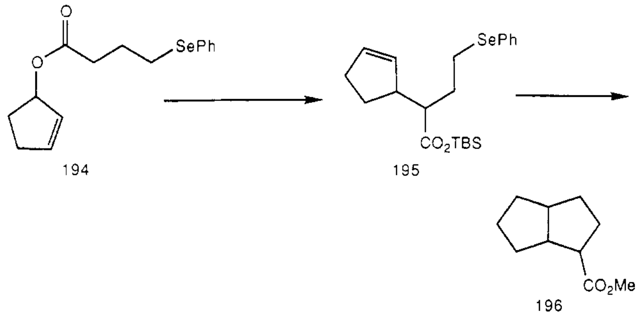




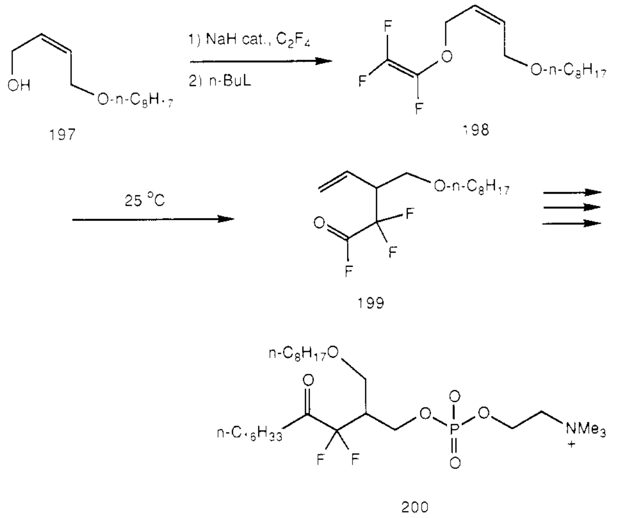
An intriguing variation on the preceding themes employs triethyl orthoacrylate (**188**).[114] The presence of the acrylate double bond in exchange product **189** prohibits elimination to a ketene acetal until a nucleophile (ethanol or propionic acid) adds to the highly stabilized carbocation **190**. The use of catalytic acid is deleterious as the cation consumes the acid (**191a**).[115] Use of excess acid (1.5 equiv) provides **192a** and **192b** in 66 and 16% yields, respectively. While the major product undergoes elimination with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), the use of potassium *tert*-butoxide, as described by Raucher,[113] should also afford acrylate **193**.



The 4-(phenylseleno)butyrate ester **194** serves as a source for radical-initiated carbocyclization. Rearrangement of the silyl ketene acetal of **194** provides the cyclopentene **195**, which is subject to reductive cyclization with triphenylstannane followed by transesterification to methyl ester **196**.[116]



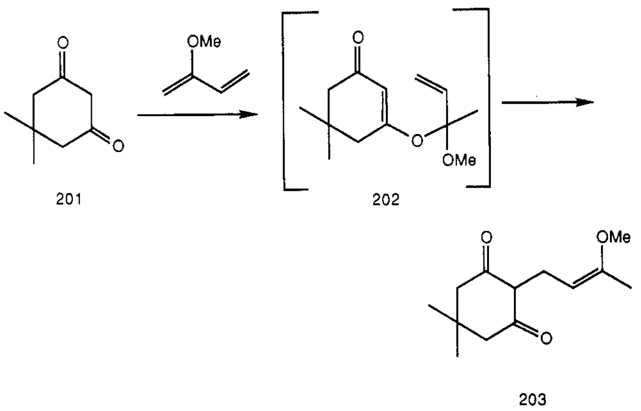
The fluorine-containing phospholipid **200**, designed as an inhibitor of cobra venom phospholipase A_2, has been prepared via rearrangement of trifluorovinyl ether **198**.[117] Not only is the vinyl ether prepared by a unique method not available in the protio series, but the rearrangement is markedly accelerated by the presence of the fluorine atoms.[48]

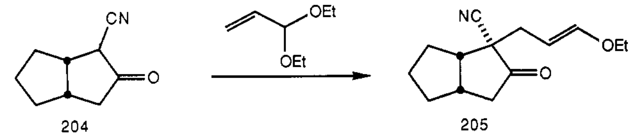


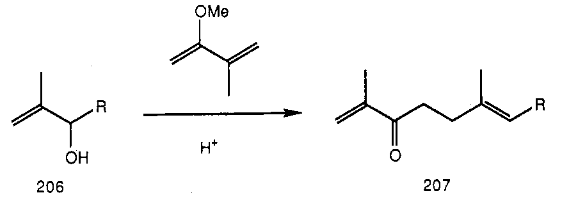
B. The Allylic Group

1. Oxygen Substituents

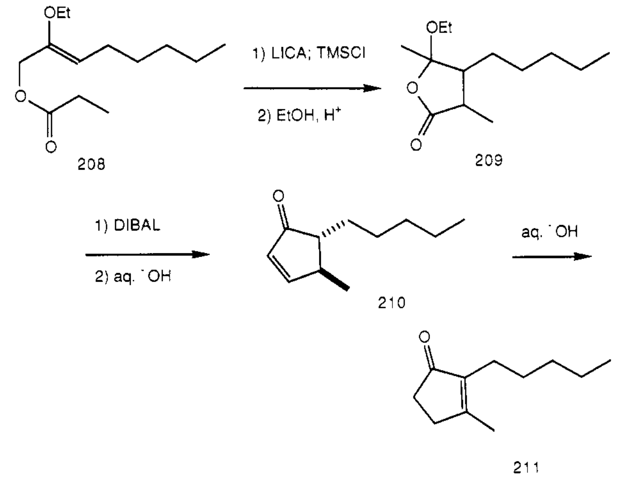
Dimedone (**201**) is in facile equilibrium with its enol, which can effect autocatalytic exchange with 2-methoxy-1,3-butadiene to generate the 4-methoxy allyl vinyl ether **202**. Rearrangement affords enol ether **203**, whose hydrolysis product is the equivalent of having effected a Michael addition of dimedone to methyl vinyl ketone.[118] Similarly, β-keto nitrile **204** reacts with the diethyl acetal of acrolein in refluxing benzene to provide enol ether **205**, with bond formation occurring on the convex face of the bicyclooctanone ring system.[119] In the transformation **201** → **203**, the 3,4 double bond of 2-methoxy-1,3-butadiene functions as an allyl component. The 1,2 double bond of the diene may also serve as a vinyl component in reactions with allylic alcohols (**206** → **207**).[25] These processes are also accomplished with ketals of α,β-unsaturated ketones.[120]



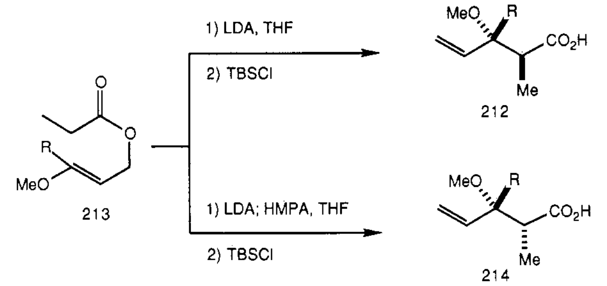




The use of C_5-oxygen-substituted allyl vinyl ethers can serve as 1,4-dicarbonyl compounds that lead to cyclopentenones via an intramolecular aldol condensation. This process had been implemented by Ireland and Mueller[21a] in their early studies on the ester enolate rearrangement. Rearrangement of vinyl ether **208**, having C_5 at a ketone oxidation level, results in the isomeric vinyl ether that undergoes facile lactonization to **209**. Generation of an intermediate hemiacetal by reduction with DIBAL and subsequent mild base treatment realizes cyclopentenone **210**; more vigorous base treatment isomerizes enone **210** to the more stable dihydrojasmone (**211**).[121]

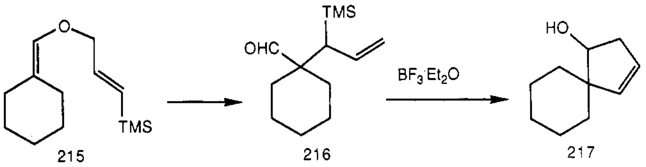


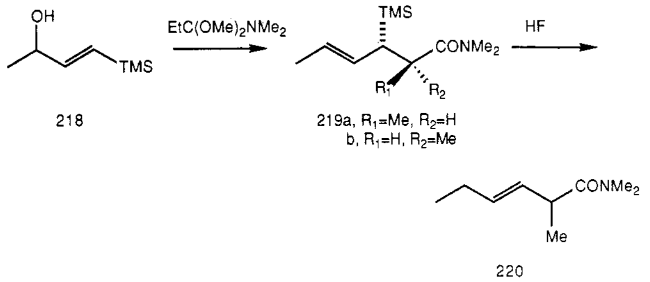
The rearrangement of systems bearing C_6-oxygen substituents has been explored by Ireland as a prelude to the synthesis of ionophores.[105c,122] The preparation of β-alkoxy alcohols and their acyl derivatives is troublesome because they are susceptible to polymerization and isomerization. The Claisen rearrangement of ester **213** (R = H, Me) is ~70–80% diastereoselective, presumably the result of a lack of control over enolate geometry. Secondary allylic alcohols in this series are extremely unstable, requiring in situ generation of the acylation products, enolization, and rearrangement. Operationally, the preparation of acids **212** and **214** is equivalent to a diastereoselective aldol condensation.

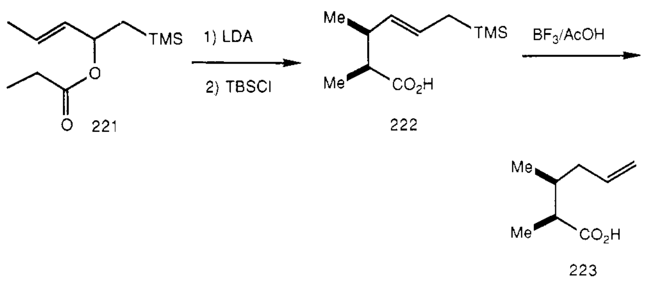


2. Silicon Substituents

The ability of silicon to direct and facilitate the reactions of olefins has led to the introduction of silicon substituents into the framework of allyl vinyl ethers. Kuwajima[123] has formed C_6-substituted allyl vinyl ether **215** in situ by the exchange of α-ethoxymethylenecyclohexane and (E)-β-(trimethylsilyl)allyl alcohol in the presence of acid. Rearrangement gives allylsilane **216**, which provides the spiro-β,γ-unsaturated alcohol **217** upon Lewis acid catalysis. In a related experiment,[124] the propionamide acetal rearrangement of allylic alcohol **218** affords amides **219a** and **219b** in a 3:1 ratio, respectively. Protodesilylation of either isomer gives the β,γ-unsaturated amide **220**. The formation of alcohol **217** and amide **220** involves the migration of the γ,δ-double bond from the initial Claisen products toward the carbonyl carbon.

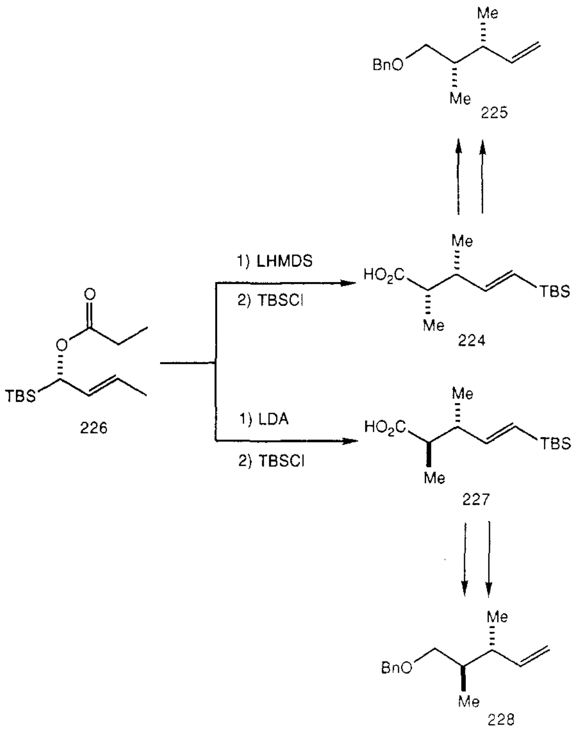






The olefin migration may be practiced in the opposite sense. Rearrangement of the (E)-O-silyl ketene acetal of ester **221** occurs with 90% stereoselectivity, providing acid **222** as the major diastereomer. Acid-catalyzed migration of the olefin away from the carbonyl realizes the δ,ϵ-acid **223**.[125,126] A severe erosion of stereochemistry has been observed when the rearrangement of the allylic alcohol component of **221** is conducted as its Eschenmoser variant,[127] similar to the selectivity in the formation of **219a** and **219b**.

A silicon substituent at C_4 serves to introduce asymmetry into achiral allylic alcohols. Propionate ester **226** is prepared from the resolved alcohol and subjected to stereospecific rearrangement. Reduction, alkylation, and protodesilylation of acids **224** and **227** give enantiomerically pure ethers **225** and **228**, respectively.[128]

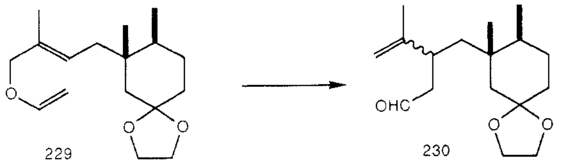


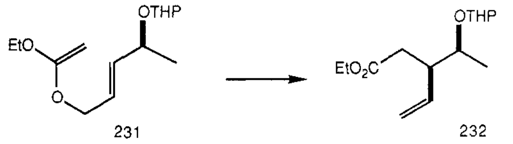
V. Remote Asymmetry

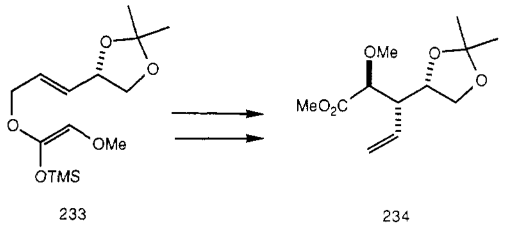
A. Acyclic Substrates

The only asymmetric effects discussed thus far have been related strictly to the C_4 carbon, an integral part of the Claisen rearrangement framework. But what of remote asymmetry and its ability to induce diastereoselective reactions?

The rearrangement of allyl vinyl ether **229**, wherein the remote asymmetry at the quaternary center (C_6 β-substituent) renders the faces of the olefin diastereotopic, shows no sign of diastereoselection; both isomers **230** are produced in equal amounts.[129] When the center of asymmetry is located vicinal to the developing center of asymmetry, modest selectivity is observed. Thus, ketene acetal **231**, derived from (*S*)-ethyl L-lactate,[130] rearranges with 3:1 diastereoselectivity (**232**, major diastereomer), while D-glyceraldehyde acetonide derived silyl ketene acetal **233** affords principally **234** (75% ds).[131,132] In each instance, the predominant stereoisomer has the same relative stereochemistry at the β- and γ-positions and has been suggested to be in accord with Felkin[133] and Houk[134] transition-state models.[135]





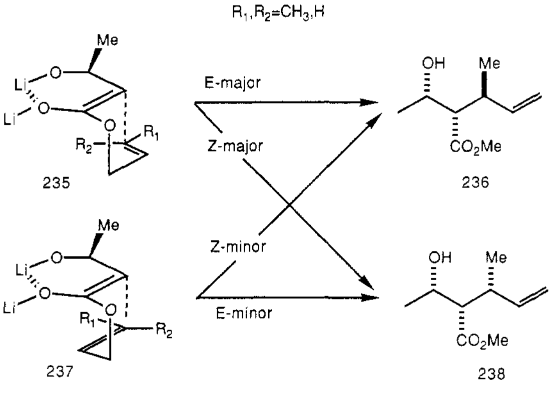


Kurth has examined the rearrangement of the dianion of the (*E*)- and (*Z*)-butenyl esters of β-hydroxybutyric acid in THF (Scheme VIII) and has applied the reaction to the synthesis of the mycotoxin botryodiplodin.[136,137] In principle, the reaction can provide four diastereomers; only two are detected. Bond formation cis to the methyl group of the ring formed by chelation is inoperative on steric grounds while bond formation trans to the methyl occurs via the chairlike and the boatlike transition states. The *E* isomer provides an 81:19 mixture and the *Z* isomer gives a 15:85 ratio of β-hydroxy esters **236** and **238**, respectively. In both instances the chairlike transition states predominate.[138] The availability of enantiospecific enzymatic reductions of β-keto esters[139] makes this rearrangement amenable to the preparation of enantiomerically pure products. Indeed, the hydroxyethyl unit functions as a "chiral auxiliary"[140] as it can be oxidized to a ketone and the resultant β-keto ester can undergo Haller–Bauer deacylation or decarboxylation.[138,141]

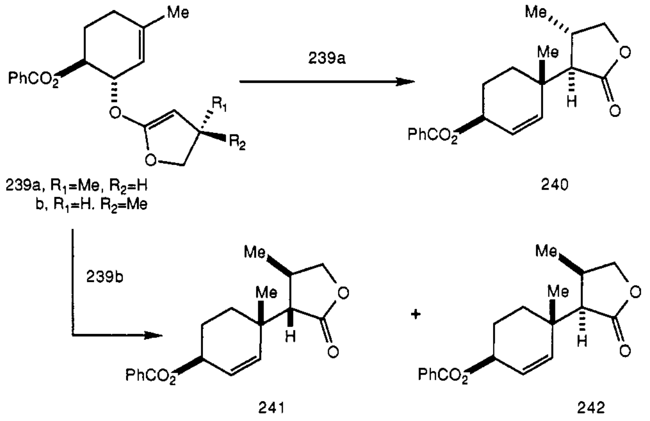
B. Ring-Bearing Substrates

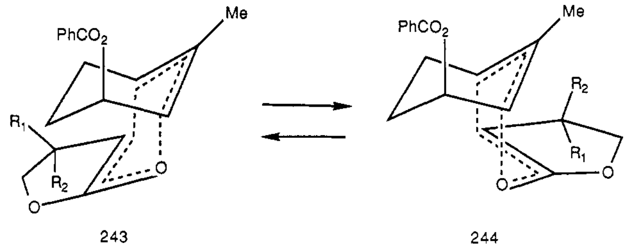
The effect of the chelated ring discussed in the previous section leads logically to the influence of remote ring substituents on stereochemistry. A more elaborate version of the Lythgoe experiments[102b] (**153** → **154**) involves the union of an enantiomerically pure reactant, 6(*S*)-(benzoyloxy)-3-methylcyclohex-2-en-1(*S*)-ol, with the *R* or *S* enantiomers of 2,2-diethoxy-3-methyltetrahydrofuran. Ketene acetal **239a**, derived from the

SCHEME VIII



(*S*)-ortholactone, rearranges to give exclusively diastereomer **240** through the boatlike transition state. However, the diastereomeric reaction with the (*R*)-ortholactone via **239b** affords a 70:30 mixture of diastereomers **241** and **242**, respectively, with the chairlike transition state leading to the major isomer. The transition state for the rearrangement of these systems normally favors the boat **156** (no substituents on the heterocyclic ring). The presence of the substituent in **239a** (R_1 = Me) serves only to destabilize further the chairlike transition state **243** relative to the boatlike transition state **244**. On the other hand, **239b** possesses the methyl substituent in a sterically demanding position in the boatlike transition state **244** that is mitigated in the chairlike transition state **243**. The preference for the chairlike transition state in the latter example requires the substituent effect to be more influential than the chair–boat factor.

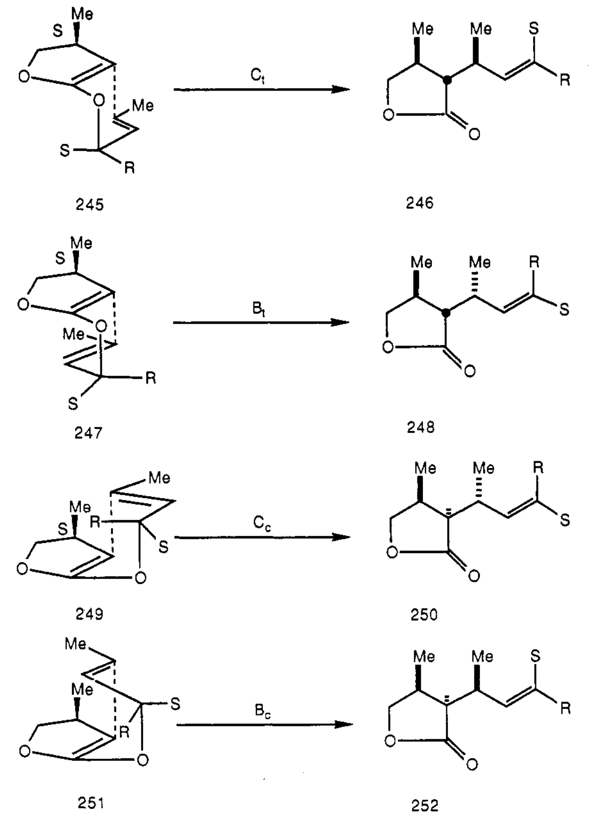




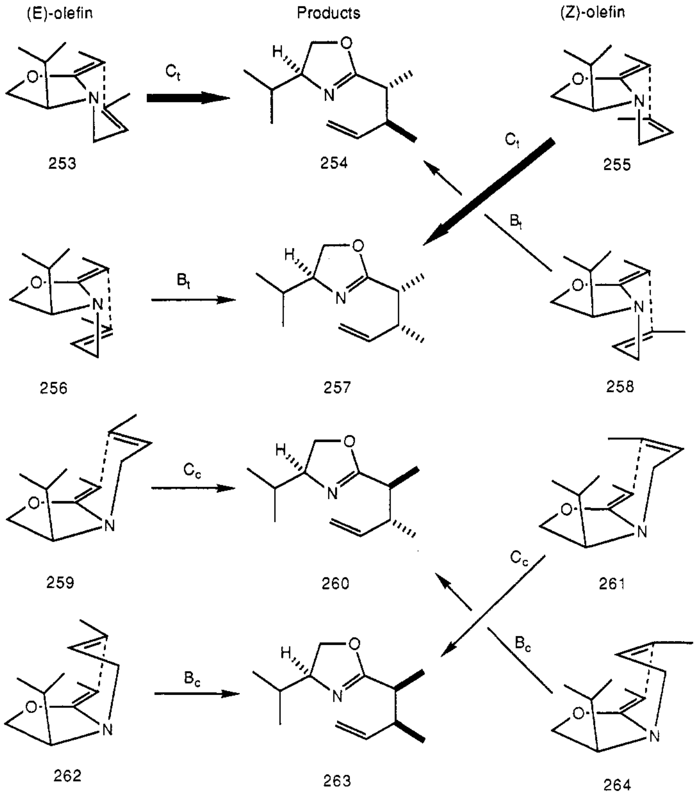
In this laboratory, the reaction of the enantiomers of the ortholactones of 3-methyl-γ-butyrolactone with enantiomerically pure secondary (*E*)-allylic alcohols has been studied.[142,143] Scheme IX provides details on the stereochemistry of these reactions. The transition states **245**, **247**, **249**, and **251** represent the four possible permutations of olefin facial selectivity. The four control elements are chair (C) vs boat (B) and trans (t) (to the methyl group) vs cis (c). The four products are derived from the (*S*)-ortholactone with the R and S substituents representing the absolute configuration of the allylic alcohol residue when an isopropyl group occupies the R or S position. When the (*R*)-alcohol is employed, only the lactone **246** is obtained. Transition states **247** and **249** are precluded as they lead to products **248** and **250**, respectively, bearing (*Z*)-olefins. While boatlike transition state **251** would lead to an (*E*)-olefin, steric interactions make this pathway less favorable than **245** → **246**. Indeed, when R = S = H, (i.e., (*E*)-2-buten-1-ol), no product having the stereochemistry of **252** is formed.

Alternatively, the (*S*)-alcohol excludes transition states **245** and **251**; transition states **247** and **249** provide lactones **248** and **250**, respectively, in a 55:45 ratio. In spite of this mixture, either diastereomer is able to be prepared from the other by chemical means.

SCHEME IX



SCHEME X



The aza Claisen rearrangement,[144] in conjunction with an amino acid derived type I chiral auxiliary, has been employed by Kurth[145] to provide 2′- and 3′-alkyl, and 2′,3′-dialkyl 2-substituted oxazolines.[146] The starting

N-allyl-*N*,*O*-acetals are prepared by N-alkylation of the 2-ethyloxazoline with the requisite allylic tosylate followed by stereoselective *n*-butyllithium deprotonation of the oxazolinium salt. The removal of the oxazoline moiety liberates an enantiomerically pure carboxylic acid. Scheme X illustrates this principle for the formation of the four possible diastereomeric 2′,3′-dimethyl-2(*S*)-oxazolines. When an (*E*)-butenyl residue is employed, the four operative transition states **253**, **256**, **259**, and **262** lead to products **254**, **257**, **260**, and **263**, respectively, in a ratio of 81:15:2:2. Thus, the isopropyl group is an effective control element for the facial selectivity of bond formation at the oxazoline double bond (96%, facial excess (fe) = 92%),[147] while the chair vs boat selectivity is not as effective (fe = ~67%). When the (*Z*)-butenyl group is employed, the products **254**, **257**, **260**, and **263** are formed in a ratio of 14:82:2:2, respectively. While the energetics of the transition states remain the same as for the (*E*)-olefin, the major product **257**, arising through the C_t transition state, provides a product with the opposite configuration at the β-position of the chain from that which was obtained in the (*E*)-butenyl series.

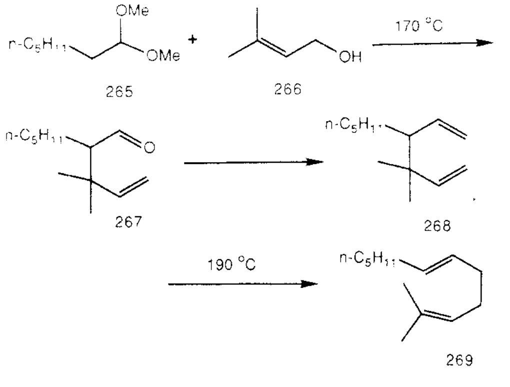
The synthetic success of type I chiral auxiliaries is dependent on the facility with which diastereomers **254** and **260** can be separated from **257** and **263** and the ease with which the members of each pair (or their hydrolysis products prepared without epimerization) can be separated from one another.

VI. Consecutive Rearrangements

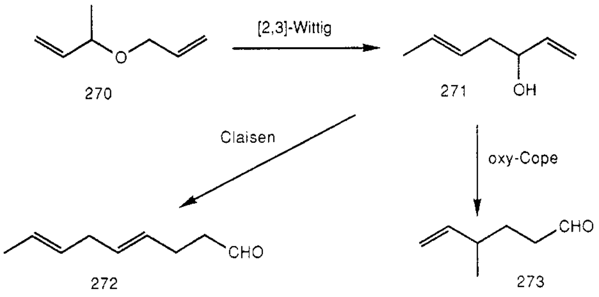
The Claisen rearrangement and its associated sigmatropic processes create the opportunity for the design and execution of consecutive rearrangements. These processes may be divided into three categories: sequential, tandem, and iterative. A sequential rearrangement requires derivatization of a rearrangement product prior to a subsequent rearrangement. A tandem rearrangement has all the atoms for consecutive rearrangements installed in the starting substrate prior to the first rearrangement. An iterative rearrangement requires a number of transformations to be conducted on a rearrangement product prior to a subsequent "identical" rearrangement.[148]

A. Sequential Rearrangements

Cookson and Hughes[149] have performed a sequential Claisen and Cope rearrangement in preparing the diene **269**. When the acetal **265** is heated with β,β-dimethylallyl alcohol (**266**) in mesitylene with *o*-nitrobenzoic acid as a catalyst, rearrangement of the intermediate allyl vinyl ether produces the aldehyde **267**. Isolation of the aldehyde and subsequent Wittig methylenation provide the 1,5-diene, which undergoes a Cope rearrangement to the more substituted, thermodynamically more stable diene **269**.

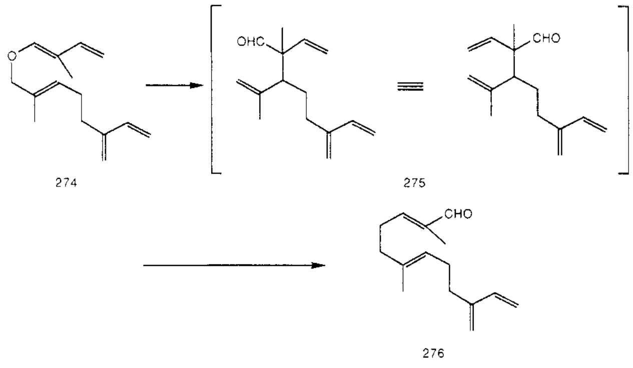


As an outgrowth of their extensive studies on the [2,3] Wittig rearrangement of diallyl ethers,[54] Nakai and his collaborators[150] have executed a sequential [2,3] Wittig–Claisen rearrangement. Selective metalation of diallyl ether **270** at the allyl residue followed by rearrangement produces dienol **271**. Subsequent Claisen rearrangement provides the 4,7-dienal **272**. The sequence is also successful when the Johnson and Ireland variants are employed. Dienol **271** provides the opportunity for an oxy-Cope rearrangement to unsaturated aldehyde **273**. The oxy-Cope process provides an unsaturated aldehyde bearing one more carbon between the functional groups than is obtained in the Claisen rearrangement.



B. Tandem Rearrangements

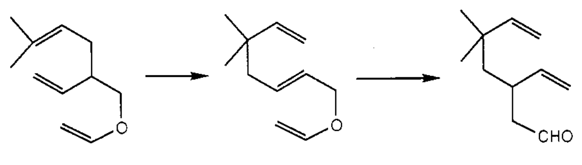
The seminal studies on aliphatic,[151] tandem rearrangements—namely, the Claisen–Cope rearrangement, have come from the laboratories of Thomas[152] and Cookson.[153-155] These investigations are best exemplified by the synthesis of β-sinesal (**276**), an essential oil of the Chinese orange.[152a] The dienyl ether function of **274** is generated from (*E*)-1-ethoxy-2-methyl-1,3-butadiene with mercuric ion catalysis. The intermediate aldehyde(s) **275** from Claisen rearrangement undergo Cope rearrangement to form the (2*E*,6*E*)-β-sinesal (**276**). The presence of the 6(*E*)-olefin requires the chain bearing the 1,3-diene of **275** to be equatorial in the transition state for the Cope rearrangement. The 2(*E*) configuration may arise either by direct means from the rearrangement or by isomerization of any 2(*Z*)-olefin produced. The success of the tandem [3,3] sigmatropic process requires a substituent (in this instance a methyl group) at C_1 of allyl vinyl ether **274** to avoid conjugation of the β,γ double bond of **275**, which



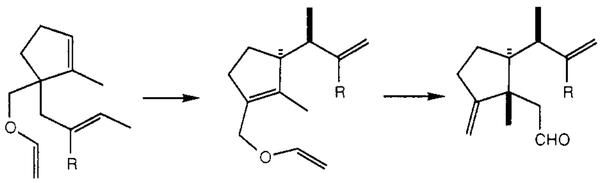
would short-circuit the Cope rearrangement.[153b,155b] For the purpose of synthetic planning, the reaction should be recognized as a formal γ-allylic alkylation of an (*E*)-2-butenal.

The tandem Claisen–Cope rearrangement has two other important characteristics. First, the Claisen rearrangement, which generally has the lower activation energy, precedes the Cope rearrangement, thereby creating the opportunity for the isolation of intermediates. Second, the success of the reversible Cope rearrangement depends upon the judicious choice of target substrate because the more stable product is the 1,5-diene having the more substituted double bonds.

In the context of several synthetic projects, the reverse order of these sigmatropic processes—namely, the Cope–Claisen rearrangement has been explored in this and other laboratories. An unfavorable equilibrium in the Cope step would be inconsequential as the irreversible Claisen rearrangement would drive the reaction; no intermediates would be anticipated. The Cope rearrangement of triene **277** to **278** is a thermodynamically unfavorable process that is driven to aldehyde **279** by the Claisen rearrangement. Similarly, the Cope rearrangement of trienes **280** (R = H, Me) gives rise to **281**, the stereochemistry of which is created through a chairlike transition state. The olefin facial selectivity of the Claisen rearrangement (**281** → **282**) occurs principally trans to the substituent at the newly created center of asymmetric of the ring to afford aldehyde **282**. The process permits the generation of three contiguous, stereodefined centers of asymmetry.[156,157]



277 278 279

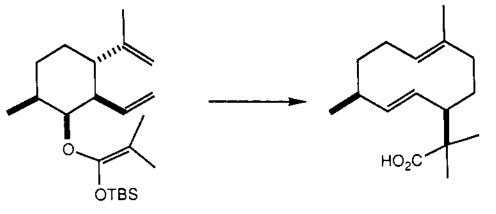


280 281 282

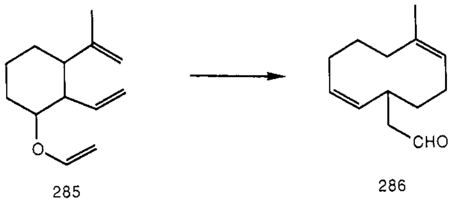
An excellent test for the tandem Cope–Claisen rearrangement is the formation of (*E*,*E*)-1,6-cyclodecadienes from the more stable 1,2-divinylcyclohexanes. Raucher[158] has successfully converted the isobutyrate-derived silyl ketene acetal **283** to the decadiene **284**. The use of the disubstituted silyl ketene acetal is critical in obtaining the desired product. Since the starting material is prepared from (*S*)-(+)-carvone, the product is obtained in enantiomerically pure form. This method has been utilized in the preparation of the sesquiterpene, (+)-dihydrocostunolide.[159] In an earlier study, three of the four diastereomers of triene **285** gave aldehyde **286** as the only 10-membered ring product.[156a,160]

C. Iterative Rearrangements

The use of 3-methoxyisoprene[84] and related ketals permits the repetitive formation of olefinic residues.

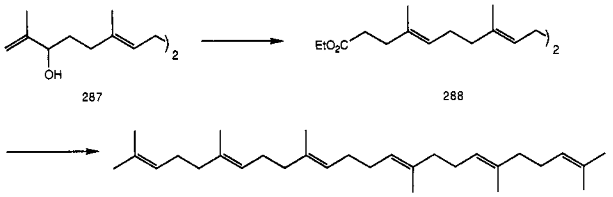


283 284



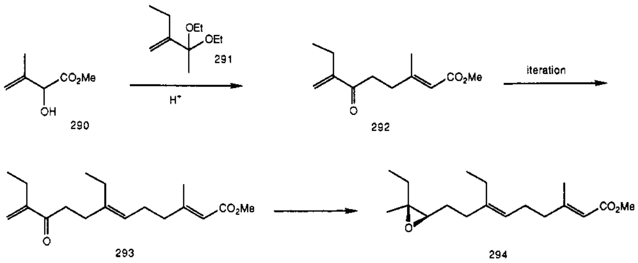
285 286

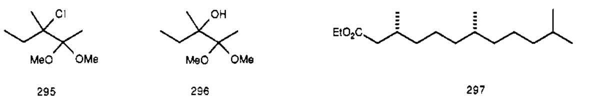
Bis(allylic alcohol) **287** (cf., **206** → **207**), prepared by the reduction of the enone, is subject to chain extension using the Johnson variant. Conversion of the terminal esters of **288** to propylidene groups provides an "inside–outside" synthesis of the symmetrical triterpene squalene (**289**), with each of the four central double bonds having their stereochemistry controlled by the Claisen rearrangement.[25]



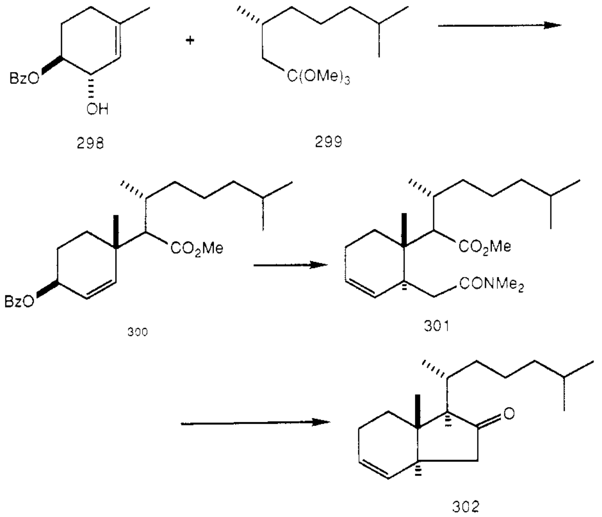
287 288 289

The C_{18}-*Cecropia* juvenile hormone (JH) (**294**) has lent itself to iterative synthesis. Olefinic ketal **291** serves as the agent for two chain extensions (**290** → **292** → **293**). The enone functionality of **293** is readily converted into JH (**294**). The iteration of **292** has also been accomplished with both enantiomers of the chiral ketals, **295**[161] and **296**,[162] which has led to the synthesis of both diastereomers and the enantiomers of the hormone. An iterative process has converted ester **133b** to ester **297**, a unit utilized in the synthesis of the vitamin E side chain.[93a,94a]





Lythgoe and co-workers[71a,102a] have employed an iterative Claisen sequence to construct the enantiomerically pure ketone **302**, an intermediate in the synthesis of tachysterol and precalciferol. The relative stereochemistry of the two oxygen functionalities of **298** sets the stereochemistry of the acetic acid residues of **301** and thereby assures the trans-fused ring system of **302**. The lack of stereocontrol adjacent to the ester group in ester **300** is inconsequential as equilibration during the Dieckmann ring closure (**301** → **302**) achieves the required stereochemistry.[163,164]



298 299

300 301

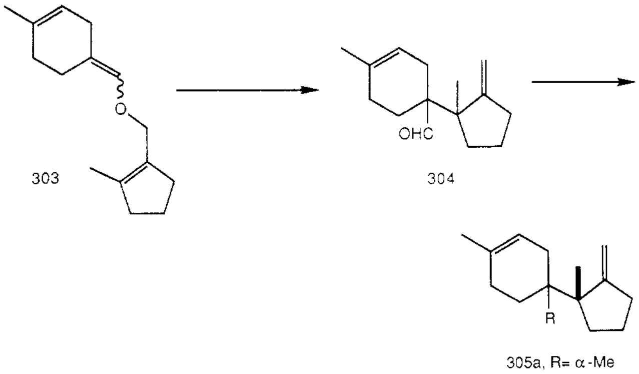
302

VII. Synthetic Applications

Although numerous synthetic applications of the aliphatic Claisen rearrangement have been discussed in previous sections to illustrate various aspects of the reaction, this section considers additional applications from the perspective of the tethered rings attending the rearrangement nucleus.

A. {1,1}-Rearrangements

This system is typified by efforts to synthesize trichodiene (**305a**), the biogenetic progenitor of the trichothecenes, via a {1,1;5,6} Claisen rearrangement. Allyl vinyl ether **303**, as an undetermined mixture of geometrical isomers, gives rise to a 1:1 mixture of aldehydes **304** and, ultimately, to the same mixture of trichodiene and bazzanene (**305b**).[165] The chairlike transition state is recognized as the dominant pathway,[166a] but the inability to control vinyl ether or ester enolate geometry[166b-d] has made this route nonselective.[167]

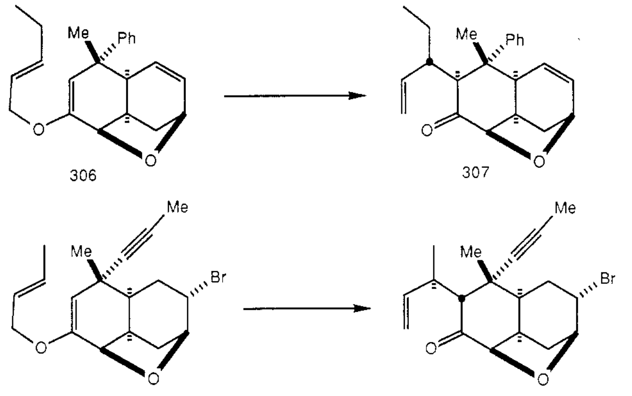


303 304

305a, R= α-Me
b, R= β-Me

B. {1,2}-Rearrangements

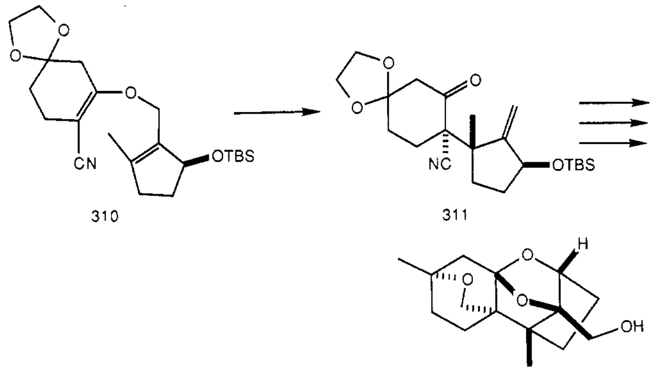
The rearrangement of the allyl enol ether of cyclohexanone to 2-allylcyclohexanone is the prototype of this group.[168] In a study related to the synthesis of the fungal phytotoxins betaenone B and stemphyloxin I, Hopkins[169] has investigated the rearrangement of allyl vinyl ethers **306** and **308**. While both rearrangements occur through the chairlike transition state, the steric bulk of the phenyl substituent in **306** directs bond formation to the concave face of the tricyclic nucleus. The less sterically demanding acetylenic residue of **308** allows bond formation to occur on the inherently more accessible convex face.



306 307

308 309

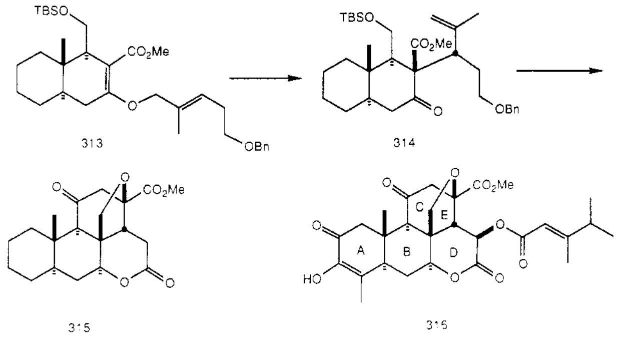
The lack of stereochemical control in the {1,1;5,6}-rearrangement of **303** → **304** has been overcome by employing a different construction of the vinyl ether residue. The {1,2;5,6}-rearrangement of nitrile **310** provides ketone **311** having vicinal quaternary centers with the desired stereochemistry of the trichodiene-derived trichothecenes. The rearrangement occurs exclusively on the face of the cyclopentene ring remote from the oxygen substituent with 16:1 chair/boat selectivity. Ketone **311** serves as an intermediate in the synthesis of neosporol (**312**).[170]



310 311

312

In a model study directed toward the synthesis of the quassinoid bruceantin (**316**), the {1,2}-rearrangement of unsaturated ester **313** results in bond formation on the α-face of ring B, remote from the angular methyl group through a chairlike transition state. With the stereochemistry set in the side chain, the sequential construction of rings C, E, and D is accomplished to provide pentacyclic lactone **315**.[171,172]

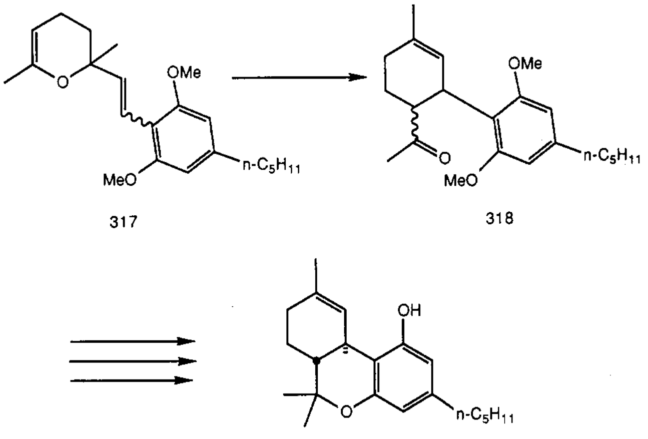


313 314

315 316

C. {1,4}-Rearrangements

The {1,4} group was discussed earlier (III.D.5) in the context of a "meta-Diels–Alder reaction",[103] a method that creates carbocycles from heterocycles. Pinnick[173] has employed the {1,4}-rearrangement in the synthesis of the cannabinoid, *trans*-Δ^1-THC (**319**). A 1:1 mixture of styrenes **317** gives the same mixture of ketones **318**. Remarkably, the reaction proceeds at ambient temperature as opposed to the elevated temperatures (200–400 °C) often required for this class of rearrangement. *O*-Methoxystyrene **317** appears to be ideally suited for dissociation at the allylic ether bond, suggesting the possibility of extensive bond breaking in the transition state, or even the intercedence of an ionic process.



317

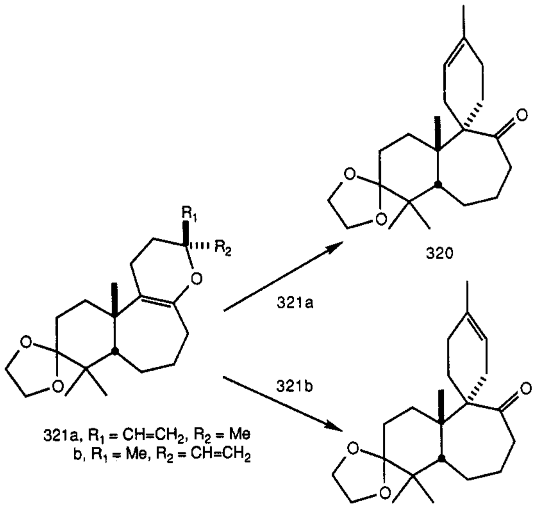
318

319

In an investigation directed toward the total synthesis of aphidicolin (**322**), Ireland and Aristoff[174] have realized the stereospecific {1,2;1,4}-rearrangement of allyl vinyl ethers **321**. While olefin **320** provides the correct substitution pattern to solve the synthetic problem, isomer **323** is suitable as an intermediate in the synthesis for the closely related stemodane skeleton. This good fortune is not always withstanding, and the success of such a venture is predicted upon the stereoselective introduction of the substituents R_1 and R_2 in allyl vinyl ethers such as **321**. In this instance, a hetero Diels–Alder reaction between methyl methacrylate and the appropriate *exo*-methylene α,β-unsaturated ketone is regioselective, but not stereoselective.

Danishefsky and his collaborators have extended the {1,4}-rearrangement to silyl ketene acetals. Thus, the lactone **324** rearranges as its silyl ketene acetal through the obligatory boatlike transition state[175a] to give rise to acid **325**. Subsequent oxidative decarboxylation provides the sesquiterpene widdrol (**326**).[175b,176]

The ionophore antibiotic indanomycin (X-14547A, **327**) provides two opportunities for the application of the {1,4}-rearrangement. The obvious application is the construction of the perhydroindane ring system. Burke[177] has utilized the Danishefsky approach to this end, but not without a surprise. Rearrangement of silyl ketene acetal **328** at 135 °C affords a mixture of four diastereomers (31:9:5:1) of **329**, the major component of which is the product allegedly arising from the {1,4}-rearrangement (**329**, α-H, α-Et). However, at 95–100 °C, the triene **330** is isolated, thermolysis of which at 135 °C produces the same mixture of diastereomers. A similar result is obtained with the diastereomer of **328** that is epimeric at the vinyl center, although a single ester **329** (β-H, α-Et) is realized. An additional caveat is warranted. Since the source of the lactones for these reactions is invariably derived from the 1,2-addition of a vinyl organometallic to an aldehyde



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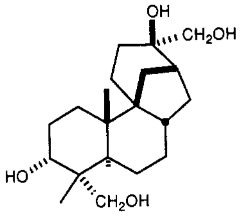

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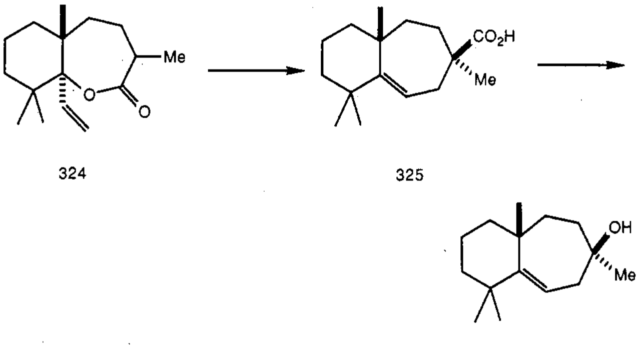

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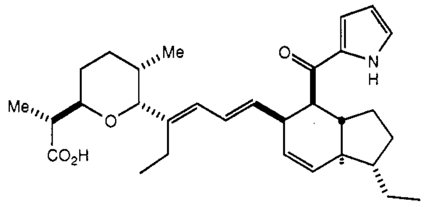

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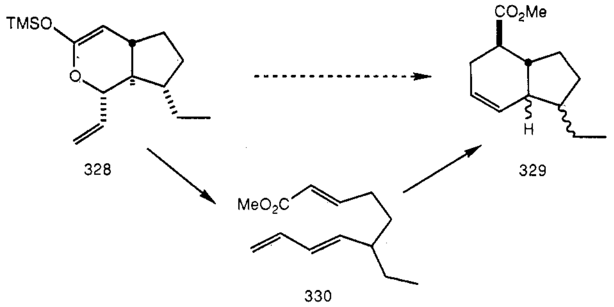

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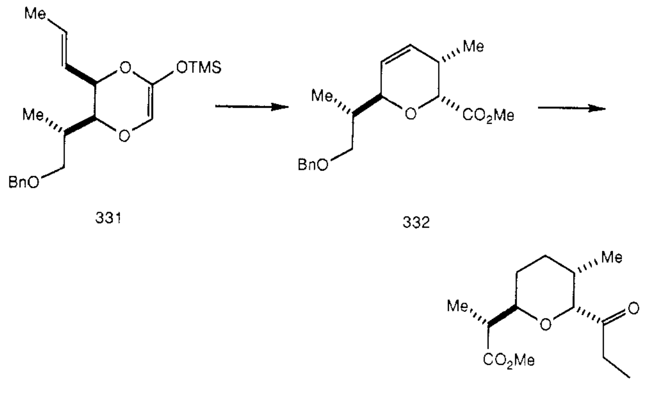
followed by lactonization, it is important to control the stereoselectivity of the addition, whether or not the Diels–Alder pathway is operative.[175c]



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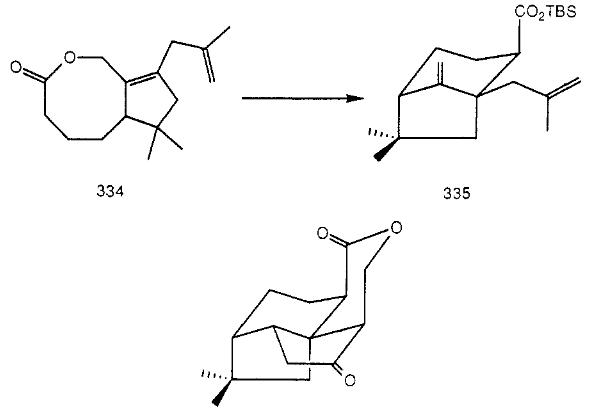
Although the propionic acid residue in the "left-wing" of indanomycin seemingly dictates the Ireland strategy (**144** → **145** + **146**), an alternative analysis reveals that the ester **332** is accessible via the {1,4} route.[178] Its conversion to ketone **333** creates a viable synthon for further elaboration. The caveat offered above is also applicable to the formation of the lactone precursor to **331**.[178c]

D. {1,5}-Rearrangements

The {1,5}-rearrangement results in a two-atom ring contraction. In an approach to the synthesis of quadrone (**336**), Funk[179] has demonstrated that fused lactone **334**, by way of its silyl ketene acetal, gives rise to the bridged, ring-contracted ester **335**. Mechanistic restraints require the ester group to be axial to the newly formed ring, thereby setting the stage for further transformations directed toward quadrone.

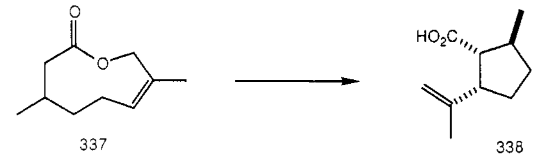


334 335 336

E. {1,6}-Rearrangements

The {1,6}-rearrangement permits ring contraction by four atoms wherein the newly formed ring bears vicinally substituted vinyl and carbonyl substituents. Thus far, the examples studied have been medium to macrocyclic lactones for which there are ample methods for their synthesis. Funk[180] and Knight[181] have provided the seminal contributions to this class of Claisen rearrangement.

In a synthesis of the iridoid iridomyrmecin (**339**), Funk[104] has demonstrated that the key intermediate **338** is formed upon rearrangement of the (*E*)-*O*-silyl ketene acetal of lactone **337**. The boatlike transition state **340** ($n = 1$), bearing the tethered chain in a cis relationship, accounts for the observed stereochemistry. For (*E*)-*O*-silyl ketene acetals, the cis-fused ring system is observed for $n = 1$–4. Transition state **341** is found to be operable, in part, when $n = 7$. Similarly, Knight[181b] has accomplished the stereoselective ring contraction of lactone **342** to afford ester **343**, an intermediate in a proposed route to guaianolide and pseudo-guaianolide sesquiterpenes.



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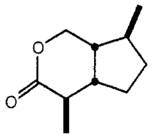

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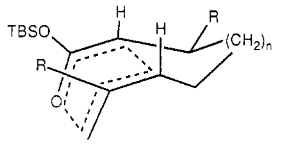

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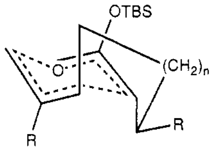

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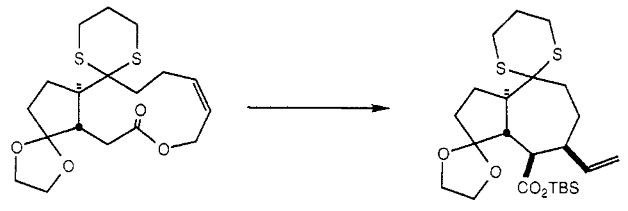

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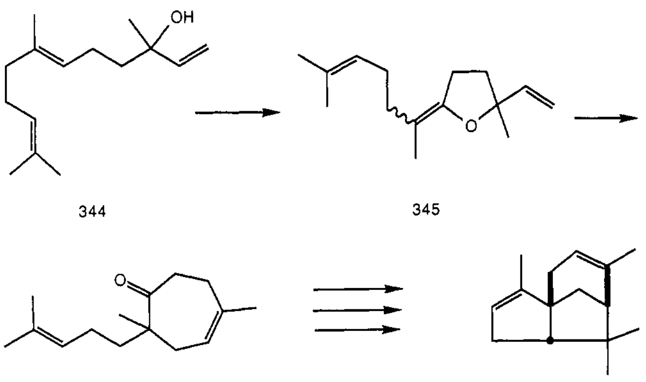
F. {2,4}-Rearrangements

This class of Claisen rearrangements permits ring expansion by two carbons and is the exocyclic vinyl ether analogue of the {1,4}-rearrangement. The vinyl ether functionality can be generated by intramolecular bromoetherification followed by base-catalyzed elimination of HBr,[182] alkoxide-promoted addition to an acetylene,[183] dehydration,[184] or radical cyclization.[185] For example, nerolidol (**344**) affords allyl vinyl ether **345** upon implementation of the bromoetherification procedure and elimination. Subsequent thermolysis of **345** gives the cycloheptenone **346**. Several operations convert the cycloheptenone into 2,5-cedradiene (**347**).[182b]

A variation on the bromoetherification theme has been developed by Petrzilka—namely, selenoxide elimination to generate ketene acetals.[186a,b] This technique is exemplified by the synthesis of the decenolide **350**, phoracantholide J. The eight-membered acetal is prepared under high-dilution conditions by intramolecular phenylselenenyl etherification of an acyclic chain bearing allylic alcohol and vinyl ether termini. Oxidation of selenide **348** to the selenoxide, subsequent elimination to ketene acetal **349**, and rearrangement afford the target substance. The formation of the (*Z*)-olefin is derived from transition state **351** (assuming

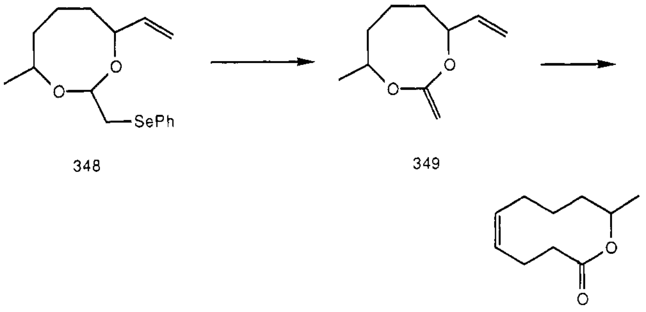


344 345

346 347

a chairlike transition state) rather than the seemingly more strained transition state **352** that would lead to the (*E*)-olefin.[186c,187]

One of the difficulties associated with this class of rearrangement is the problem of vinyl ether isomerization that can partition products between the {1,4}- and {2,4}-manifolds.[184] An intriguing case of this process is seen in the Paquette synthesis of the sesquiterpene precapnelladiene (**355**).[188] Epimeric allyl vinyl ethers **353** and **356**, both prepared from their respective lactones with Tebbe's reagent $(Cp_2TiCH_2ClAlMe_2)$,[17] undergo rearrangement via different pathways. Isomer **353**, bearing the β-methyl group, rearranges to give the desired cyclooctenone **354**. On the other hand, the α-isomer **356** is susceptible to prototropic isomerization of the vinyl ether double bond. Rearrangement via the {1,4} pathway gives the cyclohexene **358**. The prototropic shift appears less favorable in isomer **353** as the allylic proton is less accessible on the concave face than it is on the convex face of **356**.



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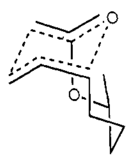

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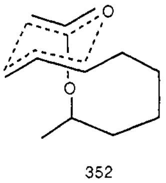

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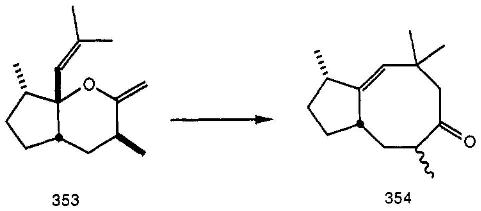

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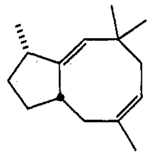

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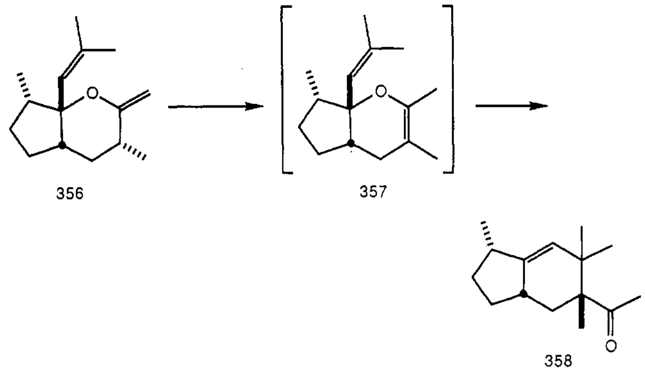

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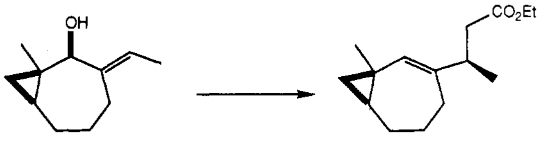
G. {4,5}-Rearrangements

This type of rearrangement has been utilized by Paquette[189] in the synthesis of the sesquiterpene dactylol (**361**). The reaction permits the control of allylic side chain stereochemistry (**360**) if the geometry of the exocyclic double bond and the stereochemistry of the hydroxyl group can be controlled. In the case at hand, allylic alcohol **359**, the former requirement is readily met by introduction of the ethylidene group via condensation between a 1-methyl[5.1.0]bicyclooctan-2-one and acetaldehyde followed by dehydration. The latter condition is achieved by selective Luche reduction $(CeCl_3/NaBH_4)$ of the enone.



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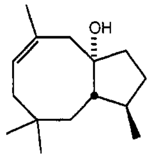

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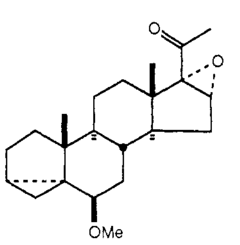
The {4,5}-rearrangement has served admirably in the steroid field to provide a route for the stereospecific introduction of the C_{20} side-chain stereochemistry and clearly indicates how product stereochemistry may be controlled if double-bond geometry and alcohol stereochemistry can be appropriately manipulated. Pregnane (**362**), readily available by α-face epoxidation of the D-ring enone, is reduced under Wharton conditions[190] to a mixture of allylic alcohols **364a** (63%) and **365** (27%). Carroll rearrangement of (*E*)-alcohol **364a** affords the C_{20} α-stereochemistry of **363a** while (*Z*)-olefin **365** provides the C_{20} β-stereochemistry (**363b**).[191] Side-chain stereoisomers **363a** and **363b** are converted to cholesterol and C_{20}-isocholesterol, respectively.[192] Alcohol **364b**, formed by oxidation and α-face reduction of the intermediate enone, gives rise to aldehyde **366**. Thus, *Z* α-allylic alcohol **365** and *E* β-allylic alcohol **364b** are operationally equivalent as they both yield the same relative stereochemistry at C_{20}.[193]



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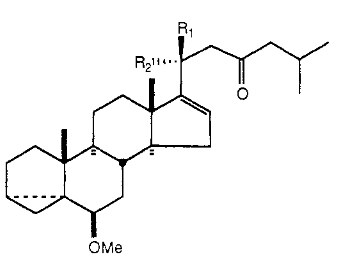
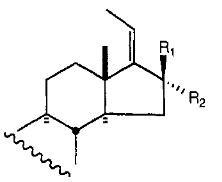
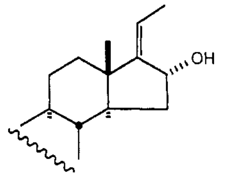


363a, R_1=H, R_2=Me
b, R_1=Me, R_2=H



364a, R_1=H, R_2=OH
b, R_1=OH, R_2=H



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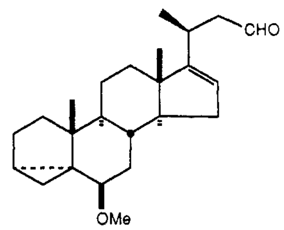

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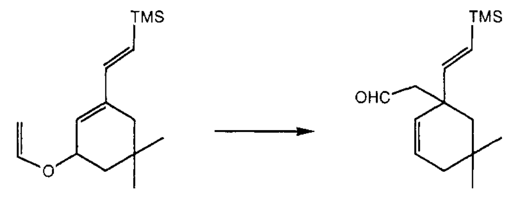
H. {4,6}-Rearrangements

The perceptive reader will have recognized many examples of this common version of the Claisen rearrangement in earlier discussions. The {4,6}-rearrangement is typified by the formal S_N2' addition of an acetic acid residue to an endocyclic cycloalkenol and provides a convenient route to quaternary allylic carbon atoms.[194] In a synthesis of quadrone (336), Burke[195] has employed two {4,6}-rearrangements. The first, **367** → **368**, creates a quaternary allylic center that serves to form subsequently a spirocyclopentenone. Whereas the allylic alcohol precursor of vinyl ether **367** arises via 1,2-reduction of the parent enone, the α-allylic alcohol progenitor of vinyl ether **370** would not, owing to the steric effect of the *gem*-dimethyl group, be accessible by the same pathway. Accordingly, the accessible α-face of the six-membered ring is exploited by employing the isomeric enone **369** in conjunction with the Wharton rearrangement.[190] The stereochemistry of the carbon–oxygen bond in the sequence is established during the α-face epoxidation of enone **369**. The combination of the Wharton and Claisen rearrangements results in the net substitution of the carbonyl of **369** by the acetaldehyde moiety of **371** with retention of the site of the double bond.

Another method for the all-important control of allylic alcohol stereochemistry, albeit target-dictated, is illustrated in the preparation of the Inhoffen–Lythgoe diol **375**,[196] a critical intermediate in vitamin D syntheses, and the steroid C/D ring synthon **379**.[197] Both approaches utilize cis-fused [3.3.0] bicyclic lactones (**372** and **376**, respectively) to generate the correct allylic alcohol stereochemistry. In each instance, a Baeyer–Villiger oxidation of a bicyclo[2.2.1]heptenone serves as the source of the lactones.



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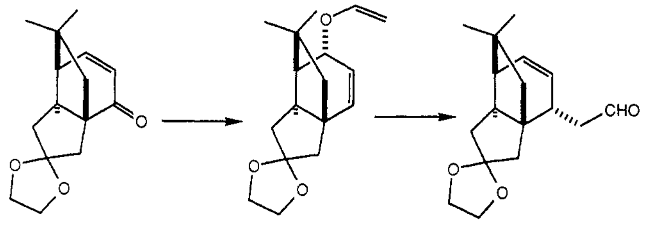

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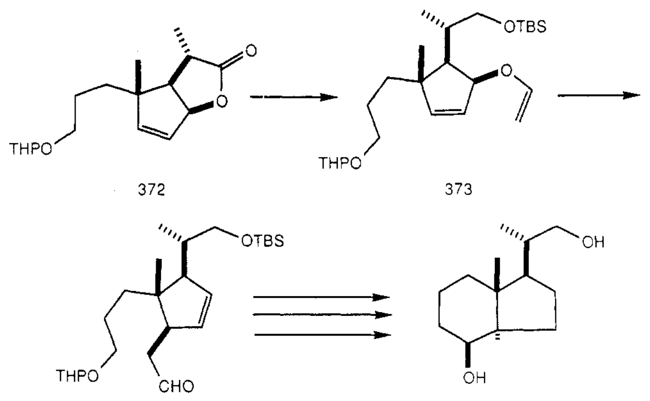

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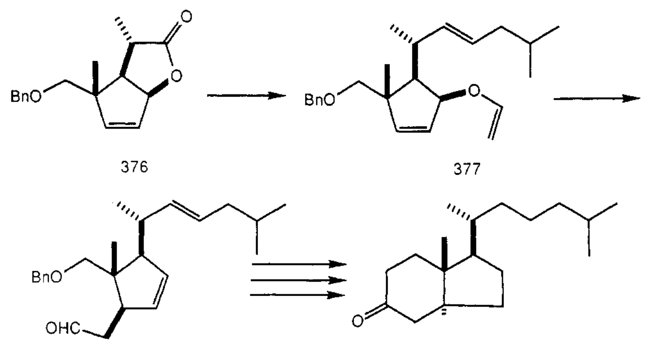

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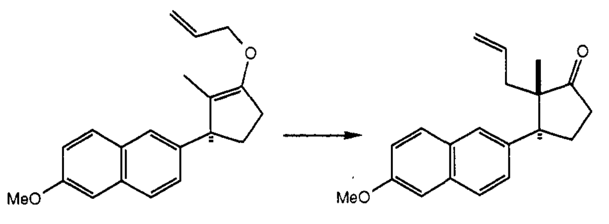
I. {5,6}-Rearrangements

The {5,6}-rearrangement is closely related to the {1,2}-rearrangement as the two processes serve to interchange carbonyl and olefin functionality. Horeau[198] has observed the stereoselective {1,2}-rearrangement of allyl vinyl ether **380** to allyl ketone **381**, an intermediate in a synthesis of equilenin. Application of the {5,6} variant as the second step of the tandem rearrangement **382** → **383** → **384** results in aldehyde **384** that is transformed into estrone **385** in several operations.[156b] Both seco derivatives **381** and **384** are the major stereoisomers from their respective rearrangements as the bulky naphthalene and dihydronaphthalene groups direct the bond formation.

The propensity for this class of rearrangement to give axial bond formation in cyclohexenyl systems with the attendant ring in a chair conformation has been demonstrated by Ireland.[199] This tendency is often observed



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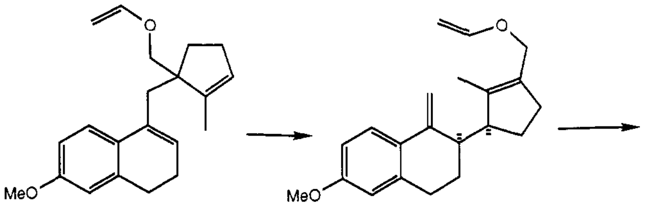

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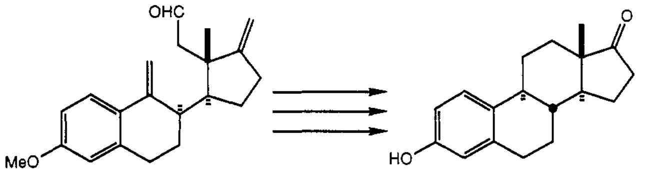

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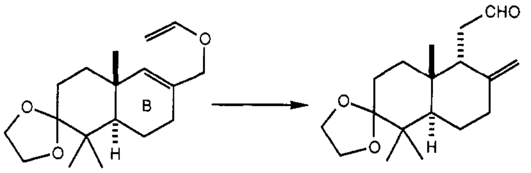
in rigid systems as typified by the conversion **386** → **387**.[200a] Bond formation occurs axially from the α-face of **386** with ring B in a chairlike conformation. However, steric factors can play an important role in altering the course of events. In a synthetic route to the clerodane diterpene annonene (**388**). Kakisawa[201] has observed an 85:15 ratio of aldehydes **390** and **391**, respectively, upon rearrangement of allyl vinyl ether **389**.



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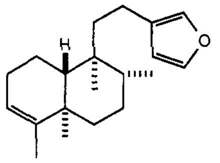

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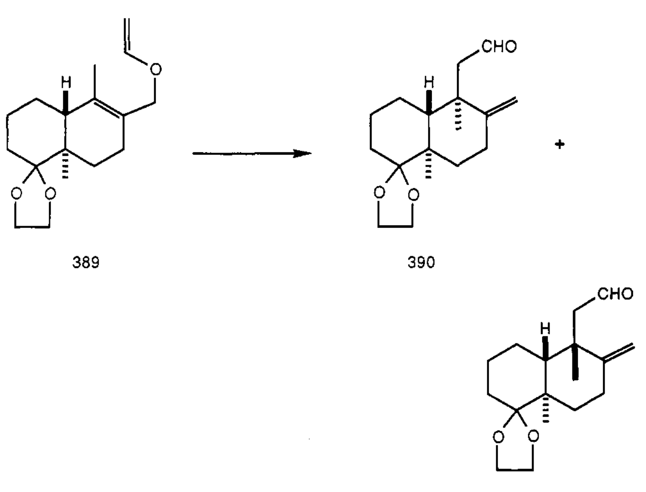

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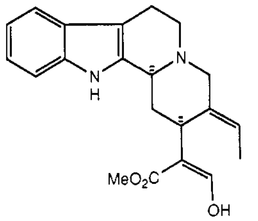
The major isomer arises from equatorial, β-face attack on ring B (chair conformation), avoiding the 1,3-diaxial interaction with the axial methyl group of the α-face.

The use of secondary allylic alcohols in the {5,6}-rearrangement generally follows the tendency of secondary allylic alcohols in {0,0}-rearrangements to give "trans" double bonds. An unsuccessful approach to the synthesis of the alkaloid geissoschizine (**392**) utilizes the rearrangement of a 1:1 mixture of the stereoisomers **393**[202,203] that provides stereoisomeric (*Z*)-olefins **394** and **395**. Allyl vinyl ether **393a** rearranges through



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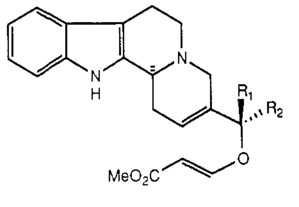
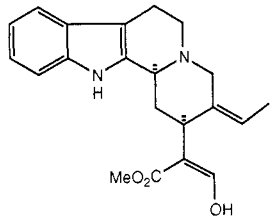


393a, R_1=Me, R_2=H
b, R_1=H, R_2=Me



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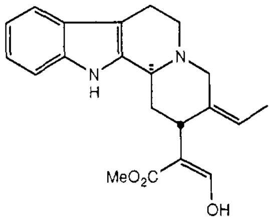

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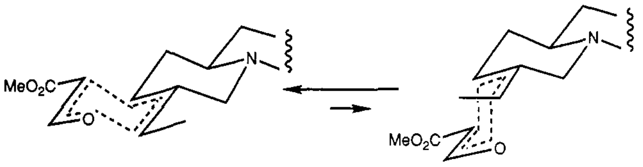
chairlike transition state **396** as opposed to its alternative chair conformation **397** which can encounter 1,3-diaxial interactions. Similarly, isomer **393b** rearranges through transition state **398** rather than **399**. In addition, transition state **399**, if late enough, can suffer from $A^{1,3}$ interactions (cf. the ground-state equivalent, **392**).



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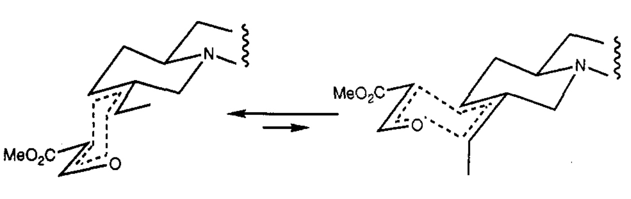

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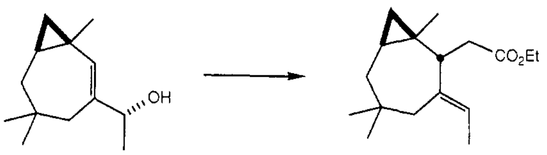
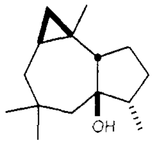
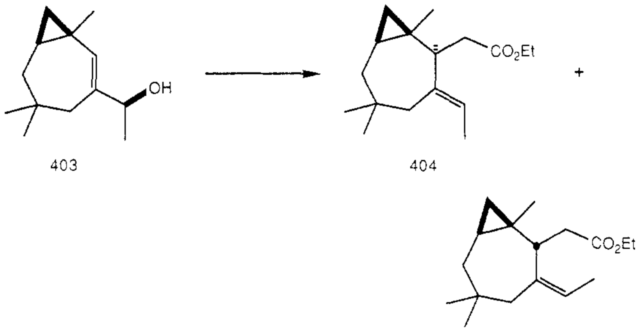
Unfortunately, high stereospecificity in this rearrangement is not always the case. In a synthesis of africanol (**402**), Paquette[189] has observed the expected ester product **401** from orthoester rearrangement of alcohol **400**. However, the rearrangement of epimeric alcohol **403** gave a 1:1 mixture of isomers **404** ((*E*)-olefin) and **405** ((*Z*)-olefin). Ester **404**, the anticipated product, encounters steric interactions with the *gem*-dimethyl group in the transition state for its formation, thereby allowing bond formation to occur trans to the cyclopropane ring in spite of the axial methyl group in the transition state for the formation of **405**.[204]



400 401



402

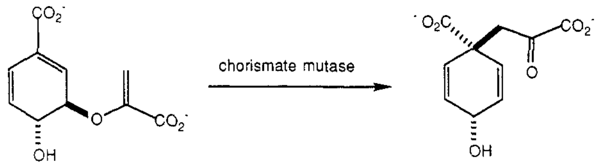


403 404 405

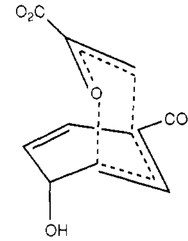
VIII. Biochemical Aspects

All the rearrangements that have been discussed thus far are inventions developed over the course of 76 years. The elucidation of the structure and absolute stereochemistry of chorismate (**406**)[205] and the discovery of its [3,3] sigmatropic rearrangement to prephenate (**407**),[206] the precursor to aromatic amino acids via the shikimic acid pathway, demonstrates that Nature has been regularly executing the "Claisen" rearrangement for some time. The synthesis of racemic chorismic acid[207a,b] and labeled[207c] chorismate was followed by the studies of Knowles, who has shown that chorismate rearranges through a chairlike transition state both in vivo and in vitro.[208] The process is catalyzed in vivo by the enzyme chorismate mutase by a factor of 10^6.[209] The accrued evidence suggests that rearrangement under either set of conditions proceeds through dipolar transition state **408** with both the hydroxyl and enol pyruvate units diaxial.[210] Bartlett has recently prepared transition-state analogue **409a** and has found it to be a potent inhibitor of chorismate mutase-prephenate dehydrogenase from *Escherichia coli*.[211,212]

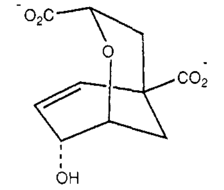
Monoclonal antibodies have recently been employed to catalyze the chorismate to prephenate rearrangement. The transition-state model **409a** is bound to the carrier protein using the diazonium salt **409b**, and monoclonal antibodies are isolated that catalyze the conversion of chorismate to prephenate with a rate enhancement of 10 000.[213]



406 407



408



409a, R=H
b, R=C(O)NHCH2CH2CH2-C6H4-N2+

IX. Concluding Remarks

From what began as a casual introduction to a paper 76 years ago has blossomed a reaction of considerable significance. The Claisen rearrangement has stimulated the interest of several generations of chemists. Physical organic chemists have been provided with a mechanistic challenge, the synthetic organic community has had the opportunity to expand the scope of the reaction and apply it to complex syntheses, and bioorganic chemists have solved a formidable challenge in the chemistry of enzymes. Perhaps a new and imaginative generation will see new opportunities for this reaction and expand upon the chemistry discussed in this review.

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(213) Jackson, D. Y.; Jacobs, J. W.; Sugasawara, R.; Reich, S. H.; Bartlett, P. A.; Schultz, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 4841.

The Ireland-Claisen Rearrangement

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Introduction

The Ireland-Claisen rearrangement, first reported in 1972,[1] has developed over the ensuing years to become a powerful tool in organic synthesis. The importance of this rearrangement derives from the flexibility it provides the synthetic organic chemist to control the diastereoselectivity of two newly generated stereocenters as well as the predictability of product stereochemistry. This review covers the development of this reaction from its inception to its current role in synthetic methodology.

The Ireland-Claisen rearrangement refers to the [3,3]-sigmatropic rearrangement of allylic esters (**1**) as ester enolates (**2**) to give 3,4-unsaturated acids (**3**) (**Scheme 1**).[1] The rearrangement is a suprafacial, concerted, non-synchronous, pericyclic process. When the sp^2-hybridized C$_1$ and C$_6$ positions of the allyl vinyl ether are substituted, the rearrangement can proceed via two achiral transition states to give two racemic diastereomers, bearing two centers of asymmetry at C$_2$ and C$_3$ of the product.

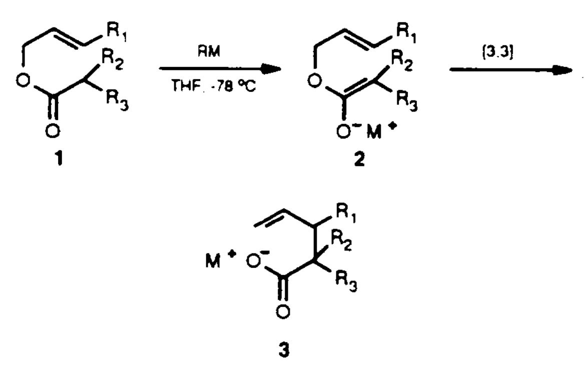
Prior to the development of Ireland's modification, other popular variants of the aliphatic Claisen rearrangement included the vinyl ether[2], the Johnson orthoester[3] and the amideacetal rearrangements.[4] Base-catalyzed reactions of allylic esters were also reported, but employed harsh conditions and gave low yields.[5] The major advantage of the Ireland modification over these base-catalyzed rearrangements is the ease of preparation and subsequent facile rearrangement of allyl vinyl ethers as their lithium enolates.

Generation of Ester Enolates

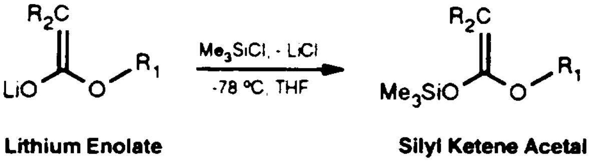
Theoretically, alpha allyloxy enolates can undergo either [3,3]-sigmatropic or competing [2,3]-Wittig type rearrangements. Surprisingly, ester enolates, especially silyl ketene acetals, do not undergo a [2,3]-Wittig rearrangement.[6]

In his initial work, Ireland employed lithium ester enolates generated by the method of Rathke,[7] but these proved unsatisfactory as they rearranged to give unwanted aldol condensation side products.[1] However, the lithium enolates, when silylated by TMSCl, afford trimethylsilyl ketene acetals (**Scheme 2**) which in turn rearrange readily to give 3,4-unsaturated acids. One problem with this approach is the formation of 2-6% C-silylated product.[1] This was overcome by using *tert*-butyldimethylchlorosilane (TBSCl) as the silylation reagent which provides predominantly the O-silylated ketene acetal.[8]

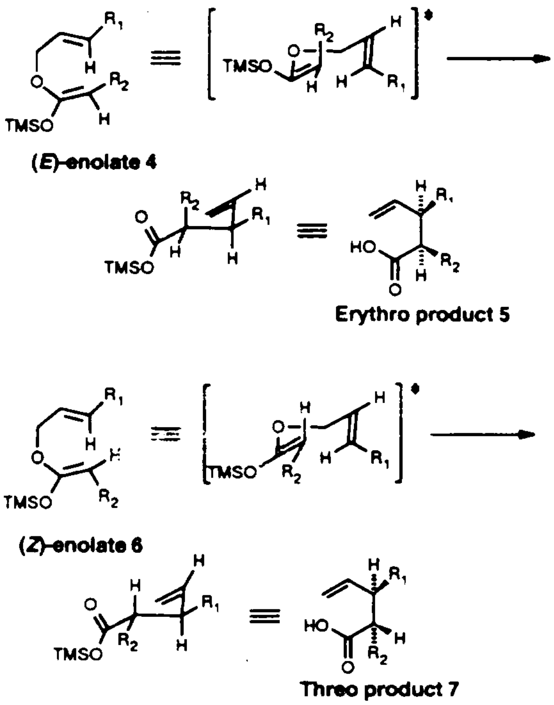
Scheme 1



Scheme 2



Scheme 3



Stereoselective Generation of Ester-Enolates

The geometry of the products of the Ireland-Claisen rearrangement can be predicted by the stereochemistry of the double bonds involved in the ketene acetal rearrangement. The (*E*)-enolate (**4**) gives predominantly an erythro product (**5**), while the (*Z*)-enolate (**6**) gives a threo compound (**7**) as the main product (**Scheme 3**).[9] The rearrangement is proposed to proceed through a four centered "chairlike" transition state as shown, thus allowing stereoselection of the products.[9,10]

The geometry of the silyl ketene acetal can be controlled during the ester enolization process by varying the solvent system. The formation of (*Z*)-enolates is favored by THF as the solvent, while the use of 23% HMPA/THF favors the formation of the (*E*)-enolate (lithium enolate). Regardless of the allylic bond configuration (*cis* or *trans*), the stereochemistry is retained on silylation and the two compounds give predominantly the erythro and threo isomers, respectively, on rearrangement (**Scheme 4**).[9]

Mechanism of Ester-Enolate Control - Thermodynamic or Kinetic?

It was initially proposed that the *E*:*Z* ratio of the enolate esters was kinetically determined, regardless whether THF or a mixture of HMPA/THF was used.[9,11] The two possible transition states **1** and **2** are shown in **Figure 1**. In the absence of HMPA, the lithium atom is strongly coordinated to the carbonyl oxygen leading to an unfavorable interaction between R and R_1. In the presence of HMPA, the lithium atom is highly solvated. In this case, favorable steric interactions between R and R_1 lead preferentially to (*Z*)-enolate formation. Note that these steric considerations had initially been used to explain ketone enolate selectivity and can also be used to explain ester enolate selectivity.

Corey's studies on enolate selectivity led to the conclusion that the use of hindered bulky bases like lithium *tert*-octyl butyl amide (LOBA) gave superior selectivity to (*E*)-enolates as compared to LDA (**Table 1**).[12] He argued that the stereochemical outcome in the presence of HMPA was not a kinetic effect, but was due to equilibration to the more thermodynamically stable (*Z*)-enolate. Corey's conclusion was based on his experiments using TMSCl as an internal quenching agent during the enolization with a lithium base (**Table 2**). The investigations of Rathke also support this conclusion (**Scheme 5**).[13]

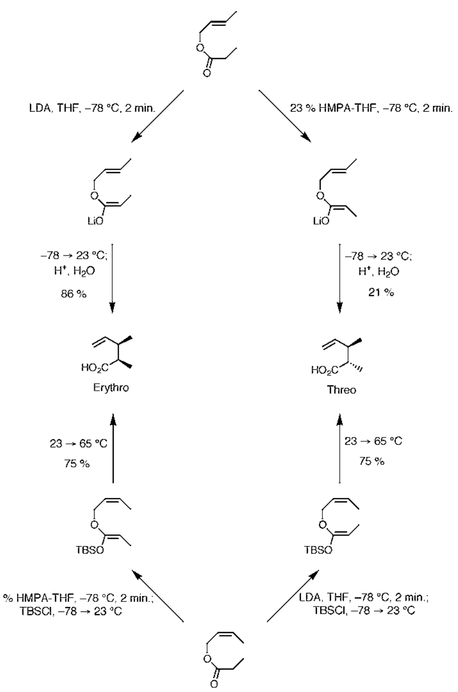
The addition of 1-4 equivalents of HMPA or TMEDA did not change the *E*:*Z* ratio, but the addition of 0.2 equivalent of 3-pentanone caused rapid isomerization to an equilibrium mixture of enolates with an *E*:*Z* ratio of 16:84. Rathke suggested the reverse aldol condensation isomerization mechanism illustrated in **Scheme 6**.[13] It was possible to control the deprotonation of 3-pentanone in THF solution so as to produce predominantly the (*E*)-isomer (**8**) by addition of the ketone to 10% excess lithium 2,2,6,6-tetramethyl piperidide (LiTMP) at 0° C (*E*:*Z* ratio 87:13), or to produce predominantly the (*Z*)-isomer (**9**) by addition of the ketone to a slight deficiency of LiTMP (*E*:*Z* ratio 16:84). He concluded that the formation of the (*E*)-enolate could be the result of kinetically controlled deprotonation, but the formation of the (*Z*)-enolate is thermodynamically favored.

To thoroughly examine the aspects of selectivity in ketene acetal formation, Ireland conducted a number of experiments, varying different parameters and using ethyl propionate as the ester.[14]

Solvent Effects

The effect of solvent on the stereoselectivity of silyl ketene acetal formation of ethyl propionate with LDA is indicated in **Table 3**. The addition of metal-chelating solvents such as HMPA, TMEDA and DMPU reversed the selectivity in favor of the (*Z*)-isomer, as opposed to the predominant formation of the (*E*)-isomer in pure THF. The best selectivity was attained by increasing the amount of DMPU to 45%. However, when the amount of TMEDA is increased, the yield decreases substantially.

Scheme 4 Redux



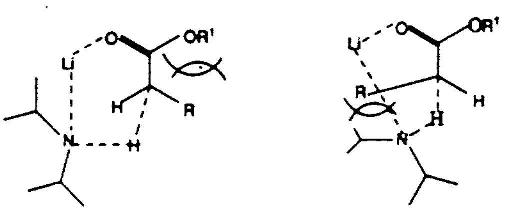
Note: The yields obtained from TBS-ketene acetals are often better than for the corresponding lithium enolates.

Adapted from Ireland, R. E.; Willard, A., K. *Tetrahedron Lett.* **1975**, *46*, 3975-3978.

Figure 1

Possible configurations of the T.S. of the of the Li ester-enolate

with THF as the solvent **Threo Product 7**



Transition State **1** **2**

Favored in absence of HMPA Favored in presence of HMPA

Table 1. ENOLATE SELECTIVITY WITH DIFFERENT BASES

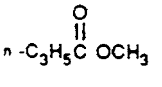
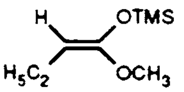
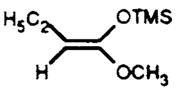
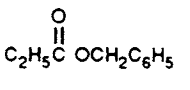
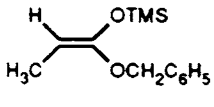
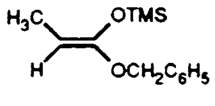
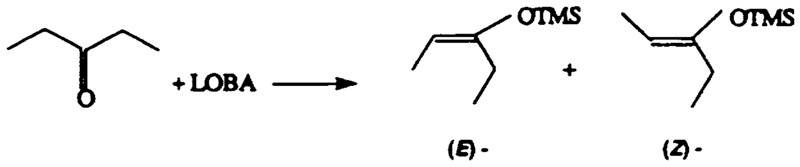
Substrate	TMS Ketene Acetal		*E*:*Z*	
	E	*Z*	LDA	LOBA
 $n\text{-}C_3H_5C(=O)OCH_3$			91:9	95:5
 $C_2H_5C(=O)OCH_2C_6H_5$			80:20	95:5

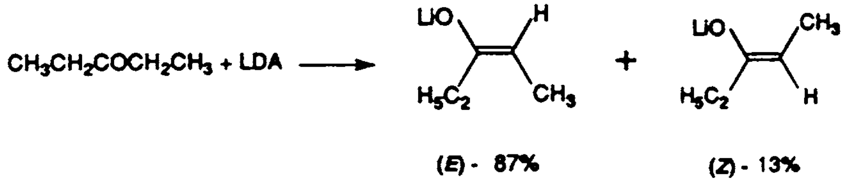
Table 2. Enolate selectivity with Corey's internal quench experiments



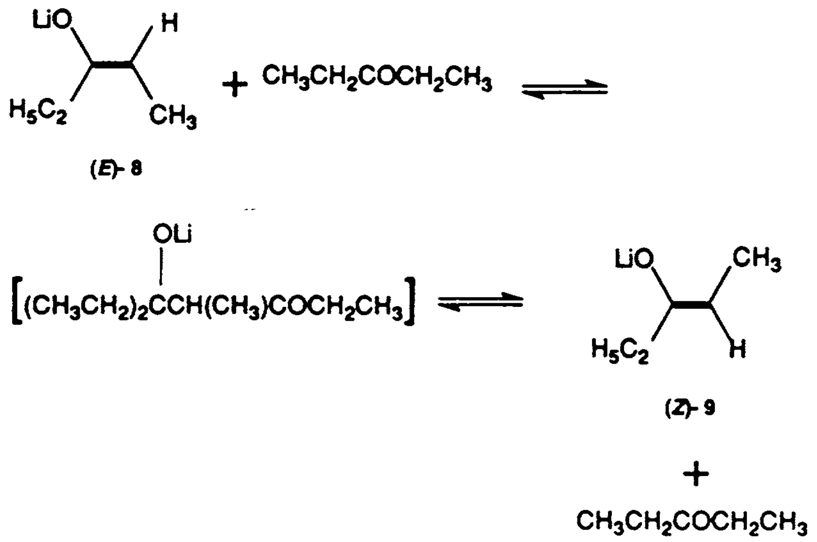
Method	Solvent	(E)-		(Z)-
internal quench	THF	98	:	2
internal quench (8 equiv. TMSCl)	HMPA/THF	37	:	63
internal quench (17 equivs. TMSCl)	HMPA/THF	46	:	54
two step procedure*	HMPA/THF	18	:	82

*slow addition of ketone to LDA followed by silylation

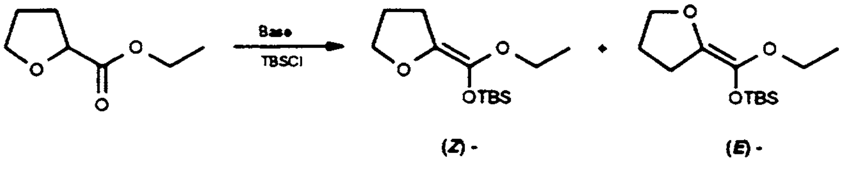
Scheme 5



Scheme 6



Scheme 7



Ester to Base Ratio

Table 4 summarizes Ireland's ester to base ratio experiments. In THF, a decrease in the ester to base ratio from 1:1 to 0.6:1 does not change the selectivity or yield. However, an increase in that ratio from 1:1 to 1:4 drastically reduces the yield from 90% to 5%. A decrease in the ester to base ratio in the mixed THF/chelating solvent system lowers the (*Z*)-selectivity and decreases the yield. Conversely, a slight increase in the ester to base ratio leads to an increase in (*Z*)-selectivity, accompanied by a drop in yield. Thus, increased (*Z*)-silylketene acetal selectivity can be obtained by adding a slight excess of the ester solution. It is also pertinent that addition of small amounts of a polar solvent like DMSO after enolization also increases the (*Z*)-selectivity.[14]

Effect of the Base

The comparison of LDA with a slightly bulkier base, i.e. lithium hexamethyl disilazide (LHMDS), showed that LHMDS is slightly more efficient for (*E*)-selective enolate formation than LDA in 23% HMPA/THF solvent mixture.[14]

Effect of an Alpha Oxygen Substituent on the (*Z*)-Enolate

The formation of the (*Z*)-enolate predominates due to chelation with an alpha O-atom as shown in **Scheme 7**. When the solvent is THF, the *Z*:*E* ratio is 90:10, whereas when 23% HMPA/THF is used the ratio drops to 63:37 with the (*Z*)-isomer still favored.

Ireland pointed out that the conclusions of Rathke and Corey were based on ketone enolates and not directly applicable to ester enolates. An aldol type equilibrium would be too slow and irreversible with acid derivatives such as esters and amides. To support his claim Ireland set up an analogous experiment with ethyl propionate in THF and TMSCl. After enolization of one equivalent of the ester by one equivalent of LDA, addition of 30% DMPU led to a *Z*:*E* silyl ketene acetal ratio of only 1:4. Furthermore, addition of 0.1 equivalents of ester to 2 equivalents of a preformed 60:40 mixture of (*E*)- to (*Z*)-lithium ester enolates led to only a small change in ratio to 69:31 (**Scheme 8**).

These observations suggest a kinetic resolution process. A preformed ratio of (*Z*)- and (*E*)- ester enolates can be altered by addition of a small amount of trapping agent that reacts at different rates with the two isomers, thus making it possible to carry out the reaction with the more reactive enolate. Ireland then set up a series of experiments using competitive trapping of the more reactive enolate with TBSCl (**Scheme 9; Table 5**).

The change in ratios is due to a competition for silylation between the two enolates (competition constant, K=k*Z*/k*E*, of 2.6 with DMPU and 1.4 with HMPA). It was concluded that "...kinetically controlled enolization in combination with a kinetic resolution process accounts for the selective formation of (*E*)- and (*Z*)- silyl ketene acetals in THF and THF/dipolar solvent systems with bases such as LDA, LHMDS, and KHMDS."[14] Ireland's experiments thus shift the evidence in favor of a kinetic resolution process in the case of ester enolates, but do not account for the observations made by Rathke and Corey on the mechanism of enolate formation from ketones (3-pentanone).

Chelation Control of Enolate Selectivity

The lithium enolates' preference for the *Z*-conformer is well established. Investigations by Bartlett,[15] Fujisawa[16] and Burke[17] showed that in the case of a heteroatom substituent that can undergo chelation with the lithium atom, the major isomer formed is the *E*-conformer (**Scheme 10**). Although the ratio of the isomers was not measured, it could be determined from the ratio of the final products. This coordination effect has been utilized in stereoselective syntheses, wherein control of the prostereogenic sp^2 sites is achieved by an allylic oxygen substituent.[18]

Yet another method for enolate control has been developed by Corey and Kim.[19] A chiral boron reagent (**Figure 2**) has been used to promote enantioselective aldol reactions of achiral propionate esters to give either syn or anti aldol products with excellent enantioselectivity and diastereoselectivity.

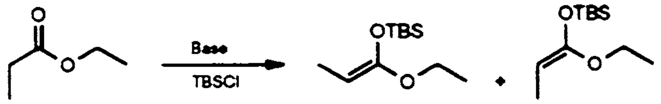
The enolate of choice can easily be controlled by use of the proper solvent:base combinations. When the chiral boron reagent [R_2BBr] and TEA in a toluene/hexane/CH_2Cl_2 solvent is used with *tert*-butyl propionate at -78°C, the transoid boron enolate is formed (O-B and methyl are *trans* to each other; *Z*-isomer by priority group nomenclature). These enolates react with aldehydes to give the expected anti aldol products in 90-97% e.e. However, when the base is the sterically demanding diisopropylethylamine and the solvent the more polar CH_2Cl_2, the cisoid enolate is formed to give the syn aldol product in 83-97% e.e.

The Transition State - Chair or Boat?

Prior investigations of [3,3]-sigmatropic rearrangements showed that unhindered 1,5-diene systems undergo rearrangement via a chair transition state.[20] Later evidence suggested the possibility of a chair, boat, twist helix or twist plane transition state for the closely related Claisen rearrangement.[21] Since Ireland's variant takes place at moderately low temperatures, the twist configurations are not likely. Further transition state studies of the Cope rearrangement led to the conclusion that substituents on the 1,5-hexadiene play a major role. In fact, a boat transition state is favored due to the nature of the substituents on certain ester enolates.[21]

From previous studies on the Cope[22,23] and Claisen[24,25] rearrangements, it was generally

Table 3. Effect of solvent on ester enolate selectivity



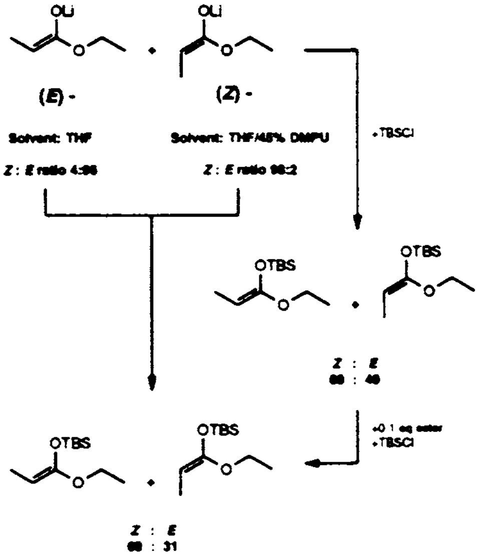
ENTRY	SOLVENT	ESTER:BASE	*Z*:*E*	YIELD
1	THF	1:1	6:94	90
2	THF/25%TMEDA	1:1	60:40	50
3	THF/50%TMEDA	1:1	--	0
4	THF/15%DMPU*	1:1	37:63	90
5	THF/30%DMPU	1:1	69:31	85
6	THF/45%DMPU	1:1	93:7	90
7	THF/23%HMPA	1:1	85:15	90

*DMPU=N,N'-dimethyl-N,N'-propylene urea

Table 4. Effect of ester to base ratio on the stereoselectivity in silyl ketene acetal formation of ethyl propionate with LDA

ENTRY	SOLVENT	ESTER:BASE	*Z*:*E*	YIELD
1	THF	1.4:1	1:1	5
2	THF	1.2:1	20:80	35
3	THF	1.1:1	6:94	90
4	THF	0.6:1	6:94	90
5	THF/30%DMPU	1.2:1	98:2	70
6	THF/30%DMPU	0.95:1	67:33	90
7	THF/30%DMPU	0.8:1	68:32	85
8	THF/30%DMPU	0.5:1	60:40	95

Scheme 8



Scheme 9

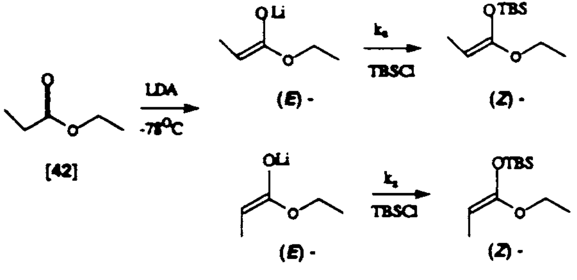
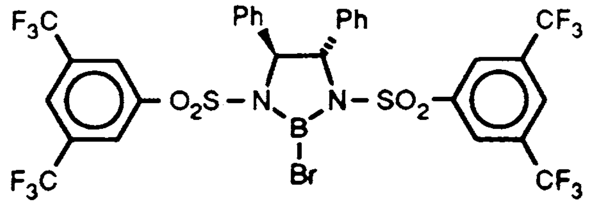


Table 5. Results of competitive trapping of the enolate with TBSCl

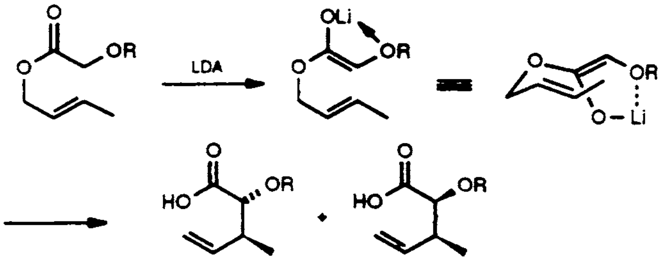
ENTRY	SOLVENT	ESTER:BASE	TBSCl	Z:E
1	THF/15%DMPU	0.8:1	0.9	30:70
2	THF/15%DMPU	0.8:1	0.08	14:86
3	THF/23%DMPU	0.8:1	0.9	73:27
4	THF/23%DMPU	0.8:1	0.08	66:34
5	THF	1:1	1.1	94:6
6	THF	1:1	0.9	4:96

Figure 2



Chiral Boron Reagent

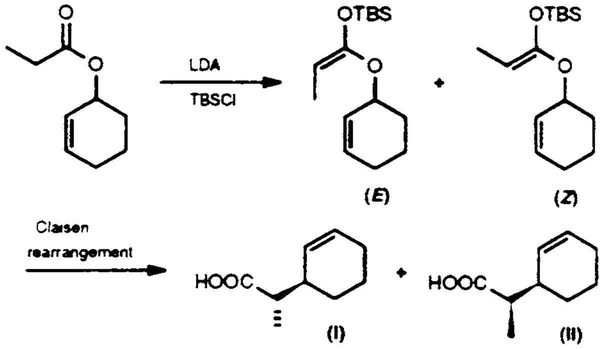
Scheme 10



R=	MAJOR:MINOR	YIELD
-Me	10.2:1	65
$-CH_2Ph$	9.6:1	77
MEM*	7.2:1	70
H	2.4:1	38

*(2-methoxyethoxy)methoxy

Scheme 11



SOLVENT	E:Z	(I):(II)	%YIELD	FAVORED T.S.
THF	83:17	84:16	79	chair
THF/45%DMPU	4:96	72:28	91	boat
THF/23%HMPA	14:86	73:27	60	boat

found that in cyclic systems a boat transition state is preferred. Another interesting observation was made by Bartlett in his studies of the ester enolate rearrangement of cyclohexenal propanoate.[26] The (*E*)-silyl ketene acetal rearranged via a chair transition state, while the (*Z*)-silyl ketene acetal rearranged via a boat transition state. Bartlett explained his observations by considering the transition states involving the chair and boat forms (**Figure 3**).

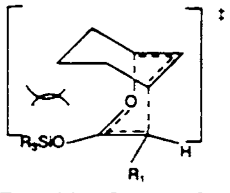
In the case of the (*Z*)-isomer there is an unfavorable interaction between the $-OSiR_3$ group and the methylene proton of the cyclohexene ring if the transition state proceeds through chair form **1**. Thus, the boat form is favored. However, the boat transition state of the (*E*)-isomer has greater steric interaction between the R group and the cyclohexene ring as in **2** (**Figure 3**), thus favoring the chair form.

Ireland carried out a systematic investigation of the effects of various cyclic and acyclic systems on the rearrangement to determine the underlying factors leading to stabilization of either the chair or boat transition state.[27]

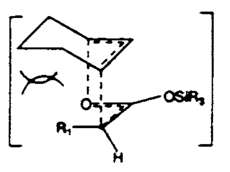
Cyclohexene and Pyranoid Derivatives

Ireland's results with cyclohexenyl propionate were identical to those of Bartlett's. Though diastereoselectivity was observed with both the (*E*)- and the (*Z*)-silyl ketene acetals, the (*E*)-isomer rearranged via a chair transition state while the (*Z*)-silyl ketene acetals rearranged via a boat transition state (**Scheme 11**). The rearrangement employing a pyranoid derivative involved a boat transition state for either (*E*)- or (*Z*)- silyl ketene acetals (**Scheme 12**). These results suggest that the ring oxygen atom can contribute between 1.0 kcal/mol (*Z*-silyl ketene acetal) and 2.2 kcal/mol (*E*-silyl ketene acetal) to the relative stabilization of a boat over a chair transition state. Since both the cyclohexene and the pyranoid rings are sterically similar, the stabilization of the boat transition state is, most likely, due to stereoelectronic rather than steric factors.

Figure 3



Transition State 1 (*Z*)-



Transition State 2 (*E*)-

A more useful picture of the rearrangement can be obtained by considering the chair and boat forms of the transition states of both (*E*)- and (*Z*)- conformers of the enolate (**Figure 4**).

Cyclopentene and Furanoid Derivatives

In the case of a cyclopentene derivative both the (*E*)- and the (*Z*)- isomers rearrange by a chair transition state (**Scheme 13**). However, the furanoid derivative rearranged by a boat transition state for both the ketene acetal configurations, thereby supporting the results of the pyranoid-cyclohexene series. The O-atom leads to relative stabilization of the boat form of the transition state over the chair form on the order of 1.4 kcal/mol (*E*-conformer) and 1.9 kcal/mol (*Z*-conformer).

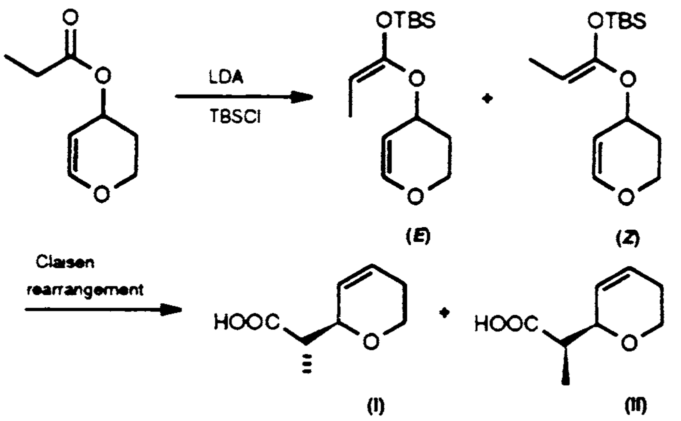
The chair and boat forms of the transition states of the (*E*)- and (*Z*)-enolates of cyclopentene-furanoid glycal derivatives are depicted in **Figure 5**.

Methoxy Allyl Propionate Derivative

The (*E*)- and (*Z*)-silyl ketene acetals of methoxy allyl propionate gave a mixture of carboxylic acids with a preference for the isomer expected via the chair transition state. Thus, in the acyclic series, the effect of the O-atom is not as important as it is in the cyclic series for stabilizing the boat transition state.

Using alpha-secondary deuterium isotope effects, Gajewski proposed that the transition state of the aliphatic Claisen rearrangement resembles an oxoallyl radical-allyl radical pair, rather than a 2-oxocyclohexane-1,4-diyl (**Scheme 14**).[28] This results in a transition state with much more advanced

Scheme 12



SOLVENT	(I):(II)	%YIELD	FAVORED T.S.
THF	29:71	77	boat
THF/45%DMPU	86:14	35	boat

Scheme 13

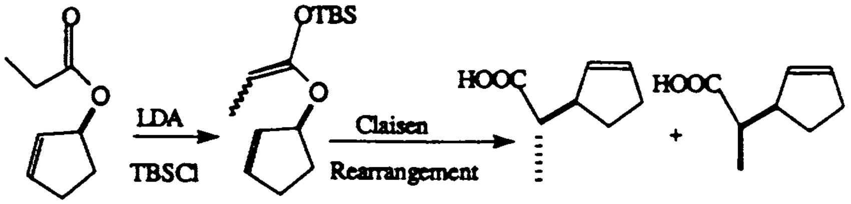


Figure 4. Transition states of cyclohexene-pyranoid glycal derivatives

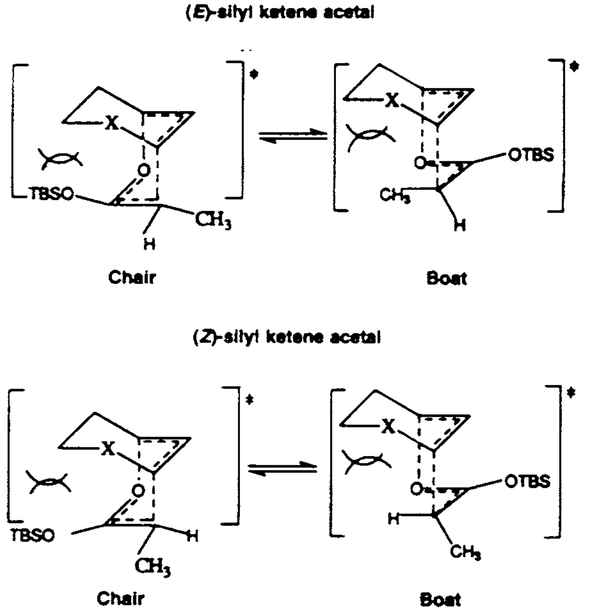
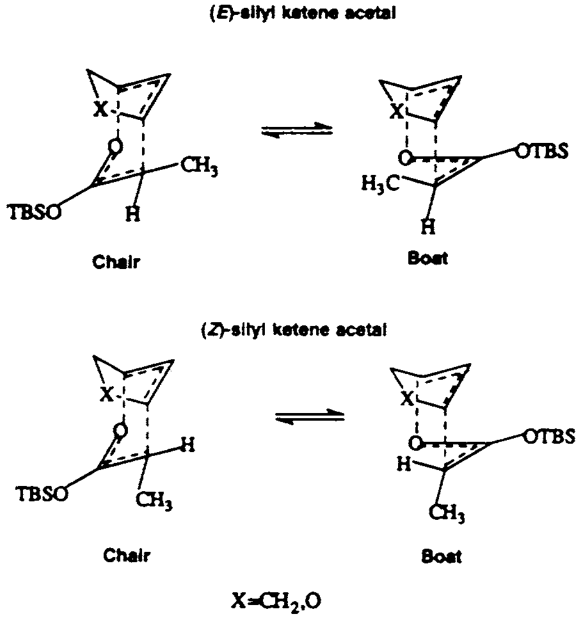
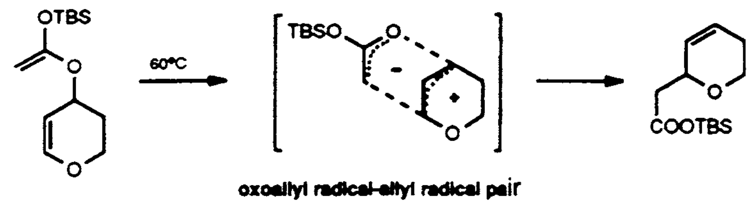


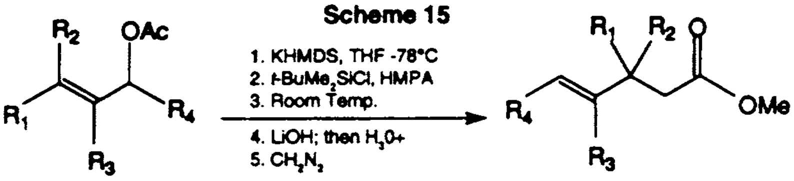
Figure 5



Scheme 14



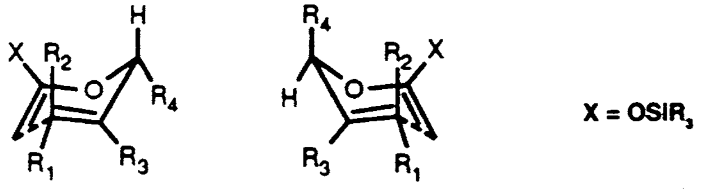
Scheme 15



8 [a-c] **9 [a-c]**

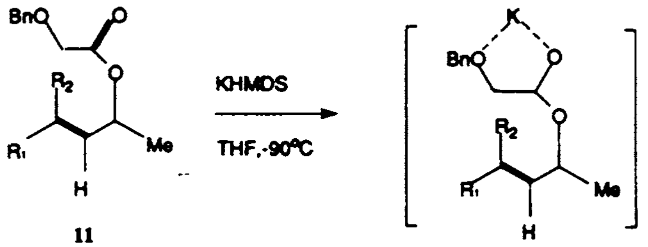
ESTER	R1	R2	R3	R4	%YIELD
8a&9a	Me	H	H	$SnBu_3$	60
8b&9b	Me	Me	H	$SnBu_3$	62
8c&9c	$SnBu_3$	H	H	Me	54

Figure 6. Possible Transition States of the Enolate



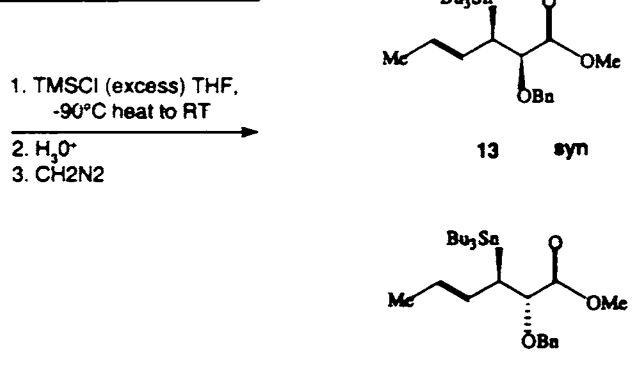
10a **10b**

Scheme 16



11 **12**

Config.	R_1	R_2
11 (E)-	$SnBu_3$	H
11 (Z)-	H	$SnBu_3$



13 **syn**

14 **anti**

O(3)-C(4) bond breaking than in the parent unsubstituted system. Thus, one would expect a rate enhancement effect from a C(6)-donor substituent to be especially effective in glycal systems.

Ireland concluded that there is a definite stereoelectronic effect which stabilizes the boat over the chair form. The energy differences between the chair and the boat forms in the transition state are small and hence tend to be influenced by substituent interactions. In the absence of steric interactions, the pyranoid and furanoid systems will rearrange by a boat transition state. A simple acyclic substituent with a C(6)- oxygen atom will not rearrange via the chair form.

Variations of the Ireland-Claisen Rearrangement

An interesting variation of the Ireland-Claisen rearrangement developed by Ritter uses an organotin ester and the chelation effect of the counterion to produce primarily the (*Z*)-enolate from the O-protected butenyl stannane (**8**). This rearrangement gives a high diastereoselectivity ratio (**Scheme 15**).[29]

The chair transition state (**10a**), with R_4 in the pseudoequatorial position, is energetically favored over (**10b**), with R_4 in the pseudoaxial position, resulting in the exclusive formation of the (*E*)-isomers (**9a - c**). The (*E*)-tributylstannylbutenol reacted six times faster than the (*Z*)-isomer, reflecting the energy difference between the transition states with the tributyltin moiety in a pseudo-equatorial (**10a**) or pseudoaxial (**10b**) position (**Figure 6**).

Ritter also investigated the chelation effect of the counterion to form predominantly the (*E*)-enolate from O-protected butenyl glycolates. The rearrangement of (*Z*)- or (*E*)-4-tributylstannyl-3-buten-2-yl (benzyloxy)acetate (**11**) (**Scheme 16**), through intermediate **12**, gave (*E*)-2-benzyloxy-3-tributylstannyl-4-hexenoic acid methyl ester in a 92% yield.

Due to the chelation control of enolate geometry, the syn ester (**13**) is the main product (syn:anti ratio 39:1) from the glycolate ester (**11**) (*E*). The glycolate ester (**11**) (*Z*) rearranges to give an anti:syn ester ratio of 40:1, thus emphasizing the utility of the rearrangement of organotin compounds to afford diastereoselective products.

Brown and co-workers recently reported a useful method for controlling enolate geometry through the use of dialkylboron reagents of the type R_2BX (X = Cl, OTf) in the presence of tertiary amines.[30] They found that the formation of the (*E*)-enol borinate is favored by the following:

(i) use of R_2BCl instead of R_2BOTf;
(ii) use of Et_3N instead of i-Pr_2EtN;
(iii) use of a dialkylboron group with a larger steric requirement (i.e. dicyclohexylboron instead of 9-BBN).

A recent publication by Corey extends this work to the highly enantioselective and diastereoselective Ireland-Claisen rearrangement of achiral allylic esters.[31] The rearrangement utilizes a recyclable chiral boron reagent (**Scheme 17**), resulting in greater than 97% e.e. in some cases.

The (*E*)- or (*Z*)-enolate is selected using the specific solvent combinations along with the chiral catalyst as shown in **Tables 6 and 7**. The (*E*)-isomer rearranged to give predominantly threo products while the (*Z*)-isomer rearranged to form mainly the erythro carboxylic acids. The diastereoselectivity of the rearrangements is consistent with the assigned geometry of the boron enolate and the expectation of the preferred chair geometry of the transition state.

Applications of the Ireland-Claisen Rearrangement

The rearrangement has been used in the synthesis of polyether antibiotics,[21,32] sesquiterpenes,[33] steroids,[34] iridoids,[35] tetronates,[36] marine natural products,[37] amino acids,[38] C-glycosides,[39] large carbocycles[40] and chiral stannanes[29] and silanes.[41] Recent applications include the synthesis of long chain or large ring molecules and demonstrate the utility of this rearrangement in controlling stereocenters.

A clever strategy utilizing a boron mediated aldol condensation in tandem with the Ireland-Claisen rearrangement provided a synthetic route to ebelactone-A, an esterase inhibitor.[42] Furthermore, a general method for the synthesis of unsaturated diesters with a high degree of stereocontrol at four chiral centers as well as two trisubstituted double bonds was devised (**Scheme 18**). Interestingly, the rearrangement could be carried out without protection of the keto group at C_7.

After the rearrangement of the diester **16A**, the resulting diacid was esterified to give the desired meso all syn diester **18A** (63% yield, 86% d.s.). The unsymmetrical diester **18B** is obtained in 53% yield and 95% d.s. from **16B**. An important aspect is that the electrophilic ketone carbonyl group is not attacked and there is no epimerization at the adjacent stereocenters. This is probably due to the flanking methyl groups which protect it from the sterically hindered base LDA and also blocks intramolecular aldol condensation. This synthesis demonstrates the use of a "double" Ireland-Claisen rearrangement to create two contiguous stereocenters.

A new, high yield synthesis of coumarin derivatives employing the rearrangement was reported by Collado and is shown in **Scheme 19**.[43] The rearrangement does not occur unless the phenolic hydroxyls are protected as, for example, their benzyl ethers.

Curran and co-workers have used the Ireland-Claisen rearrangement in a stereoselective synthesis of chiral iridoid aglycones (**Scheme 20**).[44] The iridoids are a family of natural products which have an oxygenated fused cyclopentapyran ring system possessing anti-microbial to anti-leukemic properties.

The best stereoselectivity was obtained by the generation of the (*E*)-silyl ketene acetal. This proceeded with good diastereoselectivity by a chair transition state to give **23** and its diastereomer in a 5:1 ratio. The rearrangement of the (*Z*)-silyl ketene acetal also gave **23** as the major product in a 3:2 ratio, but this time via the boat transition state, a result in keeping with the findings of Bartlett and Ireland.

Schreiber and co-workers have described the asymmetric synthesis of the cyclohexyl moiety of FK-506, a macrolide antibiotic with potent immunosuppressive properties (**Scheme 21**).[45] The rearrangement from **27** to **28** proceeded in 71% overall yield via the boat transition state. Wang has also used this rearrangement in the synthesis of the C_{10}-C_{24} fragment of FK-506.[46]

Jasperse and Curran have used the rearrangement to form two contiguous quater-

Scheme 17

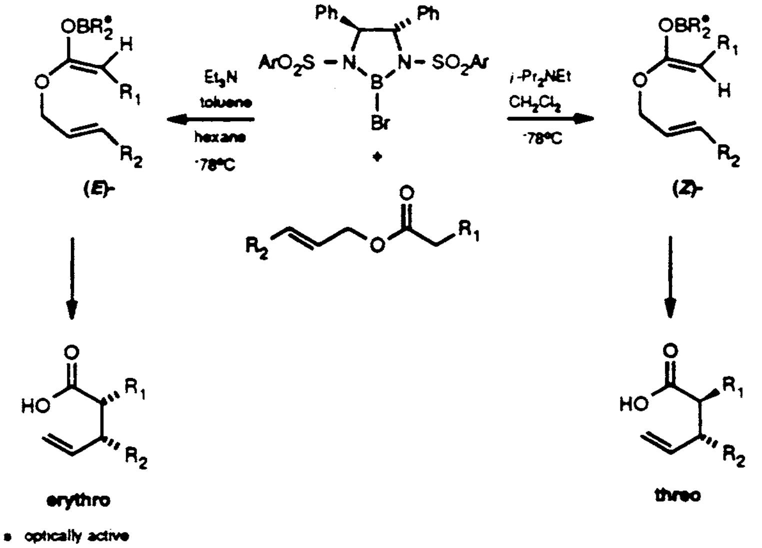


Table 6. Enantioselective rearrangement in CH_2Cl_2 via the (*E*)-boron enolate

ENTRY	R1	R2	%YIELD	THREO: ERYTHRO	e.e.%
1	Me	Me	75	99:1	<97
2	Et	Me	79	98:2	95
3	Me	Me	75	91:9	>97
4	Et	Ph	72	91:9	>97
5	Ph	Ph	100	23:77	>97
6	SPh	Me	52	39:61	>97
7	CH_2Ph	H	70	---	82
8	CH_2-l-naphthyl	H	48	---	77

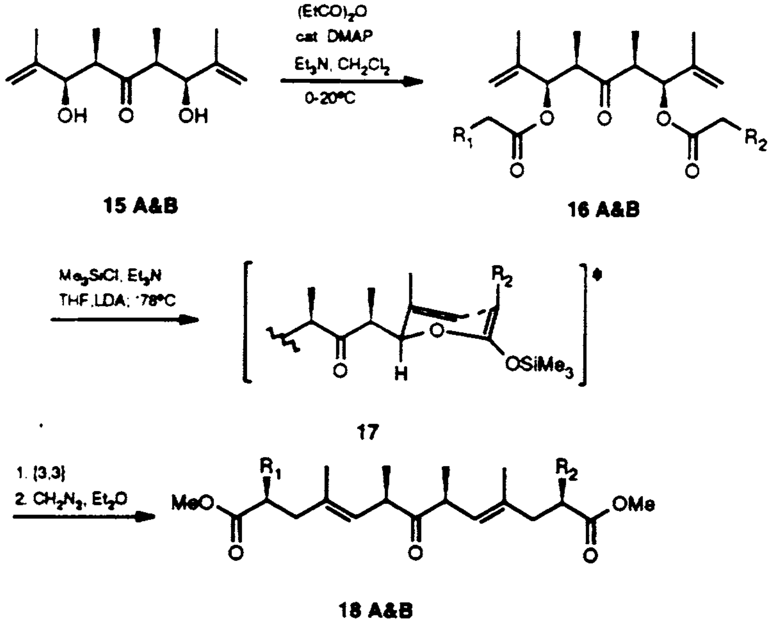
Diastereomeric ratios were determined by GC analysis of benzyl or methyl esters. e.e. values were determined by HPLC analysis of methyl esters using a Diacel OJ column.

Table 7. Enantioselective rearrangement in toluene-hexane via the (*E*)-boron enolate

ENTRY	R1	R2	%YIELD	THREO: ERYTHRO	e.e.%
1	Me	Me	65	90:10	96
2	Et	Me	79	89:11	>97
3	Me	Ph	88	96:4	>97
4	Et	Ph	69	95:5	>97
5	Ph	Ph	100	98:2	>97
6	SPh	Me	56	95:5	>97
7	SPh	Ph	45	91:9	>97
8	CH_2Ph	H	57	---	84
9	CH_2-1-naphthyl	H	63	---	79

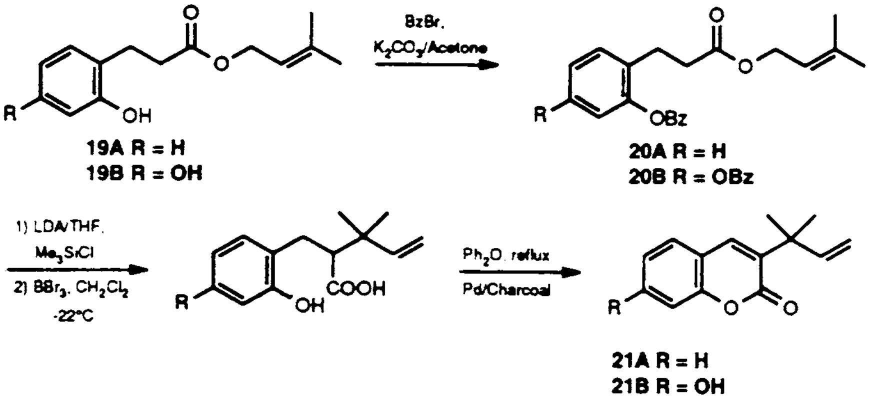
Diastereomeric ratios were determined by GC analysis of benzyl or methyl esters. e.e. values were determined by HPLC analysis of methyl esters using a Diacel OJ column.

Scheme 18

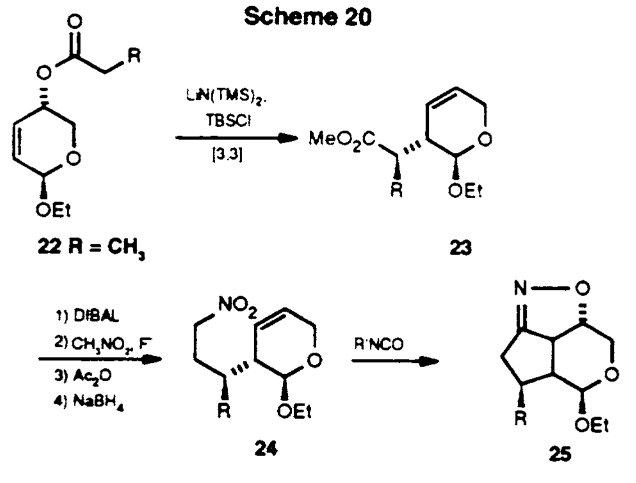


[A] R1 = R2 = Me
[B] R1 = Me; R2 = Et

Scheme 19



Scheme 20



nary centers needed for the intermediate in their synthesis of modhephene in 50% yield (**Scheme 22**).[47]

Intermediates to polyoxins which are structurally related to nucleoside peptide antibiotics were prepared by Duthaler.[48] As shown in **Scheme 23** the (*Z*)-allyl ester rearranges in a highly stereoselective manner to give predominantly the *trans*-substituted lactone, while the (*E*)-allyl ester rearranges to give mainly the *cis*-lactone.

The rearrangement was evaluated for application to the synthesis of macrocyclic lactones. Brunner and Borschberg investigated the potential synthesis of (R,S)-muscone (**37**) as shown in **Scheme 24**.[40] On rearrangement, **33** gave a mixture of **34**, **35** and **36**. The stereoselectivity of this rearrangement is rather low compared to that of acyclic systems. While of no consequence to the synthesis of the target molecule, this result highlights the fact that C-silylation may still be a problem in the case of large molecules. These findings supplement the model studies on the synthesis of medium and large carbocycles using the Ireland-Claisen rearrangement carried out by Knight, where a lack of stereospecificity was reported, and by Danishefsky.[49]

Burke has used the reaction to prepare the hydropyran subunit in his synthesis of macrodiolide and macrotriolide ionophores. He was able to effect the rearrangement of **38** to **39** in 76% yield (**Scheme 25**).[50]

In their paper titled "Stereocontrolled Synthesis of a Polyether Fragment", Bartlett describes the use of the Ireland-Claisen rearrangement to synthesize a tetrahydropyran lactone with several chiral centers.[51] The stereoselective step using the rearrangement is shown in **Scheme 26**.

The ratio of **40** to **41** is 10:1 since the use of HMPA favors the formation of the (*Z*)-enolate-ester, which in turn gives **10**.

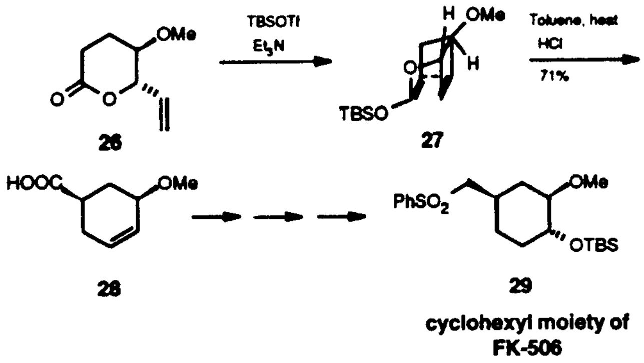
Cane and co-workers have used the rearrangement in the synthesis of chain elongation intermediates of the Monensin biosynthetic pathway.[52] They have been able to prepare **43** from **42** in 50-75% yield (Scheme 27).

Danishefsky has ingeniously used the Ireland-Claisen rearrangement to merge awkwardly positioned chiral centers in his synthesis of the C_{23}- C_{49} unit of Rapamycin, a metabolite of *Streptomyces hygroscopicus*, an antibiotic with immunosupressive properties (**Scheme 28**).[53]

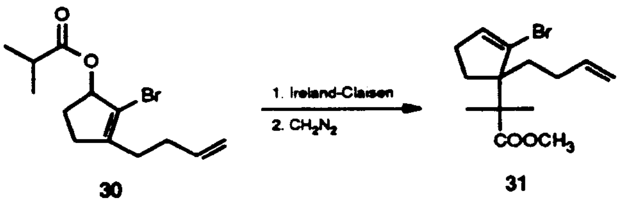
After preparing alcohol **44** and acid **45** separately, esterification in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) and DMAP gave **46** which, in turn, after rearrangement of the silyl enol ether furnished **47**.

The rearrangement of lactones to carbocycles has also been carried out by Danishefsky in his synthesis of the *Fusarium* toxin equisetin.[54] Keto-lactone **48** was converted to its bisilyl derivative **49** and subsequently rearranged to yield ester **50** in 52% yield (**Scheme 29**).

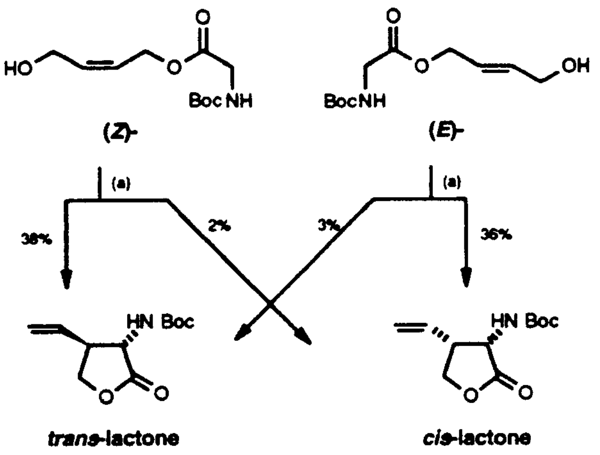
Scheme 21



Scheme 22

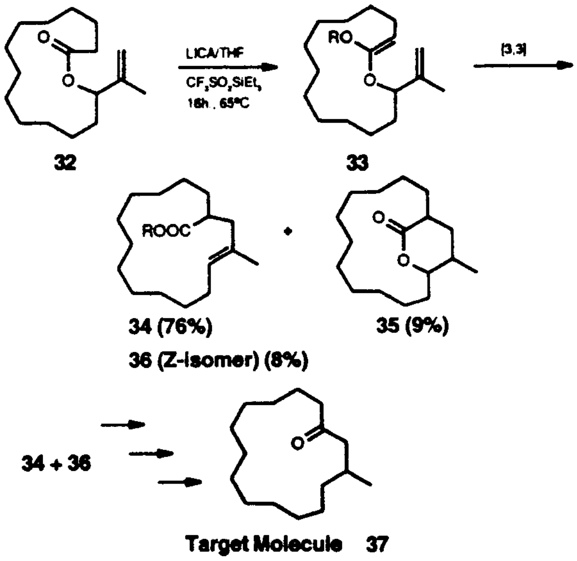


Scheme 23

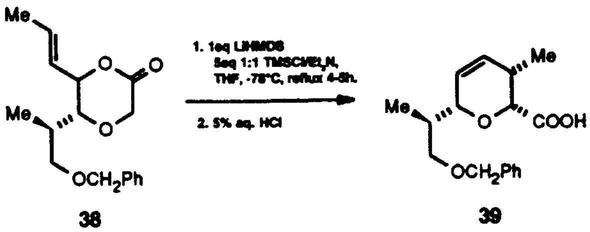


(a): 1. hexamethyldisilazane/reflux
2. LICA/THF/-76°C
3. TMSCl/-78°C to reflux

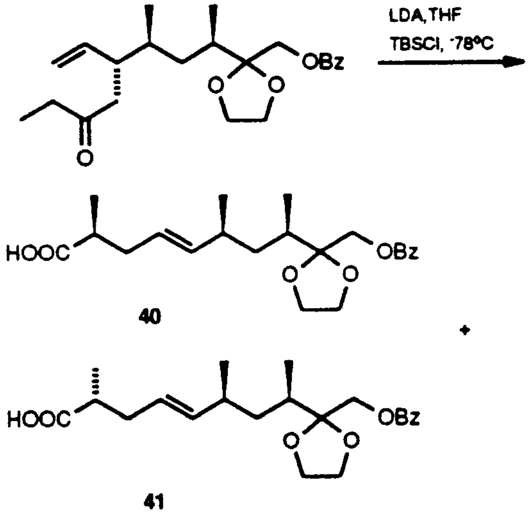
Scheme 24



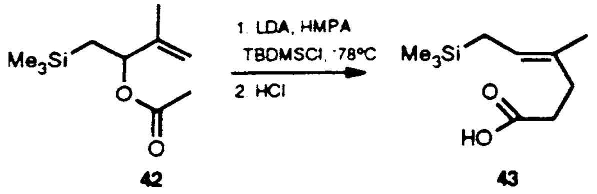
Scheme 25



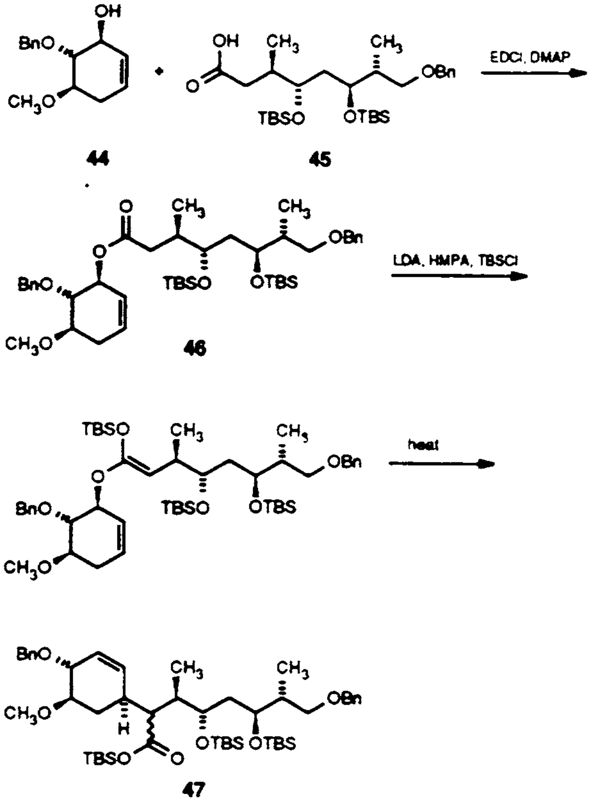
Scheme 26



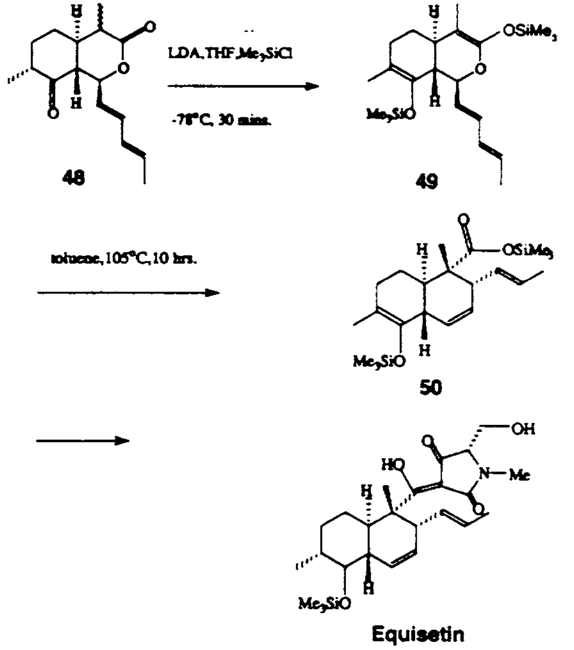
Scheme 27



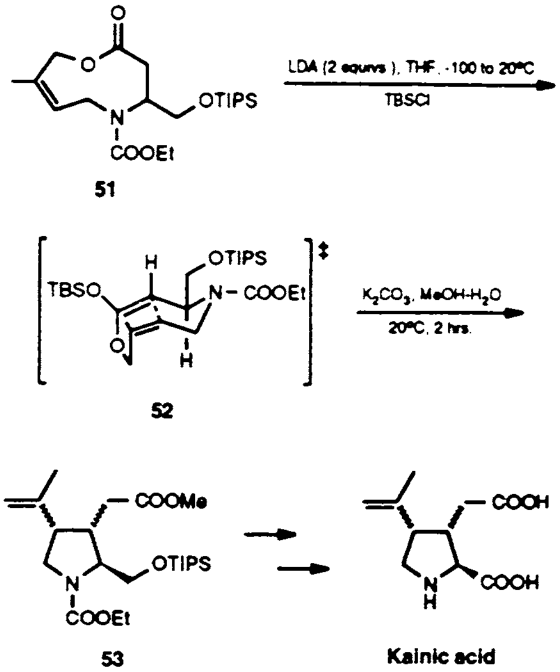
Scheme 28



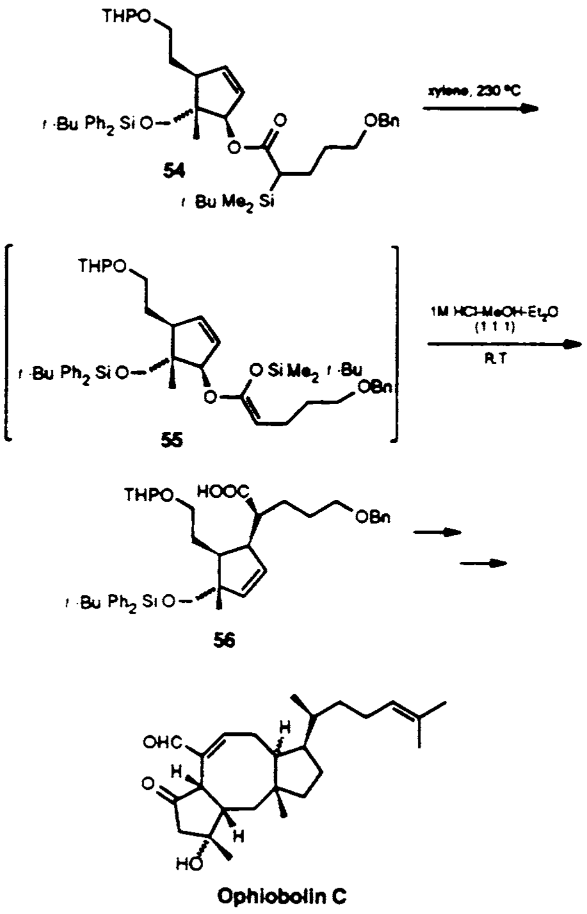
Scheme 29



Scheme 30



Scheme 31



The Ireland-Claisen rearrangement has also been used in syntheses involving the ring contraction of lactones (Claisen contraction). For example, Knight and co-workers have devised a strategy for the enantiospecific total synthesis of (-)-α-kainic acid using ring contraction of lactone (**51**) to pyrrolidinedicarboxylic acid (**53**) in 55% overall yield (**Scheme 30**).[55] The silyl ketene acetal **52** was proposed to rearrange through a boat transition state.

Another excellent example of Claisen ring contraction was reported by Funk for the preparation of the in,out-bicyclo[4.4.1]undecan-7-one core of the potent tumor promoter ingenol G49.[56]

In Kishi's total synthesis of ophiobolin C the silyl ketene acetal **55** prepared from **54** rearranged to stereoisomer **56** in 72% overall yield and 6:1 diastereoselectivity (**Scheme 31**).[37]

Conclusion

Over the years the discipline of synthetic organic chemistry has seen a trend towards the catalyzed stereoselective synthesis of natural products. These natural products often contain large carbocyclic rings and polyether fragments of well defined stereochemistry. The Claisen rearrangement,[57] reported more than 80 years ago, has remained an important synthetic tool.[58] The Ireland modification of this rearrangement enables the chemist to have better control over diastereoselectivity and to apply it to unsaturated esters. The Ireland-Claisen rearrangement has often been used to synthesize large carbocyclic structures with complex stereochemistry and will continue to be an important synthetic strategy in this class of compounds. The discovery that the Claisen rearrangement is routinely used by nature in the synthesis of aromatic amino acids via the shikimic acid pathway emphasizes the importance of the rearrangement in the synthetic preparation of these chiral natural products and others.[58]

Recent developments involving the use of organotin and organoboron chemistry have given excellent enantioselectivities (ca. 98% e.e.). In an age where high enantiomeric excesses and stereoselectivity are the order of the day, the rearrangements with organotin and organoboron reagents will be used more frequently in the future.

However, there are several areas that still have not been actively researched. Synthetic work involving the Claisen rearrangement (though not the Ireland-Claisen rearrangement) has already been investigated using organoaluminum as the diastereoselective agent, and has shown great promise for higher diastereoselectivity.[59] These, as well as other organometallic agents, should be utilized in the Ireland-Claisen rearrangements and may well enhance the diastereomeric selectivity currently achieved.

The effect of electron withdrawing substituents on the allylic ester is also significant. Welch and co-workers have studied the ester enolate rearrangement of allyl α-fluoroacetates and propanoates and demonstrated these rearrangements to be fairly selective.[60]

The aspect of diastereoselective synthesis of large carbocycles also leaves ample room for improvement of the rearrangement. For example, this topic has not been systematically investigated with the use of organometallic or lanthanide catalysts/diastereoselective agents which are now known to exert a significant chelation effect. The "double" Ireland-Claisen rearrangement described earlier could well be investigated for various chain lengths and cyclic compounds.

Another area which has received considerable attention is that of biochemical catalysis. A recent publication reports a highly stereospecific Claisen rearrangement catalyzed by an antibody.[61]

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About the Authors

Schubert Pereira was born in Bombay, India in 1967. He received his BSc and MSc from the Bombay University in 1987 and 1989 respectively. After working in the cosmetics R & D industry in India for a few years, he joined the University of Toledo's doctoral program in chemistry where he is engaged in the synthesis of siderophores for magnetic resonance imaging.

Professor Morris Srebnik received his PhD from the Hebrew University in Jerusalem in 1984, under the direction of Raphael Mechoulam. In 1985/86 he went to Purdue University on a Lady Davis Fellowship where he worked with Professor H.C. Brown on the asymmetric chemistry of organoboranes. Except for a sojourn during 1986/87 at the Aldrich Chemical Company, he remained at Purdue until 1990 when he moved to the Department of Chemistry at the University of Toledo. His research group, consisting of MSc, PhD and undergraduate students, is exploring the chemistry of organozincs, organoboranes, transmetallations and asymmetric catalysis.

Below are a few of the products discussed in the previous article

24,661-1	**Lithium diisopropylamide,** 97%	**25g $61.20; 100g $176.20**
29,696-1	**Lithium diisopropylamide,** 10 wt.% suspension in hexanes	**75g $15.70; 500g $66.40**
36,179-8	**Lithium diisopropylamide,** 2.0*M* solution in heptane/THF/ethylbenzene	**100ml $20.90; 800ml $99.00**
38,441-0	**Chlorotrimethylsilane,** 1.0*M* solution in THF	**100ml $10.00; 800ml $59.00**
38,543-3	**Chlorotrimethylsilane,** 1.0*M* solution in dichloromethane	**100ml $10.00; 800ml $59.00**
38,652-9	**Chlorotrimethylsilane,** redistilled, 99+%	**100ml $22.00; 800ml $130.00**
C7285-4	**Chlorotrimethylsilane,** 98%	**5ml $5.50; 100ml $10.20; 500ml $22.80**
19,050-0	*tert*-**Butyldimethylsilyl chloride,** 97%	**1g $5.70; 5g $14.40; 25g $46.60; 100g $130.00**
37,295-1	*tert*-**Butyldimethylsilyl chloride,** 1.0*M* solution in THF	**100ml $39.00**
38,442-9	*tert*-**Butyldimethylsilyl chloride,** 1.0*M* solution in dichloromethane	**100ml $39.00**
H1160-2	**Hexamethylphosphoramide,** 99%	**5g $10.65; 100g $21.20**
T2250-0	***N,N,N',N'*-Tetramethylethylenediamine,** 99%	**5ml $8.50; 100ml $13.75; 500ml $44.10**
25,156-9	**1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone,** 99%	**25g $10.10; 100g $17.70; 500g $59.00**
13,206-3	**Triethylamine,** 99%	**500ml $20.00; 2L $43.80**
23,962-3	**Triethylamine,** 99+%	**50g $19.80**
25,452-5	*tert*-**Butyl propionate,** 99%	**25g $31.20; 100g $85.65**
38,764-9	***N,N*-Diisopropylethylamine**, redistilled, 99.5%	**100ml $23.00; 800ml $135.00**
D12,580-6	***N,N*-Diisopropylethylamine,** 99%	**5ml $10.65; 100ml $19.85; 500mL $64.85**
37,921-2	**1,1,1,3,3,3-Hexamethyldisilazane,** 99.9%	**25ml $11.00; 100ml $30.00**
H1000-2	**1,1,1,3,3,3-Hexamethyldisilazane,** 98%	**25ml $7.90; 100ml $17.05; 500ml $39.45**
10,770-0	**4-Dimethylaminopyridine,** 99%	**5g $9.10; 25g $28.85; 100g $85.15**
33,245-3	**4-Dimethylaminopyridine,** 99+%	**5g $16.20**
23,953-4	**Diisopropylamine,** 99+%	**50g $9.70**
11,001-9	**Diisopropylamine,** 99%	**100ml $9.20; 500ml $13.20; 2L $32.10**
38,646-4	**Diisopropylamine,** redistilled, 99.5%	**100ml $19.00**
18,617-1	**Butyllithium,** 1.6*M* solution in hexanes	**100ml $14.50; 800ml $32.80; 8L $191.10; 18L $375.60**
23,070-7	**Butyllithium,** 2.5*M* solution in hexanes	**100ml $17.90; 800ml $45.60; 8L $275.60; 18L $497.00**
23,071-5	**Butyllithium,** 10.0*M* solution in hexanes	**100ml $31.10; 800ml $183.90; 8L $789.15; 18L $1520.80**
30,210-4	**Butyllithium,** 2.0*M* solution in pentane	**100ml $13.10; 800ml $63.90**
30,212-0	**Butyllithium,** 2.0*M* solution in cyclohexane	**100ml $13.10; 800ml $63.90**
19,559-6	*sec*-**Butyllithium,** 1.3*M* solution in cyclohexane	**100ml $17.00; 800ml $40.90**
40,365-2	*sec*-**Butyllithium,** 1.3*M* solution in cyclohexane/heptane (90:10)	**100ml $21.00; 800ml $41.00**
18,619-8	*tert*-**Butyllithium,** 1.7*M* solution in pentane	**100ml $17.50; 800ml $57.60; 8L $407.70; 18L $801.40**
24,172-5	**Triisopropylsilyl chloride,** 98%	**1g $7.45; 10g $41.60; 50g $125.80**
19,553-7	*tert*-**Butylchlorodiphenylsilane,** 98%	**2g $6.90; 10g $21.40; 50g $75.10**
D2800-0	**Diazald,** 99%	**25g $8.85; 100g $26.75; 500g $79.65; 1kg $137.50**
Z10,025-0	**Diazald Kit**	**$402.30**
Z10,889-8	**Mini Diazald apparatus,** with ₮ 19/22 clear-seal joints	**$179.00**
Z10,851-0	**Macro diazald kit,** with ₮ 24/40 clear-seal joints	**$595.00**
Z21,353-5	**Macro diazald kit,** ₮ 24/40, with a 1000ml receiver flask	**$595.00**
12,994-1	**1-Methyl-3-nitro-1-nitrosoguanidine,** 97%	**10g $23.00; 25g $41.45**
Z10,100-1	**MNNG-Diazomethane generation apparatus,** millimole size, with "O"-ring	**$75.40**
Z10,148-6	**Rubber septum and cap,** for millimole-size MNNG apparatus	**$14.30/12**
Z10,159-1	**MNNG Diazomethane generation apparatus,** millimole size/clear seal joints	**$69.45**
Z10,151-6	**"O"-ring,** for millimole-size MNNG apparatus	**$28.50/12**

General References:

Organometallics in Organic Synthesis, Schlosser, M., Ed.; Wiley: New York, 1994.

Organolithium Methods, Wakefield, B. J.; Academic Press: London, 1988.

The Chemistry of Organolithium Compounds, Wakefield, B. J.; Pergamon, New York, 1974.

Industrial Production of Organolithium Reagents:

$$\underset{}{RCl} + \underset{\text{(dispersion, 0.5-2\% Na)}}{2\ Li} \longrightarrow RLi + LiCl + \Delta$$

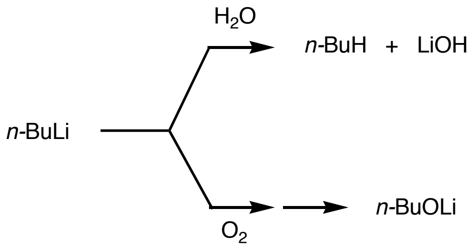
- Organolithium formation is carried out in hydrocarbon solvents. Afterwards, lithium chloride is removed and the solution is concentrated to as much as 90% w/w.
- Metalation occurs through a radical pathway. Sodium intitates and accelerates this highly exothermic reaction.

Availability (conc. in w/w):

n-butyllithium	15%, 23%, 50%, and 90% in hexane 20% in cyclohexane 20% in toluene
sec-butyllithium	10% in isopentane 12% in cyclohexane
tert-butyllithium	15% in pentane 15% in hexane
methyllithium	5% in ethyl ether 6.4% in ethyl ether containing *ca* 10% LiBr 2.6% in cumene-THF containing 0.5% methylmagnesium
ethyllithium	2% in hexane
phenyllithium	20% in cyclohexane-ethyl ether
lithium acetylide	solid complex with ethylenediamine

Organometallics in Organic Synthesis, Schlosser, M., Ed., p. 170, Wiley: New York, 1994.

Handling of Organolithium Reagents:



- Contact with oxygen or water leads to stoichiometric loss of alkyllithium titre.

$$n\text{-BuLi} \xrightarrow[> 50\ °C]{\Delta} CH_2{=}CHCH_2CH_3 + LiH$$

Ziegler, K.; Gellert, H. G. *Liebigs Ann. Chem.* **1950**, *567*, 179.

- Thermal decomposition of *n*-butyllithium produces butene and lithium hydride.

Decomposition Rates (% material lost per day)

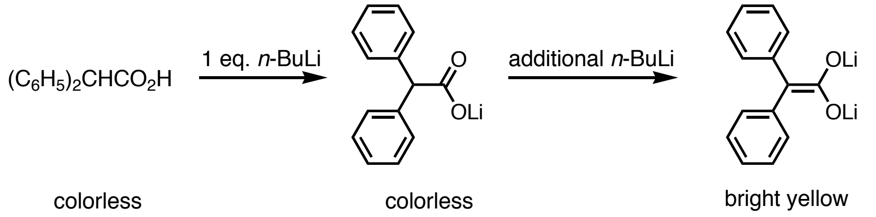
Storage Temperature (°C)	*n*-BuLi 15-20% in hexane	*n*-BuLi 90% in hexane	*sec*-BuLi 10-12% in isopentane
0	0.00001	0.0005	0.003
5	0.0002	0.0011	0.006
10	0.0004	0.0025	0.012
20	0.0018	0.013	0.047
35	0.017	0.11	0.32

Organometallics in Organic Synthesis, Schlosser, M., Ed., p. 171, Wiley: New York, 1994.

- These factors, along with solvent evaporation, can cause concentrations of alkyllithium reagents to fluctuate over time. For careful experimental work it is important to titrate alkyllithium reagents regularly.

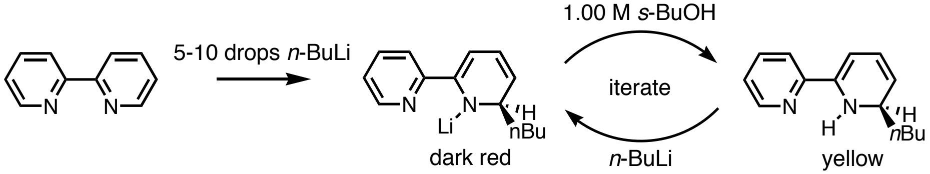
Dionicio Siegel, Jason Brubaker

Titration:



Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

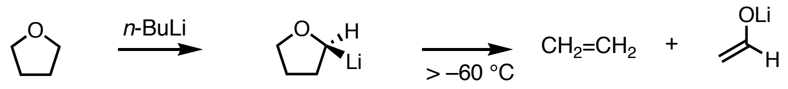
- Treatment of non-hygroscopic diphenylacetic acid with one equivalent of *n*-BuLi results in the formation of the lithium carboxylate. Additional *n*-BuLi generates the corresponding enolate, producing a slight yellow color and indicating that one equivalent has been added.

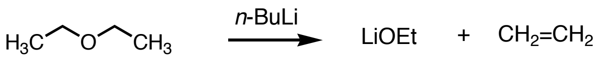


Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
Gau, M.; House, H. O. *Org. Syn.* Collective Volume VI, 121.

- Double titration methods allow for multiple titrations in a single flask, and in this case only *n*-BuLi is measured.

Organolithium Reactions with Ethereal Solvents:





- In general, the relative rates of reaction of alkyllithium reagents with ethers are DME (100 X) > THF (100 X) > diethyl ether.

- The reaction of *n*-BuLi with THF produces the enolate of acetaldehyde, which is difficult to form cleanly by direct deprotonation of acetaldehyde.

Reaction of *n*-butyllithium with ethers

Ether	Temp (°C)	$t_{1/2}$
ethyl ether	25	6 d
	35	31 h
isopropyl ether	25	18 d
DME	25	10 min
THF	0	23.5 h
	–30	5 d

Organometallics in Organic Synthesis, Schlosser, M., Ed., p. 172, Wiley: New York, 1994.

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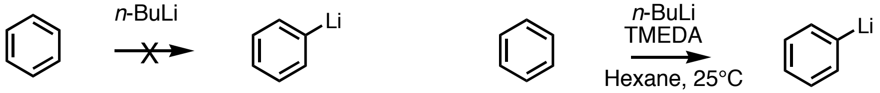
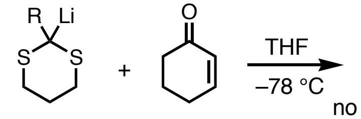
Additives:

- Additives are often used to enhance the reactivity of alkyllithium reagents. Common additives are tetramethylethylenediamine (TMEDA), hexamethylphosphoramide (HMPA), and potassium *tert*-butoxide.



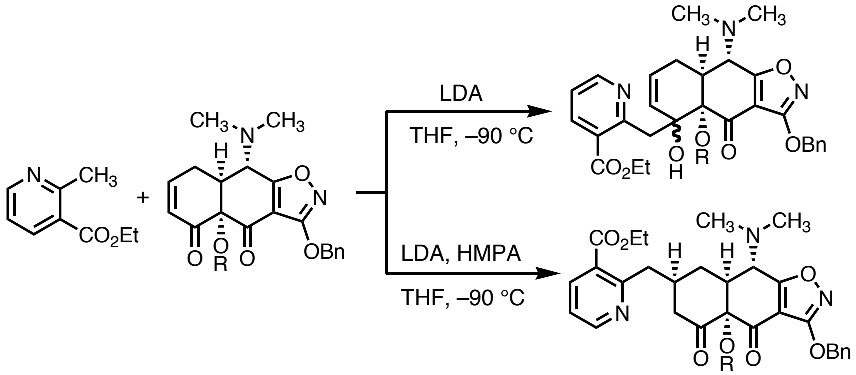
Chalk, A. J.; Hoogeboom, T. J. *J. Organomet. Chem.* **1968**, *11*, 615.

- Treatment of benzene with *n*-BuLi leads to little or no reaction, where as addition of TMEDA leads to quantitative lithiation.



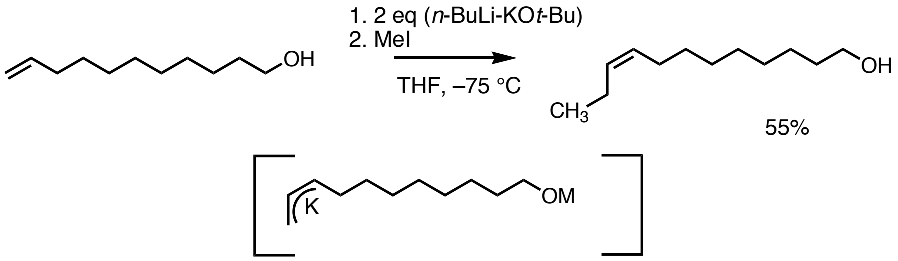
	1,2 addition	1,4 addition
no additive:	>99	0
HMPA:	<5	>95

Sikorski, W. H., Reich, H. J.; *J. Am. Chem. Soc.* **2001**, *123*, 6527.



Brubaker, J. D.; Myers, A. G.; *unpublished*

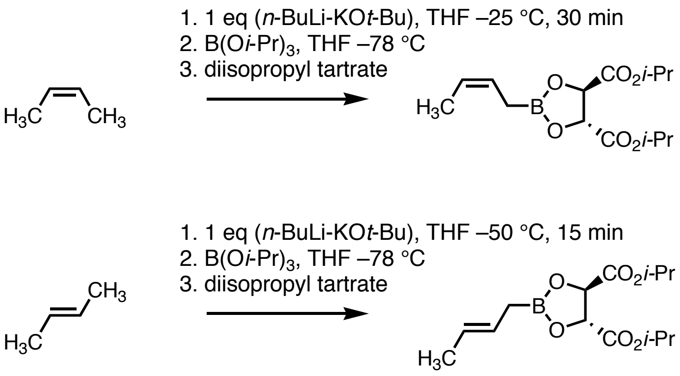
- HMPA (1-2 equiv) can sometimes change the regioselectivity from 1,2- to 1,4- in the addition of stabilized organolithium reagents to α,β-unsaturated carbonyl compounds.



Z–η^3-allylpotassium intermediate

Schlosser, M. *Pure Appl. Chem.* **1988**, *11*, 1627.

- Alkyllithium reagents combined with potassium alcoholates ("LICKOR" reagents) provide highly activated and yet selective organometallic reagents. The reaction depicted above provides an η^3-allylpotassium reagent. The Z isomer is favored (ratio 20:1 Z:E at –50 °C). Alkylation of allylpotassium reagents usually occurs at the unsubstituted terminus.



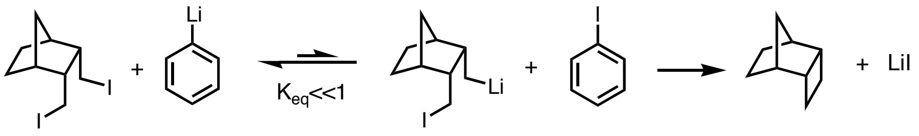
Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579.

- The LICKOR base system allows for the stereospecific preparation of synthetically important crotylboronate reagents from butene.

$$\text{RLi} + \text{R'X} \rightleftharpoons \text{RX} + \text{R'Li}$$

- Lithium-halogen exchange reactions are kinetically controlled. The position of the equilibrium varies with the stabilities of the carbanion intermediates involved (sp >> sp_2 >> sp_3).

$$n\text{-PrLi} + \text{PhI} \underset{1:10{,}000}{\rightleftharpoons} n\text{PrI} + \text{PhLi}$$



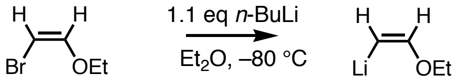
- In the above example, internal trapping of the newly formed alkyllithium reagent by alkylation drives an otherwise unfavorable exchange reaction.

- Alkyliodides are more reactive than the corresponding bromides. Alkylchlorides are essentially inert.

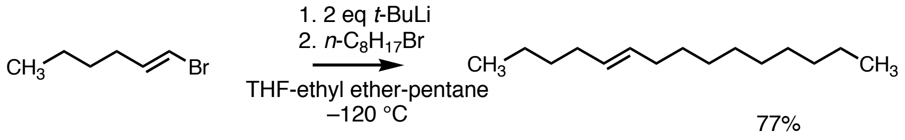
$$2\ t\text{-BuLi} + \text{RI} \rightleftharpoons t\text{-BuI} + \text{RLi}$$

$$t\text{-BuI} \xrightarrow{t\text{-BuLi}} \text{isobutene} + \text{isobutane} + \text{LiI}$$

- Lithium-halogen exchange reactions using *t*-BuLi typically employ two or more equivalents of *t*-BuLi. The first equivalent is used for the exchange and the second equivalent reacts with the *t*-BuI produced, to form isobutene, isobutane, and lithium iodide.

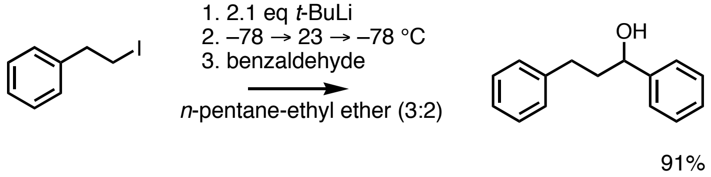


Lau, K. S.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.



Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, *52*, 4839.

- Lithium-halogen exchange of vinyl halides is stereospecific, proceeding with retention of configuration.



Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

- Aliphatic alkyllithium reagents are normally prepared from the corresponding primary iodides at low temperature in a pentane-ether solvent system.

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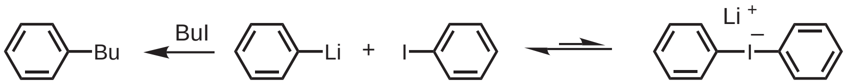
Mechanism of Lithium-Halogen Exchange:

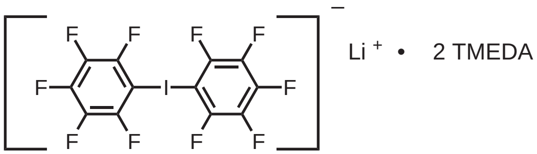
Review:

Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.



Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101.

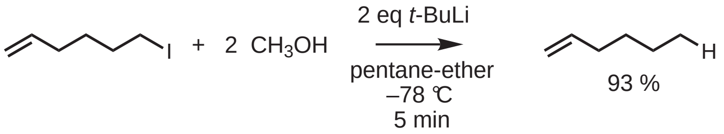
- Added phenyl iodide slows the reaction of butyl iodide with phenyllithium, providing evidence for the intermediacy of a less reactive "ate-complex".



Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449.

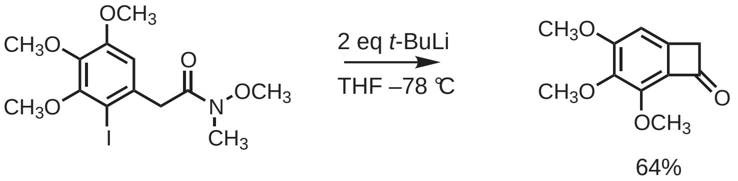
- An X-ray crystal structure of lithium bis(pentafluorophenyl) iodinate complexed with TMEDA has been obtained, providing support for the intermediacy of ate complexes during lithium-halogen exchange.

- Lithium-halogen exchange is extremely fast. In some instances, the rate of lithium-halogen exchange can exceed the rate of proton transfer.

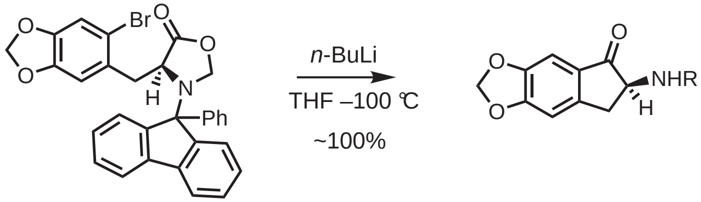


Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861.

- Lithium-halogen exchange is typically more rapid than addition reactions that might compete.



Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.



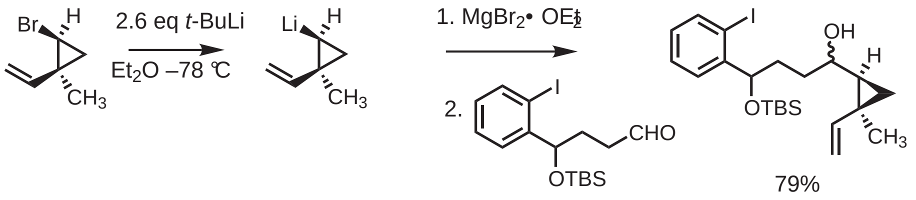
Paleo, M. R.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1993**, *58*, 2763.

- The 9-phenylfluorenyl protecting group is particularly useful in minimizing the rate of epimerization of adjacent labile centers, such as the α-amino ketone above.

Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

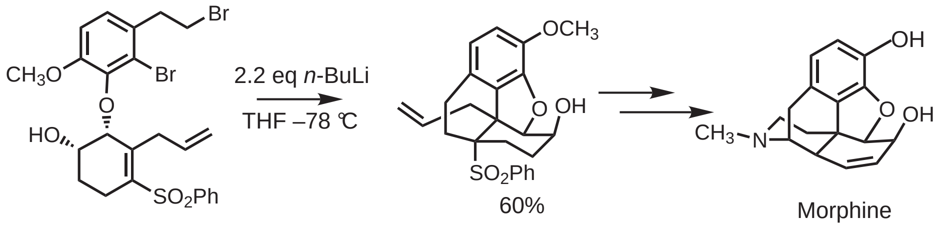
Dionicio Siegel

Examples of Lithium-Halogen Exchange in Synthesis:



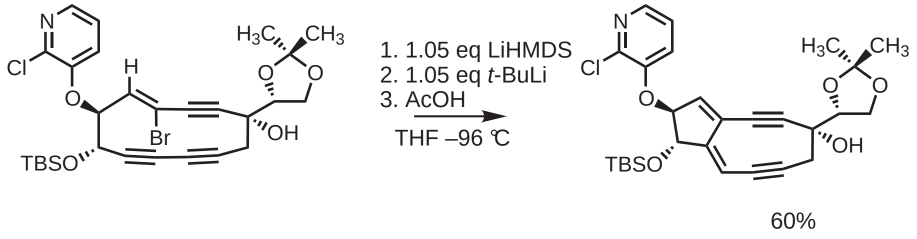
Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031.

- Cyclopropyl bromides, unlike normal aliphatic bromides, can be reliably converted to the corresponding organolithium reagents. Pretreatment of the cyclopropyl anion with magnesium bromide ethyl etherate in the example above prevents a second, unwanted lithium-halogen exchange reaction from occuring between the cyclopropyllithium reagent and the aryl iodide.

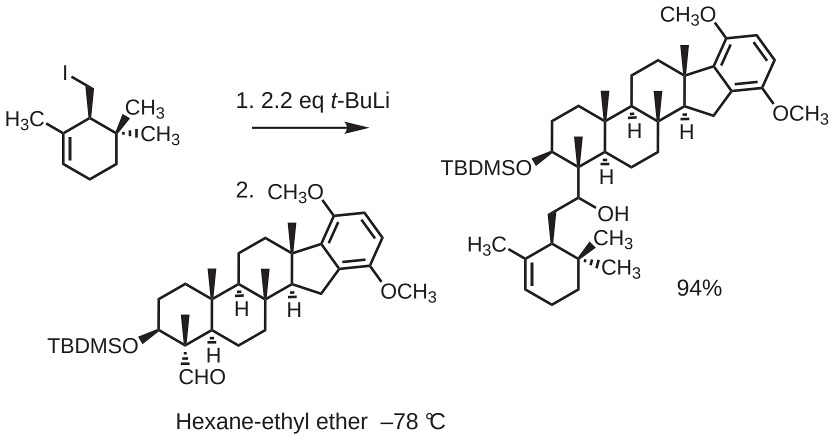


Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1986**, *52*, 473.

- Consider the relative rates of the processes that must occur in the above transformation.



Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2732.



Bogenstatter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206.

Review:

Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Ahn Vu, V. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4302.

General References on the Preparation and Reactions of Grignard Reagents:

Main Group Metals in Organic Synthesis, Yamamoto, H., Oshima, K., Eds.; John Wiley and Sons: New York, **2004**.

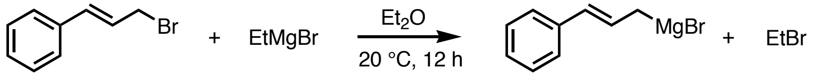
Handbook of Grignard Reagents, Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, **1996**.

Organomagnesium Methods in Organic Synthesis, Wakefield, B. J.; Academic Press: San Diego, **1995**.

Development and General Aspects:

$$\boxed{\mathrm{RX} + \mathrm{R'MgX'} \rightleftharpoons \mathrm{RMgX'} + \mathrm{R'X}}$$

- Analogous to lithium-halogen exchange. The position of the equilibrium varies with the stabilities of the carbanion intermediates involved (sp >> sp^2 >> sp^3).



Prévost, C. *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.

- Although the first example was reported in 1931 (above), the preparation of Grignard reagents via metal-halogen exchange has not been widely used until recently. Knochel and coworkers have demonstrated the functional-group tolerance of magnesium-halogen exchange, which is now the method of choice for the preparation of highly functionalized organomagnesium reagents.

- *i*-PrMgCl or *i*-PrMgBr are the most common reagents. In most cases, these reagents can be used interchangeably. *i*-PrMgBr is made by the Grignard reaction of isopropyl bromide and magnesium turnings. It is less soluble than the chloride (solutions are ~0.8 M), and the titre must be checked more often. *i*-PrMgCl is commercially available as a 2.0 M solution in THF or diethyl ether.

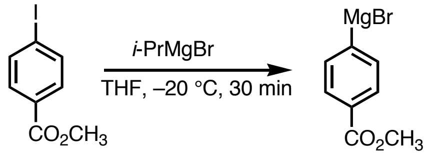
- Solutions of *i*-PrMgX are titrated by the method of Paquette (Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.) According to this procedure, a flame-dried flask is charged with menthol (a non-hygroscopic solid), 1,10-phenanthroline (indicator) and THF. The Grignard reagent is then added until a distinct violet or burgundy color persists.

- Unlike many lithium-halogen exchange protocols, only one equivalent of *i*-PrMgX is used in typical experimental procedures.

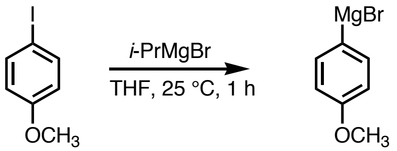
- THF is the most common solvent. Ethyl ether has been employed as a solvent for selective exchange of geminal dihalides to generate magnesium carbenoids.

- The reactivity of Grignard reagents is highly temperature dependant. Only highly reactive electrophiles such as aldehydes and ketones react at significant rates below 0 °C. This allows for the preparation of organomagnesium reagents containing cyano, nitro, ester, and imine functional groups, provided that the rate of the exchange reaction is fast enough to allow for exchange at temperatures below 0 °C.

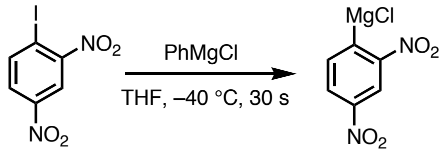
- The rate of magnesium-halogen exchange is accelerated by electron-withdrawing groups on the aromatic ring, and is slowed by electron-donating groups:



Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Ahn Vu, V.; Knochel, P. *Synthesis* **2002**, 565.



Cali, P.; Begtrup, M. *Synthesis* **2002**, 63.



Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1610.

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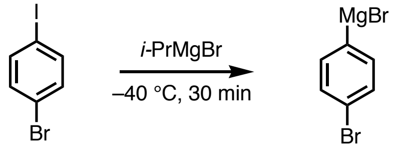
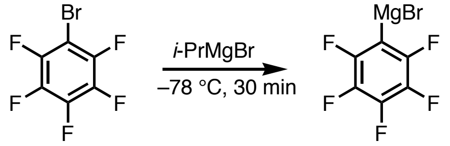
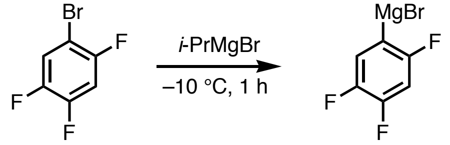
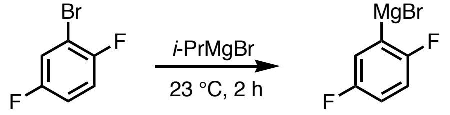
- Aryl bromides undergo exchange more slowly than iodides, but electron-poor aryl bromides can still react at temperatures below 0 °C.



Bomond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701.



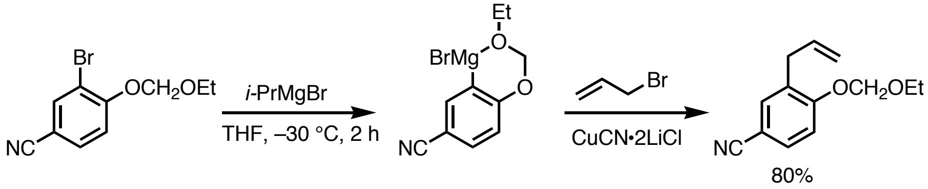




Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

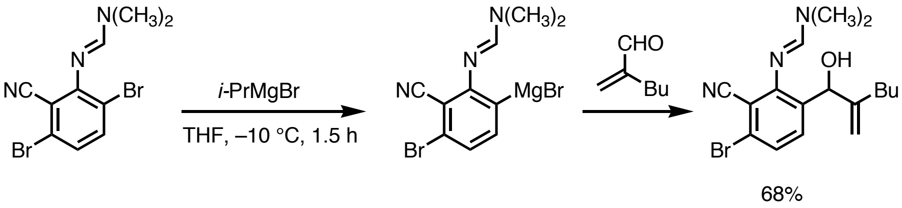
Ortho- **Directing Groups:**

- The presence of an chelating *ortho-* group facilitates exchange; increases the rate of reaction, and allows for low-temperature exchange.



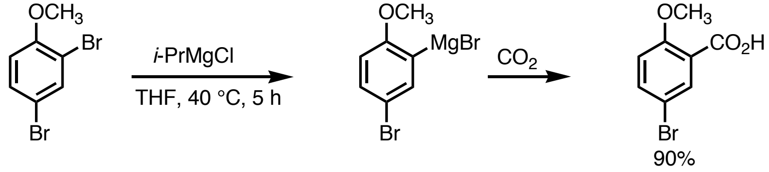
Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Ahn Vu, V. *Angew . Chem., Int. Ed. Engl.* **2003**, *42*, 4302.

- Dibromides undergo regioselective exchange of the bromine *ortho-* to a chelating group. Note also the compatibility of the amidine group with the exchange reaction.



Varchi, G.; Jensen, a. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 477.

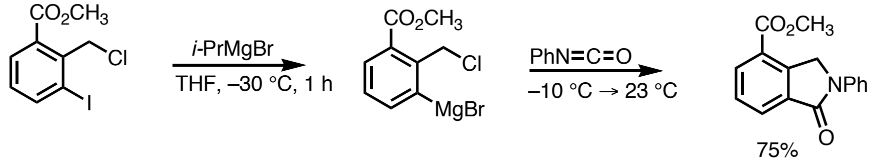
- Higher temperatures are required for the selective exchange with less effective chelators.



Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407.

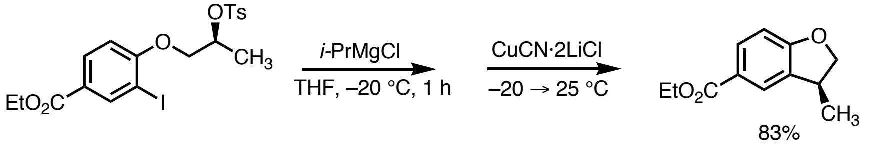
Functional Groups Compatible with the Magnesium-Halogen Exchange:

- Ester, benzylic chloride:



Delacroix, T.; Berillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108.

- Secondary alkyl tosylate:



Kneisel, F. F.; Monguchi, Y.; Knapp, K. M.; Zipse, H.; Knochel, P. *Tetrahedron* **2002**, *43*, 4875.

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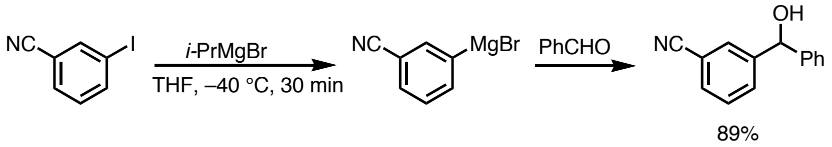
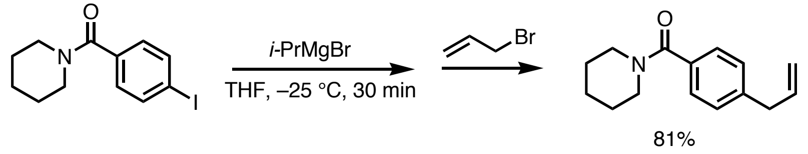
- Nitrile:

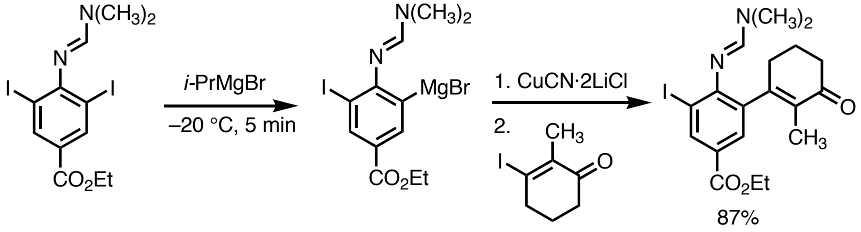


- Tertiary amide:



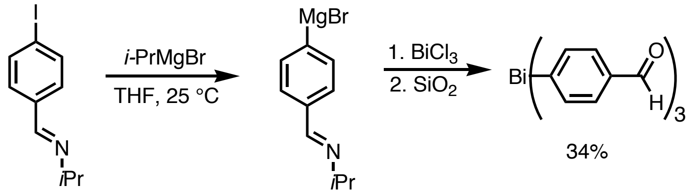
Bomond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701.

- Amidine, note also the selective exchange of a diiodide:



Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, *477.*

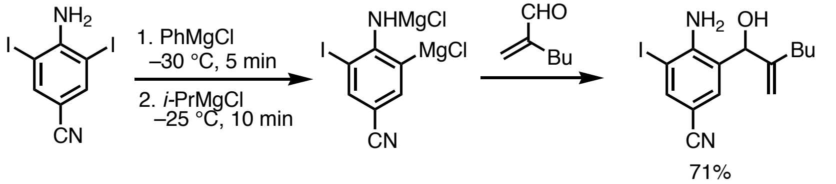
- Imine:



Murafuji, T.; Nishio, K.; Nagasue, M.; Tanabe, A.; Aono, M.; Sugihara, Y. *Synthesis* **2000**, 1208.

- Imines can be used to mask aryl aldehydes during the magnesium halogen exchange. The low yield of the reaction sequence above is likely attributable to the second step of the procedure.

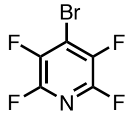
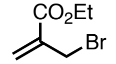
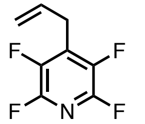
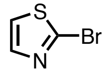
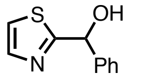
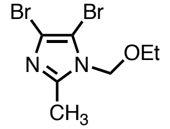
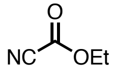
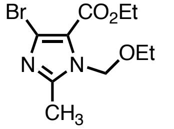
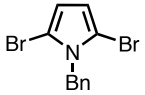
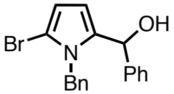
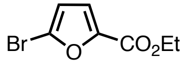
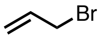
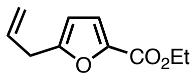
- Unprotected anilines:



Varchi, G.; Kofink, C.; Lindsay, D. M.; Ricci, A.; Seconi, G.; Knochel, P. *Chem. Commun.* **20**

- In the above example, phenyl magnesium chloride is first added because it is a strong base and as a magnesium-halogen exchange reagent it is less reactive than *i*-PrMgX. This allows for quantitative deprotonation before exchange.

- Heteroaromatics:

Heterocycle	Conditions[a] (°C, h)	Electrophile	Product	Yield (%)
	–40, 0.5	 (CuCN added)		80
	25, 1.5	PhCHO		75
	–20, 1			59
	–5, 1	PhCHO		73
	–30, 1	 (CuCN added)		80

[a] *i*-PrMgBr (1.2 equiv), THF

Abarbi, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

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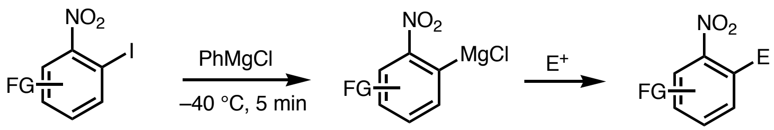
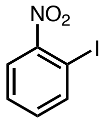
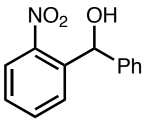
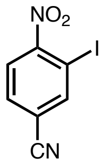
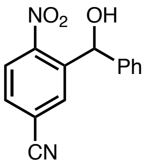
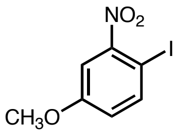
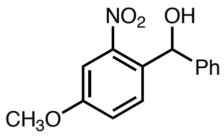
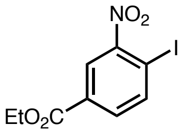
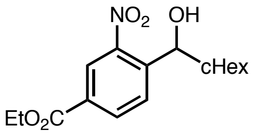
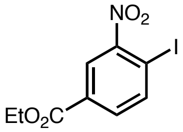
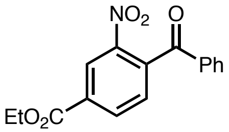
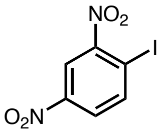
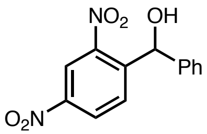
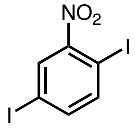
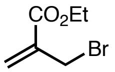
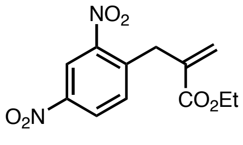
- Nitro arenes:



Nitro arene	Electrophile	Product	Yield (%)
	PhCHO		87
	PhCHO		94
	PhCHO		72
	cHexCHO		64
	PhCOBr		76
	PhCHO		81
			74

Sapountzis, Ioannis; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1610.

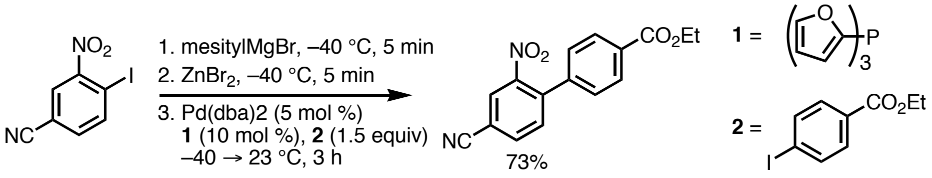
- Nitro-substituted organometallic reagents are difficult to prepare through classical methods. These electron-deficient arenes tend to undergo electron-transfer reactions, and direct oxidative addition with elemental magnesium or zinc often leads to reduction of the nitro group. This new procedure is the best method to date for the preparation of nitroarene organometallics.

- The nitro group must be *ortho* to the iodide exchanged. *Meta-* and *para*-nitro substituted aryl iodides give complex mixtures.

- PhMgCl is necessary for a successful reaction. More reactive Grignard reagents such as *i*-PrMgCl give complex mixtures.

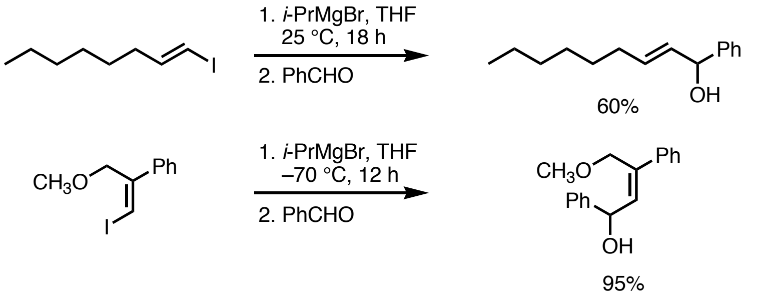
- For successful reactions with reactive electrophiles such as allyl bromides and acid halides, transmetallation of the organomagnesium intermediate with CuCN·2LiCl is necessary.

- Pd-catalyzed Negishi cross-coupling reactions are possible after transmetallation with $ZnBr_2$:



- In the case above, mesityl magnesium bromide is used to prevent competing oxidative addition of the aryl iodide generated in the magnesium-iodide exchange reaction.

Magnesium-Halogen Exchange of Vinyl Iodides:



Rottlander, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.

- Vinyl Iodides are also suitable substrates for magnesium-halogen exchange. Higher temperatures and longer reactions times are required, which limits the functional-group tolerance of this method.

- When the vinyl iodide is substituted with electron-withdrawing groups or chelating heteratoms, the rate of exchange is enhanced.

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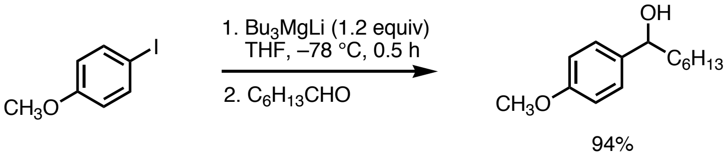
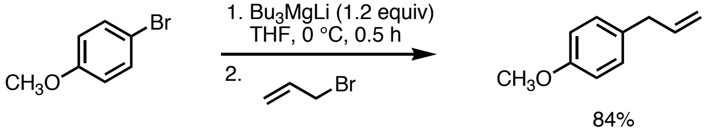
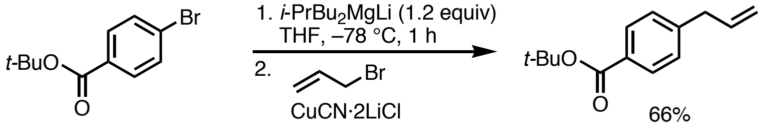
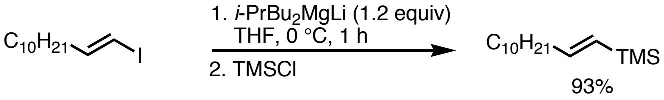
Alternative, More Reactive Reagent Combinations for Magnesium-Halogen Exchange:

- Lithium Trialkyl Magesium Ate Complexes:









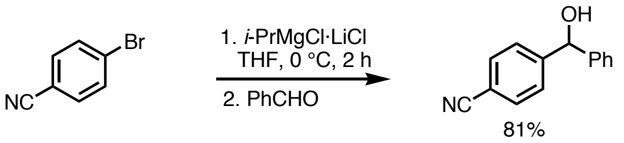
Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.

- The lithium trialkyl magnesiates are prepared in situ by the addition of an alkyl lithium (2 equiv) to an alkyl magnesium halide (1 equiv).

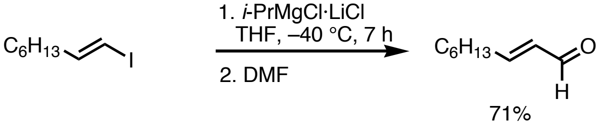
- Magnesiates exhibit a reactivity somewhere between alkyllithium and alkylmagnesium reagents.
- The exchange reaction is faster and less sensitive to electronic effects (arene substitution).

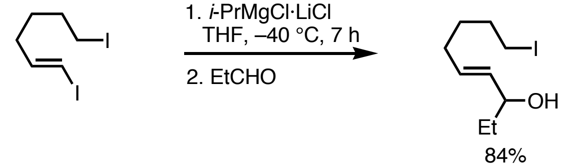
- In accord with their greater reactivity, aryl magnesiates show less funtional group tolerance.

- Enhanced Reactivity by Addition of Lithium Chloride to *i*-PrMgCl prior to exchange (1 equiv):



Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2004***, 43*, 3333.



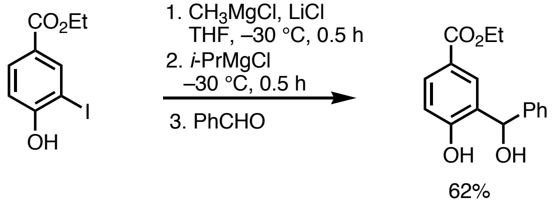


Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004***, 6*, 4215.

- Addition of LiCl to the Grignard reagent produces a more active magnesium-halogen exchange reagent

- It has been proposed that LiCl breaks up aggregates of organomagnesium reagents.

- This more active reagent combination is successful in the exchange of the *ortho*-phenoxy aryl iodide shown below:

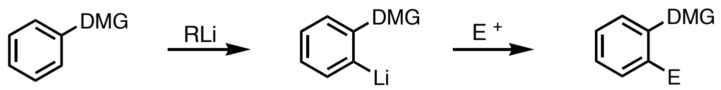


Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288.

Jason Brubaker

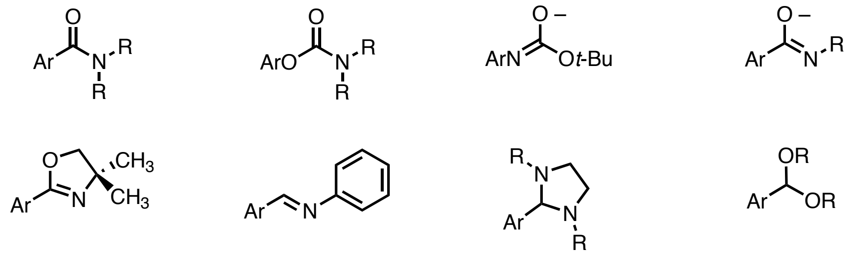
Review:

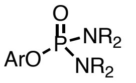
Snieckus, V. *Chem. Rev.* **1990**, 879.

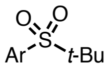


Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, *73*, 1197.

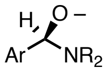
- Directed metalation of anisole with *n*-BuLi was discovered independently in 1939-1940 by Gilman and Wittig. This led to the discovery of more than 40 directing groups.







$ArCF_3$



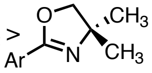
$ArOCH_2OCH_3$ $ArOCH_3$ ArO^- $ArCH_2O^-$

ArF ArCl $ArCH_2N(CH_3)_2$ $ArN(CH_3)_2$

Relative Rates of Directed Metalation:

SO_2NR_2, $CO\overline{N}R$, $CH_2NR_2 >$ $OCH_3 > CH_2CH_2NR_2$, CF_3, F, NR_2

Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.

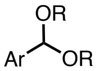
$CO\overline{N}R \geq CONR_2 >$  $> SO_2NR_2$, $SO_2\overline{N}R$, CH_2NR_2, OCH_3, Cl

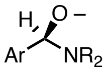
Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

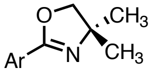
Beak, P.; Tse, A.; Hawkins, J.; Chen, C.; Mills, S. *Tetrahedron* **1983**, *39*, 1983.

- Protective groups that also serve as strong directing groups are especially useful:

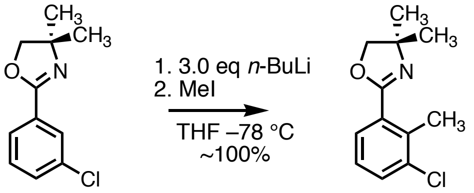
$ArOCH_2OCH_3$







- Meta oriented directing groups almost always direct metalation to the position ortho to both groups.



Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.

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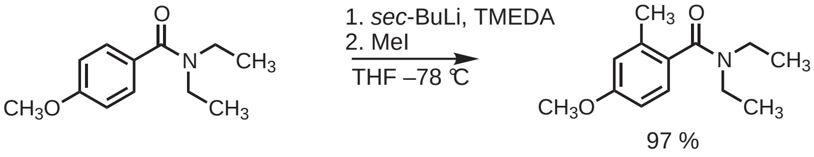
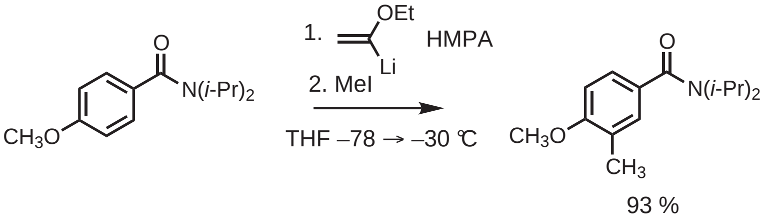
- Lithiation occurs ortho to the stronger directing group in cases were two lithiation sites are possible.



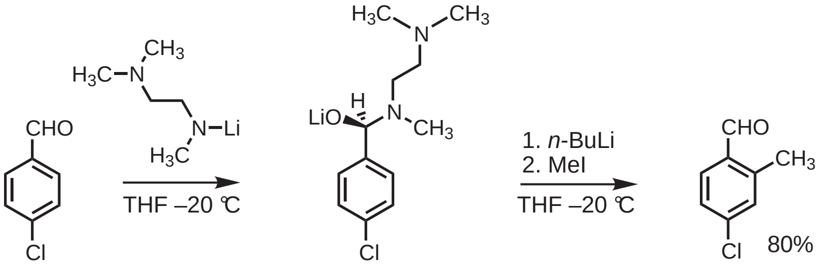
Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4386.

- Ethoxyvinyllithium (EVL) with HMPA shows a reversal in selectivity; the proton ortho to the methoxyl group is removed.



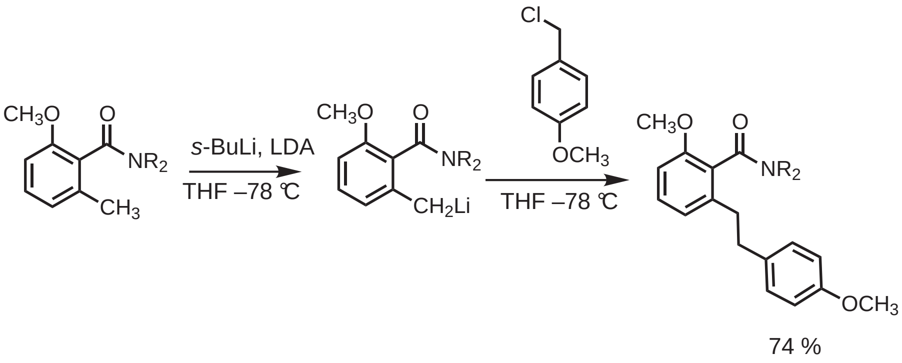
Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.

- Aldehydes can be transiently protected and, at the same time, transformed into a directing group by amide anion addition



Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

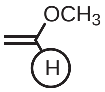
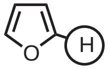
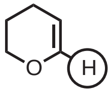
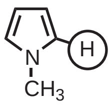
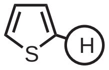
- Ortho tolyl anion formation is facile by directed metalation.



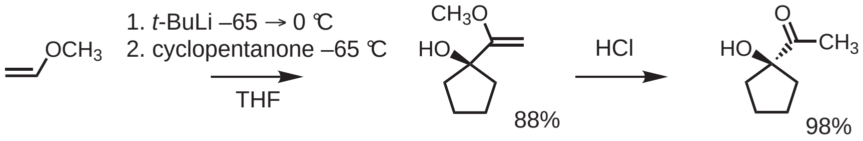
Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375.

Heterocycle and Vinyl Ether Metalation:

- Metalation of vinyl ethers and heterocycles occurs readily at the positions indicated.

- Vinyl ether anions provide an acyl anion equivalent.



Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

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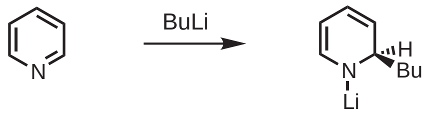
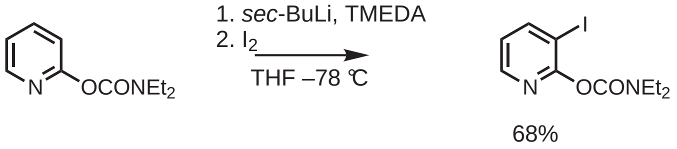
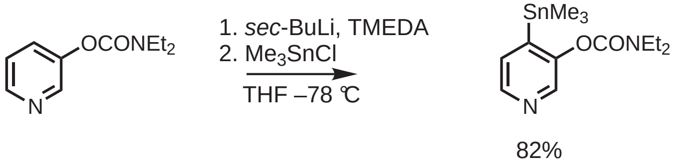
- Metalation of pyridine is complicated by 1,2-addition of the organometalic into the pyridine ring.



- With appropriate directing groups, lithiation of the pyridine ring can be efficient.

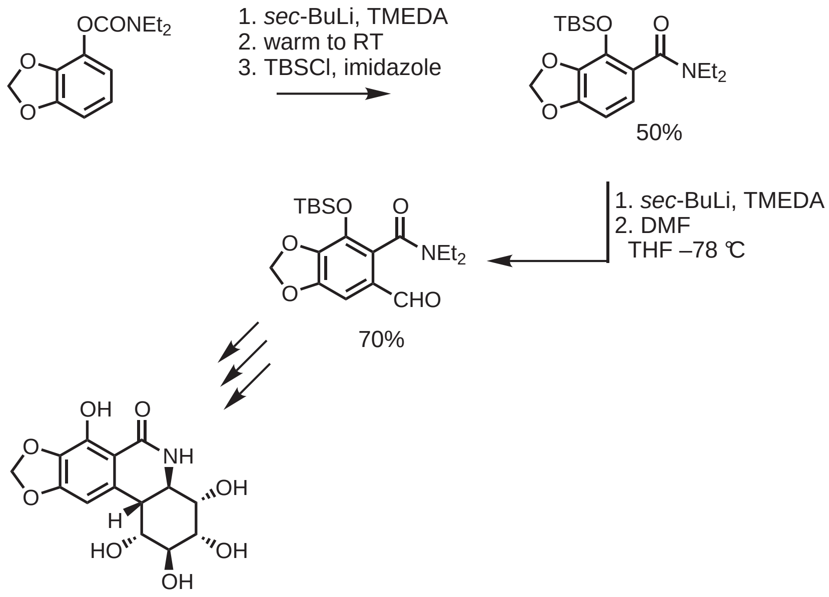




Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.

Examples of Directed Ortho Metalation in Synthesis:

- Carbamate directing groups can rearrange upon warming after lithiation. The resulting amide can be used for a second metalation reaction.



Pancratistatin

Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

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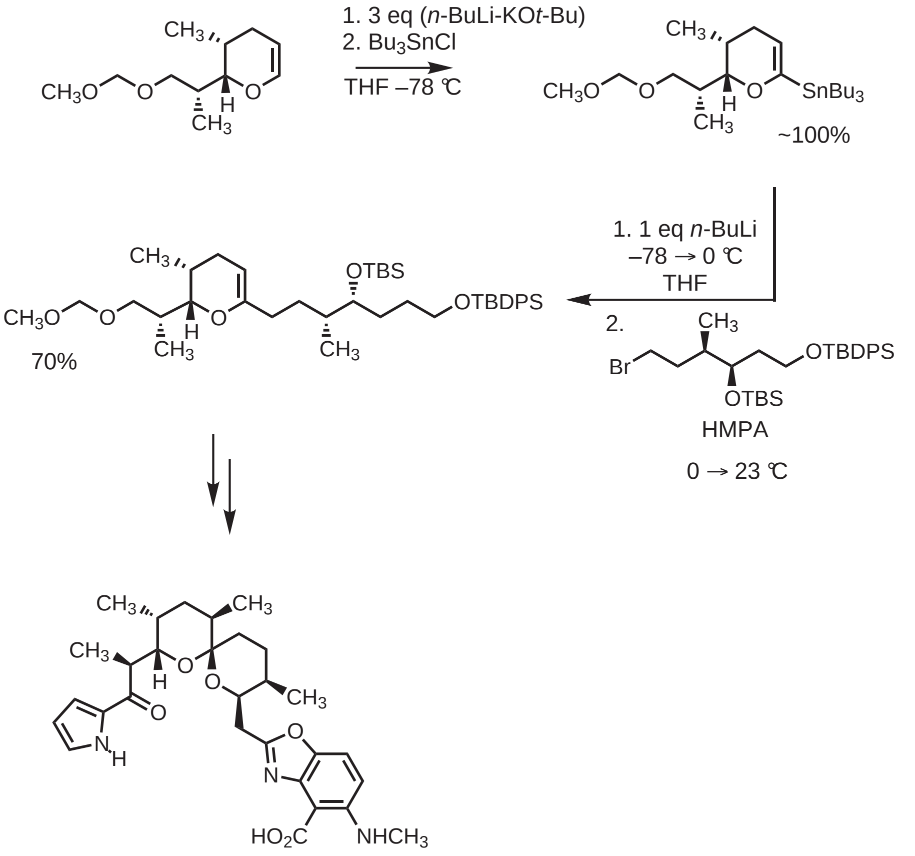
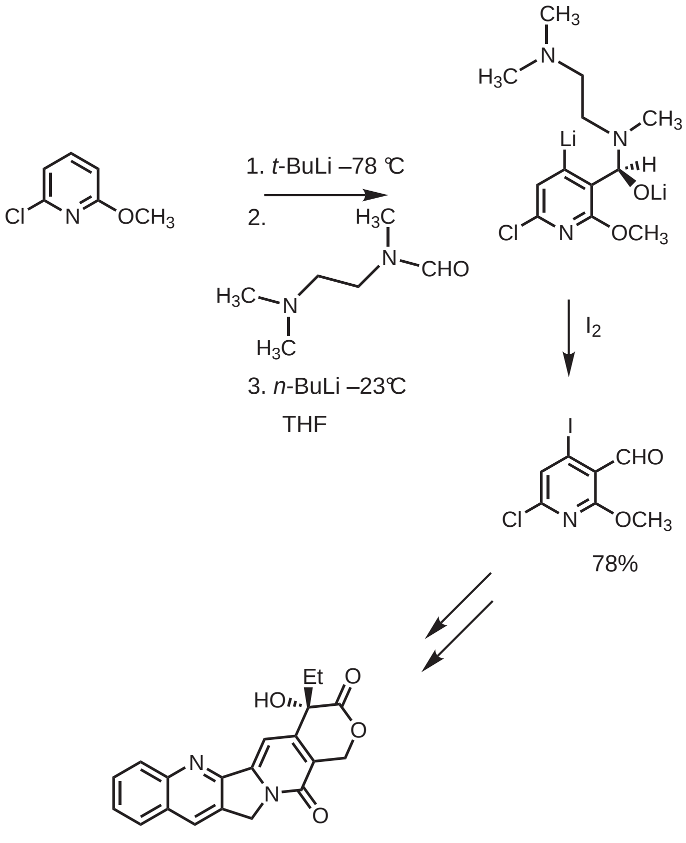


Calcimycin



(*S*)-camptothecin

- Note that treatment with *t*-BuLi alone failed to provide the desired anion. Trapping the anion under LICKOR conditions with tin provided a substrate that could be readily converted to the corresponding organolithium reagent.

Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.

- Lithiation adjacent to the methoxyl group followed by trapping with the formamide shown provides an α-amino alkoxide to direct a second metalation reaction.

Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

Dionicio Siegel

Reviews:

Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1–652.

Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, pp. 167–202.

Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; John Wiley & Sons: New York, **1998**.

Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

- Intramolecular:

Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246.

- Solid phase:

Franzén, R. *Can. J. Chem.* **2000**, *78*, 957–962.

Generalized Cross-Coupling:

$$R{-}X \quad + \quad R'{-}M \xrightarrow{\text{catalyst}} R{-}R' \quad + \quad M{-}X$$

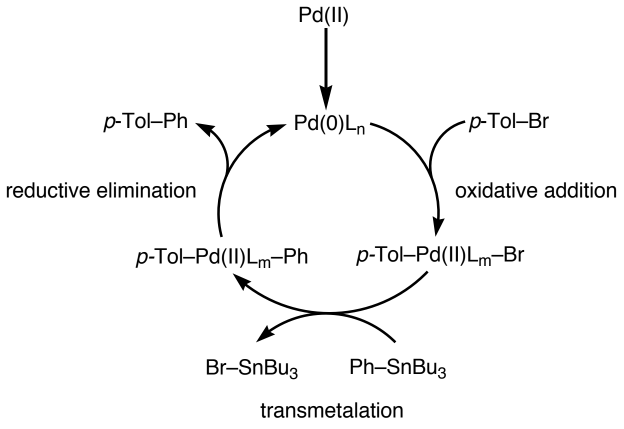
Typically:

- R and R' are sp^2–hybridized
- M = Sn, B, Zr, Zn
- X = I, OSO_2CF_3, Br, Cl
- catalyst = Pd (sometimes Ni)

Mechanism:

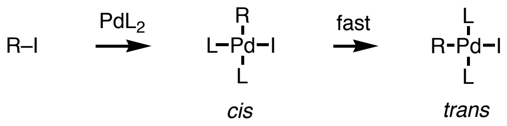
- A specific example:

$$p\text{-Tol–Br} \quad + \quad Ph{-}SnBu_3 \xrightarrow{\text{Pd catalyst}} p\text{-Tol–Ph} \quad + \quad Bu_3Sn{-}Br$$



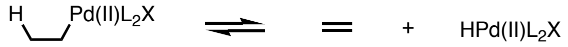
- Many functional groups are tolerated (e.g., CO_2R, CN, OH, CHO).

- Oxidative addition initally gives a *cis* complex that rapidly isomerizes to its *trans* isomer:



Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954–959.

- β-hydride elimination can be a serious side reaction within alkyl palladium intermediates.



- Oxidative addition and reductive elimination steps occur with retention of configuration for sp^2-hybridized substrates.

- Transmetalation is proposed to be the rate determining step with most substrates.

- Relative order of ligand transfer from Sn:

alkynyl > alkenyl > aryl > allyl = benzyl > α-alkoxyalkyl > alkyl

- The details of the mechanism are still being elucidated, and the mechanism may change with different reaction conditions:

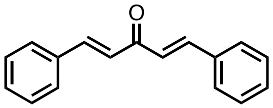
Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985.

Stille Reaction conditions:

- Catalyst: Commercially available Pd(II) or Pd(0) sources. Examples:

$Pd(PPh_3)_4$ $\quad$ $Pd(OAc)_2$ $\quad$ $Pd_2(dba)_3$

dba =



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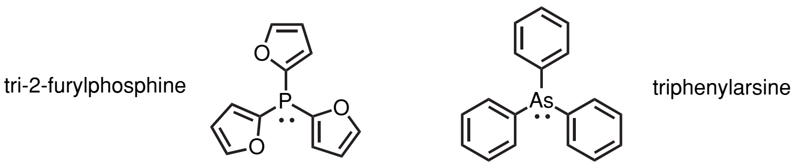
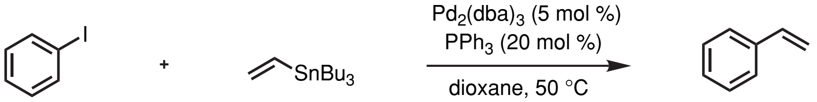
- Ligands: Phosphine (PR_3) ligands are often added when the Pd source doesn't contain strong ligands.

  Large rate enhancements (10^2–10^3) occur with poorly electron-donating ligands:



Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.

- Additives: CuI can increase the reaction rate by $>10^2$.

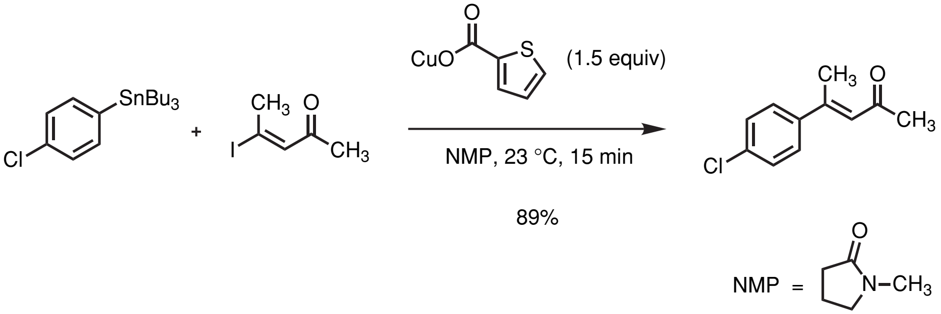


mol % CuI	relative rate
0	1
10	114

- The rate increase is attributed to the free ligand scavenging ability of CuI; strong ligands in solution are known to inhibit the rate-limiting transmetalation step.

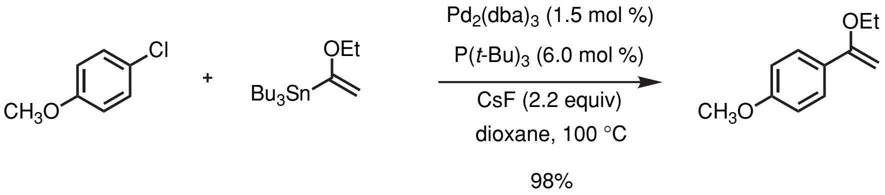
Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.

- Stoichiometric Cu itself can mediate cross-coupling reactions under mild conditions, without Pd.



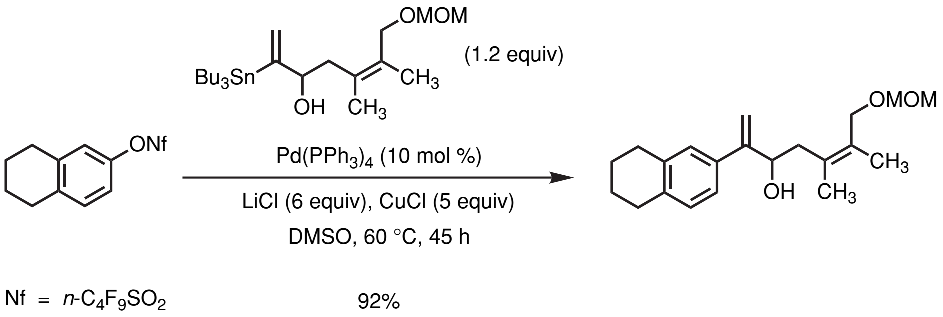
Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.

- A general Stille cross-coupling employing aryl chlorides (which are more abundant and less expensive than aryl iodides, aryl bromides, and aryl triflates) has been developed.

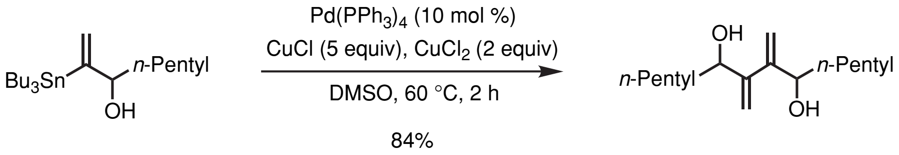


Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411-2413.

- 1-substituted vinylstannanes can be poor substrates for the Stille reaction, probably due to steric constraints. However, conditions have been discovered that afford the desired Stille coupling product in excellent yields.



- Transmetalation of Bu_3Sn with CuCl is proposed to increase the rate of this reaction. Isolation of the homocoupling product in the following experiment was taken as evidence for a transmetalation event.



Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.

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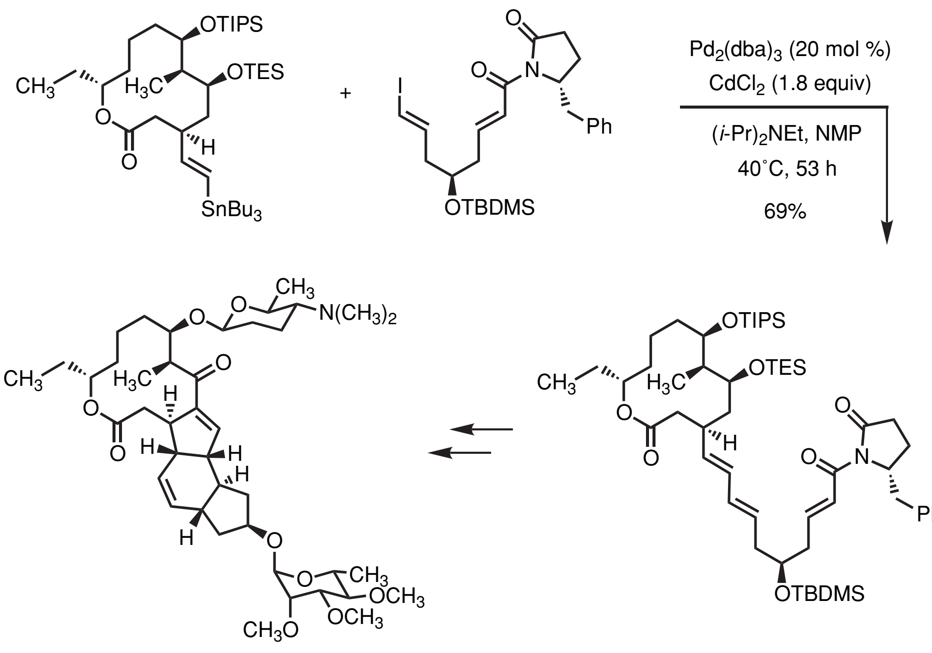
Examples:

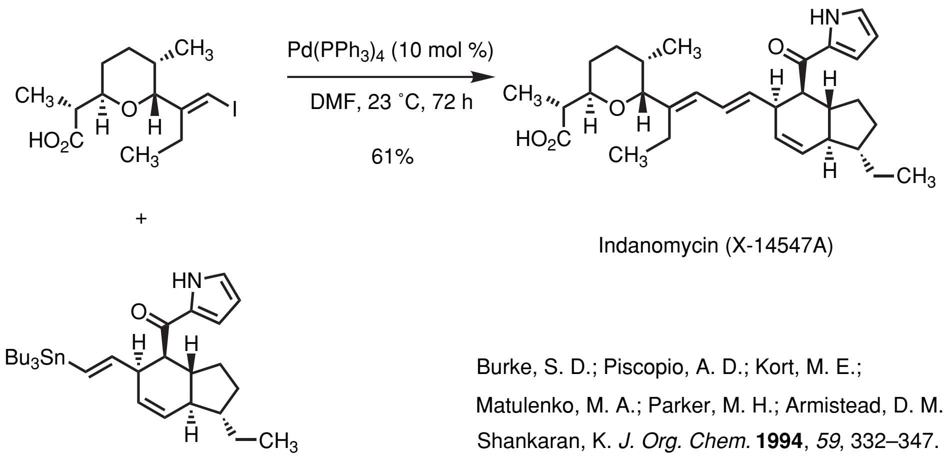
- Alkenes as coupling partners:



(+)-A83543A, (+)-Lepicidin

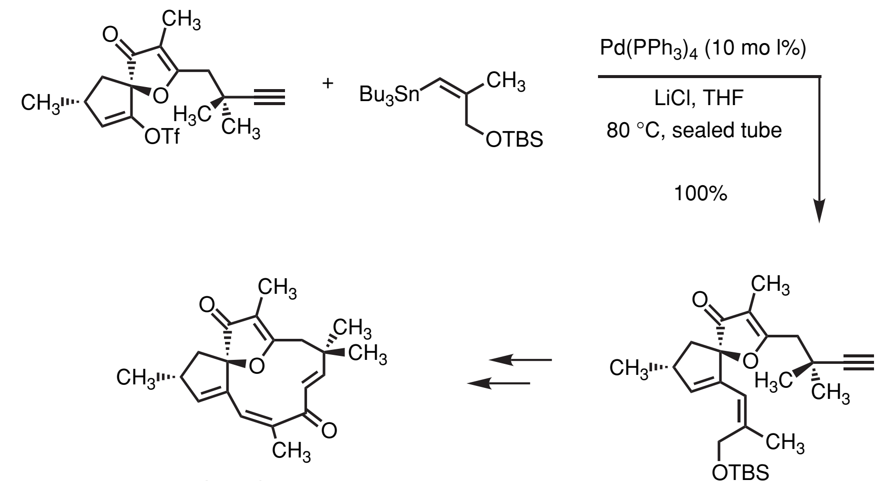
- CdCl$_2$ serves as a transmetalation cocatalyst. Without it, homodimerization of both coupling partners was observed.

Evans, D. A.; Black, W. D. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.



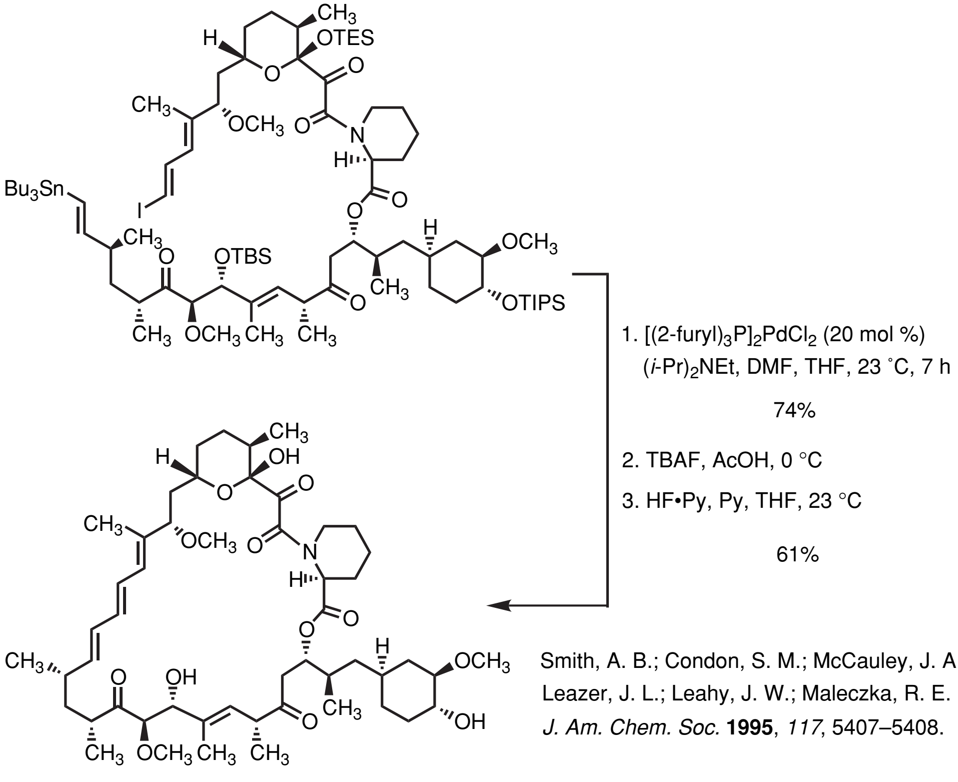
Indanomycin (X-14547A)

Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332–347.



Jatrophone

Han, Q; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697.



Rapamycin

Smith, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E. *J. Am. Chem. Soc.* **1995**, *117*, 5407–5408.

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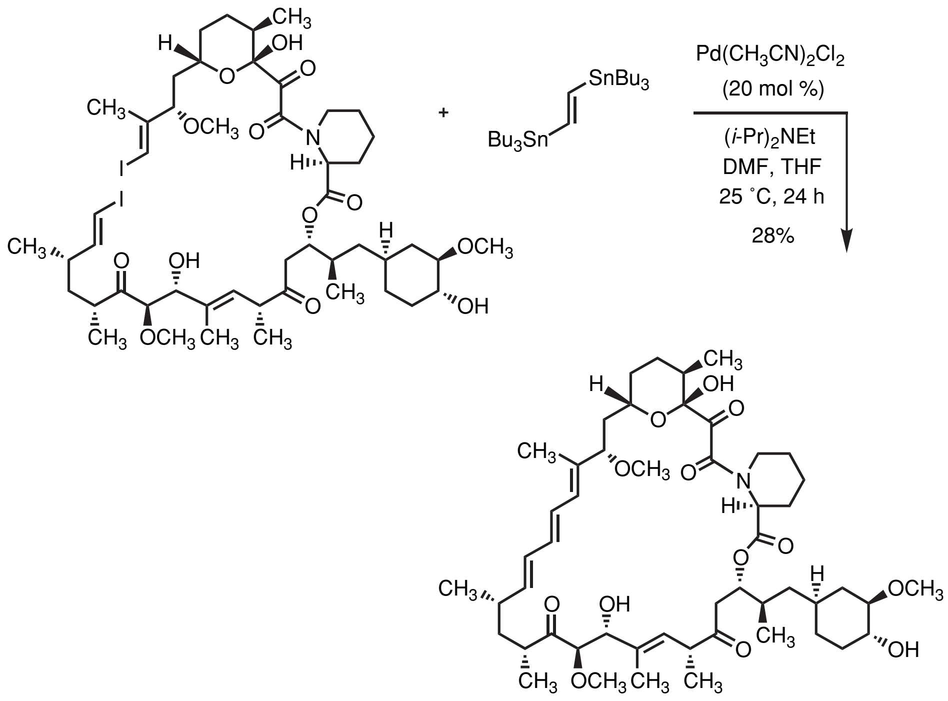
Further Examples:

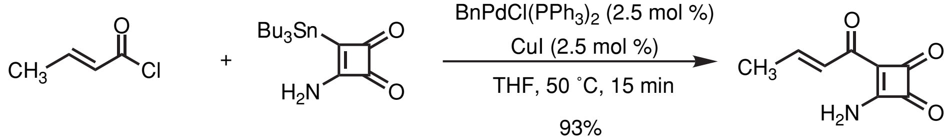


Rapamycin

Nicolaou, K. C.; Chakraborty, T. K; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420.

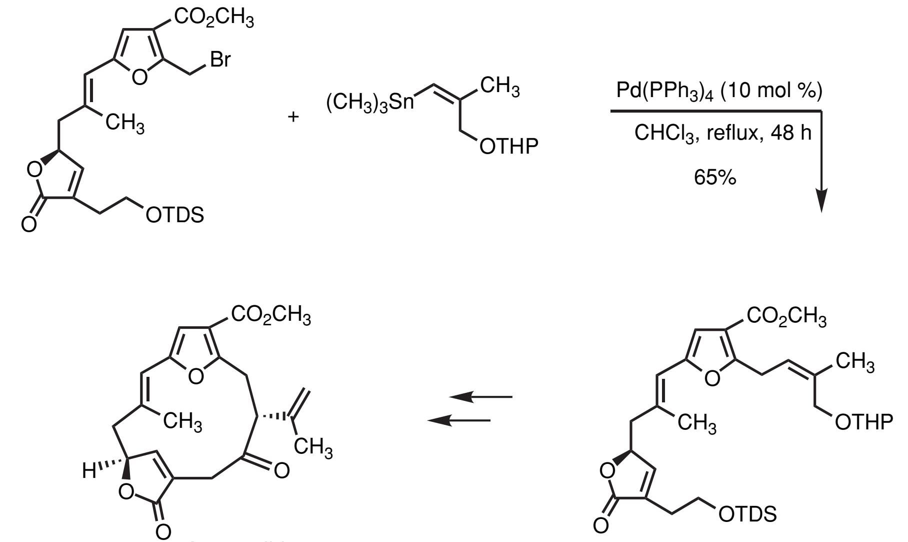
- Acid chlorides can be used as coupling reagents (the Stille reaction, as first reported, used acid chlorides).

Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.



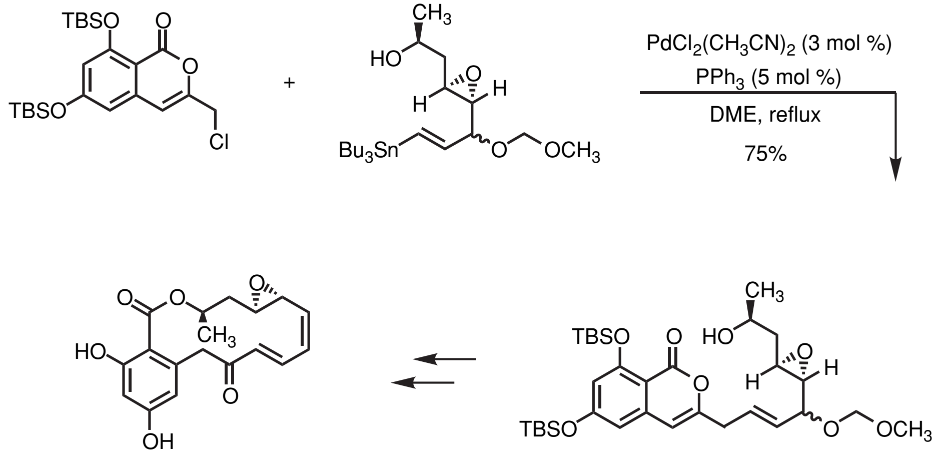
Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543–3549.

- Allylic, benzylic halides:



Acerosolide

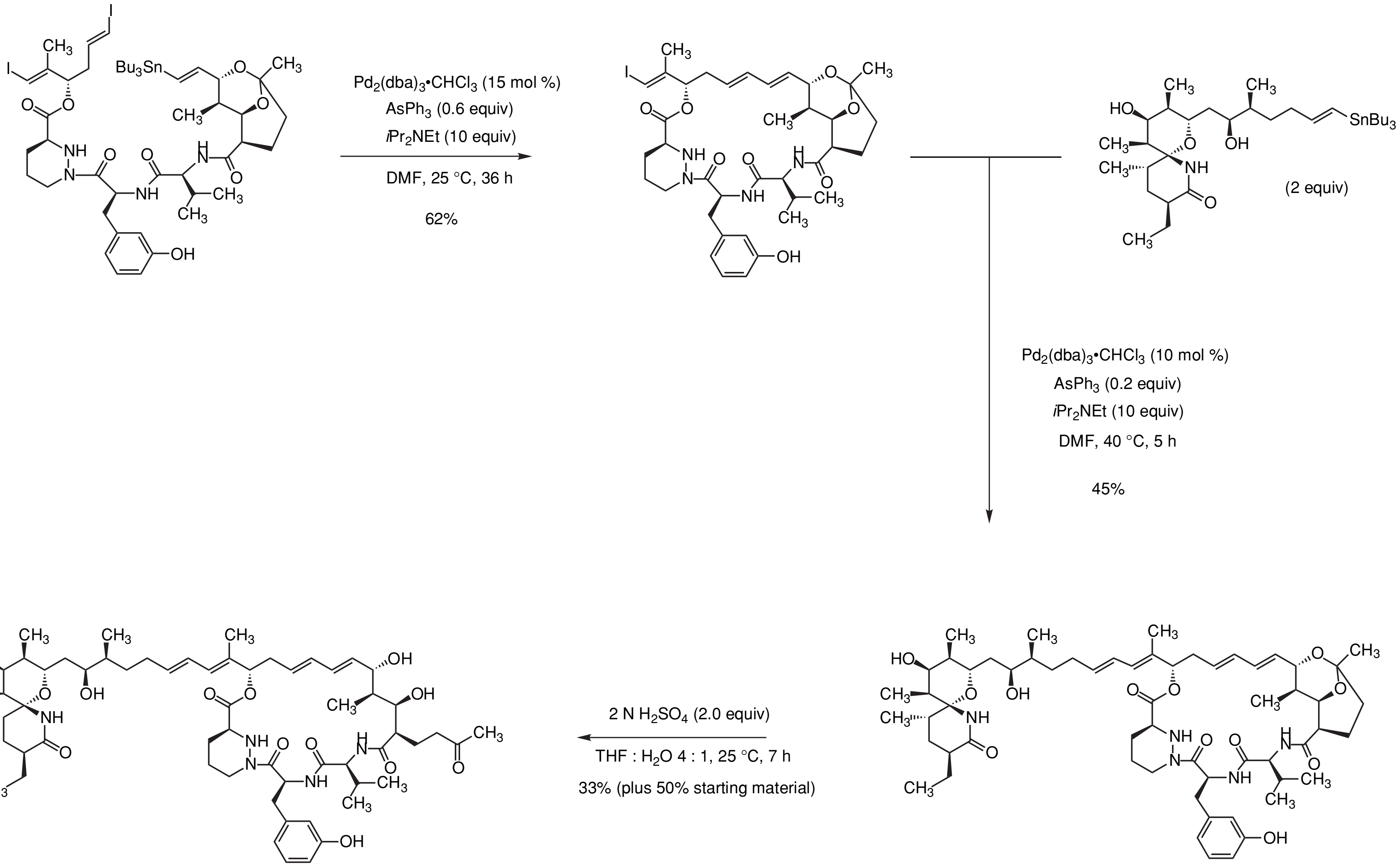
Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169.



Monocillin I

Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 777–780.

Further Examples:



Pd$_2$(dba)$_3$•CHCl$_3$ (15 mol %)
AsPh$_3$ (0.6 equiv)
*i*Pr$_2$NEt (10 equiv)
DMF, 25 °C, 36 h
62%
(2 equiv)
Pd$_2$(dba)$_3$•CHCl$_3$ (10 mol %)
AsPh$_3$ (0.2 equiv)
*i*Pr$_2$NEt (10 equiv)
DMF, 40 °C, 5 h
45%
2 N H$_2$SO$_4$ (2.0 equiv)
THF : H$_2$O 4 : 1, 25 °C, 7 h
33% (plus 50% starting material)

Sanglifehrin A

- In the first Stille coupling, none of the regioisomeric coupling product was isolated.

Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830–3838.

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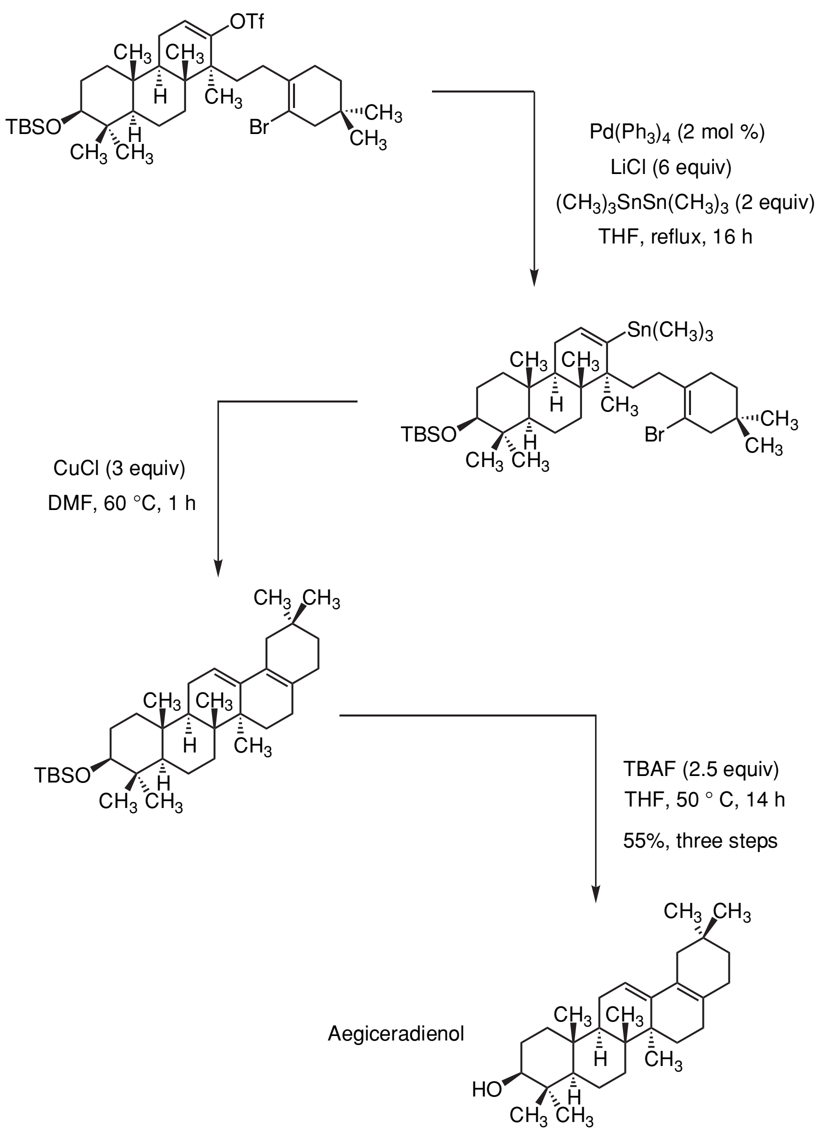
Examples involving copper(I):

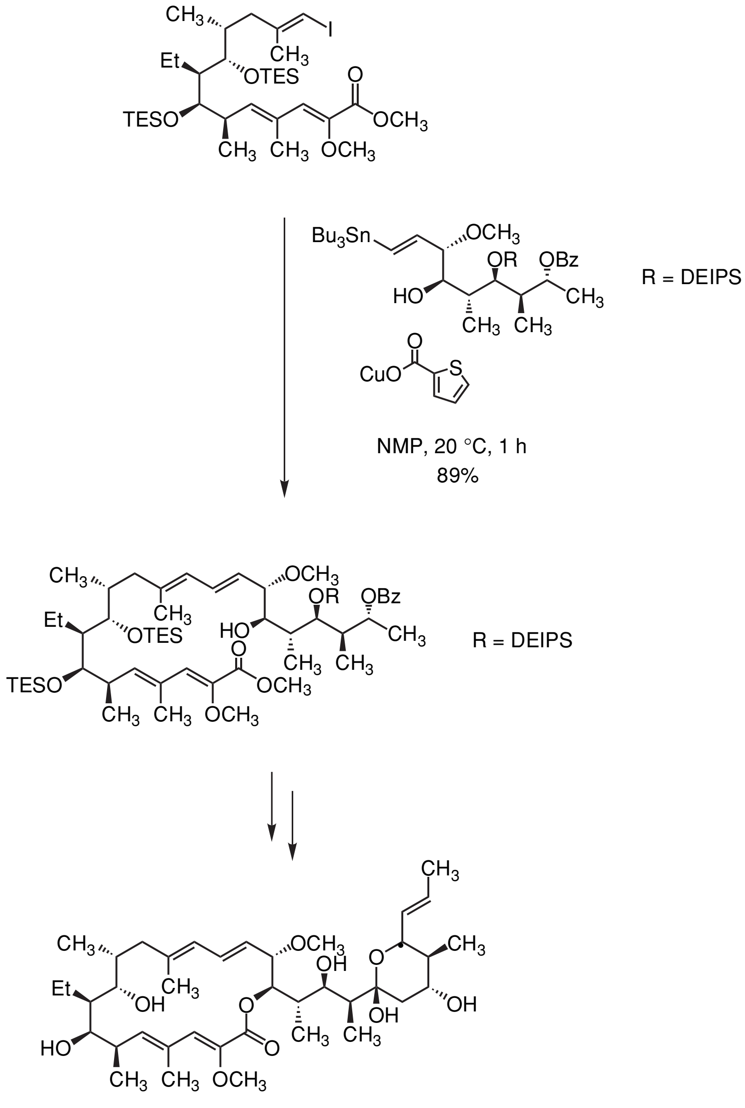
- The copper(I)-mediated coupling of a vinyl stannane and a vinyl bromide succeeded when palladium catalysis failed. Note the selective transformation of the vinyl triflate to the vinyl stannane in the presence of the vinyl bromide.



Aegiceradienol

Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.

- Liebeskind's copper(I) thiophene-2-carboxylate promoted coupling reaction was used for the total synthesis of concanamycin F. This reaction failed intramolecularly when the two coupling partners had already been joined via the ester linkage.



Concanamycin F

Paterson, I.; Doughty, V. A.; McLeod, M. D.; Trieselmann, T. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1308–1312.

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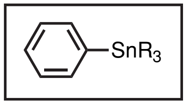
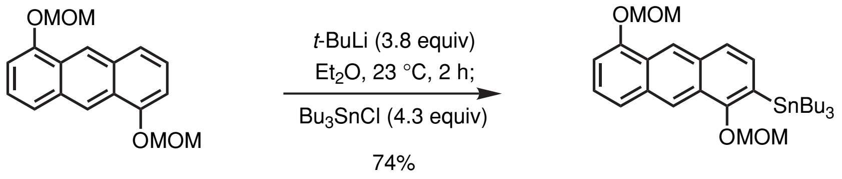
Synthesis of Aryl and Vinyl Stannanes:

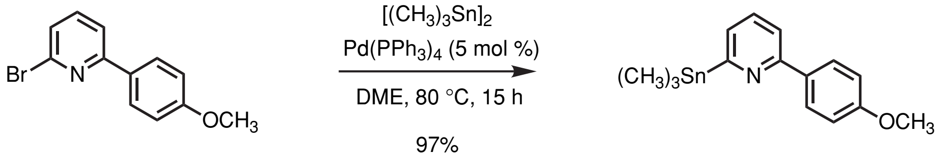


- Directed *ortho* metalation followed by addition of a stannyl chloride is a standard method.

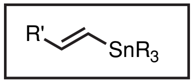
Snieckus, V. *Chem. Rev.* **1990**, *90*, 923–924.

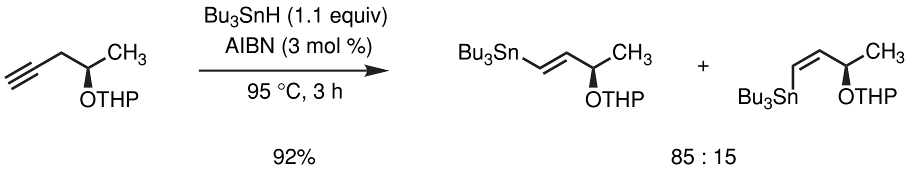


Tius, M. A.; Gomez-Galeno, J.; Gu, X.; Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 5775-5783.



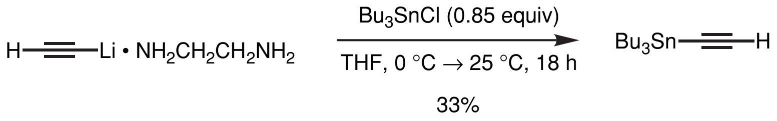
Benaglia, M.; Toyota, S.; Woods, C. R.; Siegel, J. S. *Tetrahedron Lett.* **1997**, *38,* 4737-4740.

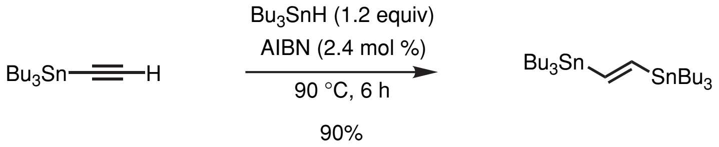




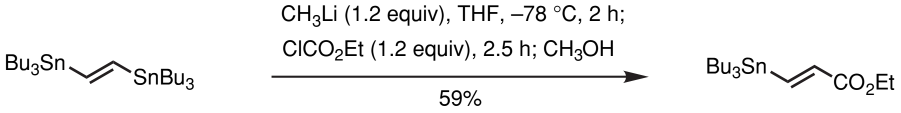
- The addition of stannyl radicals to alkynes is reversible under these conditions. The product ratio reflects the thermodynamic equilibrium.

Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222–224.

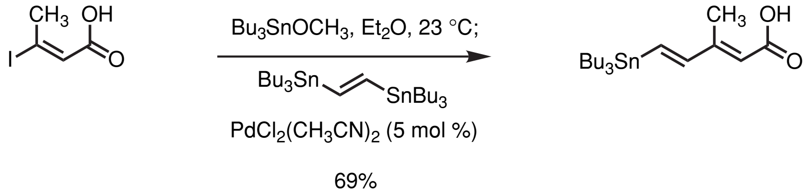




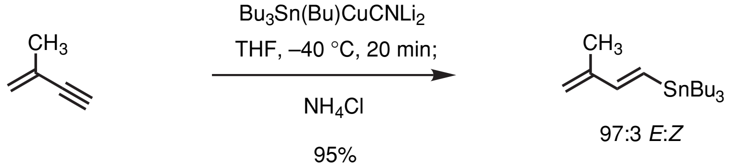
Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.


Bu_3Sn
$SnBu_3$
CH_3Li (1.2 equiv), THF, –78 °C, 2 h;
$ClCO_2Et$ (1.2 equiv), 2.5 h; CH_3OH
59%
Bu_3Sn
CO_2Et

Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



Thibonnet, J.; Abarbi, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771–772.



Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163–1176.

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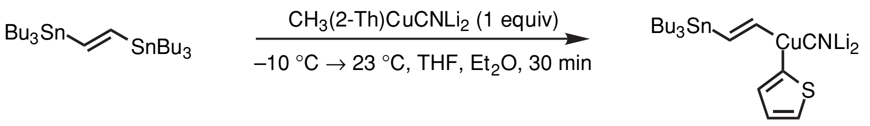
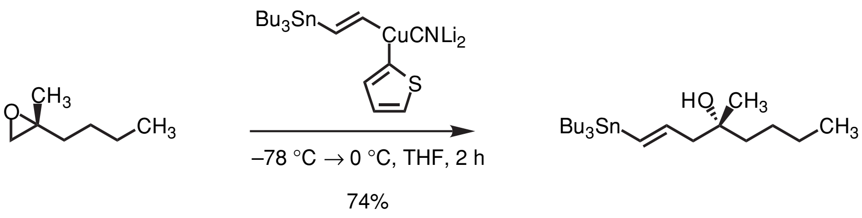
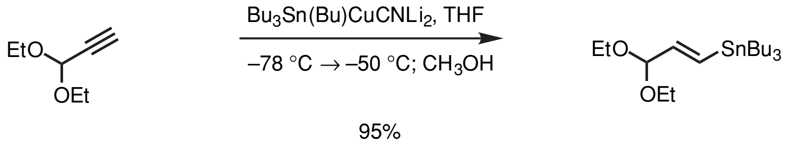
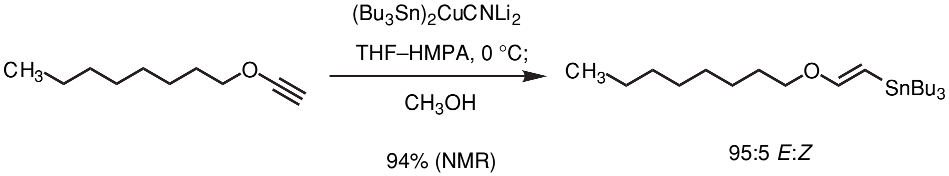




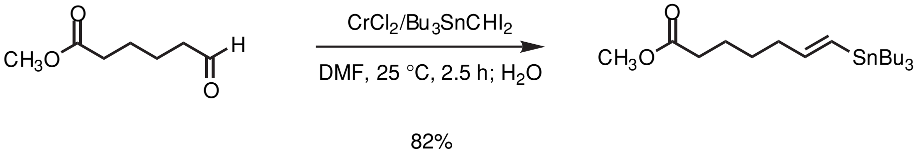
Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H.
Tetrahedron Lett. **1989**, *30*, 27–30.



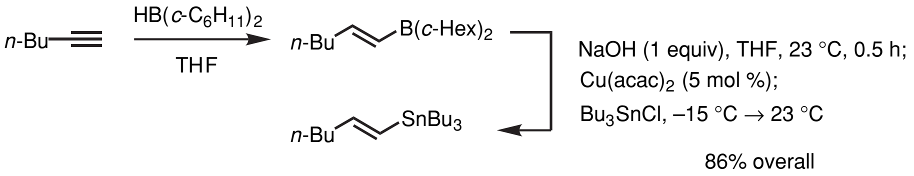
Marek, I.; Alexakis, A.; Normant, J.–F. *Tetrahedron Lett.* **1991**, *32*, 6337–6340.



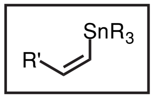
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.

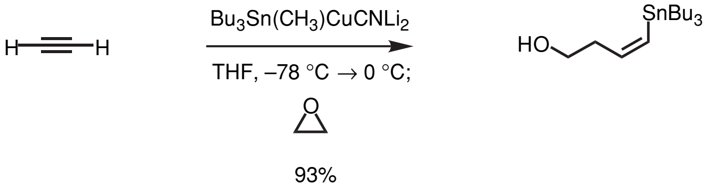


Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Tetrahedron Lett.* **1998**, *39*, 6419–6420.

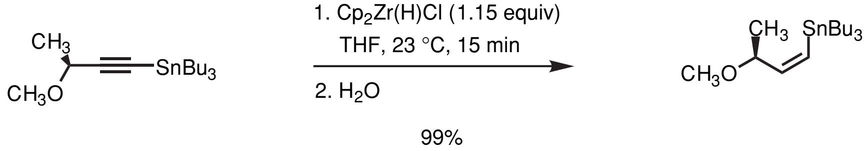


Hoshi, M.; Takahashi, K.; Arase, A. *Tetrahedron Lett.* **1997**, *38*, 8049–8052.





Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzalez, A. M.; Pulido, F. J. *J. Chem. Soc., Chem. Commun.* **1992**, 351–353.



Lipshutz, B. H.; Kell, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861–5864.

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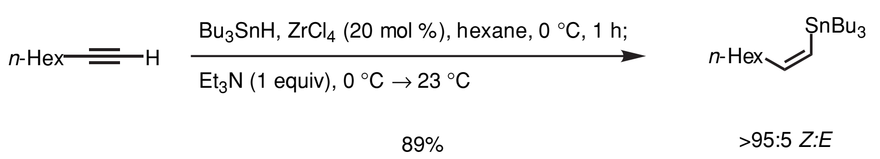
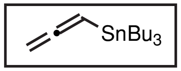
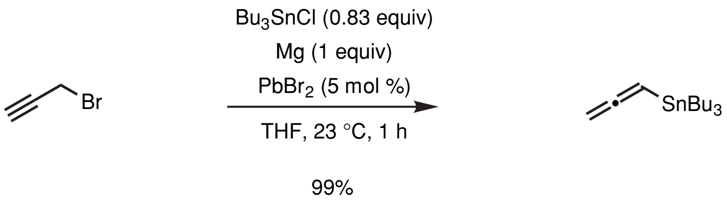
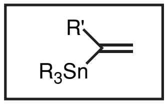

n-Hex
H
Bu_3SnH, $ZrCl_4$ (20 mol %), hexane, 0 °C, 1 h;
Et_3N (1 equiv), 0 °C → 23 °C
n-Hex
$SnBu_3$
89%
>95:5 *Z:E*

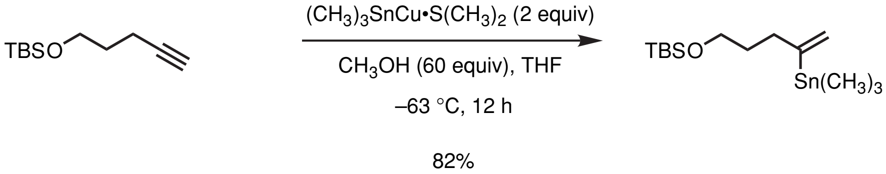
Asao, N.; Liu, J.–X.; Sudoh, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 2405–2406.



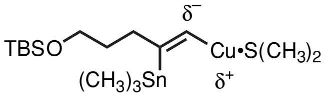


Tanaka, H.; Abdul Hai, A. K. M.; Ogawa, H.; Torii, S. *Synlett* **1993**, 835–836.

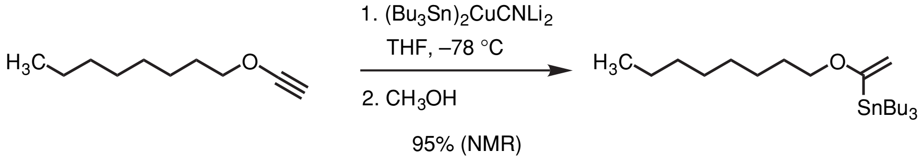




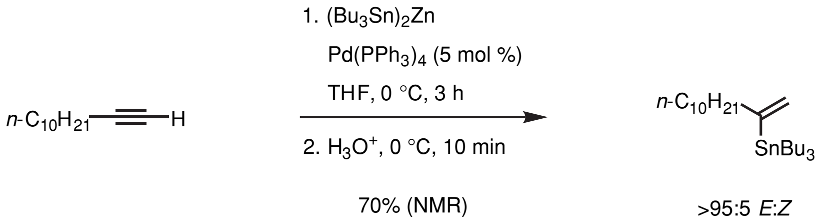
- The addition of the cuprate reagent is reversible. The authors attribute the observed regioselectivity to the higher stability of the polarized carbon-copper bond when copper is attached to the less electronegative terminal carbon.



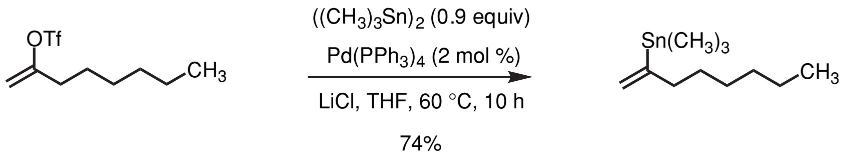
Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66*, 1425–1429.



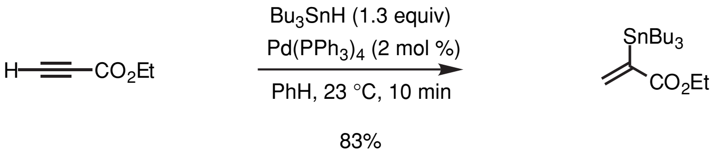
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.



Matsubara, S.; Hibino, J.–I.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Organomet. Chem.* **1985**, *285*, 163–172.

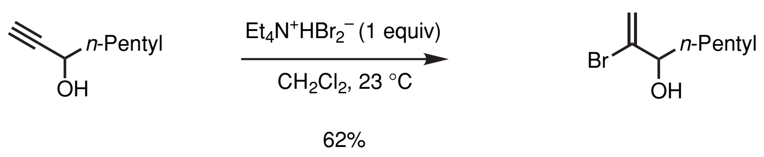


Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277–279.

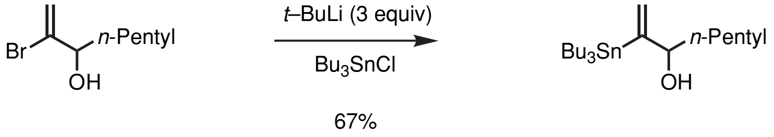


Miyake, H.; Yamamura, K. *Chemistry Lett.* **1989**, 981–984.

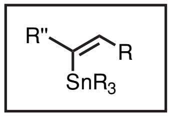
- An alternate route:

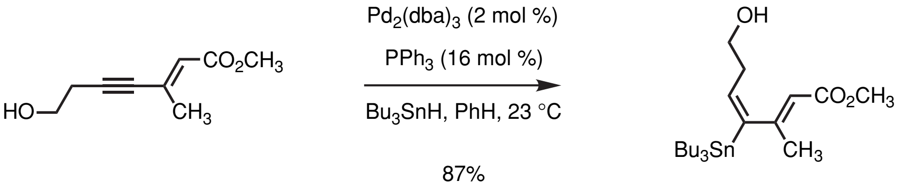


Marshall, J. A.; Sehon, C. A. *Org. Synth.* **1999**, *76*, 263–270.



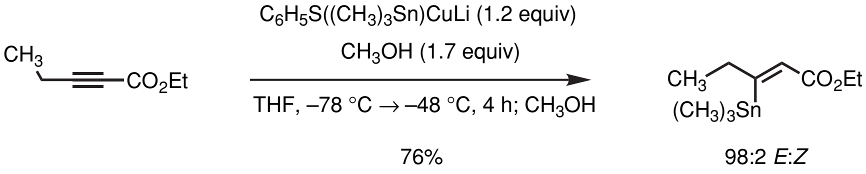
Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.



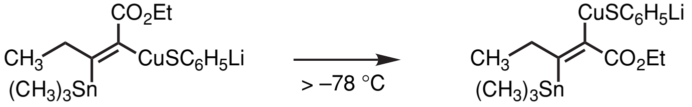


- The regiochemistry of the addition is explained as the result of hydride addition to the more electron-deficient terminus of the acetylene.

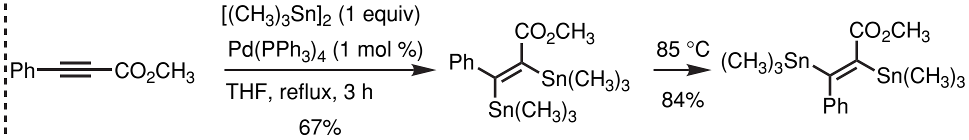
Trost, B. M.; Li, C–J. *Synthesis* **1994**, 1267–1271.


CH_3
CO_2Et
$C_6H_5S((CH_3)_3Sn)CuLi$ (1.2 equiv)
CH_3OH (1.7 equiv)
THF, –78 °C → –48 °C, 4 h; CH_3OH
76%
CH_3
CO_2Et
$(CH_3)_3Sn$
98:2 E:Z

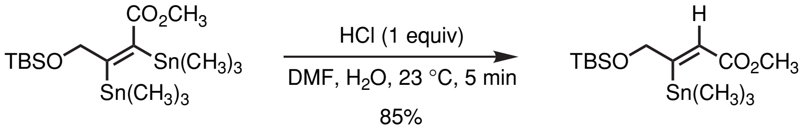
- The initially formed *cis* adduct is stable at –100 °C, but at higher temperatures (–48 °C), the equilibrium favors the Cu/Sn *trans* isomer.



Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264.



Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034–6040.



Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034–6040.

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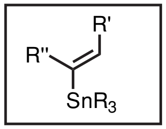
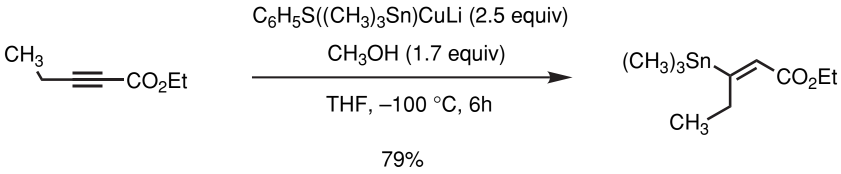
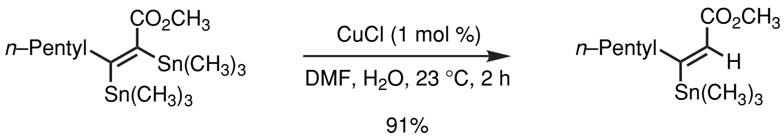
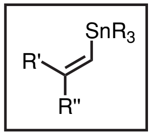


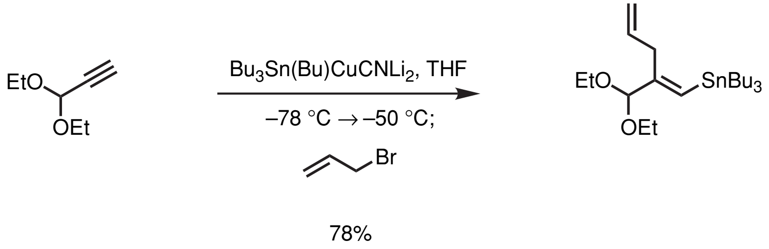


Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264.

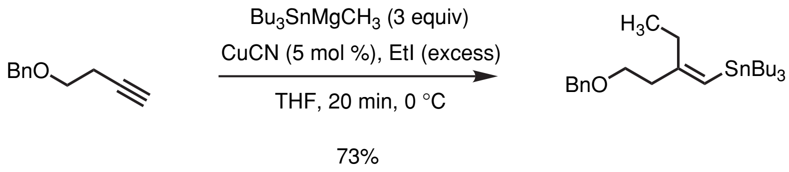


Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034–6040.





Marek, I.; Alexakis, A.; Normant, J.–F. *Tetrahedron Lett.* **1991**, *32*, 6337–6340.

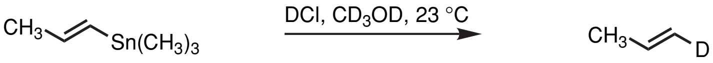


Matsubara, S.; Hibino, J.-I.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Organomet. Chem.* **1985**, *285*, 163–172.

Vinylstannanes:

- are sensitive to acids, undergoing protodestannylation with retention of stereochemistry.

Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133–2136.



Cochran, J. C. et al. *Organometallics* **1982**, *1*, 586–590.

- frequently are unstable to chromatography on silica gel (addition of triethylamine to the eluent can prevent decomposition during chromatography).

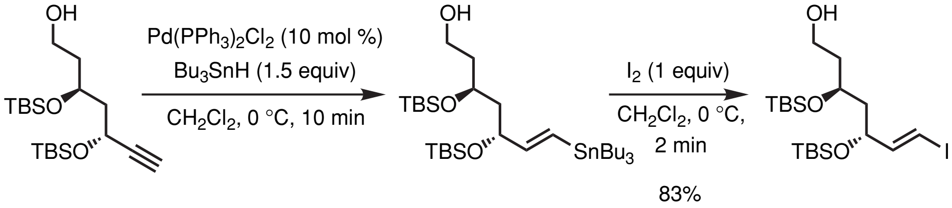
- can be purified by a chromatographic technique that uses C-18 silica, which has been made hydrophobic by capping the silanol residues with octadecyldimethylsilyl groups.

Farina, V. *J. Org. Chem.* **1991**, *56*, 4985–4987.

- can be difficult to separate from unwanted tin by-products after the reaction. For leading references on the work-up of tin reactions, see:

Renaud, P.; Lacôte, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123–2126.

- react cleanly and efficiently with I_2 to form vinyl iodides with retention of stereochemistry. For example:



Smith, A. B.; Ott, G.R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948.

Andrew Haidle

Reviews:

Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*, Diederich, F., and Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, pp. 49-97.

Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

Suzuki, A. *J. Organometallic Chem.* **1999**, *576*, 147–168.

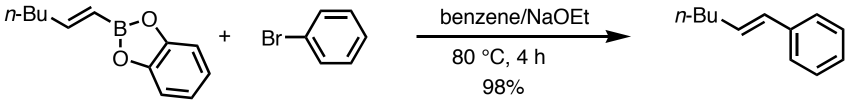
- *B*-Alkyl Suzuki reaction:

Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4544–4568.

- Solid phase:

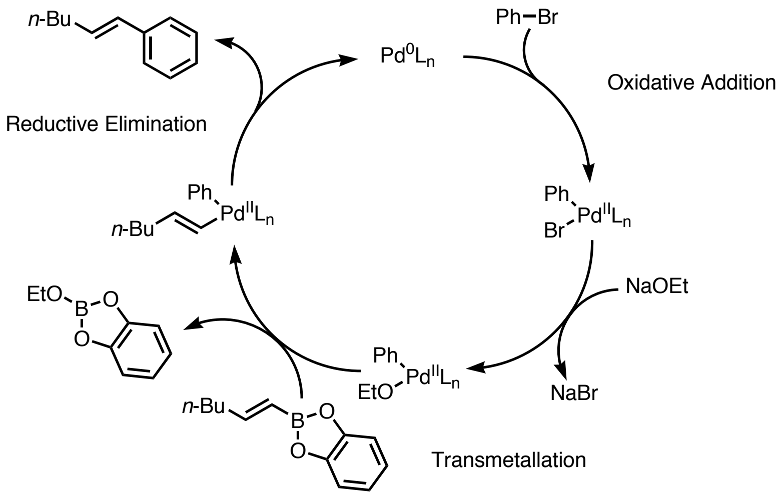
Franzén, R. *Can. J. Chem.* **2000**, *78*, 957–962.

- The Suzuki reaction is the coupling of an aryl or vinyl boronic acid with an aryl or vinyl halide or triflate using a palladium catalyst. It is a powerful cross coupling method that allows for the synthesis of conjugated olefins, styrenes, and biphenyls:



Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.

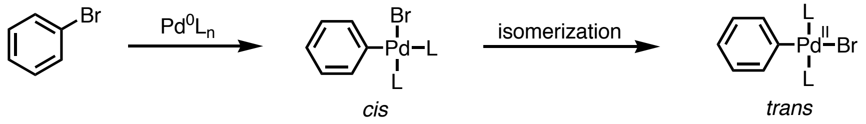
Mechanism:



Suzuki, A. *Pure & Appl. Chem.* **1985**, *57*, 1749–1758.

Analysis of Elementary Steps in the Reaction Mechanism

Oxidative Addition



- Relative reactivity of leaving groups: $I^- > OTf^- > Br^- \gg Cl^-$.

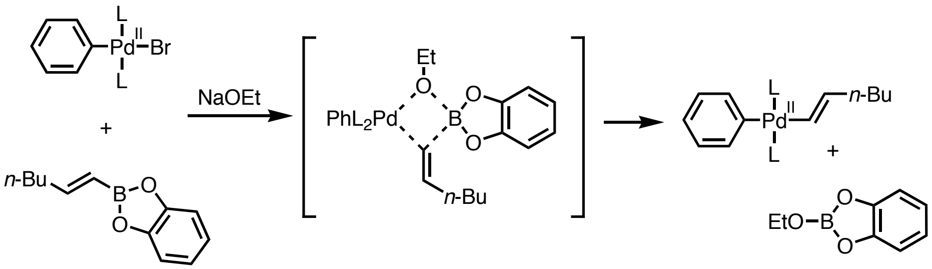
- Oxidative addition is known to proceed with retention of stereochemistry with vinyl halides and with inversion with allylic and benzylic halides.

Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434–442.

- Oxidative addition intially gives a *cis* complex that rapidly isomerizes to its *trans* isomer.

Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954–959.

Transmetallation

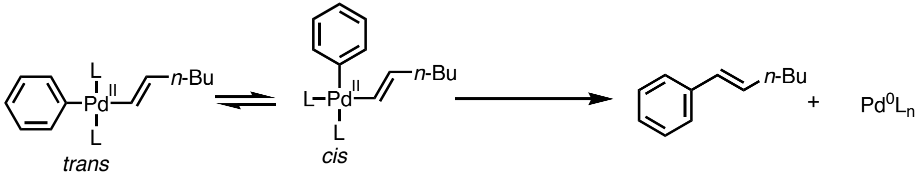


- Organoboron compounds are highly covalent in character, and do not undergo transmetallation readily in the absence of base.

- The role of the base during transmetalation is unresolved. Boron "ate" complexes, formed via quaternization of the boron with a negatively charged base, are frequently invoked.

Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.

Reductive Elimination



- Isomerization to the *cis* complex is required before reductive elimination can occur.

- Relative rates of reductive elimination from palladium(II) complexes:

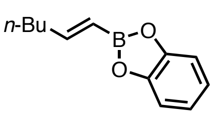
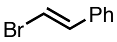
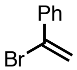
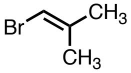
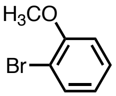
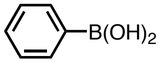
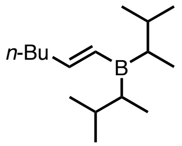
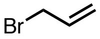
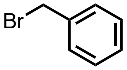
aryl–aryl > alkyl–aryl > *n*-propyl–*n*-propyl > ethyl–ethyl > methyl–methyl

Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

Andrew Haidle/Chris Coletta

Conditions

$$R{-}BY_2 \quad + \quad X{-}R' \xrightarrow[\text{benzene, 80 °C}]{P(PPh_3)_4} R{-}R'$$

		base	time (h)	yield (%)
		NaOEt	2	80[a]
		NaOEt	2	80[a]
		NaOEt	2	81[a]
	I−Ph	NaOEt	2	100[b]
	Br−Ph	NaOEt NaOEt	2 4	63[b] 98[b]
	Cl−Ph	NaOEt	2	3[b]
		NaOEt	4	93[b]
	I−Ph	2M NaOH	6	62[c]
	Br−Ph	2M Na_2CO_3	6	88[c]
	Cl−Ph	NaOEt	6	0[c]
		2M NaOH	2	87[d]
		2M NaOH	2	99[d]

- The conditions shown above are the original conditions developed for the cross coupling by Suzuki and Miyaura.

- The reaction is stereo- and regiospecific, providing a convenient method for the synthesis of conjugated alkadienes, arylated alkenes, and biaryls.

- Note that under the conditions shown above, aryl chlorides are not acceptable substrates for the reaction, likely due to their reluctance to participate in oxidative addition.

[a] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

[b] Miyaura, N.; Suzuki, A. J. Chem. Soc.*, Chem. Commun.* **1979**, 866–867.

[c] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.

[d] Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865–2868.

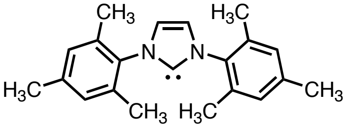
Catalyst and Ligands: The most commonly used system is $Pd(PPh_3)_4$, but other palladium sources have been used including Pd^{II} pre-catalysts that are reduced to the active Pd^0 *in situ:*

- $Pd_2(dba)_3 + PPh_3$
- $Pd(OAc)_2 + PPh_3$
- $PdCl_2(dppf)$ (for sp3-sp2 couplings-see section on *B*-alkyl Suzuki reaction)

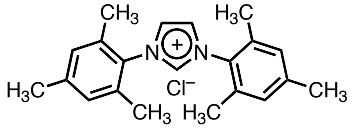
- "Ligand-free" conditions, using $Pd(OAc)_2$, have also been developed. Side reactions often associated with the use of phosphine ligands (phosphonium salt formation and aryl-aryl exchange between substrate and phosphine) are thus avoided.

Goodson, F. E.; Wallow, T. I.; Novak, B. M. *Org. Synth.* **1997**, *75*, 61–68.

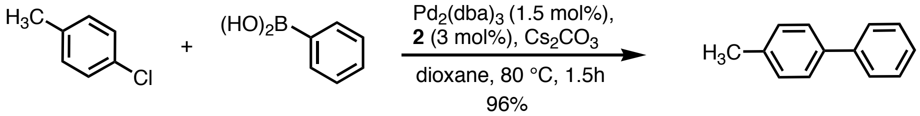
- Use of N-heterocyclic carbenes as an alternative to phosphine ligands:



1



2



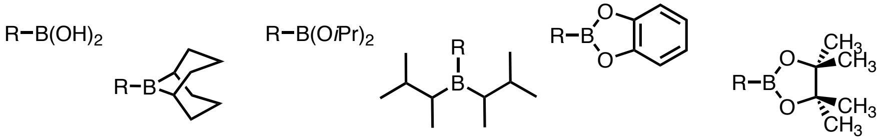
- The nucleophilic *N*-heterocyclic carbene **1** is the active ligand, and is formed *in situ* from **2**.

- The use of ligand **1** allows for utilization of aryl chlorides in the Suzuki reaction (see the section on bulky, electron rich phosphines as ligands for use of aryl chlorides as coupling partners as well).

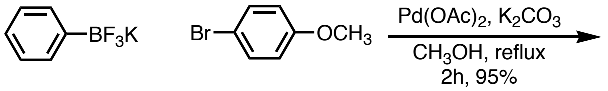
Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804-3805.

Organoboranes: A variety of organoboranes may be used to effect the transfer of the organic coupling partner to the reactive palladium center via transmetallation. Choice of the appropriate organoborane will depend upon the compatability with the coupling partners and availability (see section on synthesis of organoboranes).

Some of the more common organoboranes used in the Suzuki reaction are shown below:



- Use of Aryltrifluoroborates as Organoboranes for the Suzuki Reaction:



- The aryltrifluoroborates are prepared by treatment of the corresponding arylboronic acid with excess KHF_2.
- According to the authors, aryltrifluoroborates are more robust, more easily purified, and less prone to protodeboronation compared to aryl boronic acids.

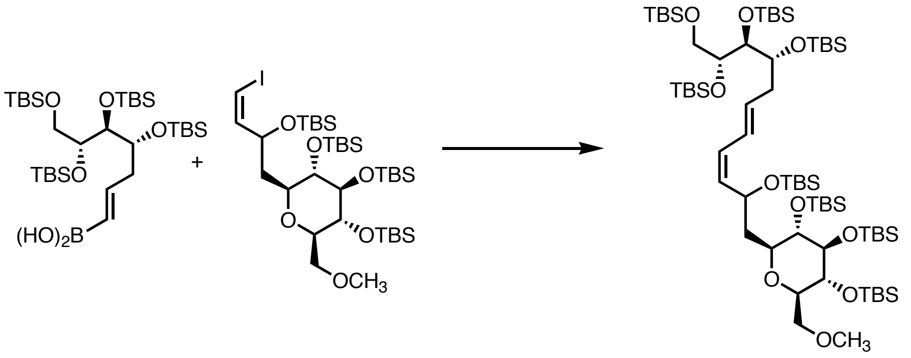
Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.

Solvent: The Suzuki reaction is unique among metal-catalyzed cross-coupling reactions in that it can be run in biphasic (organic/aqueous) or aqueous environments in addition to organic solvents.

Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330.

Andrew Haidle/Chris Coletta

TlOH and TlOEt as Rate-Enhancing Additives for the Suzuki Reaction

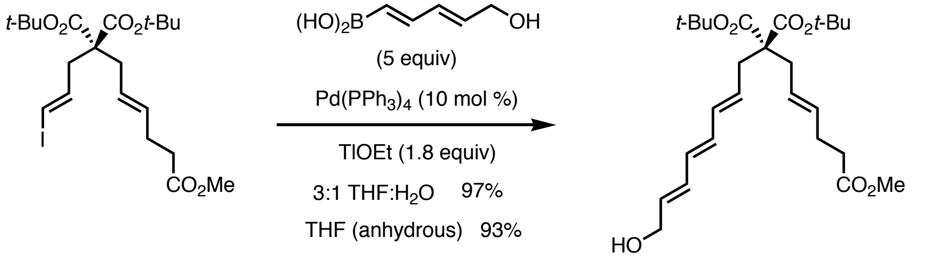


base	temp (°C)	time	yield	relative rate
KOH	23	2 h	86	1
TlOH	23	<<30 sec	92	1000

- TlOH greatly increases the rate of coupling, which the authors attribute to acceleration of the hydroxyl–halogen exchange at palladium.

Uenishi, J.; Beau, J.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4658.

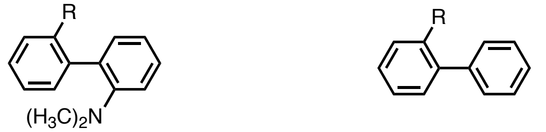
- TlOH vs. TlOEt



- Roush has found that TlOEt is a generally superior source of Tl for Suzuki couplings. Pure TlOH is available from only a single source, aqueous solutions of TlOH have a poor shelf life, and the aqueous solutions are both air- and light-sensitive.
- The largest problem with using TlOEt is that some boronic acid–TlOEt adducts are not very soluble. Using water as a cosolvent helps to alleviate this problem in many cases.

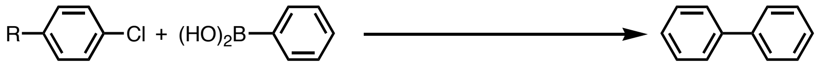
Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691–2694.

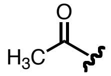
Bulky, Electron-Rich Phosphines as Ligands for the Suzuki Reaction



R = PCy_2 (**1**)
R = $P(t\text{-}Bu)_2$ (**2**)

R = PCy_2 (**3**)
R = $P(t\text{-}Bu)_2$ (**4**)



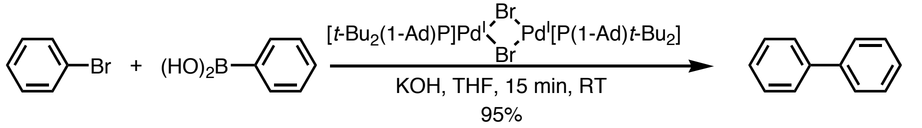
R	ligand	Pd source	base	solvent	temp (°C)	time (h)	yield (%)
CH_3	PPh_3	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	0[a]
CH_3	$Pt\text{-}Bu_3$	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	86[a]
	4	$Pd(OAc)_2$	KF	THF	23	6	95[b]
CH_3O	$Pt\text{-}Bu_3$	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	89[a]
	4	$Pd(OAc)_2$	KF	THF	45	6	93[b]
NH_2	$Pt\text{-}Bu_3$	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	92[a]
	$Pt\text{-}Bu_3$	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	91[a]

- Previous to the introduction of the bulky, electron-rich phosphine ligands shown above, most aryl chlorides were not suitable substrates for the Suzuki reaction.
- These ligands are either commercially available ($Pt\text{-}Bu_3$) or readily synthesized from commercial starting materials (**1**-**4**).
- The increased activity of the ligands shown above allows for the Suzuki reaction of aryl bromides at room temperature.

[a] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[b] Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.

- **Alkyl Di-*tert*-butylphosphane-Ligated Palladium(I) dimers as catalyst for the Suzuki Reaction**

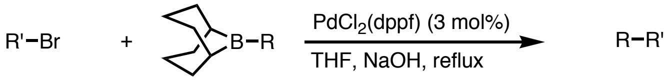

Br
+
$(HO)_2B$
$[t\text{-}Bu_2(1\text{-}Ad)P]Pd^I$
Br
Br
$Pd^I[P(1\text{-}Ad)t\text{-}Bu_2]$
KOH, THF, 15 min, RT
95%

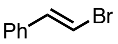
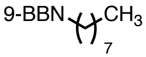
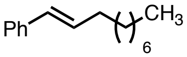
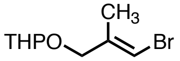
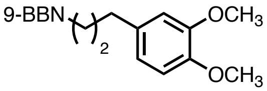
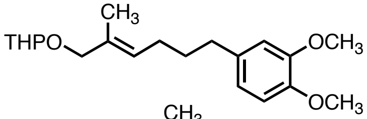
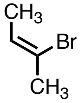
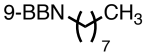
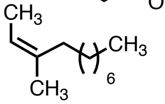
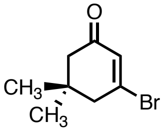
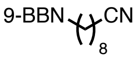
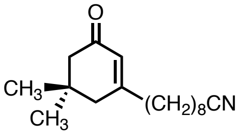
- As a solid, the catalytic complex is stable indefinitely in the air. it is believed that the catalyst fragments to form the monomeric subunits under the reaction conditions.
- Reactions of phenyl boronic acids with (deactivated) aryl chlorides occurred rapidly at room temperature, but conversion did not exceed 70%.

Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 4746-4748.

Chris Coletta

B-Alkyl Suzuki Reaction



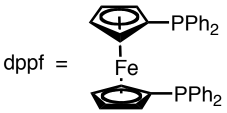
vinyl bromide	9-alkyl-9-BBN	product	yield (%)
			85
			80
			98
			81

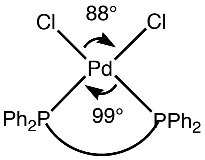
- With the advent of the $PdCl_2$(dppf) catalyst, primary alkyl groups can be transferred by Suzuki coupling, typically using 9-BBN reagents.
- Other suitable coupling partners include aryl or vinyl triflates and aryl iodides.
- Secondary alkyl boron compounds are not suitable coupling partners for this reaction.
- Alkyl boronic esters are also be viable substrates in the B-alkyl Suzuki reaction when thallium salts such as TlOH or Tl_2CO_3 are used as the base.

Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

Sato, M.; Miyaura, Suzuki, A. *Chem. Lett.* **1989**, 1405-1408.

- The large bite angle of the dppf ligand has been noted and is believed to provide a catalyst with a more favorable ratio of rate constants for reductive elimination versus β-hydride elimination.



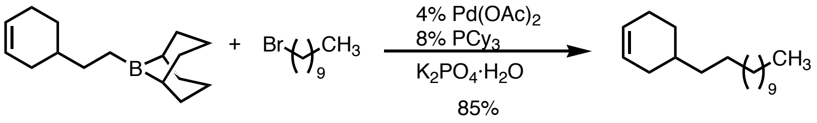


Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158–163.

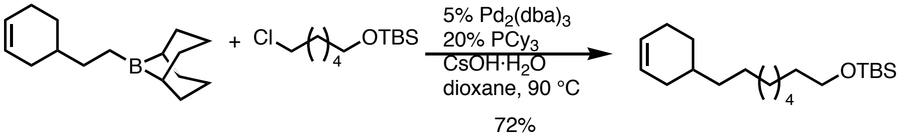
Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta.* **1994**, *220*, 249–259.

sp^3-sp^3 Suzuki Coupling

- By employing a bulky, electron-rich ligand (similar to the ligands used in aryl chloride Suzuki couplings) Fu and coworkers are able to effect the Suzuki coupling of primary alkyl bromides or chlorides and 9-alkyl-9BBN:



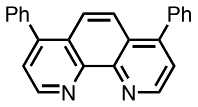
Netherton, M. R.; Dai, C.; Klaus, N.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099-10100.



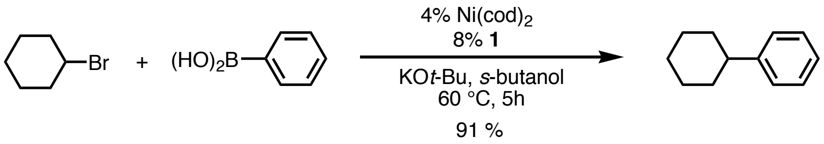
Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1945-1947.

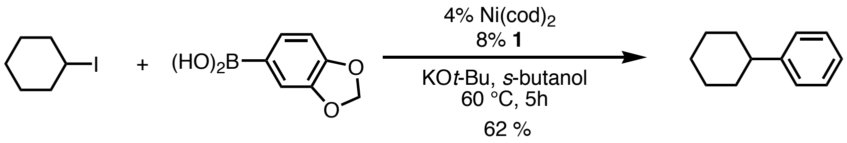
Suzuki Cross-Coupling of Unactivated Secondary Alkyl Halides

- Recently, Fu and coworkers have developed a Ni^0-catalyzed Suzuki coupling of unactivated alkyl bromides and iodides:



1

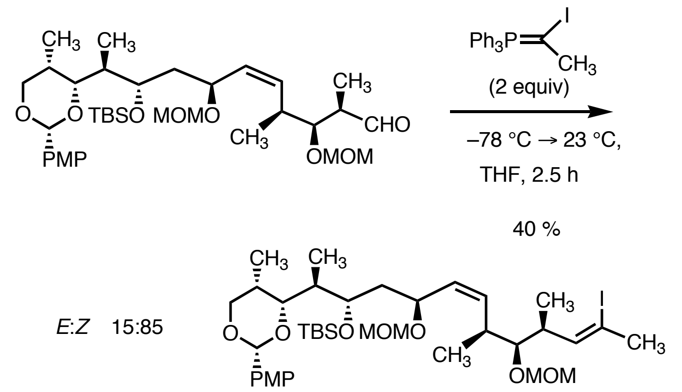




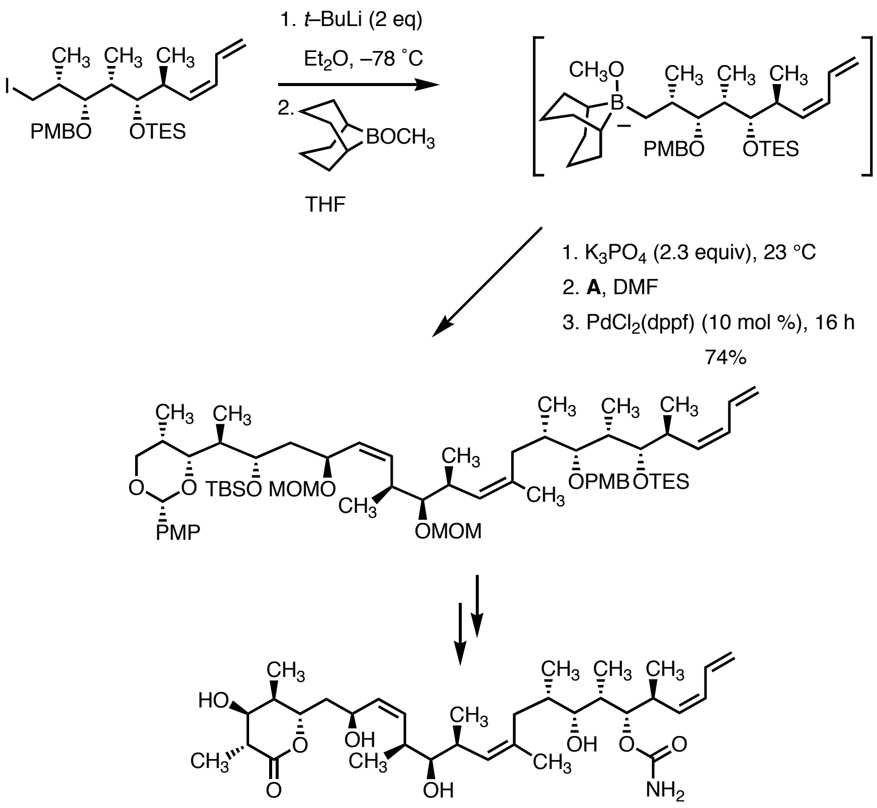
Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341.

Chris Coletta

(+)-Discodermolide (*B*-Alkyl Suzuki Reaction)



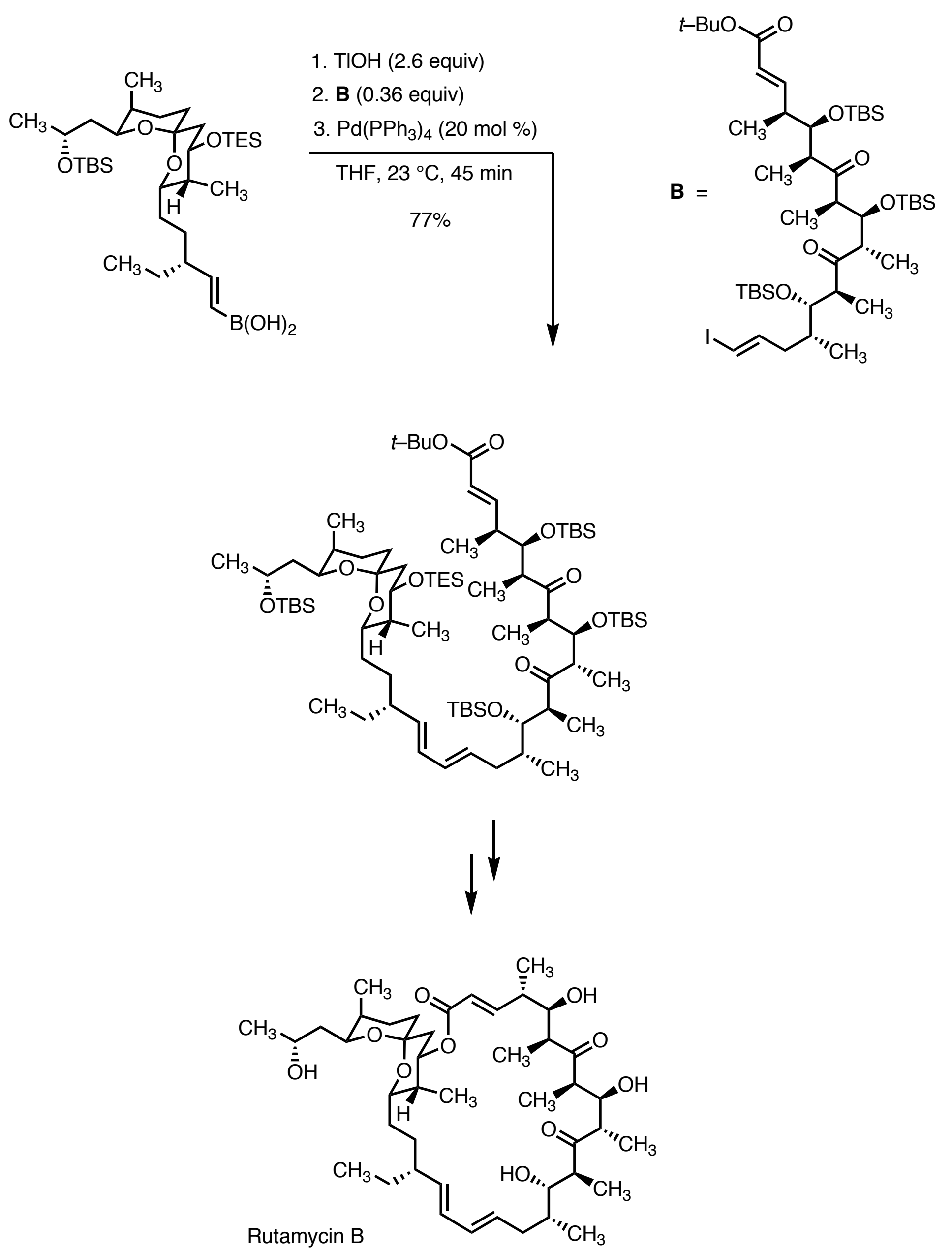
A



(+)-Discodermolide

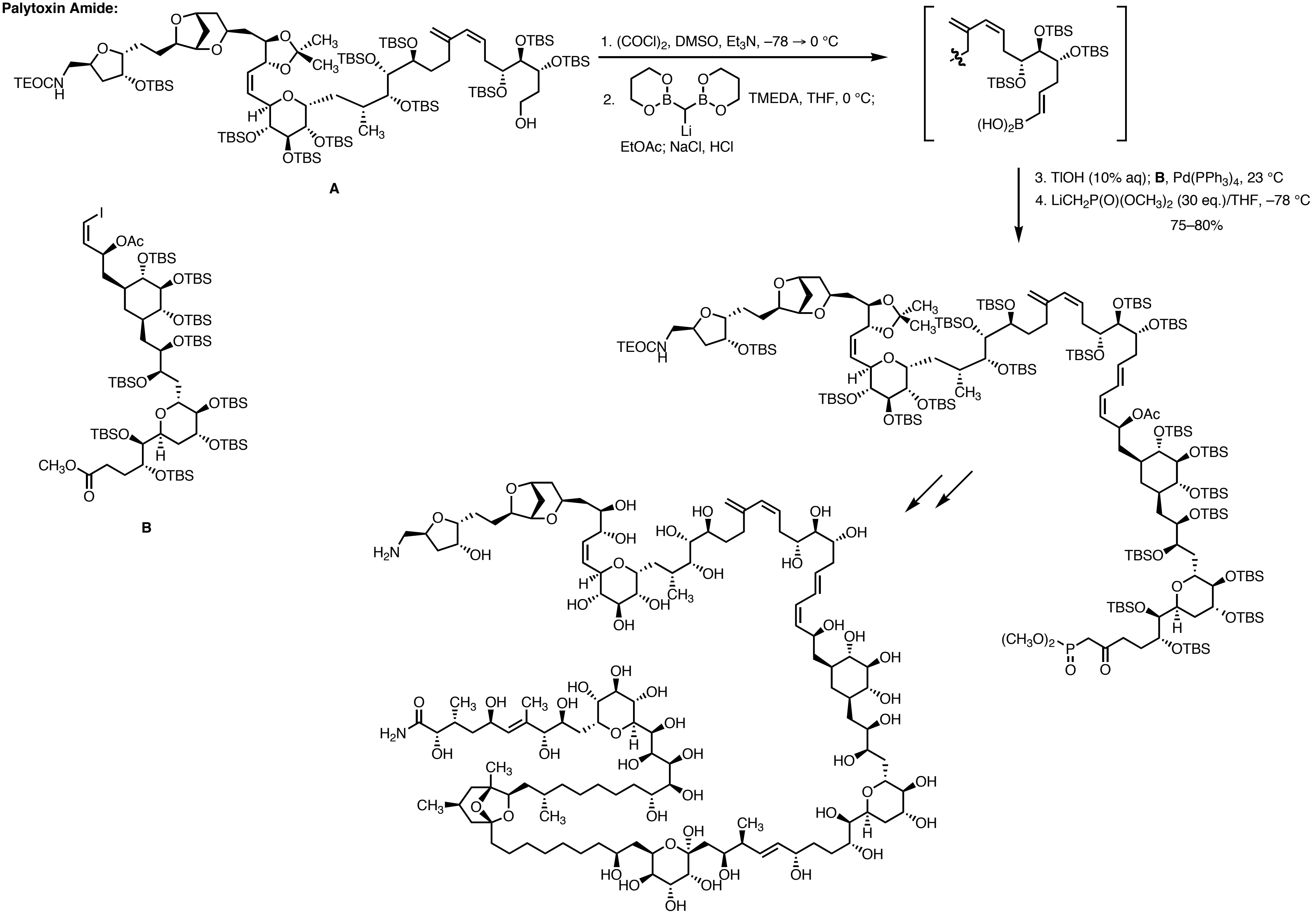
Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885–7892.

Rutamycin B



Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459.

Palytoxin Amide:



1. (COCl)$_2$, DMSO, Et$_3$N, –78 → 0 °C

2. TMEDA, THF, 0 °C; EtOAc; NaCl, HCl

3. TlOH (10% aq); **B**, Pd(PPh$_3$)$_4$, 23 °C

4. LiCH$_2$P(O)(OCH$_3$)$_2$ (30 eq.)/THF, –78 °C

75–80%

Kishi, Y., et al. *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530.

Kishi, Y., et al. *J. Am. Chem. Soc.* **1989**, *111*, 7530–7533.

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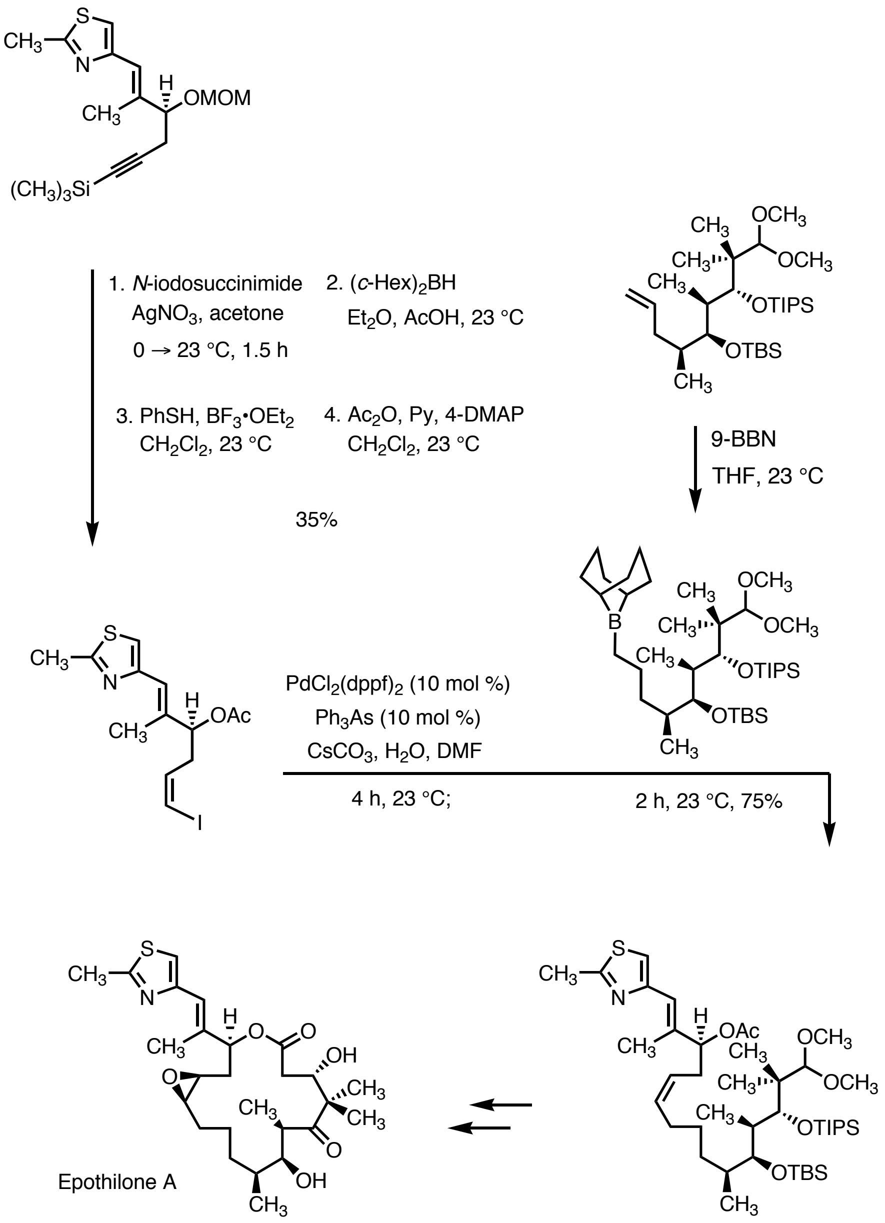
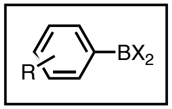
Epothilone A:

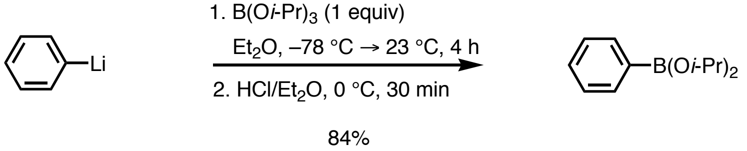


Epothilone A

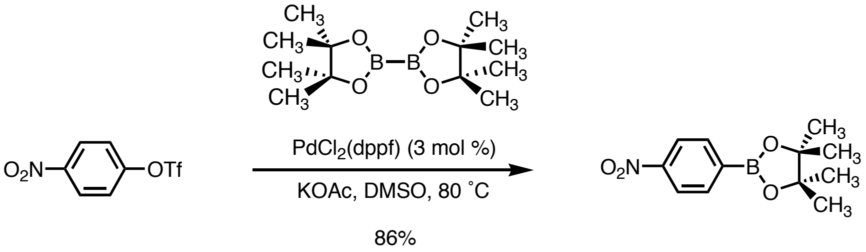
Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S., J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.

Synthesis of organoboron compounds:




Li
1. B(Oi-Pr)3 (1 equiv) Et2O, –78 °C → 23 °C, 4 h
2. HCl/Et2O, 0 °C, 30 min
84%
B(Oi-Pr)2

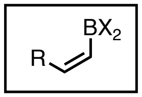
Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316–1319.

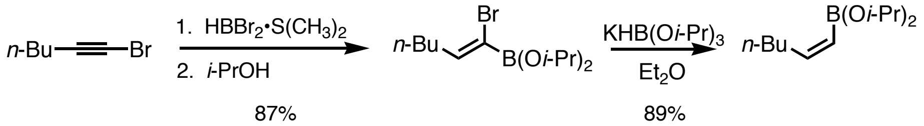


- Aryl bromides and chlorides can also be used.

Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450.

Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.





Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392–1395.

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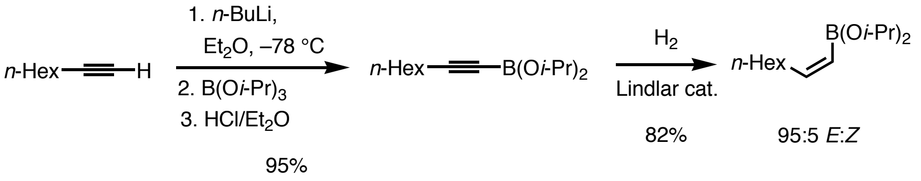
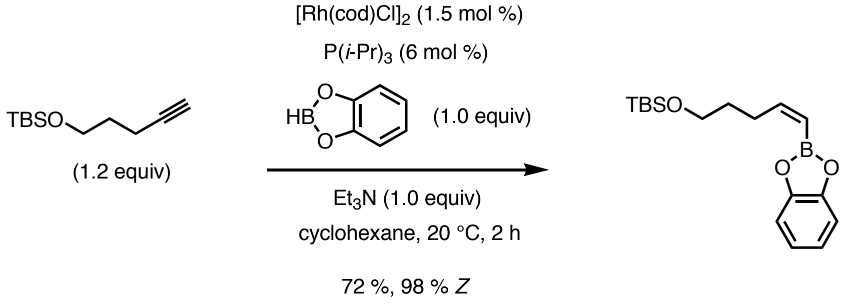
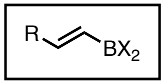


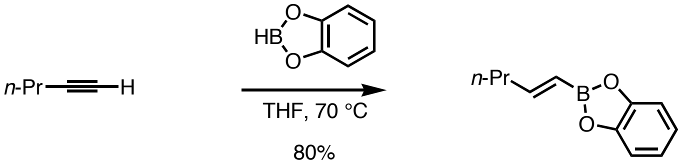
Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.

Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635–2638.

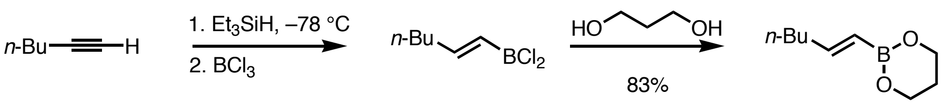


Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991.

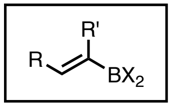


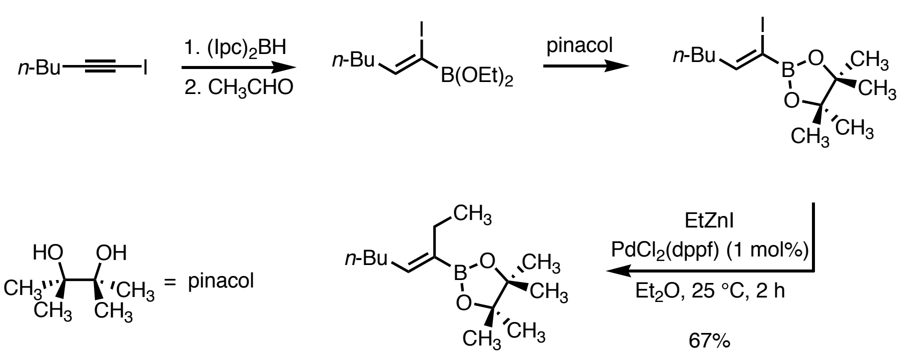


Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.

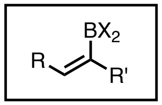


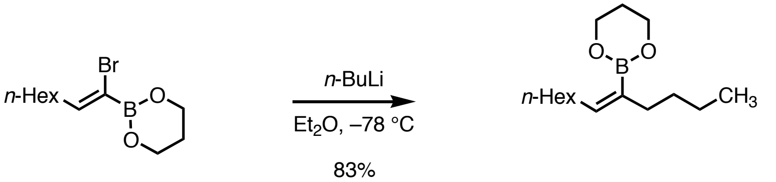
Soundararajan, R.; Matteson, D. S. *J. Org. Chem.* **1990**, *55*, 2274–2275.





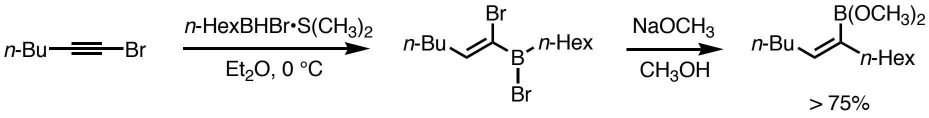
Moriya, T.; Miyaura, N.; Suzuki, A. *Chemistry Lett.* **1993**, 1429–1432.





- Grignard reagents can also be used.

Brown, H. C.; Imai, T.; Bhat, N. G. *J. Org. Chem.* **1986**, *51*, 5277–5282.



- Exact yield not specified because the vinyl borane shown was oxidized to a ketone.

Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Org. Chem.* **1982**, *47*, 3808–3810.

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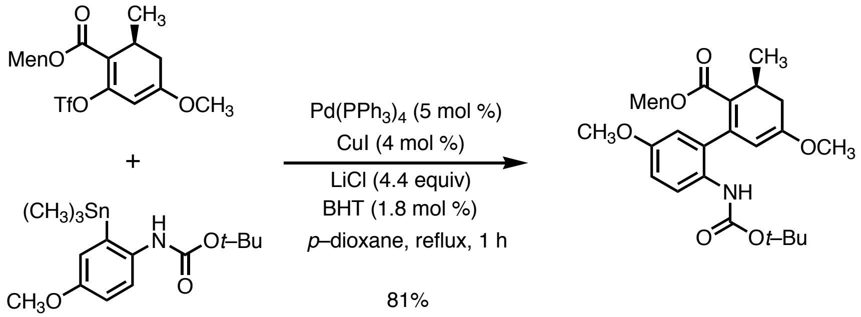
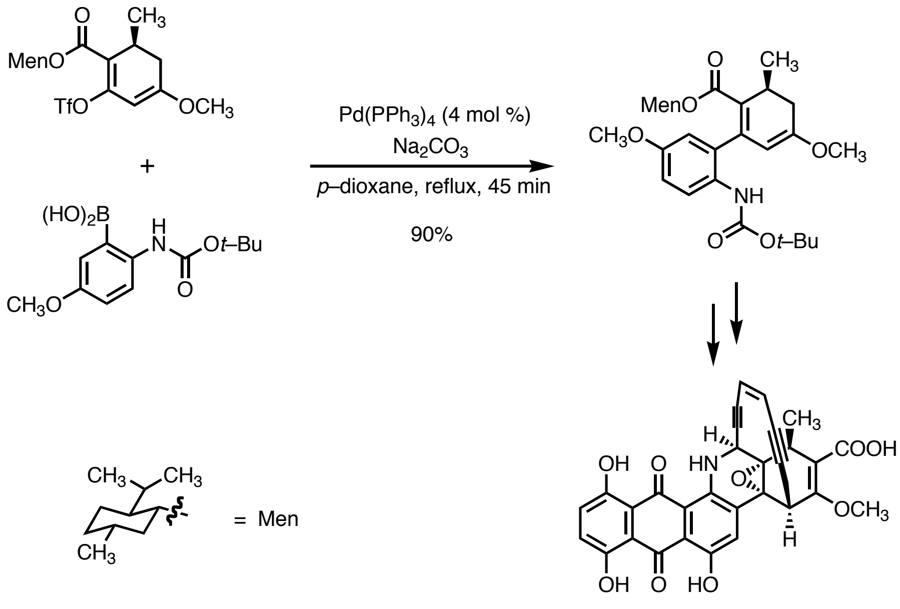
Comparison of the Stille and Suzuki cross-coupling methods:

- The yields are often comparable:

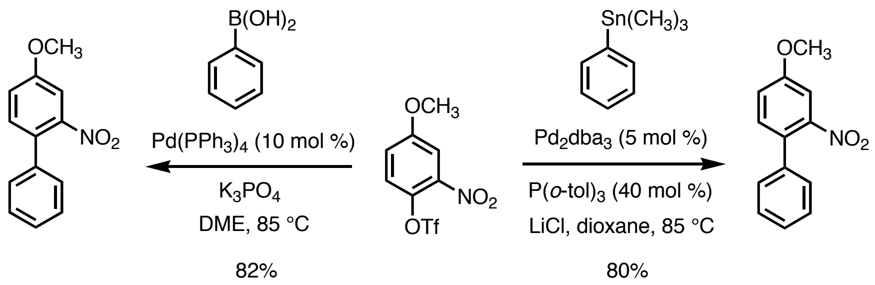




(+)-Dynemicin A

- The higher cost and toxicity of organostannanes makes the Suzuki coupling the preferred method.

Myers, A. G.; Tom., N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072–6094.

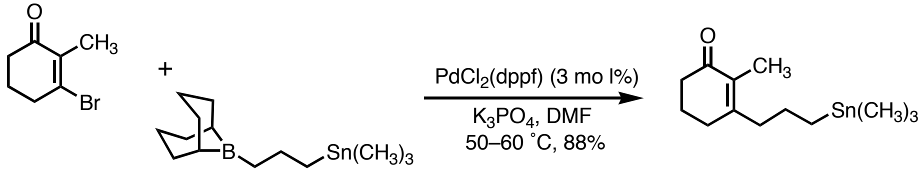


Holzapfel, C. W.; Dwyer, C. *Heterocycles* **1998**, *48*, 1513–1518.

- Some highly sensitive compounds do not tolerate the basic conditions of the Suzuki reaction.

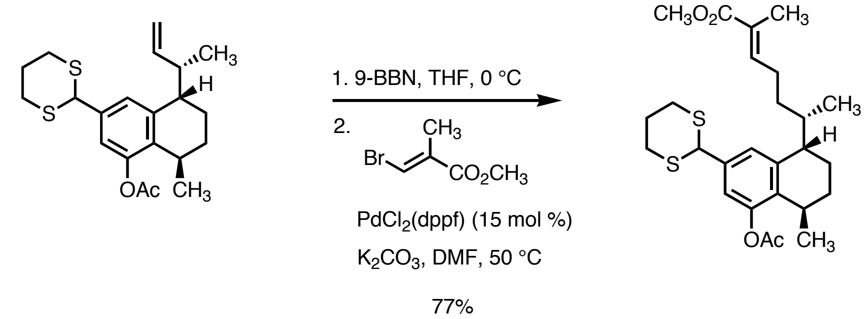
Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1–652.

- When alkylboron and alkylstannane groups are present in the same molecule, the organoboron groups react preferentially under basic conditions.



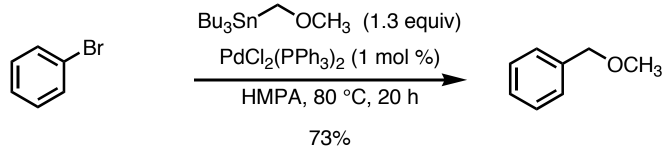
Ishiyama, T.; Miyaura, N.; Suzuki, A. *Synlett* **1991**, 687–688.

- The cross-coupling reaction of primary organoboranes is possible, while primary organostannanes are not typically used.



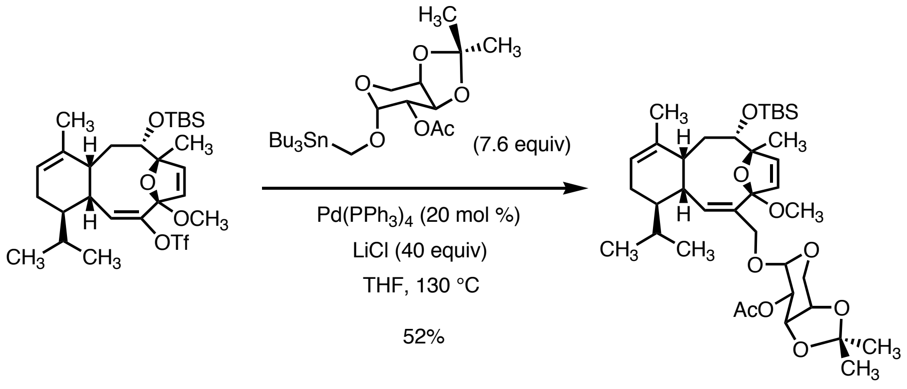
Uemura, M.; Nishimura, H.; Minami, T.; Hayashi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 5402–5410.

- Stille couplings with primary organostannanes typically involve special structural features, such as an α-heteroatom, and typically cannot undergo β-hydride elimination.



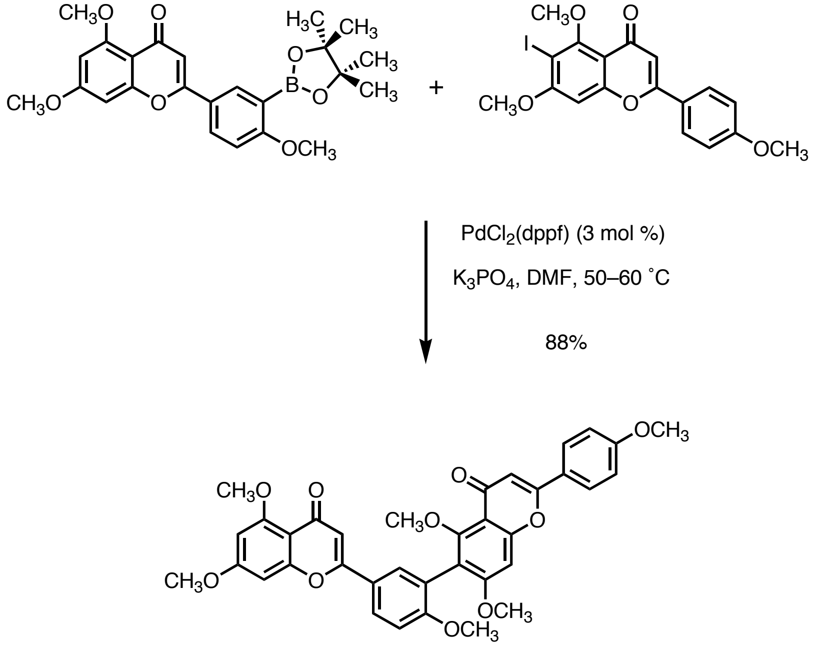
Kosugi, M.; Sumiya, T.; Ogata, T.; Sano, H.; Migita, T. *Chemistry Lett.* **1984**, 1225–1226.

- The Stille coupling has been used for the introduction of glycosylmethyl groups.

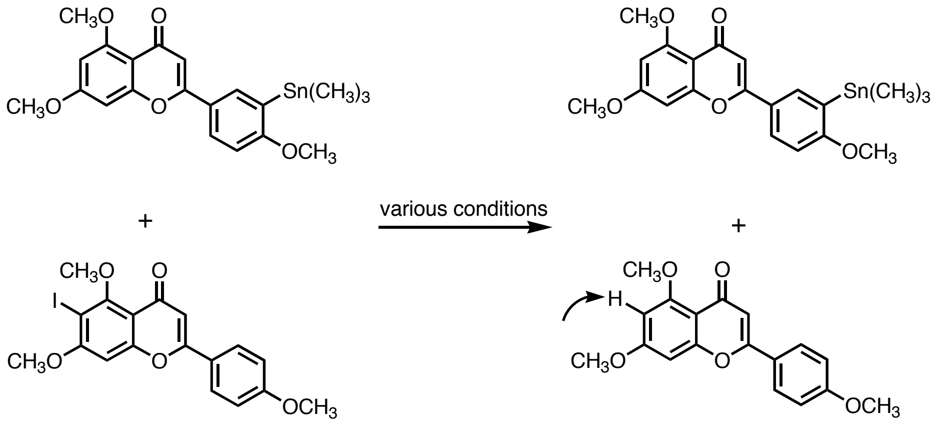


Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579.

- In the following examples, the Suzuki coupling was successful but the corresponding Stille reaction failed. This was attributed to a proposed slower rate of transmetalltion in the Stille reaction.



versus



Zembower, D.E.; Zhang, H. *J. Org. Chem.* **1998**, 9300–9305.

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The Heck Reaction

Reviews:

Belestskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

Brase, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, pp. 99–166.

Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28,* 2–7.

de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411.

- Intramolecular:

Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Eds.; Wiley-VCH: New York, **1998**, pp. 231–269.

Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447–471.

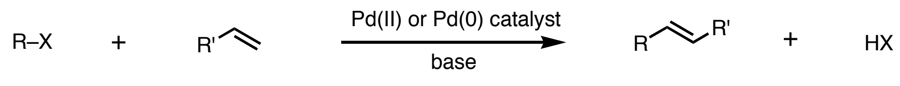
- Asymmetric:

Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7393.

- Solid phase:

Franzén, R. *Can. J. Chem.* **2000**, *78*, 957–962.

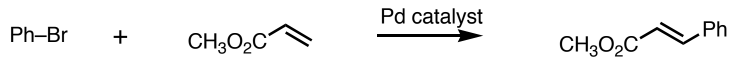
General transformation:

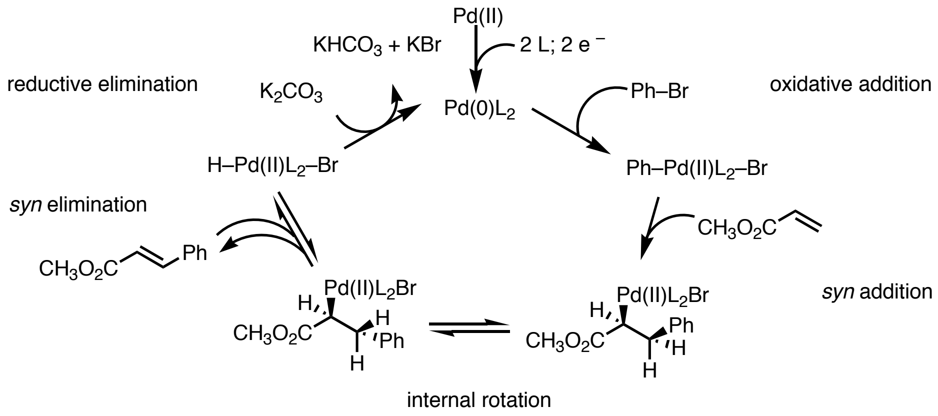


R = alkenyl, aryl, allyl, alkynyl, benzyl X = halide, triflate R' = alkyl, alkenyl, aryl, CO_2R, OR, SiR_3

Mechanism:

- Proposed mechanism involving neutral Pd:





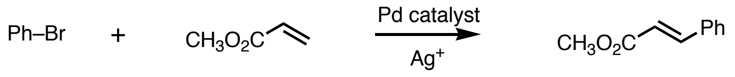
- Pd(II) is reduced to the catalytically active Pd(0) in situ, typically through the oxidation of a phosphine ligand.

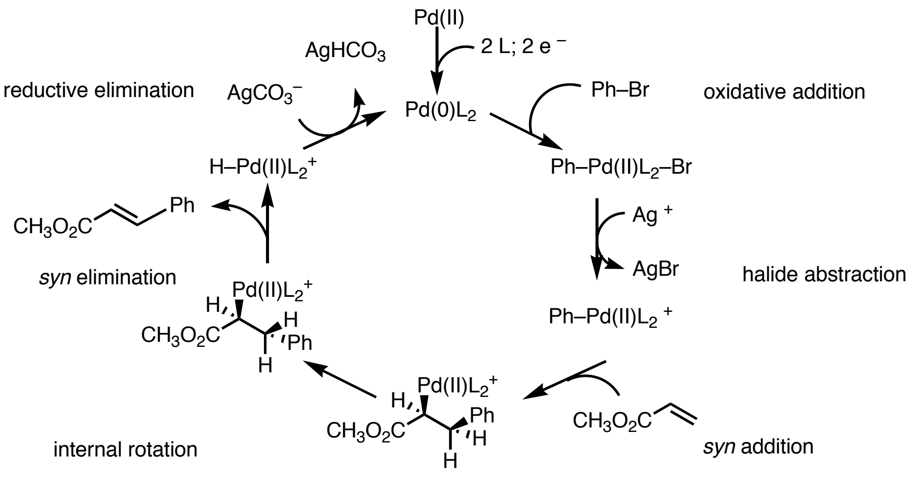
$$Pd(OAc)_2 + H_2O + nPR_3 + 2R'_3N \longrightarrow Pd(PR_3)_{n-1} + O{=}PR_3 + 2R'_3N{\bullet}HOAc$$

Ozawa, F.; Kubo, A.; Hayashi, T. *Chemistry Lett.* **1992**, 2177–2180.

- Ag^+ / Tl^+ salts irreversibly abstract a halide ion from the Pd complex formed by oxidative addition. Reductive elimination from the cationic complex is probably irreversible.

- An example of a proposed mechanism involving cationic Pd:





Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133–4135.

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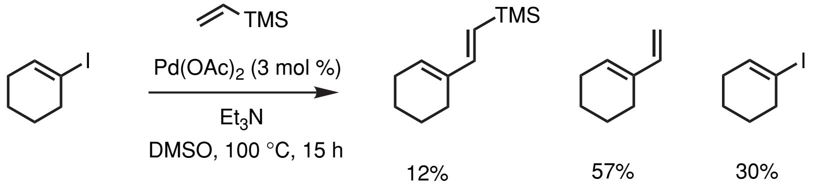
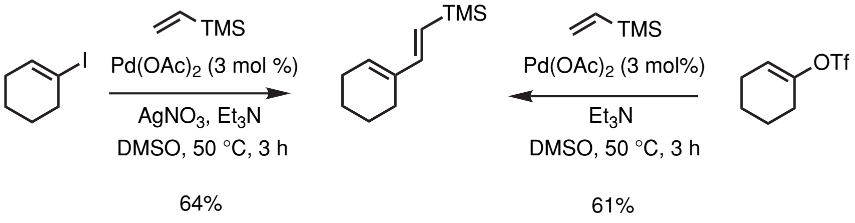
- Reactions with vinyl or aryl triflates often parallel those of the corresponding halides in the presence of silver salts.

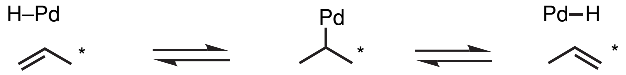


GC yields

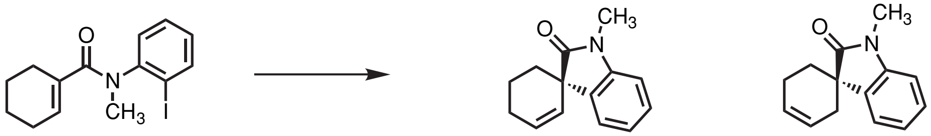


Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909–4914.

- Reversible β-hydride elimination can lead to alkene isomerization.

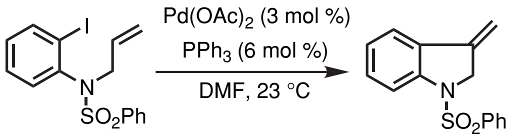


- Use of silver salts can minimize alkene isomerization.



Conditions	
$Pd(OAc)_2$ (1 mol %) PPh_3 (3 mol %) Et_3N (2 equiv) acetonitrile, 3h, reflux	1 : 1
as above, plus $AgNO_3$ (1 equiv) and 23 °C	26 : 1

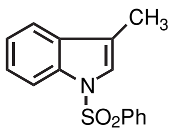
Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133–4135.



Ag_2CO_3, eq	Time, h	Yield, %
1	24	50
1	48	35
2	5	80

Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1941–1942.

By-product:



- With some ligands, experimental evidence points to a Pd(II)/Pd(IV) catalytic cycle, although the debate is ongoing.

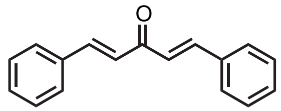
Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.

Shaw, B. L.; Perera, S. D.; Staley, E. A. *J. Chem. Soc., Chem. Commun.* **1998**, 1361–1362.

Conditions:

• Catalysts:	$Pd(OAc)_2$	$Pd_2(dba)_3$
	most common	stable Pd(0) source; useful if substrate is sensitive to oxidation

dba =



- Ligands: Phosphines (PR_3), used to prevent deposition of Pd(0) mirror.

- Solvents: Typically aprotic; a range of polarities.

Solvent	toluene	THF	1,1-dichloroethane	DMF
Dielectric constant	2.4	7.6	10.5	38.3

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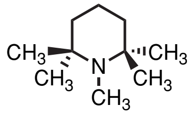
- Bases: Both soluble and insoluble bases are used.

Soluble examples



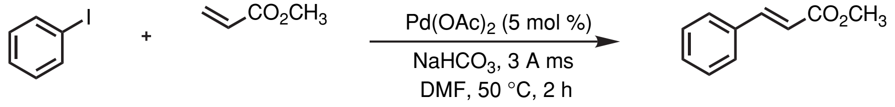
1,2,2,6,6-pentamethylpiperidine (PMP)

Et_3N

Insoluble examples

K_2CO_3 Ag_2CO_3

- Jeffery conditions: The combination of tetraalkylammonium salts (phase-transfer catalysts) and insoluble bases accelerates the rate to the extent that lower reaction temperatures are possible.



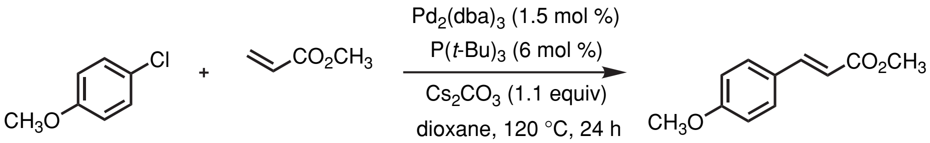
Equiv. of *n*–Bu_4NCl	GC Yield(%)
0	2
1	99

Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

- One proposed explanation for this rate enhancement is based on the fact that palladium complexes can be stabilized by the coordination of halide ions; thus, the catalyst is less likely to decompose under the Heck reaction conditions.

Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384.

- Conditions for the Heck coupling of aryl chlorides have been developed.

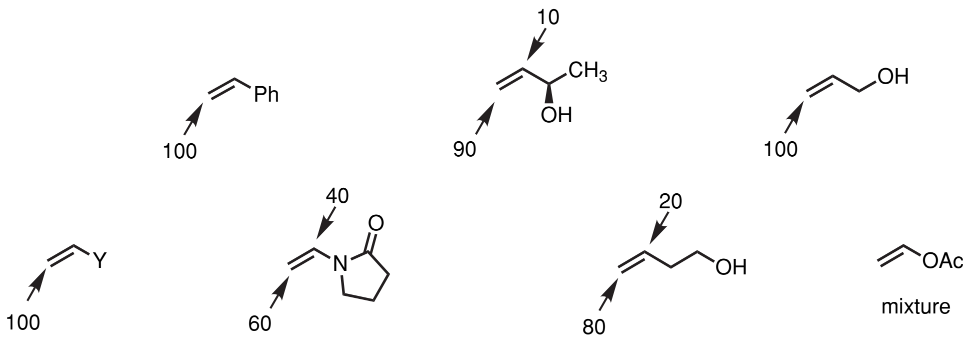


82%

Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.

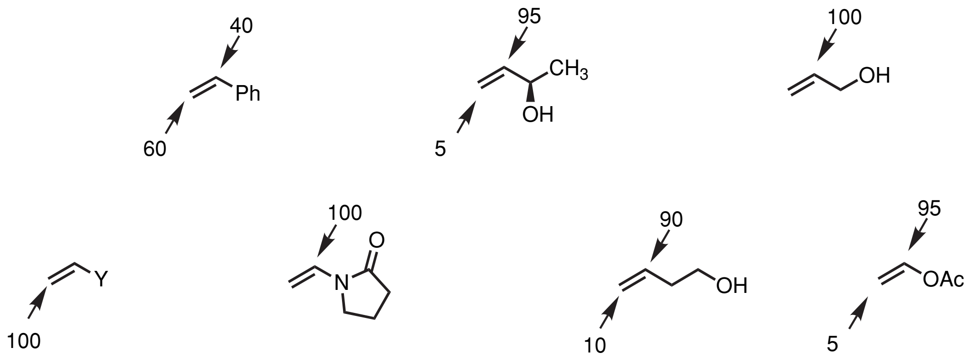
Regiochemistry of addition:

- Neutral Pd complexes: regiochemistry is governed by sterics; position of Ar attachment:



Y = CO_2R
CN
$CONH_2$

- Cationic Pd complexes: regiochemistry is affected by electronics. The cationic Pd complex increases the polarization of the alkene favoring transfer of the vinyl or aryl group to the site of least electron density.



Y = CO_2R
CN
$CONH_2$

Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28,* 2–7.

Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481–1486.

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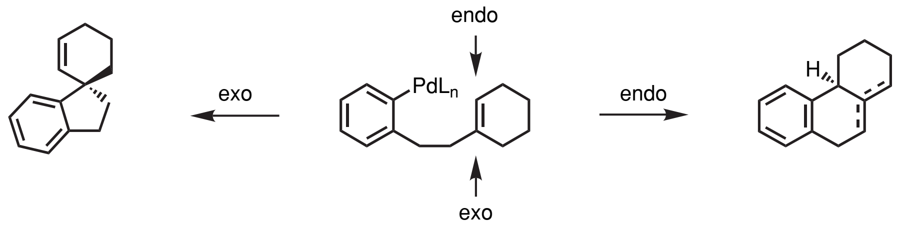
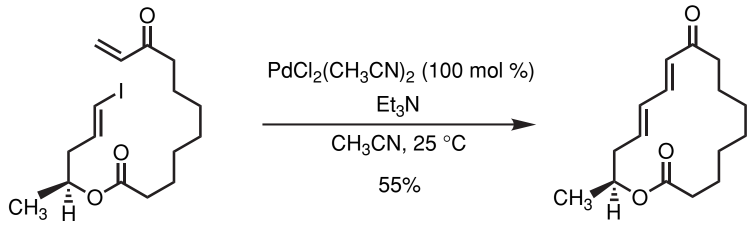
- A major issue in intramolecular Heck reactions is the mode of ring closure, i.e., *exo* versus *endo.*



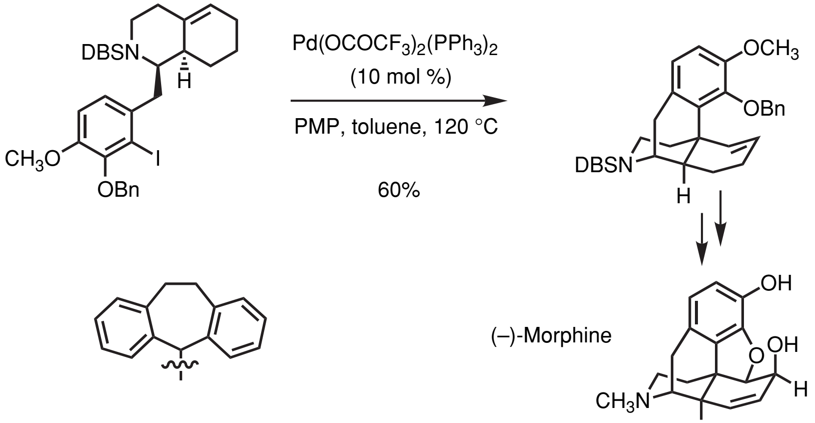
- For large rings, conformational effects can be minimal. If a neutral Pd complex is used, sterics enforce *endo* selectivity.

- The Heck reaction is useful for macrocylization.



Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035–4040.

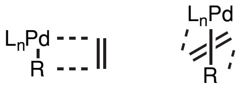
- Five-, six-, and seven-membered ring closures (the most efficient Heck ring closures) give predominantly *exo* products.



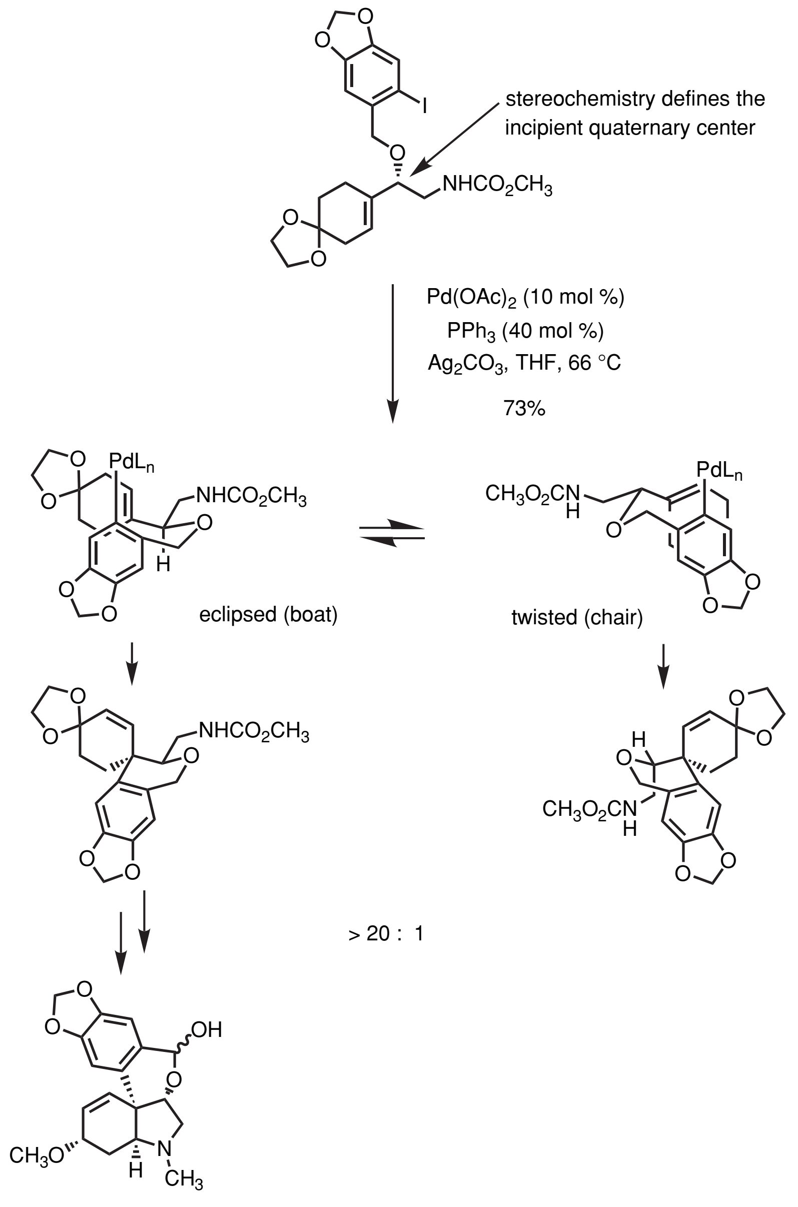
DBS = dibenzosuberyl

Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029.

- Conformational effects are more important when forming smaller rings. The eclipsed orientation is preferred for the reaction, even if this means the rest of the molecule must adopt a less than ideal conformation.



eclipsed twisted



(±)-6a-epipretazettine

Overman, L. E. *Pure & Appl. Chem.* **1994**, *66*, 1423–1430.

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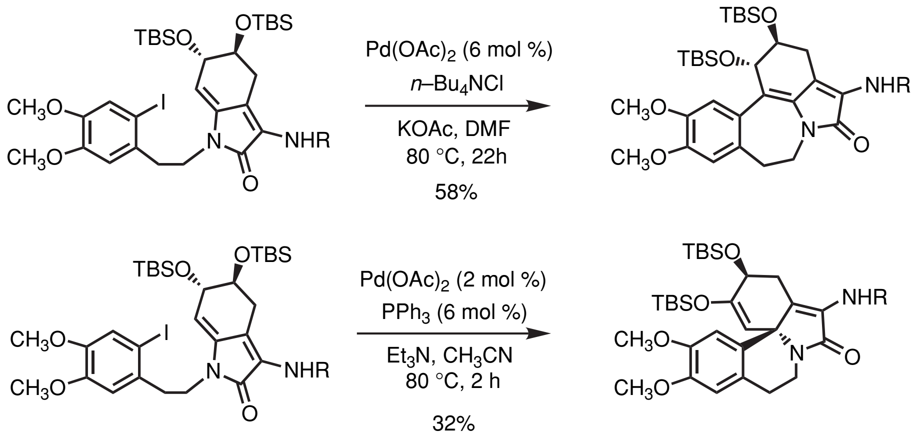
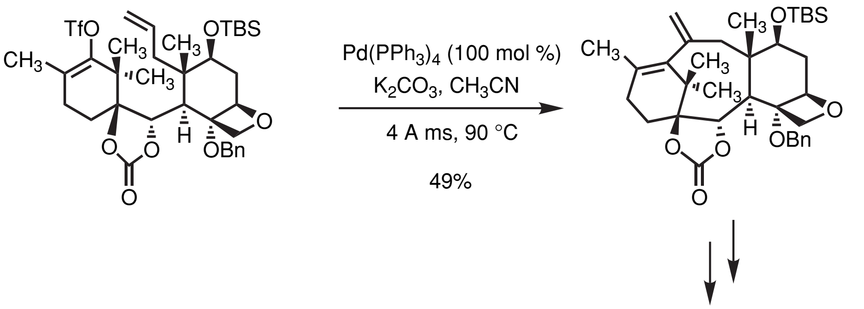
- Variation of reaction conditions can greatly influence *exo* versus *endo* selectivity in small rings.

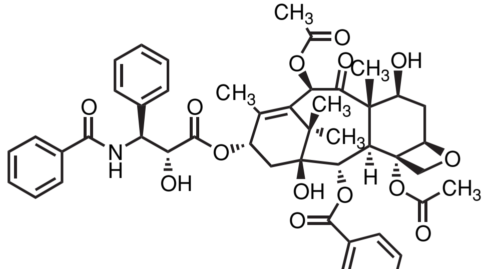


- The authors' rationale for these results is that under the Jeffery conditions, the coordination sphere of palladium is relatively smaller, and thus the metal can be accommodated at the more substituted alkene site during migratory insertion.

Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835.



- Steric and electronic effects begin to compete with conformational effects when forming medium–sized rings.

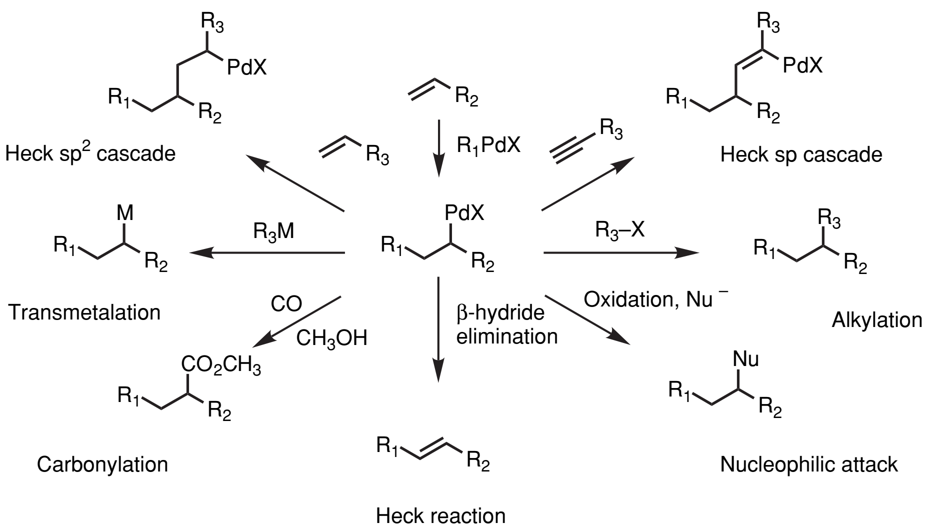


Taxol

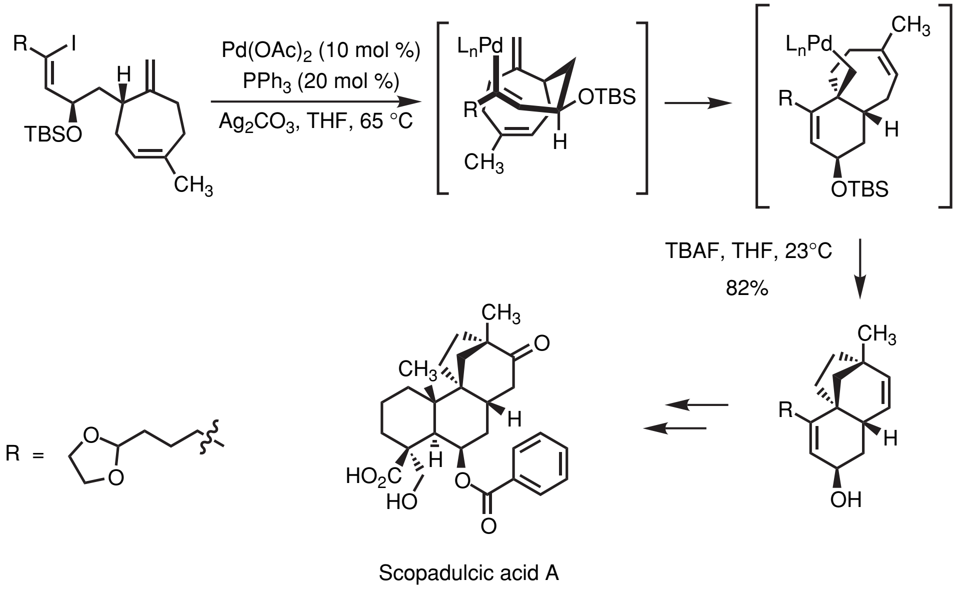
Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723–1726.

Tandem Reaction:

- Additional reaction pathways become available when the initial Pd–C species does not (or can not) decompose via β-hydride elimination.



- Tandem Heck reactions:



Scopadulcic acid A

Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304–5306.

Fox, M. E.; Li, C; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.

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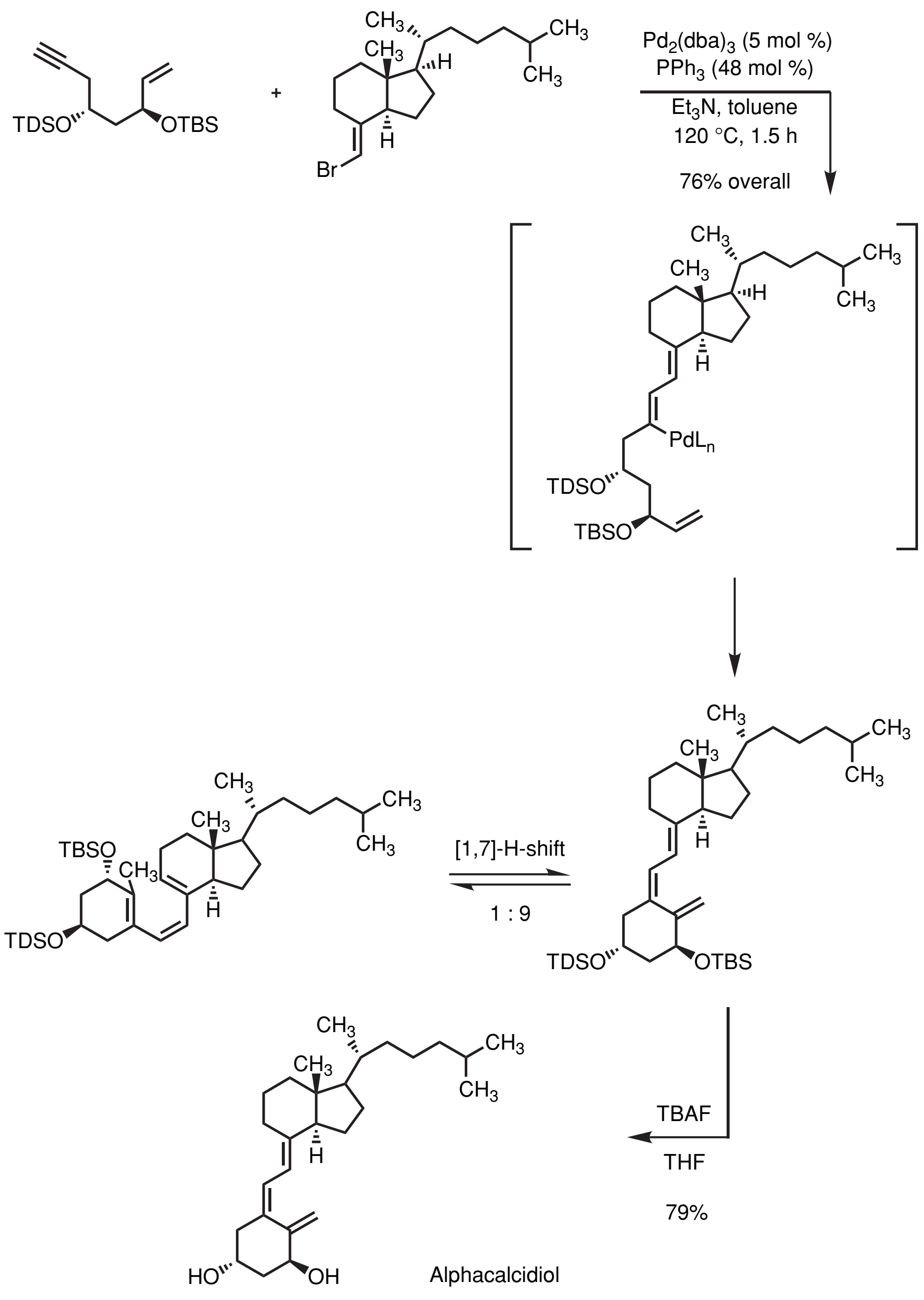
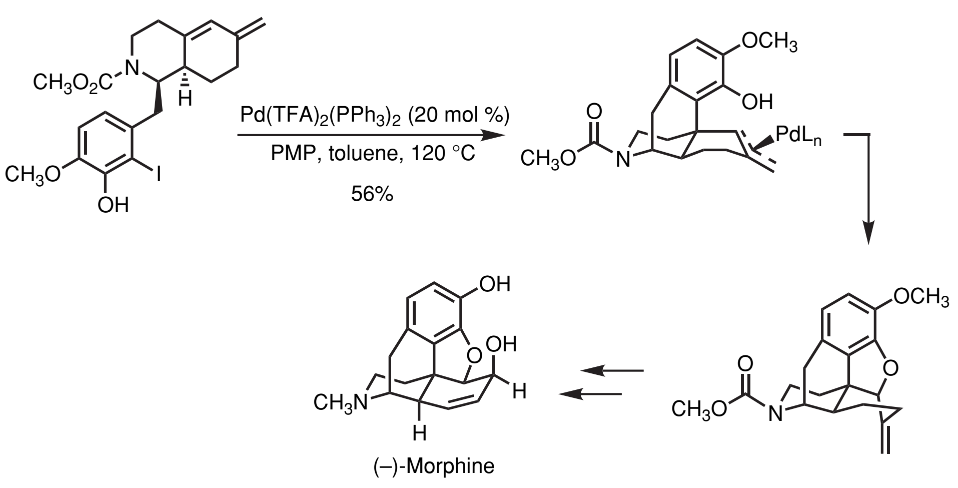
- Tandem Heck reaction, intermolecular



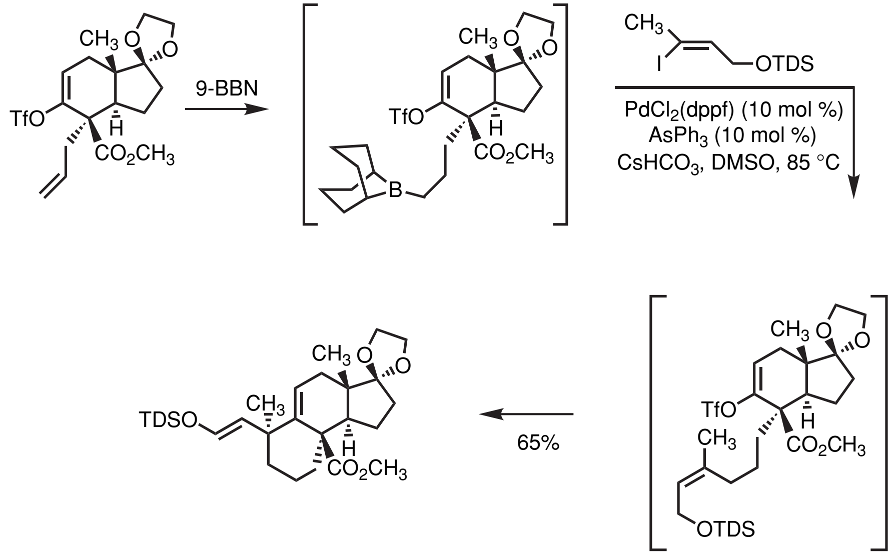
Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845.

- Tandem Heck/π–allylpalladium reactions



Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453–3456.

- Tandem Suzuki/Heck reactions



Kojima, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3455–3458.

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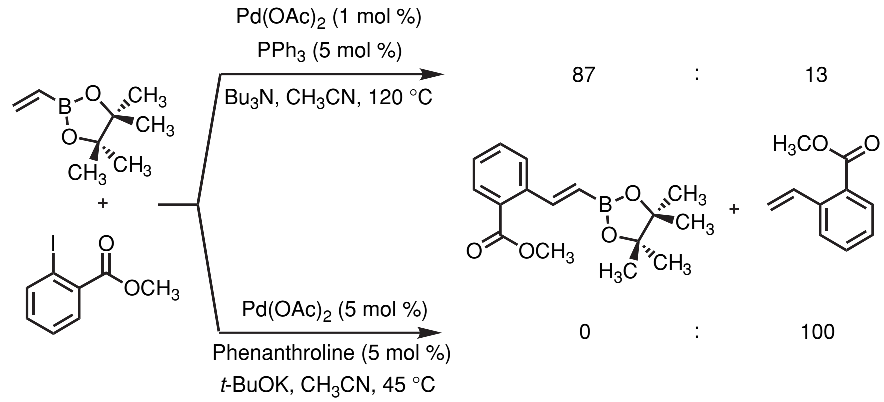
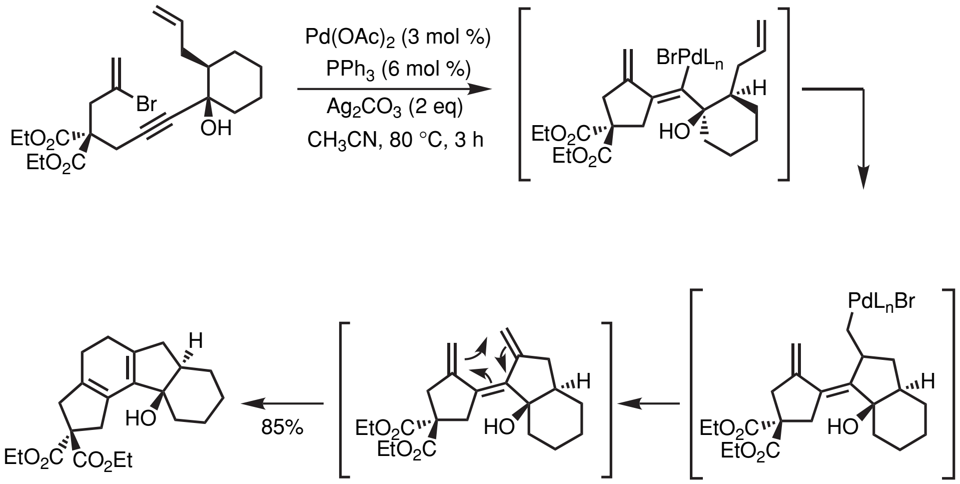
- The ease of reaction (Heck versus Suzuki) is highly dependent upon the reaction conditions:



Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.*, **1993**, *34*, 3599–3602.

- Tandem Heck/6π-electrocyclization reactions:

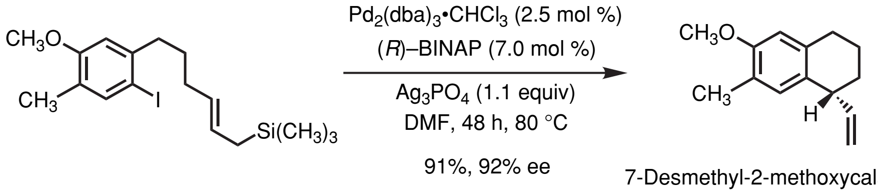


Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11545–11578.

Enantioselective Heck Reactions:

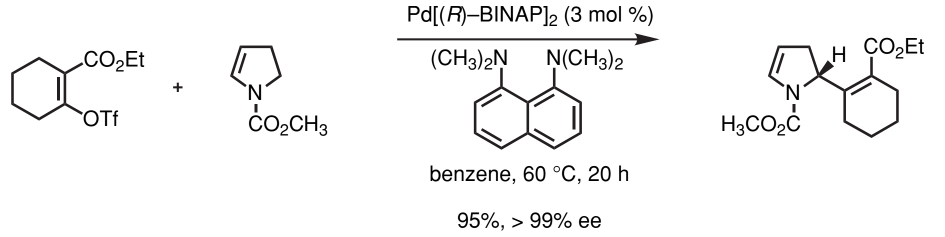
- Typical yields = 50–80%
- Typical ee's = 80–95%

- Formation of tertiary stereocenters:



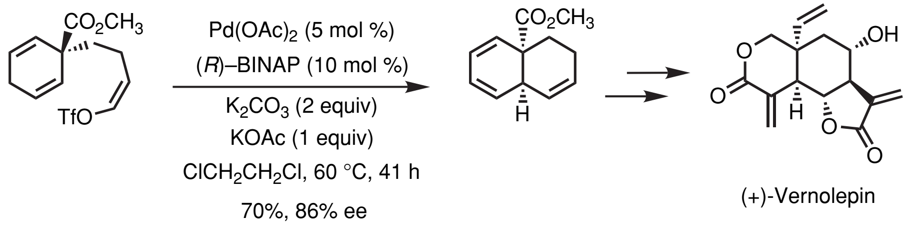
7-Desmethyl-2-methoxycalamenene

Tietze, L. F.; Raschke, T. *Synlett* **1995**, 597–598.



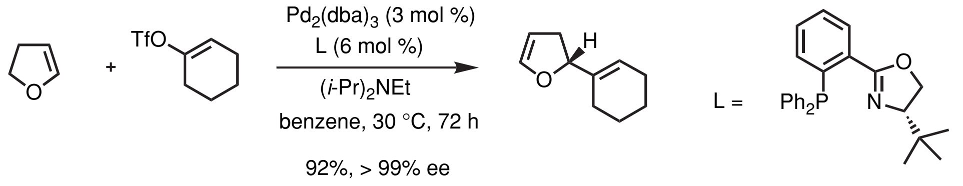
- Note that the alkene within the intially formed pyrrolidine has migrated under the reaction conditions.

Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505–2508.



(+)-Vernolepin

Ohari, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737–11748.



Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338–1345.

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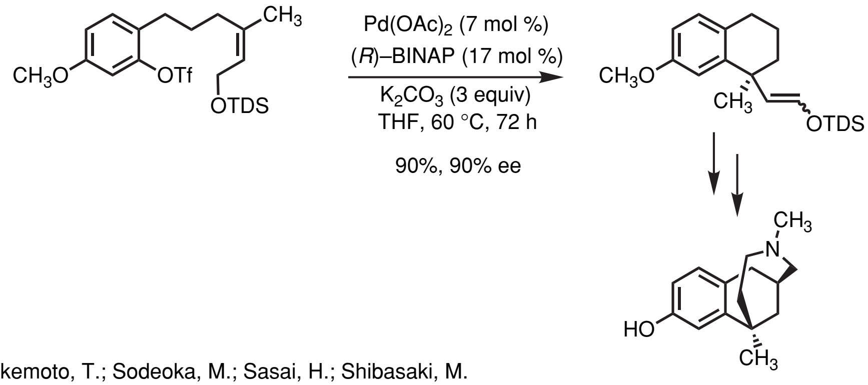
- Formation of quaternary stereocenters:

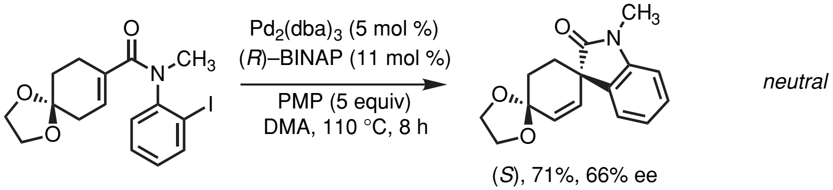


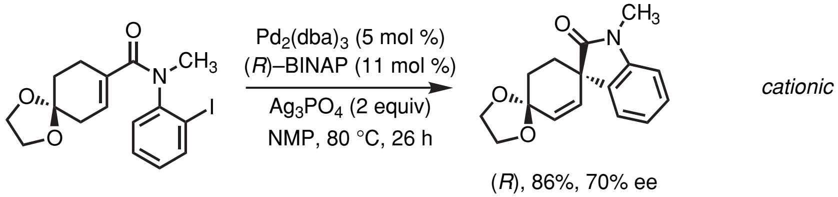
Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M.

J. Am. Chem. Soc. **1993**, *115*, 8477–8488.

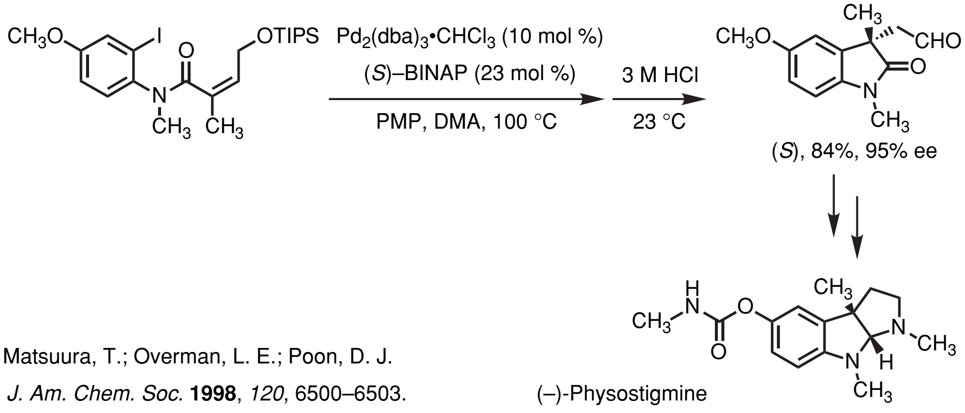
(–)-Eptazocine

- The choice of base influences whether the Pd complex is neutral or cationic; this in turn can influence the stereochemical outcome.





Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487.

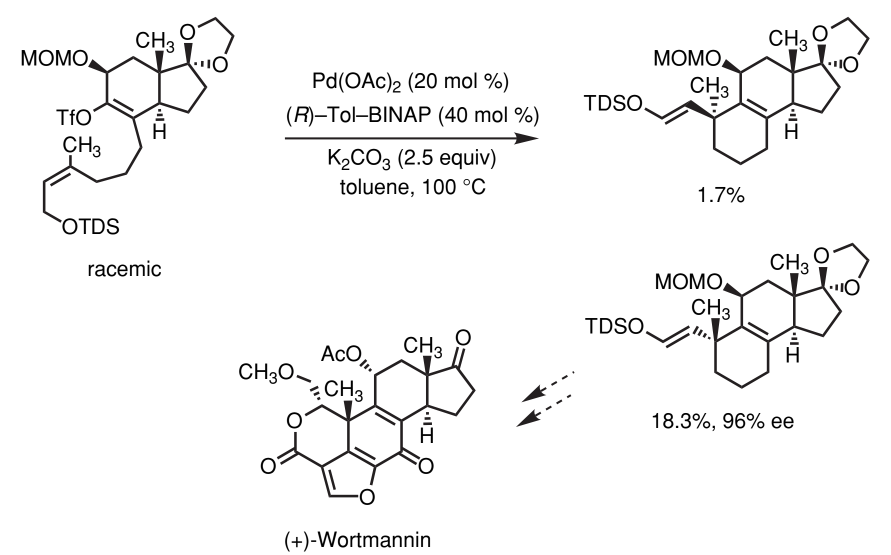


Matsuura, T.; Overman, L. E.; Poon, D. J.

J. Am. Chem. Soc. **1998**, *120*, 6500–6503.

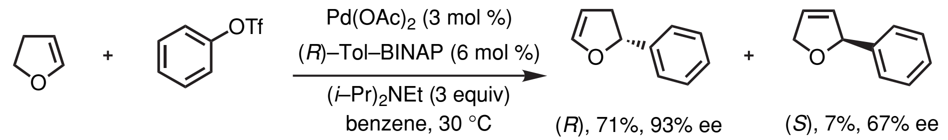
(–)-Physostigmine

- Kinetic Resolution:



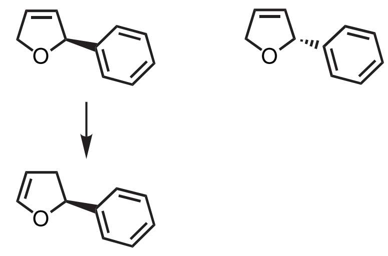
- The enantiomer of the major product not observed. Instead, a complex mixture of products was formed.

Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311–314.



- Initial products are 2,3 dihydrofurans:

- Only the (*R*) isomer can isomerize due to the asymmetric environment of the ligand.



Ozawa, F.; Kubo, F.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K.

Organometallics **1993**, *12*, 4188–4196.

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Pure & Appl. Chem., Vol. 64, No. 3, pp. 343–350, 1992.
Printed in Great Britain.
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Applications of Ni(II)/Cr(II)-mediated coupling reactions to natural products syntheses

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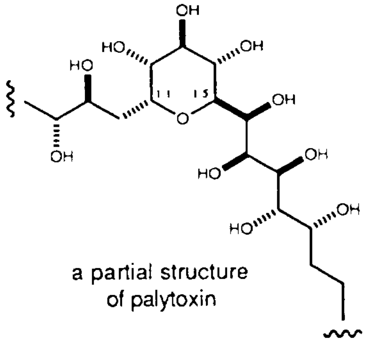
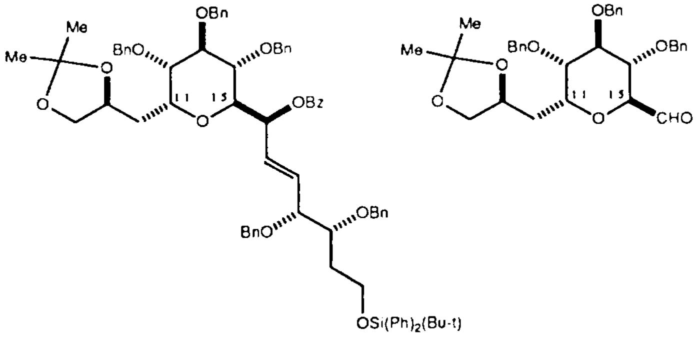
Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, MA 02138 USA

ABSTRACT - This paper presents a brief review on the history of the development of Ni(II)/Cr(II)-mediated coupling reaction and its application to natural products syntheses.

During the synthetic studies on the marine natural product palytoxin, we recognized the *trans*-allylic benzylether benzoate to be the key intermediate for the synthesis of the C.8-C.22 segment (ref. 1-4). We had planned to synthesize this substance from the aldehyde or its synthetic equivalent, which seemed possible through routine synthetic operations. However, we soon realized that standard synthetic routes such as Wittig and aldol approaches were not as practical as we had hoped. Among the many possibilities attempted, a coupling reaction utilizing organocuprates gave, at least in the model series, very promising results. However, in spite of extensive efforts, we were unable to generate the desired organocuprate reagent from the *trans*-iodoolefin.

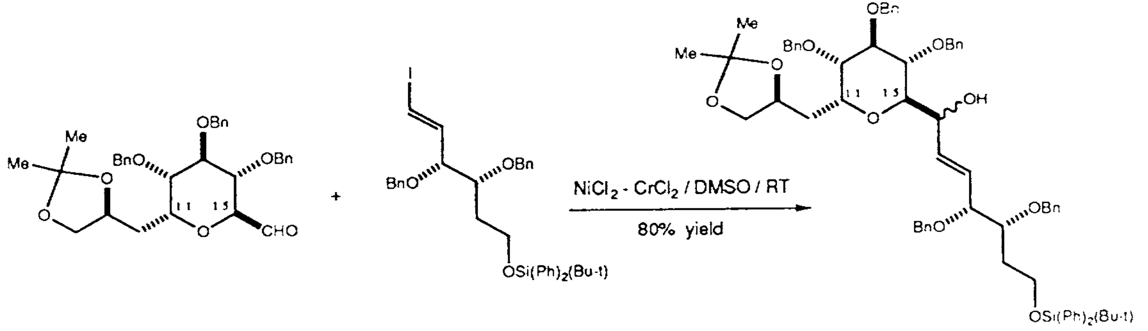


a partial structure of palytoxin



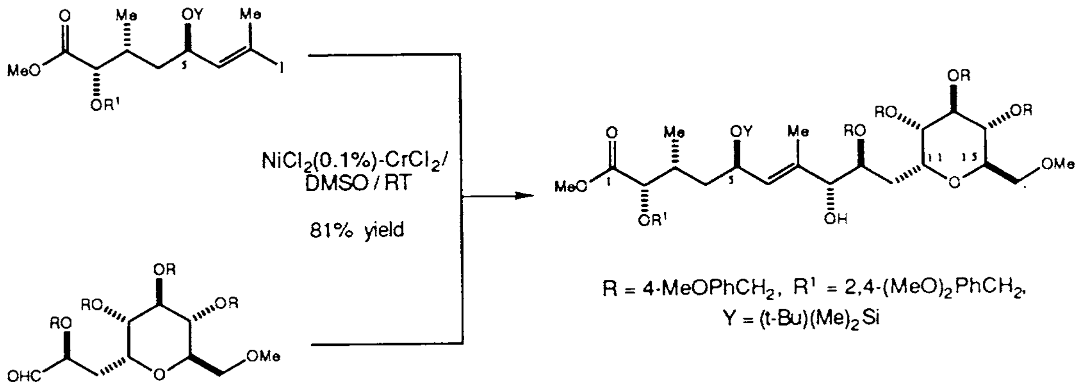
The clue to the solution came from the timely work of Professor Nozaki and co-workers on the Cr(II)-mediated addition of alkenyl halides to aldehydes (ref. 5). After much trial-and-error, we were able to realize the required coupling by adding $CrCl_2$ to a DMSO solution of aldehyde and iodoolefin at room temperature in the absence of oxygen. This reaction warrants several comments. First, we examined a large number of highly-oxygenated substrates, and found the coupling to be remarkably effective even for polyfunctional cases, including α-oxygenated aldehydes with iodoolefins or β-iodoenones. Second, the stereochemistry of *trans*- as well as *cis*-iodoolefins is retained at least in the cases of disubstituted iodoolefins and trisubstituted *trans*-iodoolefins. Third, with respect to the newly introduced chiral center, this process produces a mixture of two possible diastereomers with a moderate-to-good preference for one stereoisomer. It is worth mentioning that the major products produced from α-alkoxy and α,β-bisalkoxy aldehydes have the stereochemistry opposite to cuprate or Grignard products.

The Cr(II)-mediated coupling reaction provided an excellent solution to our problem except for one technical difficulty. Unlike the Cr(II)-mediated coupling of allyl halides with aldehydes (ref. 6), the success of this coupling mysteriously depended on the source and batch of $CrCl_2$. We also tested a home-made Cr(II)-reagent without success. These facts naturally suggested an intriguing possibility that the success of this coupling might depend on some unknown contaminant in $CrCl_2$. For this reason, we examined the effect of transition metals on the Cr(II)-mediated coupling reaction and found that $NiCl_2$, when added to the reaction medium, has a dramatic effect. Although we did not establish whether the effectiveness of the commercially available $CrCl_2$ sample was because of Ni salt or some other metal contaminant, it is now possible to achieve the coupling using $CrCl_2$ from any source with excellent reproducibility. It is important to keep the $NiCl_2$ content in $CrCl_2$ low [about 0.01%~1% (w/w)] to avoid formation of dienes from iodoolefins by homocoupling. Reactions are fast in DMF, THF, or a mixture of DMF and THF, which is usually the choice of solvent for coupling of iodoenones. Reactions are slower in DMSO but this often gives much cleaner results for the coupling of iodoolefins (ref. 7, 8).



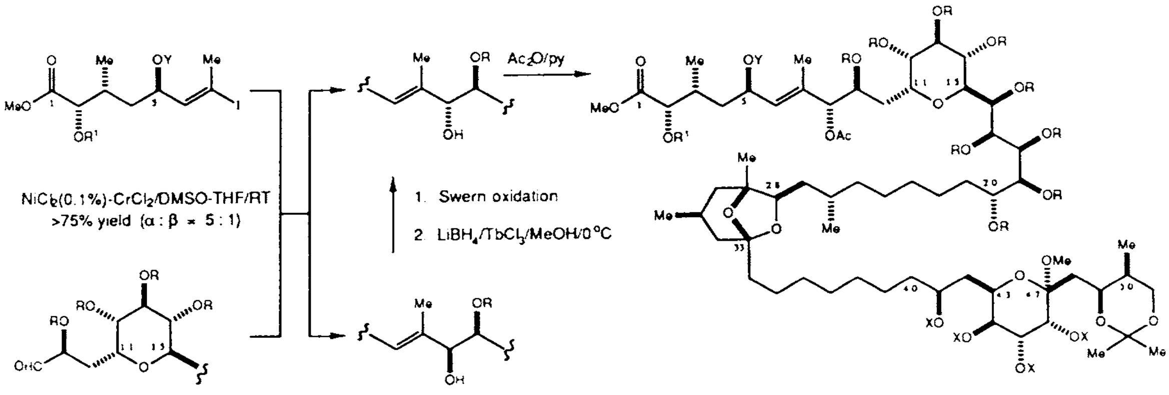
With respect to the possible mechanism for the activation of an alkenyl iodide, this process may involve an initial reduction of Ni(II) into Ni(I) or Ni(0) by Cr(II), oxidative addition of an alkenyl iodide to Ni(I) or Ni(0), and then transmetallation with Cr(II) or Cr(III), to generate the organometallic reagent which then couples with an aldehyde. On the other hand, Ni(II) is regenerated and completes the cycle.

It became obvious that the Ni(II)/Cr(II)-mediated coupling would provide a unique solution to the C.7-C.8 bond formation for the palytoxin synthesis, if we could overcome one additional technical difficulty. Namely, it was important to use an excess of vinyliodide to achieve the Ni(II)/Cr(II)-mediated coupling reaction efficiently, which was not a serious problem as long as the vinyliodides were inexpensive. Unfortunately, the vinyliodide required for the C.7-C.8 bond formation was not cheap by any means, forcing us to search for a method to increase the efficiency of the catalytic cycle. For this reason, we studied the effect of C.5 protecting group on the coupling reaction using a model system. The results were dramatic; with a silyl protecting group at the C.5 position, the coupling reaction could be achieved in excellent yield even with 2 equivalents of the vinyliodide (ref. 9). Although the reason(s) for the dramatic improvement in the efficiency of the catalytic cycle still remains unclear, this observation, i.e. a high efficiency on the substrate with a silyl protecting group(s), is quite general. We found one additional bonus from this model study. The C.8-stereoselectivity was improved up to the level of 10:1, favoring the desired diastereomer.



R = 4-MeOPhCH$_2$, R^1 = 2,4-(MeO)$_2$PhCH$_2$,
Y = (t-Bu)(Me)$_2$Si

The Cr(II)-mediated coupling allows a carbon-carbon bond formation between alkenyl halides and aldehydes, which can usually be achieved by traditional organometallic reagents such as Grignard, lithium, or cuprate. However, there are several unique characteristics of this reaction. Experimentally, activation of a carbon-iodine bond in the presence of an aldehyde offers an attractive convenience for many cases. In our view, this coupling reaction has demonstrated its potential and uniqueness for polyfunctional substrates, for which conventional organometallic reagents are difficult to apply. The coupling reaction of the C.1-C.7 segment with the C.8-C.51 segment best illustrates this point; the Ni(II)/Cr(II)-mediated coupling reaction under standard conditions using 2 equivalents of the vinyliodide yielded the expected product in 75% yield as a 5:1 mixture of the C.8 diastereomers, favori the desired product (ref. 7). The minor undesired stereoisomer was converted into the desired stereoisomer via an oxidation-reduction process. After acetylation, hydrolysis of the acetonide group under mild acidic conditions furnished the complete left half of palytoxin.

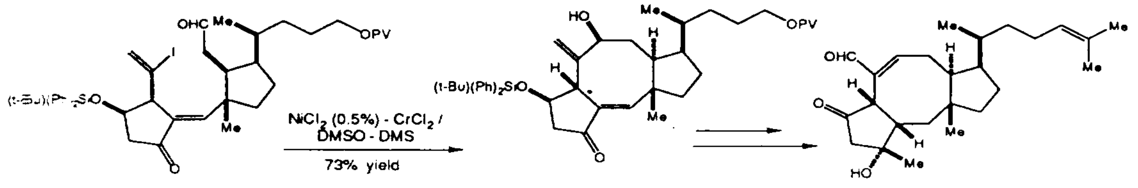

NiCl$_2$(0.1%)-CrCl$_2$/DMSO-THF/RT
>75% yield (α : β = 5 : 1)
Ac$_2$O/py
1. Swern oxidation
2. LiBH$_4$/TbCl$_3$/MeOH/0 °C

R = 4-MeOPhCH$_2$, R^1 = 2,4-(MeO)$_2$PhCH$_2$, X = Bz, Y = (t-Bu)(Me)$_2$Si

Functional groups stable under the coupling conditions :

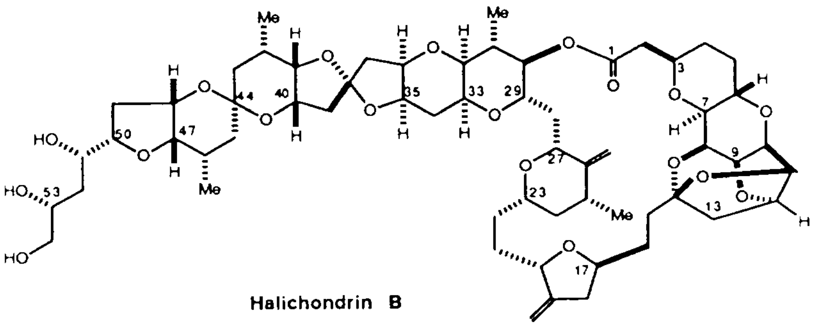
esters, amides, nitriles, ketones, acyls, acetals, ketals, ethers, silyl ethers, alcohols, olefins. . . . .

We have used the Ni(II)/Cr(II)-mediated coupling reaction as the key bond-forming step for the synthesis of various natural and non-natural products. Among them, the synthesis of ophiobolin C deserves comment (ref. 10). This work demonstrates the usefulness of the Ni(II)/Cr(II)-mediated coupling reaction for ring formation, even for medium ring formation; construction of the highly functionalized eight-membered ring was effectively accomplished by treatment of the vinyliodide aldehyde with CrCl$_2$ containing NiCl$_2$ (0.5%) in a mixture of DMSO and dimethyl sulfide (1% v/v) at room temperature for 2 hours. It is worth noting that a single stereoisomer was formed in this cyclization, and its stereochemistry was found to be the one anticipated on the basis of steric considerations.



Ophiobolin C

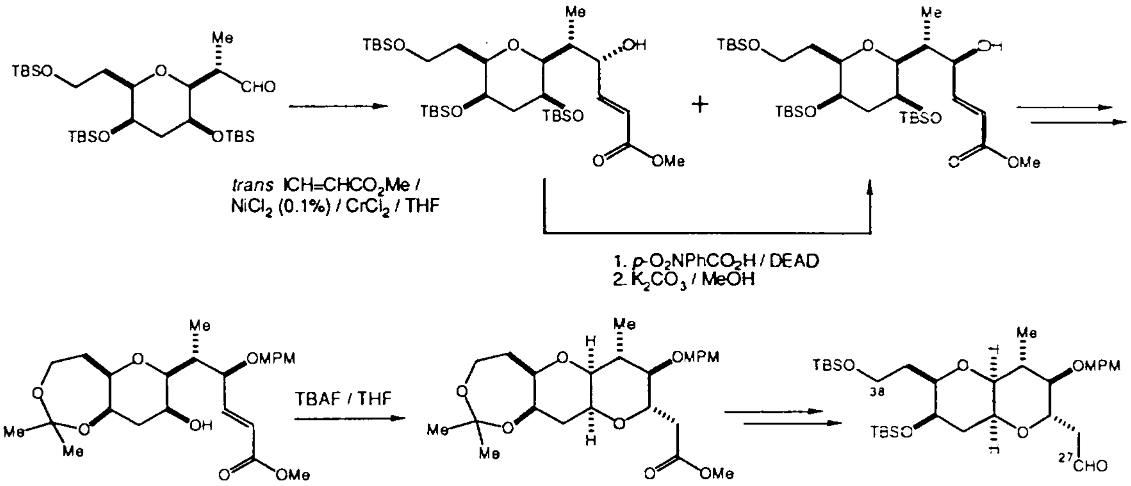
In order to further illustrate the scope and limitation of the Ni(II)/Cr(II)-mediated coupling reaction, we now outline the five carbon-carbon bond forming steps used in the synthesis of halichondrins, a class of polyether macrolides isolated from the marine sponge *Halichondria okadai* (ref. 11). Halichondrins, especially halichondrin B and homohalichondrin B, exhibit an extraordinary in-vitro and in-vivo antitumor activity (ref. 11). However, the very limited supply of halichondrins from natural sources has prevented further evaluation for their potential clinical application thus far. Their intriguing and challenging structural features, coupled with this fact, have encouraged us to undertake synthetic efforts toward this class of natural products (ref. 12, 13).



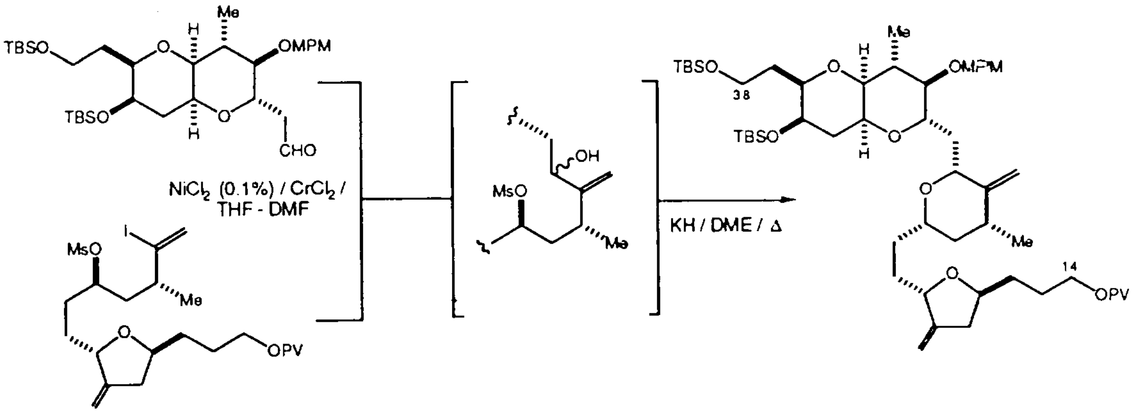
Halichondrin B

The first Ni(II)/Cr(II)-mediated coupling reaction used in this work is depicted below. It allowed an efficient carbon-carbon bond formation between the aldehyde and the β-position of acrylate to form a γ-hydroxy-*trans*-acrylate in 90-95% yield. This example once again demonstrates the uniqueness of this coupling reaction. However, it also shows its limitation; namely, the product formed was approximately a 2:1 mixture of the two possible diastereomers, favoring the desired stereoisomer. The minor, undesired alcohol was subjected to the Mitsunobu procedure (ref. 14) to invert the stereochemistry. There is a distinct possibility that the stereochemical outcome of this type of coupling reaction could be dictated by using a suitable chiral ligand. We have made some efforts along this line, but have met with only limited success thus far. Undoubtedly, some device of controlling the stereochemical course should give additional versatility to this process.

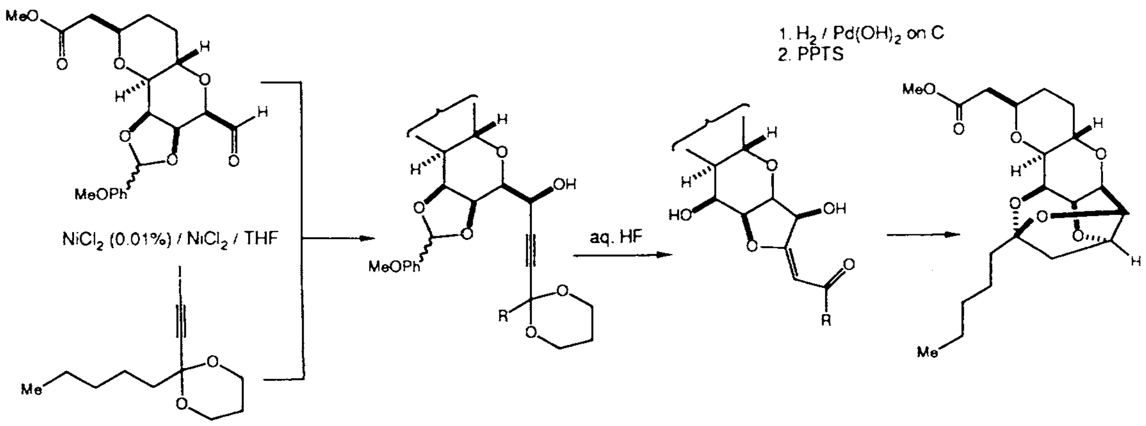
After protection of the allylic alcohol as an MPM group, deprotection of the silyl groups, and protection of the two-out-of-three resultant alcohols as an acetonide, the Ni(II)/Cr(II)-coupling product was subjected to a Michael reaction in the presence of commercially available tetrabutylammonium fluoride in THF at room temperature, to furnish the desired cyclized product with an excellent stereoselectivity (>20:1). Using routine synthetic reactions, this Michael product was transformed into the C.27-C.38 segment.


TBSO
Me
CHO
TBSO
OTBS
trans ICH=CHCO$_2$Me / NiCl$_2$ (0.1%) / CrCl$_2$ / THF
OH
+
OMe
1. p-O$_2$NPhCO$_2$H / DEAD
2. K$_2$CO$_3$ / MeOH
OMPM
TBAF / THF
OH
H
38
27
CHO

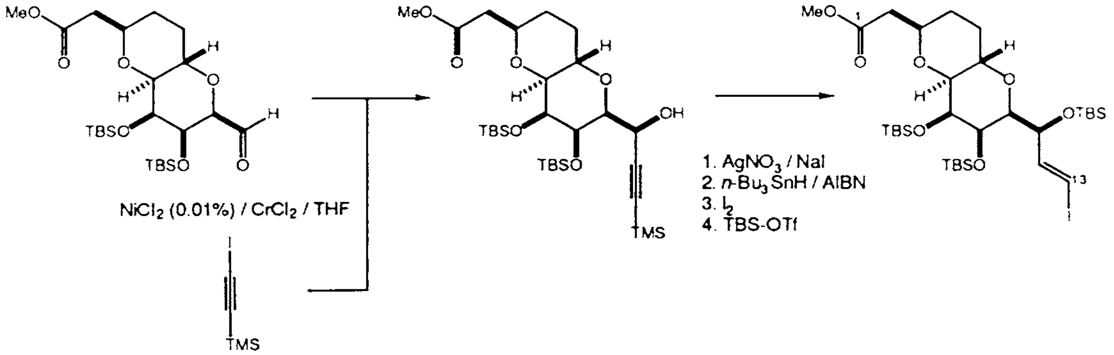
The second Ni(II)/Cr(II)-mediated coupling reaction used in the synthesis of halichondrins is shown below. This reaction allowed us to couple the two segments with the fragile functional groups and to complete a highly convergent synthesis of the C.14-C.38 portion. The overall yield for this process was 50-60%, and the stereoselectivity was approximately 6:1 favoring the desired product.



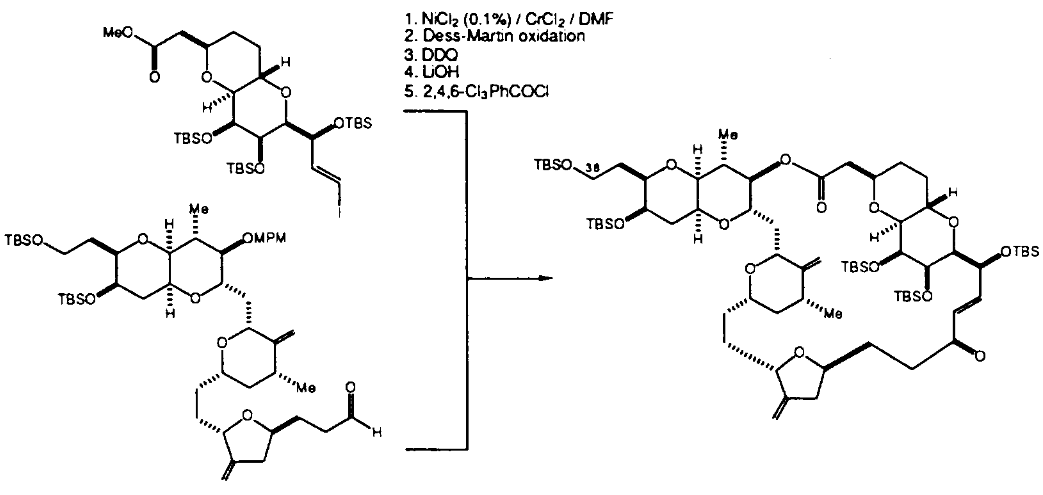
We recognized the possibility to construct the intriguing polycyclic ring system around the C.1-C.15 moiety by using the Ni(II)/Cr(II)-mediated coupling reaction, and studied its feasibility first in the model series. The aldehyde was subjected to the Ni(II)/Cr(II)-mediated coupling reaction with the iodoacetylene (1.4 equivalents), to yield the expected, desired propargyl alcohol in excellent yield. This coupling reaction warrants several comments. First, as described before, this process is exceptionally well suited for cases where the aldehyde is labile. In this case, the aldehyde can potentially give problems associated with enolization such as epimerization and dehydration. However, under the Ni(II)/Cr(II)-mediated coupling conditions, we observed no complications. Second, the stereoselectivity was slightly over 8:1, favoring the desired product, which was anticipated on the basis of steric considerations. Third, the $NiCl_2$ content in $CrCl_2$ needs to be much lower for iodoacetylenes than for iodoolefins.



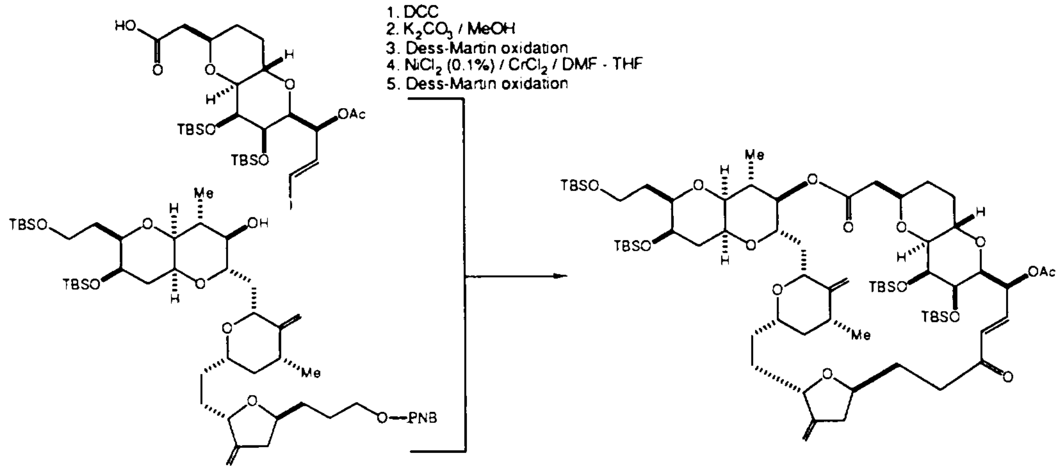
The propargyl alcohol thus obtained was subjected to acid treatment to form the vinylogous ester, hydrogenation, then mild acid treatment, to furnish the desired the polycyclic compound in excellent overall yield. This model study yielded a solution for the synthesis of the polycyclic system around the C.1-C.15 moiety. However, we realized that some modification on this approach should be considered for two major reasons. First, the Ni(II)/Cr(II)-mediated coupling reaction is most effectively accomplished with a slight excess, typically 1.5-2.0 equivalents, of iodoolefins or iodoacetylenes. We had planned to use the C.12-C.38 segment as the iodoacetylene component in the real system. Not surprisingly, the synthesis of the C.12-C.38 segment required more effort than the synthesis of the C.1-C.11 segment. Second, hydrogenation was needed stereospecifically to introduce the C.12 chiral center, but the intact C.12-C.38 segment contains two exocyclic olefinic bonds. In order to overcome these potential difficulties, we decided to modify the original plan slightly. Namely, the aldehyde and trimethylsilyliodoacetylene were first subjected to the Ni(II)/Cr(II)-mediated coupling reaction, to yield the expected TMS-acetylene in over 90% yield (stereoselectivity=8:1), which was then converted to the *trans*-iodoolefin by using routine synthetic reactions.



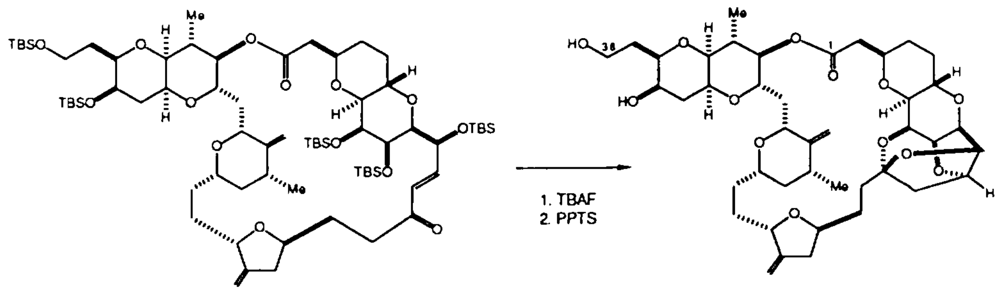
This *trans*-iodoolefin provided the opportunity of using the Ni(II)/Cr(II)-mediated coupling reaction to assemble the entire C.1-C.38 backbone. Obviously, this process could be used intermolecularly or intramolecularly to achieve the goal. We tested the intermolecular approach first; under standard conditions with two equivalents of vinyliodide, the expected coupling product was isolated in 70-80% yield. After oxidation with Dess-Martin reagent (ref. 15), MPM deprotection with DDQ (ref. 16), and ester hydrolysis with lithium hydroxide, this product was subjected to the Yamaguchi macrolactonization conditions (ref. 17), to furnish the C.1-C.38 enone in excellent overall yield.



As demonstrated in the synthesis of ophiobolin C, the Ni(II)/Cr(II)-mediated coupling reaction could be used in an intramolecular fashion. Indeed, we found the Ni(II)/Cr(II)-mediated macrocyclization to be amazingly effective, particularly for the substrate with an acyl group at the C.11 position. With respect to overall efficiency, however, the intermolecular version was found to be slightly better than the intramolecular version.



The C.1-C.38 enone thus obtained was subjected to deprotection of the TBS groups with tetrabutylammonium fluoride (neutral) in THF at room temperature. In addition to the expected deprotection of the TBS groups, the resultant C.9 alcohol was added to the enone in a Michael fashion under these conditions. A brief acid treatment of the crude product facilitated the intramolecular ketalization, to furnish the complete right half of halichondrins in excellent overall yield.



In concluding this presentation, we are pleased to note that the complete right half of halichondrins has recently been transformed into norhalichondrin B.

Acknowledgement I would like to express my warmest appreciation to the co-workers whose spirit, dedication, stamina, and skill have enabled us to bring this stimulating, exciting, challenging, and rewarding venture to its successful conclusion. The co-workers who have energetically and enthusiastically participated in the projects outlined are acknowledged in the references. Financial assistance for the palytoxin, ophiobolin C, and halichondrin programs is provided from the National Institutes of Health (NS 12108), the National Science Foundation (CHE 89-09762), and the National Institutes of Health (CA 22215), respectively.

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2. For the gross structure of palytoxin, see: (a) D. Uemura, K. Ueda, Y. Hirata, H. Naoki, and T. Iwashita, Tetrahedron Lett., 22, 2781-2784 (1981) and references cited therein. (b) R. E. Moore and G. Bartolini, J. Am. Chem. Soc., 103, 2491-2494 (1981) and references cited therein.
3. For the stereochemistry assignment primarily based on organic synthesis, see: J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi, L. L. Klein, S. S. Ko, J. Leder, W. W. McWhorter, Jr., K.-P. Pfaff, M. Yonaga, D. Uemura, and Y. Hirata, J. Am Chem. Soc., 104, 7369-7371 (1982) and preceding papers. (b) For the stereochemistry assignment primarily based on spectroscopic methods, see: R. E. Moore, G. Bartolini, J. Barchi, A. A. Bothner-By, J. Dadok, and J. Ford, J. Am. Chem. Soc., 104, 3776-3779 (1982).
4. For the total synthesis of palytoxin carboxylic acid and palytoxin amide, see: R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J. Uenishi, J. B. White, and M. Yonaga, J. Am Chem. Soc., 111, 7530-7533 (1989) and preceding paper.
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6. Y. Okude, S. Hirano, T. Hiyama, and H. Nozaki, J. Am. Chem. Soc., 99, 3179-3181 (1977).
7. H. Jin, J. Uenishi, W. J. Christ, and Y. Kishi, J. Am. Chem. Soc., 108, 5644-5646 (1986).
8. Professor Nozaki and co-workers simultaneously discovered a catalytic effect of $NiCl_2$ on the activation of vinyl triflates: K. Takai, M. Tagashira, T. Kuroda, T. Oshima, K. Utimoto, and H. Nozaki, J. Am. Chem. Soc., 108, 6048-6050 (1986).
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13. For the synthetic studies towards halichondrins from other groups, see: (a) S. Kim and R. G. Salomon, Tetrahedron Lett., 30, 6279-6282 (1989). (b) A. J. Cooper and R. G. Salomon, Tetrahedron Lett., 31, 3813-3816 (1990). (c) S. D. Burke, J. L. Buchanan, and J. D. Rovin, Tetrahedron Lett., 32, 3961-3964 (1991).
14. For a review on this subject, see: O. Mitsunobu, Synthesis, 1-28 (1981).
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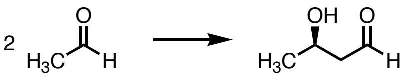
Stereoselective, Directed Aldol Reaction

Reviews:

Heathcock, C. H. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 133-238.

Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 239-275.

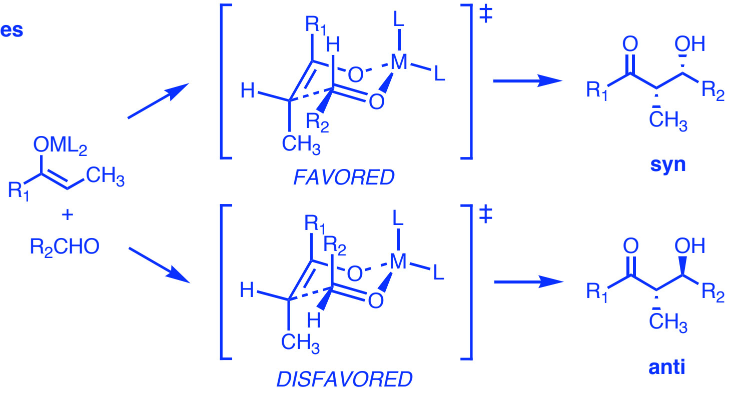
Paterson, I. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 301-319.



- The aldol reaction was discovered by Aleksandr Porfir'evich Borodin in 1872 where he first observed the formation of "aldol", 3-hydroxybutanal, from acetaldehyde under the influence of catalysts such as hydrochloric acid or zinc chloride.

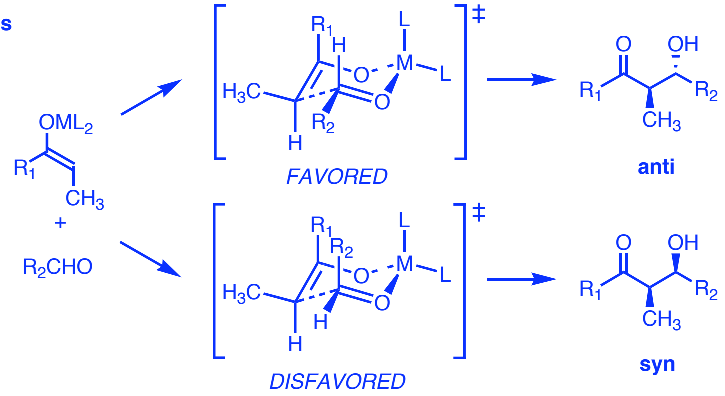
Diastereofacial Selectivity in the Aldol Addition Reaction-Zimmerman-Traxler Chair-Like Transition States

(*Z*)-enolates



- Note: the enantiomeric transition states (not shown) are, by definition, of equal energies. The pericyclic transition state determines syn/anti selectivity. To differentiate two syn or two anti transition states, a chiral element must be introduced (e.g., R_1, R_2, or L), thereby creating diastereomeric transition states which, by definition, are of different energies.

(*E*)-enolates



- Zimmerman and Traxler proposed that the aldol reaction with metal enolates proceeds via a chair-like, pericyclic process. In practice, the stereochemistry can be highly metal dependent. Only a few metals, such as boron, reliably follow the indicated pathways.

- (*Z*)- and (*E*)-enolates afford *syn*¯ and *anti*-aldol adducts, respectively, by minimizing 1,3-diaxial interactions between R_1 and R_2 in each chair-like TS‡.

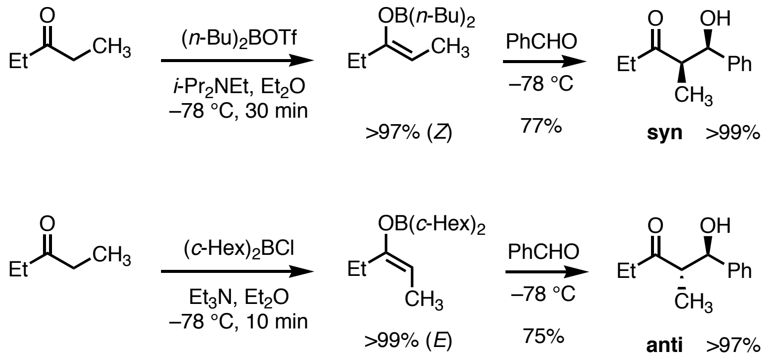
Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225-1228.

Heathcock, C. H.; Buse, C. T.; Kleschnick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081.

M. Movassaghi

Preparation of (*Z*)- and (*E*)-Boron Enolates



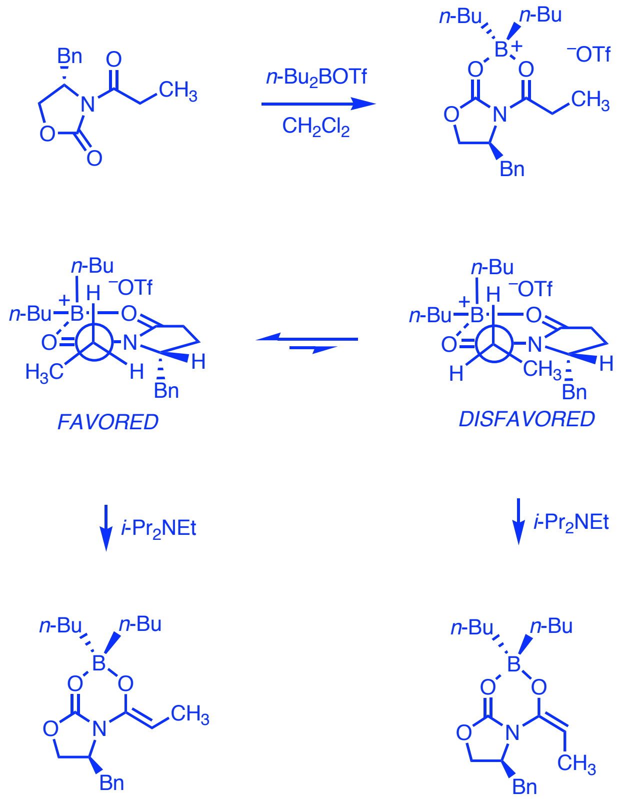
- Dialkylboron triflates typically afford (*Z*)-boron enolates, with little sensitivity toward the amine used or the steric requirements of the alkyl groups on the boron reagent.
- In the case of dialkylboron chlorides the geometry of the the product enolates is much more sensitive to variations in the amine and the alkyl groups on boron.
- The combination of (*c*-Hex)$_2$BCl and Et$_3$N provides the (*E*)-boron enolate preferentially.

Evans, D. A.; Vogel, E.; Nelson, J. V.; *J. Am. Chem. Soc.* **1979**, *101*, 6120-6123.

Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

Brown, H. C.; Dhar, R. K. Bakshi, R. K. Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442.

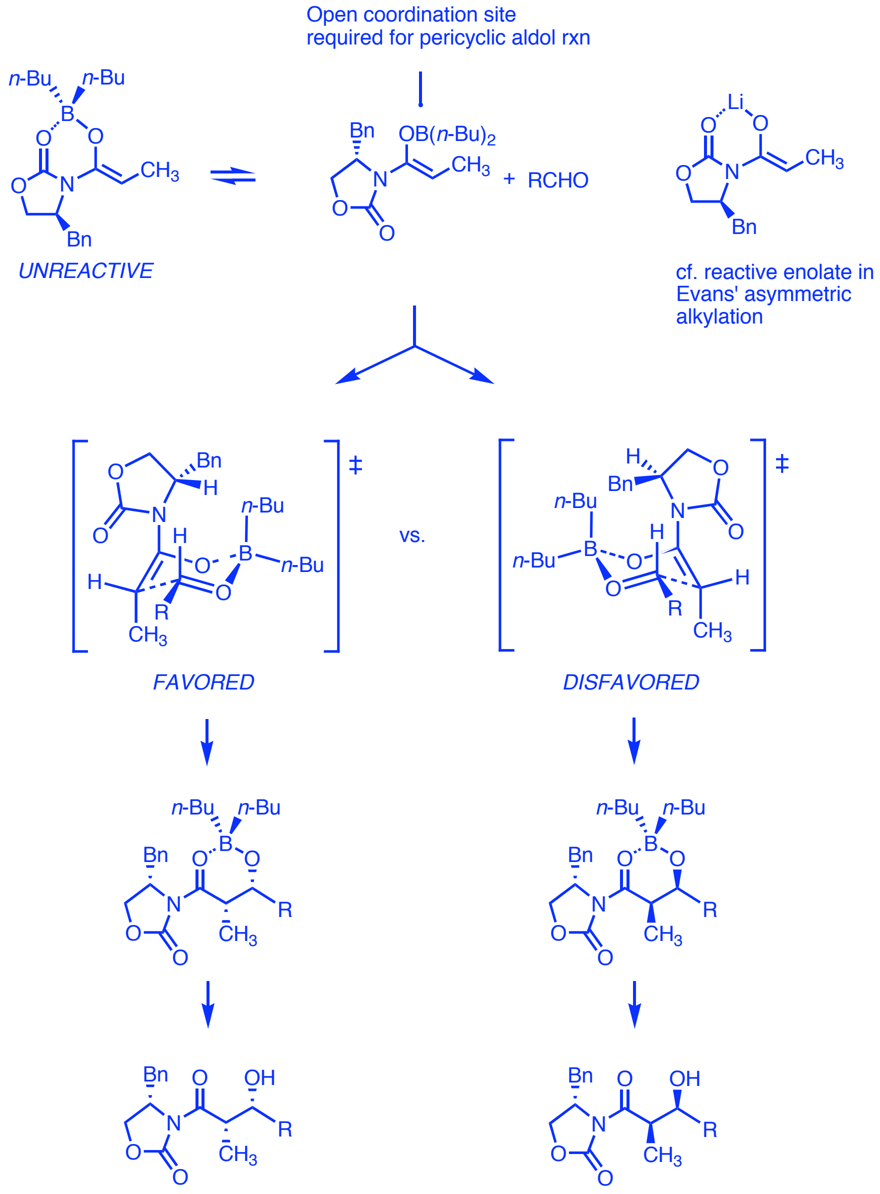
(*Z*)-Selective Preparation of Boron Enolates from Evans' Acyl Oxazolidinones (Imides)



- Observed selectivity: ≥100:1 *Z* : *E*

Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

Syn-Selective Aldol Reactions of Imide-Derived Boron (*Z*)-Enolates



Open coordination site required for pericyclic aldol rxn

UNREACTIVE

cf. reactive enolate in Evans' asymmetric alkylation

FAVORED

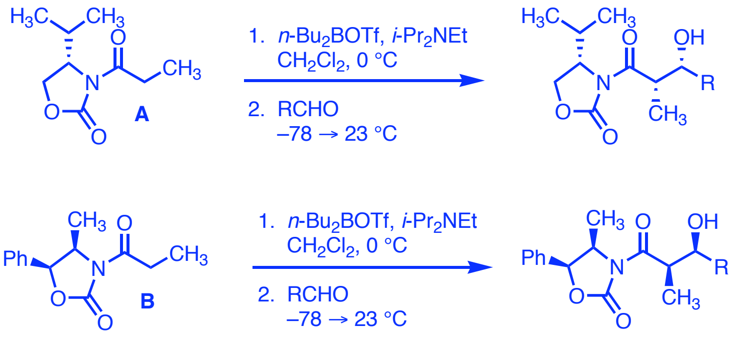
vs.

DISFAVORED

Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

- Chiral controller group biases enolate π-faces such that one of the two diastereomeric (syn) transition states is greatly favored.

- Dipole-dipole interactions within the imide are minimized in the reactive conformation (see: Noe, E. A.; Raban, M *J. Am. Chem. Soc.* **1975**, *97*, 5811-5820).



A

1. n-Bu$_2$BOTf, i-Pr$_2$NEt
   CH$_2$Cl$_2$, 0 °C
2. RCHO
   −78 → 23 °C

B

1. n-Bu$_2$BOTf, i-Pr$_2$NEt
   CH$_2$Cl$_2$, 0 °C
2. RCHO
   −78 → 23 °C

imide	aldehyde	diastereomeric[a] ratio	yield
A	$(CH_3)_2CHCHO$	497:1	78
B	$(CH_3)_2CHCHO$	<1:500	91
A	n-C_4H_9CHO	141:1	75
B	n-C_4H_9CHO	<1:500	95
A	C_6H_5CHO	>500:1	88
B	C_6H_5CHO	<1:500	89

[a] Ratio of major syn product to minor syn product.

- A variety of chiral imides can be used for highly selective aldol reactions.

- Anti products are typically formed in less than 1% yield.

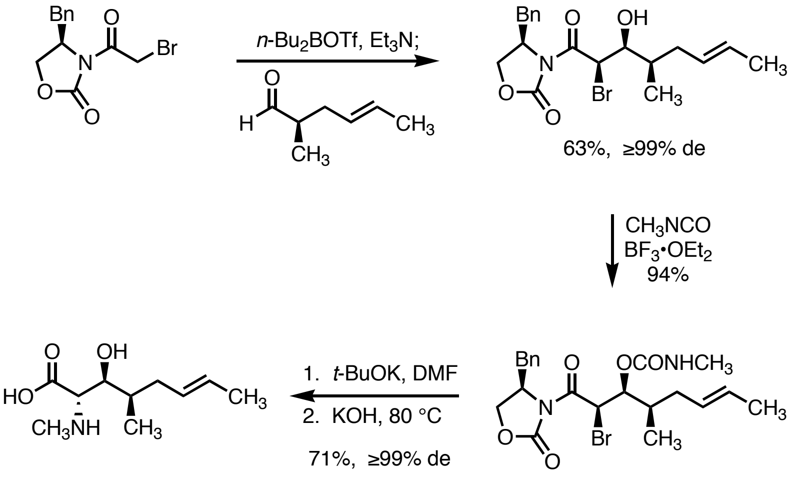
- Often, a single crystallization affords diastereomerically pure product.

Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

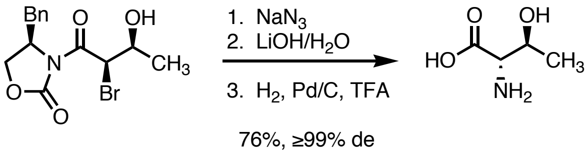
Evans, D. A.; Gage, J. R. *Org. Syn.* **1990**, *68*, 83.

M. Movassaghi

Asymmetric Synthesis of Anti β-Hydroxy-α-Amino Acids



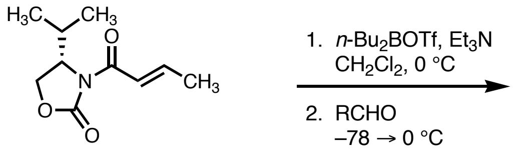
- 2-Chloro- and 2-Bromoacetyl imides undergo aldol addition with high diastereoselectivity (88-96% de, 63-79% yield).



- Bromide displacement occurs with clean inversion.

Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39-42.

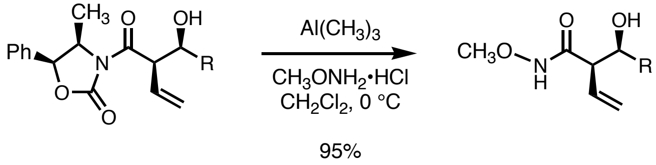
Aldol Addition Reactions of Chiral Crotonate Imides



aldehyde	yield (%)[a]
CH_3CHO	82
$(CH_3)_2CHCHO$	90
C_6H_5CHO	92

[a] >96% de.

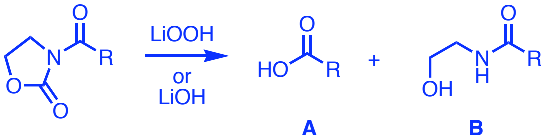
- The use of triethylamine rather than diisopropylethylamine is essential in these examples because self-condensation (Michael addition) can compete with enolization.



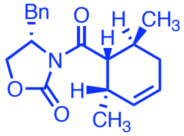
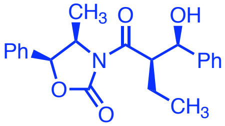
- Although the aldol adducts are sensitive to base-induced retro-aldol reaction, aluminum amides are found to cleave the auxiliary efficiently.

Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957-4960.

Carboximide Hydrolysis with Lithium Hydroperoxide

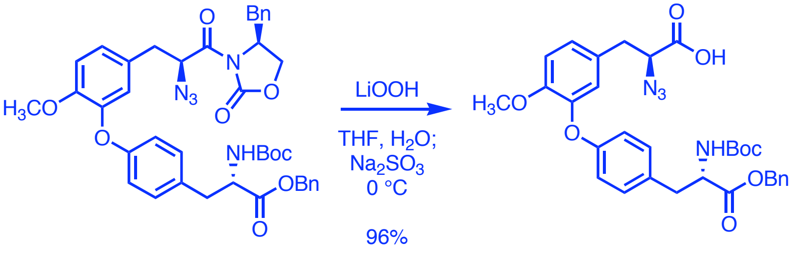


A **B**

substrate	reagent	yield of **A** (%)[a]	yield of **B** (%)[a]
	LiOOH	76	16
	LiOH	0	100
	LiOOH	98	<1
	LiOH	43	30

[a] Yield of diastereomerically pure (>99:1) product.

- LiOOH displays the greatest regioselectivity for attack of the exocyclic carbonyl group.
- This selectivity is most pronounced with sterically congested acyl imides.
- This is a general solution for the hydrolysis of all classes of oxazolidinone-derived carboximides and allows for efficient recovery of the chiral auxiliary.

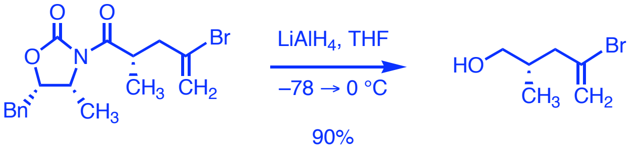


- The selective hydrolysis of carboximides can be achieved in the presence of unactivated esters using LiOOH.

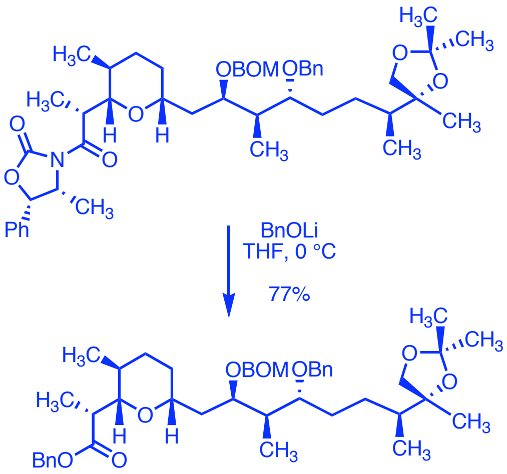
Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.
Gage, J. R.; Evans, D. A. *Org. Syn.* **1990**, *68*, 83-91.

Other Methods for Removal of the Chiral Auxiliary

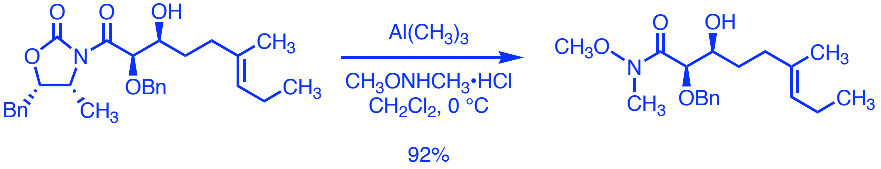
- Reductive cleavage:



- Esterification:



- Transamination (as before):

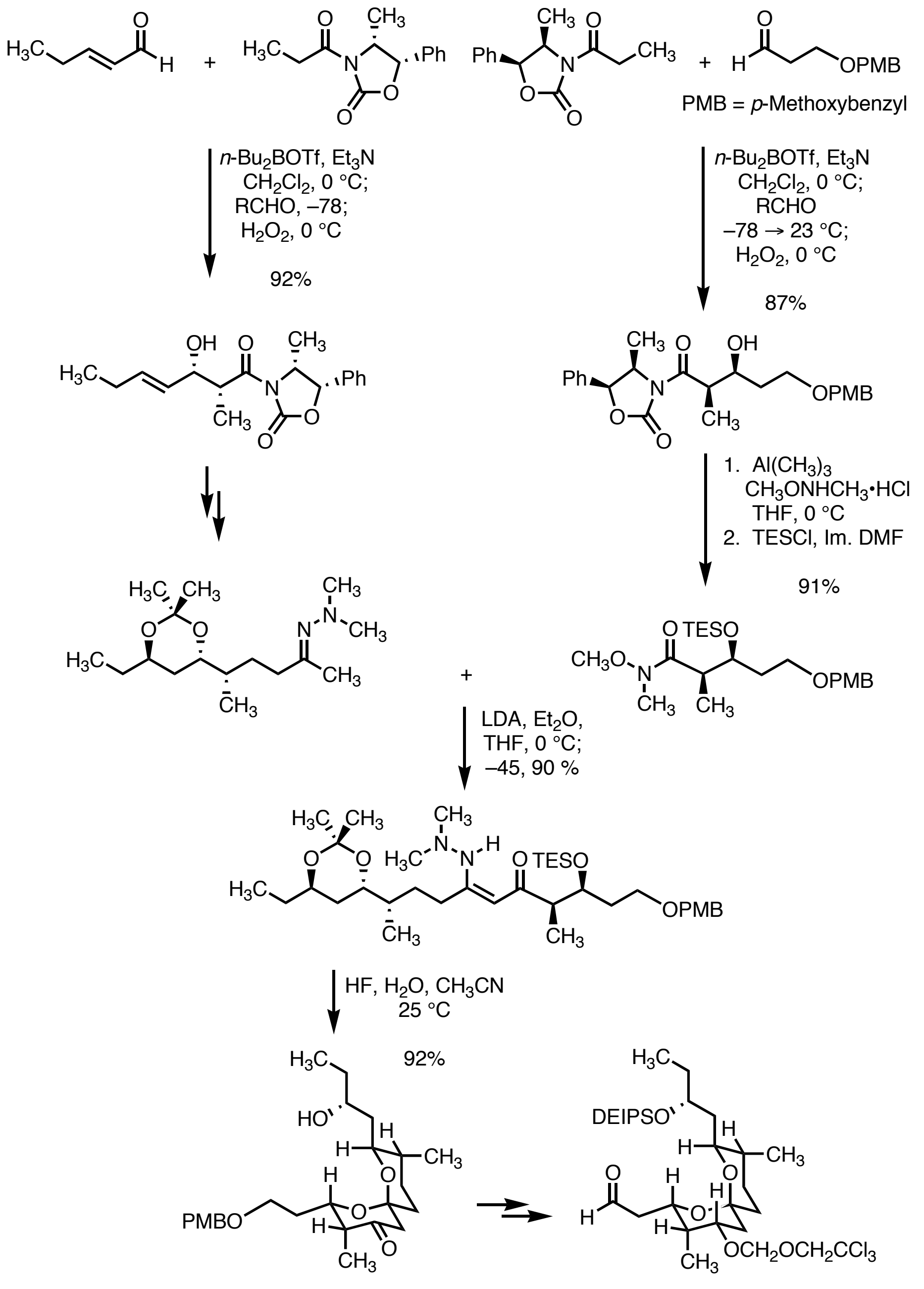


- A free β-hydroxyl group is required.
- Weinreb amides can be readily converted into ketones or aldehydes (see: Nahm, S.; Weinreb., S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818).

Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

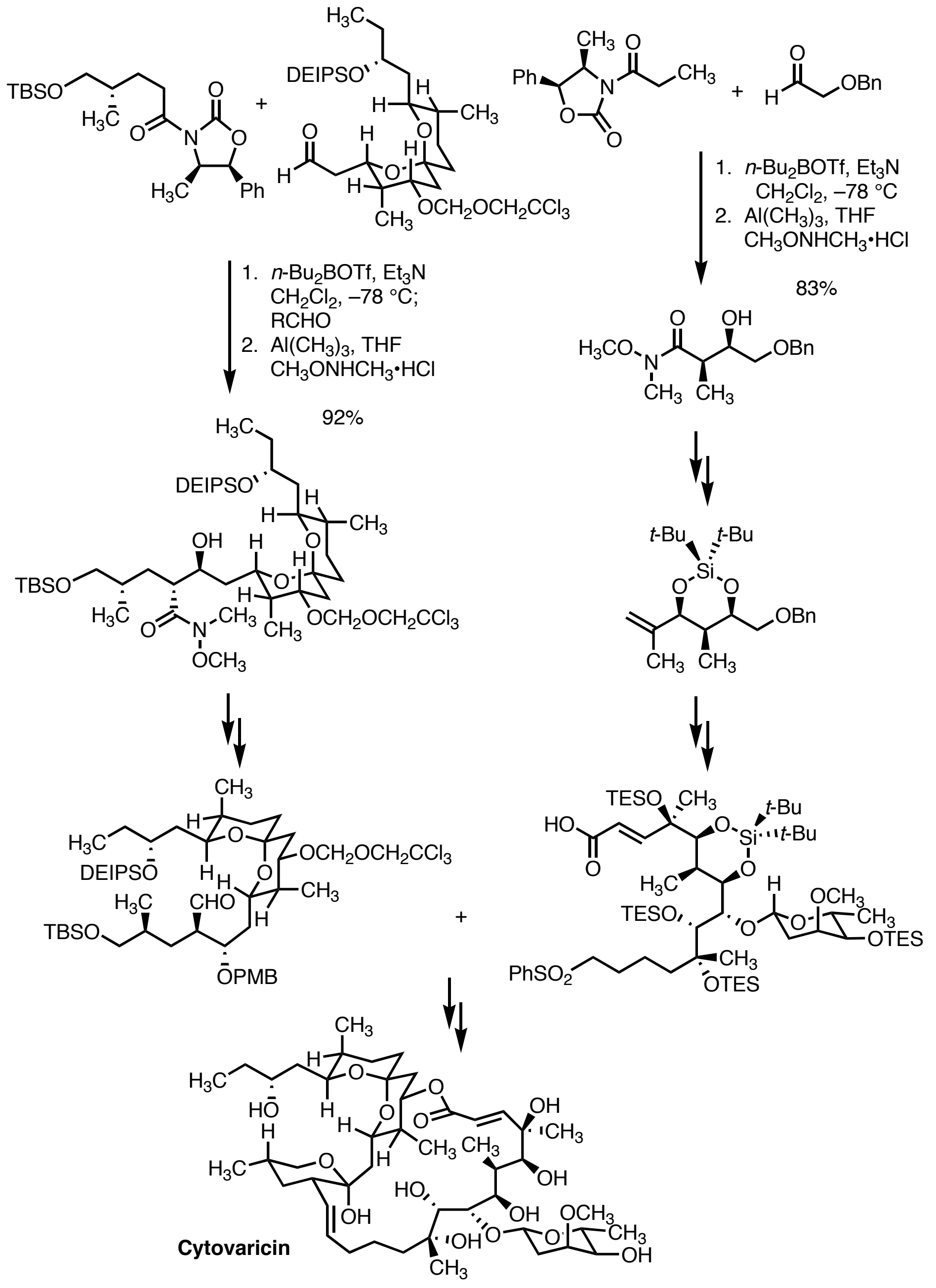
M. Movassaghi

Cytovaricin:



PMB = *p*-Methoxybenzyl

DEIPS = diethylisopropylsilyl

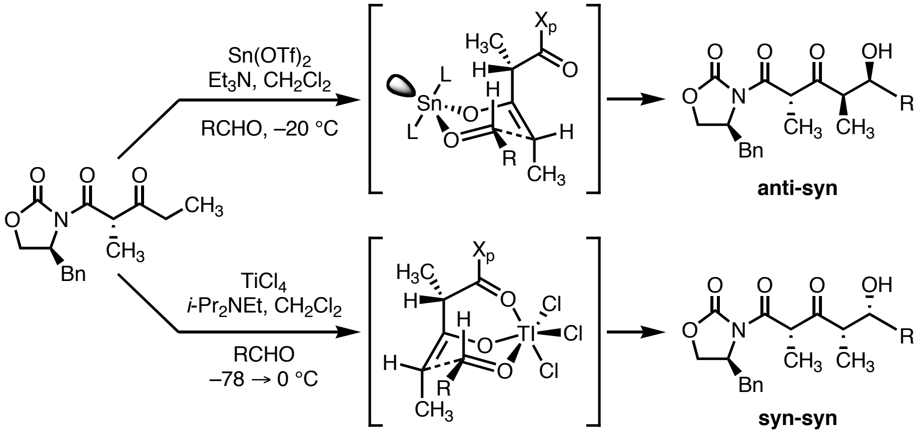


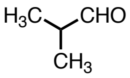
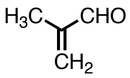
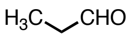
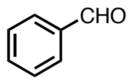
Cytovaricin

Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

M. Movassaghi

Diastereoselective *Syn*-Aldol Reaction of β-Ketoimides



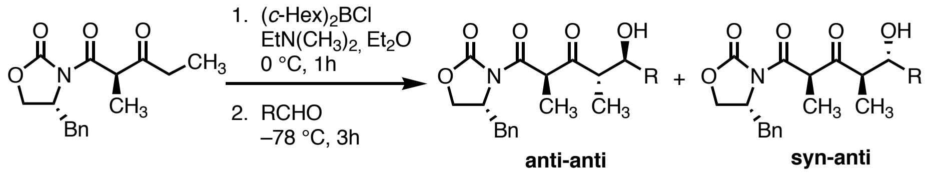
enolization conditions	RCHO[a]	yield %[b]	ratio anti-syn : syn-syn
A		83	95:5
B		86	<1:99
A		77[c]	95:5
B		64[c]	2:98
A		71	79:21
B		86	<1:99
A		85	89:11
B		81	4:96

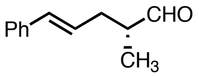
A: Sn(OTf)$_2$, Et$_3$N; B: TiCl$_4$, *i*-Pr$_2$NEt. [a]1.0-1.1 equiv [b]Isolated yield of major diastereomer (>99% purity). [c]3-5 equiv of RCHO was used.

- Both enolization methods provide (*Z*)-enolates and (diastereomeric) syn aldol products.
- The stereochemical outcome of both reactions is dominated by the C$_2$ methyl-bearing stereocenter, as shown in the proposed transition states above.
- Use of excess aldehyde (3-5 equiv) is necessary where polymerization of the aldehyde is a problem (i.e., α-methacrolein).
- The chirality of the oxazolidinone has little influence on the diastereoselectivity of these reactions.

Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868.

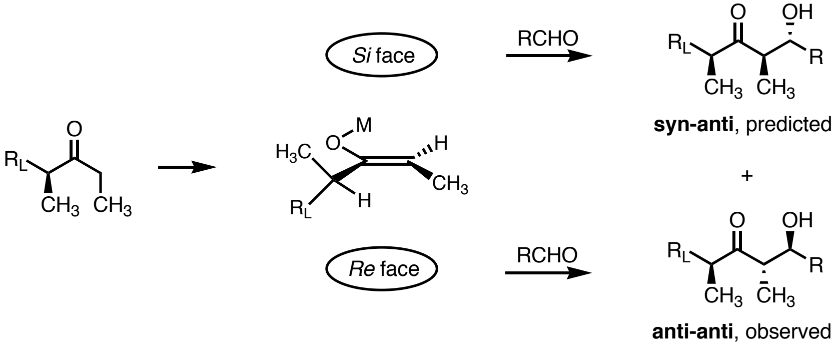
Diastereoselective *Anti*-Aldol Reactions of β-Ketoimides



aldehyde	yield %[a]	ratio anti-anti : syn-anti
$(CH_3)_2CHCHO$	78	84:16
$CH_2{=}C(CH_3)CHO$	72	92:8
CH_3CH_2CHO	70[b]	80:20
$PhCH_2CH_2CHO$	84[b]	88:12
	84	97:3

[a]Isolated yield of major diastereomer. [b]Yield of purified mixture of diastereomers.

- Enolization of the less hindered side of the ketone under Brown's conditions affords the (*E*)-boron enolate.
- The C2 stereocenter is the dominant control element in these aldol reactions; "matched" vs. "mismatched" effects of the remote auxiliary are negligible.

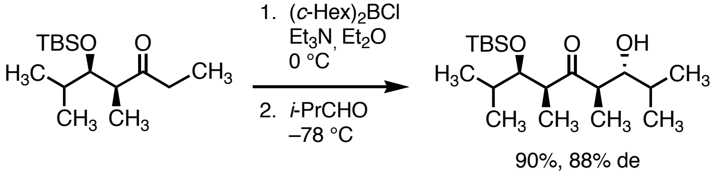


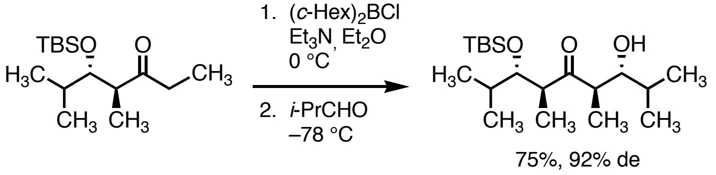
- The sense of asymmetric induction observed in these reactions was unexpected and opposite to a prediction based on a reactant-like transition state model minimizing A$_{(1,3)}$ strain.

Evans, D. A.; Ng, H. P.; Clark, J. S.; Reiger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142.

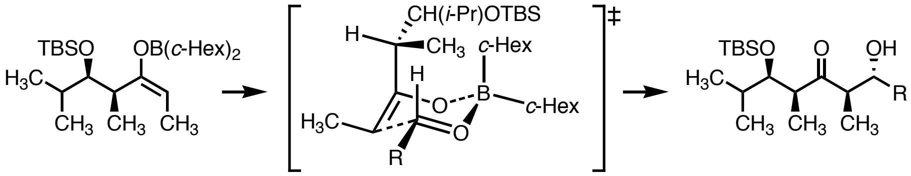
M. Movassaghi

Anti-Selective Aldol Reactions in Related Systems





- The C2 stereocenter is believed to be the dominant control element for both substrates.

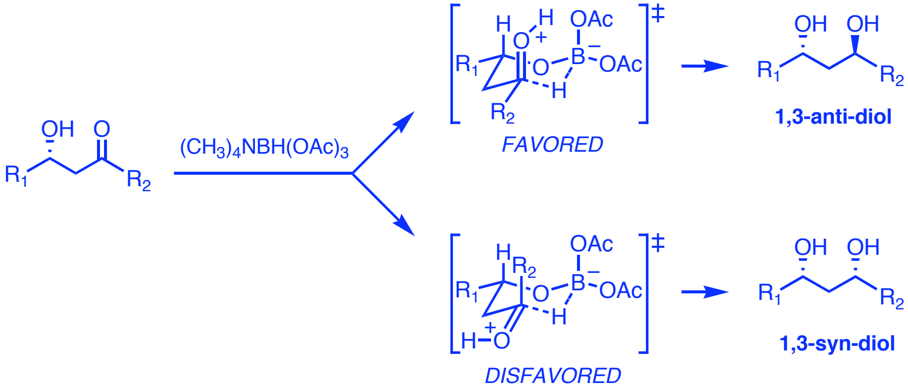


- Minimization of $A_{(1,3)}$ interactions in the enolate biases the approach of the aldehyde to the methyl-bearing π-face of the enolate, while the (*E*)-enolate geometry affords anti-aldol products.

Evans, D. A.; Ng H. P.; Clark, J. S.; Reiger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142.

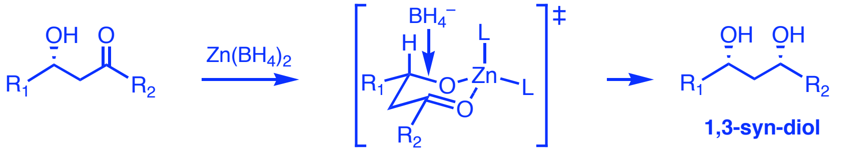
Directed Reduction of β-Hydroxy Ketones

Internal hydride delivery:

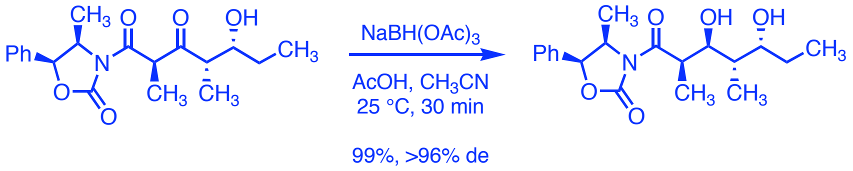


- The reactivity of the reagent is attenuated such that the reduction of ketones proceeds at convenient rates only intramolecularly, favoring formation of 1,3-anti-diols.

External hydride delivery:



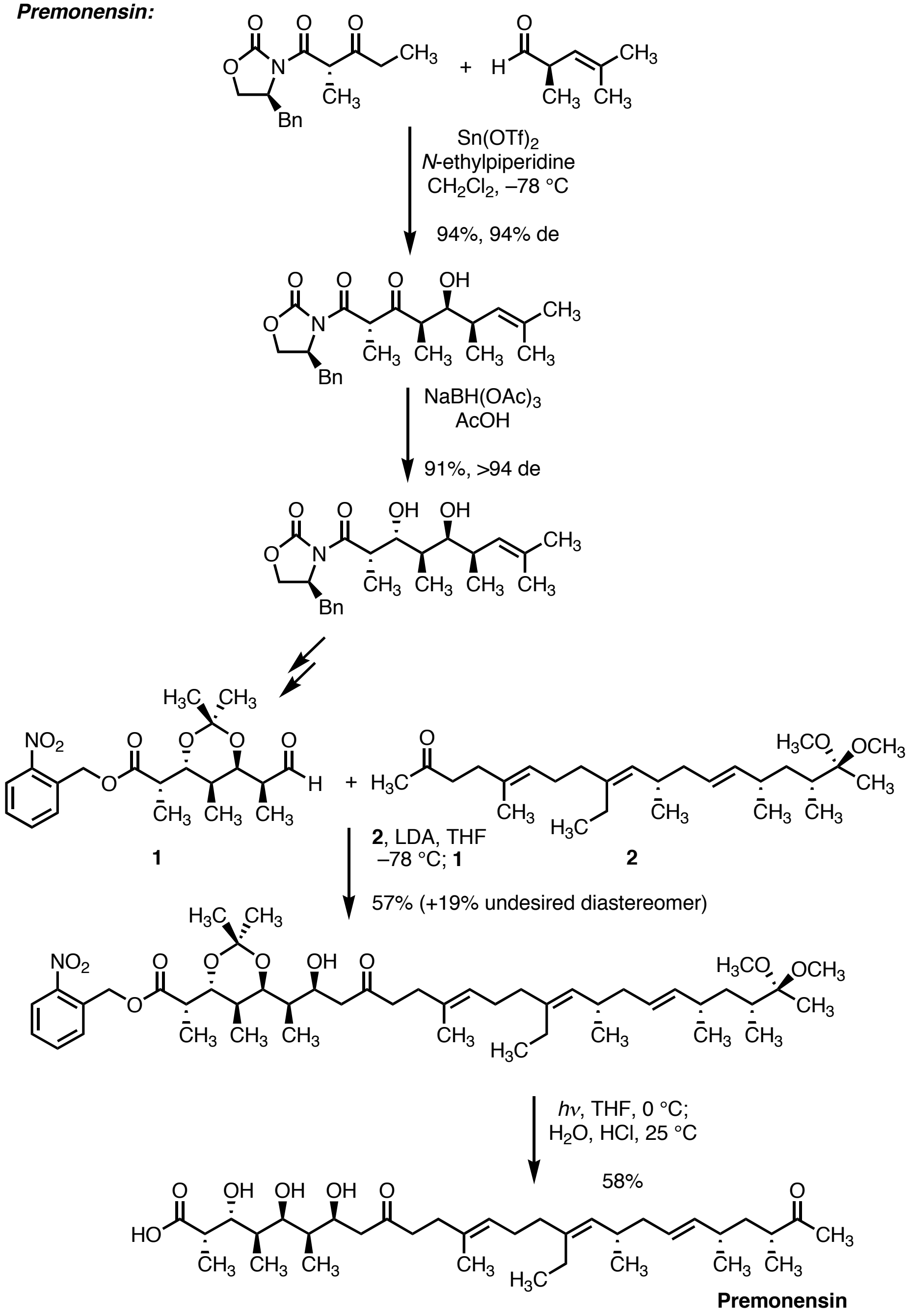
- Chelated transition state, axial attack provides 1,3-syn-diol.
- These directed reductions are applicable to δ-hydroxy-β-ketoimides:



Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

M. Movassaghi

Premonensin:



Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476-2478.

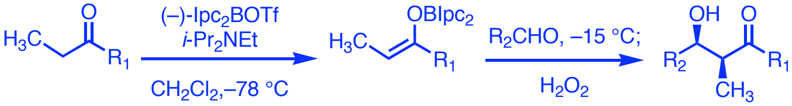
Paterson Aldol

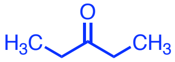
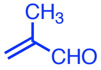
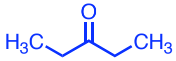
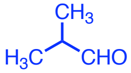
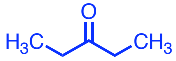
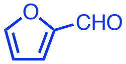
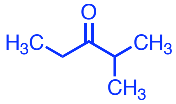
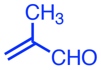
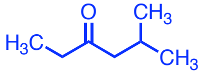
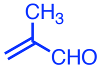
Reviews:

Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317.

Syn-Aldol Adducts via Enol Diisopinocamphenylborinates



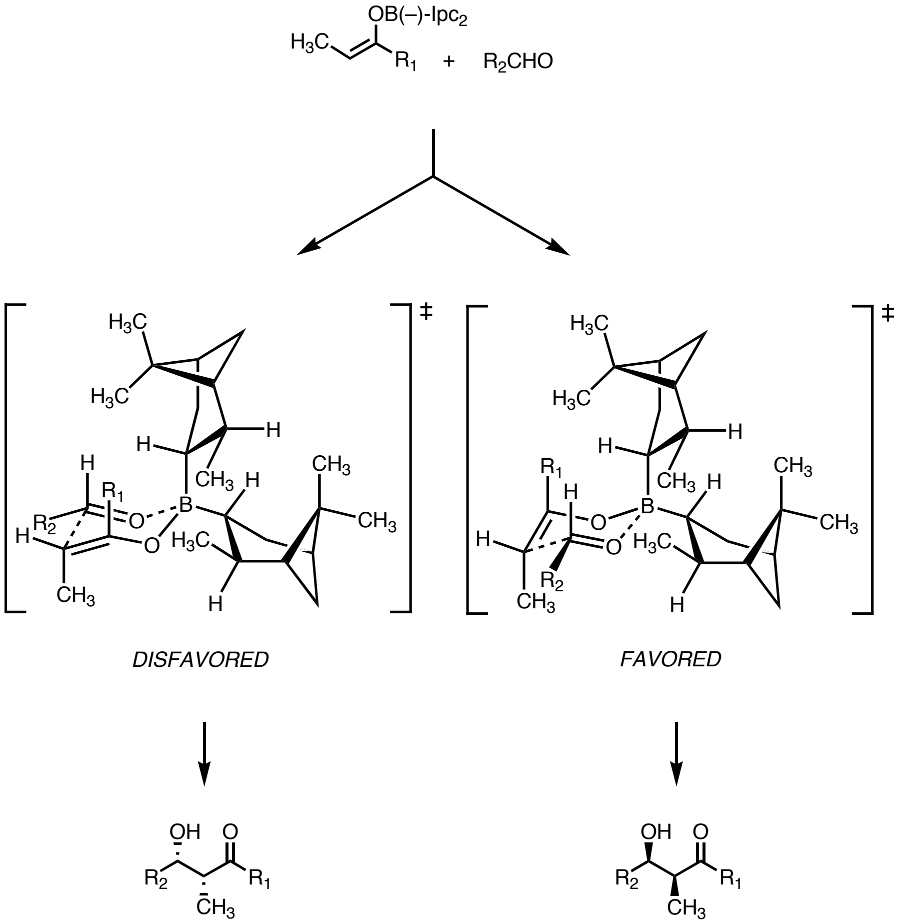
ketone	aldehyde	syn:anti	ee (%)	yield (%)
		98:2	91	78
		96:4	66	45
		96:4	80	84
		95:5	88	99
		97:3	86	79

- Enolization occurs selectively on the less hindered side of the ketone and with (*Z*)-selectivity.
- The (*E*)-Enolate, generated in low yield using (–)-Ipc$_2$BCl, does not lead to a selective *anti*-aldol reaction.
- Highest enantioselectivities are obtained with unhindered aldehydes.
- Aldol additions of methyl ketones are not highly enantioselective (53-73%).

Paterson, I.; Goodman, J. M.; Lister, M. A.; Scumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663-4684.

M. Movassaghi

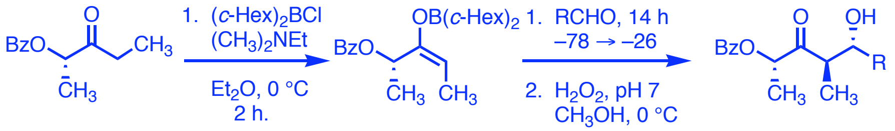
Proposed Origin of Selectivity:

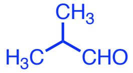
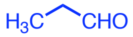
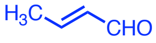
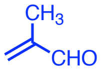


- Diastereofacial selectivity is believed to be due to a favored transition state wherein steric interactions between the (–)-Ipc ligand on boron and the R_1 substituent on the ketone are minimized.

Paterson, I.; Goodman, J. M.; Lister, M. A.; Scumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663-4684.

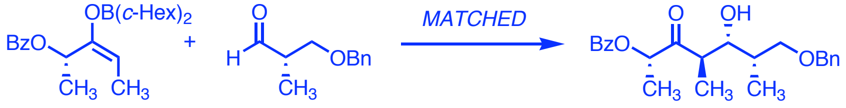
Anti-Aldol Reactions of Lactate-Derived Ketones



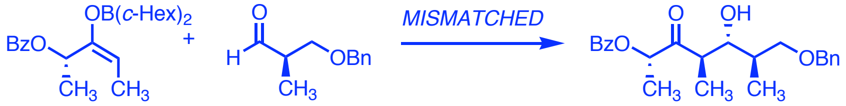
aldehyde	de (%)	yield (%)[a]
	94	95
	99	82
	90	97
	96	97
PhCHO	99	85

[a]Isolated yield for 3 steps.

- Diastereofacial selectivity is very high; α-chiral aldehydes afford anti-aldol adducts with high diastereoselectivity regardless of their stereochemistry.

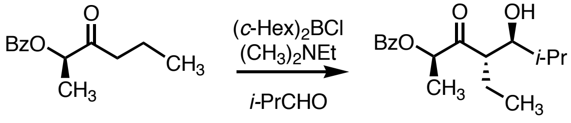


80%, >94% de

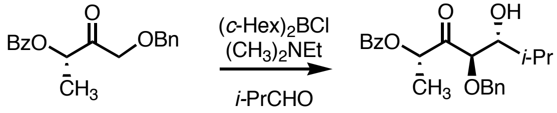


61%, 84% de

- Other examples:



95%, 86% de



77%, 98% de

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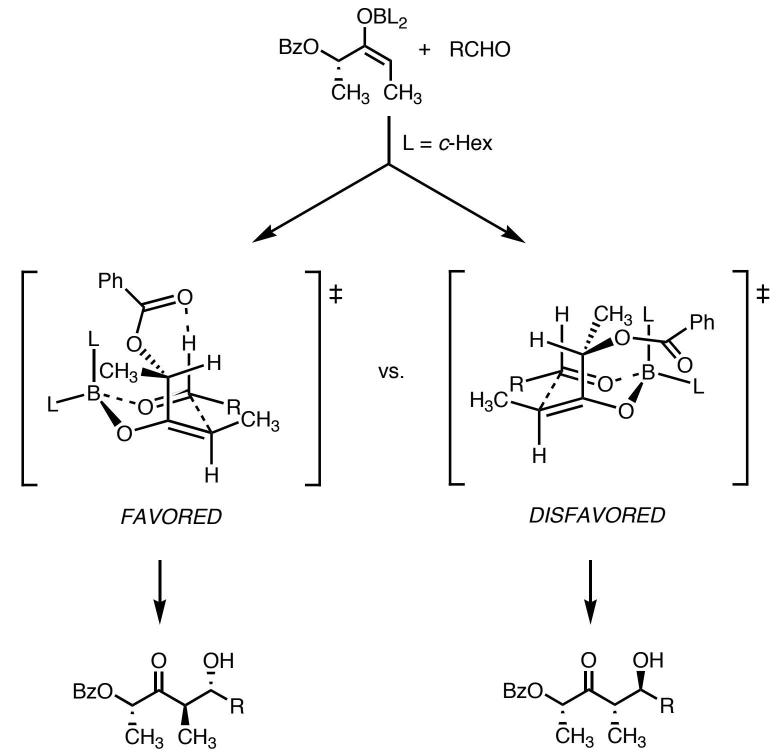
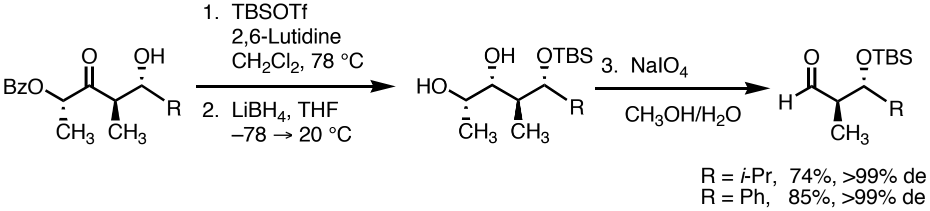
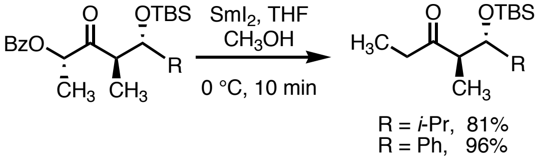
- The origin of the diastereoselectivity is proposed to be due to a formyl hydrogen bond in the favored transition state.

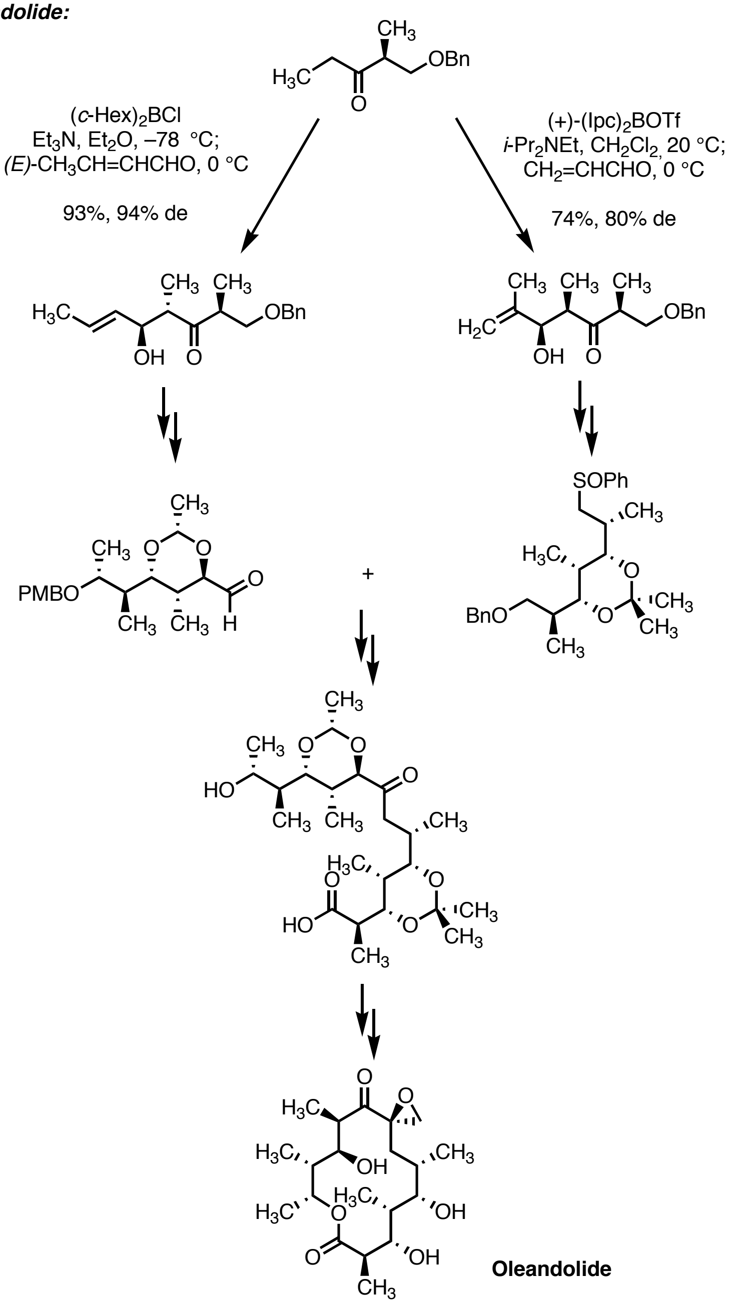






- Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639-652.

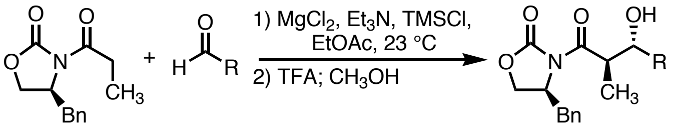
Oleandolide:

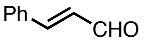
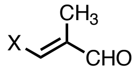

(*c*-Hex)$_2$BCl
Et$_3$N, Et$_2$O, –78 °C;
(E)-CH$_3$CH=CHCHO, 0 °C
93%, 94% de
(+)-(Ipc)$_2$BOTf
i-Pr$_2$NEt, CH$_2$Cl$_2$, 20 °C;
CH$_2$=CHCHO, 0 °C
74%, 80% de
+

Oleandolide

Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287-11314.

Anti-Aldol Reactions of Chiral N-Acyloxazolidinones and N-Acylthiazolidinethiones

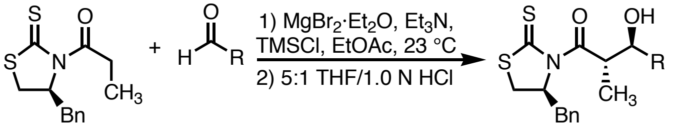


aldehdye		dr	yield (%)
p-$CH_3C_6H_4CHO$		24:1	-
p-$CH_3OC_6H_4CHO$		32:1	91
p-$NO_2C_6H_4CHO$		7:1	71
		21:1	92
	X = Ph	28:1	92
	X = H	16:1	77
α-naphthaldehyde		14:1	91
furfural		6:1	80

- Only aromatic and unsaturated aldehydes are suitable substrates for this reaction.
- This method does not allow for β-branching on the acyl substituent.

Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392-393.

- Use of the analogous N-acylthiazolidinethione chiral auxilary affords products with the opposite *anti*-diastereoselectivity.



- The yields, dr and substrate scope are comparable to the $MgCl_2$ catalyzed *anti*-aldol reactions of chiral N-acyloxazolidinones shown above.

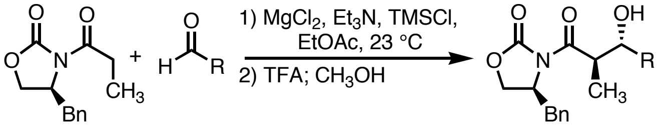
Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S.. *Org. Lett.* **2002**, *4*, 1127-1130.

Summary of Anti-Aldol Methodology

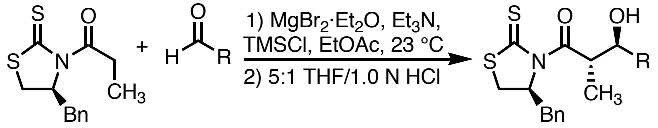
- Currently there is not a good general method for the enantoselective formation of *anti*-aldol products. Listed below are the best current methods for their formation, along with a brief description of their shortcomings. Note that the Evans and Paterson *anti*-aldol reactions are covered in this handout.

Evans

Comments

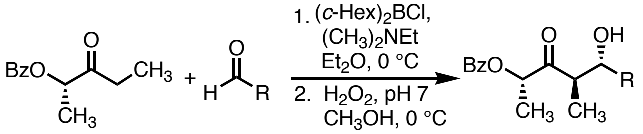


Only aromatic and unsturated aldehydes are suitable substrates for this reaction.



Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392-393.

Paterson

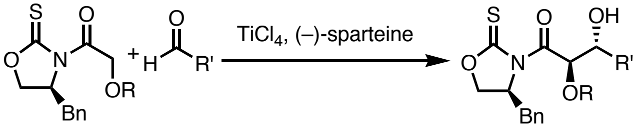


1. $(c\text{-Hex})_2BCl$, $(CH_3)_2NEt$, Et_2O, 0 °C
2. H_2O_2, pH 7, CH_3OH, 0 °C

Only lactate derived ketones are suitable substrates for this reaction.

Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639-652.

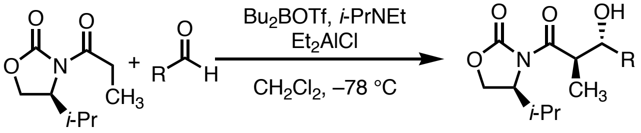
Crimmins



Crimmins, M. T.; McDougall, P.J. *Org. Lett.* **2003**, *5*, 591-594.

Excess Lewis Acid is required for complexation to the aldehyde in both the Crimmins and Heathcock methods. It is proposed that when the aldehyde is complexed to a Lewis acid these reactions go through an open transition state.

Heathcock

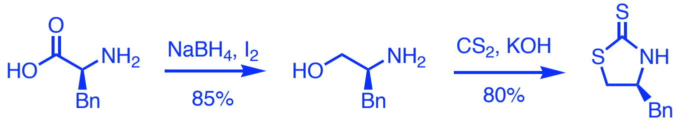


Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747-5750.

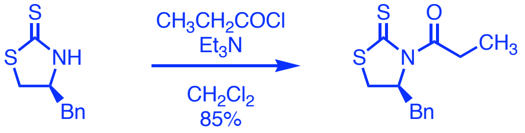
Chris Coletta

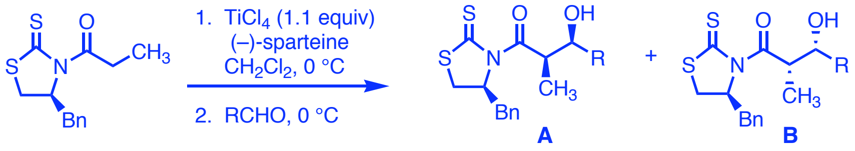
Asymmetric Aldol Reactions with Titanium Enolates of Acyloxazolidinethiones

- Synthesis of thiazolidinethione auxiliary:



- Acylation of thiazolidinethione auxiliary:





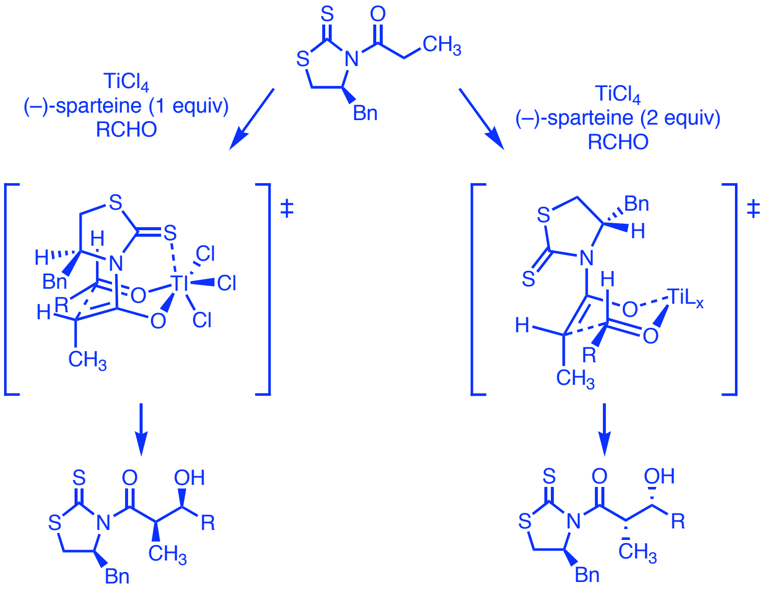
RCHO	(–)-sparteine (equiv)	yield (%)	**A** : **B**
CH_2=CHCHO	1.0	49	>99:1
i-PrCHO	1.0	60	98:2
CH_2=CHCHO	2.0	77	<1:99
i-PrCHO	2.0	75	3:97

- Selectivities are generally >95:5 for syn:anti products.

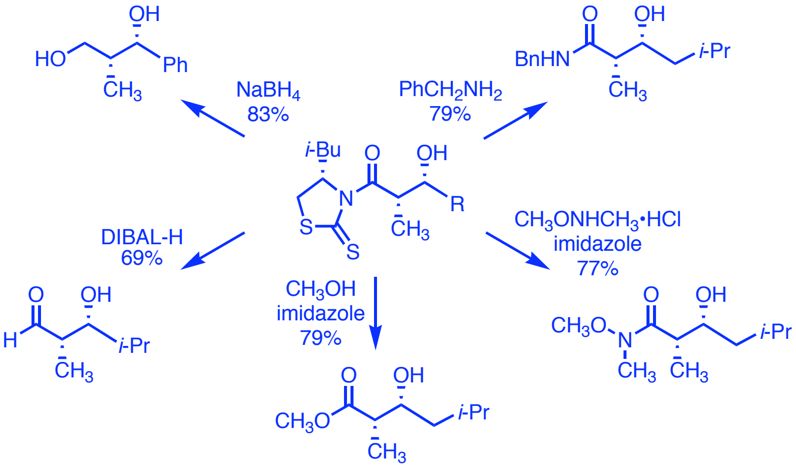
- Both the yield and diastereoselectivities are high and synthetically useful, although they are typically lower than the corresponding oxazolidine aldol reactions.

- An advantage of this method is that a single acyloxazolidinethione can provide either syn aldol product by changing the amount of sparteine in the reaction mixture.

- Proposed transition states provide a rationale for the selectivity dependence on amine equivalents:



- The oxazolidinethione auxiliary is easily removed under mild conditions:

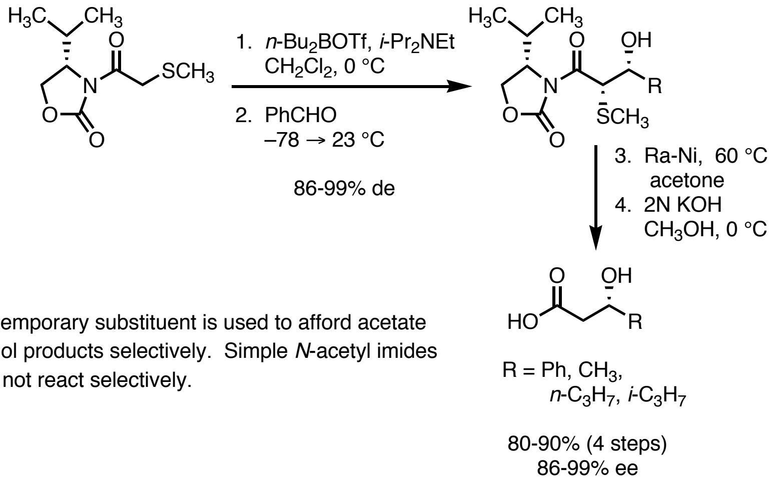


- The thiazolidinethione auxiliary is recovered by basic extraction (1 M NaOH) of the product mixture (not compatible with aldehyde products due to competing epimerization).

Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884.
Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775-777.

M. Movassaghi

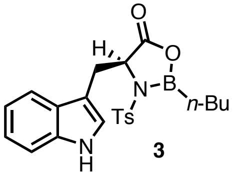
An Approach to the Acetate Aldol Problem



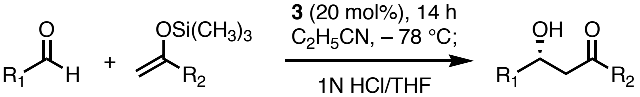
- A temporary substituent is used to afford acetate aldol products selectively. Simple *N*-acetyl imides do not react selectively.

Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

An Enantioselective Mukaiyama Aldol Reaction Catalyzed by a Tryptophan-Derived Oxazaborolidine



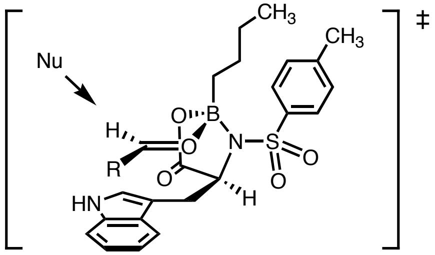
3



R_1	R_2	yield (%)	ee (%)
Ph	C_6H_5	82	89
c-C_6H_{11}	C_6H_5	67	93
2-furyl	C_6H_5	100	92
c-C_6H_{11}	n-C_4H_9	56	86

- The Lewis-acid catalyzed addition of silyl enol ethers to aldehydes is known as the Mukaiyama Aldol reaction: Kobayashi, S.; Uchiro, H.; Shina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761-1772.

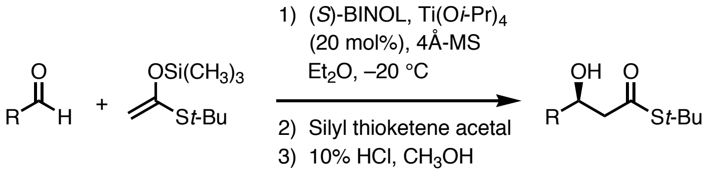
- Use of terminal trimethylsilyl enol ethers provide the highest level of enantioselectivities.



- A transition state is proposed in which the *si* face of the aldehyde is blocked by the indole ring.

Corey, E. J.; Cywin, C. L; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907-6910.

Catalytic, Enantioselective Mukaiyama Aldol Condensation of Silyl Thioketene Acetals



aldehyde	yield (%)	ee (%)
PhCHO	90	97
$PhCH_2CH_2CHO$	80	97
furylCHO	88	>98
c-$C_6H_{11}CHO$	70	89
$PhCH_2OCH_2CHO$	82	>98

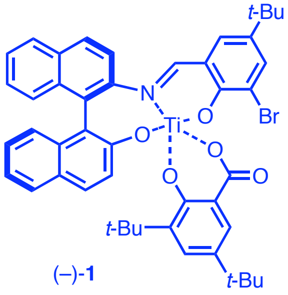
- This reaction is highly sensitive to the solvent and to reactant concentrations.

Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363-2364.

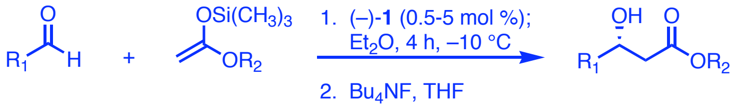
Catalytic, Enantioselective Acetate Aldol Additions with Silyl Ketene Acetals

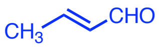
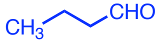
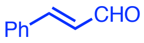
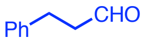
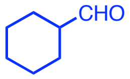
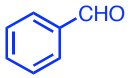
Review

Carreira, E. M.; Singer, R. A. *Drug Discovery Today* **1996**, *1*, 145-150.



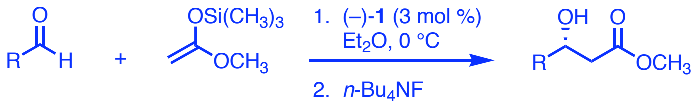
(–)-**1**

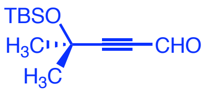


Aldehyde	%ee: R_2 = Et	%ee: R_2 = CH_3	%ee: R_2 = Bn
	92	97	-
	88	95	-
	93	97	96
	89	94	91
	94	95	-
	93	96	96

Yields for two steps (addition and desilylation) range from 72-98%.

- Catalyst **1** is formed by condensation of the chiral amino alcohol with 3-bromo-5-tert-butylsalicylaldehyde followed by complexation with Ti(O*i*-Pr)$_4$ and 3,5-di-tert-butylsalicylic acid. Both enantiomeric forms are available.
- Complete removal of *i*-PrOH during catalyst preparation is key to achieving high yields and selectivities. This may be done by azeotropic removal of *i*-PrOH with toluene or by its silylation in an in situ catalyst preparation (TMSCl, Et$_3$N).
- The reaction can be carried out in a variety of solvents, such as toluene, benzene, chloroform, diethyl ether, and *tert*-butyl methyl ether.
- Alkenyl and alkynyl aldehydes are particularly good substrates for this catalytic process.



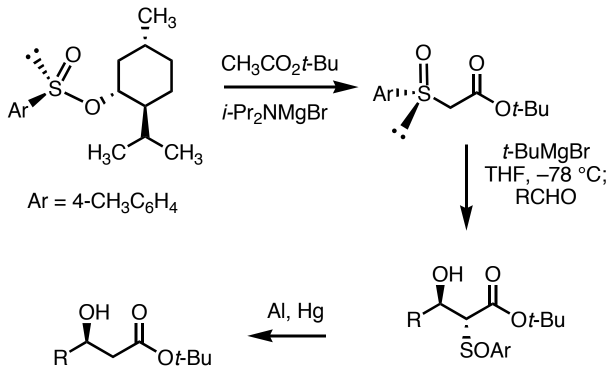
aldehyde	yield (%)	%ee
$\mathrm{TBSOCH_2{-}{\equiv}{-}CHO}$	88	96
$\mathrm{Ph{-}{\equiv}{-}CHO}$	96	94
$\mathrm{TIPS{-}{\equiv}{-}CHO}$	88	97
	88	96

Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837-8838.
Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927-930.
Singer, R. A.; Shepard, M. S.; Carreira, E. M. *Tetrahedron* **1998**, *54*, 7025-7032.

M. Movassaghi

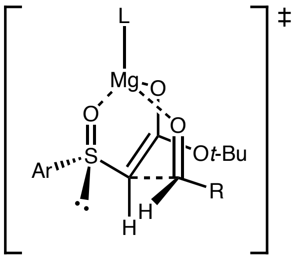
Acetate Aldol

Addition of a Chiral α-Sulphinylester Enolate to Aldehydes



- The β-hydroxy ester products are isolated in 50-85% yield and 80-91% ee.

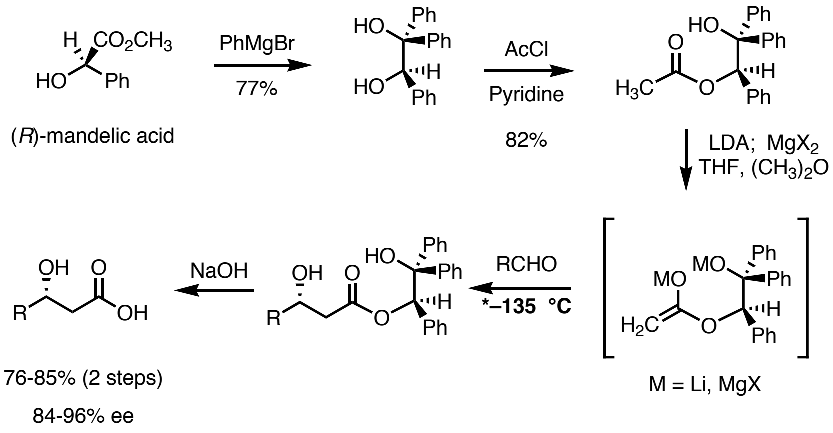
Proposed Transition State



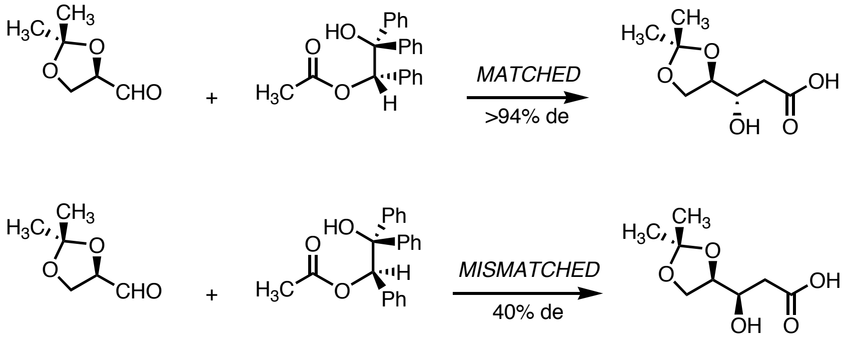
- Approach of the aldehyde is proposed to occur from the side of the non-bonding electron pair of the sulfur atom with the R-group of the aldehyde anti to the sulfinyl substituent. A chelated enolate is proposed.

Mioskowski, C.; Solladie, G. *J. Chem. Soc.*, *Chem. Commun.* **1977**, 162-163.

Addition of a Chiral Acetate Enolate to Aldehydes



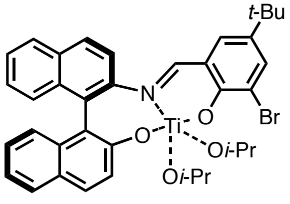
- Both (*R*)- and (*S*)-mandelic acids are commerically available.



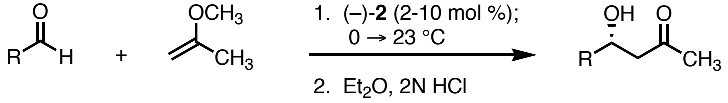
- Low diastereoselectivities are obtained with mismatched chiral aldehydes.
- A mechanistic rationale has not been proposed.

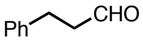
Braun, M. *Angew. Chem.*, *Int. Ed. Engl.* **1987**, *26*, 24-37.

Catalytic, Enantioselective Aldol Additions of an Acetone Enolate Equivalent



(–)-**2**

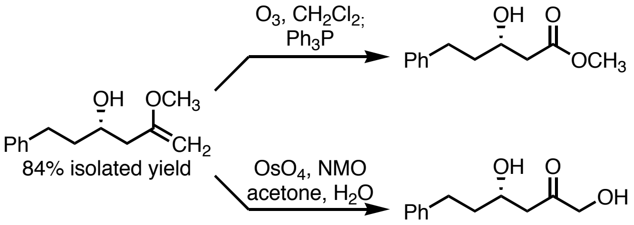


aldehdye	temp. (°C)	yield	%ee
$Ph(CH_2)_3—\equiv—CHO$	0	99	98
$TBSOCH_2—\equiv—CHO$	0	85	93
$Ph—\equiv—CHO$	0	99	91
	0 → 23	98	90
PhCHO	0 → 23	83	66
c-$C_6H_{11}CHO$	0 → 23	79	75

- 2-methoxypropene is used as the reaction solvent.
- Unhindered aldehydes afford products with the highest enantioselectivities.
- 2,6-di-*tert*-butyl-4-methylpyridine (0.4 equiv) is used in the reaction to prevent decomposition of the product by adventitious acid.

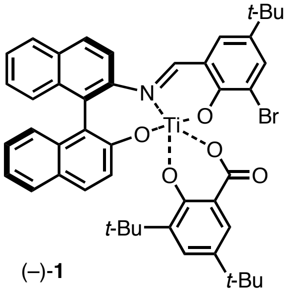
Carreira, E. M; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649-3650.

- The vinyl ether products can be isolated, or transformed into other useful products:

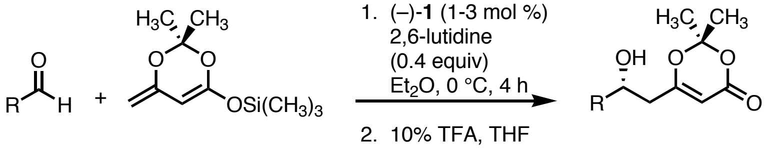


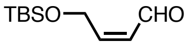
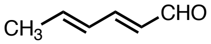
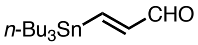
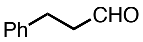
Carreira, E. M; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649-3650.

Catalytic, Enantioselective Dienolate Additions to Aldehydes



(–)-**1**

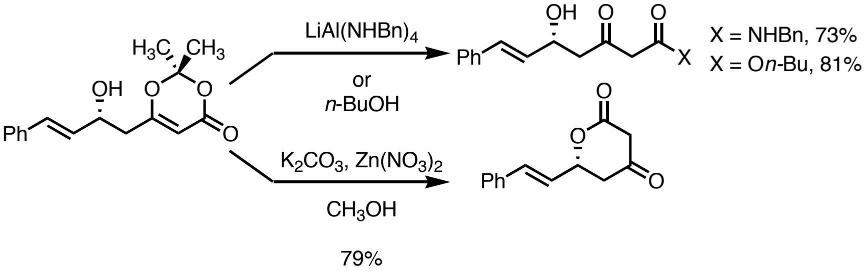


aldehyde	yield (%)	%ee
$TIPS—\equiv—CHO$	86	91
	97	94
	88	92
	79	92
	97	80
PhCHO	83	84 (96)[a]

[a] after recrystallization.

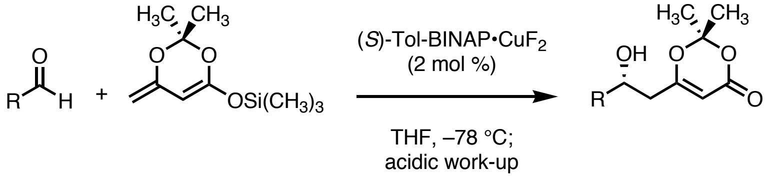
M. Movassaghi

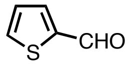
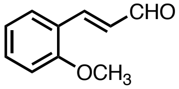
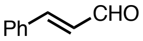
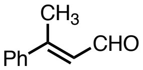
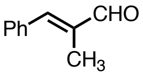
- The silyl dienolate is easily prepared, purified by distillation, and is stable to storage.
- The absolute sense of induction parallels that of acetate-derived silyl enol ether and 2-methoxypropene addition reactions.
- The protected acetoacetate adducts are versatile precursors for the preparation of optically active δ-hydroxy-β-keto esters, amides, and lactones.



Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360-12361.

Catalytic, Enantioselective Dienolate Additions to Aldehydes Using a Nucleophilic Catalyst.

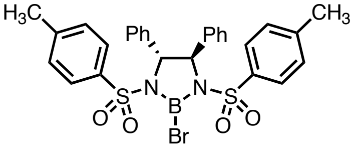


aldehyde	yield (%)	%ee
PhCHO	92	94
	98	95
	82	90
	48	91
	81	83
	74	65

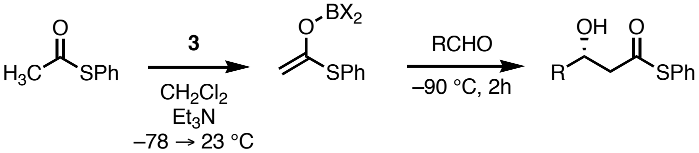
- (*S*)-Tol-BINAP-CuF_2 is readily prepared in situ by mixing (*S*)-Tol-BINAP, $Cu(OTf)_2$, and (n-Bu_4N)Ph_3SiF_2 in THF.
- This process is efficient for non-enolizable (α,β-unsaturated, aromatic, and heteroaromatic) aldehydes.
- Enolizable, aliphatic aldehydes give products with high enantioselectivity, but in poor yield (<40%).
- Spectroscopic evidence supports a catalytic process involving a chiral transition metal dienolate as an intermediate.

Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837-838.
Pagenkopt, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Engl. Ed.* **1998**, *37*, 3124-3126.

Enantioselective Acetate Aldol Addition Using a Chiral Controller Group



3



aldehdye	yield (%)	ee (%)
C_6H_5CHO	84	91
i-PrCHO	82	83

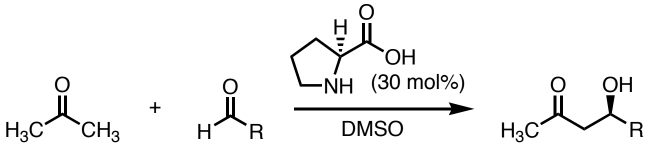
- Bromide **3** is produced from the corresponding (*R*,*R*)-bissulfonamide by reaction with BBr_3 in CH_2Cl_2.

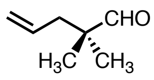
- Upon completion of the reaction the (*R*,*R*)-bis-sulfonamide can be recovered and reused.

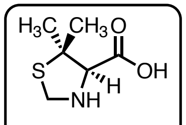
Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493-5495.

M. Movassaghi

Proline-Catalyzed Asymmetric Aldol Reaction of Acetone



aldehdye	yield	%ee
p-NO$_2$C$_6$H$_4$CHO	68 (60)	76 (86)
C$_6$H$_5$CHO	62 (60)	60 (89)
p-BrC$_6$H$_4$CHO	74 (85)	65 (67)
o-ClC$_6$H$_4$CHO	94 (71)	69 (74)
α-napthaldehyde	54 (60)	77 (88)
i-PrCHO	97 (65)	96 (96)
c-C$_6$H$_{11}$CHO	63 (45)	84 (83)
t-BuCHO	81	>99
	85	>99


DMTC

- Typically a 20-30 equivalent excess of acetone is used in relation to the aldehyde.

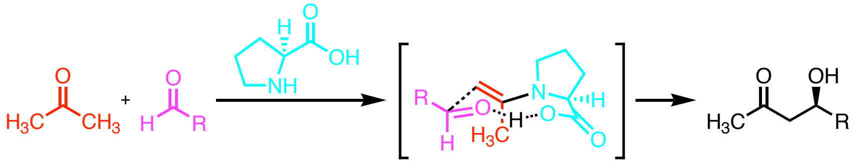
- Tertiary and α-branched aldehydes result in the highest yields and enantioselectivities, while unbranched aliphatic aldehdes give poor yields and enantioselectivities.

- 5,5-Dimethyl thiazolidinium-4-carboxylate (DMTC) has also been found to be an efficient amino acid catalyst for the acetone aldol reaction. Results with this catalyst are shown above in parentheses.

List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

Kandasamy S.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.

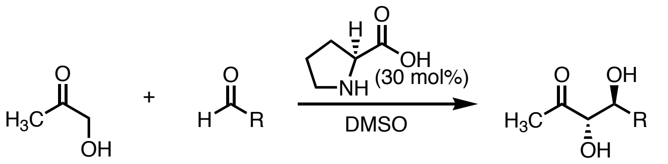
- The transition state shown below has been proposed to account for the stereoselectivity of proline-catalyzed aldol reactions.

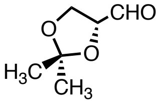
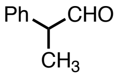


Rankin,K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A.* **2002**, *106*, 5155-5159.

Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

Proline-Catalyzed Asymmetric Aldol Reaction of Hydroxyacetone



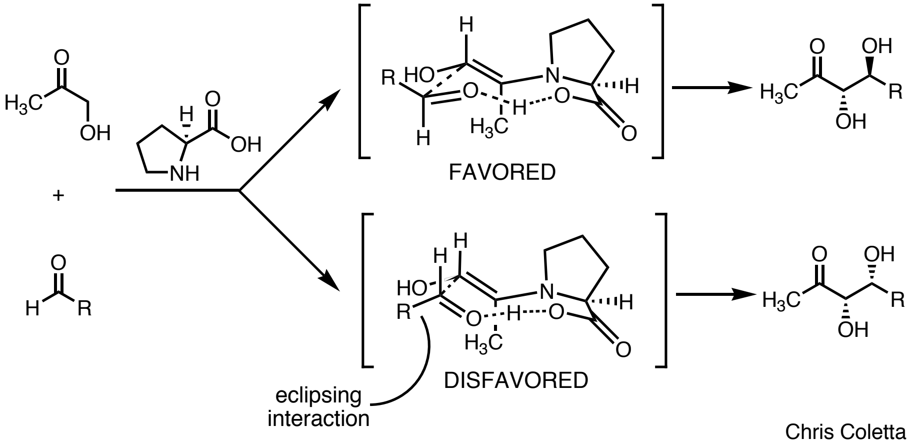
aldehdye	yield (%)	*anti*:*syn*	%ee (of *anti* product)
c-C$_6$H$_{11}$CHO	60	>20:1	>99
i-PrCHO	62	>20:1	>99
o-ClC$_6$H$_4$CHO	95	1.5:1	67
t-BuCH$_2$CHO	38	1.7:1	>97
	40	2:1	>97
	51	>20:1	>95

- The *anti*-diol product formed is not readily accessible via asymmetric dihydroxylation, making this reaction complementary to the Sharpless asymmetric dihydroxylation.

- The reaction is highly regioselective, and with suitable substrates (α-branched aliphatic aldehydes) the *anti:syn* ratio (dr) and enantioselectivity are excellent. In the case of α-unbranched aldehydes and aromatic aldehydes, the poor *anti:syn* selectivity is thought to result from a decrease in an eclipsing interaction between the alcohol and the aldehyde in the disfavored boat transition state shown below.

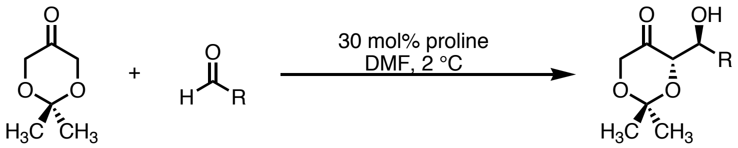
Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387.

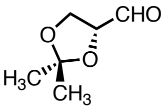
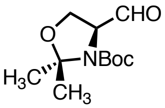
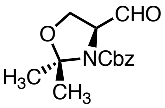
Proposed Origin of Selectivity:



Chris Coletta

Proline-Catalyzed Asymmetric Aldol Reaction of Acetonide Protected Dihydroxyacetone



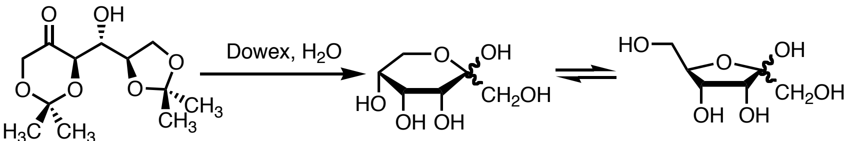
aldehdye	organocatalyst	yield	*anti/syn*	%ee
i-PrCHO	(S)-proline	97	>98:2	94
c-C_6H_{11}CHO	(S)-proline	86	>98:2	90
BnOCH_2CHO	(S)-proline	40	>98:2	97
$(CH_3O)_2$CHCHO	(S)-proline	69	94:6	93
	(R)-proline	76	>98:2	>98
	(S)-proline	80	>98:2	>96
	(R)-proline	31		>96
	(S)-proline	80	>98:2	>96

- The use of linear aldehydes in this reaction leads to poor yields, likely due to self condensation.

- Aromatic aldehydes form products with low diastereoselectivity (e.g., a 4:1 *anti:syn* ratio was reported for*ortho*-chlorobenzaldehyde).

- With the α-chiral α-aminoaldehyde shown above, the mismatched case results in a poor yield, but excellent dr and ee.

- Certian hexoses have been synthesized by this method.

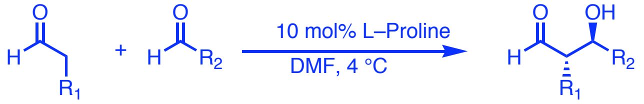


d-psicose

Enders, D.; Grondal, C. *Angew.Chem. Int. Ed.* **2005**, *44*, 1210-1212.

Chris Coletta

Proline-Catalyzed Enantioselective Cross-Aldol Reaction of Aldehydes



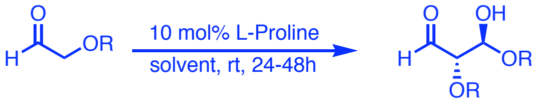
R_1	R_2	yield (%)	*anti:syn*	%ee
Me	Et	80	4:1	99
Me	*i*-Bu	88	3:1	97
Me	*c*-C_6H_{11}	87	14:1	99
Me	Ph	81	3:1	99
Me	*i*-Pr	82	24:1	>99
n-Bu	*i*-Pr	80	24:1	98
Bn	*i*-Pr	75	19:1	91

- Slow addition via syringe pump of the donor aldehyde to a solution of the acceptor aldehyde and proline is required in order to avoid dimerization of the donor aldehyde.

- The acceptor aldehyde must not be amenable to enamine formation upon extended exposure to proline in order to avoid self condesation. Either non-enolizable aldehydes or aldehydes containg α- or β-branching are suitable acceptor aldehydes for this reaction.

Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

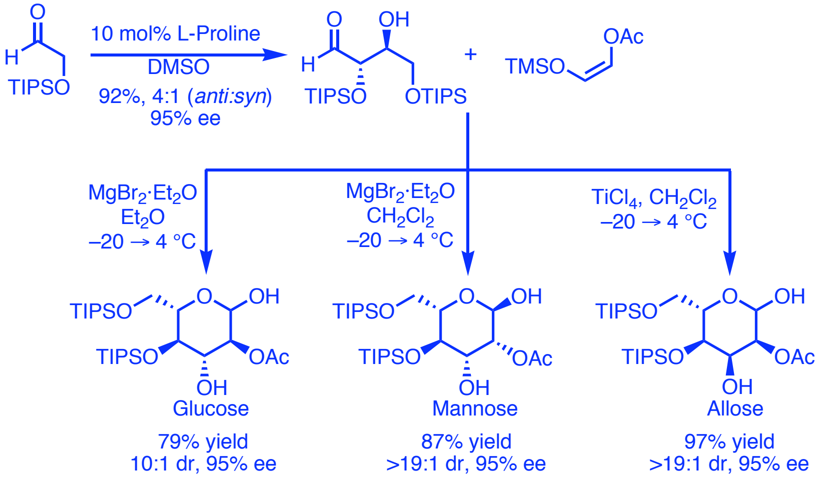
Proline-Catalyzed Direct and Enatioselective Aldol Reaction of α-Oxyaldehydes



R	Solvent	yield (%)	*anti:syn*	%ee
Bn	DMF	73	4:1	98
PMB	DMF	64	4:1	97
MOM	DMF	42	4:1	96
TBDPS	DMF/dioxane	61	9:1	96
TIPS	DMSO	92	4:1	95
TBS	dioxane	62	3:1	88

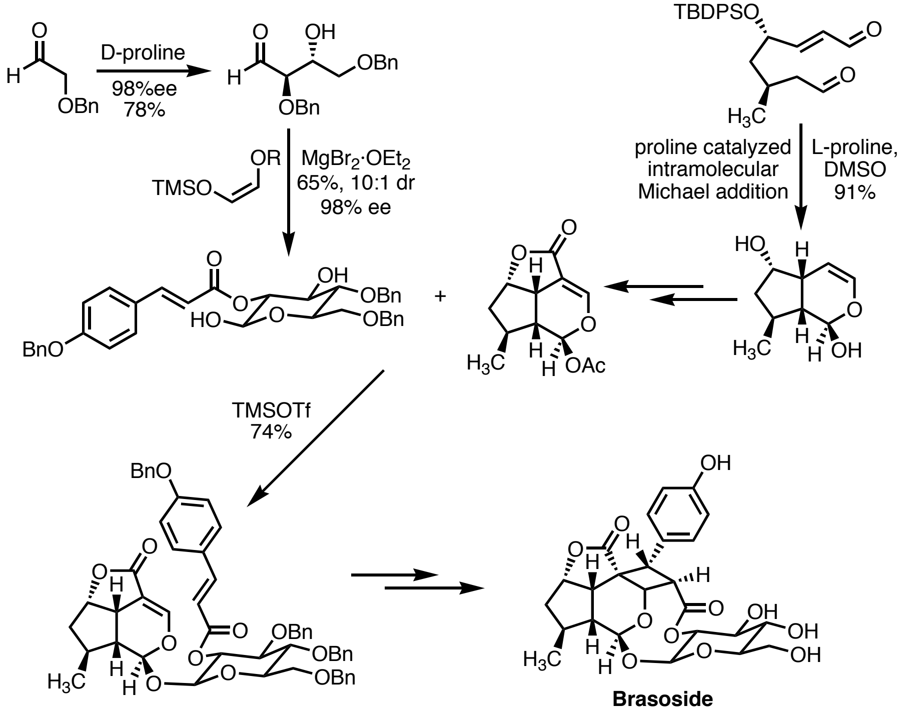
Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

- The aldol products from α-oxyaldehydes can be further elaborated as part of a two-step synthesis of carbohydrates.



Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305,* 1752-1755.

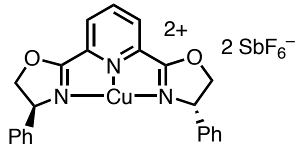
Application in Total Synthesis: Brasoside



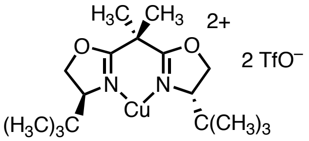
Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696-3697.

Chris Coletta

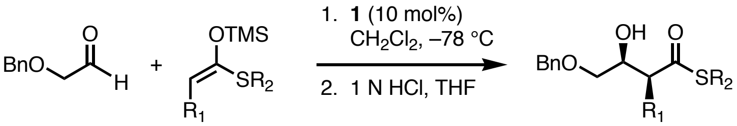
Catalytic, Enantioselective Aldol Additions of Silyl Thioketene Acetals and Silyl Enol Ethers



1

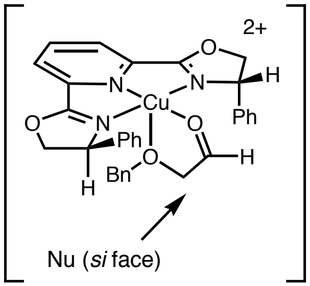


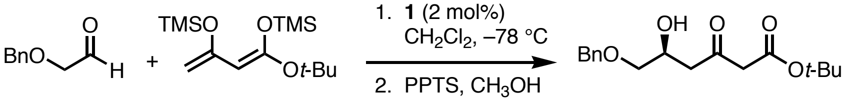
2



R_1	R_2	enol silane geometry	time (h)	T (°C)	syn:anti	%ee	yield (%)
H	*t*-Bu	–	24	–78	–	99	99
CH_3	Et	(*Z*)	4	–78	97:3	97	90
CH_3	Et	(*E*)	1d	–50	86:14	85	48
i-Bu	Et	(*Z*)	2d	–50	95:5	95	85

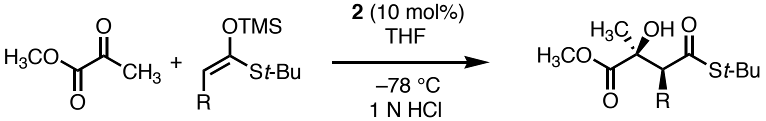
- Experimental data, including an X-ray structure of a catalyst-substrate complex, suggest a two-point binding model for the aldehyde during catalysis.





85%, 99% ee

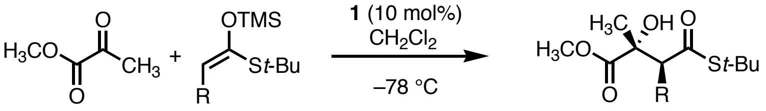
Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669-685.



R = H, CH_3, Et, *i*-Bu
77-97%
≥96% ee
≥94:6 syn:anti

- Based on structural data acquired with catalyst **1**, a bidentate coordination of methyl pyruvate to the copper complex **2** has been proposed.

Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893-7894.

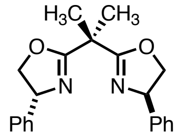


R = CH_3, Et, *i*-Bu
81-94%
≥96% ee
≥98:2 anti:syn

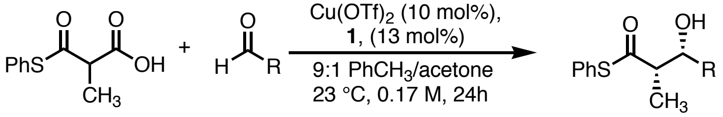
Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859-10860.
Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335.

M. Movassaghi

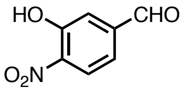
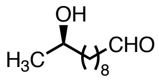
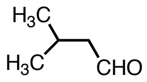
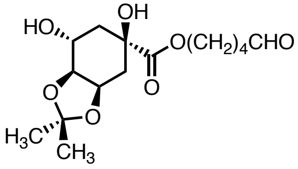
Catalytic, Enantioselective Thioester Aldol Reactions



1



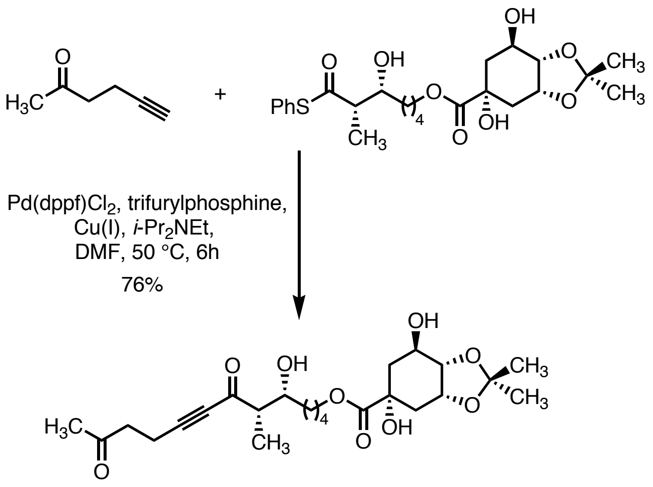
Cu(OTf)$_2$ (10 mol%),
1, (13 mol%)
9:1 PhCH$_3$/acetone
23 °C, 0.17 M, 24h

aldehdye	yield (%)	*syn:anti*	%ee
$CH_3(CH_2)_6CHO$	80	9:1	92 (R)
$CH_3O_2C(CH_2)_4CHO$	83	10:1	94
	83	9:1	93 (S)
	79	8:1	91
$CH_3(CH_2)_5{-}C{\equiv}C{-}CHO$	59	2.2:1	96 (S)
	73	7.5:1	89
c-C_6H_{11}CHO	48 (71)	36:1	93
	70	5.5:1	92

- This method is compatible with aldehyde substrates containing unprotected hydroxyl groups, including phenols.

- Aromatic aldehydes and β-branched aldehydes are generally poor substrates.

- The thioester group of the aldol products can be transformed by Pd-catalyzed cross coupling to give ketones.



Pd(dppf)Cl$_2$, trifurylphosphine,
Cu(I), *i*-Pr$_2$NEt,
DMF, 50 °C, 6h
76%

Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284-7285.

Chris Coletta

Horner-Wadsworth-Emmons Olefination

Reviews:

Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73-253.

Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.

Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99.

Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I. Ed.; Pergamon: Oxford, **1991**, Vol. 1, pp. 729-817.

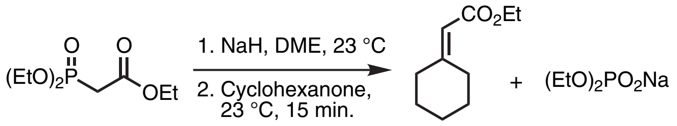
Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, **1979**, pp. 155-205.

Applications in Natural Product Synthesis: Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recueil* **1997**, 1283-1301.

Asymmetric Wittig-Type Reactions: Rein, T.; Reiser, O. *Acta. Chem. Scand.* **1996**, *50*, 369-379.

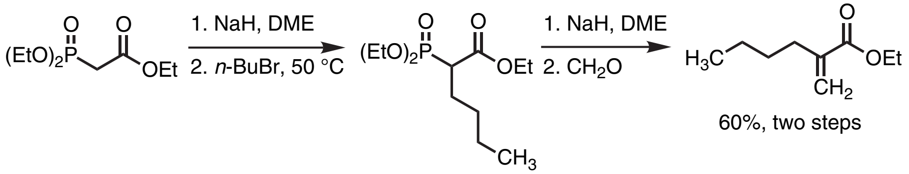
Development and General Aspects:

- Olefin synthesis employing phosphonium ylides was introduced in 1953 by Wittig and Geissler. Wittig, G.; Geissler G. *Liebigs Ann.* **1953**, *580*, 44-57.
- In 1958, Horner disclosed a modified Wittig reaction employing phosphonate-stabilized carbanions; the scope of the reaction was further defined by Wadsworth and Emmons.



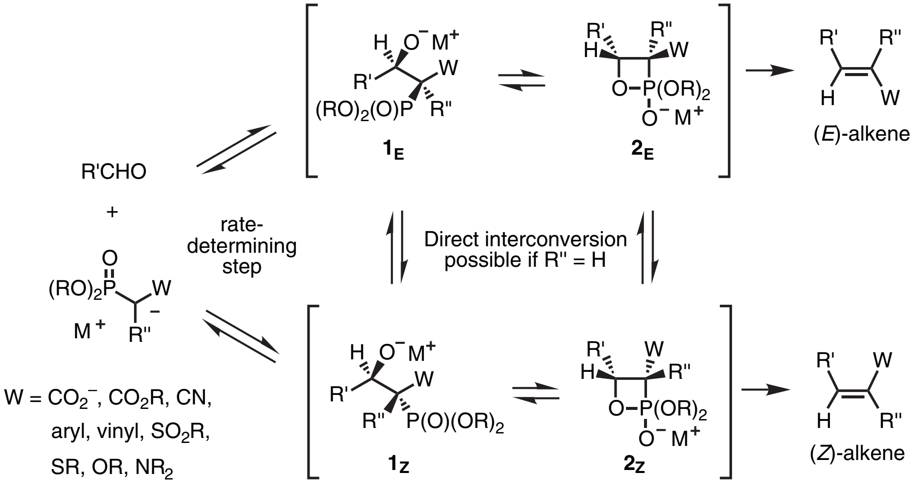
70%

- Phosphonate-stabilized carbanions are more nucleophilic (and more basic) than the corresponding phosphonium ylides.
- The by-product dialkylphosphate salt is readily removed by aqueous extraction.
- In contrast to phosphonium ylides, phosphonate-stabilized carbanions are readily alkylated:



Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61-63.
Horner, L.; Hoffmann, H. M. R.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499-2505.
Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1961**, *83*, 1733-1738.

Mechanism:



W = CO_2^-, CO_2R, CN, aryl, vinyl, SO_2R, SR, OR, NR_2

- Phosphonate anion addition to the carbonyl is rate determining (determined for olefination of aromatic aldehydes employing sodium ethoxide):

  Larsen, R. O.; Aksnes, G. *Phosphorus Sulfur* **1983**, *15*, 219-218.

- Carbanion-stabilizing group (W) at the phosphonate-substituted carbon is necessary for elimination to occur; nonstabilized phosphonates (W = R or H) afford stable β-hydroxyphosphonates.

  Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654-5656.

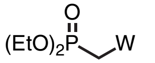
- Direct interconversion of intermediates **1**$_{E,Z}$ or **2**$_{E,Z}$ is possible when R'' = H:

  Lefèbvre, G.; Seyden-Penne, J. *J. Chem Soc., Chem. Commun.* **1970**, 1308-1309.

- The ratio of olefin isomers is dependent upon the stereochemical outcome of the initial addition and upon the ability of the intermediates to equilibrate.

Kent Barbay

Acidity of Stabilized Phosphonates in DMSO:



W	p*K*a
CN	16.4
CO_2Et	18.6
Cl	26.2
Ph	27.6
$SiMe_3$	28.8

Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.;
Bordwell, F. G. Unpublished results.
(http://daeiris.harvard.edu/DavidEvans.html)

- Phosphonium salts are considerably more acidic than the corresponding phosphonates:

$(Ph_3P^+CH_2CN)Cl^-$: $pK_a = 6.9$

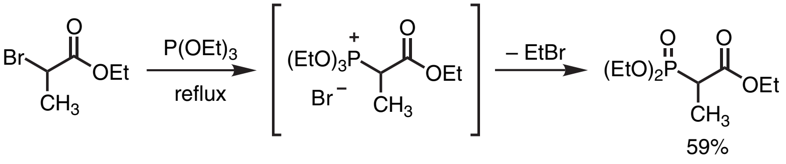
$(Ph_3P^+CH_2CO_2Et)Cl^-$: $pK_a = 8.5$

Bordwell, F. G.; Zhang, X.-M. *J. Am. Chem. Soc.* **1994**, *116*, 968-972.

Preparation of phosphonates:

Michaelis-Arbusov Reaction:

Review: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

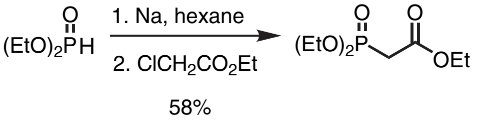


Arbusov, A. E.; Durin, A. A. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 295.

Michaelis-Becker Reaction:

Worms, K. H.; Schmidt-Dunker, M. In *Organic Phosphorus Compounds*; Kosolapoff, G. M. and Maier, L. Ed.; Wiley: New York, **1976**, Vol. 7, pp. 27-28.

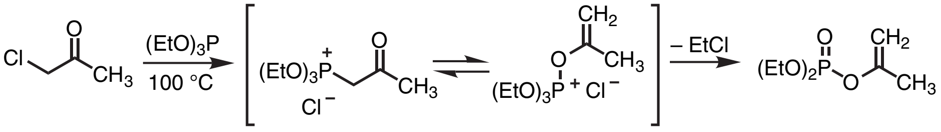
Muller, E. (ed.) *Methoden der Organishen Chemie* (Houben-Weyl); George Theime Verlag: Stuttgart, **1964**, Vol 12/1, p. 446.



Kosolapoff, G. M. *J. Am. Chem. Soc.* **1946**, *68*, 1103-1105.

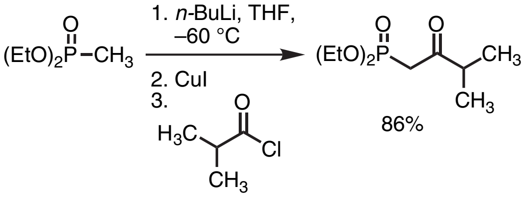
Acylation of Alkylphosphonate Anions:

- The synthesis of β-ketophosphonates from α-haloketones by the Michaelis-Arbusov reaction is impractical due to competing formation of dialkyl vinyl phosphates by the Perkow reaction:



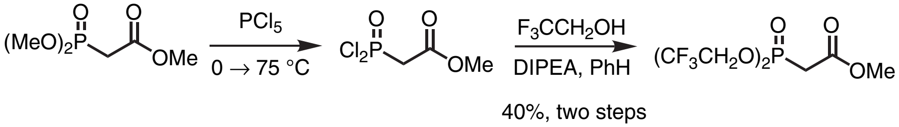
Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

- β-ketophosphonates are prepared by acylation of alkylphosphonate anions:



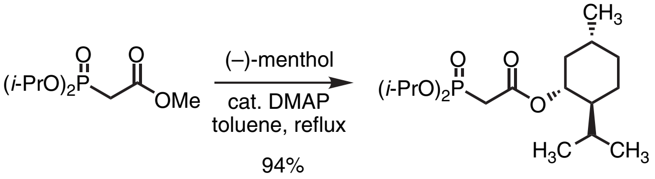
Mathey, F.; Savignac, P. *Tetrahedron*, **1978**, *34*, 649-654.

Phosphonate Ester Interchange:



Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.
Bodnarchuk, N. D.; Malovik, V. V.; Derkach, G. I. *Zh. Obshch. Khim.* **1970**, *40*, 1210.

Ester Interchange:



- The use of isopropyl phosphonates minimizes alkoxy exchange at phosphorus.

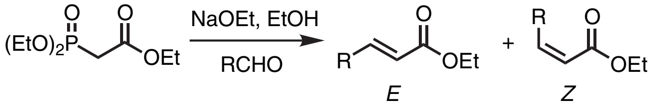
Hatakeyama, S.; Satoh, K.; Kuniya, S.; Seiichi, T. *Tetrahedron Lett.* **1987**, *28*, 2713-2716.

Kent Barbay

Stereoselectivity of HWE Olefination:

Disubstituted Olefins:

- Reaction of phosphonates with aldehydes favors formation of (*E*)-alkenes.



Aldehyde	Ratio of products (*E* : *Z*)
PhCHO	98 : 2
n-PrCHO	95 : 5
i-PrCHO	84 : 16

Larsen, R. O.; Aksnes, G. *Phosphorus Sulfur*, **1983**, *16*, 339-344.

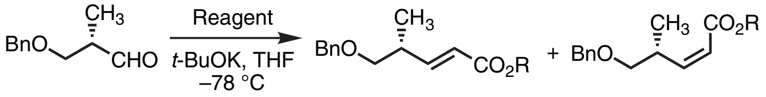
- In a systematic study of the synthesis of disubstituted olefins by HWE, *E* : *Z* ratio increases:

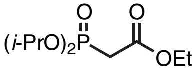
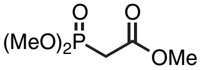
(1) in DME relative to THF,
(2) at higher reaction temperatures,
(3) M^+ = Li > Na > K,
(4) with increasing α-substitution of the aldehyde.

In general, conditions which increase the reversibility of the reaction (i.e., increase the rate of retroaddition relative to the rate of elimination) favor the formation of *E*-alkenes.

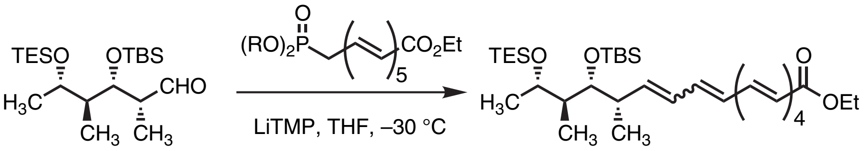
Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386-3388.

- Bulky phosphonate and ester substituents enhance (*E*)-selectivity in disubstituted olefin synthesis:



Reagent	Ratio of products (*E* : *Z*)
	95 : 5
	1 : 3

Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873-3888.



68% for R = *i*-Pr

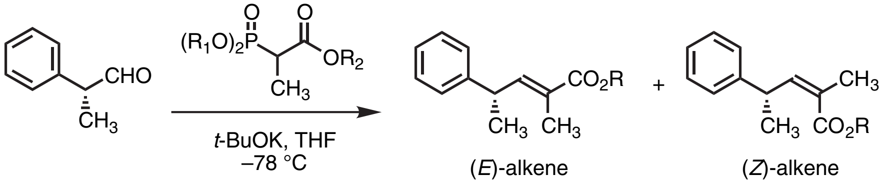
R	Ratio of products (*E* : *Z*)
Me	1 : 1.2
Et	1.75 : 1
i-Pr	E only
$CH(Et)_2$	E only

Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239-5242.

Trisubstituted Olefins:

Reaction of α-Branched Phosphonates with Aldehydes:

- The size of the phosphonate and ester substituents plays a critical role in determining the stereochemical outcome in the synthesis of trisubstituted olefins – large substituents favor (*E*)-alkenes.



R_1	R_2	Ratio of products (*E* : *Z*)
Me	Me	5 : 95
Me	Et	10 : 90
Et	Et	40 : 60
i-Pr	Et	90 : 10
i-Pr	*i*-Pr	95 : 5

Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873-3888.

- (*Z*)-selective olefination with the trimethyl phosphonate (R_1, R_2 = CH_3) is unsuccessful with aromatic aldehydes. The Still modification of the HWE olefination (see below) can be applied for (*Z*)-selective olefination of aromatic aldehydes.

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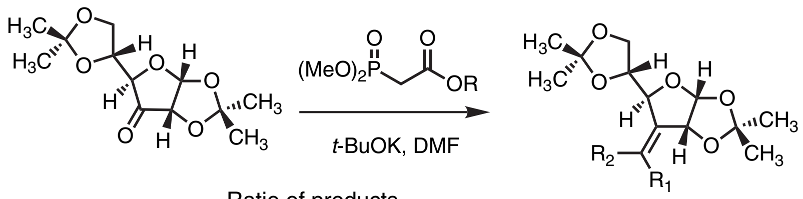
Olefination of Ketones:

- (*E*)-selectivities are typically modest in condensations with ketones. In some cases, use of a bulky ester increases the selectivity:



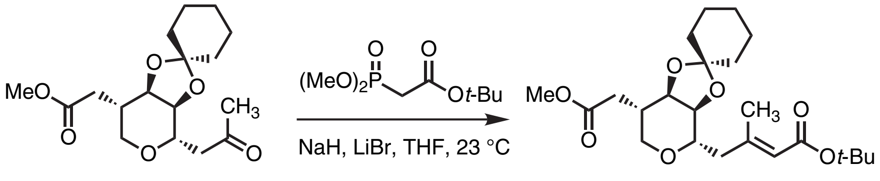
R	Ratio of products (**A** : **B**)
Me	2.7 : 1
t-Bu	9 : 1

A: $R_1 = CO_2R$, $R_2 = H$
B: $R_1 = H$, $R_2 = CO_2R$

- The failure of this hindered ketone to react with $Ph_3P{=}CHCO_2Et$ (benzene, reflux) provides an example of the increased reactivity of phosphonates in comparison to phosphonium ylides.

Mulzer, J.; Steffin, U.; Zorn, L.; Schneider, C.; Weinhold, E.; Münch, W.; Rudert, R.; Luger, P.; Hartl, H. *J. Am. Chem. Soc.* **1988**, *110*, 4640-4646.

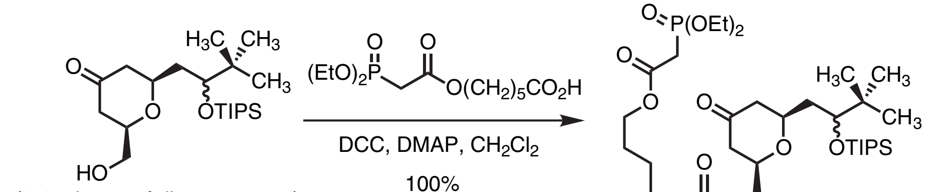
Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1201-1210.



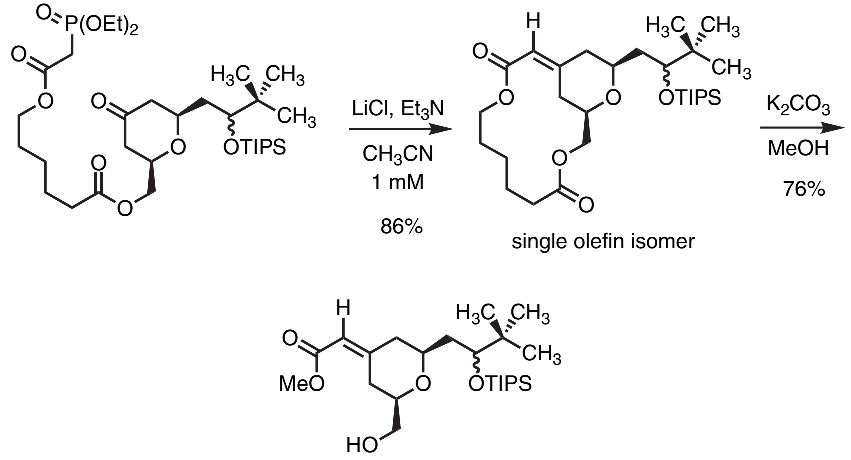
77%, 7:1 *E* : *Z*

White, J. D.; Theramongkol, P.; Kuroda, C.; Engelbrecht, J. R. *J. Org. Chem.* **1988**, *53*, 5909-5921.

- Control of double-bond geometry in tri-substituted olefin synthesis has been accomplished by the use of a tethered HWE reagent:

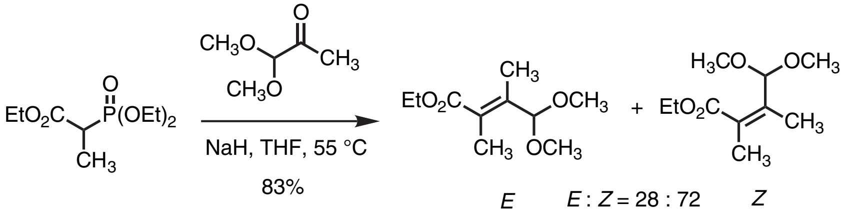


(1:1 mixture of diastereomers)



Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703-4706.

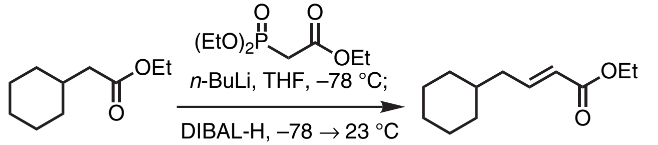
- Tetrasubstitued olefins can be prepared in some cases, but isomeric mixtures are obtained:



E : *Z* = 28 : 72

Bestmann, H. J.; Ermann, P.; Rüppel, H.; Sperling, W. *Liebigs. Ann. Chem.* **1986**, 479-498.

Single-step two-carbon homologation of esters:



81%, 91 : 9 *E* : *Z*

- Ester reduction in the presence of the phosphonate minimizes overreduction of the intermediate aldehyde.

Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257-1260.

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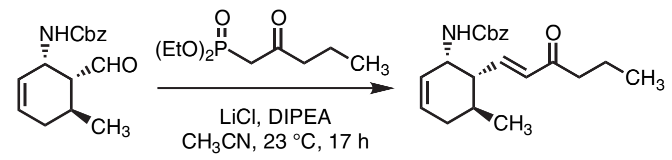
Olefination of Base-Sensitive Substrates (Masamune-Roush Conditions):

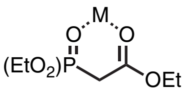
- Masamune and Roush reported mild conditions (LiCl, amine base, ambient temperature) for olefinations employing base-sensitive substrates or phosphonates:



90%

- This aldehyde substrate epimerizes under standard HWE conditions (NaH as base).

- Addition of LiCl enhances acidity of phosphonate, allows use of weak bases (DBU, i-Pr$_2$NEt) and ambient temperature.

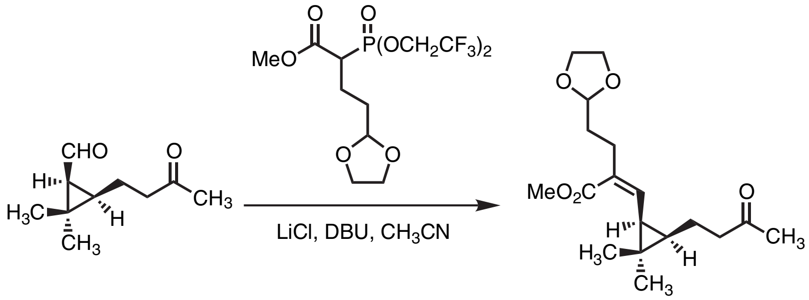


M	solvent	pKa
K	DMSO	19.2
Li	diglyme	12.2

- Application of the Masamune-Roush conditions does not alter the inherent (*E*)-selectivity of the HWE reaction.

Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

- Application of mild HWE conditions to (*Z*)-selective olefin synthesis (see adjacent column):

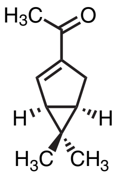


80%, 3 : 1 *Z* : *E*

- Application of the normal conditions for (*Z*)-selective HWE (KHMDS, 18-crown-6) yielded only the internal aldol product **A**.

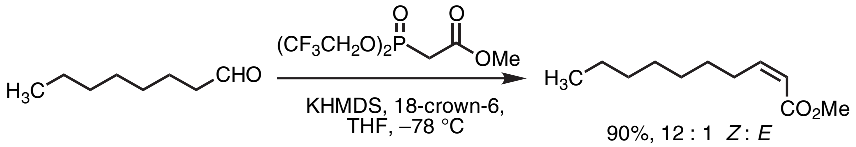
Hammond, G.S.; Cox Blagg, M.; Weimer, D. F. *J. Org. Chem.* **1990**, *55*, 128.

A

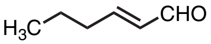
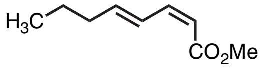
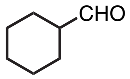
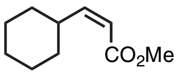
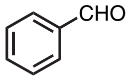
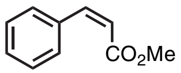
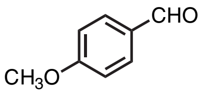
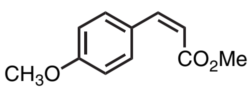
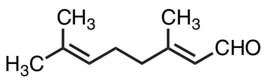
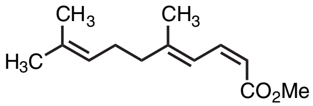


(*Z*)-Selective Olefination – Still Modification of HWE Olefination:

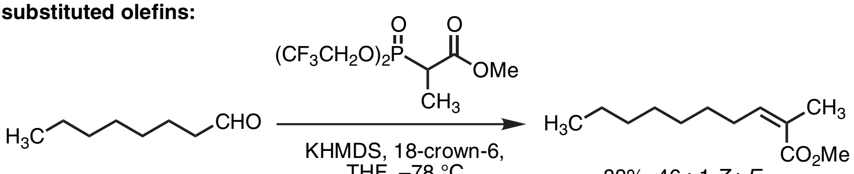
Disubstituted olefins:



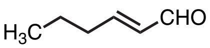
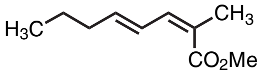
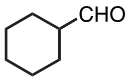
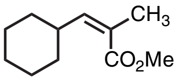
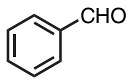
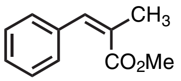
90%, 12 : 1 *Z* : *E*

aldehyde	product	*Z* : *E*	yield, %
		>50 : 1	87
		4 : 1	74
		>50 : 1	>95
		>50 : 1	>95
		22 : 1	81

Trisubstituted olefins:



88%, 46 : 1 *Z* : *E*

aldehyde	product	*Z* : *E*	yield, %
		>50 : 1	79
		>50 : 1	80
		30 : 1	>95

From: Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

- The electrophilic phosphonate and the use of strongly dissociating conditions favor rapid elimination, resulting in excellent (*Z*)-selectivity.

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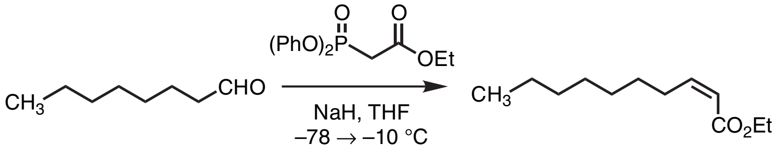
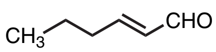
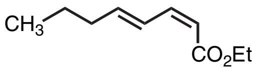
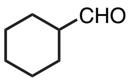
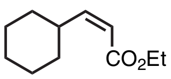
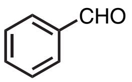
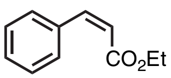
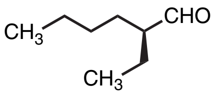
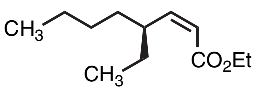
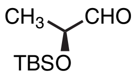
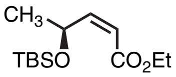
(Z)-Selective Olefination – (Diarylphosphono)acetates:

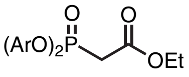
Disubstituted olefins:



100%, 90 : 10 *Z* : *E*

aldehyde	product	base	*Z* : *E*	yield, %
		Me_3NBuOH	89 : 11	97
		NaH	91 : 9	98
		Me_3NBuOH	93 : 7	98
		NaH	94 : 6	100
		NaH	97 : 3	78

- (*Z*)-Selectivity was further enhanced using *ortho*-alkyl substituted (diarylphosphono)acetates:



Ar = *o*-MePh, *o*-EtPh, *o*-*i*-PrPh

- 93 : 7 – 99 : 1 (*Z*)-selectivity, 92–100% yield.
- Aryl, α,β-unsaturated, alkyl, branched alkyl, and α-oxygenated aldehydes are suitable substrates.

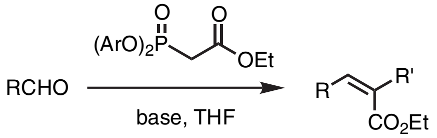
- In analogy to Still's (*Z*)-selective HWE reaction employing [bis(trifluoroethyl)phosphono]acetates, (*Z*)-selectivity is attributed to the electron-withdrawing nature of the aryloxy substituent, which accelerates elimination relative to equilibration of oxaphosphatane intermediates.

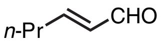
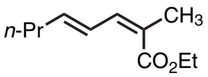
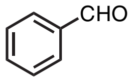
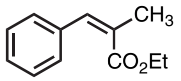
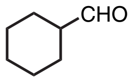
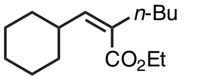
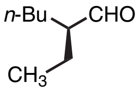
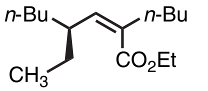
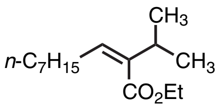
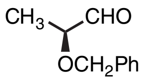
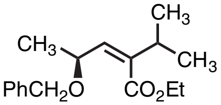
Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.

- For (diphenylphosphono)acetate esters, (*Z*)-selectivity increases with increasing steric bulk of the ester moiety.

Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408.

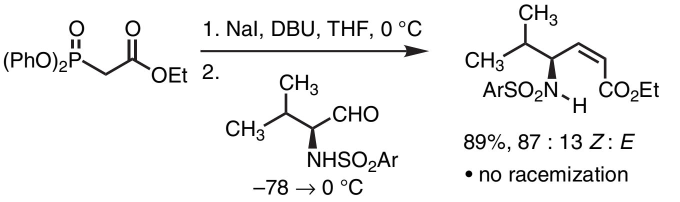
Trisubstituted olefins:



aldehyde	Ar	R'	product	base	*Z* : *E*	yield, %
	*o*-MePh	Me		Me_3NBuOH	89 : 11	97
	*o*-*i*-PrPh	Me		*t*-BuOK	97 : 3	100
	Ph	*n*-Bu		NaH	96 : 4	91
	Ph	*n*-Bu		NaH	95 : 5	85
n-C_7H_{15}CHO	Ph	*i*-Pr		NaH–LiBr	91 : 9	75
	Ph	*i*-Pr		NaH	98 : 2	65

Ando, K. *J. Org. Chem.* **1998**, *63*, 8411–8416.

- Masamune and Roush's mild conditions have been adapted for (*Z*)-selective olefin synthesis using (diarylphosphono)acetates:



89%, 87 : 13 *Z* : *E*
- no racemization

Ar = 2,4,6-trimethylphenyl

Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

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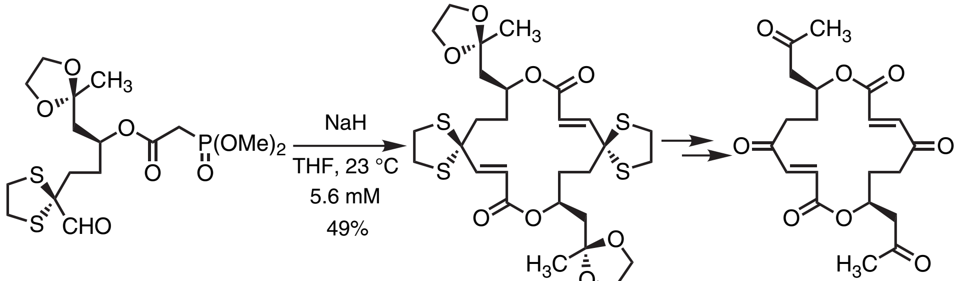
HWE Reaction in Macrolide Synthesis:

(–)-Vermiculine:

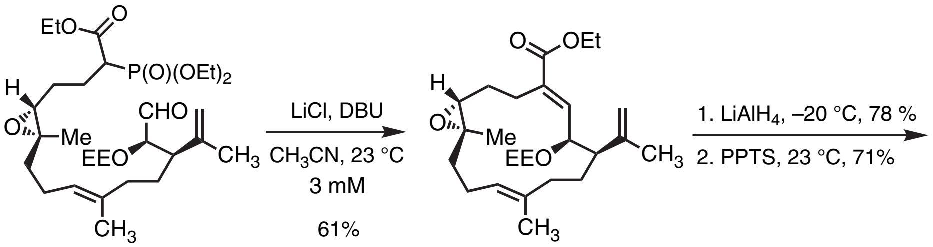


(–)-Vermiculine

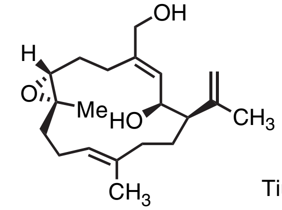
- High-dilution or syringe-pump additions are frequently required to achieve high-yielding macrocyclizations.

Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069-7071.

(–)-Asperdiol:



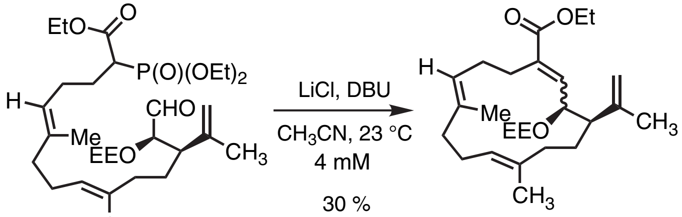
(*E*) only



(–)-Asperdiol

Tius, M.A.; Fauq, A. *J. Am. Chem. Soc.* **1986**, *108*, 6389-6391.

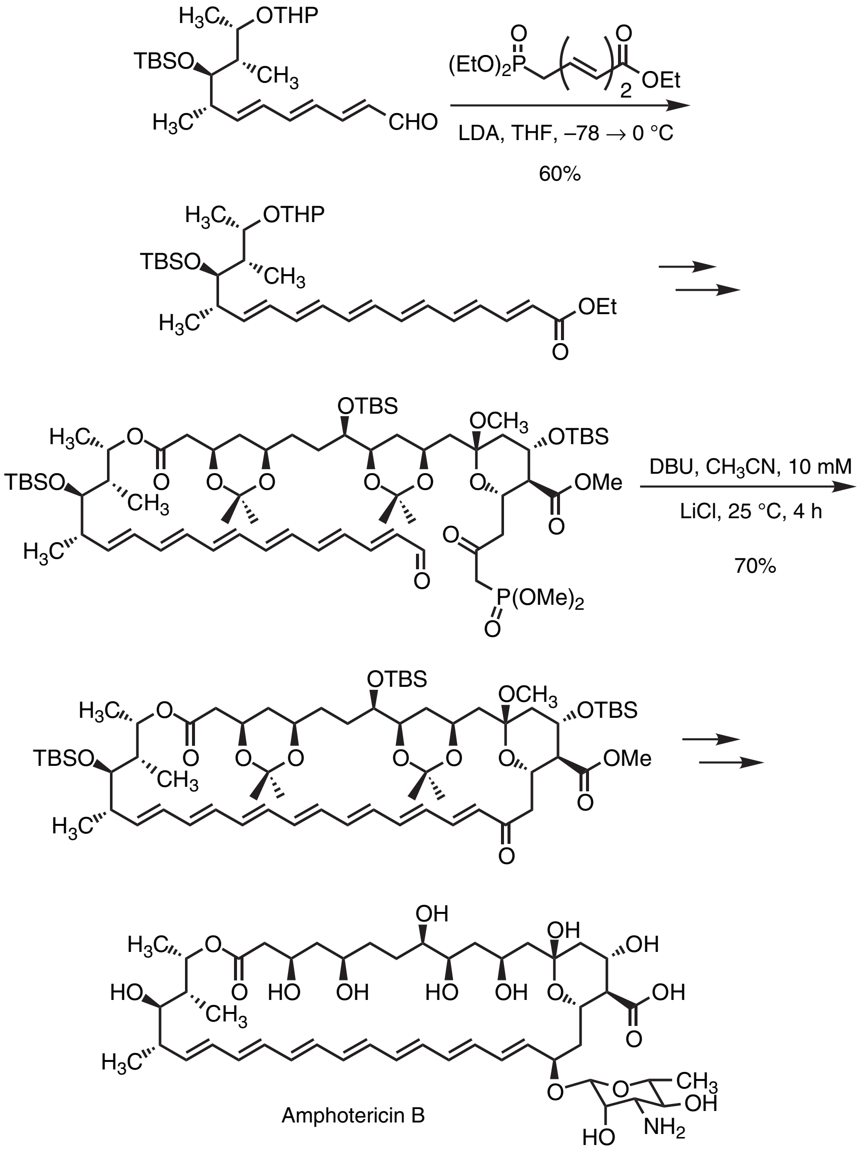
- Intramolecular HWE olefinations are usually selective for (*E*)-alkenes, but the selectivity can vary based on ring size and substitution. For example, compare to above:



2 : 1 *E* : *Z*

Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035-1039.

Amphotericin B:



Amphotericin B

Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685-4696.

Nicolaou, K.C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696-4705.

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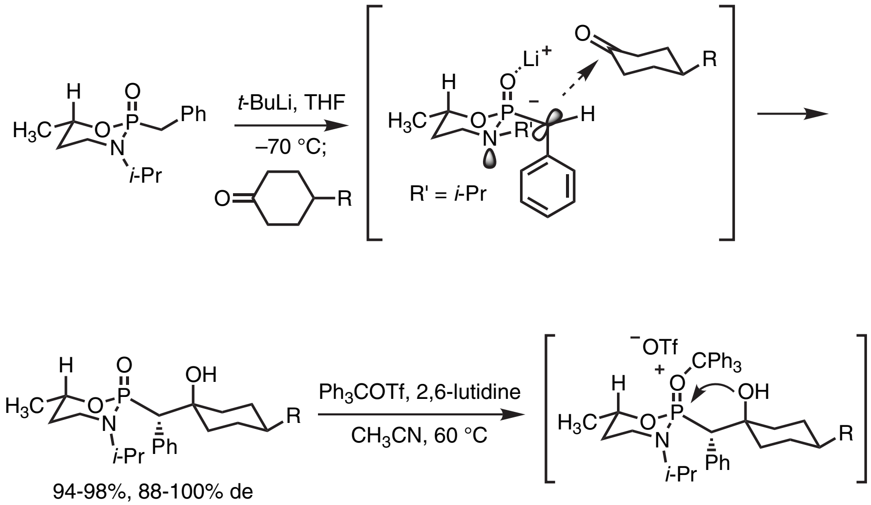
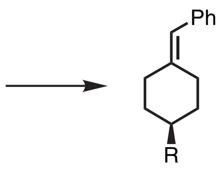
Asymmetric HWE:

Chiral Phosphonamidates:



94-98%, 88-100% de



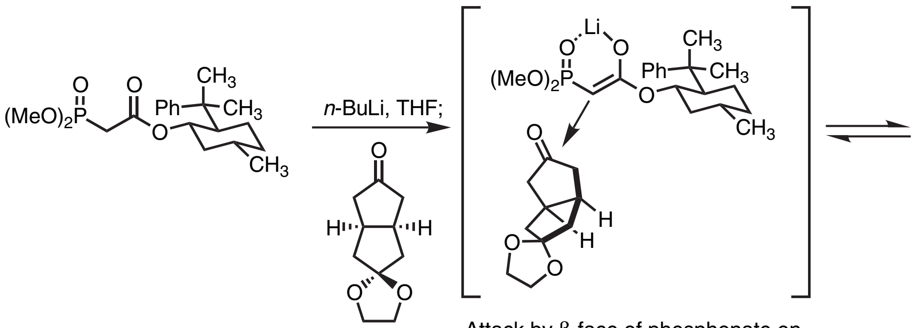
R	yield, %	ee, %
t-Bu	65	>99
Me	72	86
Ph	71	>99
CO_2*t*-Bu	75	95

- Electrophilic attack occurs from the less hindered α-face of the phosphonamidate-stabilized carbanion. Bulky nucleophiles display high selectivity for equatorial attack on cyclohexanones.

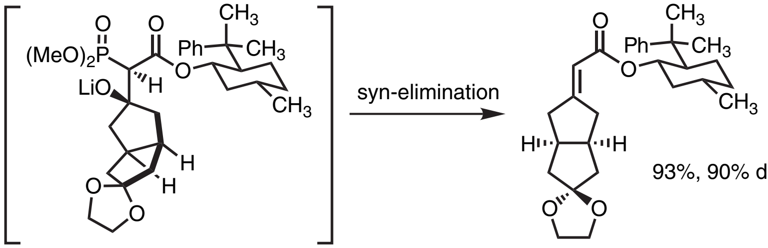
- Stable β-hydroxy phosphonamidates are isolated and transformed to alkenes by electrophilic activation with trityl salts. This procedure results in stereospecific syn-cycloelimination. (Attempted base-catalyzed olefin formation led to retroaddition.)

Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674-10676.
Denmark, S. E.; Chen, C.-T. *J. Org. Chem.* **1994**, *59*, 2922-2924.

Asymmetric Olefin Synthesis – Chiral Ester:



Attack by β-face of phosphonate on convex face of ketone



93%, 90% de

Gais, H.-J.; Schmeidl, G.; Ball, W. A.; Bund, J.; Hellmann, G.; Erdelmeier, I. *Tetrahedron Lett.* **1988**, *29*, 1773-1774.

8-phenylmenthol: Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.

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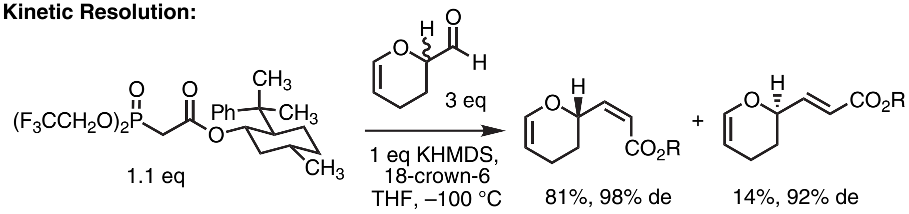
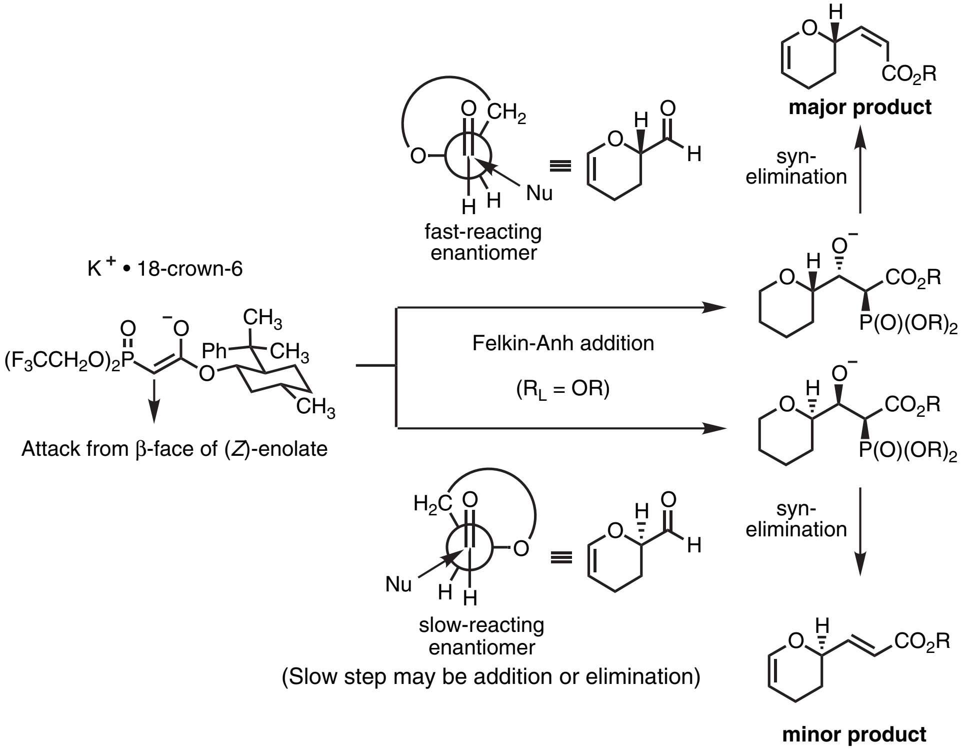
Kinetic Resolution:



Crude *Z* : *E* = 85 : 15

- *E* and *Z* products are formed from different enantiomers of the starting aldehyde.

- Mechanistic hypothesis:

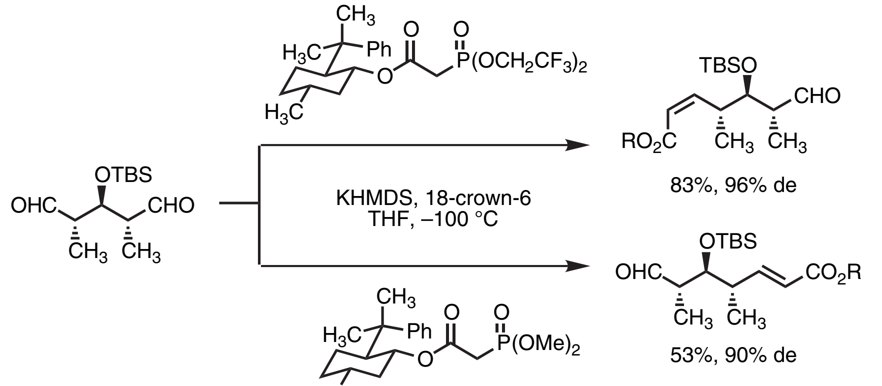


- For consideration of the stereochemical outcome of addition to α-alkyloxy aldehydes, see: Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353-3361.

Rein, T.; Kann, N.; Kreuder, R.; Benoit, G.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 556-558.

Rein, T.; Reiser, O. *Acta. Chem. Scand.* **1996**, *50*, 369-379.

Discrimination of enantiotopic or diastereotopic carbonyls:

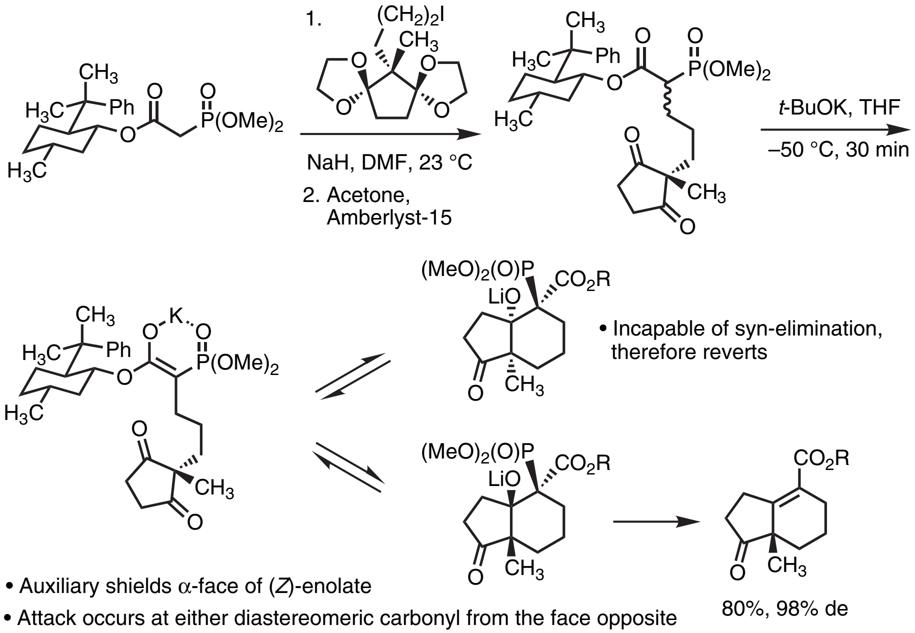


- Diastereoselectivity is depend on conversion, because the minor diastereomeric products are preferentially bis-olefinated.

See: Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, 109, 1525-1529.

Exercise: Based on the previous example, rationalize the stereochemical outcome of these olefinations. (Note that the phosphonate used in this example is enantiomeric to that used in the previous example).

Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284-8294.



- Auxiliary shields α-face of (*Z*)-enolate
- Attack occurs at either diastereomeric carbonyl from the face opposite the methyl group.

Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847-5849.

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Reviews:

Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B.M. and Fleming, I. Eds.; Pergamon: Oxford, 1991, Vol. 5, pp. 315-399.

Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019.

Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, Heidelberg, 1986, Vol 4, pp. 262-306.

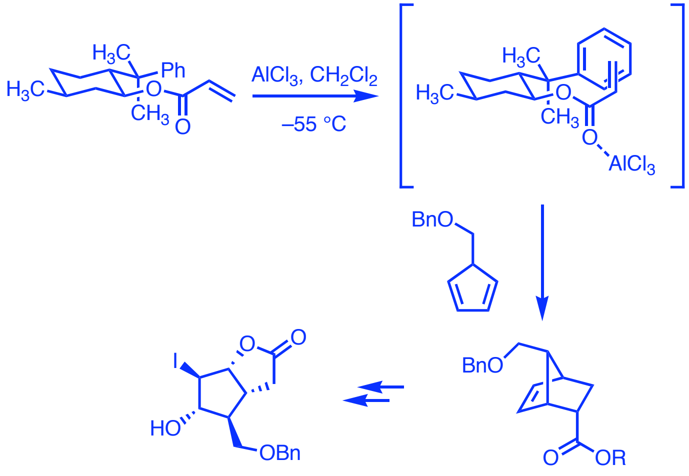
Reilly, M.; Oh, T. *Org. Prep. Proceed. Int.* **1994**, *26*, 131-158.

Maruoka, K.; Yamamoto, H. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; Wiley-VCH: New York, 1993, Chapter 9, pp. 413-440.

Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, 1999; Vol III, pp. 1177-1235.

Chiral Auxiliaries – Dienophiles:

(–)-8-Phenylmenthol:



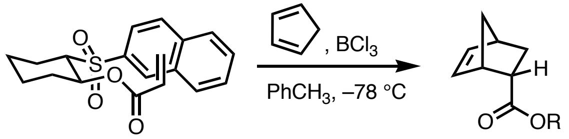
(Intermediate in prostaglandin synthesis)

89%, 97% de

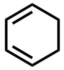
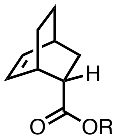
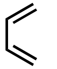
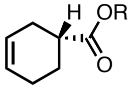
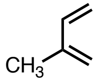
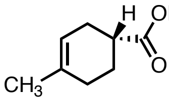
- Endo-selective cycloaddition is proposed to occur from the unblocked β-face of the *s-trans* acrylate-Lewis acid complex.
- A favorable π-stacking interaction is proposed to enhance the stereoselectivity of this process. (Acrylates derived from menthol afford lower diastereoselectivity – ca. 40%).
- (–)-8-phenylmenthol, derived from (–)-pulegone, is commercially available. Recovery of the auxiliary was accomplished in 94% yield following reductive removal.

Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.
Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **1978**, *43*, 1610-1612.

- The stereochemical model for chiral induction by the 8-phenylmenthol controller has recently been applied in the design of a practical auxiliary for asymmetric Diels-Alder reactions:

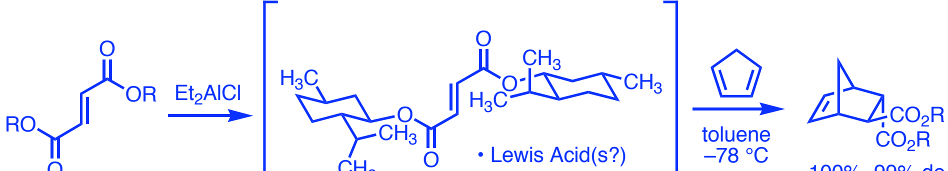


99% yield, 98.5 : 1.5 endo : exo, 97% de

diene	product	yield (%)	endo : exo	de (%)
		94	> 99 : 1	97
		97	--	94
		98	--	94

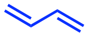
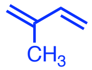
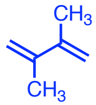
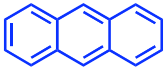
Corey, E. J.; Sarakinos, G. *Org. Lett.* **1999**, *1*, 1741-1744.

Dimenthyl Fumarate:



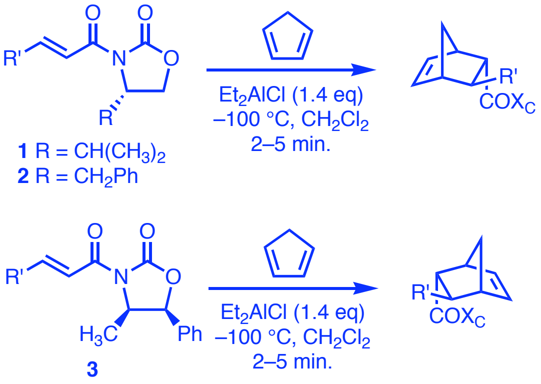
100%, 99% de

- The menthyl auxiliaries exhibit cooperative asymmetric induction in the case of the fumarate ester, resulting in excellent selectivity for cycloaddition from the back face.

Diene	Lewis Acid	Temperature (°C)	Yield	de (%)
	*i*-Bu$_2$AlCl	–40	56	95
	*i*-Bu$_2$AlCl	–20	94	95
	Et$_2$AlCl	–20	70	96
	AlCl$_3$	25	92	99

From: Furuta, K.; Iwanaga, K. Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507-4510. Kent Barbay

***N*-Acyloxazolidinone Dienophiles:**

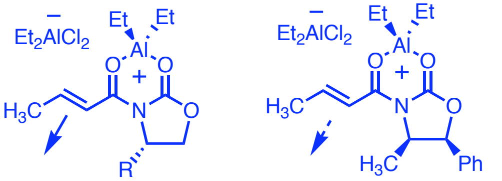


dienophile	endo : exo	endo dr	isolated yield	isolated dr
1, R' = H	>100 : 1	93 : 7	81	>99 : 1
2, R' = H	>100 : 1	95 : 5	78	97 : 3
3, R' = H	100 : 1	5 : 95	82	<1 : 99
1, R' = CH_3	48 : 1	95 : 5	82	>99 : 1
2, R' = CH_3	55 : 1	97 : 3	83	99 : 1
3, R' = CH_3	60 : 1	2 : 98	88	<1 : 99
1, R' = Ph[a]	b	93 : 7	83	>99 : 1

a. Reaction run at –20 °C, 2.5 h.
b. Exo product not observed by 500 MHz ^{1}H-NMR.

- The high reactivity of the unsaturated carboximides is highlighted by tolerance of β-substitution on the dienophile, which is not typically the case for chiral ester dienophiles.

- The stereochemical results are consistent with the following models:



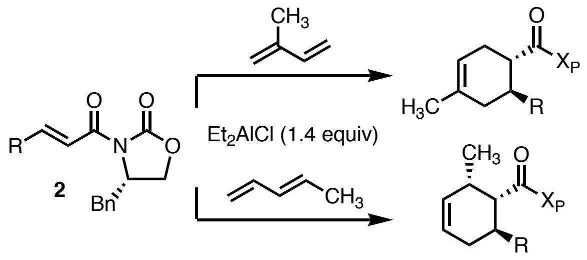
- cycloaddition occurs from the less sterically encumbered face
- the reactive dienophile is a chelated cationic species
- the *s-cis* conformation of chelated acyl oxazolidinones is assumed to be favored

- (*Z*)-unsaturated imides and β,β-disubstituted imides have limited applicability due to competing isomerization or low reactivity.

Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263.

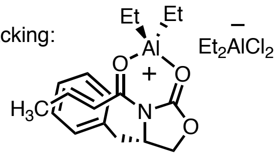
Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

- Diene scope: includes dienes less reactive than cyclopentadiene (e.g. acyclic dienes). In this case, imide **2** afforded uniformly higher diastereoselectivities than **1** or **3**.



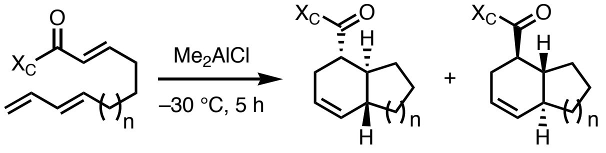
R	diene	dr	isolated yield (%)	isolated dr
H	isoprene	95 : 5	85	> 99 : 1
H	piperylene	>100 : 1	84	> 99 : 1
CH_3	isoprene	94 : 6	83	> 99 : 1
CH_3	piperylene	95 : 1 : 2 : 2	77	> 99 : 1

- The enhanced stereoselectivity of dienophile **2** is attributed to π-stacking:

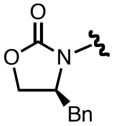
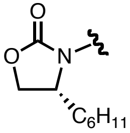


Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184-1186.

- The oxazolidinone auxiliaries have been applied to asymmetric intramolecular Diels-Alder reactions:



Endo I   Endo II

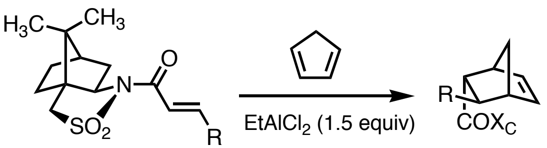
X_C	n	dr (Endo I : Endo II)	Isolated yield (%)[a]
	1	95 : 5	73
	2	97 : 3	88
	1	3 : 97	65
	2	6 : 94	70

a. Refers to purified products, de >99%.

Evans, D. A.; Chapman, K. T.; Bisaha, J. *Tetrahedron Lett.* **1984**, 25, 4071-4074.

Kent Barbay

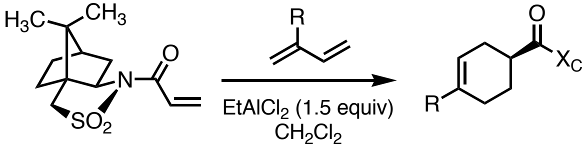
Camphor-derived *N*-Enoyl Sultams:



R	Temperature (°C)	Time (h)	endo : exo	endo dr	yield
H	–130	6	99.5 : 0.5	97.5 : 2.5	83[a]
CH_3	–78	18	96 : 4	99 : 1	91[b]

a. Recrystallized yield, de ≥ 99%.
b. Crude yield of material with indicated isomeric purity.

- Acyclic dienes are suitable substrates in the case of (unsubstituted) *N*-acryloyl sultams:



R	Temperature (°C)	Time (h)	dr	yield[a]
H	–78	6	98.5 : 1.5	81
CH_3	–94	6	97 : 3	64

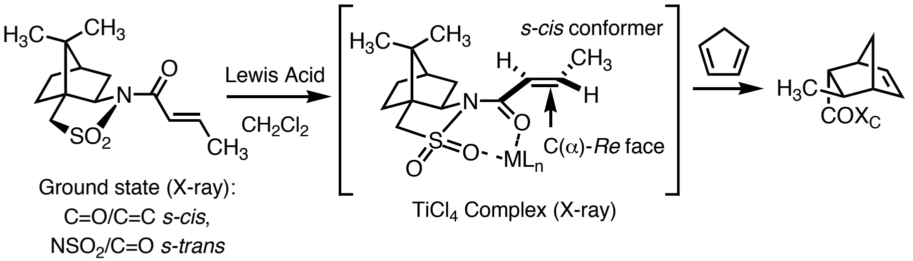
a. Recrystallized yield, de ≥ 99%.

- Both antipodes of the chiral auxiliary are available; they are synthesized in two synthetic steps from camphor-10-sulfonyl chloride.
- Recovery of the auxiliary is possible after reductive or hydrolytic removal.
- The cycloadducts tend to be crystalline solids, facilitating purification.

Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chem. Acta.* **1984**, *67*, 1397-1401.

Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B.M. and Fleming, I. Eds.; Pergamon: Oxford, 1991, Vol. 5, pp. 315-399.

- The stereochemical outcome is rationalized by the following model, involving a chelated complex:

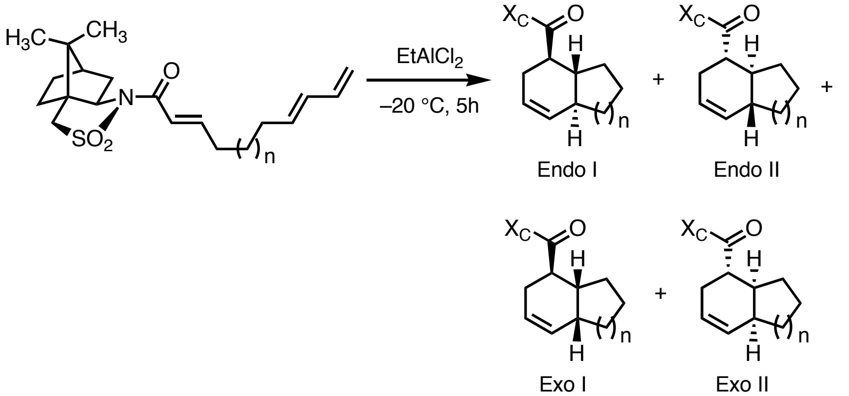


Oppolzer, W.; Rodriquez, I.; Blagg, J.; Bernardinelli, G. *Helv. Chem. Acta.* **1989**, *72*, 123-131.

- α,β-unsaturated amides display a general preference for the *s-cis* conformer.

Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365-6370.

- The camphor-derived sultam auxiliary has also been applied to intramolecular reactions:



n	dr (Endo I : Endo II : [Exo I + Exo II])	Isolated yield (%)[a]
1	>97.4 : 2.5 : <0.1	75
2	94.0 : 2.6 : 3.4	53

a. Refers to crystallized Endo I, de >99%.

Oppolzer, W.; Dupuis, D. *Tetrahedron Lett.* **1985**, *26*, 5437-5440.

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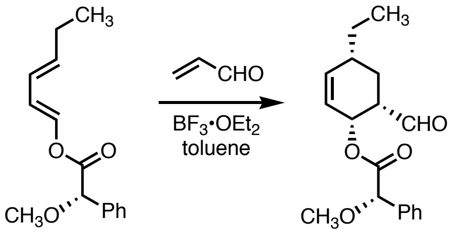
Chiral Auxiliaries – Dienes:

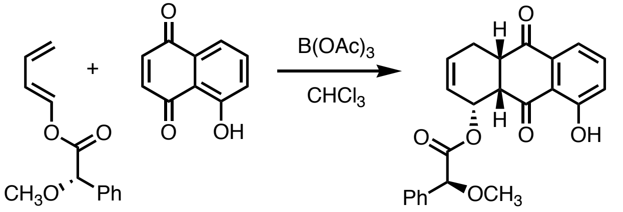
Review: Barluenga, J.; Suárez-Sobrino, A.; López, L. A. *Aldrichimica Acta.* **1999**, *32*, 4–15.

Chiral 1-heterosubstituted dienes:

- 1-*O*-methylmandeloxy substituted dienes (Trost's dienes):



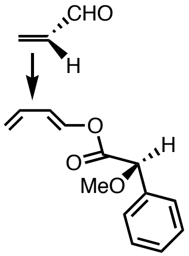
endo only
60% de, 92% yield



endo only
> 97% de, 98% yield

Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596.

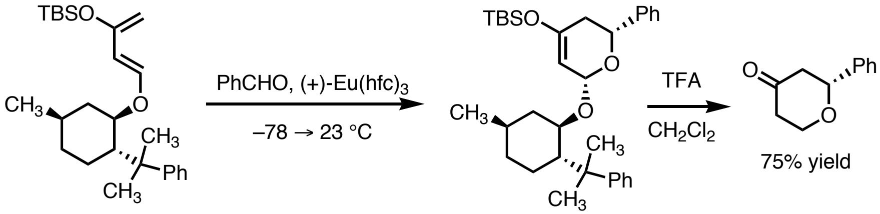
- A stereochemical model rationalizing these results has been presented by Thornton:



- a transition state conformation in which the phenyl substituent is perpendicular to the plane of the diene is proposed, favoring approach from the top face.

Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225–5228.
Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630–7640.

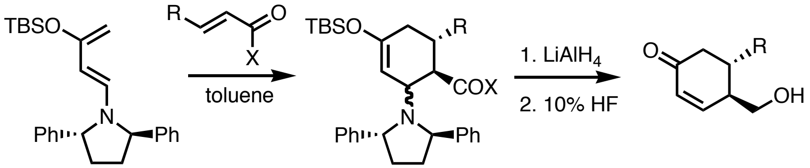
- 1-Alkoxy-3-silyloxy-1,3-butadienes (auxiliary-modified analogs of Danishefsky's diene):

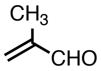
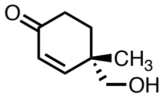
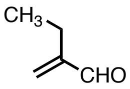
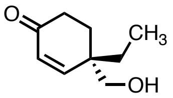
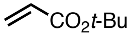
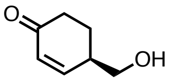
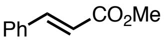
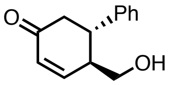
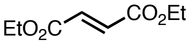
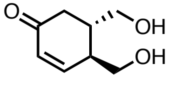
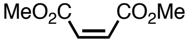
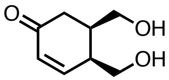


92% de

Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060–7067.

- 1-amino-3-silyloxy dienes:



dienophile	product	yield (%)	ee(%)
		79	88
		87	88
		86	98
		66	96
		82	92
		64	98

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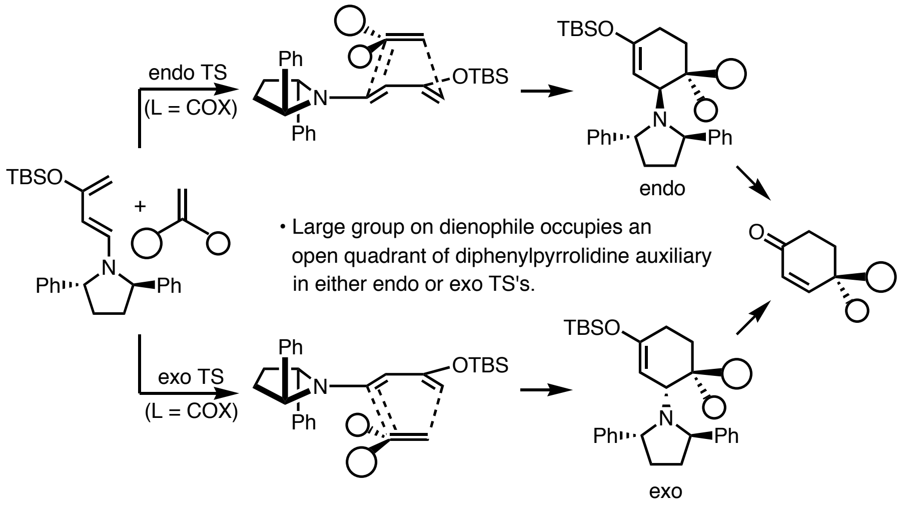
- Stereochemical Model:



- Large group on dienophile occupies an open quadrant of diphenylpyrrolidine auxiliary in either endo or exo TS's.

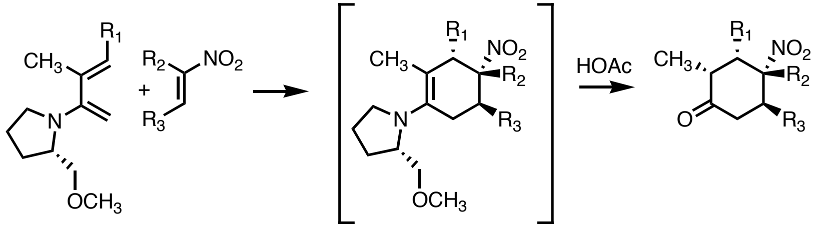
- Both endo and exo cycloadducts are transformed to the same enantiomer of the cyclohexenone product, allowing the use of dienophiles that do not undergo cycloaddition with high endo/exo selectivity.

Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562–9573.

Chiral 2-heterosubstituted dienes:

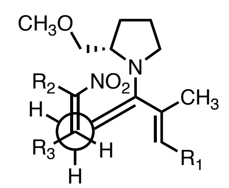
- 2-amino dienes:

Review: Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023–1035.



R_1	R_2	R_3	yield (%)	ee (%)
H	H	Ph	48	98
CH_2OTBS	H	Ph	63	94
CH_2OTBS	H	Me	48	95
CH_2OTBS	H	*i*-Pr	56	92
CH_2OTBS	-$(CH_2)_4$-		70	94

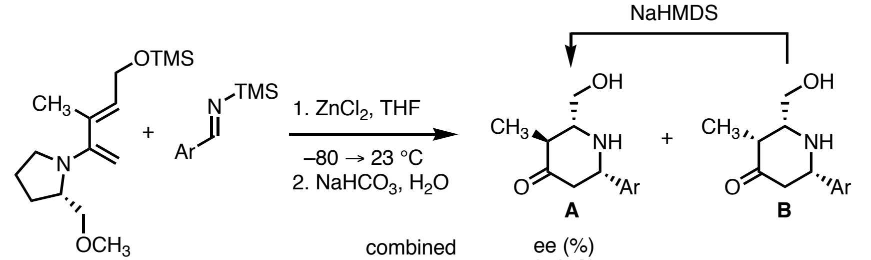
- These cycloadditions are proposed to proceed by a stepwise mechanism:



- Alkyl substitution at C_3 of the diene appears to be required, probably to restrict the conformation of the prolinol group as shown.

Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1997**, *62*, 6746–6753.

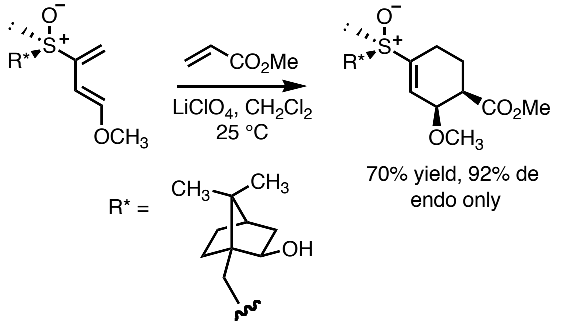
Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242–1244.



Ar	combined yield (%)	ee (%) (pdt **A**)
3-furyl	51	> 98
4-MeOPh	43	90
Ph	65	95

Barluenga, J.; Anzar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805–811.

- Sulfinyl-substituted dienes:



70% yield, 92% de
endo only

Aversa, M. C.; Barattuci, A.; Bonaccorsi, P.; Giannetto, P.; Jones, D. N. *J. Org. Chem.* **1997**, *62*, 4376–4384.

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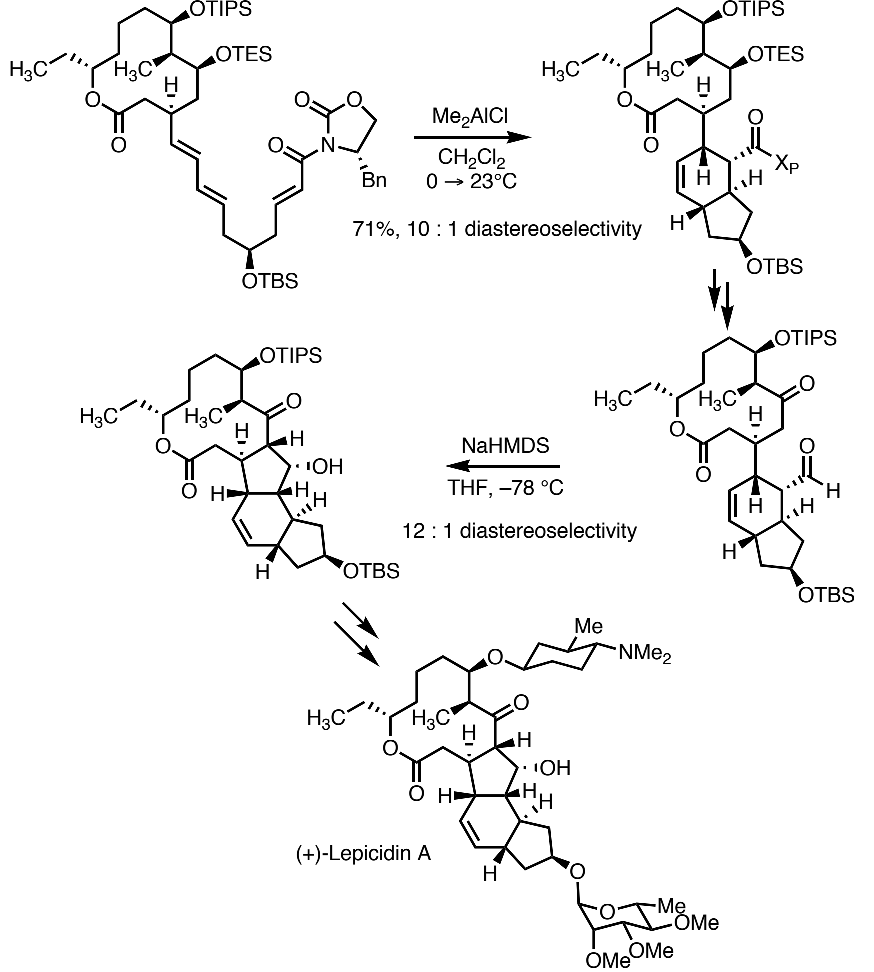
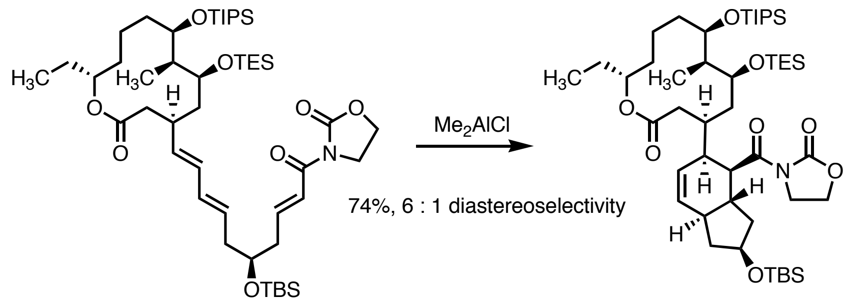
Chiral Auxiliaries for Asymmetric Diels-Alder Reations – Applications in Synthesis:

(+)-Lepicidin A:

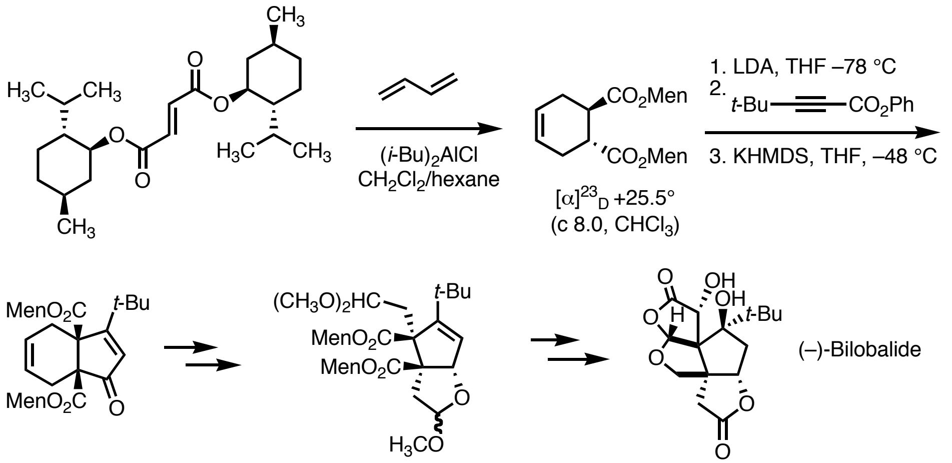


- A control experiment demonstrated that the imide auxiliary overcame an inherent stereochemical bias in the substrate:



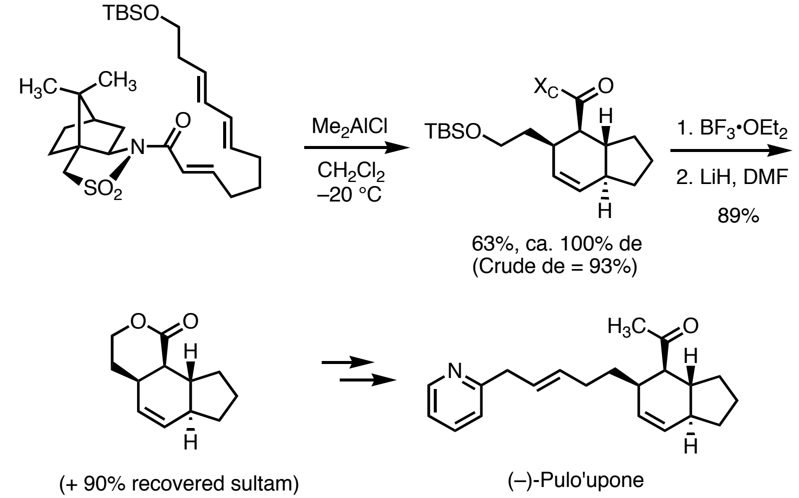
Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513.

(–)-Bilobalide:



Corey, E. J.; Su, W.-G. *Tetrahedron Lett.* **1988**, *29*, 3423-3426.

Pulo'upone:



Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. R.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, 29, 5885-5888.

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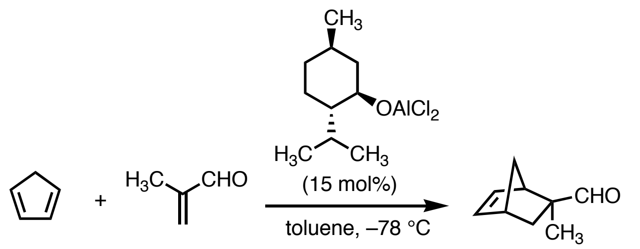
Catalytic, Asymmetric Diels-Alder Reactions:

- The first reported catalytic, asymmetric Diels-Alder reaction:

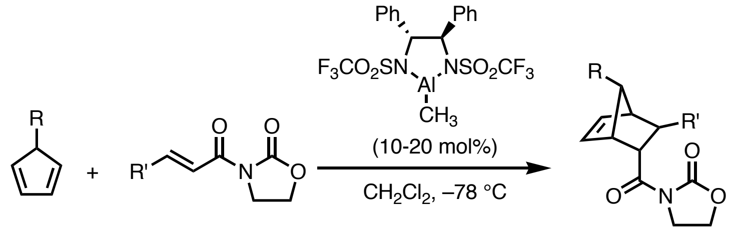


69%, 72% ee
exo : endo = 98 : 2

- The exo selectivity of α-substituted acroleins is general.

Hasimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437-438.

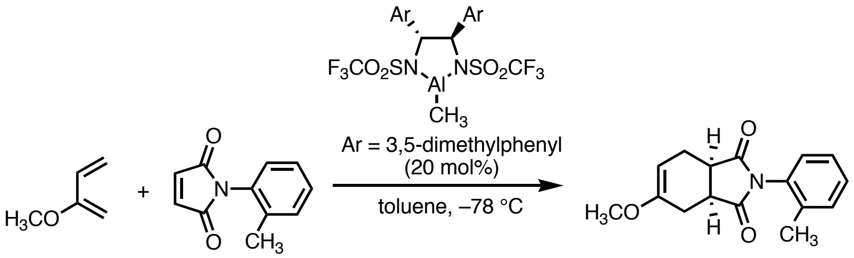
C_2-symmetric Diazaaluminolidine Catalysts:



R	R'	endo : exo	ee (%)	yield (%)
H	H	>50 : 1	91	92
H	CH_3	96 : 4	94	88
CH_2OBn	H	–	95	94

Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5493-5495.

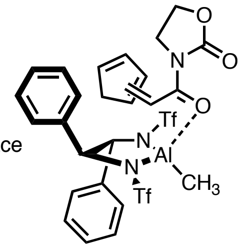
- A modified catalyst expanded the scope of this system to include maleimide dienophiles:



98%, 93% ee

Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089-12090.

- Both antipodes of the 1,2-diaryl-1,2-diaminoethane ligands are available, via resolution employing tartaric acid: Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3-6.
- Proposed transition-state assembly:

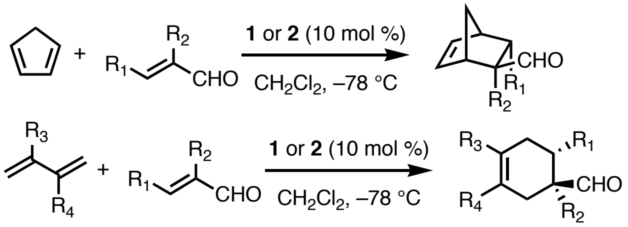


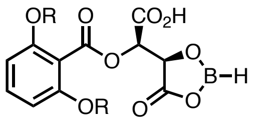
- Non-chelated binding mode
- *s-trans* dienophile conformer
- Phenyl blocks front face

- This model is supported by ^1H, ^{13}C, and ^1H NOE data for the 1 : 1 dienophile : catalyst complex, as well as X-ray diffraction analysis of the catalyst dimer.

Corey, E. J.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 7938-7939.

Chiral (Acyloxy)borane (CAB):





1 R = Me
2 R = *i*-Pr

catalyst	R_1	R_2	R_3	R_4	endo : exo	ee (%)	yield (%)
1	H	H	–	–	88 : 12	84	90
1	H	H	CH_3	CH_3	–	84	53
1	H	CH_3	–	–	11 : 89	96	85
1	H	CH_3	CH_3	CH_3	–	97	61
1	H	CH_3	CH_3	H	–	91	65
1	CH_3	CH_3	–	–	3 : 97	90	91
2	H	Br	–	–	6 : 94	95	100
2	H	Br	CH_3	CH_3	–	95	80
2	CH_3	Br	–	–	>99 : 1	98	100

- α-substituted α,β-unsaturated aldehyde dienophiles give optimal selectivities.
- Both enantiomers of the CAB catalyst are available, from (+) and (–)-tartaric acid.

Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1483-1484.
Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917-6919.

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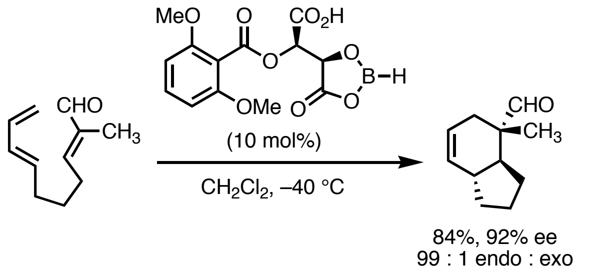
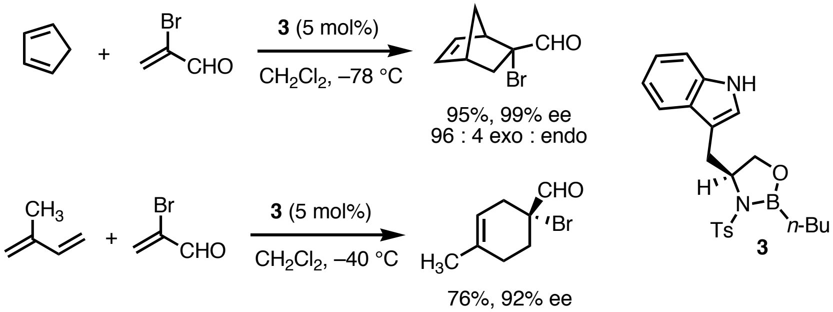
- Yamamoto's CAB catalyst has been applied to intramolecular reactions:



Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231-7232.

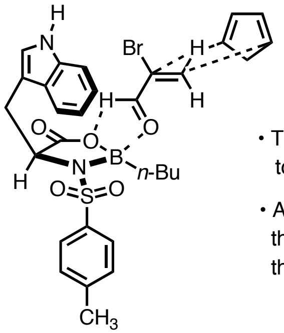
Oxazaborolidine Catalysts:



- α-substitution on the aldehyde component is required for high enantioselectivity.
- The tryptophan-derived ligand was efficiently recovered.

Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966-8967.

- Physical and chemical studies of this system led to the following transition-state model:



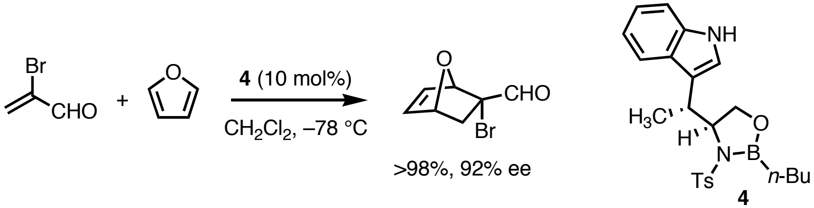
- The complex of the *s-cis* conformer is proposed to be the reactive species.
- Attractive π-stacking interactions between the indole and the dienophile organize the TS, and result in reaction from the unblocked (back) face.

Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290-8292.

- Lewis acids complex aldehydes *syn* with respect to the formyl proton – for a review on the conformations of carbonyl-Lewis acid complexes, see: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256-272.

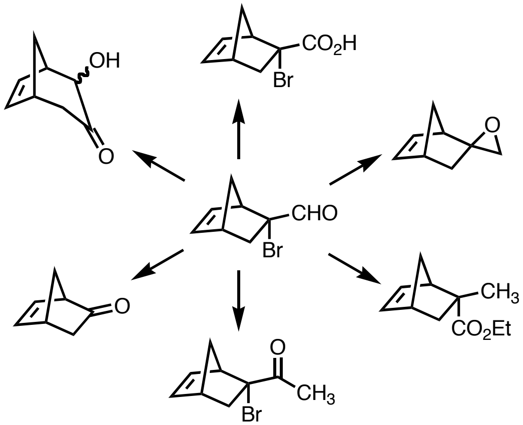
- Formyl CH--O hydrogen bonding is proposed as an additional organizational element leading to the excellent enantioselectivities observed. For the application of the formyl CH--O hydrogen bond postulate to the understanding of enantioselective reactions involving chiral boron Lewis acids and aldehydes, see: Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37-40.

- A modified oxazaborolidine catalyzes cycloadditions to furan:



Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979-3982.

- Corey has demonstrated the synthetic versatility of the 2-bromoacrolein/cyclopentadiene cycloaddition adducts:



Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966-8967.

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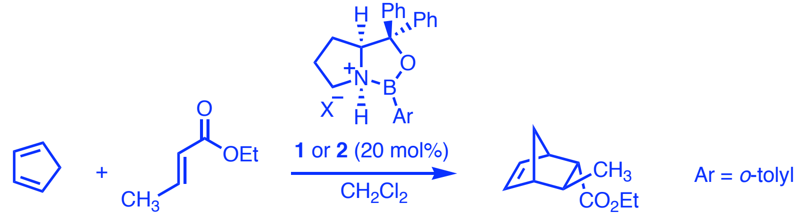
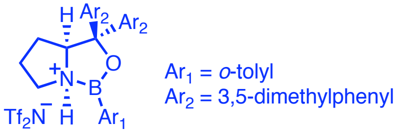
Cationic Oxazaborolidine Catalysts:

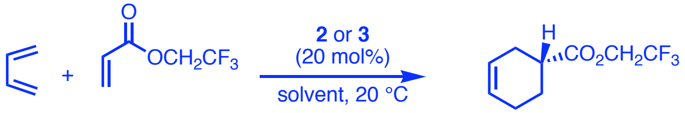


catalyst	X	temp (°C)	time (h)	yield (%)	endo:exo	ee (%, endo)
1	OTf	4	72	46	91:9	>98
2	NTf_2	20	16	94	89:11	97

- The neutral oxazaborolidine catalyst does not exhibit catalytic activity in the Diels-Alder reaction of cyclopentadiene with methacrolein.
- Early experiments were conducted with catalyst **1**; it was subsequently shown that the triflimide-activated catalyst **2** exhibits greater thermal stability and higher catalytic activity.
- When using less reative dienes, the related 3,5-dimethylphenyl catalyst **3** is often superior to **2**.



3

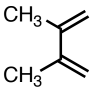
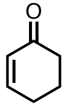
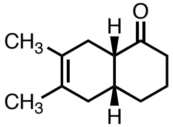
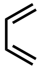
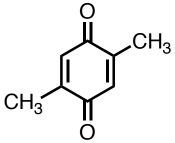
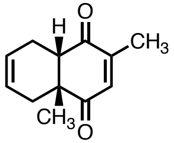
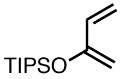
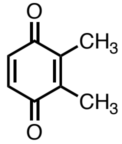
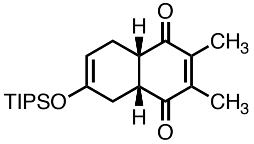
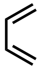
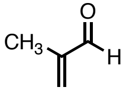
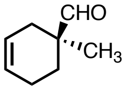
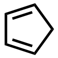
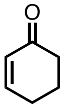
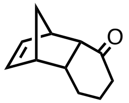


catalyst	solvent	time (h)	yield (%)	ee (%)
2	toluene	40	78	88
3	neat	24	96	95

Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.
Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.
Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

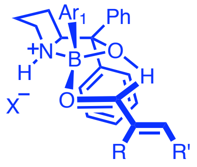
- A useful set of predictive selection rules has been developed for the oxazaborolidinium-mediated Diels-Alder reaction of substituted quinones:
  Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800.

- Catalysts **1**, **2**, and **3** exhibit broad substrate scope and predictable selectivities. Enantioselectivities are typically >90%; *endo:exo* ratios are uniformally high (4:1→>99:1).

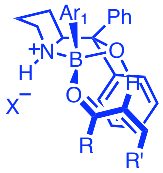
catalyst^a	diene	dienophile	product	time (h), temp (°C)	yield, ee (%)
2 **3**				16, 20 24, 4	99, 64 99, 77
2				48, –78	97, 91
2				2, –95	98, >99
1				24, –78	85, 94
1				16, –20	97, 93^b

^{a} 20 mol% catalyst. ^{b}*endo:exo* = 91:9.

- Corey has proposed the following pre-transition-state complexes:



enals

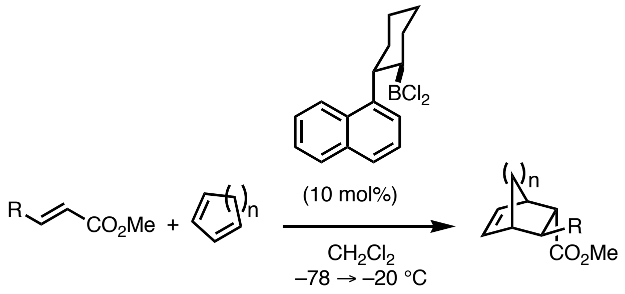


quinones, enones, and α,β-unsaturated esters

- The phenyl [or 3,5-dimethylphenyl in the case of **3** (not shown)] substituent is proposed to engage in π-stacking with the dienophile.
- The diene approaches the catalyst–dienophile complex from the face opposite the phenyl substituent.
- The existence of an O—HC interaction is supported by studies of enal-, and enone-BF_3 complexes.
- Note the sense of stereoinduction for enals is opposite that of quinones, enones, and α,β-unsaturated esters.

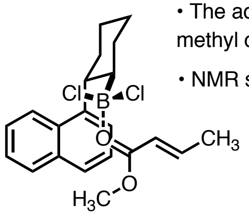
Seth B. Herzon

Alkyldichloroboranes:



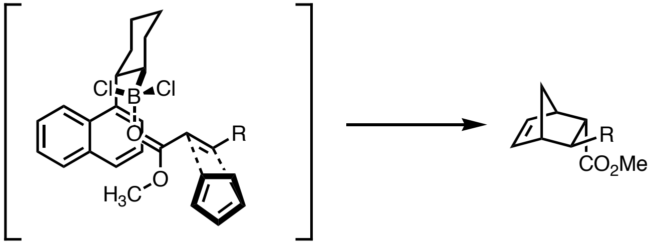
R	n	ee (%)	yield (%)
H	1	97	97
CH_3	1	93	91
CO_2Me	1	90	92
H	2	86	83

- The catalyst was prepared by resolution with (–)-menthone.



- The adjacent figure illustrates the approximate conformation of the catalyst•methyl crotonate complex (X-ray).
- NMR studies suggest this conformation is retained in solution.
  - The *s-trans* crotonate conformer is observed.
  - The carbonyl is positioned over and parallel to the naphthylene, within van der Waals contact (3.2 Å) (π-stacking interaction).
  - Complexation of Lewis acids *anti* to ester C–O bonds appears to be a general phenomenon.

- The absolute stereochemical configuration of the products is consistent with a transition-state model closely related to the observed ground state complex:

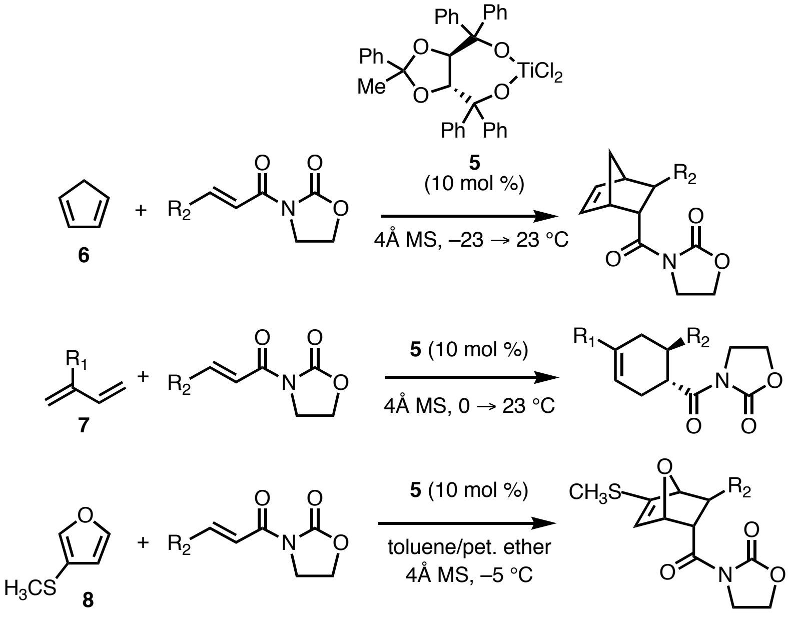


- The naphthalene substituent forces the dienophile to approach from the front face.

Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794-7795.

Titanium-TADDOL:

- Narasaka's Ti complex catalyzes a wide variety of Diels-Alder reactions with high selectivities:



Diene	R_1	R_2	endo : exo	ee (%)	yield (%)	reference
6	–	H	n.d.	88	81	2
6	–	CH_3	87 : 13	94	91	1
6	–	Ph	92 : 8	80	76	1
7	H	H	–	93	81	2
7	H	CO_2Me	–	91	84	1
7	CH_3	H	–	>96	93	2
7	CH_3	CO_2Me	–	94	94	1
8	–	H	85 :15	87	97	3
8	–	CO_2Me	78 : 22	86	99	3

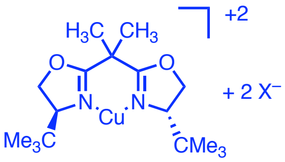
1. Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340-5345.
2. Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387-391.
3. Narasaka, K.; Yamamoto, I. *Chem. Lett.* **1995**, 1129-1130.

- A number of transition-state models have been proposed; the analysis is complicated by the number of coordination possibilities available in octahedral complexes.

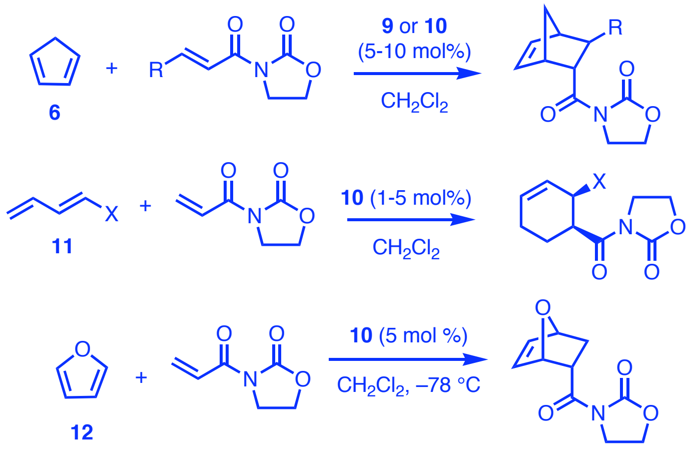
Kent Barbay

Bis(oxazoline) Copper Complexes:

- Evan's copper (II) catalysts have been successfully applied to a wide array of cycloaddition substrates:



9 X = OTf
10 X = SbF_6

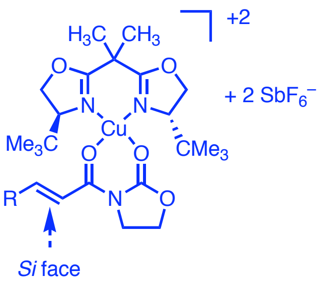


Catalyst	Diene	X	R	endo : exo	ee (%)	yield (%)
9	**6**	–	H	98 : 2	>98	86
9	**6**	–	CO_2Et	94 : 6	95	92
9	**6**	–	CH_3	96 : 4	97	85
10	**6**	–	Ph	91 : 9	96	96
10	**6**	–	Cl	86 : 14	95	96
10	**11**	OAc	–	85 : 15	96	75
10	**11**	SPh	–	98 : 2	98	84
10	**11**	NHCbz	–	72 : 28	90	54
10	**12**	–	–	80 : 20	97	97

- Catalyst **10** (X = SbF_6) uniformly provides higher reactivity and higher levels of asymmetric induction than **9** (X = OTf), which was reported earlier.

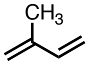
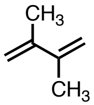
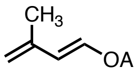
Evans. D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798-800.

- The stereochemical results are in all cases consistent with the following model:



- Square planar geometry about Cu
- Imide binds in a bidentate fashion
- *s-cis* dienophile configuration
- diene approaches from the back face; the front face is blocked by the *t*-Bu group

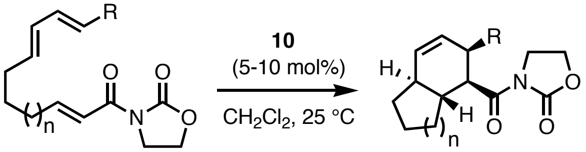
- Acyclic dienes unsubstituted at the 1-position afforded lower enantioselectivities:

Catalyst	Diene	endo : exo	ee (%)	yield (%)
10		–	59	81
10		–	65	78
10		27 : 73	98	57[a]

a. Isolated yield of enantiomerically and diastereomerically pure material.

- These dienes are proposed to approach via an exo transition state. The exo transition state is apparently only selective in the case of 1-substituted dienes.

- Catalyst **10** is also effective for intramolecular Diels-Alder reactions:

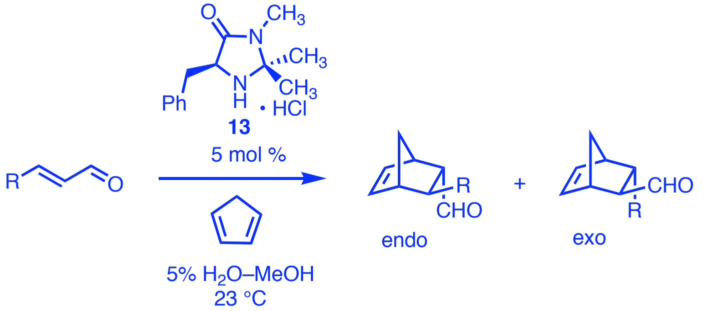


R	n	endo : exo	ee (%)	yield (%)
H	1	>99 : 1	86	89
Ph	1	>95 : 5	92	86
Ph	2	84 : 16	97	97

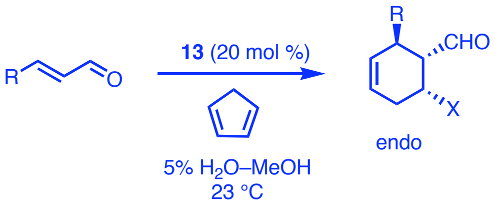
Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460-6461.
Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559-7573.
Evans, D. A.; Barnes, D. M.; Johnson, J.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582-7594.

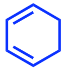
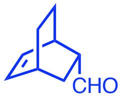
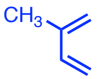
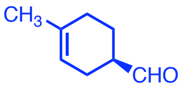
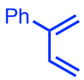
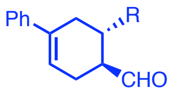
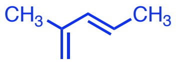
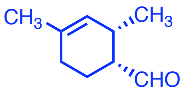
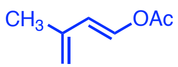
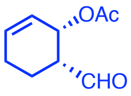
Kent Barbay

Asymmetric Catalysis of the Diels-Alder Reaction with a Chiral Amine through Reversible Iminium Ion Formation:

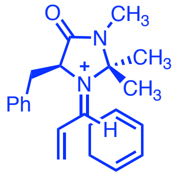


R	yield	exo : endo	exo ee (%)	endo ee (%)
Me	75	1 : 1	86	90
n-Pr	92	1 : 1	86	90
i-Pr	81	1 : 1	84	93
Ph	99	1.3 : 1	93	93
Furyl	89	1 : 1	91	93



diene	R	product	yield	endo : exo	ee (%)
	H		82	14 : 1	94
	H		84	–	89
	H		90	–	83
	CH_3		75	–	90
	H		75	5 : 1	90
	H		72	11 : 1	85

- Stereochemical model:

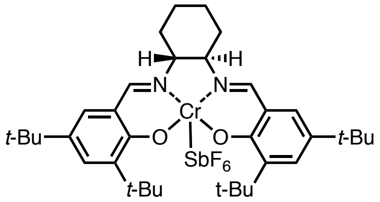


- Selective formation of the (illustrated) (*E*)-iminium isomer is proposed, avoiding unfavorable interactions between the substrate olefin and the geminal dimethyl substituents.
- The benzyl substituent shields the β-face of the dienophile.

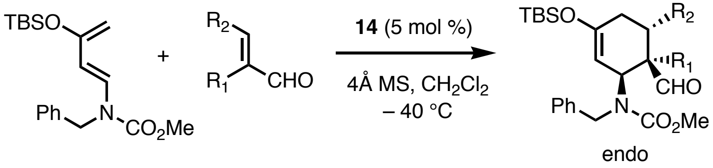
Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

Jacobsen's Catalyst:

- Jacobsen's Cr (III) salen complex **14** catalyzes highly enantioselective Diels-Alder reactions of 1-amino-3-silyloxydienes and acroleins:



14



R_1	R_2	yield	ee (%)
Me	H	93	97
Et	H	91	97
i-Pr	H	92	>97
TBSO$(CH_2)_2$	H	93	95
TBSO	H	86	>97
–$(CH_2)_3$–		76	96

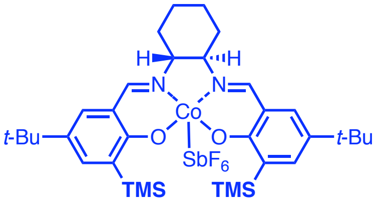
- No exo products were observed in these cycloadditions.

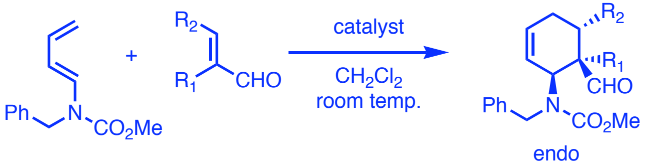
Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843–7844.

Kent Barbay

- X-ray analysis of the (1*R*, 2*R*)-salen–Co(III)-SbF_6•2PhCHO complex suggested that replacing the *t*-butyl groups with bulkier trimethylsilyl substituents might create a steric interaction (between the trimethylsilyl groups) that would twist the aromatic rings out of plane.

- This modification has resulted in an exceptionally selective and active Diels-Alder catalyst:





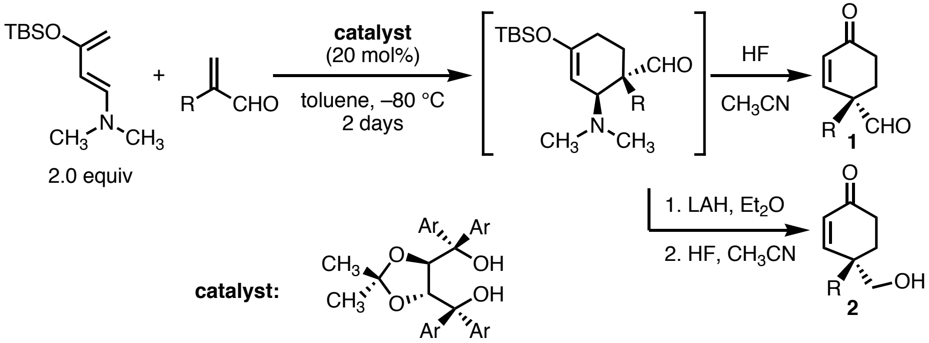
entry	R_1	R_2	mol % cat.	time (h)	yield	ee (%)
1	CH_3	H	4	1	98	98
2	CH_3	H	0.05	72	93	98
3	CH_2CH_3	H	0.1	30	93	>97
4	$TBSO(CH_2)_2$	H	0.5	18	100	>97
5[a]	H	H	0.1	18	100	85
6[b]	H	H	2	40	90	>97
7	$–(CH_2)_4–$		2	72	78	>95

[a] Reaction performed at 0 °C. [b] Reaction performed at –78 °C.

- Entry 2 represents the lowest substrate/catalyst ratio (s:c = 2000) reported for an asymmetric Diels-Alder reaction.

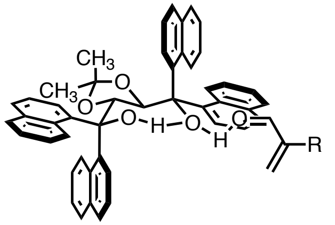
Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950.

Catalysis via Hydrogen Bonding



entry	R	% yield **1**	% yield **2**	% ee of **2**
1	H	—	77	73
2	CH_3	85	82	91
3	CH_2CH_3	80	83	88
4	*i*-Pr	77	81	92
5	Bn	84	82	89
6	CH_2CH_2OTBS	80	80	86

•The following stereochemical model has been proposed:

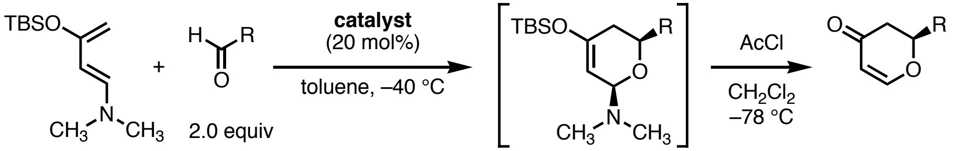


- The diene approaches from the face opposite the napthyl group.

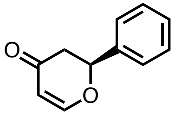
Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846.

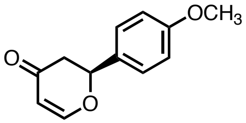
Catalytic, Asymmetric Hetero Diels-Alder Reactions:

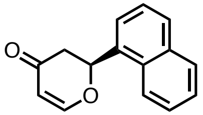
The same TADDOL derivative catalyzes hetero Diels-Alder reactions:

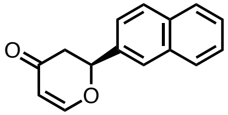


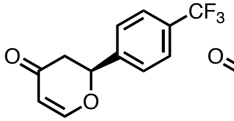
- Products:

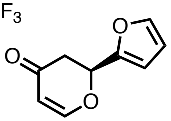

70%, >98% ee

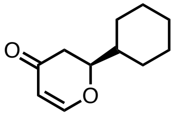

68%, 94% ee

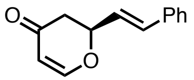

69%, >98% ee


97%, 94% ee


68%, 94% ee


67%, 92% ee


64%, 86% ee


52%, >94% ee

Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature*, **2003**, *424*, 146.

- A 2nd-generation catalyst was developed, expanding the substrate scope. See: Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

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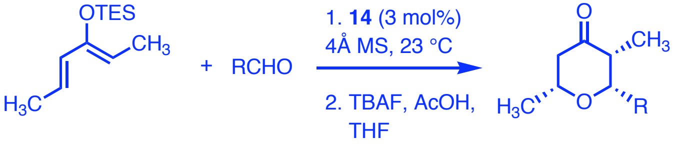
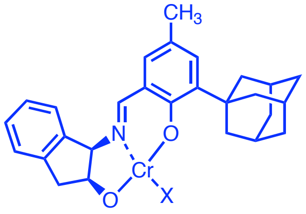


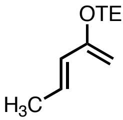
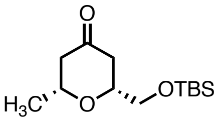
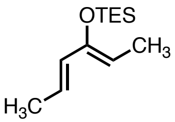
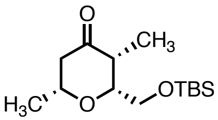
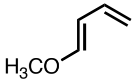
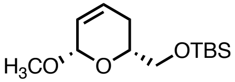
R	ee (%)	yield (%)
Ph	90	72
CH$_2$OTBS	>99	97
CH$_2$OBn	94	94
n-C$_5$H$_{11}$	98	85
(CH$_2$)$_4$CH=CH$_2$	98	78
CH$_2$CH$_2$Ph	98	78
2-furyl	95	77



14 X = SbF$_6$
15 X = Cl

- The diastereoselectivity was >95% in all cases, favoring the illustrated endo product.
- Use of acetone as solvent in the cycloaddition generally improves enantioselectivities, and is critical in the case of aromatic aldehydes.
- Both enantiomers of the aminoindanol ligand are commercially available.

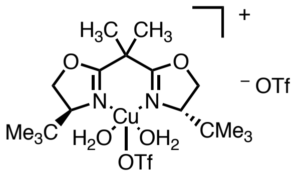
- Excellent enantioselectivities were maintained with several other dienes in reactions catalyzed by **15**:

Diene	Product	ee (%)	yield (%)
		98	78
		91	50
		>99	91

- This is the first effective method for the asymmetric HDA reaction between dienes with less than two oxygen substituents and unactivated carbonyl compounds.

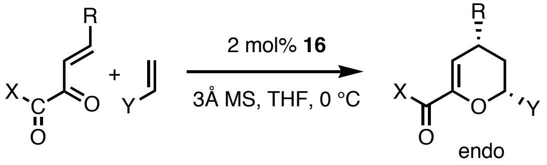
Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2398-2400.

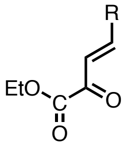
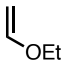
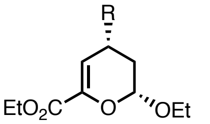
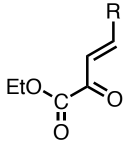
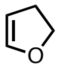
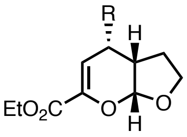
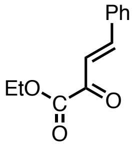
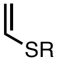
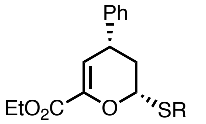
Inverse Electron Demand Hetero Diels-Alder Reactions catalyzed by Bis(oxazoline) Copper(II) Complexes:



16

- air-stable, solid catalyst



hetero diene	hetero dienophile	product	endo : exo	yield (%)	ee (%)
					
		R = Me	24 : 1	87	97
		R = Ph	> 20 : 1	93	97
		R = *i*-Pr	22 : 1	95	96
		R = OMe	59 : 1	90	98
					
		R = Ph	16 : 1	96	97
		R = *i*-Pr	16 : 1	94	95
					
		R = Et	> 20 : 1	94	97
		R = Ph	> 20 : 1	91	99

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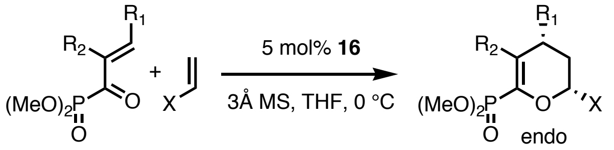
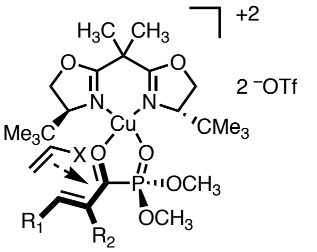


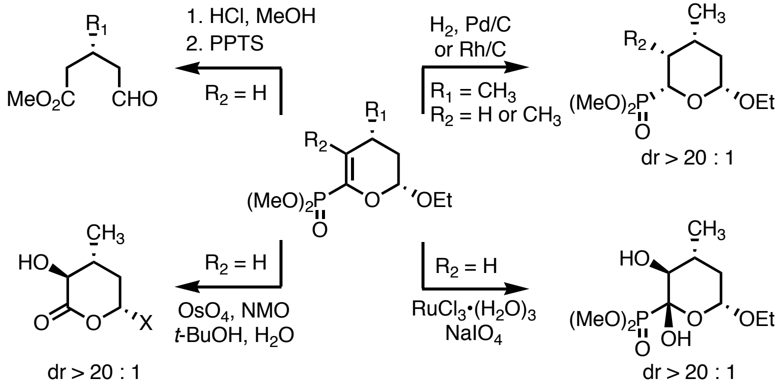
R$_1$	R$_2$	X	yield (%)	endo : exo	ee (%)
Me	H	OEt	84	36 : 1	93
Ph	H	OEt	95	22 : 1	97
i-Pr	H	OEt	92	22 : 1	95
OEt	H	OEt	92	44 : 1	97
Me	Me	OEt	98	25 : 1	≥90
Me	H	SEt	75	16 : 1	96

- The hetero Diels-Alder reactions catalyzed by **16** display a favorable temperature-enantioselectivity profile, affording dihydropyrans with high enantioselectivities even at 0 °C.
- Stereochemical Model:



- square planar transition structure
- heterodiene binds in a chelated fashion
- attack of heterodienophile occurs from the less hindered α-face

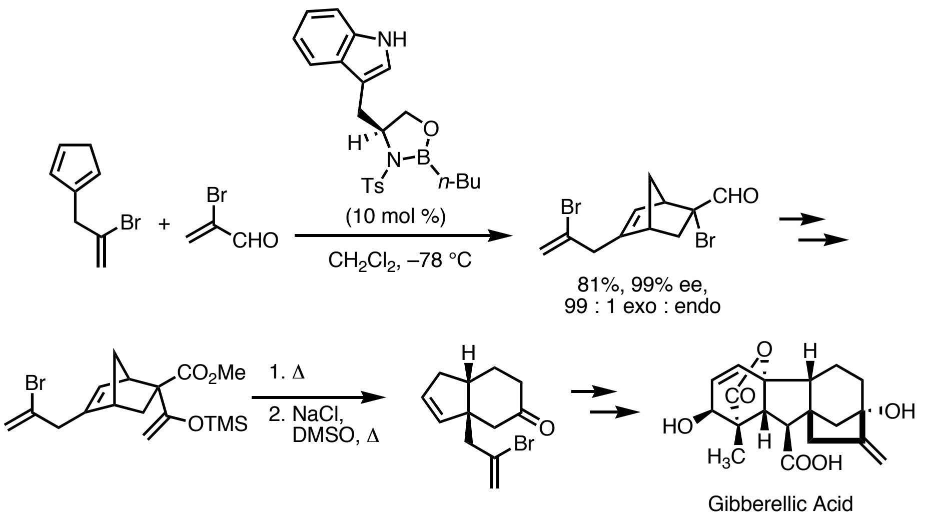
- The product dihydropyrans are synthetically versatile:



Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

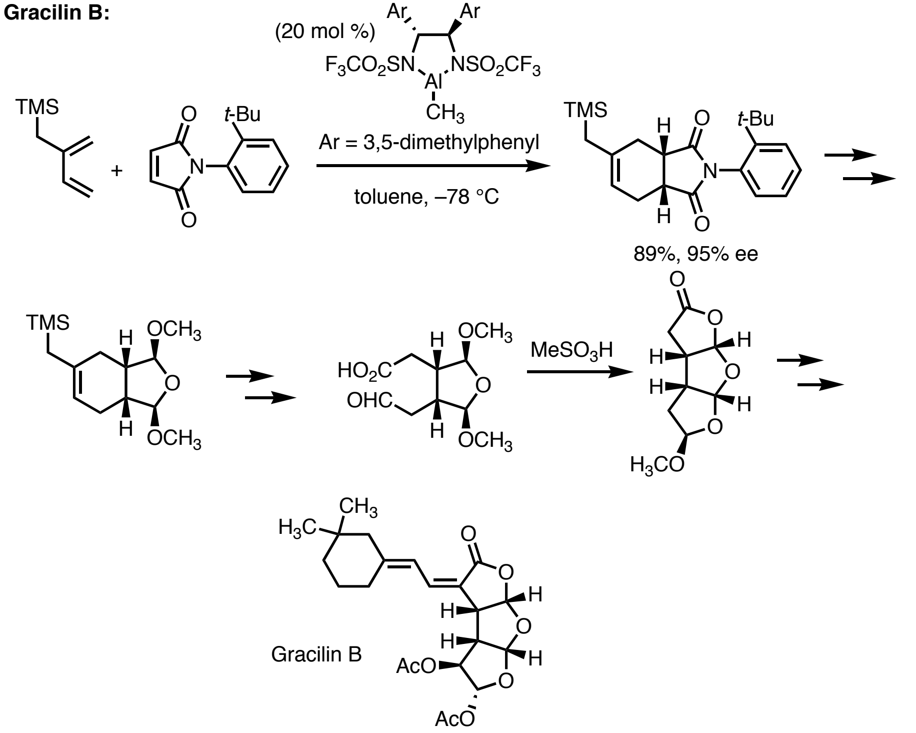
Catalytic, Asymmetric Diels-Alder Reactions – Applications in Synthesis:

Gibberellic Acid:



Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611-3612.

Gracilin B:



Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616-9617.

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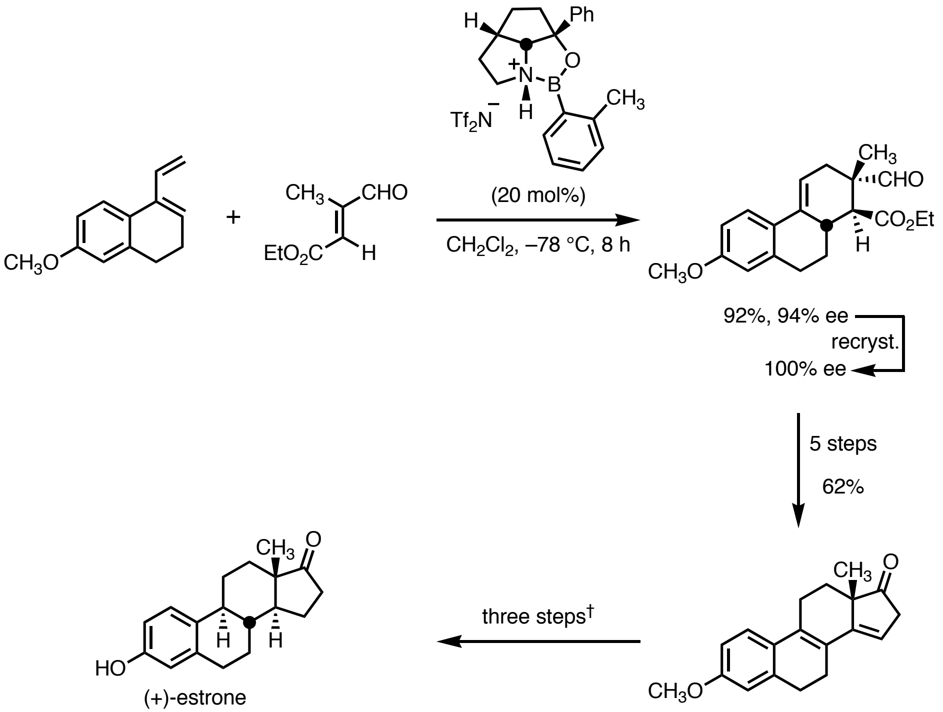
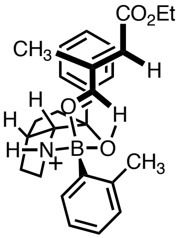
Estrone



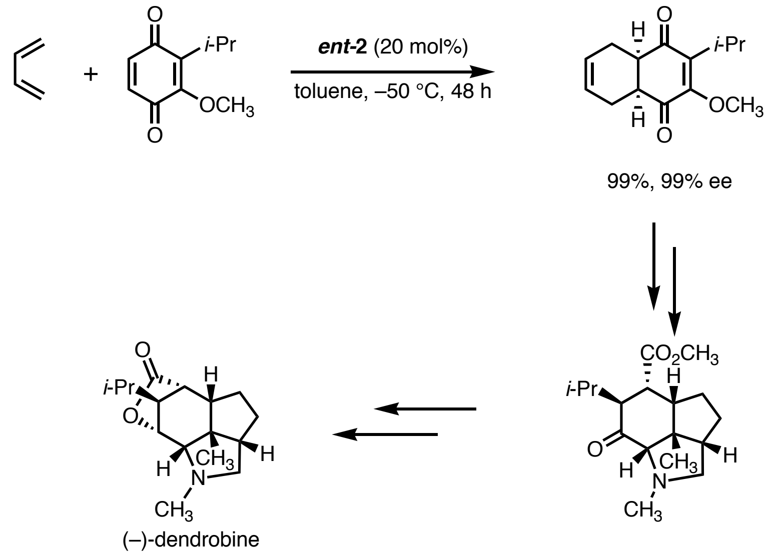
Hu, Q.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004,** *126*, 5984.

† (a). Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *4*, 1553.
(b) Quinkert, G.; Grosso, M. D.; Dõring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, *78*, 1345.

- Both enantiomers of the catalyst are accessible.
- The following pre-transition-state assembly was suggested:

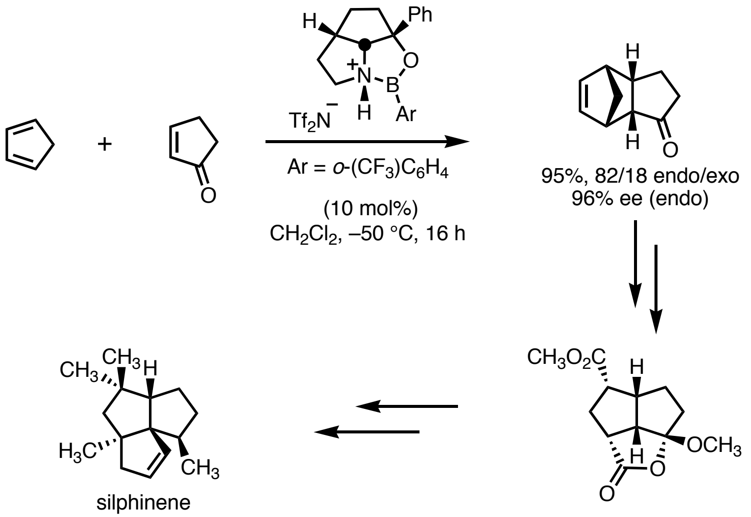


The application of the oxazaborolidinium catalysts to once racemic syntheses has been demonstrated:



racemic synthesis: Kende, A. S.; Bentley, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 4332.

Hu, Q.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 12708.



racemic synthesis: Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83.

Hu, Q.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 12708.

Seth B. Herzon

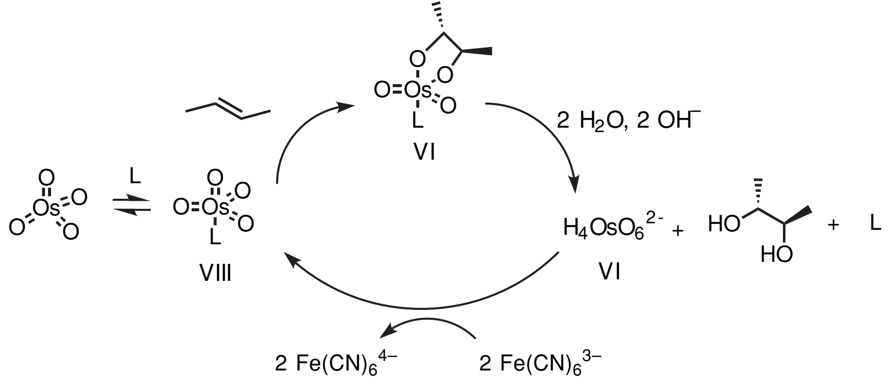
Sharpless Asymmetric Dihydroxylation Reaction

Review:

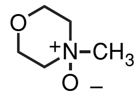
Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

Ligands such as pyridine accelerate the osmylation of olefins (Criegee, R.; Marchand, B.; Wannowius, H. *Liebigs Ann. Chem.* **1942**, *550*, 99-133.)

Catalytic Cycle:



Turnover is achieved by re-oxidation with stoichiometric oxidants:



UpJohn Process: VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973-1976.

$K_3Fe(CN)_6$ Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766-768.

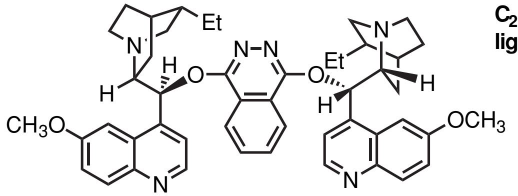
In the original Sharpless procedure, using NMO, reoxidation was believed to compete with hydrolysis, leading to a competing 2nd-cycle oxidation that was less enantioselective:

Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965-3968.

Balance of evidence appears to favor 3 + 2 Mechanism (vs. 2 + 2 pathway).

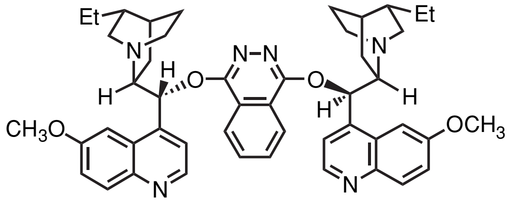
See, e.g., Corey, E.J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1996**, *37*, 4899-4902.

DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907-9908.



(DHQD)$_2$-PHAL
Ligand for AD-mix-β

C$_2$-symmetric, pseudo-enantiomeric ligands:



(DHQ)$_2$-PHAL
Ligand for AD-mix-α,
(slightly less
enantioselective)

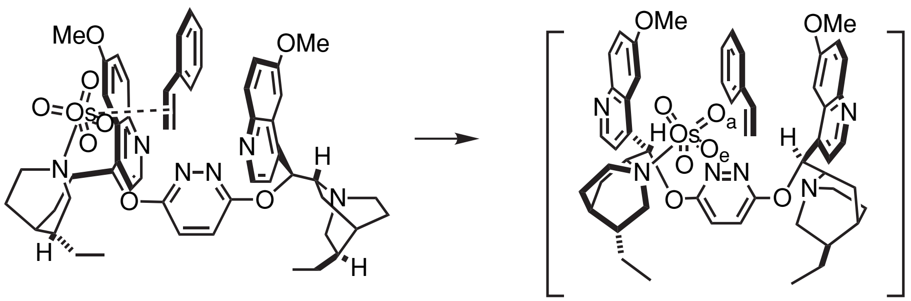
AD-mix reagents are commercially available:

1.4 g AD-mix-β will oxidize 1 mmol olefin, contains:
0.98 g $K_3Fe(CN)_6$ (3 mmol)
0.41 g K_2CO_3 (3 mmol)
0.0078 g (DHQD)$_2$-PHAL (0.01 mmol)
0.00074 g $K_2OsO_2(OH)_4$ (0.002 mmol)

Conditions: *t*-BuOH, H$_2$O (1:1), 0 °C, 6-24 h

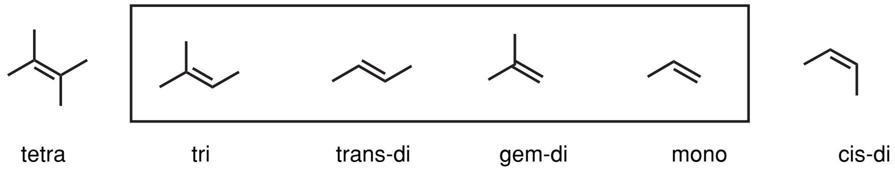
Sharpless, K. B., et al. *J. Org. Chem.* **1992**, *57*, 2768-2771.

Corey proposes a U-shaped binding pocket:

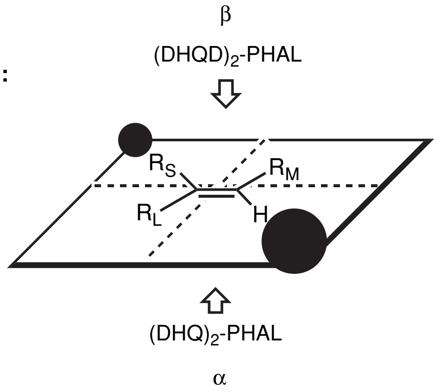


Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481-3484.

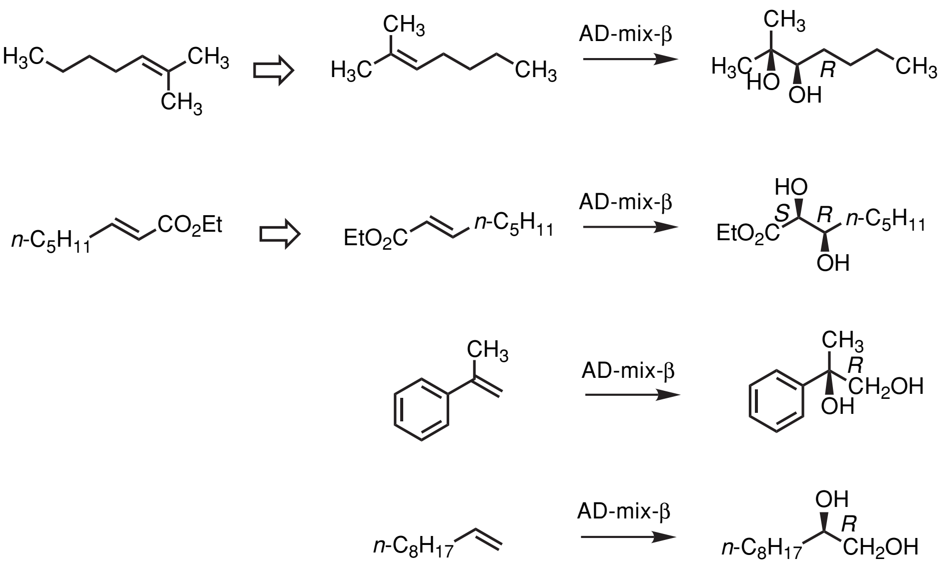
4 of 6 Olefin substitution classes are successfully dihydroxylated:

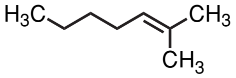
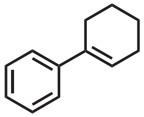
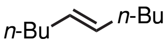
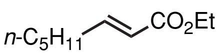
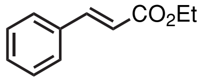
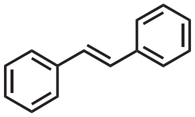
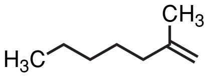
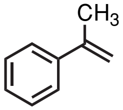
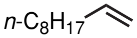
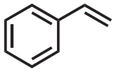


Mnemonic:



Application of Mnemonic:



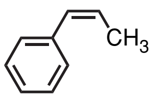
	AD-mix-β [(DHQD)$_2$-PHAL] % ee, config.	AD-mix-α [(DHQ)$_2$-PHAL] % ee, config.
 *	98, *R*	95, *S*
 *	99, *R,R*	97, *S, S*
 *	97, *R,R*	93, *S, S*
 *	99, 2*S*, 3*R*	96, 2*R*, 3*S*
 *	97, 2*S*, 3*R*	95, 2*R*, 3*S*
 *	>99.5, *R,R*	>99.5, *S,S*
	78, *R*	76, *S*
	94, *R*	93, *S*
	84, *R*	80, *S*
	97, *R*	97, *S*

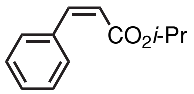
* addition of $CH_3SO_2NH_2$ leads to faster reaction

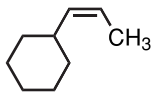
from: Sharpless, K. B., et al. *J. Org. Chem.* **1992**, *57*, 2768-2771.

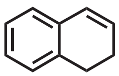
Cis-Disubstituted Olefins are generally poor substrates. With a modified catalyst, DHQD-IND, fair to good enantioselectivities can be obtained:

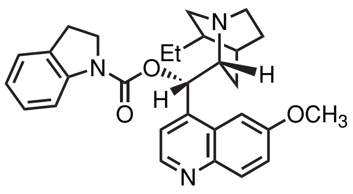
ee at 0 °C


72 (1*R*, 2*S*)


80, (2*S*, 3*R*)

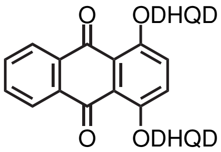

56, (1*R*, 2*S*), 44% ee of enantiomer with DHQ-IND

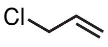

16, (1*R*, 2*S*)

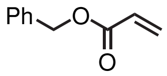

DHQD-IND

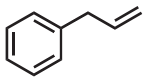
Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568-7570.

(DHQD)$_2$AQN is often a superior ligand:


(DHQD)$_2$AQN

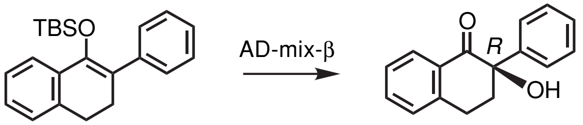

90% ee vs. 63% ee, (DHQD)$_2$PHAL


88% ee vs. 77% ee, (DHQD)$_2$PHAL


78% ee vs. 44% ee, (DHQD)$_2$PHAL

Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448-451.

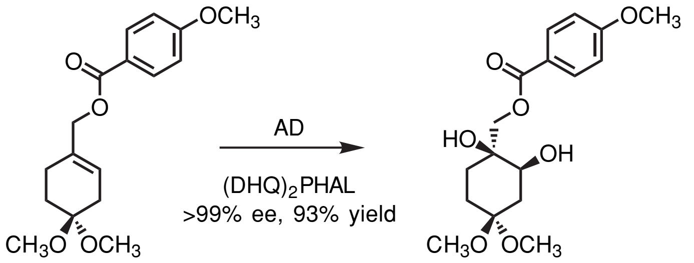
a few tetra-substituted olefins work well, see:
Sharpless, K. B., et al. *J. Am. Chem. Soc.* **1993**, *115,* 8463-8464.



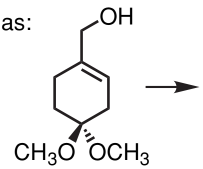
93% ee, 94% yield

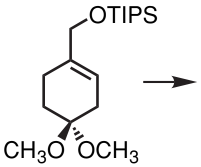
a best case, ee's and yields are not yet generally high

Allylic 4-methoxybenzoates are particularly good substrates:

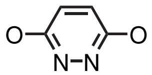


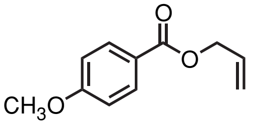
whereas:

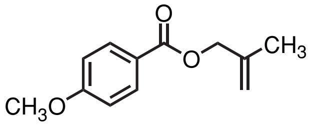

18% ee

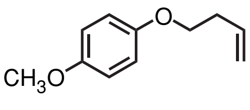

13% ee

AD, (DHQD)$_2$PYDZ

PYDZ = 

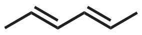
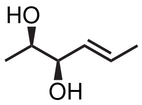
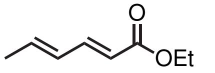
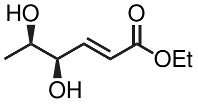
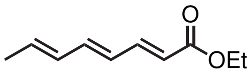
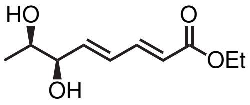
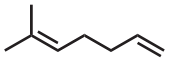
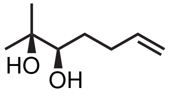
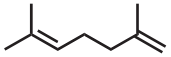
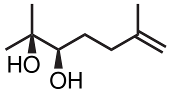

>99% yield, 98% ee


98% yield, 97% ee


96% yield, 91%ee

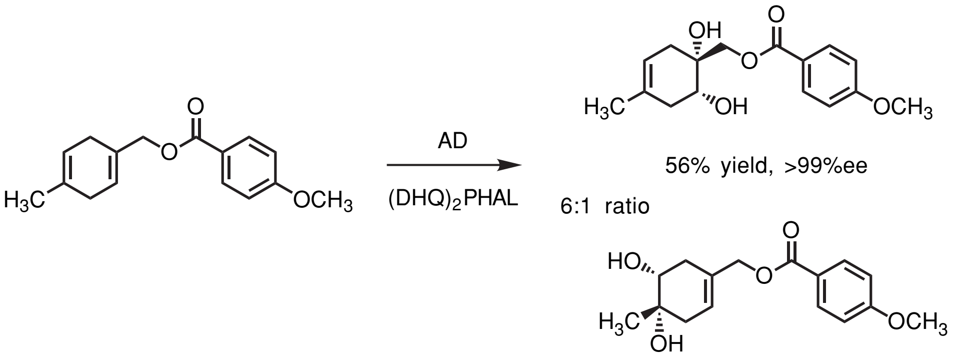
Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805-10816.

Regioselectivity of AD with Diene Substrates (($(DHQD)_2$-PHAL as Ligand):

Substrate	Product	% yield, % ee
		78, 93
		78, 92
		93, 95
		73, 98
		70, 98

in general, AD is selective for more electron-rich double bond

Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.



56% yield, >99%ee

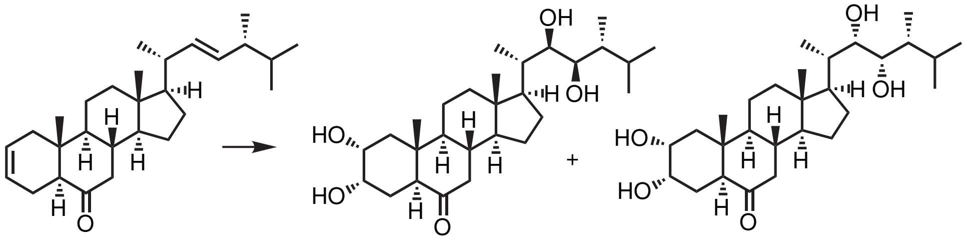
6:1 ratio

with OsO_4, NMO ratio is ≤1:10

10% yield, 96%ee

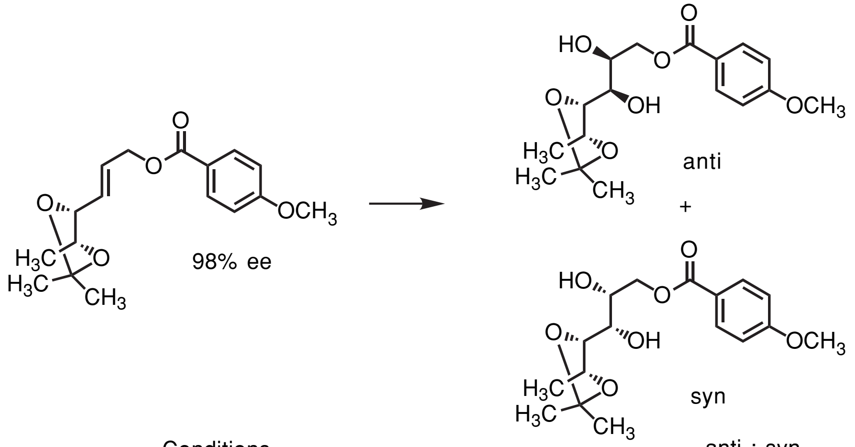
Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805-10816.

Use of AD with Chiral Olefins:



OsO_4 alone	1 : 1.6
$(DHQD)_2$-PHAL	10 : 1

Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547, and refs. therein.



Conditions		anti : syn
OsO_4, NMO	88% yield (mixture)	1.9 : 1
$(DHQ)_2PHAL$ (matched)	86% yield (anti)	54 : 1
$(DHQD)_2PYDZ$ (mismatched)	86% yield (syn)	1 : 35

Guzman-Perez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *38*, 5941-5944.

Sharpless Asymmetric Epoxidation Reaction

Reviews:

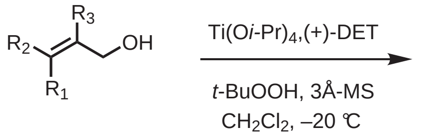
Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1-300.

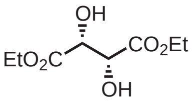
Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, pp. 103-158.

Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 7*, pp. 389-436.

Pfenninger, A. *Synthesis* **1986**, 89-116.

Asymmetric Epoxidation of Allylic Alcohols:



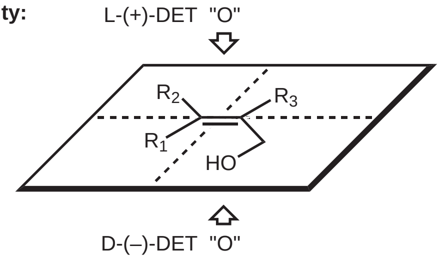
(+)-DET = 

$EtO_2C\text{–}CH(OH)\text{–}CH(OH)\text{–}CO_2Et$

- 5-10 mol% catalyst in the presence of 3 or 4 Å-MS.
- 10-20 mol% excess tartarate vs. Ti(O*i*Pr)$_4$ required.
- (+)- and (–)-DET are readily available and inexpensive.
- (+)- and (–)-DIPT, diisopropyl tartarate, are also available and sometimes lead to higher selectivity.

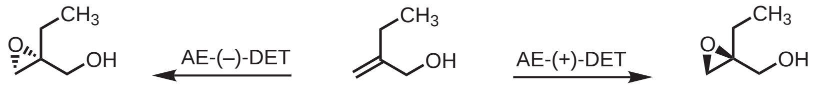
Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

Mnemonic for selectivity:



Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

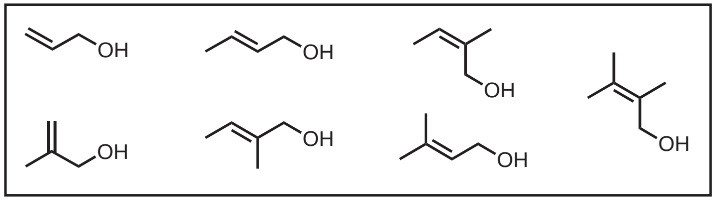
Application of Mnemonic:

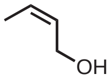


97%, 86% ee

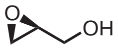
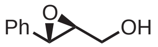
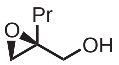
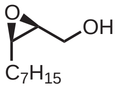
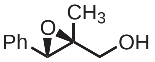
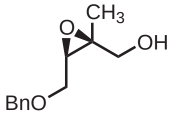
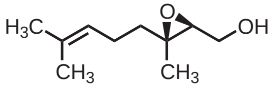
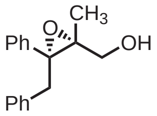
97%, 86% ee

Substitution patterns:



- *Z*-disubstituted olefins are least reactive and selective. 

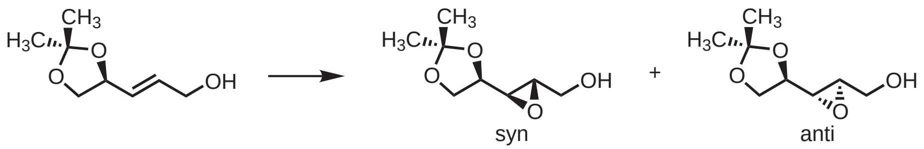
Examples of Sharpless Epoxidation:

product	Ti(%)	tartarate (%)	℃	h	yield (%)	ee (%)
	5	(+)-DIPT (6.0)	0	2	65	90
	5	(+)-DIPT (7.5)	–20	3	89	>98
	4.7	(+)-DET (5.9)	–12	11	88	95
	10	(+)-DET (14)	–10	29	74	86
	5	(+)-DIPT (7.5)	–35	2	79	>98
	100	(+)-DET (142)	–20	14	80	80
	5	(+)-DET (7.4)	–20	0.75	95	91
	120	(–)-DET (150)	–20	5	90	94

From: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780 and Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**; pp. 103-158.

M. Movassaghi

Chiral Substrate:



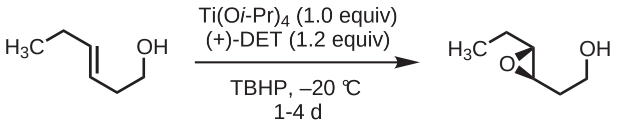
Reagent	Ratio (syn : anti)	
m-CPBA	1 : 1.4	
VO(acac)$_2$-TBHP	1 : 1.8	
Ti(O*i*Pr)$_4$-TBHP	1 : 2.3	
Ti(O*i*Pr)$_4$-(–)-DIPT-TBHP	1 : 90	MATCHED
Ti(O*i*Pr)$_4$-(+)-DIPT-TBHP	22 : 1	MISMATCHED

- Products are diastereomeric.
- Sense of induction is dominated by the catalyst.
- The C4 center reinforces and erodes this in "MATCHED" and "MISMATCHED" cases, respectively, as shown.

Ko, S. Y.; Lee, A. W. M.; Masamune, S; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245-264.

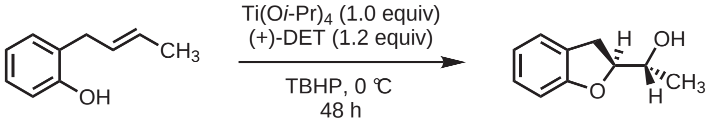
Homoallylic, bishomoallylic and trishomoallylic:

- Rates of epoxidation are usually slower.
- Enantiofacial selectivity of the catalyst is reversed for all three.
- Enantiofacial selectivity is generally lower.



50%, 41% ee

Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707-3711.

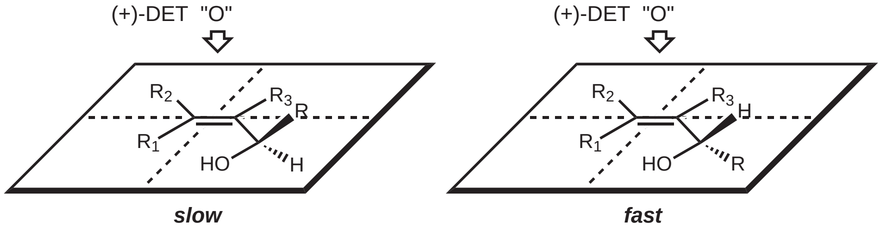


22%, 29% ee

Hosokawa, T.; Kono, T.; Shinohara, T.; Murahashi, S.-I. *J. Organometal. Chem.* **1989**, *370*, C13-C16.
For other examples see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, pp. 103-158 and Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1-300.

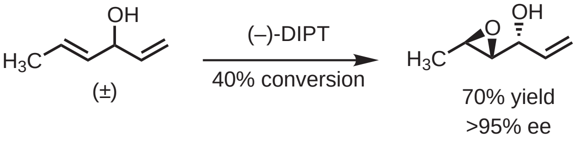
Kinetic Resolution:

- Products are diastereomeric.
- Using the Sharpless mnemonic, contact between the C1 substituent (R) and the catalyst predicts slow reacting isomer.



$k_{rel} = k_{fast}/k_{slow}$

- With the exception of *Z*-disubstituted allylic alcohols, k_{rel} > 25.
- When k_{rel} = 25, the ee of unreacted alcohol is essentially 100% at 60% conversion.
- Allylic tertiary alcohols are not successfuly epoxidized under Sharpless conditions.
- Factors may combine for high selectivity:

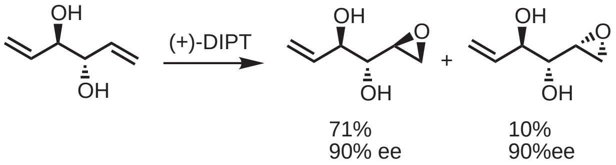


- Disubstituted olefin is more reactive than monosubstituted olefin (k_{rel} ~100).
- k_{fast}/k_{slow} for chiral *E*-propenylcarbinols is ~100.

Excercise: Apply the Sharpless mnemonic to predict the stereochemistry of this product.

Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem*. **1983**, *55*, 589.

- Allylic 1,2-diols do not follow the Sharpless mnemonic:



Excercise: What isomer would you have predicted using the Sharpless mnemonic?

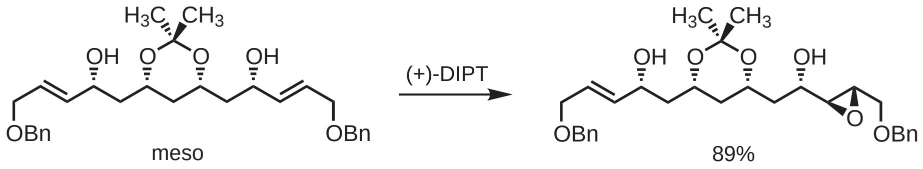
Takano, S.; Iwabuchi, Y.; Ogasawara *J. Am. Chem. Soc.* **1991**, *113*, 2786-2787.

M. Movassaghi

C2-Symmetric Substrates:

- Any minor diastereomer that is produced is rapidly removed by bis-epoxidation.

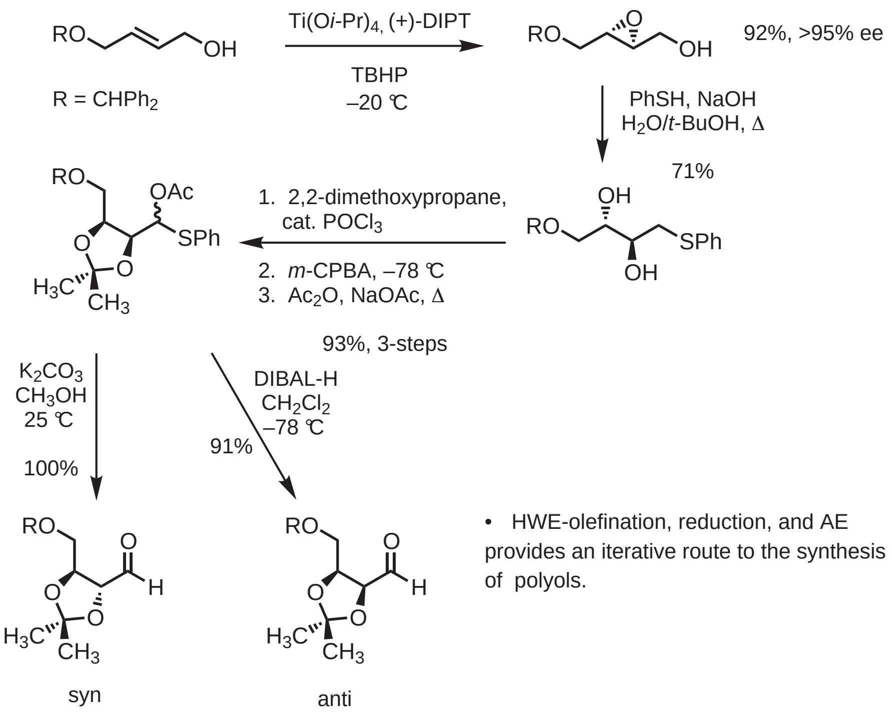
Excercise: Why?



Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529.
Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718-4720.

Applications in Synthesis:

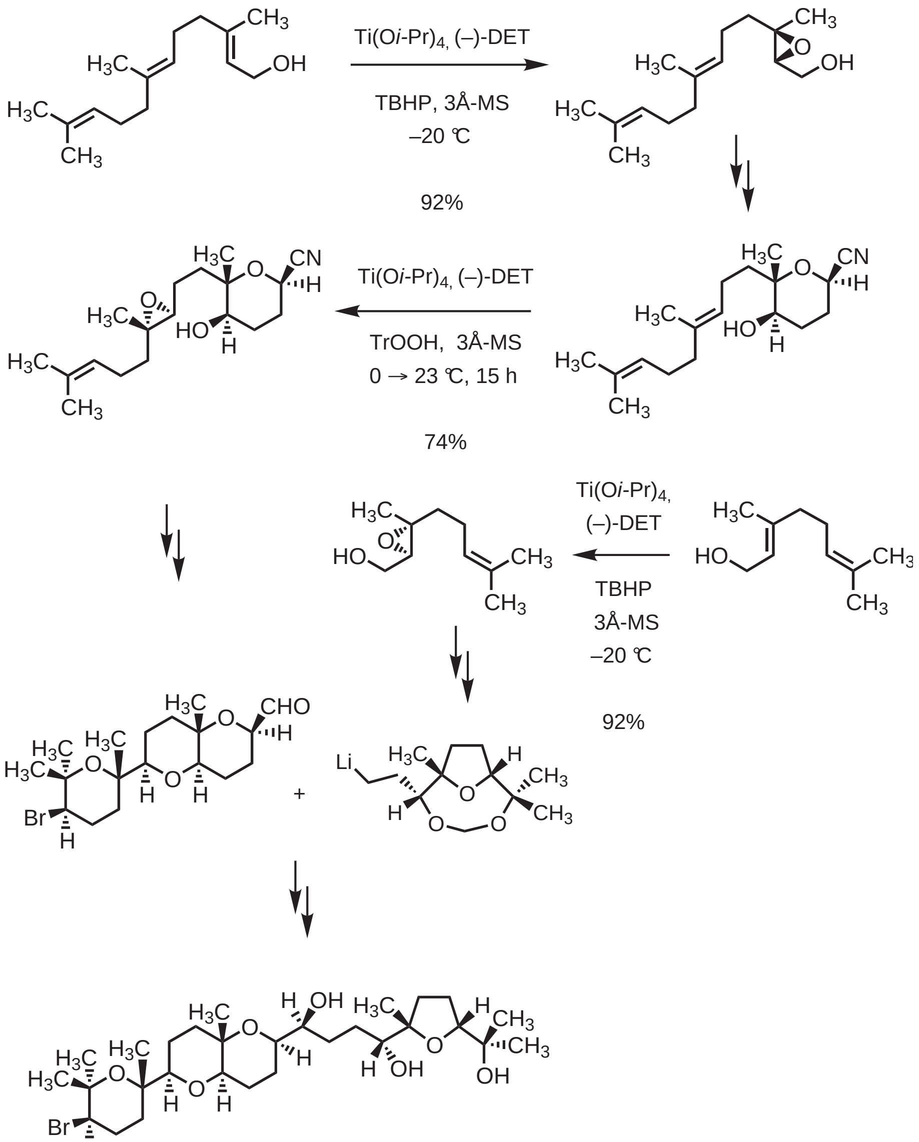
L-Hexoses:



- HWE-olefination, reduction, and AE provides an iterative route to the synthesis of polyols.

Ko, S. Y.; Lee, A. W. M.; Masamune, S; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245-264.

Venustatriol:

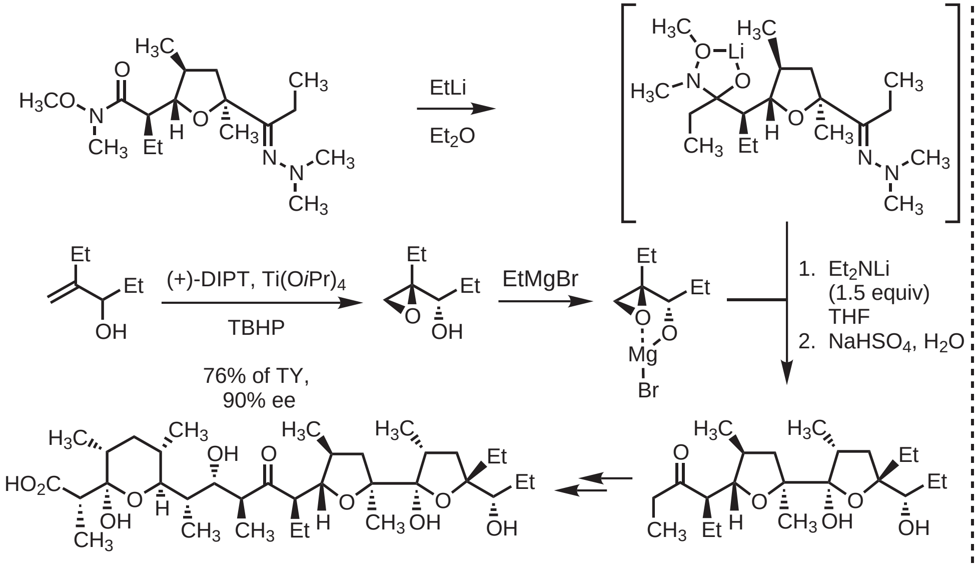


Venustatriol

Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171-3174.

M. Movassaghi

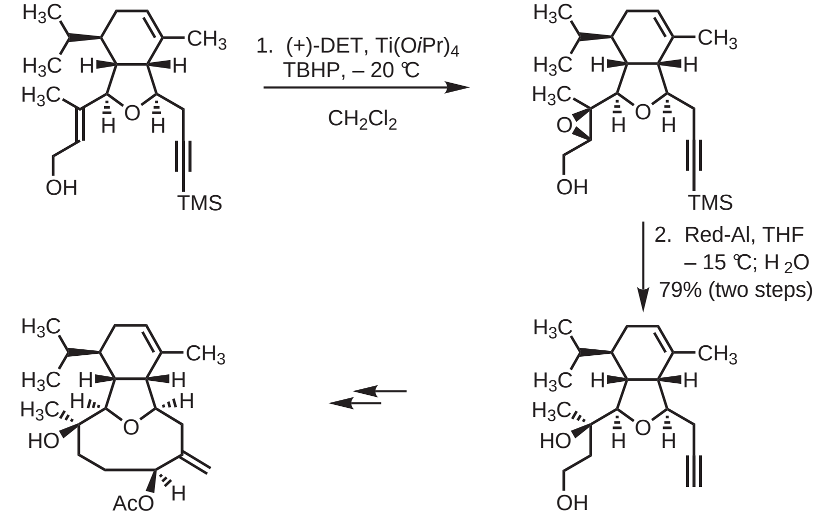
Ferensimycin B:



Ferensimycin B

Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613-7630.

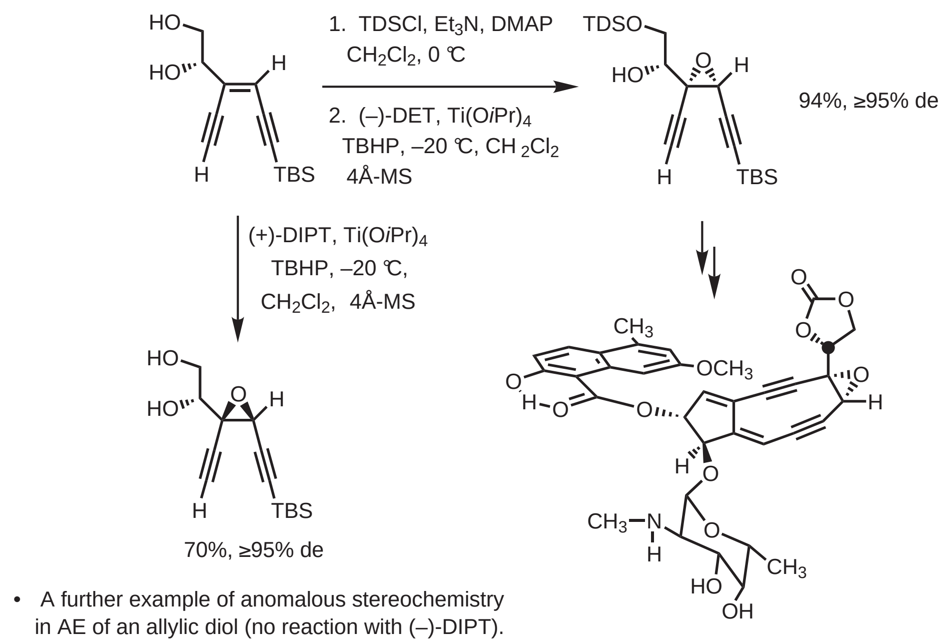
(–)-7-Deacetoxyalcyonin Acetate:



(–)-7-Deacetoxyalcyonin Acetate

MacMillan, D. W. C.; Overman, L, E. *J. Am. Chem. Soc.* **1995**, *117*, 10391-10392.

(+)-Neocarzinostatin Chromophore:



- A further example of anomalous stereochemistry in AE of an allylic diol (no reaction with (–)-DIPT).

(+)-Neocarzinostatin Chromophore

Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.-N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006-10007.
Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Yusheng, W.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319-5320.

Chem. Rev. 1993, 93, 1307–1370

Substrate-Directable Chemical Reactions

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I. Introduction

Control of the regio- and stereochemical aspects of reaction selectivity[1] is a continuing challenge to organic chemists. *Nonbonding interactions* contributed by substrate substituents generally provide the dominant stereochemical control element in the preferential attack of a reagent onto the more accessible face of a prostereogenic carbon center. Such interactions between reacting partners which are repulsive in nature are modulated by *stereoelectronic effects*,[2] which either enhance, diminish, or override the "steric bias" in the vicinity of a given reaction site. In certain instances,

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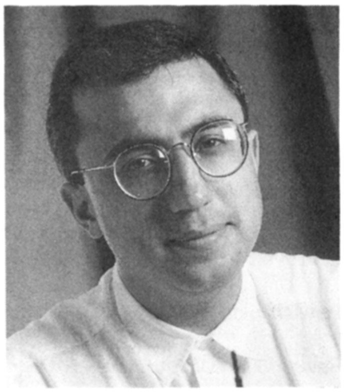
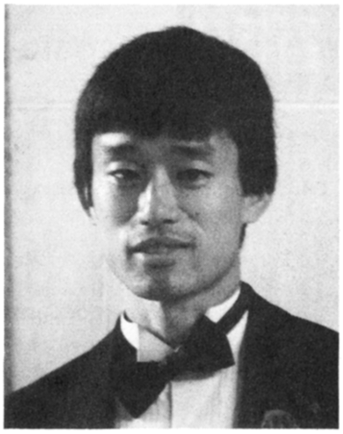


Amir Hoveyda received his undergraduate degree at Columbia, where he was introduced to organic chemistry by Tom Katz and Nick Turro. He received his graduate education with Stuart Schreiber at Yale, where he examined the mechanism and synthetic applications of furancarbonyl photocycloaddition. After postdoctoral work with David Evans at Harvard as an American Cancer Society Postdoctoral Fellow, he assumed the position of Assistant Professor of Chemistry at Boston College in 1990. His research interests include development of new methods in synthesis and study of metal-catalyzed carbon–carbon bond-forming transformations with particular attention to reaction mechanism and asymmetric catalysis. He is an NSF National Young Investigator, an Eli Lilly Grantee, and the recipient of an American Cancer Society Junior Faculty Award.

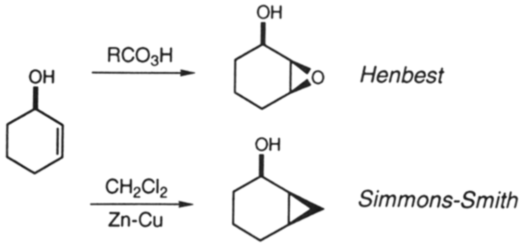
David Evans was born in Washington, DC, in 1941. He received his A.B. degree from Oberlin College in 1963 and his Ph.D. from the California Institute of Technology in 1967 under the supervision of Robert Ireland. In that year he joined the faculty at the University of California, Los Angeles. In 1973 he was promoted to the rank of Full Professor, and shortly thereafter returned to Caltech where he remained until 1983. In 1983 he moved to his present position at Harvard University where he is currently the Abbott and James Lawrence Professor of Chemistry. His interests are focused in the area of organic synthesis. His laboratory is engaged both in the development of new stereoselective reactions and asymmetric synthesis methodology as well as the application of these concepts to the synthesis of a range of targets of biological significance.



Greg Fu was born in Ohio in 1963. He received his S.B. degree in chemistry in 1985 from M.I.T., where he worked in the laboratory of K. Barry Sharpless. In 1991, he earned a Ph.D. in organic chemistry from Harvard University under the guidance of David A. Evans. His thesis dealt with the scope and the mechanism of the transition metal-catalyzed hydroboration reaction. He is currently a National Science Foundation postdoctoral fellow with Robert H. Grubbs at Caltech and will join the faculty at MIT this summer.

reagents have been documented to preassociate with polar functional groups in the vicinity of the reaction center and to influence the sterochemical outcome of the process. Such interactions between substrate and reagent, which are attractive rather than repulsive in nature, frequently provide a stereochemical outcome that is opposite to that predicted on the basis of an analysis of steric effects alone. Those cases wherein such contrasteric selectivity has been observed invariably involve substrates that carry polar, oxygen-containing functional groups and metal-based reagents. Preassociation of the reacting partners either through hydrogen bonding, covalent, or Lewis acid–base union is followed by the maintainance of this interaction during the ensuing chemical transformation. Such reactions characteristically proceed through highly ordered transition states, frequently with exceptional levels of stereoselection.

Two of the earliest examples of such *directed reactions* are the Henbest epoxidation of 2-cyclohexen-1-ol and the Simmons–Smith cyclopropanation of the same substrate. In these stereoselective processes, hydroxyl participation results in the delivery of the reagent to the sterically more congested olefin diastereoface, syn to the allylic heteroatom. As a class, such transformations afford the opportunity for overriding steric factors in stereoselective bond constructions. Accordingly, these reactions are of great importance in stereoselective synthesis.

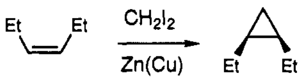


The principal aim of this article is to present a general overview of heteroatom-directed organic reactions, a topic which has not previously been reviewed. Processes that are covered in the following discussion are those which have explicitly been demonstrated to involve *transient* interaction of a substrate functional group with the incoming reagent, or those reactions where the most plausible explanation for their regio- and stereochemical outcome would invoke such an interplay. That is, reactions where the delivered reagent is covalently bound to the starting material are not discussed. In addition, this review is limited to those reactions where the directing functionality itself does not undergo a transformation and is recovered intact in the final product.[3] Finally, we have only included processes where the delivery of the reagent[4] and the determination of the stereochemical identity of the products transpires in a unimolecular step.

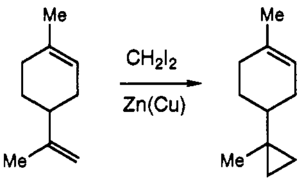
II. Directed Cyclopropanation Reactions

A. Introduction

In 1958, Simmons and Smith reported that treatment of simple alkenes with a mixture of methylene iodide and zinc–copper couple results in the high yield formation of cyclopropanes.[5] Several important features of this process were later presented in a more detailed account.[6] The reaction of alkenes with the "zinc reagent" is stereospecific with regard to the correlation of olefin geometry and product stereochemistry (eq 1) and is influenced by both steric and electronic factors.[7] The transformation is kinetically first order in both the organometallic reagent and the olefin.



(1)

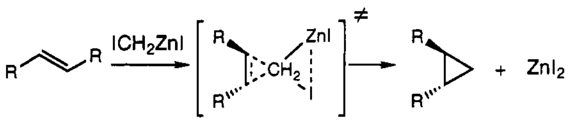


(2)

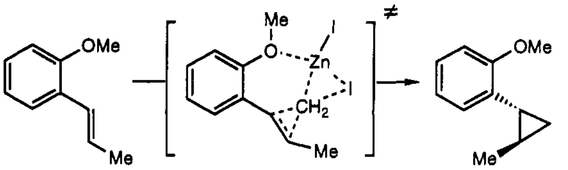
Simmons and Smith subsequently outlined a mechanism, where (iodomethyl)zinc iodide, the product of the initial reaction of methylene iodide and zinc metal, was proposed to be the active cyclopropanation reagent (Scheme 1).[8] Accordingly, the organometallic entity "could be considered as a relatively strongly bonded complex of methylene and zinc iodide, the carbon atom of which is electrophilic in character". A three-centered transition structure was proposed to account for the observed stereoselectivities. The preference of the cyclopropanation reagent for the less encumbered alkenes (eq 2) was attributed to the sterically demanding nature of the organometallic reagent.

Scheme 1

$CH_2I_2 + Zn \longrightarrow ICH_2ZnI$

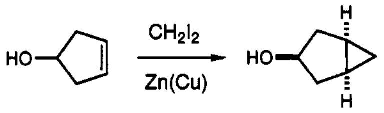


The initial indications that the cyclopropanation reaction may be affected by resident heteroatoms surfaced when it was discovered that the influence of steric factors can be somewhat unpredictable.[6] For example, the more hindered *o*-methoxyphenylpropene gives a higher yield of the cyclopropane adduct than either the meta or para isomers.[9] This unanticipated behavior was attributed to initial coordination of the Lewis basic ether oxygen with the Lewis acidic (iodomethyl)zinc iodide, thereby stabilizing the transition structure for the ortho-substituted anisole derivative (eq 3). Simmons and Smith thus made the important observation that internal functional groups can "assist and direct addition" in the zinc-mediated cyclopropanation.



(3)

The notion of utilizing a "steering" interaction between a suitably disposed heteroatom and the incoming zinc reagent was first exploited in 1961.[10] Winstein and co-workers reported that treatment of 3-cyclopenten-1-ol with methylene iodide and zinc–copper couple afforded the syn cyclopropyl carbinol as a single stereoisomer in 75% yield (eq 4). Cyclopropanation of the cyclopentenyl acetate and cyclopentadiene proved to be considerably more sluggish (3% conversion). Winstein surmised that *in the reaction of 3-cyclopenten-1-ol, prior coordination of the zinc reagent with the hydroxy group both directs the addition of methylene to the neighboring alkene and enhances the rate of the overall transformation.*[11]

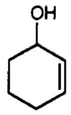
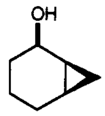
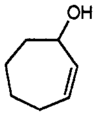
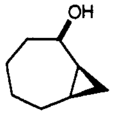
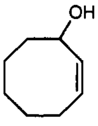
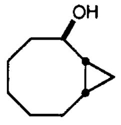


(4)

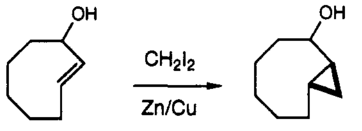
B. Cyclopropanation of Allylic Alcohols

The utility of hydroxyl-directed cyclopropanation reactions has been demonstrated in a number of cyclic systems (Table 1) and incorporated in several natural product syntheses. 2-Cyclohexen-1-ol and its derived methyl ether are reported to undergo cyclopropanation to afford the *syn*-cyclopropyl alcohol product exclusively.[12] Winstein and co-workers performed a comprehensive study of the addition reaction of cyclic allylic alcohols and confirmed earlier reports[13] that syn addition is predominant in the reaction of 2-cyclohepten-1-ol.[14] In contrast, 2-cycloocten-1-ol and 2-cyclononen-1-ol yield anti bicyclic carbinols stereoselectively (entry 3).

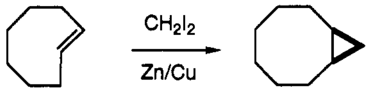
Table 1. Stereoselective Cyclopropanation of Cyclic Allylic Alcohols

Entry	Substrate	Major Product	Selectivity
1			>99 : 1
2			9 : 1
3			>99 : 1

Rate enhancement by a neighboring hydroxy group is such that *trans*-2-cycloocten-1-ol affords the *anti*-cyclopropyl alcohol (eq 5), whereas the reaction of the parent hydrocarbon is impaired by an intervening trans-to-cis isomerization (eq 6).[15]

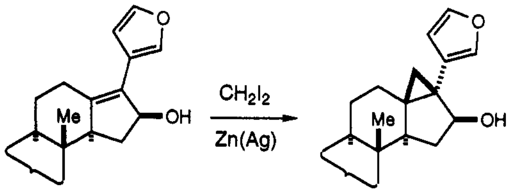


(5)

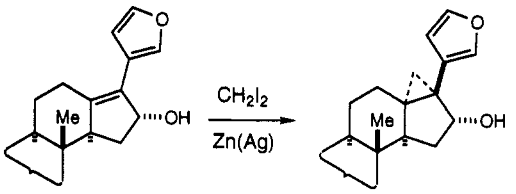


(6)

Use of a zinc–silver couple instead of the original zinc–copper mixture is advantageous in several regards.[16] Cyclopropanations of enamines,[17] enol ethers, enol esters, and α,β-unsaturated aldehydes and ketones,[18] which often proceed in low yield under the Simmons–Smith conditions, can be effected satisfactorily with zinc–silver couple. Moreover, the usual hydrolytic workup is replaced by the simple addition of an amine (e.g., pyridine) and filtration of the resulting zinc salts. In studies on synthetic routes to the limonoid system, Conia's modifications facilitated the preparation of both the α- and the β-cyclopropyl isomers in ~90% yield (eqs 7 and 8).[19] Through subsequent oxidation and lithium–ammonia reduction of the resultant ketones, the difficult task of introducing the C/D angular methyl group was accomplished.

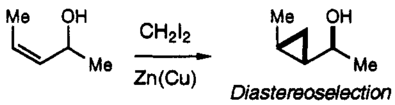


(7)



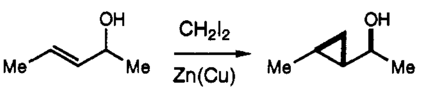
(8)

The stereochemical outcome of the Simmons–Smith reaction on acyclic allylic alcohols has been examined. Addition reactions of cis-disubstituted substrates are highly stereoselective, whereas the related trans isomers exhibit only modest levels of stereocontrol (eqs 9 and 10).[20]



(9)

Diastereoselection >99 : 1

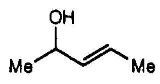
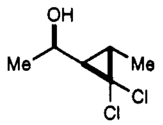
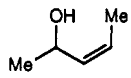
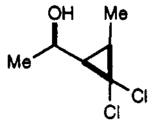
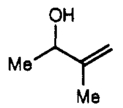
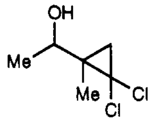
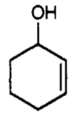
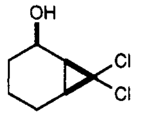


(10)

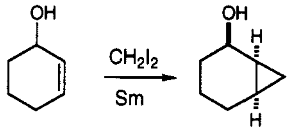
No Diastereoselection

In a stereochemically related reaction, dichlorocarbene ($CHCl_3$, NaOH, $BnNEt_3Cl$) was also found to selectively react with allylic alcohols to give syn cyclopropyl carbinols (Table 2).[21] The last entry of Table 2 indicates that the dichloromethylene group is introduced predominantly syn to the neighboring hydroxyl group. (The *tert*-butyldiphenylsilyl ether of *trans*-pent-3-en-2-ol reacts in a stereorandom manner.) Association of dichlorocarbene and the olefinic substrate through a hydrogen bond, in conjunction with restriction of conformational mobility to minimize allylic strain, accounts for the observed stereoselectivities.[22]

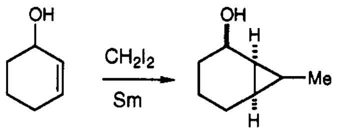
Table 2. Stereoselective Cyclopropanation of Allylic Alcohols with Dichlorocarbene

Entry	Substrate	Major Product	Selectivity
1			8 : 1
2			51 : 1
3			1 : 1
4			10 : 1

Samarium-derived carbenoids are also effective agents for the cyclopropanation of allylic alcohols.[23] The reaction often occurs at −60 °C, in contrast to the Simmons–Smith conditions which require above-ambient temperatures. When samarium is used, 2-cyclohexen-1-ol affords the syn cyclopropyl carbinol as a single isomer (eq 11, 92%). As illustrated in eq 12, ethylene iodide may be used in the samarium-mediated cyclopropanations: contrary to the Simmons–Smith conditions, higher levels of exo/endo stereoselectivity are observed.



(11)

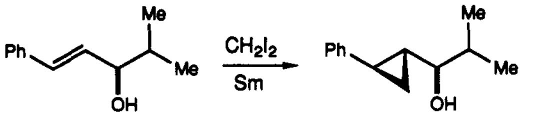


(12)

	Exo : *Endo*
Sm / CH_3CHI_2	5 : 1
Et_2Zn / CH_3CHI_2	1.6 : 1

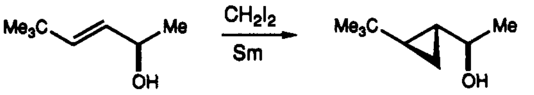
Samarium carbenoids react with acyclic allylic alcohols to afford cyclopropyl carbinols with diastereocontrol (eqs 13–15). The samarium-promoted, directed cyclopropanation reaction is highly site selective. In the cyclopropanation of geraniol, reaction of the olefin adjacent to the hydroxyl group occurs with >95% selectivity.

Nonracemic cyclopropyl ketones may be obtained through methylenation of the corresponding β-hydroxysulfoximine.[24] As shown in eq 16, this technology has been employed in the preparation of (−)- and (+)-thujospene (eq 16).



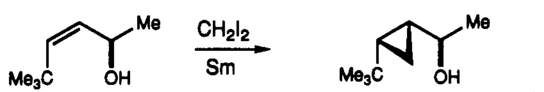
(13)

Diastereoselection >200 : 1



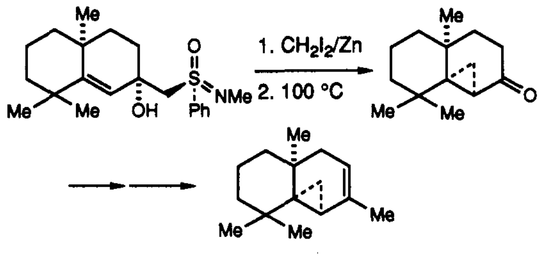
(14)

Diastereoselection >200 : 1



(15)

Diastereoselection >200 : 1



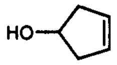
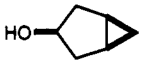
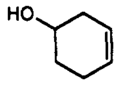
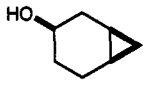
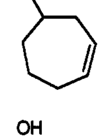
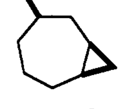
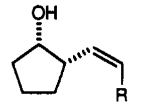
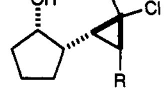
(16)

(-)- m-ospene

C. Cyclopropanation of Homoallylic Alcohols

Cyclopropanation of homoallylic alcohols is subject to directivity by a resident heteroatom. 3-Cyclopenten-1-ol,[11] 3-cyclohexen-1-ol,[25] and 3-cyclohepten-1-ol[25] afford the corresponding syn cyclopropyl carbinols with equally high levels of stereochemical control (Table 3). As illustrated in entry 4 of Table 3, cyclopropanation of a homoallylic alcohol with dichlorocarbene may also proceed with high levels of stereochemical control.[26]

Table 3. Stereoselective Cyclopropanation of Homoallylic Alcohols

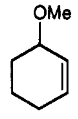
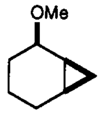
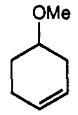
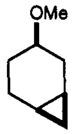
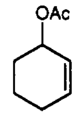
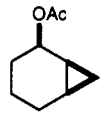
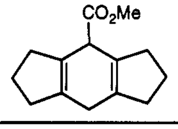
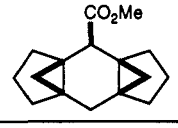
Entry	Substrate	Major Product	Selectivity
1			>20:1
2			>20:1
3			>20:1
4			>20:1

R = $(CH_2)_3$-OTBS

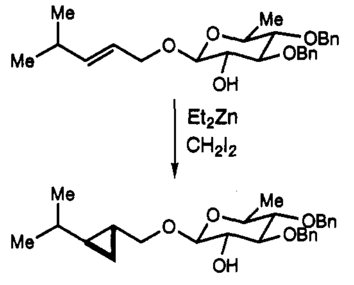
D. Cyclopropanation of Olefinic Ethers and Esters

Table 4 illustrates a number of cases where the stereochemical course of the cyclopropanation process is influenced by functionality other than a hydroxyl group. The methyl ethers derived from both 2-cyclohexen-1-ol[27] and 3-cyclohexen-1-ol[28] afford syn cyclopropyl carbinols exclusively. In apparent contrast to Winstein's early reports,[10] carboxylic esters, even from the homoallylic position, direct the stereochemical course of the cyclopropanation reaction, as illustrated by entries 3 and 4 of Table 4.[29]

Table 4. Stereoselective Cyclopropanation of Unsaturated Ethers and Esters

Entry	Substrate	Major Product	Selectivity
1			>99 : 1
2			>99 : 1
3			4 : 1
4			>99 : 1

Recently, carbohydrate-derived allylic acetals have been employed in diastereoselective cyclopropanation (eq 17). Presumably both the allylic ether and the neighboring hydroxyl are responsible for the delivery of the methylenation reagent: protection of the alcohol or removal of the ether functionality leads to significant diminution in stereocontrol ($\sim$2:1).[30]



(17)

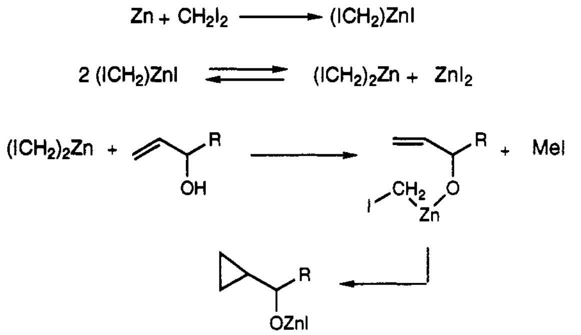
Diastereoselection >50 : 1

E. Mechanistic Considerations

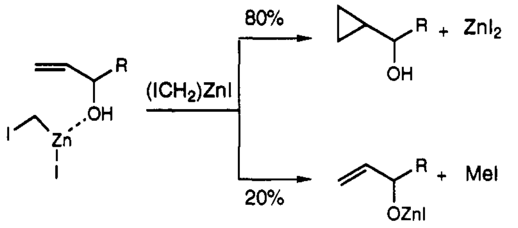
In 1964, Simmons proposed that the reaction of unsaturated alcohols involves the formation of an intermediate zinc alkoxide, since in the cyclopropanation of 3-cyclopenten-1-ol, 1 mol of iodomethane is formed for each mole of the desired bicyclic alcohol.[31] It was suggested that upon formation of (iodomethyl)zinc iodide, a Schlenk equilibrium is established, resulting in the formation of bis(iodomethyl)zinc (Scheme 2). Reaction of the latter species with the allylic alcohol yields equimolar amounts of the corresponding zinc alkoxide and iodomethane; intramolecular methylene transfer would then afford the final product.[32]

Dauben later showed that an iodometrically equivalent amount of (iodomethyl)zinc iodide and 2-cyclopentene-1-ol gives the cyclopropane product in 80%

Scheme 2



Scheme 3



yield.[12] This observation is in contrast to Simmons' postulate where 2 equiv of the zinc reagent are required for completion of the reaction. Dauben therefore suggested that the first step in the methylenation process is the formation of a *dative* complex between the zinc reagent and the hydroxy group (Scheme 3). Generation of iodomethane as a side product would be the result of competitive decomposition of (iodomethyl)-zinc iodide by the alcohol moiety.

The exact nature of the reacting complex in the cyclopropanation reactions of allylic alcohols remains an unresolved issue. It is likely that initial complexation is followed by formation of a zinc alkoxide and that both types of species, covalent and dative, are capable of directing the methylenation process. A transient dative oxygen–zinc complex has been proposed to account for the stereochemical preferences in reactions of allylic ethers and esters (Table 3).[33] Although these data indicate that directivity by certain oxygen-containing functional groups occurs without formation of a covalent oxygen–zinc bond, there is no conclusive evidence that dative complexes are exclusively involved in the reaction of allylic alcohols.

Homoallylic alcohols react more slowly than the corresponding allylic systems, but immeasurably faster than simple alkenes. It appears that the practical limit of heteroatom directivity is at the homoallylic position, since the bishomoallylic alcohol in entry 3 of Table 5 exhibits a reaction rate comparable to that of cyclohexene (however, compare with entries 3 and 4 of Table 4).

The influence of substrate structure on both the rate and the stereochemical outcome of the cyclopropanation of various cyclohexenols can offer insight into the mechanism and conformational preferences involved in the cyclopropanation reaction (Table 6).[7] 2-Cyclohexen-1-ol reacts only twice as fast as its derived methyl ether (entries 1 and 2). It was suggested that if the reaction of the parent alcohol did proceed through a covalently bound zinc alkoxide intermediate, as opposed to the cyclopropanation of the methyl ether which must involve a dative complex, it is likely that a larger difference in rate would have been observed. As entries 3 and 4 of Table 6 show, both *syn*- and *anti*-5-methyl-2-cyclohexen-1-ol afford a single cyclopropane adduct, with the anti isomer reacting about 3 times faster.

Table 5. Relative Rates and Stereoselectivity in Cyclopropanation of Cyclic Unsaturated Alcohols

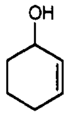
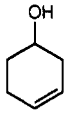
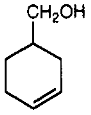
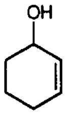
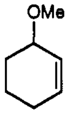
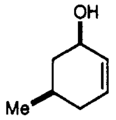
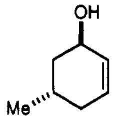
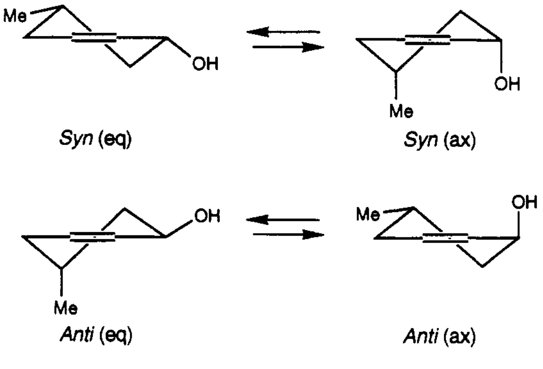
Entry	Substrate	Relative Rate (k)	Selectivity *Syn* : *Anti*
1		1.00	>99 : 1
2		0.091 ± 0.012	>99 : 1
3		Very slow	1 : 1

Table 6. Relative Rates and Stereoselectivity in Cyclopropanation of Cyclic Allylic Alcohols

Entry	Substrate	Relative Rate (k)	Selectivity *Syn* : *Anti*
1		1.00	>99 : 1
2		0.50 ± 0.05	>99 : 1
3		1.54 ± 0.10	>99 : 1
4		0.46 ± 0.05	>99 : 1

To account for these data, Rickborn considered four half-chair conformers, two each for the axial and equatorial alcohols (Scheme 4). If the reaction proceeds through the pseudoaxial hydroxyl–zinc complex, the anti isomer should react faster, as it contains a pseudoequatorial rather than an energetically unfavorable pseudoaxial methyl substituent. Nonetheless, the opposite trend was observed: the syn isomer exhibits

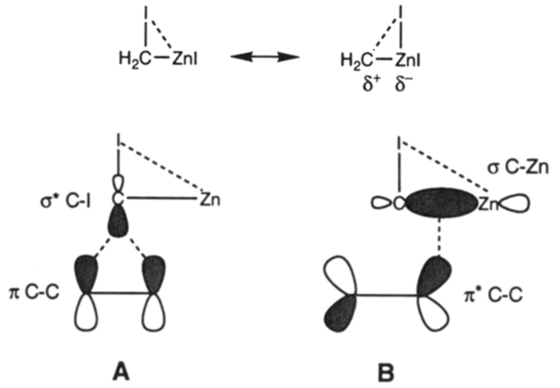
Scheme 4



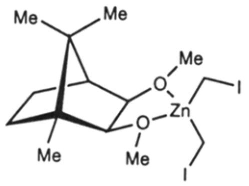
greater reactivity. It is therefore proposed that cyclopropanation occurs through the pseudoequatorial metal alkoxide.

The geometric and stereoelectronic requirements of the methylenation reaction may offer insights into the structure of the most reactive transition structure involved in this process. It is plausible that formation of the carbon–carbon bonds of the cyclopropane is triggered by two interactions: (1) The overlap of the π_{C-C} and the σ^*_{C-I} orbitals (Scheme 5, A), and (2) The overlap of the σ_{C-Zn} and the π^*_{C-C} orbitals (Scheme 5, B). Additionally, the incipient Zn–I bond should lower the energy level of σ^*_{C-I}, thereby accommodating the mixing of π_{C-C} with σ^*_{C-I}.

Scheme 5

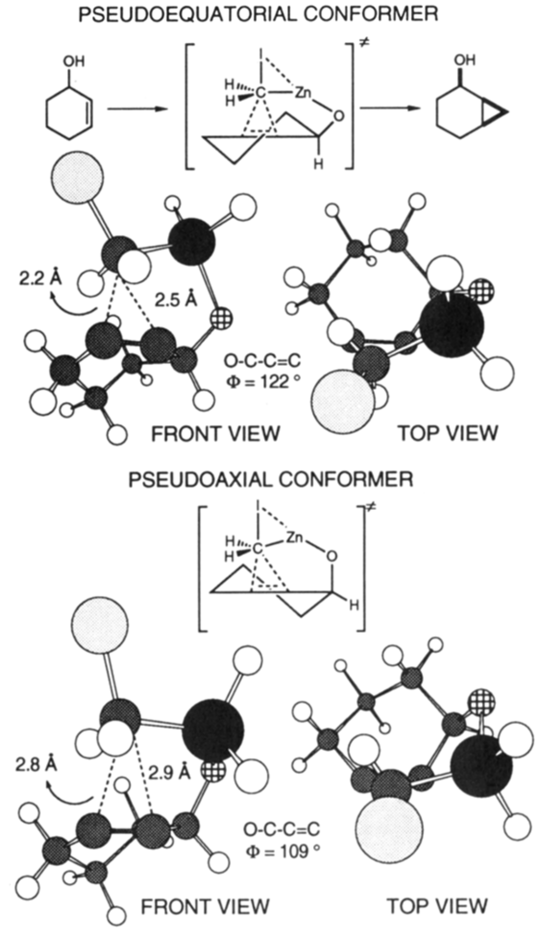


Recently, a solid-state structure of the cyclopropanation reagent has been reported (see below). The exo iodomethyl groups possess particularly smaller Zn–C–I angles and shorter Zn–I distances. It is claimed that "this close contact is reminiscent of the internal activation proposed by Simmons in the methylene transfer step".[34]



The model illustrated in Scheme 5 agrees with the original Simmons' supposition that the carbon atom in the zinc reagent is electrophilic in character but reserves a significant role for the C–Zn bond in the mechanism of the cyclopropanation reaction. In the case of cyclohexenyl allylic alcohols, analysis of molecular models reveals that both the pseudoaxial and the pseudoequatorial complexes of the half-chair conformers can orient for maximum overlap of the π_{C-C} and the σ^*_{C-I} orbitals or σ_{C-Zn}, π^*_{C-C} overlap (Scheme 6; available ligation site on Zn may be occupied by solvent molecules).[35] However, in the axial conformer, with the smaller O—C—C=C dihedral angle of 109°, the organometallic agent and the alkene center are unable to achieve the distance that is requisite for formation of carbon–carbon bonds.[36] It is noteworthy that the proposed interaction between the σ_{C-Zn} and the π^*_{C-C} orbitals closely parallels the interaction of a peracid lone pair with the π^*_{C-C} in directed peracid epoxidation reactions (section III).

Scheme 6



An additional stereoelectronic effect, which may also provide a bias for preferential reaction through the pseudoequatorial conformer, involves the overlap of the low-lying hydroxyl σ^*_{C-O} and the alkene π_{C-C}. This interaction, which is present to a larger degree in the pseudoaxial hydroxyl orientation, attenuates the nucleophilic character of the olefin and should thereby render the pseudoaxial conformer less reactive (Figure 1).[37] Within this context, measurement of the relative rates and levels of stereoinduction in cyclopropanation reactions of *cis*- and *trans*-5-*tert*-butyl-2-cyclohexen-1-ols may prove enlightening.

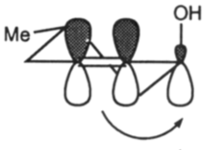
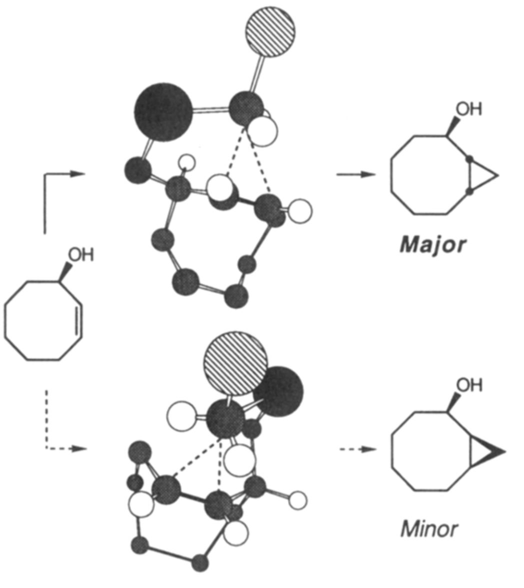


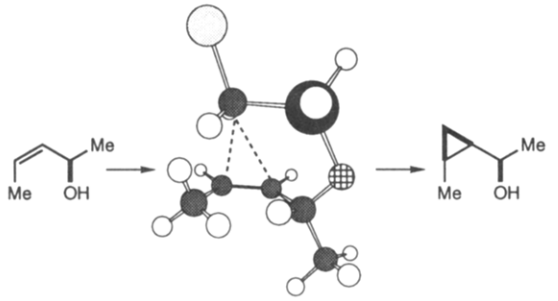
Figure 1. Overlap of π_{C-C} and σ^*_{C-O} in the allylic system leads to attenuation of the nucleophilic character of the olefin.

The stereoelectronic requirements delineated above account for the trend in the stereochemical outcome of the cyclopropanation reactions of 2-cyclohepten-1-ol (syn cyclopropyl carbinol; Table 1, entry 2) and 2-cycloocten-1-ol (anti cyclopropyl carbinol; Table 1, entry 3). Both the pseudoaxial and pseudoequatorial zinc alkoxides may afford the major product diastereomer. However, as is illustrated in Scheme 7, in the cyclopropanation of 2-cycloocten-1-ol the pseudoequatorial conformer is favored on simple steric grounds,

Scheme 7



Scheme 8



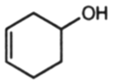
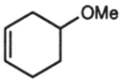
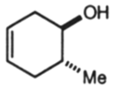
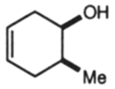
and as a result of the larger O—C—C=C dihedral angle, offers a more desirable alignment of the interacting orbitals, leading to the predominant formation of the anti diastereomer.[38]

The observed stereochemical preferences in the cyclopropanation of acyclic allylic alcohols (eqs 9–10 and 13–15 and Table 2) may be rationalized in a similar fashion. For *cis*-alkenes, A(1,3) allylic strain[22] favors the transition state conformation shown in Scheme 8; formation of the erythro product is thus preferred. As this destabilizing interaction is absent in trans-disubstituted alkenes, the cyclopropanation occurs nonstereoselectively.

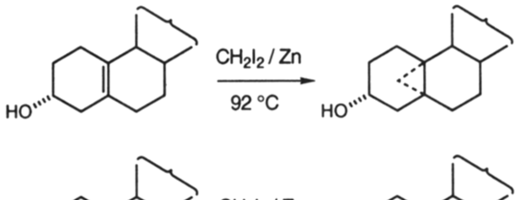
It is noteworthy that the staggered model offers a plausible representation of the more reactive transition state. On the one hand, the aforementioned deactivating overlap of the π_{C-C} with the σ^*_{C-O} is attenuated, and on the other, this orientation allows for the hyperconjugative interaction between the σ_{C-C} and the π^*_{C-C} orbitals, which should in turn enhance the nucleophilicity of the olefin. These effects require a O—C—C=C dihedral angle of ~130°, which closely resembles the values predicted for the more reactive conformers of six-, seven-, and eight-membered cyclic allylic systems. Similar arguments apply to samarium-mediated cyclopropanation reactions.

Studies on the conformational aspects of the directive effect in the cyclopropanation of cyclic homoallylic alcohols[7] indicate that these compounds mainly react through conformers with an axial hydroxy group (Table 7), in contrast to the corresponding allylic systems. This is perhaps to be expected, since when the directing group adopts the pseudoaxial position, the alkene is more accessible to the hydroxy-organometallic complex. The deactivating interaction between the π_{C-C} and σ^*_{C-O}, proposed to exert an influence in the allylic systems (Figure 1), is no longer operative and therefore does not disfavor the pseudoaxial zinc hydroxy conformer. Entries 3 and 4 of Table 7 show that substituents which enforce the axial hydroxy conformer effect an increase in the rate of cyclopropanation.

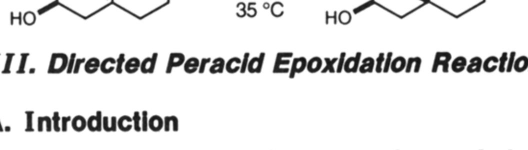
Table 7. Relative Rates and Stereoselectivity in Reactions of Homoallylic Alcohols

Entry	Substrate	Relative Rate (k)	Selectivity *Syn : Anti*
1	 OH	1.00	>99 : 1
2	 OMe	0.18 ± 0.2	>99 : 1
3	 OH Me	2.6 ± 0.2	>99 : 1
4	 OH Me	5.2 ± 0.4	>99 : 1

In the case of the homoallylic substrates, the difference in rate between the cyclopropanation of the parent alcohol and the derived methyl ether is larger than that observed for the corresponding allylic substrates (see entries 1 and 2, Tables 6 and 7). However, as has been suggested by Rickborn, such differences in reaction rates are too small to support different mechanisms for alcohol and ether substrates.[26] A related observation is that the highly stereoselective cyclopropanation of 5-α-hydroxy steroidal substrates requires unusually elevated temperatures (92 °C), whereas the related β isomers undergo cyclopropanation smoothly at 35 °C (eqs 18 and 19).[39] It has been demonstrated that the preferred half-chair conformation of the A ring in these compounds favors a pseudoequatorial orientation for the α-hydroxy and a pseudoaxial disposition for the β-hydroxy isomers.[40] The aforementioned data serve as further evidence that reactions of homoallylic alcohols preferentially occur through conformers which possess a pseudoaxial heteroatom. Furthermore, in support of Simmons' mechanistic paradigm, formation of the zinc alkoxide takes place prior to cyclopropanation in the case of the α-hydroxy isomer.[41]



(18)

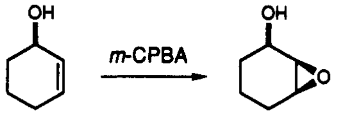


(19)

III. Directed Peracid Epoxidation Reactions

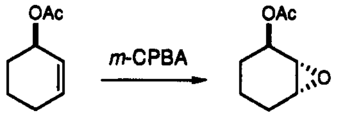
A. Introduction

In 1959, Henbest and Wilson observed that upon treatment with perbenzoic acid "formation of epoxides from cyclic allylic alcohols occurs on the side cis to the hydroxyl group".[42] Whereas oxidation of 2-cyclohexen-1-ol results in the predominant formation of the syn epoxy alcohol, the derived acetate or methyl ether affords the anti isomer as the major product (eqs 20 and 21; *m*-CPBA = *m*-chloroperbenzoic acid).



(20)

Diastereoselection 10 : 1

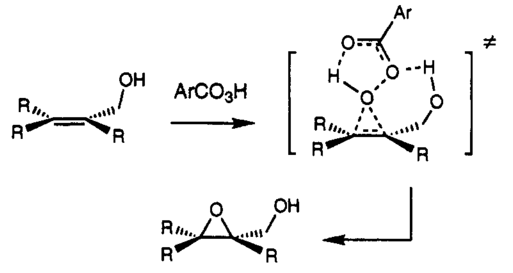


(21)

Diastereoselection 4 : 1

The difference in the stereochemical outcome of the above transformations was rationalized through a transition structure largely based on the "butterfly" mechanism of Bartlett, involving the interaction of the *nucleophilic* alkene with the *electrophilic* peracid.[43] It was postulated that a hydrogen bond formed between the hydroxy group and one of the peracid oxygens leads to delivery of the reagent to the olefin face syn to the hydroxy group (Scheme 9). Subsequently, the concept of heteroatom-directed peracid epoxidations was demonstrated in a number of cyclic and acyclic systems. In addition, the question of the mechanism of the "Henbest effect" formed the basis of several studies.[44]

Scheme 9



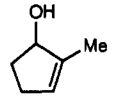
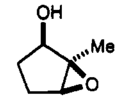
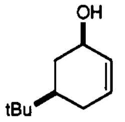
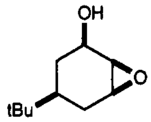
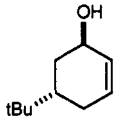
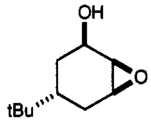
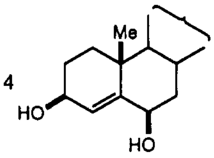
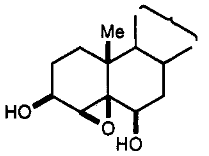
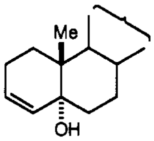
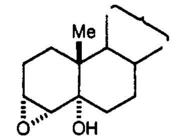
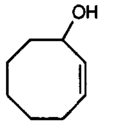
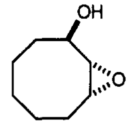
B. Peracid Epoxidation of Cyclic Olefins with Allylic Directing Groups

Table 8 illustrates cases where the stereochemical course of the peracid epoxidation of a cyclopentenol is controlled by a hydroxyl group.[45] Whereas oxidation (perlauric acid) of 2-cyclopenten-1-ol in cyclopentane produces the syn epoxy carbinol predominantly, under identical conditions the reaction of the derived methyl ether affords the anti isomer as the major product (11.5: 1).[46] 2-Cyclopenten-1-ol is stereorandomly oxidized when methanol is used as solvent, as protic media preempt the formation of the necessary hydrogen bond.

A comparison of the outcome of the reactions shown in entries 2 and 3 (Table 8) suggests that a hydroxyl group is more efficient in directing epoxidation from a pseudoequatorial than a pseudoaxial position.[47] Entries 4 and 5 illustrate two bicyclic allylic alcohols which are oxidized stereoselectively regardless of the position of the directing group.[42,48] Peracid epoxidation of 2-cycloocten-1-ol affords the anti product isomer with high selectivity (entry 6).

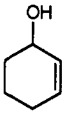
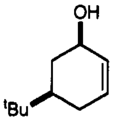
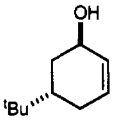
Epoxidation of allylic alcohols with trifluoroperacetic acid offers significantly higher levels of stereocontrol than perbenzoic acids.[49] Comparison of the stereochemical outcomes in entries 2 and 3 of Table 9 implies that the heteroatom functionality directs the oxidation reaction more effectively from the pseudoequatorial orientation (O—C—C=C dihedral angle of 140°).

Table 8. Stereoselective Epoxidation of Cyclic Allylic Alcohols[a]

Entry	Substrate	Major Product	Selectivity
1			>20 : 1
2			24 : 1
3			5 : 1
4			"highly selective"
5			"highly selective"
6			"highly selective"

[a] Conditions: Perbenzoic acid, perlauric acid, or *m*-chlorobenzoic acid in benzene.

Table 9. Stereoselective Epoxidation of Cyclic Allylic Alcohols with CF_3CO_3H

Entry	Substrate	*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
1		24 : 1	50 : 1
2		24 : 1	100 : 1
3		5 : 1	100 : 1

With *m*-chloroperbenzoic acid (*m*-CPBA) as the oxidant, epoxidation reactions of unsaturated cyclic silyl ethers are not subject to heteroatom directivity; however, when trifluoroperacetic acid is employed, syn epoxy silyl ethers are formed selectively (Table 10). The ability of silyl ethers to direct the epoxidation process when trifluoroperacetic acid is used may be

Table 10. Stereoselective Epoxidation of Silyl Ethers with CF_3CO_3H

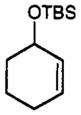
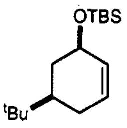
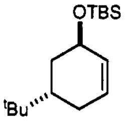
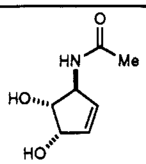
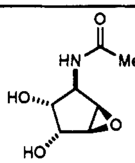
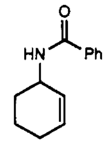
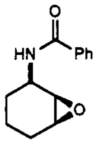
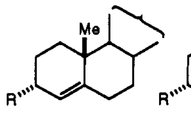
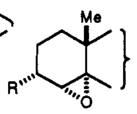
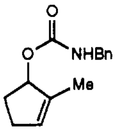
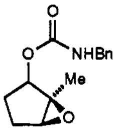
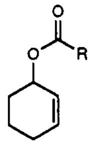
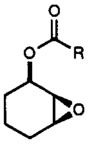
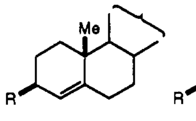
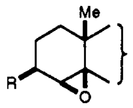
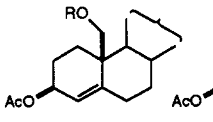
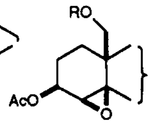
Entry	Substrate	*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
1		1 : 7	5 : 1
2		1 : 8	12 : 1
3		1 : 4	1 : 6

Table 11. Epoxidation of Cyclic Olefins with Amide-, Urea-, and Urethane-Directing Groups[a]

Entry	Substrate	Major Product	Selectivity
1			'highly selective'
2			'highly selective'
3		 a. R = NHCONHAc b. R = NHCONH₂ c. R = NHCOMe	2 : 1 'highly selective' 'highly selective'
4			>20 : 1
5		 a. R = NH₂ b. R = NHBn c. R = NMe₂	3 : 1 5 : 1 10 : 1
6		 a. R = OCONHBn b. R = OCONMe₂	>20 : 1 >20 : 1
7		 a. R = CONH₂ b. R = CONHBn c. R = CONMe₂	6 : 1 >10 : 1 2 : 1

[a] Conditions: Perbenzoic acid or *m*-chlorobenzoic acid in benzene.

attributed to the higher acidity of this reagent compared to *m*-CPBA.

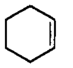
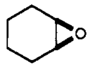
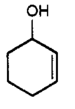
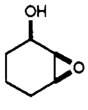
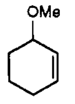
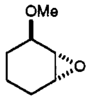
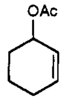
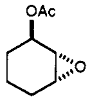
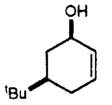
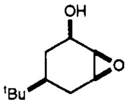
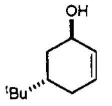
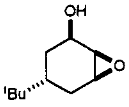
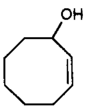
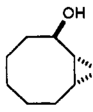
Table 11 illustrates cases where amide, urea, and urethane groups direct the stereochemical course of the epoxidation. The examples in entries 1[50] and 2[51] indicate that a carboxamide group effectively delivers the peracid reagent onto the syn face of the adjacent alkene. Moreover, the stereochemical outcome shown in entry 1 implies that amides may effectively direct the oxidation reaction in the presence of a competing hydroxyl group. Entries 3 and 4[52] of Table 11 offer instances where urethanes, ureas, and amides control the stereochemical course of the epoxidation process. Reaction of the acylurea shown in entry 3a proceeds with little selectivity, since *intramolecular* hydrogen bonding of the allylic NH preempts *intermolecular* association with the peracid.[45a] With regard to the substrates shown in entries 5–7, it has been proposed that the Lewis basic carbonyl, through its interaction with the peracid proton, plays the role of the proton *acceptor*. The case illustrated in entry 6b attests to the ability of the carbonyl group of a carbamate to direct the course of the epoxidation.

C. Mechanistic Considerations

Henbest and Chamberlain reported the relative rates of peracid oxidation of a number of olefinic substrates; these data are summarized in Table 12.[46,47] Entries 1–4 illustrate that 2-cyclohexen-1-ol reacts *slower* than cyclohexene, but significantly *faster* than its nondirecting methyl ether and ester derivatives. The higher rate of epoxidation of *cis*-5-*tert*-butyl-2-cyclohexen-1-ol (entry 5) relative to that of its trans isomer (entry 6) is consistent with differences in the levels of stereochemical induction reported for these substrates (24:1 vs 5:1, respectively). The *cis*-*tert*-butyl derivative is oxidized faster and more selectively than 2-cyclohexen-1-ol; this observation supports the proposal that the adjacent hydroxyl functionality is a more effective directing group when oriented pseudoequatorially.

2-Cycloocten-1-ol is oxidized slower than cyclooctene (relative rate = 2.16), but 15 times faster than the

Table 12. Relative Rates of Epoxidation of Representative Cyclic Olefins[a]

Entry	Substrate	Major Product	Relative Rate (k)
1			1.00
2			0.55
3			0.067
4			0.046
5			0.75
6			0.10
7			1.80

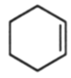
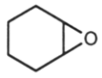
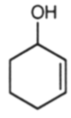
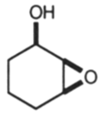
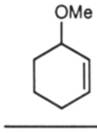
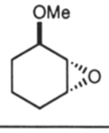
[a] Conditions: Perbenzoic acid, benzene, 5 °C.

derived methyl ether (relative rate = 0.12). It is significant that both the cyclopropanation and the peracid epoxidation of 2-cycloocten-1-ol result in the anti functionalization of the allylic alcohol. The rationale for the anti selectivity in the epoxidation of 2-cycloocten-1-ol closely parallels that which was presented for the cyclopropanation of this compound (see above).

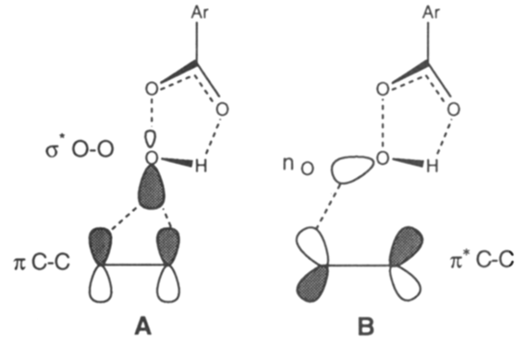
The values for the enthalpies and entropies of activation ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) in the epoxidation reactions of three of the aforementioned substrates are shown in Table 13. The enthalpy of activation ($\Delta H^{\ddagger}$) for the allylic alcohol is ~2 kcal/mol lower than that of the parent cycloalkene. This value is probably the net effect of two opposing factors: (1) stabilization of the transition structure as a result of hydrogen bonding between the hydroxyl group and the peracid reagent and (2) reduction in the nucleophilic character of the alkene, stemming from the electron-withdrawing ability of the adjacent heteroatom and the larger steric bulk of a methoxy versus a hydrogen group. Comparison of the activation parameters for epoxidations of cyclohexene and 2-cyclohexen-1-ol reveals that in the reaction of the latter substrate the diminution in $\Delta H^{\ddagger}$ is countered by a decrease in $\Delta S^{\ddagger}$, which results in an overall increase in the free energy of activation. Therefore, it is largely the variation in the activation entropy that leads to the reduction of the reaction rate in the epoxidation of the alcohol substrate. The values reported for the entropies of activation suggest a more organized transition structure for the peracid oxidations of the hydroxylic versus nonhydroxylic alkenes and thus support the directing influence of the resident alcohol moiety. With regard to the epoxidation of the allylic ether, in the absence of the steering influence of a hydroxy group, the entropy of activation is nearly identical to that of cyclohexene. The deactivating inductive effect of the ether functionality, in addition to the larger steric bulk of a methoxy, result in a higher enthalpy of activation.

For the peracid epoxidation of allylic alcohols, the interactions between the olefin π-system and the peracid shown in Scheme 10 can be suggested. A number of experimental data and theoretical considerations support this proposal. The role of the alkene as the nucleophile and that of the peracid as the electrophile[53] implies backside displacement of the peroxide bond and requires proper alignment of the π_{C-C} and σ^*_{O-O} orbitals (A).[54] The intramolecular hydrogen bonding in the oxidant facilitates the epoxidation process, as the carboxylic acid and not the corresponding carboxylate anion will be the leaving group.

Table 13. Activation Energy Parameters for Epoxidation of Representative Cyclohexenes

Substrate	Major Product	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (cal/deg/mol)
		10.42	-32.9
		8.35	-41.0
		12.36	-30.7

Scheme 10



Hanzlik and Shearer observed small peracid isotope effects in epoxidations of a number of simple olefins (e.g., stilbene), and thus proposed that "the peracid hydrogen remains hydrogen-bonded, or at least is not being transferred in the transition state".[55] This paradigm is supported by two independent observations: added acids do not catalyze the epoxidation reaction of simple olefins,[50] and basic solvents inhibit oxidation since the internally hydrogen-bonded structure of the peracid monomer is disrupted.[56] Transition structures with O—C—C═C dihedral angles of ~140° are preferred (equatorial OH), so that the deactivating effect of the adjacent heteroatom on the nucleophilic character of the π-cloud is minimized (see Figure 1). It is worthy of mention that, with regard to the favored O—C—C═C dihedral angle, similar arguments were presented in the case of Simmons–Smith cyclopropanation reactions of allylic alcohols.

Sharpless has proposed that a dihedral angle of ~60° between the planes defined by the two molecules orients one of the nonbonding electron pairs for donation into the π^*_{C-C} orbital, thus initiating formation of the second C–O bond of the incipient epoxide (Scheme 10, B).[57] Such association of the peroxide oxygen nonbonding pair and the π^*_{C-C} is reminiscent of the interaction between σ_{C-Zn} and π^*_{C-C} in the Simmons–Smith cyclopropanation. Moreover, it has been suggested that such an orientation properly disposes the second lone pair of the terminal peracid oxygen for hydrogen bonding with the adjacent hydroxyl group.[58]

The unsymmetrical transition structure illustrated in Figure 2 is based on the theoretical and mechanistic work of Hanzlik and Shearer.[52] Examination of the kinetic isotope effects of several peracid epoxidations indicates that extensive bond formation occurs at the site adjacent to the heteroatom such that the developing partial positive charge resides at the carbon more distant from the electron-withdrawing oxygen substituent. Molecular models imply that in the case of pseudoequatorial alcohol (O—C—C═C dihedral angle of ~140°), with the commonly depicted symmetrical transition structures, the hydroxyl proton and the peracid oxygen are too distant for effective hydrogen bonding (~2.6 Å).[59] However, in an unsymmetrical structure, where the peracid has slipped closer to the directing group, these atoms may lie easily within an acceptable distance for formation of a hydrogen bond (~1.9 Å).[60] Hanzlik and Shearer suggest that the developing carbocationic character of the β-carbon is in turn ameliorated through electron donation by the

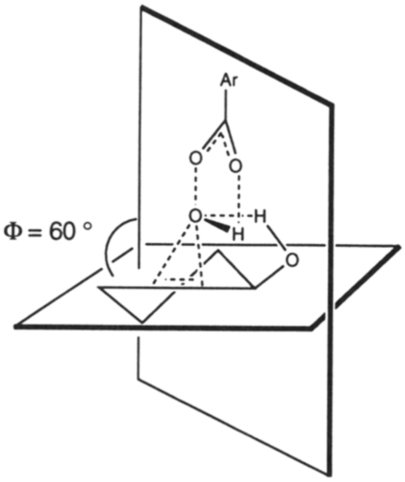


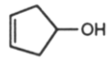
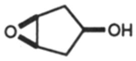
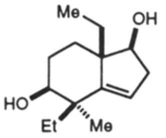
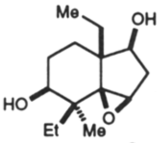
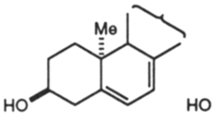
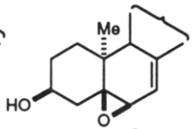
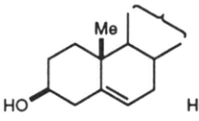
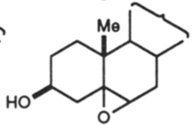
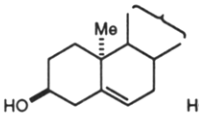
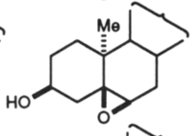
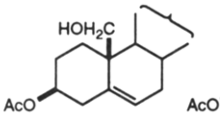
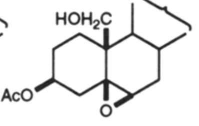
Figure 2. Transition structure for the peracid epoxidation of cyclic alcohols.

nonbonding electrons of the peracid oxygen; this interaction is illustrated in Scheme 10, B. As mentioned previously, Sharpless has proposed that this latter overlap eventually leads to the formation of the second epoxide C–O bond. With allylic amides and urethanes (Table 11), a transition structure involving formation of a hydrogen bond between the terminal peracid oxygen and the amide NH, similar to that proposed for the oxidation of allylic alcohols, readily accounts for the observed stereoselectivities.

D. Peracid Epoxidation of Cyclic Olefins with Homoallylic Directing Groups

Table 14 illustrates instances where a homoallylic hydroxyl group directs the course of the peracid epoxidation reaction.[61] Entries 1[62] and 2[63] show cases where a cyclopentenyl alkene is oxidized with stereochemical control. 3-Cyclopenten-1-ol is epoxidized stereoselectively in cyclopentane but stereorandomly in methanol. Regardless of the solvent employed, the reaction of the derived methyl ether affords the anti isomer as the major product (4:1).[46] Entry 3[64] illustrates a regio- and stereoselective peracid oxidation; the derived acetate reacts less selectively (7:1) and with a rate 4 times slower. With the substrate in entry 4, where the alcohol function is disposed pseudoequatorially, epoxidation proceeds nonselectively; in contrast the corresponding axial isomer affords the expected epoxide with excellent selectivity (entry 5).[65] Thus, with homoallylic alcohols directivity is more efficient with a pseudoaxially disposed hydroxyl group. The example in entry 6 indicates that the more flexible primary carbinols may not direct epoxidation reactions as efficiently as the secondary or tertiary derivatives.[66] Hydroxy groups in bishomoallylic cyclic alcohols exert little or no influence on the course of peracid epoxidation reactions.[67]

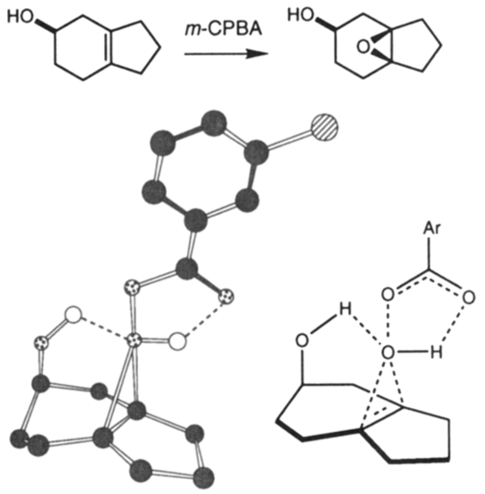
Table 14. Epoxidation of Cyclic Homoallylic Alcohols[a]

Entry	Substrate	Major Product	Selectivity
1			9 : 1
2			"highly selective"
3			16 : 1
4			1 : 1
5			21 : 1
6			5 : 1

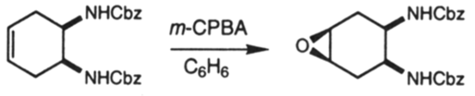
[a] Conditions: Perbenzoic acid, or *m*-chloroperbenzoic acid in benzene or cyclopentane.

A transition structure for the epoxidation of homoallylic alcohols is proposed on the basis of the same principles described for the reaction of allylic systems (vide supra). The transition structure depicted in Scheme 11 may serve as an example.

Scheme 11

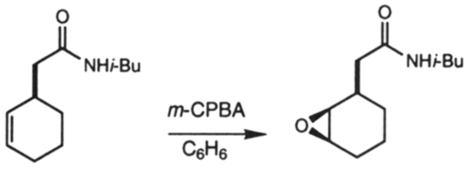


Equations 22[68] and 23[69] illustrate cases where a homoallylic carbamate and a homoallylic amide may affect the stereochemical course of the epoxidation.



(22)

only diastereomer

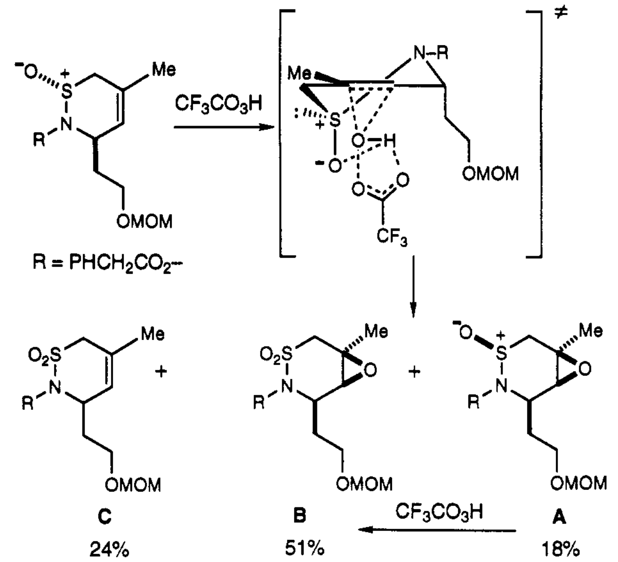


(23)

Diastereocontrol >95 : 5

With trifluoroperacetic acid as oxidant, sulfoxides may direct the epoxidation process (Scheme 12).[70] The *cis*-3,6-dihydrothiazine 1-oxide shown below is oxidized

Scheme 12



stereoselectively to afford the β-epoxy thiazineoxide (A) and the β-epoxy sultam (B) in 18% and 51% yield, respectively. The corresponding unsaturated sultam (C) was isolated as a side product (24%); this compound was shown not to be an intermediate in the formation of aforementioned epoxides, since treatment of this material with trifluoroperacetic acid affords the α-epoxide exclusively. It was proposed that the relevant transition structure contains a sidechain disposed in the pseudoaxial position, so that the unfavorable A(1,3) allylic strain[22] that would otherwise develop between this group and the neighboring carbamate functionality is avoided.

E. Peracid Epoxidation of Acyclic Olefins

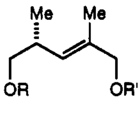
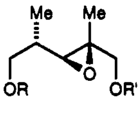
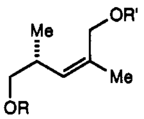
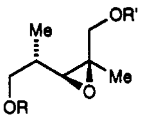
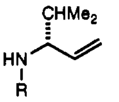
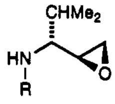
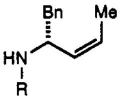
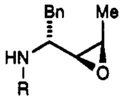
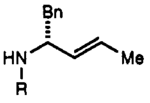
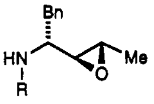
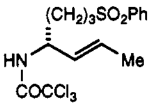
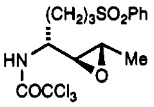
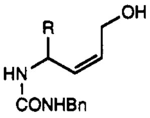
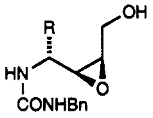
The trisubstituted alkenes shown in entries 1 and 2 of Table 15, upon treatment with *m*-chloroperbenzoic acid at 5 °C, are oxidized with varying levels of stereoselectivity, depending on whether the allylic or the homoallylic hydroxyl group is protected.[71] To account for the observed stereoselectivities, two cooperative hydrogen bonding interactions between the peracid and the olefinic substrate were proposed.

Figure 3 illustrates plausible transition structures where simultaneous association of the peracid with allylic and homoallylic hydroxyl or alkoxy groups leads to diastereoselective epoxidations. These transition states are based on the same steric and stereoelectronic principles that were discussed in detail previously (Figure 2 and Scheme 10). However, as the hydrogen bonding network involves substituents on both of the olefinic carbons, the transition-state structure is expected to be more symmetrical. Therefore, to achieve the proper interatomic distances for effective formation of hydrogen bonds, one of the heteroatom substituents must adopt the "inside" position (~30° O—C—C=C dihedral angle). It is the *allylic* hydroxyl group which projects inside and adopts the smaller O—C—C=C dihedral angle in order to avoid the destabilizing A(1,3) allylic strain. With regard to the dibenzyl ethers in entries 1d and 2d, in the absence of the directing influence of a hydroxy group, epoxidation is nonselective and proceeds at a much slower rate.

Entries 3–7[72] of Table 15 illustrate cases where the epoxidation process is directed by an amide or a urethane functionality. The observed selectivities may be explained through similar mechanisms that were discussed before for cyclic unsaturated carbamates. The transition structure for entry 4a in Table 15 is illustrative (Figure 4).

The improvement in stereoselectivity in entry 6 (Table 15) as compared to that of entry 5b may be ascribed to the additional hydrogen bonding between the peracid and the sulfone oxygens. The trends shown in entries 3–5 of Table 7 are, in general, puzzling and difficult to explain, and any plausible rationalization must await further experimental data. The stereoselectivities illustrated in entry 7 can be accounted for through similar arguments to those that were described for the reaction shown in entry 4a. In fact, the example

Table 15. Stereoselective Epoxidations of Acyclic Olefins[a]

Entry	Substrate	Major Product		Selectivity
1			a. R = H, R' = H	>25 : 1
			b. R = H, R' = Bn	6 : 1
			c. R = Bn, R' = H	>25 : 1
			d. R = Bn, R' = Bn	1 : 1
2			a. R = H, R' = H	4 : 1
			b. R = H, R' = Bn	7 : 1
			c. R = Bn, R' = H	15 : 1
			d. R = Bn, R' = Bn	1 : 1
3			a. R = CO$_2$*t*-Bu	15 : 1
			b. R = Phth	4 : 1
4			a. R = CONHPh	>19 : 1
			b. R = COCCl$_3$	3 : 1
5			a. R = CONHPh	1 : 1
			b. R = COCCl$_3$	3 : 1
6				"highly selective"
7			a. R = Me	10 : 1
			b. R = *i*-Pr	28 : 1

[a] Conditions: *m*-Chloroperbenzoic acid in benzene or CH$_2$Cl$_2$.

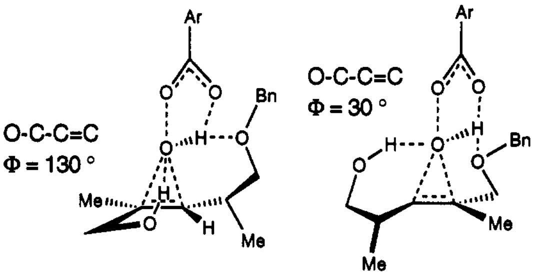


Figure 3. Transition structures for directed epoxidation of acyclic olefins containing both allylic and homoalyllic oxygen heteroatoms.

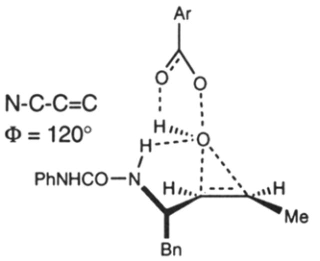
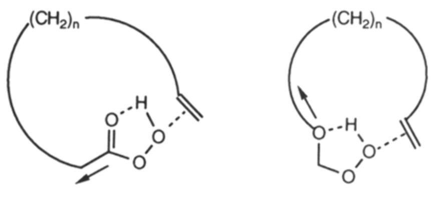


Figure 4. Transition structure for directed epoxidation of acyclic urethane shown in Table 15, entry 4a.

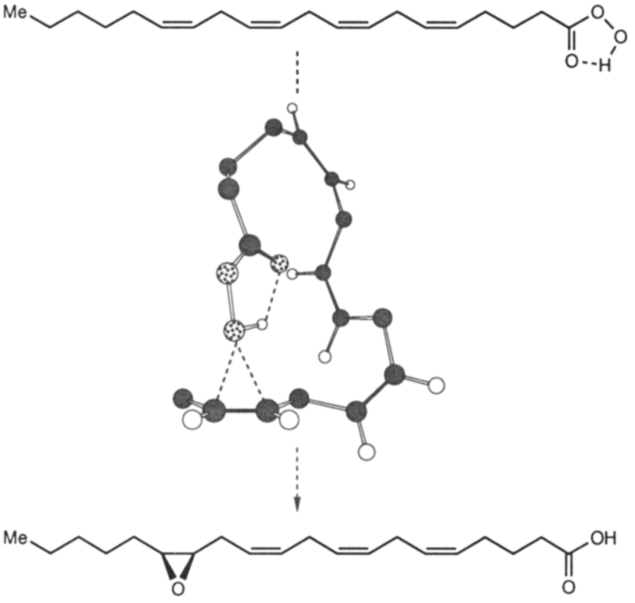
shown in entry 4a serves as a control experiment, indicating that in the oxidation of substrates in entry 7 cooperative hydrogen bonding of the primary alcohol may not be required for high stereoselectivity.

Another class of directed epoxidations are those reactions where a resident peracid or peroxy moiety is generated in situ from a suitable precursor. A remarkable example of this type of epoxidation is shown in Scheme 13.[73] Arachidonic (*cis*-5,8,11,14-tetraenoic) peracid (generated in situ from the corresponding acid), upon standing at 20 °C is epoxidized site selectively to afford a single epoxy ester in near quantitative yield (after esterification with diazomethane). In a control experiment, oxidation of arachidonic acid or the corresponding ester with *m*-CPBA is nonselective and yields a mixture of all possible epoxides. According to Corey, this unprecedented selectivity is an indication that "the 15-membered cyclic structure is energetically quite favorable compared with alternative geometries involving more proximate double bonds and smaller rings". The observed selectivity indicates that "the favored transition state for oxygen transfer may be an (S_N2 like) arrangement with...the C═C π cloud attacking oxygen back side to and collinear with the O–O bond being broken". That is, proper positioning of the alkene and the peracid moiety, as is illustrated in Figure 2, may only be geometrically possible when a certain number of atoms separate the two reacting groups (the peracid and the olefin).

The geometric requirements for intramolecular epoxidation by an internal peracid or peroxide were later investigated.[74] This study was based on the principle that analogous α-hydroperoxy ethers are expected to be highly conducive to intramolecular delivery of oxygen onto a neighboring olefin. As is illustrated below, "the direction of the first bond away from the peroxy carbon permits the geometry required for intramolecular epoxidation to be achieved with fewer connective atoms".

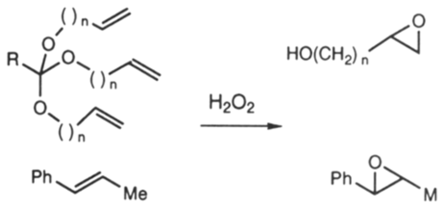


Scheme 13



The relative facility of intramolecular epoxidation of hydroperoxy substrates with variable chain lengths was examined through competition experiments, with β-methylstyrene serving as reference. The outcome of some of these experiments is shown in Table 16. With 90% H_2O_2 (α-hydroperoxy ethers are generated in situ), oxidation of the substrate in entry 1 is slower than β-methylstyrene, whereas the longer chain acetal in entry 3 reacts ~40 times faster. Furthermore, as the reaction solution is made more dilute, the ratio of the acetal oxide to the styrene oxide *decreases* for the substrate in entry 1, but *increases* for the substrate in entry 2 and significantly more so for the compound shown in entry 3. These data indicate that for the allylic substrate (Table 16, entry 1) the intramolecular component for epoxidation is relatively insignificant. The homoallylic (entry 2) and bishomoallylic (entry 3) cases, however, offer strong evidence in support of the intramolecular pathway.

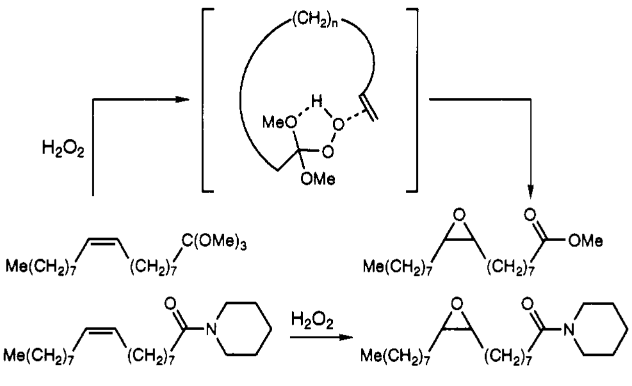
Table 16. Facility of Intramolecular Epoxidations as a Function of Chain Length



Entry	Substrate	k_{intra} / $k_{styrene}$
1	$HC[-O-CH_2-C=CH_2]_3$	<1 M
2	$MeC[-O-(CH_2)_2-C=CH_2]_3$	7 M
3	$HC[-O-(CH_2)_3-C=CH_2]_3$	40 M

Epoxidations of a structurally analogous class of α-hydroperoxy ethers, where the hydrocarbon tether is attached to the acetal *carbon* (as opposed to former cases where it is attached to the acetal *oxygen*), corroborate the above-mentioned hypotheses. Upon repeated dilutions of a 90% H_2O_2 solution of equimolar amounts of the ortho ester and the related cyclohexyl amide, the ester product/amide product ratio rises steadily (Scheme 14). It was therefore concluded that in the above reactions transient hydroperoxy ethers are generated (shown in Scheme 14), and if the resident alkene is accessible, intramolecular oxidation occurs readily.

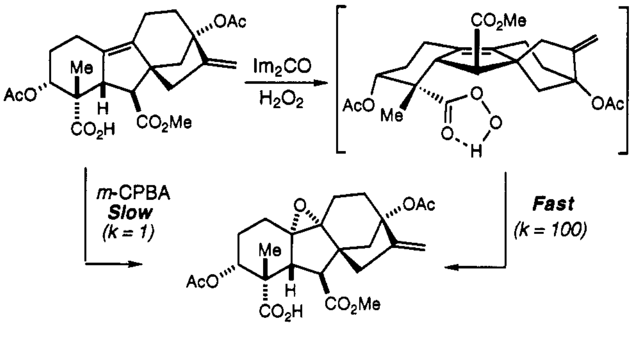
Scheme 14



[*ortho* ester] = [Amide], M	[Ester Prod.] / [Amide Prod.]
1	7
0.5	12
0.25	27

A recent report adds an interesting note to the aforementioned mechanistic proposals: treatment of the carboxylic acid shown in Scheme 15 with *m*-CPBA leads to selective formation of the α-epoxide.[75] The corresponding peracid (prepared in situ from the acid by treatment with Im_2CO and H_2O_2) also affords a single diastereomeric product but at a rate ~100 times faster than the parent carboxylic acid. It was suggested that intramolecular oxidation of the tetrasubstituted olefin by the transient peracid accounts for the above observation. Examination of molecular models clearly indicates that with an internally hydrogen-bonded peracid, alignment of the π_{C-C} and σ^*_{O-O} orbitals is impossible. However, if the peracid is *not* internally hydrogen bonded, proper association of these orbitals is feasible. Accordingly, this transformation should be further catalyzed by added acids. Nonetheless, it is intriguing that in spite of the absence of an internal hydrogen bond, prior generation of the bound peracid results in a noticeable rate acceleration.

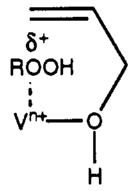
Scheme 15



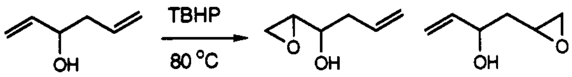
IV. Directed Metal-Catalyzed Epoxidation Reactions

A. Introduction

Interest in catalytic epoxidation increased markedly in the late 1960s following the discovery of transition metal-catalyzed *tert*-butyl hydroperoxide (TBHP)[76,77] epoxidation[78] by Indictor and Brill.[79] Soon afterward, it was established that the reactivity of an olefin typically correlates with its nucleophilicity,[80] and that the epoxidation of allylic alcohols with vanadium catalysts is anomalously rapid.[80,81] Whereas $Mo(CO)_6$ is generally a more active catalyst than $VO(acac)_2$, for allylic alcohols the reverse is true.[80] There had been earlier indications that strong inhibition by *tert*-butyl alcohol of $VO(acac)_2$-catalyzed TBHP epoxidation.[82] To account for these observations, Sheng and Zajacek postulated that the vanadium-catalyzed reaction proceeds through the ternary complex shown.[83]



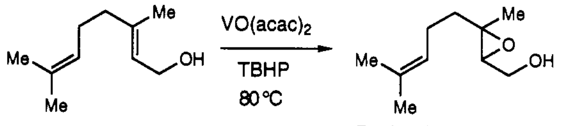
Later reports indicated that the diastereoselective epoxidation of an allylic and a homoallylic alcohol by $VO(acac)_2$/TBHP, as well as the regioselective epoxidation of 1,5-hexadien-3-ol (eq 24).[84,85]



(24)

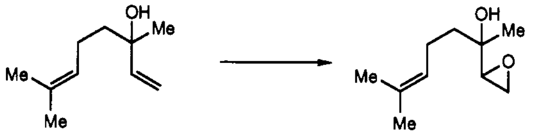
Catalyst		
	$VO(acac)_2$	4 : 1
	$Mo(CO)_6$	1 : 1

Olefinic alcohols are epoxidized with regio- and stereocontrol by TBHP in the presence of either $Mo(CO)_6$ or $VO(acac)_2$.[86] The site-selective epoxidation of geraniol and linalool (eqs 25 and 26) illustrates that hydroxyl groups are able to deliver the oxidant regioselectively to the less electron-rich alkene of a diene.



(25)

Regioselection 49:1



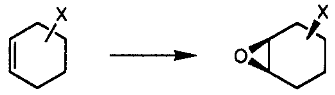
(26)

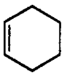
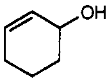
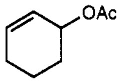
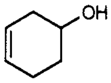
Regioselection 20:1

Sharpless and co-workers quantified the enhanced reactivity observed as a result of a directing functionality (Table 17).[87] In contrast to directed peracid epoxidation (Table 12),[88] where introduction of a hydroxyl group has a net *deactivating* impact on olefin reactivity, the metal-catalyzed reaction shows a dramatic overall *rate enhancement*.[89] Allylic, homoallylic, and even bishomoallylic alcohols are substantially more reactive toward epoxidation by $VO(acac)_2$/TBHP than are the analogues lacking an OH. In cyclic systems, high levels of syn stereoselectivity are observed (Table 17), consistent with oxygen atom transfer within an intramolecular complex.

Although a detailed mechanistic pathway for these metal-catalyzed epoxidations has not been elucidated, based on the available data, Sharpless has proposed that the vanadium-catalyzed reaction proceeds through the cycle depicted in Scheme 16.[57] The lower-valent $VO(acac)_2$ complex is oxidized by TBHP to a catalyt-

Table 17. Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives



Substrate	k_{rel}^{a,b} (diastereoselectivity^c) peracid	Mo(CO)$_6$	VO(acac)$_2$
	1.00	1.00	1.00
 OH	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
 OAc	0.046 (37 : 63)	0.07 (40 : 60)	--
 OH	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

[a] The relative rate data apply only to a given column. [b] The peracid relative rates are reported in ref 87. [c] The values in parentheses refer to the ratio of syn:anti epoxide.

Scheme 16

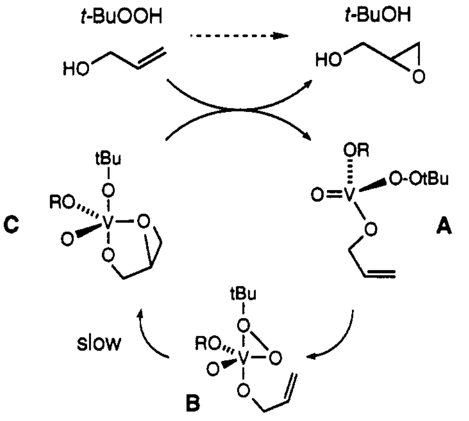
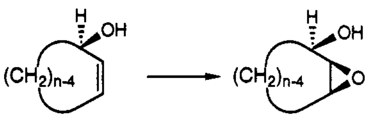


Table 18. Percent Syn Isomer in the Epoxidation of Cyclic Allylic Alcohols



n	VO(acac)$_2$	MoO$_2$(acac)$_2$	m-CPBA
5	99.2	--	84
6	99.7	98	95
7	99.6	95	61
8	97	42	0.2
9	91	3	0.2

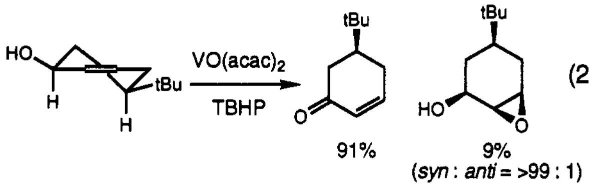
ically active d^0 vanadate ester (VO(OR)$_3$),[90-92] which undergoes rapid ligand exchange[93] to provide A. Following activation of the alkylperoxide by bidentate coordination (B),[94] nucleophilic attack by the alkene in the rate- and stereochemistry-determining step yields the epoxy alcohol complex C.

Applications of hydroxyl-directed,[95,96] metal-catalyzed epoxidation in organic synthesis are discussed below.[97-99] As the issue of diastereoselectivity constitutes the primary focus, where possible, working transition state models based on the Sharpless mechanism are provided.

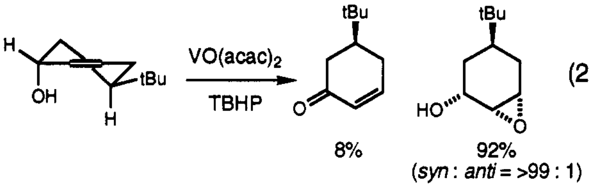
B. Metal-Catalyzed Epoxidation of Cyclic Olefins

Sharpless demonstrated that directed epoxidation of cyclohexenols occurs syn to the hydroxyl group.[86] Subsequent reports provided a more comprehensive examination of reactions of cyclic olefinic alcohols.[100,101] In contrast to epoxidations with *m*-CPBA or MoO$_2$(acac)$_2$, for which formation of the anti epoxy alcohol is favored for medium (eight- and nine-) membered rings, VO(acac)$_2$-catalyzed reactions display a preference for the syn product for all ring sizes from five to nine (Table 18).[102] Oxidation of the allylic alcohol to the enone[103] can be a significant side reaction, particularly for substrates in which the hydroxyl group is strongly disposed to lie in a pseudoequatorial position.

In the reaction of 5-*tert*-butyl-2-cyclohexenol, the pseudoaxial alcohol undergoes epoxidation 34 times faster than the pseudoequatorial diastereomer, whereas the latter alcohol is oxidized to the enone about three times faster than the former (eqs 27 and 28).[104,105] These data suggest a preferred epoxidation geometry wherein the hydroxyl group is oriented well above the nodal plane of the alkene π system.



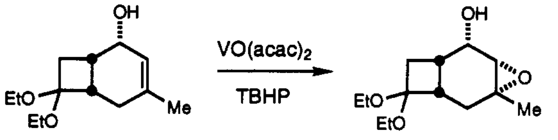
(27)



(28)

Allylic, homoallylic, and bishomoallylic alcohols direct epoxidations effectively and a range of functional groups are compatible with the reaction conditions (Table 19).[106] In the example shown in entry 5, the hydroxyl group provides regioselectivity while the topography of the substrate dictates facial selectivity.[107] Entry 6 demonstrates that electron-deficient olefins undergo directed epoxidation; the related compound lacking a hydroxyl group is unreactive under the same conditions.[108]

There have been reports of directed epoxidations in cyclic systems which proceed with comparatively low stereoselectivity.[109] For example, in studies directed toward the total synthesis of paniculide A, a 3:1 mixture of endo:exo epoxide isomers were obtained (eq 29).[110] The poor stereoselection may be attributed to steric inhibition of alcohol–vanadium complexation.

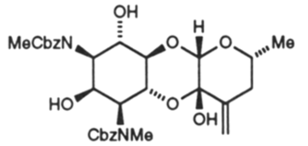
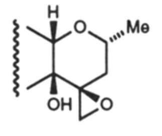
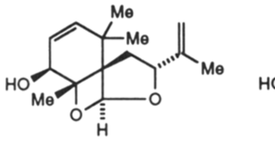
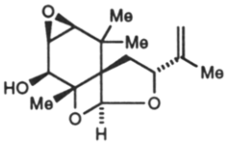
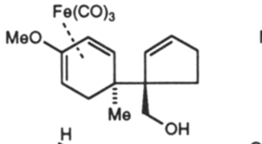
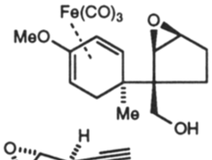
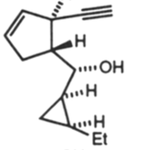
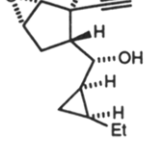
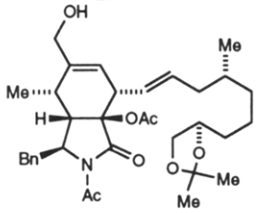
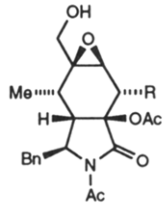
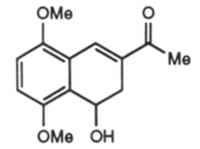
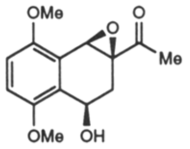


(29)

Diastereoselection 3:1

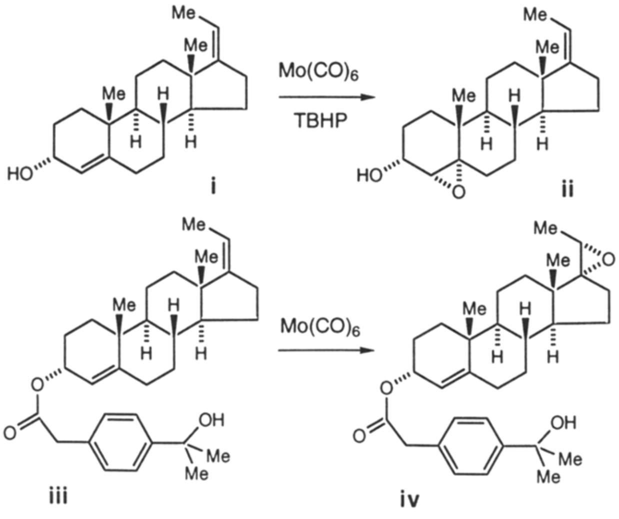
Scheme 17 illustrates an epoxidation method that involves incorporation of a removable functionality bearing a hydroxyl group positioned for delivering an

Table 19. Mo-Catalyzed Epoxidation of Cyclic Olefinic Alcohols

Entry	Substrate	Product	Yield (%)
1			78
2			94
3			90
4			87
5[a]			95
6			--

[a] Catalyst: $Mo(CO)_6$.

Scheme 17



oxidant to a nearby alkene.[111] Site-selective directed epoxidation of remote olefins was achieved, and the geometrical requirements for reaction were shown to be stringent. Whereas epoxidation of i provides ii as the only product, reaction of the derived hydroxy ester iii produces only iv. Interestingly, attempted epoxidation of the meta isomer of iii results in no detectable reaction under these conditions.

There have been numerous reports on the stereoselective directed epoxidation of complex macrocycles (Table 20).[112] The requirement of hydroxyl delivery for reaction permits regioselective epoxidation of polyene systems. Analogous regioselectivity is not observed with *m*-CPBA. For example, in the epoxidation illustrated in entry 2, reaction with peracid occurs preferentially at the *trans*-olefin. As is indicated in entry 5, treatment with *m*-CPBA produces a mixture of products resulting from competitive epoxidation of all three olefins.

C. Metal-Catalyzed Epoxidation of Acyclic Olefins

1. Allylic Alcohols

High levels of organization in the transition state of a reaction often result in high levels of acyclic stereocontrol. A systematic study of diastereocontrol in epoxidation reactions of acyclic allylic alcohols was performed by Sharpless;[113] a representative set of the data reported in this study are illustrated in Table 21.

A three-dimensional depiction of a reasonable transition structure,[114] essentially identical to the model suggested by Sharpless, is shown in Figure 5.[57] The O—C—C=C dihedral angle in the allylic alcohol is about 40°.[115] The salient interactions are (1) A(1,2) strain[22] between R_{gem} and R_1,[116] favoring the erythro isomer; (2) A(1,3) strain between R_2 and R_{cis}, favoring the threo isomer; (3) 1,3-interaction between L and R_1, favoring the erythro isomer; (4) hyperconjugative donation (σ_{C-R_2} to $\pi^*_{C=C}$), which increases the nucleophilicity of the olefin, favoring the erythro isomer.

Careful analysis of experimental data leads to the conclusion that minimization of A(1,2) or A(1,3) strain typically dictates the observed sense of epoxidation. For terminal or trans olefins, where these interactions are comparatively weak, otherwise subordinate steric and electronic effects become important (Scheme 18).

The patterns of erythro selectivity illustrated in Table 22 are consistent with the trends predicted by the above model.[117] Comparison of entry pairs (1, 2), (3, 4), and (5, 6) reveals a modest sensitivity to the steric bulk of R_α, whereas entries 1, 3, and 7 show a substantial dependence on the size of R_{gem}.

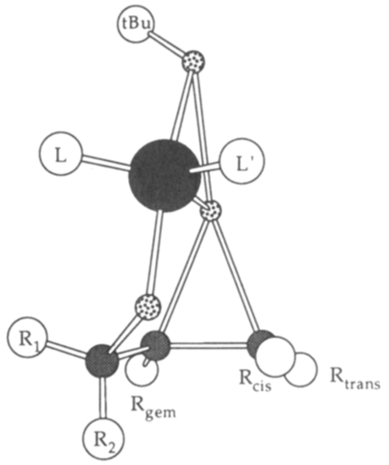
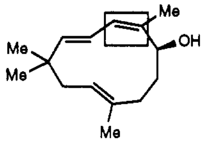
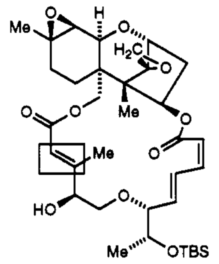
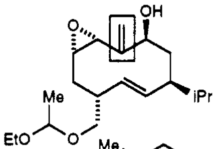
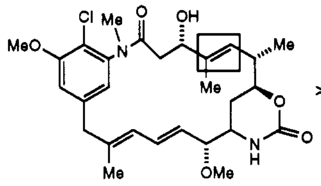
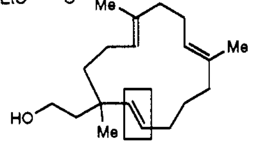


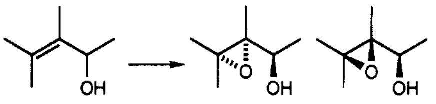
Figure 5. Transition structure for metal-catalyzed allylic alcohol epoxidation.

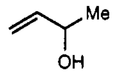
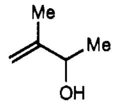
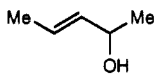
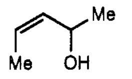
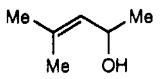
Table 20. Epoxidation of Macrocyclic Olefinic Alcohols[a]

Entry	Substrate	Selectivity	Entry	Substrate	Selectivity
1		9 : 1 (α)	4		single epoxide (α)
2		single epoxide (β)	5		>200 : 1 (β)
3		1 : 1			

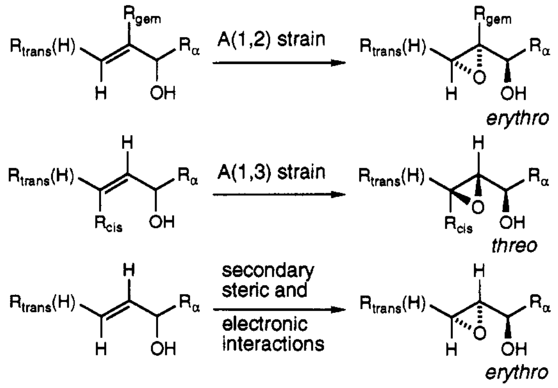
[a] Site of epoxidation indicated with a box.

Table 21. Epoxidation Selectivity of Allylic Alcohols



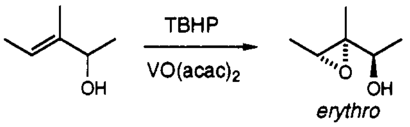
Entry	Substrate	VO(acac)$_2$	Mo(CO)$_6$	*m*-CPBA
1		4 : 1	1 : 1	1 : 1.5
2		19 : 1	5 : 1	1 : 1
3		2.5 : 1	1 : 1.5	1 : 1.7
4		1 : 2.4	1 : 5	1 : 19
5		1: 5	1 : 19	1 : 19

Scheme 18



This sensitivity of reaction diastereoselection to the bulk of R_{gem} has been exploited in a number of applications in synthesis.[118] Thus, use of a trimethylsilyl group as a dummy substituent[119,120] affords a route to diastereomerically pure erythro epoxy alcohols (diastereoselection >25:1, eq 30).[121]

Table 22. Erythro-Selective Epoxidation of Allylic Alcohols



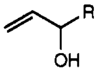
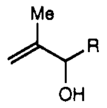
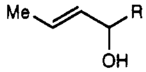
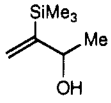
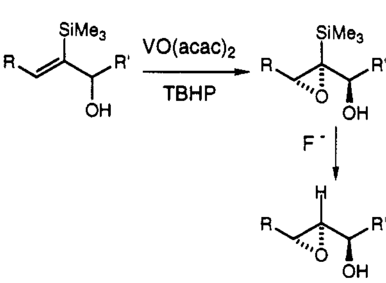
Substrate	Entry	R	*Erythro*:*Threo*
	1 2	Me *i*-Pr	4 : 1 5.6 : 1
	3 4	Me Bu	19 : 1 49 : 1
	5 6	Me *t*-Bu	2.4 : 1 3.7 : 1
	7		>99 : 1

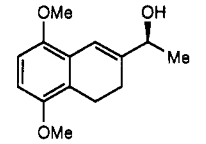
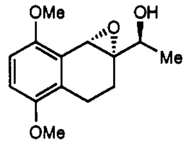
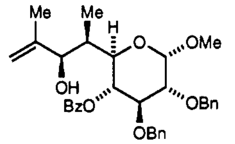
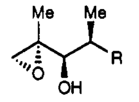
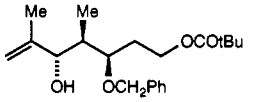
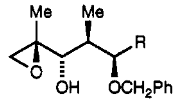
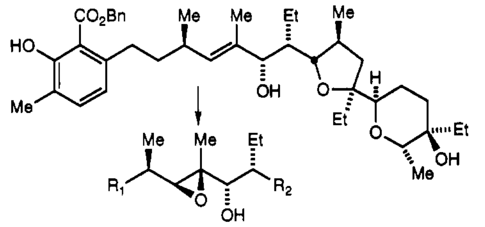
Table 23[122] presents examples of epoxidations of more highly functionalized acyclic systems.[123] The level of erythro selectivity is comparable to that observed with the simpler substrates.[124] Entries 2 and 3 indicate that the α-stereocenter is the dominant stereocontrol element.[125]



(30)

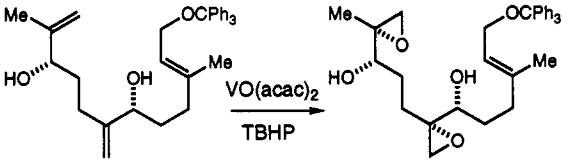
The erythro-selective epoxidation of two allylic alcohols shown in eq 31, key step in the synthesis of *dl*-C_{18} *Cecropia* juvenile hormone, has been performed by a one-pot operation.[126,127]

Table 23. Erythro-Selective Epoxidation of Allylic Alcohols: Applications

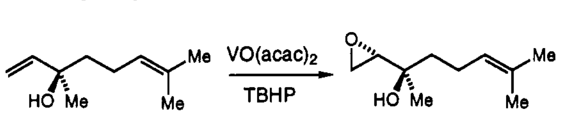
Entry	Substrate	Product	Selectivity[a]
1			24 : 1
2			only (8 : 1)
3			only
4			10 : 1 (7 : 3)

[a] Values in parentheses refer to selectivity observed with m-CPBA.

Equations 32 and 33 provide examples of stereoselective epoxidations of tertiary allylic alcohols.[128,129] In general, the reaction proceeds with low levels of selectivity, as one would predict from the A(1,2) strain-based model discussed earlier. However, the Corey synthesis of (±)-ovalicin, which employs directed epoxidation as the ultimate step (eq 33), affords a rare example of a highly stereoselective epoxidation of a tertiary allylic alcohol.[128d]

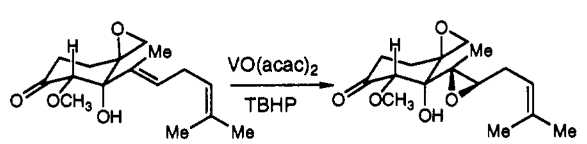


(31)



(32)

Diastereoselection 2:1



(33)

Diastereoselection >20:1

As noted above, allylic alcohols bearing R_{cis} but no R_{gem} undergo a threo-selective epoxidation. Table 24[130] shows that as the bulk of R_{cis} (entries 1 and 2) or R_{anti} (entries 2 and 3) increases, the diastereoselectivity increases, in accord with the prediction of the A(1,3)-strain[22] model. A sufficiently bulky R_{cis} substituent may override the normal erythro preference of allylic alcohols which bear R_{gem}.[118]

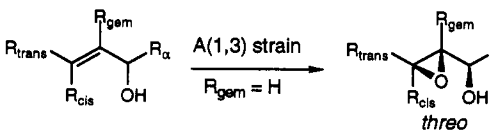
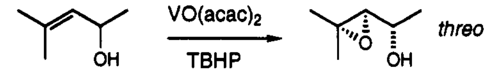
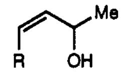
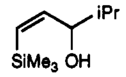
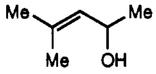
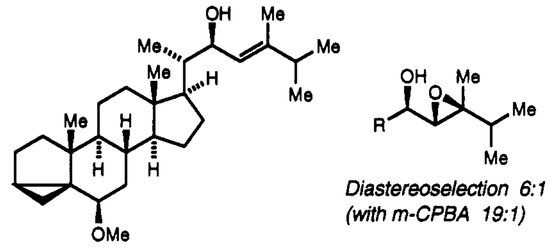


Table 24. Threo-Selective Epoxidation of Allylic Alcohols



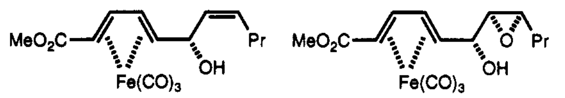
Substrate	Entry	R	*Threo* : *Erythro*
	1	Me	3 : 1
	2	SiMe$_3$	24 : 1
	3		>99 : 1
	4		6 : 1

Equations 34–36 are examples of threo-selective epoxidation in more complex systems.[131] The reaction in eq 35 demonstrates that a diene complexed to iron tricarbonyl is stable to the reaction conditions. In studies directed toward the total synthesis of tirandamycin A, a directed epoxidation of the diol shown in eq 36 was realized; no rationale was offered for the observed stereoselectivity.[131c]



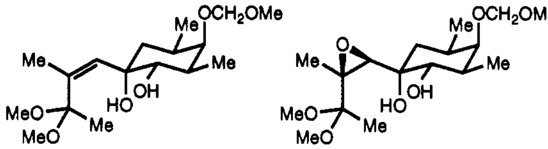
(34)

Diastereoselection 6:1 (with m-CPBA 19:1)



(35)

Diastereoselection 1.5:1



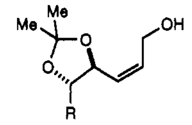
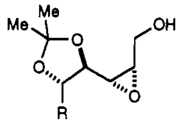
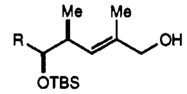
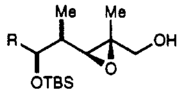
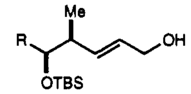
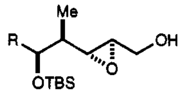
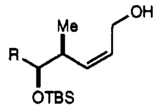
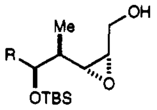
(36)

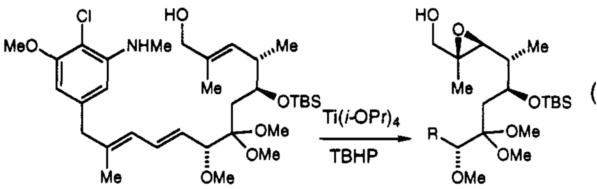
Diastereoselection >20:1 (with m-CPBA 9:1)

Diastereoselective epoxidation of allylic alcohols where the hydroxyl-bearing carbon is not a stereogenic center has been achieved (Table 25).[132] In these reactions, the role of the hydroxyl group is to enhance the reactivity of the olefin, while the allylic stereocenter dictates the facial selectivity. First-order models for electrophilic addition to olefins do not properly rationalize these results (entries 1 vs 2; 3 vs 5, Table 25).[133]

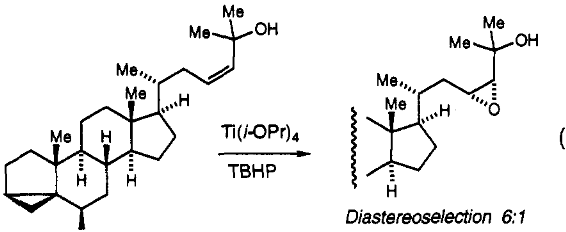
Entries 3–5 of Table 25 illustrate cases of stereoselective Ti(O*i*-Pr)$_4$-catalyzed epoxidation of allylic alcohols. Equation 37 depicts the selective oxidation performed in the synthesis of racemic maysine.[132b] Equation 38 illustrates a case of epoxidations of allylic alcohols where a remote *homoallylic* stereocenter controls the diastereoselection; no rationale was provided for these results (eq 38).[134]

Table 25. Epoxidation Diastereocontrol by Other Stereocenters

Entry	Substrate	Product	Reagent	Selectivity
1	 R = H		$VO(OEt)_3$	5 : 1
2	R = CH_2OBn		$VO(OEt)_3$	1 : 3.5
3	 R = $(CH_2)_4OTBS$		Ti(O*i*-Pr)$_4$ VO(acac)$_2$ *m*-CPBA	10 : 1 1.5 : 1 1 : 99
4	 R = CH_2CH_2Ph		Ti(O*i*-Pr)$_4$ VO(acac)$_2$ *m*-CPBA	2.3 : 1 2.5 : 1 >25 : 1
5	 R = CH_2CH_2Ph		Ti(O*i*-Pr)$_4$	5.7 : 1

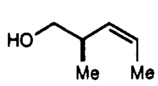
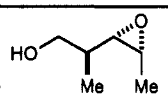
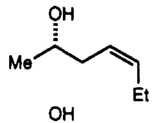
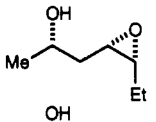
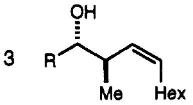
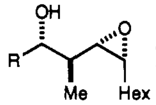
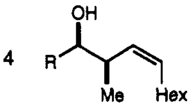
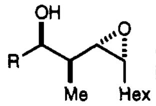

(37)

Diastereoselection >20:1


(38)

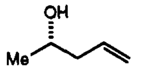
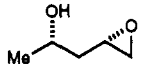
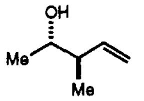
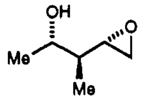
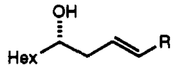
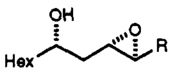
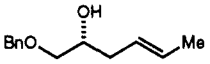
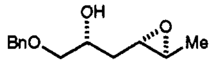
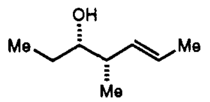
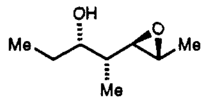
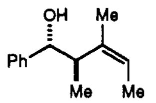
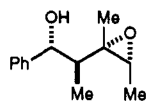
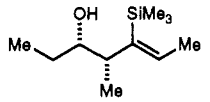
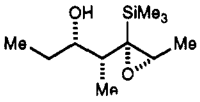
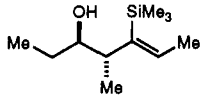
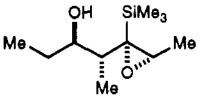
Diastereoselection 6:1 (no selectivity with m-CPBA)

Table 26. Epoxidation of Cis Homoallylic Alcohols[a]

Entry	Substrate	Product	Selectivity
1			>400 : 1
2			12 : 1
3		 a. R = Me b. R = $CH(CH_3)_2$	104 : 1 >400 : 1
4		 a. R = Me b. R = $CH(CH_3)_2$	70 : 1 2.1 : 1

[a] Conditions: TBHP, VO(acac)$_2$.

Table 27. Epoxidation of Homoallylic Alcohols[a]

Entry	Substrate	Product	Selectivity
1			2 : 1
2			4.6 : 1
3	 R = $(CH_2)_7CO_2Me$		1.4 : 1
4			"only"
5			1.5 : 1
6			8 : 1
7			>99 : 1
8			2 : 1

[a] Conditions: TBHP, VO(acac)$_2$.

2. Homoallylic Alcohols

In 1981, Mihelich reported the first systematic study of the diastereoselective epoxidation of acyclic homoallylic alcohols.[135] Substrates bearing a stereocenter either α or β to the alkene were found to undergo epoxidation with high levels of stereocontrol (entries 1 and 2). It is worthy of note that the diastereoselection observed for (*Z*)-2-methyl-3-penten-1-ol (entry 1) is higher than that observed for its allylic homologue (Table 26, entry 4). With an α- and a β-stereocenter present, the former appears to be the dominant stereocontrolling element (entries 3 and 4).

Other classes of alkenes have not been studied as systematically, but there are indications that, in general, oxidations proceed with somewhat lower levels of selectivity (Table 27, entries 1–3, 5, and 6).[136] As with allylic alcohols, use of a removable trimethylsilyl group at the R_{gem} position to control diastereoselection can be effective (entry 5 vs 7). This strategy was used in a synthesis of the C(1)–C(7) segment of 6-deoxyerythronolide B.[136d] The approach fails with the corresponding anti isomer (entry 8).

Mihelich has proposed that both the sense and the magnitude of asymmetric induction may be predicted through comparison of two diastereomeric chairlike transition states.[137] According to this model (Figure 6, box), the sense of stereoselection is governed by the minimization of A(1,3) strain between R_4 and R_7, and better selectivity is generally obtained when the substituent α to the alcohol is oriented in the less encumbered pseudoequatorial orientation. Our analysis (Figure 6) largely echoes that of Mihelich. Only geometries i and ii, which afford diastereomeric products, obey the constraints suggested by molecular models. For *cis*-olefins, i, which corresponds to the transition structure in Figure 6, is greatly preferred over ii due to the highly unfavorable R_1–R_7 interaction present in the latter. However, for substrates with R_7 = H (Table 27), low levels of diastereoselection are

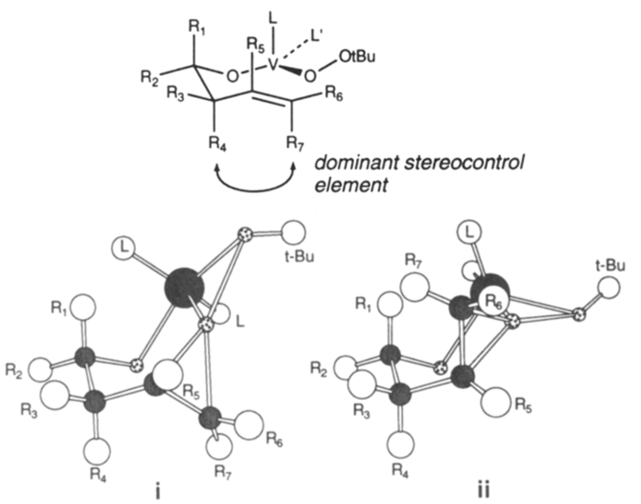
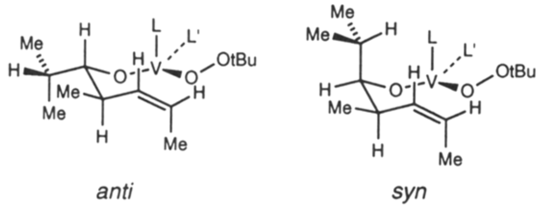


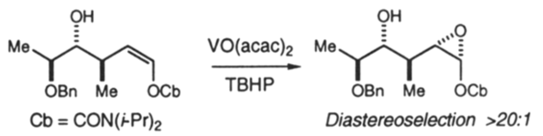
Figure 6. Transition structure for metal-catalyzed homoallylic alcohol epoxidation.

observed since structure ii is now of comparable energy to i (Figure 6).

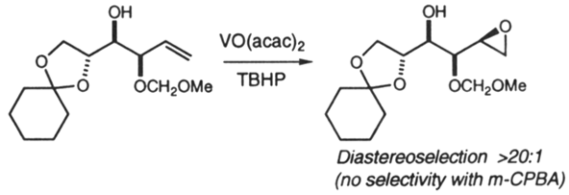
The seemingly anomalous result shown in entry 4b of Table 26 is accommodated within this analysis.[138] Structure i suggests that the anti isomer should provide slightly higher diastereoselection than the syn compound, since both substituents occupy pseudoequatorial positions in the transition state (R_2 and R_3). The relative selectivities displayed in entries 3a and 4a are consistent with this paradigm. The dramatic difference in stereoselection observed for entries 3b and 4b may at first appear puzzling. However, closer inspection of the transition structure reveals the key role played by the isopropyl group: whereas for the anti compound this group may adopt a conformation devoid of destabilizing interactions, for the syn isomer avoiding an unfavorable *syn*-pentane relationship is not feasible.



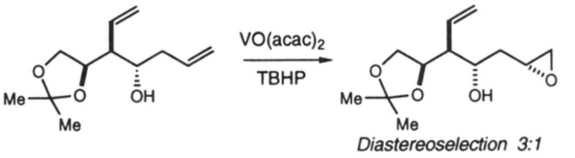
Equations 39–41 present several diastereoselective epoxidations of more highly functionalized homoallylic alcohols.[139] Enol carbamates are epoxidized with high selectivity; for the case shown in eq 39, the stereochemistry of the γ-carbon plays no appreciable role in the stereodifferentiation. The transformation shown in eq 40 offers a rare example of a highly stereoselective epoxidation of a homoallylic alcohol bearing no cis substituent.[140] The diastereoselectivity obtained in the course of a synthesis of the C_{14}–C_{20} unit of amphotericin B is more typical (eq 41). The site specificity of this reaction has been attributed to the presence of an additional 1,3-interaction in the transition state of the less reactive alkene.[141]



(39)



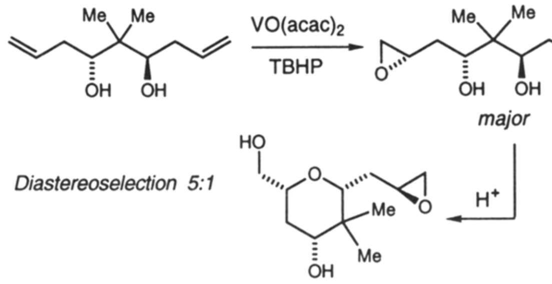
(40)



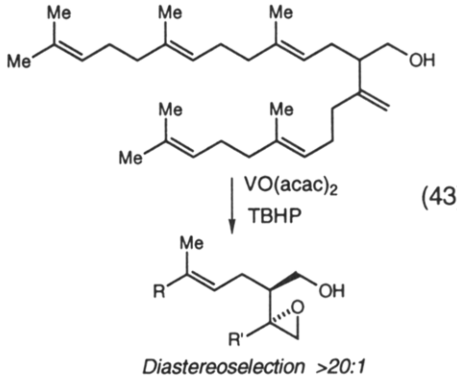
(41)

Epoxidation of alkenes in the symmetrical diene shown in eq 42, followed by acid-catalyzed cyclization results in the formation of a 5:1 mixture of pyran diastereomers.[142]

The stereo- and regiospecific epoxidation of a polyene on route to a synthesis of (±)-bifarnesol (eq 43) affords yet another example of hydroxyl-mediated regio- and stereocontrol. Oxidation through the intermediacy of transition structure i (Figure 7), where the triene unit occupies R_4 to minimize A(1,2) strain, offers a plausible rationale for the observed selectivity.[143]



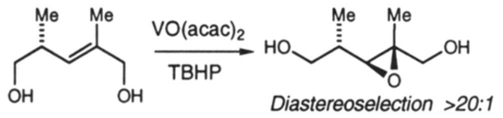
(42)



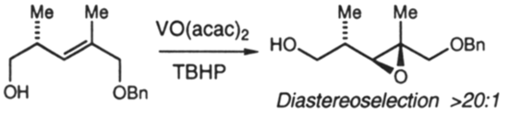
(43)

Equations 44–46 illustrate three epoxidations where either an allylic or a homoallylic heteroatom may direct the course of the reaction.[71,144] For the *trans*-olefin, epoxidation of the allylic benzyl ether affords the same sense and level of stereoselectivity as that of the diol (eq 44 and 45). In contrast, when the homoallylic alcohol is protected, epoxidation proceeds essentially stereorandomly (eq 46); this is consistent with exclusive binding of the allylic alcohol to the metal center as the source of diastereoselectivity in eq 44. These data require a transition state that involves participation of the homoallylic hydroxyl, but neither preclude nor demand the simultaneous involvement of the allylic hydroxyl group.

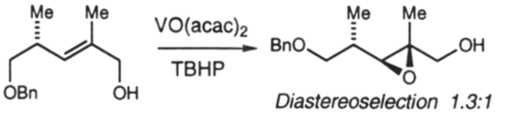
For the *cis*-alkene, the data suggest a role in diastereoselection for the allylic (eqs 47 and 48), as well as for the homoallylic, hydroxyl group; whether these groups interact independently or simultaneously (or



(44)

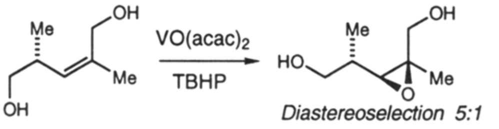


(45)

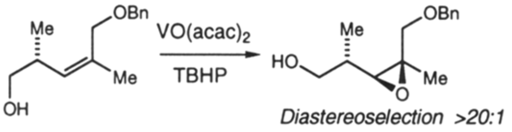


(46)

both) with vanadium is unclear. Comparison of the relative rates of epoxidation within each set of substrates might provide additional insight with regard to the nature of the vanadium-alcohol interactions responsible for the observed diastereoselectivity.[145]



(47)



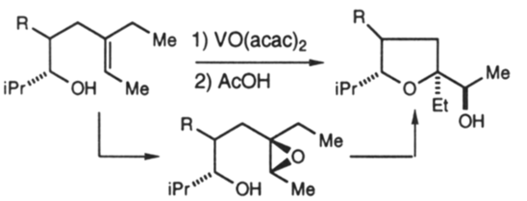
(48)

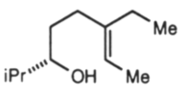
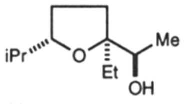
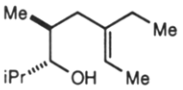
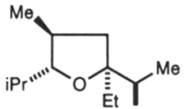
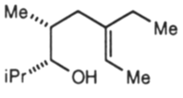
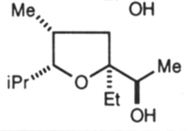
3. Bishomoallylic and Trishomoallylic Alcohols

In connection with the synthesis of lasalocid A, the first diastereoselective directed epoxidations of bishomoallylic alcohols was realized (Table 28).[146] Efficient 1,4-asymmetric induction was achieved; the stereocenter α to the alcohol appears to play a dominant role over the β-site in determining the sense of observed induction.

The two distinct transition structures illustrated in Figure 7 (box) were proposed by Kishi. Models indicate that structure I (Figure 7) best fulfills the steric, stereoelectronic, and geometrical constraints for epoxidation. To avoid a destabilizing transannular interaction, the substituent α to the hydroxyl group occupies the "outside" position in I; this accounts for the sense of stereoselection shown in entry 1 (Table 28).[147] Kishi's model offers a tenable rationale for the trends indicated in entries 2 and 3. Replacement of hydrogen with alkyl at R destabilizes I more than it does II (by an additional 1,3-interaction), leading to decreased stereoselectivity (entry 1 vs 2). Similarly, replacement of hydrogen with alkyl at R′ results in higher stereoselectivity (entry 1 vs 3).

Table 28. Epoxidation of Bishomoallylic Alcohols



Entry	Substrate	Product	Selectivity
1			9 : 1
2			6 : 1
3			>20 : 1

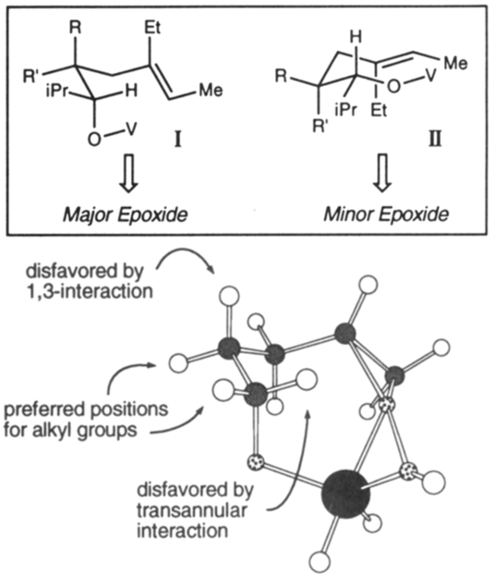
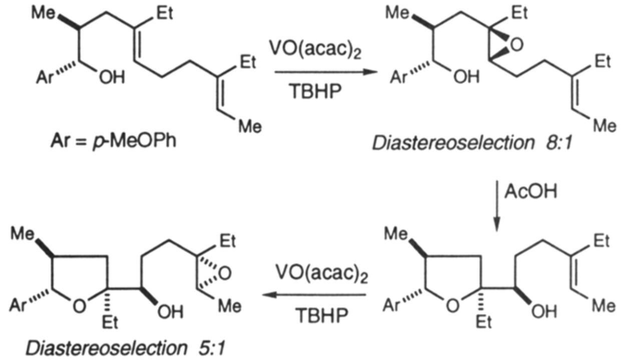
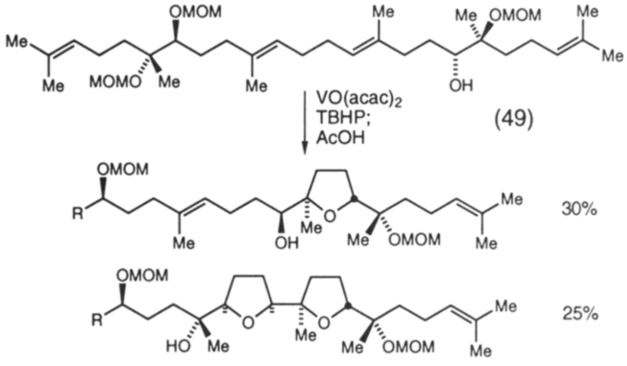

I
II
Major Epoxide
Minor Epoxide
disfavored by 1,3-interaction
preferred positions for alkyl groups
disfavored by transannular interaction

Figure 7. Transition structure for metal-catalyzed bishomoallylic alcohol epoxidation.

Scheme 19

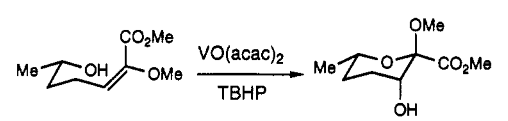


Iterative epoxidation has been utilized as a key sequence in a number of synthesis plans; Kishi's lasalocid A synthesis is illustrative (Scheme 19).[148] Other syntheses of polyether antibiotics have helped to define further the scope of the diastereoselective epoxidation of bishomoallylic alcohols.[149]



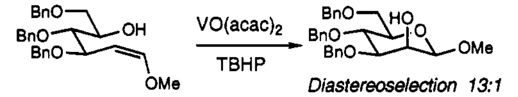
Directed epoxidation has been used for the construction of a bis(tetrahydrofuran) intermediate in the synthesis of teurilene (eq 49).[150] Despite the low yield, the reaction is worthy of note, as it represents the first report of a successful propagating epoxidation–cyclization.

The epoxidation of bishomoallylic alcohols has also found use in the synthesis of glycosides (eqs 50 and 51).[151] The first example of a stereoselective hydroxyl-directed epoxidation of a trishomoallylic alcohol is illustrated in eq 52.[152]



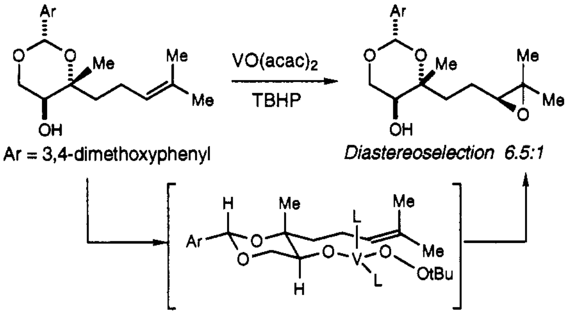
(50)

Diastereoselection 7:1
(no selectivity with m-CPBA)



(51)

Diastereoselection 13:1
(with m-CPBA 1:2)



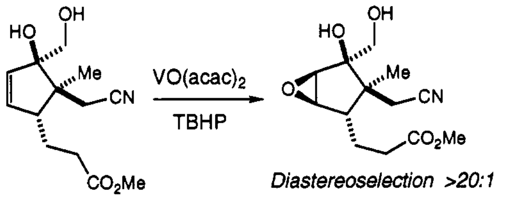
(52)

Ar = 3,4-dimethoxyphenyl

Diastereoselection 6.5:1

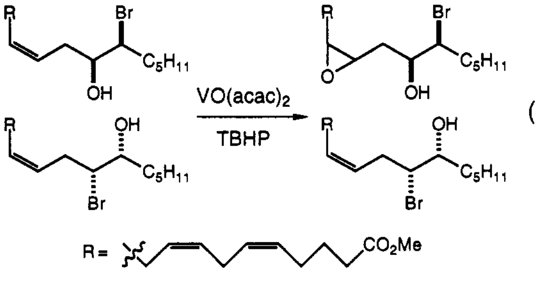
D. Relative Reactivity of Homologous Olefinic Alcohols

In general, the reactivity of an olefinic alcohol depends on the proximity of the hydroxyl group to the alkene.[80,86] In studies directed toward the synthesis of vitamin B-12, the superior directing ability of an allylic to a homoallylic hydroxyl group was demonstrated (eq 53).[153] Furthermore, as is illustrated in eq 54, the differential reactivity of homoallylic and bishomoallylic alcohols has been exploited in the separation of a mixture of bromohydrins formed in route to the synthesis of a family of eicosanoids.[154]



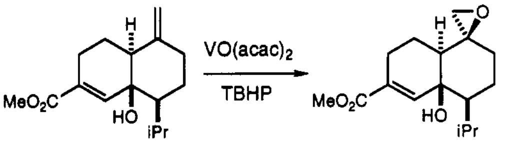
(53)

Diastereoselection >20:1

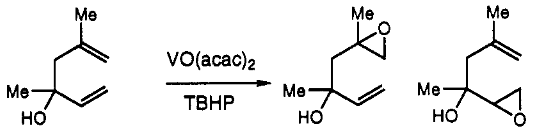


(54)

There have been several accounts of preferential epoxidations of a homoallylic alcohol in the presence of an allylic system (eqs 55–58).[155] The low nucleophilicity of an enoate π-system provides an explanation for the Mo(CO)$_6$-catalyzed epoxidation shown in eq 55;[106p] in contrast, the outcome shown in eq 56 is somewhat surprising.[155b] Equation 57 illustrates an epoxidation where either diastereomer of the diol shown affords the derived α-epoxide as a single isomer.[106f] Only the homoallylic alcohol dictates the facial selectivity, overriding the high erythro preference observed when this hydroxyl is either protected or removed (Table 23, entry 1); reaction by way of a chelated substrate–metal complex is not geometrically feasible. The transformation depicted in eq 58 is consistent with direction by a homoallylic hydroxyl in preference to an allylic hydroxyl group. Competition experiments both within each class of olefinic alcohols and among homologues would provide insight into the factors determining the relative rates of directed epoxidations.

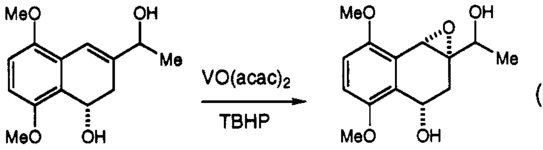


(55)

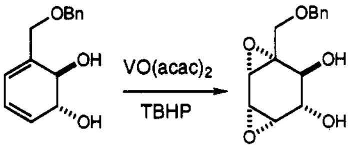


(56)

Regioselection 2:1



(57)



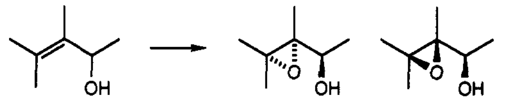
(58)

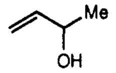
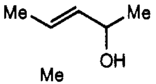
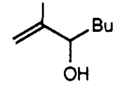
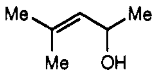
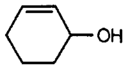
E. Other Metal Catalysts for Directed Epoxidation

A variety of reagents other than vanadium[91] and molybdenum[92] complexes selectively epoxidize allylic alcohols in the presence of isolated olefins, but most of these systems have not been examined extensively. Niobium, zirconium, tantalum, hafnium, titanium, and a number of lanthanide alkoxides effect the regioselective epoxidation of geraniol with TBHP,[156] but only Ti(Oi-Pr)$_4$ has found use in the synthesis of complex molecules.[157] Treatment of geraniol with oxo(tetraphenylporphyrinato)titanium(IV) and TBHP regiospecifically produces the 2,3-epoxy alcohol,[158] an observation which is not accommodated by a Sharpless-type mechanism, where three coordination sites on the same side of the porphyrin are required. Arenearsonic acids (ArAsO(OH)$_2$) in combination with aqueous H_2O_2 effect site-selective epoxidation of geraniol (22:1), as well as syn epoxidation of 2-cyclohexen-1-ol (20:1).[159] The reaction is postulated to occur via the allyl arsonate.

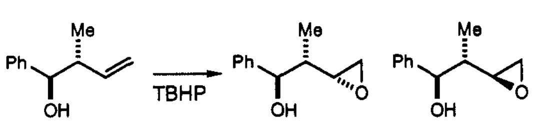
Three directed epoxidation systems have been studied in some detail: H_2WO_4/H_2O_2,[160] Al(Ot-Bu)$_3$/TBHP,[161] and Bu$_2$SnO/TBHP.[153c] For each, epoxidation of geraniol provides the 2,3-epoxy alcohol exclusively. The erythro/threo selectivity of these catalysts for typical allylic alcohols is shown in Table 29.[162] The tungstic acid diastereoselection resembles that of VO(acac)$_2$; the aluminum *tert*-butoxide, Mo(CO)$_6$. Tin-catalyzed epoxidation is responsive both to the nucleophilicity of the olefin and to the proximity of the hydroxyl group.[153c]

Table 29. Epoxidation Selectivity of Various Metal Catalysts



Substrate	V	W	Mo	Al	Sn
	80 : 20	85 : 15	56 : 44	58 : 42	--
	71 : 29	60 : 40	38 : 62	36 : 64	--
	98 : 2	95 : 5	84 : 16	87 : 13	90 : 10
	14 : 86	10 : 90	5 : 95	<0.5 : >99.5	5 : 95
	98 : 2	95 : 5	98 : 2	>99.5 : <0.5	--

The only reported example of an epoxidation of a homoallylic alcohol by Al(O*t*-Bu)$_3$/TBHP (eq 59) is promising,[163] since the reaction affords the opposite sense of diastereoselection to VO(acac)$_2$. The tungstic acid system delivers low levels of selectivity with this class of substrates, whereas epoxidation with Bu$_2$SnO is too sluggish to be useful in synthesis. More recently, a variety of lanthanide alkoxides were reported to be effective epoxidation catalysts; for example, Yb(O*i*-Pr)$_3$ (10 mol %) effects the site-selective oxidation of the allylic alcohol of geraniol (23:1).[164] The full scope and utility of these catalysts for the epoxidation of allylic and homoallylic alcohols has yet to be explored fully.



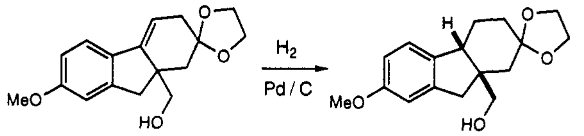
(59)

Al(O*t*-Bu)$_3$ *Diastereoselection 4 : 1*
VO(acac)$_2$ *Diastereoselection 1 : 3*

V. Directed Heterogeneous Hydrogenation Reactions

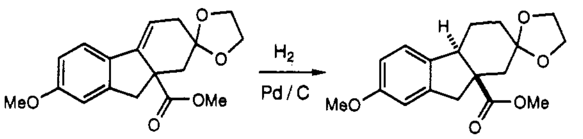
The stereochemical course of heterogeneous hydrogenation reactions may be influenced by a neighboring heteroatom.[165] Association of an internal polar group with the metal surface can lead to the delivery of hydrogen to the unsaturation site in a syn fashion. This catalyst–substrate interaction may be largely preempted or facilitated, depending on the nature of the metal, the support, or the solvent employed.

For example, catalytic hydrogenation of the tricyclic alcohol shown below affords the syn isomer as the major product (eq 60, 5% Pd/C, 15 psi H$_2$, EtOH).[166] The stereochemical outcome implies that the substrate is bound to the catalyst surface on the same side as the hydroxy group and that this affinity results in the addition of hydrogen syn to the coordinating moiety. Reduction of the corresponding ester derivative under identical conditions leads to the predominant formation of the anti system (eq 61).



(60)

Diastereoselection 95:5



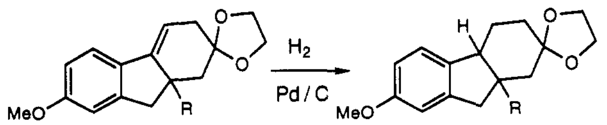
(61)

Diastereoselection 86:14

As is illustrated in Table 30, for this olefinic substrate the level and sense of asymmetric induction is greatly dependent on the nature of the heteroatom.[167] Although the primary alcohol and the aldehyde functionalities can perform well as directing groups, with an amide or a ketone the stereochemical course of the reduction is largely influenced by steric factors: the anti isomer is isolated as the major product. The stereoselectivity trends that are illustrated in Table 30 cannot be correlated with the directing group's physical properties such as its Brönsted basicity (pK_a) or its electronegativity.[168] However, solvent polarity has a more predictable influence on the course of heterogeneous reductions. That is, highly polar solvents (DMF) which compete for metal binding sites afford the anti adduct preferentially, whereas nonpolar media (hexane) enforce heteroatom–catalyst association and thereby favor formation of the syn isomer. Nonetheless, the effect of solvents on the stereochemical outcome of heterogeneous hydrogenations is not always predictable: Thompson's stereoselective reduction of the tricyclic alcohol was performed in ethanol (eq 60).

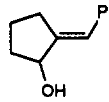
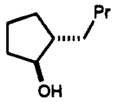
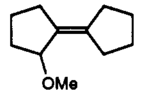
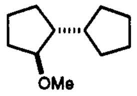
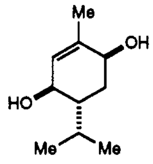
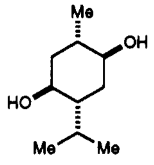
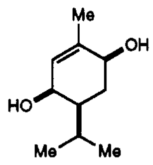
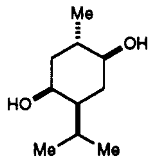
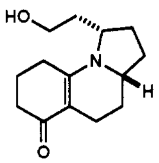
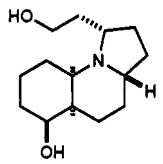
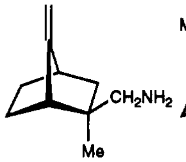
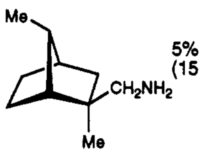
Table 31 illustrates additional examples of directed heterogeneous hydrogenation processes. 2-Butylidene-1-cyclopentanol is reduced with Raney nickel to afford the anti product preferentially (entry 1).[169] Hydrogenation of the cyclopentylidene allylic methyl ether

Table 30. Directivity by Various Functional Groups in Heterogeneous Hydrogenation



R	*Cis* : *Trans*	pK_a	Electronegativity
CH$_2$OH	19 : 1	-2	3.65
CHO	13 : 1	-8	2.90
CO$_2$Na	1 : 1	+5	2.95
CO$_2$H	1 : 4	-6	2.85
CO$_2$Me	1 : 6	-6	2.75
COMe	1 : 6	-7	2.70
CONH$_2$	1 : 9	-1	2.95

Table 31. Directed Heterogeneous Hydrogenation

Entry	Substrate	Major Product	Catalyst (H_2 Pressure)	Selectivity
1			Raney-Ni (1000 psi)	24 : 1
2			Raney-Ni (1000 psi)	12 : 1
3			Raney-Ni (30 psi)	9 : 1
4			Raney-Ni (30 psi)	2 : 1
5			5% Pt / Al_2O_3 (60 psi)	12 : 1
6			5% Pd / C (15 psi)	>99 : 1

(entry 2) indicates that, although less effectively than parent alcohols, alkyl ethers can also direct the addition reaction. Hydrogenation of the cyclohexenediol in entry 3 proceeds stereoselectively in the presence of Raney nickel, but minor modifications in substrate structure result in diminished stereodifferentation.[170] As is shown in entry 4, if hydrogen delivery is to occur from the same face as the sizeable isopropyl group, the reduction proceeds with significantly lower levels of stereocontrol. Hydrogenation of the vinylogous amide shown in entry 5 proceeds smoothly to yield the amino alcohol.[171] The directing effect of the primary alcohol was ascertained by control experiments; under identical conditions, the corresponding acetate, silyl ether, or deoxy derivatives give no reduction products. As the example in entry 6 indicates, a primary amine may also direct the course of the reduction process.[172]

Although heteroatom functional groups can influence the stereochemical course of heterogeneous reductions, a number of variables, such as the nature of the directing group, solvent, catalyst, support, and hydrogen pressure are important and often must be optimized to achieve useful levels of selectivity. These changes in reaction conditions cannot be effected predictably; poisoning is often a problem, and different catalyst batches seldom show identical reactivity. It is for these reasons that heterogeneous catalysis does not offer a general and reliable solution to the notion of heteroatom-directed hydrogenation reactions.

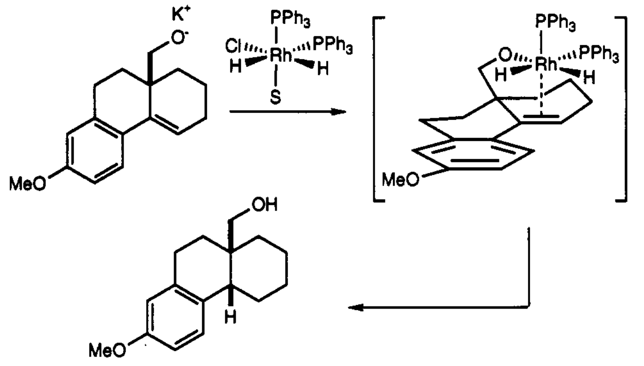
VI. Directed Homogeneous Hydrogenation Reactions

A. Introduction

Homogeneous hydrogenation catalysts were first introduced in 1961 by Halpern; a number of simple alkenes, such as maleic, fumaric, and acrylic acids, can be reduced efficiently with chlororuthenate(II) complexes.[173] Subsequently, other significant advances were made in this area, chiefly by Wilkinson and coworkers, who developed an array of effective rhodium and ruthenium catalysts.[174] Perhaps the most notable of such complexes, $RhCl(PPh_3)_3$ (Wilkinson's complex), was shown to effect hydrogenation reactions with site and diastereoselectivity.[175]

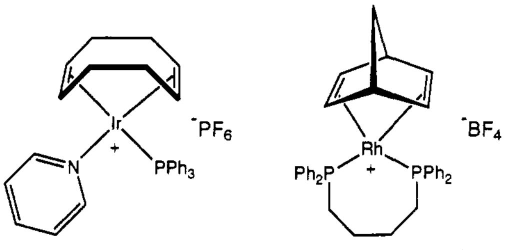
The first systematic studies of directed homogeneous hydrogenation reactions were reported in 1974.[176] The tricyclic alcohol shown in Scheme 20 is resistant to reduction by hydrogen and $RhCl(PPh_3)_3$, even at 100 psi and 50 °C. However, when the corresponding potassium alkoxide is subjected to the above conditions (100 psi H_2, 50 °C, 0.04 mol % catalyst), the syn isomer is produced exclusively. It was proposed that the reaction involves a rhodium–dihydride complex where both the solvent molecule (S; e.g., THF) and the chloride ion are replaced by the olefinic alkoxide, which in turn delivers hydrogen to the unsaturation site. In these experiments prior formation of the potassium alkoxide and subsequent displacement of the chloride ligand are *required* for efficient delivery of hydrogen. Hydrogenation reactions of this alcohol substrate and its various salts with heterogeneous palladium and platinum catalysts provide significant amounts of the anti isomer.[168]

Scheme 20



Heteroatom directivity requires binding of H_2, the alkene, and the directing group to the transition metal; three ligation sites on the metal center of the catalyst are necessary. With $RhCl(PPh_3)_3$, the active 14-electron species $RhCl(PPh_3)_2$ cannot accommodate the three groups, as this would result in the formation of an unfavorable 20-electron complex (an additional ligand (Cl) must be lost). To effect a directed reaction with a hydroxy or another polar heteroatom group which is not capable of initiating ligand displacement, an active catalyst with a 12-electron structure is required. A number of hydrogenation catalysts satisfy this criterion. Chiral cationic rhodium catalysts (e.g., $[Rh(nbd)(S,S\text{-chiraphos})]BF_4$) have been employed successfully in enantioselective reductions of dehydroamino acids,[177] where association of both the olefin and the *N*-acyl carbonyl group plays a crucial role in efficient transfer of chirality. More recently, hydrogenation of a variety of allylic and homoallylic alcohols, under the agency of chiral ruthenium complexes (e.g., Ru(*S*-binap)(O-$COCH_3)_2$), has been shown to occur with high enantioface differentiation (~98%).[178] In this instance as well, two-point binding between the catalyst and the substrate is crucial for achieving high selectivity.

This section of the article will be primarily concerned with *diastereoselective*, directed hydrogenation processes. Among the various catalysts, $[Ir(cod)py(PCy_3)]PF_6$[179] and $[Rh(nbd)(diphos\text{-}4)]BF_4$[180] have emerged as the most commonly used, and their role in directed hydrogenation reactions with be emphasized.[181]



$[Ir(cod)py(PCy_3)]PF_6$ (Ir^+)

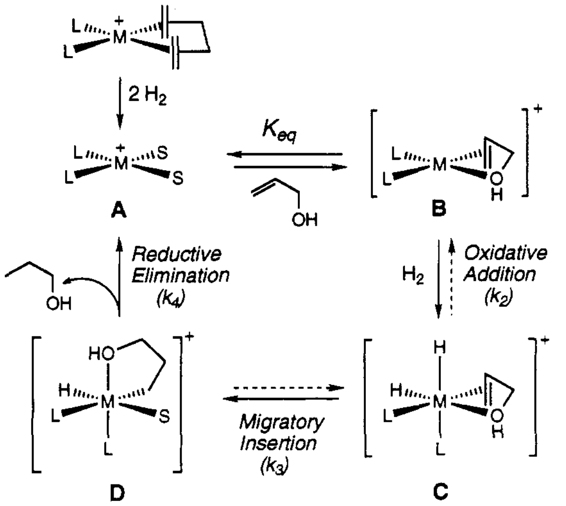
$[Rh(nbd)(diphos\text{-}4)]BF_4$ (Rh^+)

B. General Mechanistic Considerations

Upon treatment with H_2, the cyclooctadiene (cod) and norbornadiene (nbd) ligands of $[Ir(cod)py(PCy_3)]PF_6$ and $[Rh(nbd)(diphos\text{-}4)]BF_4$ are promptly reduced, and the 12-electron "IrR_2^+" and "RhL_2^+" systems are formed (A, Scheme 21). The course of the reduction process illustrated below and the intermediates involved can be inferred from Halpern's mechanistic studies on the rhodium-catalyzed hydrogenation of dehydroamino acids.[182] The heteroatom and its neighboring alkene readily bind to the coordinatively unsaturated metal complex. Coordination of the substrate is followed by oxidative addition of hydrogen and subsequent migratory insertion to afford the alkyl metal complex (D). Reductive elimination then yields the desired product and regenerates the active hydrogenation catalyst.

Whether any of the steps presented in the catalytic cycle are reversible is largely a function of the catalyst and the reaction conditions (e.g., temperature and pressure). Halpern's studies have demonstrated that in the cationic rhodium-catalyzed hydrogenation of dehydroamino acids, at 15 psi (1 atm) H_2 the oxidative addition step (B → C) is rate determining, whereas at elevated hydrogen pressure reductive elimination is the slow step (D → A).[182] In contrast, Crabtree's mechanistic work on *iridium*-catalyzed hydrogenation indicates that, at least in certain instances, formation of the alkyliridium complex is rate limiting (C → D).[179]

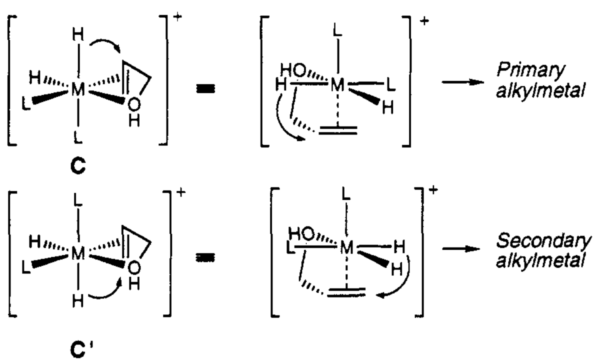
Scheme 21


2 H_2
K_{eq}
A
B
OH
Reductive Elimination (k_4)
Oxidative Addition (k_2)
H_2
Migratory Insertion (k_3)
D
C

As is indicated in Scheme 21, formation of the hydridoalkyl complex, D, could occur via the metal dihydride species (B → C → D). Although iridium dihydrides have been detected spectroscopically, the analogous rhodium complexes have not yet been observed. In the proposed catalytic cycle for the rhodium-catalyzed reduction of dehydroamino acids, the dihydride complex, (C), remains the only intermediate that has not thus far been intercepted and characterized, due to the rapid rate of the migratory insertion step ($k_3 \gg k_2$). However, the well-recognized oxidative addition reactions of hydrogen with a number of d^8 complexes, and the similarity of the related activation parameters (k_2) to those of the dehydroamino acid asymmetric reductions, render the involvement of metal dihydrides (such as C) likely.[183] The intermediacy of these complexes is therefore invoked in the ensuing discussions.

Complex C contains two diastereotopic hydrides, initial transfer of one of which is predicted to be favored. As is illustrated in Scheme 22, the parallel metal hydride (H—M—C═C dihedral angle of ~0°) is properly aligned to overlap with the olefin σ^*_{C-C} and should therefore be transferred first. The perpendicular hydride is orthogonal to the C–C π cloud (H—M—C═C dihedral angle of ~90°), and its insertion is predicted to be energetically unfavorable. Scheme 22 also demonstrates that there are two possible modes of hydride insertion wherein the above stereoelectronic effects are satisfied. In the case of a monosubstituted allylic alcohol, C′ affords a *secondary* alkylmetal complex whereas C generates the more (thermodynamically) favorable *primary* product. In the case of a 1,2-disubstituted olefin, where a secondary alkylrhodium is generated regardless of the mode of hydride transfer, steric factors may also prove to be significant (e.g., preferences for certain metallacycle ring sizes).

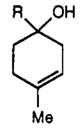
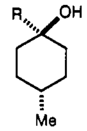
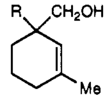
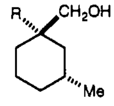
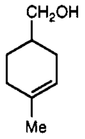
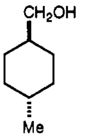
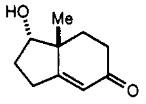
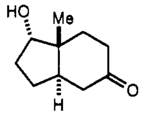
Scheme 22



C. Hydrogenation of Cyclic Olefins

In 1983, Crabtree[184] and Stork[185] demonstrated that the cationic iridium catalyst ($[Ir(cod)py(PCy_3)]PF_6$, Ir^+)

Table 32. Hydrogenation of Cyclic Homo- and Bishomoallylic Alcohols with [Ir(cod)py(PCy$_3$)]PF$_6$

Entry	Substrate	Major Product	Mol % Ir catalyst		Selectivity
1			20	a. R = H	>99 : 1
			20	b. R = Me	33 : 1
2			20	a. R = H	6 : 1
			20	b. R = Me	9 : 1
3			2		>99 : 1
4			20		24 : 1

is effective in the directed reduction of a diverse selection of cyclic olefinic alcohols. As shown in Table 32, endocyclic homoallylic carbinols are generally hydrogenated with good to excellent selectivity; the major product corresponds to addition of hydrogen syn to the hydroxy group. As is indicated in entry 2 of Table 32, homoallylic alcohols which bear a primary hydroxy group may undergo directed hydrogenation reactions with relatively lower levels of stereocontrol. Comparison of entries 2 and 3 implies that levels of diastereoselection are dependent on catalyst concentration. As will be discussed later in more detail, higher concentrations of the iridium catalyst result in significantly lower levels of stereoinduction.[186] The reaction of the enone system shown in entry 5 is significantly slower than that of unconjugated olefins, yet the desired *trans*-indanone is produced as the major product.

Table 33 illustrates several examples of stereoselective hydrogenation reactions of cyclic allylic alcohols catalyzed by [Ir(cod)py(PCy$_3$)]PF$_6$. Entries 2 and 3 of Table 33 demonstrate that the level of stereocontrol is not greatly affected by the relative stereochemistry of substituents proximal to the directing functionality.[187] Hydrogenation of the bicyclic alcohol shown in entry 4 gives the cis-fused system as the sole product.[188]

In the initial studies on iridium-catalyzed directed hydrogenations, 20 mol % of the catalyst was employed;[185] these conditions were later determined not to be optimal for achieving high levels of stereoselection.[186] For example, reductions of 3-methyl-2-cyclohexen-1-ol and 4-methyl-3-cyclohexen-1-ol with [Ir(cod)py(PCy$_3$)]PF$_6$ were shown to be more selective at lower catalyst loadings (Table 34). It is possible that at higher catalyst concentrations more than one metal complex is present. Some of these species, such as the trinuclear bridged hydride system examined by Crabtree,[189] is inactive, whereas others, although active, might not be constrained to the same directivity effects as the mononuclear complex.

The cationic rhodium complex, [Rh(nbd)(diphos-4)]BF$_4$ (Rh$^+$), has also proved to be a useful catalyst for directed hydrogenation of cyclic alkenes (Table 35). Upon treatment of 3-methylenecyclohexan-1-ol with 2 mol % of the rhodium catalyst (15 psi H$_2$), *trans*-3-methylcyclohexan-1-ol is obtained stereoselectively (>98%, entry 1).[190] In contrast, reduction of 2-methylenecyclohexanemethanol proceeds in a stereorandom fashion (entry 2). Subjection of 2-methylenecyclohexan-1-ol to the above conditions leads to the formation of hydrogenation products with low selectivity (entry 3). This transformation is plagued with olefin isomerization; 2-methylcyclohexan-1-one is produced as the major product.[191]

Table 33. Hydrogenation of Cyclic Allylic Alcohols with [Ir(cod)py(PCy$_3$)]PF$_6$

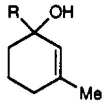
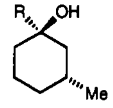
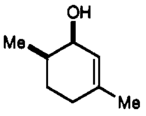
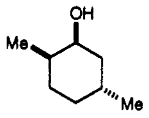
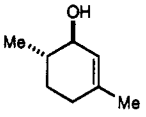
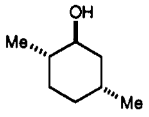
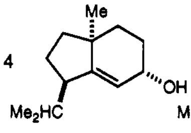
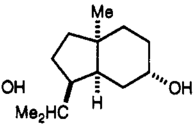
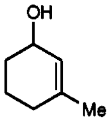
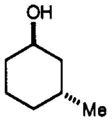
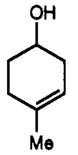
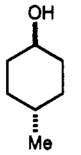
Entry	Substrate	Major Product	Mol % Ir catalyst		Selectivity
1			20	a. R = H	74 : 1
			20	b. R = Me	>100 : 1
2			2		65 : 1
3			2		36 : 1
4			20		"highly selective"

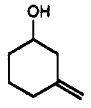
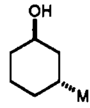
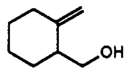
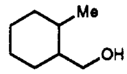
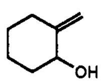
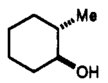
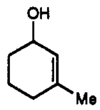
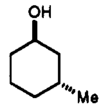
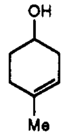
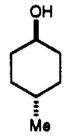
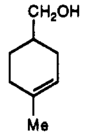
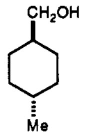
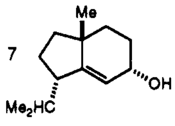
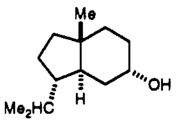
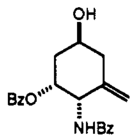
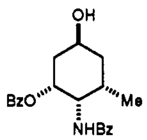
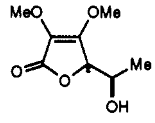
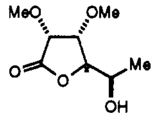
Table 34. Stereoselectivity as a Function of [Ir(cod)py(PCy$_3$)]PF$_6$ Concentration

Substrate	Major Product	Mol % Ir catalyst	Selectivity
		20.0 2.5	50 : 1 150 : 1
		20.0 2.5	33 : 1 52 : 1

Alkene isomerization in rhodium-catalyzed hydrogenation processes is largely circumvented if reactions are carried out at elevated hydrogen pressures.[191] Although reduction of 2-methylenecyclohexan-1-ol at 500 and 1000 psi H$_2$ does not result in improvement of stereoselectivity (3:1; Table 35, entry 3), generation of the undesired ketone is diminished to 20% and 13%, respectively. Hydrogenation of 3-methyl-2-cyclohexen-1-ol at 375 psi H$_2$ affords *trans*-3-methylcyclohexan-1-ol in a >200:1 ratio (entry 4, 200:1 at 15 psi).[191] As entries 5, 6, and 8 of Table 35 show, homoallylic and bishomoallylic cyclic olefins are reduced stereoselectively with the cationic rhodium catalyst at high H$_2$ pressure.[192]

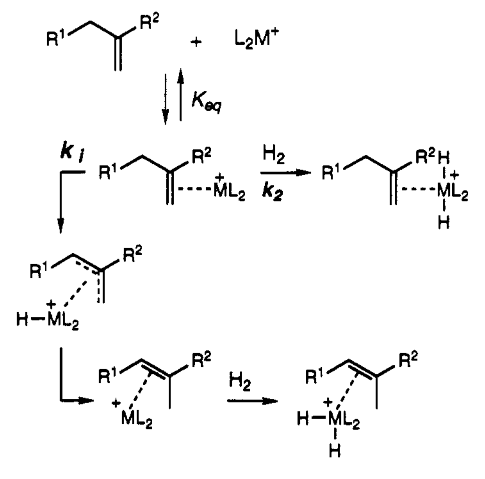
Thus, in rhodium-catalyzed hydrogenations an increase in hydrogen pressure results in diminished olefin isomerization and higher selectivity (Scheme 23, M =

Table 35. Hydrogenation of Cyclic Alcohols with [Rh(nbd)(diphos-4)]BF_4

Entry	Substrate	Major Product	Mol %, Catalyst[a] (H_2 Pressure)	Selectivity
1			2, Rh^+ (15 psi)	>49 : 1
2			2, Rh^+ (15 psi)	1 : 1
3			3.5, Rh^+ (500 psi)	3 : 1
4			3.5, Rh^+ (375 psi) 2.5, Ir^+ (15 psi)	>200 : 1 150 : 1
5			10, Rh^+ (1000 psi) 2.5, Ir^+ (15 psi)	64 : 1 52 : 1
6			10, Rh^+ (1000 psi) 20, Ir^+ (15 psi)	19 : 1 6 : 1
7			10, Rh^+ (800 psi)	70 : 1
8			35, Rh^+ (15 psi) 17.5, Ir^+ (15 psi)	>19 : 1 2 : 1
9			20, Rh^+ (1850 psi)	"highly selective"

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4 (Rh^+); [Ir(cod)py(PCY_3)]PF_6 (Ir^+).

Scheme 23



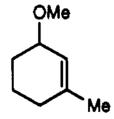
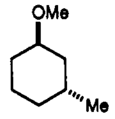
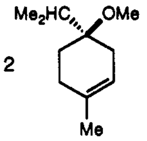
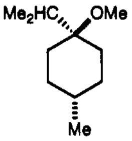
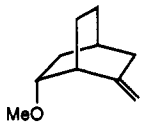
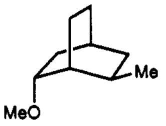
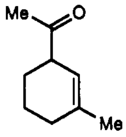
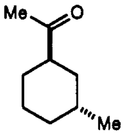
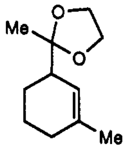
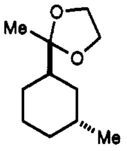
Rh). In direct analogy with the asymmetric hydrogenation of dehydroamino acids by closely related rhodium complexes,[193] in reactions of allylic alcohols at 15 psi H_2 oxidative addition of hydrogen is probably the rate-determining step. As a result, the substrate–catalyst adduct may competitively undergo alkene isomerization through a route involving the corresponding π-allyl hydride ($k_2[H_2] \cong k_i$). When pressures above 15 psi (1 atm) are employed, olefin isomerization is attenuated ($k_2[H_2] > k_i$), and formation of the putative π-allyl hydride no longer competes with the desired pathway. Another plausible explanation points to competition between a β-elimination pathway (resulting in alkene isomerization) and a reductive elimination route (affording hydrogenation product) of the intermediate alkyl hydride. It may be that H_2 at high pressures acts as a ligand which induces reductive elimination and thus favors hydrogenation of the unrearranged alkene. In the iridium-catalyzed processes (M = Ir) variations in hydrogen pressure are of little consequence.[191]

Table 35 illustrates several instances where the directed, rhodium-catalyzed hydrogenation has been employed in a synthesis strategy. In the case of the bicyclic system shown in entry 7, in spite of an exceptional level of steric congestion which is disposed to override hydroxyl directivity, the trans-fused adduct is formed as the major product.[191] Due to the instability of this substrate toward the Lewis acidic rhodium, satisfactory results are achieved only when reduction is performed in tetrahydrofuran. (Unlike dichloromethane, tetrahydrofuran effectively buffers the catalyst Lewis acidity.[194]) This transformation fails at low hydrogen pressure or with the cationic iridium complex.[188]

Rhodium-catalyzed hydrogenation of the substrate shown in entry 8 (Table 35) proceeds with high levels of stereochemical control.[195] With [Ir(cod)py(PCy_3)]PF_6 only a 2:1 ratio is obtained; the lack of stereoselectivity could be attributed to competitive binding and directivity by the amide group (vide infra). Entry 9 of Table 35 indicates that a directing group positioned on an exocyclic group can effectively control the stereochemical outcome of the reaction.[196]

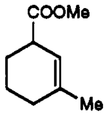
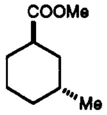
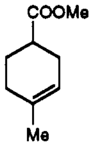
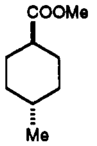
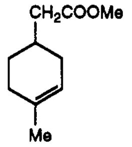
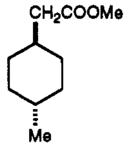
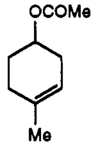
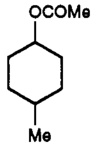
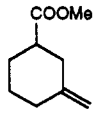
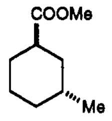
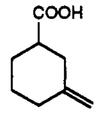
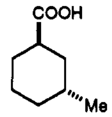
Other heteroatom-containing functional groups, such as ethers, carboxylic esters, and amides, efficiently bind to cationic rhodium and iridium complexes and direct the hydrogenation reactions of cyclic substrates.[197] As the first three entries of Table 36 demonstrate, methyl ethers are effective directing groups. The bicyclic ether of entry 3 is reduced with lower selectivity but faster than the parent alcohol, even when the more discriminating iridium complex is employed.[198] This relationship between rate and selectivity (that faster transformations are less selective) is not general and appears to depend on the nature of the directing group, at least with regard to the iridium-catalyzed reactions. For instance, with [Ir(cod)py(PCy_3)]PF_6, hydrogenation of the unsaturated ketone in entry 4 is faster and more selective than that of the carbinol derivative (>99:1 vs 6:1). Somewhat surprisingly, reduction of the ethylidene ketal shown in entry 5 occurs with low stereoselectivity and with <50% conversion.[184]

Table 36. Hydrogenation of Cyclic Olefinic Ethers and Ketones[a]

Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1			2, Ir$^+$	>99 : 1
2			2, Ir$^+$	>99 : 1
3			2, Ir$^+$ 2, Rh$^+$	32 : 1 7 : 1
4			2, Ir$^+$	>99 : 1
5			2, Ir$^+$	1.6 : 1

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4(Rh$^+$); [Ir(cod)py-(PCY_3)]PF_6(Ir$^+$). Reactions were run at 15 psi H_2.

Table 37. Hydrogenation of Cyclic Olefinic Ethers and Acids

Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1			2, Ir$^+$ 2, Rh$^+$	>99 : 1 32 : 1
2			2, Ir$^+$ 2, Rh$^+$	41 : 1 7 : 1
3			5, Ir$^+$	1 : 1
4			5, Ir$^+$	1 : 1
5			2, Ir$^+$ 2, Rh$^+$	10 : 1 4 : 1
6			2, Ir$^+$ 2, Rh$^+$	7 : 1 1 : 1

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4(Rh$^+$); [Ir(cod)py-(PCY_3)]PF_6(Ir$^+$). Reactions were run at 15 psi H_2.

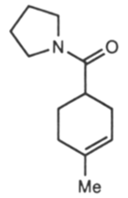
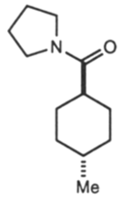
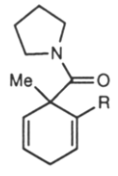
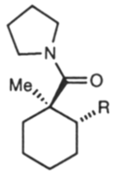
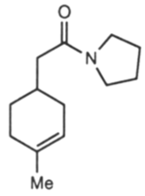
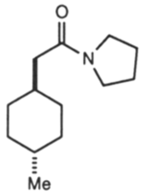
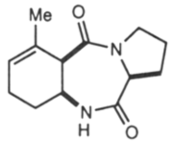
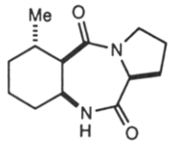
Table 37 illustrates a number of stereoselective hydrogenations where an ester functionality acts as the directing group. The β,γ-unsaturated ester in entry 1 is reduced with high selectively with both iridium and rhodium catalysts.[190] Reduction of the more distant alkene of the γ,δ-unsaturated ester in entry 2 is slower and less stereoselective. The resident heteroatom functionality in the δ,ε-unsaturated ester of entry 3 is too distant from the olefin for effective differentiation of its syn and anti faces; the same argument holds for the structurally analogous acetate in entry 4 which is also reduced in a stereorandom fashion.[185] Table 37 includes the case of an unsaturated carboxylic acid (entry 6) which is reduced selectively in presence of the iridium complex (7:1), albeit not as rapidly as the related ester (entry 5).

The carboxamide group serves admirably as a directing agent in hydrogenations with the cationic iridium catalyst.[199] Entries in Table 38 clearly indicate that delivery by an amide group is more efficient than by an ester functionality. An increase in distance between the amide carbonyl and the alkene results in little erosion of stereoselectivity, as might be expected for this more Lewis basic functional group (this is in contrast to the less Lewis basic esters). In contrast to the corresponding methyl ester which is hydrogenated stereorandomly (entry 3, Table 37), the δ,ε-unsaturated amide in entry 3 (Table 38) is reduced with >100:1 selectivity. Particularly impressive is the highly selective reduction of the Lewis-acid sensitive enol ether of entry 2b. As illustrated in entry 4, this technology has found an important application in connection with the total syntheses of pumiliotoxins.

With regard to the preferred geometry in reductions of cyclic homoallylic substrates, similar to the directed cyclopropanation reaction (vide supra), it appears plausible that the internal alkene is within reach only when the hydroxy–metal complex is in the pseudoaxial orientation (Figure 8, box). Substrates which are reduced with higher degrees of stereochemical control are those which are more strongly favored to be axially disposed. Comparison of entries 1–3 in Table 33 suggests that, unlike the directed methylenation processes, hydrogenation reactions of allylic substrates proceed through the pseudoaxial hydroxy conformer (Figure 8, parts a and b). As was discussed previously in detail (Scheme 22), one of the two diastereomeric hydrides is properly aligned with the alkene π-system and is consequently transferred first (H_A; H—M—C═C dihedral angle of 0°). There are two possible modes of hydride insertion wherein the metal hydride and π^*_{C-C} are properly aligned. From illustrations in Figure 8, it is not obvious whether one mode should be preferred over the other.

In contrast to Simmons–Smith cyclopropanations and metal-catalyzed epoxidations, the presence of a hydroxy group has been shown to *decrease* the overall efficiency of iridium-catalyzed hydrogenations. Whereas in the reaction of 1-methylcyclohexene ~4000 mol of H_2 per mole of iridium [Ir(cod)py(PCy_3)]PF_6 is consumed, with terpinen-4-ol this value is diminished to ~30 mol of H_2 per mole of the catalyst.[187] This observation implies

Table 38. Hydrogenation of Cyclic Olefinic Amides

Entry	Substrate	Major Product	Mol %, Cat^a	Selectivity
1			5, Ir$^+$	130 : 1
2		 a. R = Me b. R = OMe	5, Ir$^+$ 5, Ir$^+$	170 : 1 170 : 1
3			5, Ir$^+$	>100 : 1
4			5, Ir$^+$	>99 : 1

^{a} Catalyst: [Ir(cod)py(PCY$_3$)]PF$_6$(Ir$^+$).

that coordination of the catalyst to the hydroxyl group results in attenuation of the catalytic activity of the iridium system. Moreover, unless larger amounts of the iridium complex are used, hydrogenation of nonhydroxylic olefins usually occurs in much lower yields than hydroxylic analogues. Such reactivity patterns have been attributed to catalyst deactivation (e.g., trimerization), which is largely inhibited when the complex is bound to a heteroatom.[200] Collectively, these data imply that the resident hydroxy group rapidly binds to the metal,[179a] protects the catalyst from decomposition and directs the H_2 delivery, but at the expense of catalyst deactivation and reduction of the reaction rates.

D. Hydrogenation of Acyclic Olefins

Hydrogenation of the 1,1-disubstituted allylic alcohol shown in entry 1 of Table 39 proceeds stereoselectively with 2 mol % [Rh(nbd)(diphos-4)]BF_4.[201] Under these conditions ~20% of the corresponding methyl ketone is produced due to olefin isomerization. When the iridium catalyst (Ir$^+$) is employed, 60% of the reaction mixture consists of the ketone side product, and the reduction occurs with lower selectivity (15:1). It is noteworthy that either the syn or the anti stereochemical relationship can be generated, depending on the substitution pattern of the starting alkene. This complementarity in diastereoselective hydrogenation of di- and trisubstituted olefins, and the general stereochemical outcome in reductions of allylic systems, may be rationalized on the basis of a number of conformational preferences.

Two-point binding of the transition metal with the olefin and its neighboring heteroatom occurs in such a fashion so that the A(1,2) allylic strain between R_1 and CH_2R_2 or Me substituents is avoided (~3.0 kcal/mol; Scheme 24).[202] In this manner, simultaneous coordination of the metal with the alkene and hydroxy groups results in effective differentiation of the two diastereotopic faces.

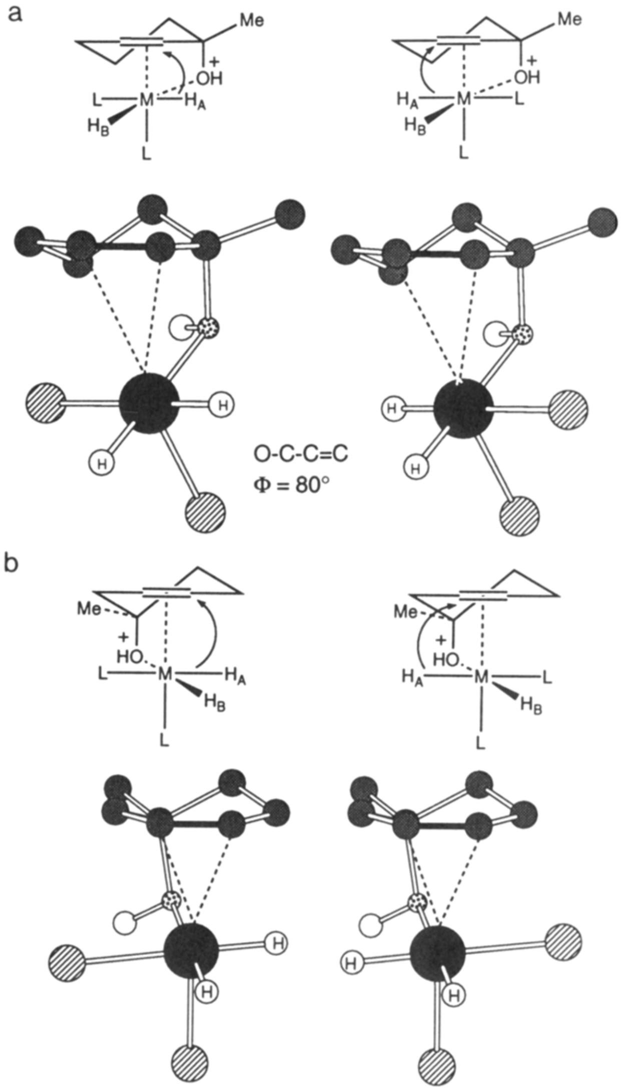
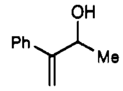
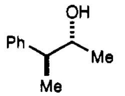
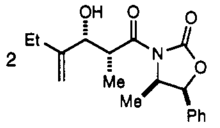
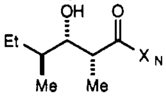
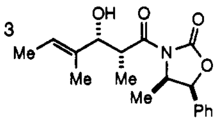
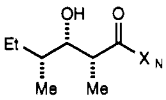
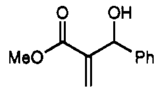
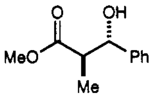
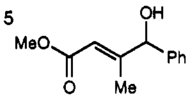
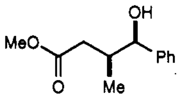


Figure 8. Preferred orientations of catalyst–olefin complexes of cyclic allylic (a) and cyclic homoallylic (b) alcohols.

The cationic rhodium complex is a uniquely effective catalyst for the stereoselective reduction of hydroxyacrylate esters (see entries 4 and 5 in Table 39). The iridium-mediated reactions are nonselective, and reductions catalyzed by Wilkinson's complex or common heterogeneous systems are slow and occur stereorandomly.[203] It is remarkable that hydrogenation of the disubstituted alkene in entry 4 proceeds with such high levels of stereocontrol at 15 psi H_2, since isomerization and formation of the β-keto ester should be prevalent under these conditions.

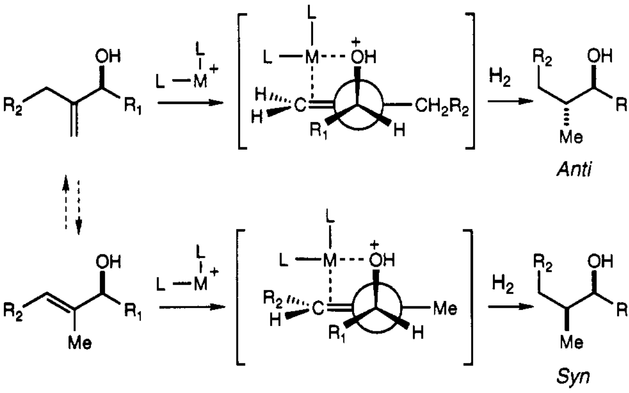
That hydrogenation of di- and trisubstituted alkenes leads to the formation of *opposite* stereo relationships has significant implications (entries 2 and 3, Table 39). If olefin isomerization occurs prior to hydrogenation, diminished overall stereoselectivities will be observed even though the individual transformations could be inherently discriminating. This complication, often inconsequential in cyclic systems, can be detrimental with acyclic substrates. At 15 psi H_2, when olefin

Table 39. Hydrogenation of Acyclic Allylic Alcohols

Entry	Substrate	Major Product	Mol %, Cat[a] (H_2 Press)	Selectivity
1			2, Rh^+ (15 psi)	32 : 1
2			17.5, Rh^+ (640 psi) 2.5, Ir^+ (15 psi)	13 : 1 6 : 1
3			17.5, Rh^+ (640 psi) 2.5, Ir^+ (15 psi)	10 : 1 3 : 1
4			0.5, Rh^+ (15 psi)	99 : 1
5			10, Rh^+ (15 psi)	32 : 1

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4(Rh^+); [Ir(cod)py-(PCY_3)]PF_6(Ir^+).

Scheme 24

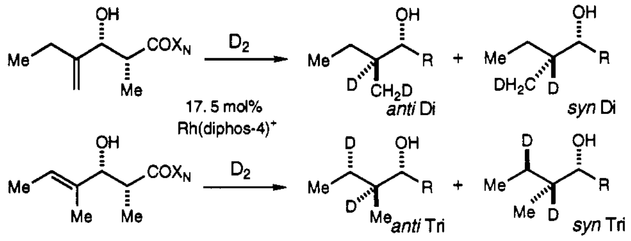


isomerization is most rampant, reduction of the disubstituted alkene affords predominantly the syn product, the product expected from hydrogenation of the trisubstituted isomer.

Studies with D_2 indicate that olefin isomerization takes place and low stereoselectivities are obtained unless elevated pressures are employed. Table 40 shows that this is especially true with disubstituted olefins; whereas at 515 psi D_2 addition occurs exclusively at the original unsaturation site, at 15 psi 75% of the product mixture corresponds to deuteration of the trisubstituted system.

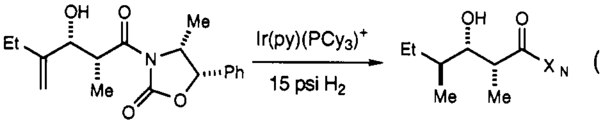
As entries 2 and 3 in Table 39 illustrate, the cationic iridium catalyst is less effective than the cationic rhodium complex in mediating stereoselective reductions of acyclic allylic alcohols. The observed levels of stereoselectivity could be due to competitive binding and directivity by the amide carbonyl. However, control experiments that rigorously address this possibility have not yet been performed. With the cationic iridium complex, changes in hydrogen pressure do not affect the observed levels of stereodifferentiation, as was also the case with the cyclic compounds. In the iridium-catalyzed hydrogenation reactions, adventitious olefin isomerization may largely be responsible for the diminished levels of stereocontrol. In further contrast to the cationic rhodium system, in iridium-catalyzed hydrogenations variations in the catalyst concentration influenced the stereoselective outcome of the reduction (eq 62).

Table 40. Effects of Variations in D_2 Pressure in Stereoselective Hydrogenations of Allylic Alcohols[a]



Substrate	D_2 Pressure (psi)	Ratio anti : syn	{anti Di / syn Di} : anti Tri : syn Tri
Disubstituted alkene	15	1 : 2	25 : 8 : 67
Disubstituted alkene	515	9 : 1	100 : 0 : 0
Trisubstituted alkene	15	1 : 6	10 : 10 : 80
Trisubstituted alkene	515	1 : 9	0 : 10 : 90

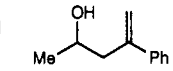
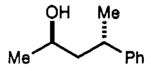
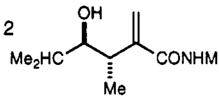
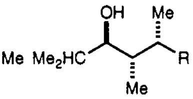
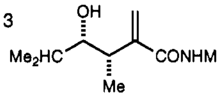
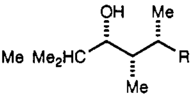
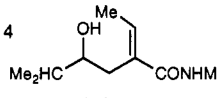
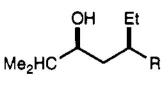
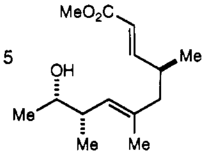
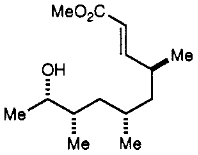
[a] Abbreviations: X_N = norephedrine oxazolidone chiral auxiliary.

 (62)

1.3 mol% catalyst, Diastereoselection 7:1
5.0 mol% catalyst, Diastereoselection 3: 1
20.0 mol% catalyst, No Diastereoselection

Entry 1 of Table 41 illustrates that, with [Rh(nbd)-(diphos-4)]BF_4 as catalyst, a homoallylic carbinol center of a 1,1-disubstituted olefin can exert modest levels of

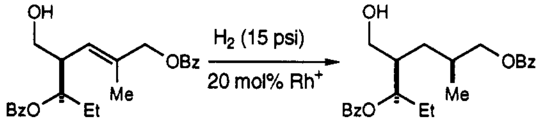
Table 41. Hydrogenations of Acyclic Homoallylic Alcohols

Entry	Substrate	Major Product	Mol %, Cat[a] (H_2 Pres)	Selectivity
1			2, Rh^+ (15 psi)	7 : 1
2			5, Rh^+ [b] (15 psi)	10 : 1
3			5, Rh^+ [b] (15 psi)	2 : 1
4			5, Rh^+ [b] (15 psi)	8 : 1
5			5, Rh^+ (15 psi)	16 : 1

[a] Catalyst: [Rh(nbd)(diphos-4)]BF_4 or [Rh(nbd)(diphos-4)]-OSO_2CF_3.

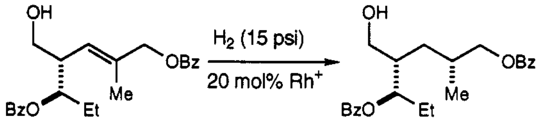
asymmetric induction in the hydrogenation process;[201] however, with a protic solvent (e.g., MeOH) the reduction proceeds nonselectively. As entries 2–3 illustrate, the level of stereodifferentiation is greatly dependent on the substitution pattern of the starting material.[204] Directed hydrogenation of trisubstituted alkenes proceeds efficiently with useful levels of diastereocontrol (entries 4 and 5, Table 41).

In hydrogenations of trisubstituted olefins, the steric requirements of the allylic substituent and the olefin geometry have a small but marked effect on the reaction diastereoselection (eqs 63–66, Rh^+ = [Rh(nbd)(diphos-4)]BF_4).[186b] Since homoallylic hydroxyl groups perform well as directing groups, alkene geometry, along with the relative stereochemistry of the homoallylic hydroxy functionality, can be manipulated for effective control of the sense of asymmetric induction.



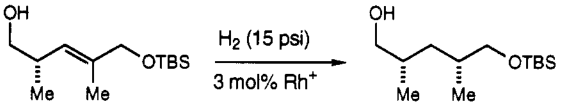
(63)

Diastereoselection 32:1



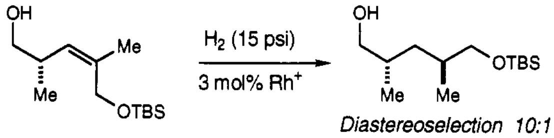
(64)

Diastereoselection 99:1



(65)

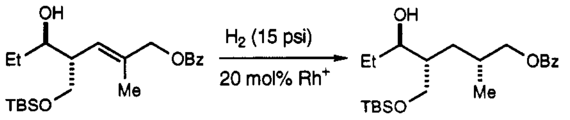
Diastereoselection 19:1



(66)

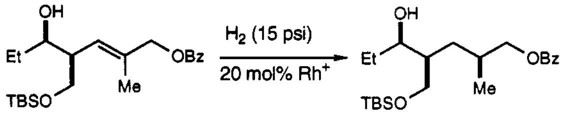
Diastereoselection 10:1

In cases where allylic and homoallylic stereogenic centers are present, alkene rearrangement is not observed at 15 psi H_2, and the cationic rhodium and the cationic iridium catalysts afford high levels of diastereoselection (eqs 67–69).[186b] Once again, it is the allylic center, not the stereogenic homoallylic carbinol site, that determines which diastereoface will be preferentially hydrogenated. Moreover, comparison of eqs 67 and 68 indicates that the anti relative stereochemistry between the hydroxy and allylic centers leads to greater levels of stereodifferentiation. Equation 69 depicts a directed hydrogenation reaction used in efforts toward the total synthesis of the immunosuppressant FK-506.[205]



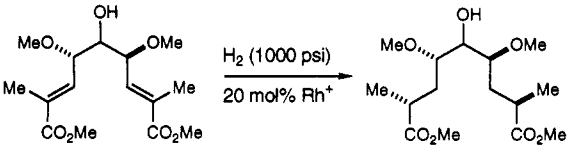
(67)

Diastereoselection 32:1



(68)

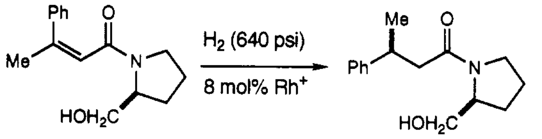
Diastereoselection 8:1



(69)

Diastereoselection 10:1

The stereoselective hydrogenation of the amide in eq 70 provides a rare example of 1,5-asymmetric induction.

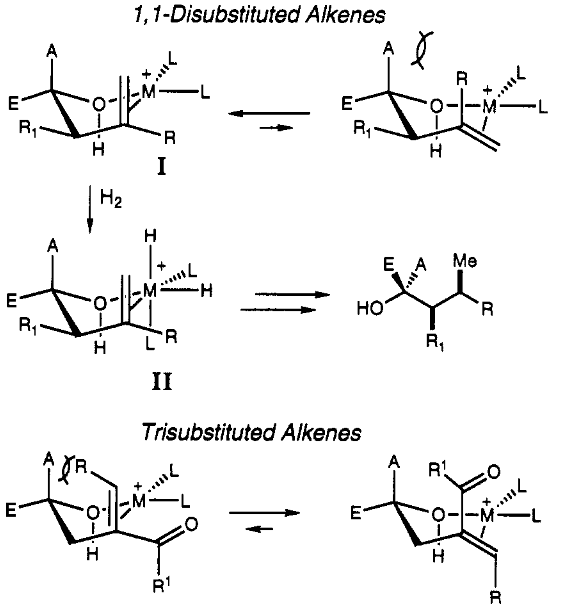


(70)

Diastereoselection 4:1

The observed stereoselectivity in the hydrogenation of the 1,1-disubstituted homoallylic alcohols can be rationalized through complexes I and II, shown in Scheme 25. Alkene conformation I is preferred; unfavorable A(1,2) interactions are minimized in this conformation. In instances where there is no allylic substituent (R_1 = H), the homoallylic group adopts the pseudoequatorial orientation. In cases with an allylic stereogenic center ($R_1 \neq$ H), this group will also prefer the pseudoequatorial disposition so that the destabilizing A(1,2) strain between R and R_1 groups is avoided (~3.0 kcal/mol). Inspection of the data presented in eqs 63 and 64 clearly indicates that in cases where there is both an allylic and a homoallylic substituent, the sense of asymmetric induction is primarily dictated by the *allylic* stereogenic center.[206]

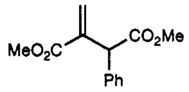
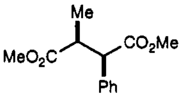
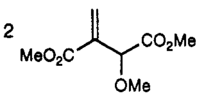
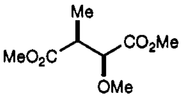
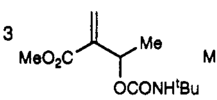
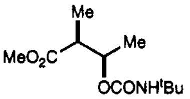
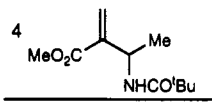
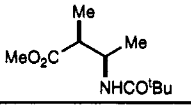
Scheme 25



The above hypotheses readily account for the lack of stereocontrol observed for the syn substrate in entry 3 of Table 41, since either the allylic or the homoallylic group would have to occupy the unfavorable pseudoaxial position. The trisubstituted olefins do not react through the same type of intermediates, as the resulting A(1,3) allylic strain[202] between R and A groups would be rather costly (~3.9 kcal/mol). Similar arguments pertain to reactions of trisubstituted alkenes that possess other substitution patterns.

In the asymmetric hydrogenation of dehydroamino acids by chiral cationic rhodium catalysts, the less

Table 42. Directed Hydrogenation of Nonhydroxylic Acyclic Alkenes

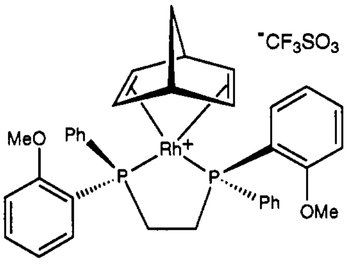
Entry	Substrate	Major Product	Mol %, Cat[a] (Solvent)	Selectivity
1			2, Rh⁺ (MeOH)	200 : 1
2			2, Rh⁺ (MeOH)	49 : 1
3			?, Rh⁺	17 : 1
4			5, Rh⁺ (CH_2Cl_2)	99 : 1

[a] Catalyst: [Rh(nbd)(diphos-4)]BF *or* [Rh(nbd)(diphos-4)]-OSO_2CF_3.

stable, *minor* metal–substrate complex reacts with H_2 far more rapidly (~500 times faster) than the major complex and thereby dictates the eventual stereochemical outcome of the reaction.[182] Therefore, in connection to the rhodium-catalyzed directed hydrogenations, if the rate-limiting step in the sequence of events is the oxidative addition process (B → C, Scheme 21), it is perhaps warranted that we base our rationalization on the relative rates of formation of the diastereomeric *dihydrides* (the oxidative insertion step) and not of the metal substrate complexes (the initial equilibrium). In the rhodium-catalyzed hydrogenations of hydroxylic olefins, unlike the asymmetric dehydroamino acid reductions, the more stable metal–catalyst complexes consistently predict the predominant product diastereomers. In the hydrogenation of these substrates, if the second step is in fact the rate-determining step, the complex with the higher thermodynamic concentration either undergoes oxidative addition faster than, or with the same rate as, the minor system. Oxidative addition of the major system could even be somewhat slower than that of the minor complex; however, this rate difference may not be large enough to overcome the initial binding preferences. Moreover, hydrogenation of dehydroamino acids proceeds less selectively under conditions which lower the effective concentration of the minor complex, namely, at lower reaction temperatures or under increased hydrogen pressure.[182] In contrast, unsaturated alcohols are reduced with higher stereochemical control when reactions are performed at high pressure or low temperature, implying that with these substrates it is primarily the *major* rhodium–hydroxy alkene complex that determines the stereochemical course of the reduction.

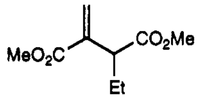
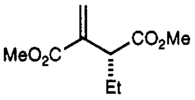
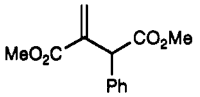
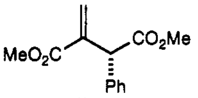
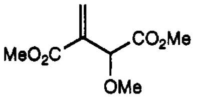
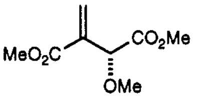
The selective hydrogenation of the 3-methyl itaconate ester shown in entry 1 of Table 42 suggests that, with [Rh(nbd)(diphos-4)]BF_4 as catalyst, methyl carboxylates can effectively direct reductions of acyclic substrates.[207] Entries 1 and 2 indicate a noticeable effect by the ether functionality on the sense of asymmetric induction in these hydrogenation reactions. The amide in entry 4 is reduced stereoselectively, but hydrogenations of the derived amine and that of the corresponding trifluoroacetate salt were nonselective.

The levels of stereocontrol observed in the hydrogenation of unsaturated alcohols is largely due to efficient substrate–metal binding, which leads to the formation of highly organized reactive complexes and results in effective diastereotopic face differentiation. Such high levels of structural organization indicate that the influence by *chiral* ligands on the *absolute* face selectivity in these reductions may be significant. Hydrogenation of a number of itaconate esters with Rh(*R*,*R*-dipamp)⁺ leads to the recovery of >80% optically pure starting material after ~60% conversion (Table 43).[208] As is illustrated in entry 1, an increase in the reaction temperature results in lower asymmetric induction. This trend is opposite to that observed forthe reductions of dehydroamino acids catalyzed by the same metal complex.[209]



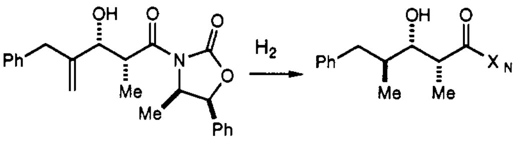
[Rh(nbd)(R,R-dipamp)]CF_3SO_3

Table 43. Kinetic Resolution in Hydrogenation of Itaconate Esters with Rh(dipamp)⁺

Entry	Substrate	Recovered Enantiomer[a]	Temp., °C (% Reaction)	ee, %[b]
1			0 (65) 50 (55)	≥96 64
2			20 (62)	82
3			20 (62)	93

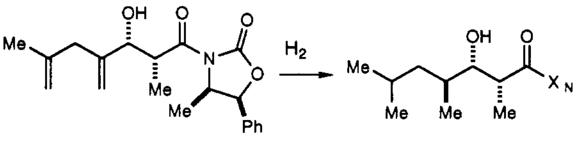
[a] All reactions were performed in MeOH at 15 psi H_2. [b] Indicates ee of the recovered starting material.

Reaction diastereoselectivity in the reductions of enantiopure allylic and homoallylic alcohols may be influenced by chiral catalysts. Two of the more dramatic examples of this phenomenon are shown in eqs 71 and 72. Noteworthy is the allylic diene of eq



(71)

Rh((+)-binap)⁺ *Diastereoselection 15:1*
Rh((-)-binap)⁺ *Diastereoselection 3:1*



(72)

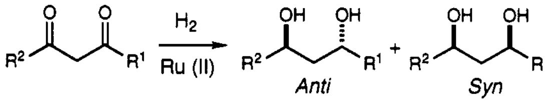
Rh((+)-binap)⁺ *Diastereoselection 200:1*
Rh((-)-binap)⁺ *Diastereoselection 1:3*

71: the hydrogenation reaction affords different diastereomeric products, depending on the catalyst antipode employed.

E. Hydrogenation of Acyclic Hydroxylic Ketones

In contrast to the directed catalytic hydrogenation reactions of alkenes, there is a paucity of instances where a ketone group is reduced stereoselectively through metal catalysis. A variety of simple 1,3-diketones can be hydrogenated to afford *trans*-1,3-diols with high diastereo- and enantioselectivity (700 psi H_2, 0.2 mol % $Ru_2Cl_4[(R)\text{-binap}]_2(NEt_3)$; Table 44.[210] In the sluggish hydrogenation of phenyl ketones, the major product is the related β-hydroxy phenyl ketone. This observation is consistent with the hypothesis that β-hydroxy ketones are intermediates in these reductions.

Table 44. Directed Hydrogenation of 1,3-Diketones



R^1	R^2	*Anti* : *Syn*	Yield
Me	Me	99 : 1	98 %
Me	Et	16 : 1	89 %
Me	*i*-Pr	32 : 1	92 %
Et	Et	49 : 1	84 %

Since simple ketones, such as pentan-2-one, are resistant to hydrogenation under the above conditions, coordination of the two carbonyl units with the ruthenium metal is believed to play an important role in the initial reduction process.[211] Association of the resulting hydroxyl group with the metal catalyst subsequently delivers the *anti*-diol selectively. Similar transition-state arguments as was put forth for the hydrogenation of the corresponding olefins (see Scheme 25) can be used to account for these cases.

More recently, Noyori and co-workers have employed RuX_2(binap) (X = Cl or Br) as a catalyst that effects stereoselective hydrogenation of a variety of ketones with neighboring nitrogen-, sulfur-, and oxygen-containing directing groups (e.g., hydroxyl, dialkylamino, alkoxy, keto, and alkylthiocarbonyl groups).[212] The sense of asymmetric induction, which is identical to that illustrated in Table 44, suggests that once again the critical factor in the stereodifferentiation is the simultaneous coordination of the carbonyl and the neighboring heteroatom-containing functionality. Nonetheless, both the Saburi and the Noyori methods reduce 1,2-diketones with only low levels of stereocontrol ($\sim$3: 1).

VII. Directed Nucleophilic Addition Reactions

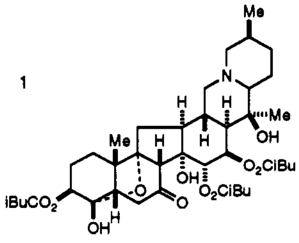
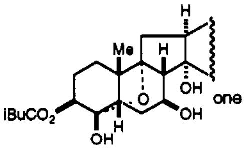
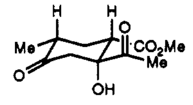
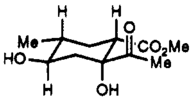
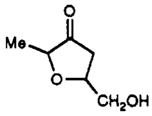
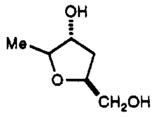
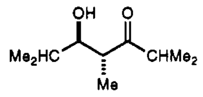
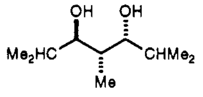
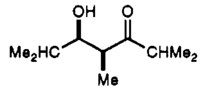
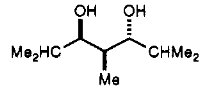
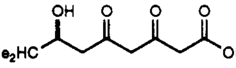
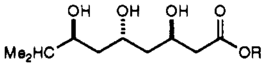
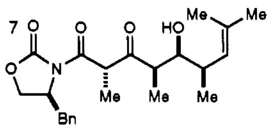
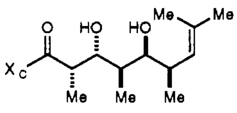
A. Reduction of C=O and C=N

The following discussion consists of two parts. The first deals with directed reductions involving tetravalent metal hydride reagents. Reductions by these species frequently involve initial reaction with an acidic substrate functional group to form a *covalent* metal hydride complex, from which H^- is subsequently delivered. The second section focuses on reductions by trivalent hydrides, which generally are bound to the substrate in a *dative* fashion prior to hydride transfer.

1. Reduction by Tetravalent Hydride Reagents

The stability of ketones, but not aldehydes, to reduction by $NaBH(OAc)_3$ was established in 1975.[213] In 1983, it was discovered that the reagent can effect the reduction of ketones bearing hydroxyl groups suitably positioned for interaction with the borohydride (for example, Table 45, entry 1).[214] To explain the observed selectivity and reactivity, a sequence involving a ligand exchange reaction at boron by the substrate (ROH) to form $NaBH(OAc)_2(OR)$, followed by intramolecular delivery of hydride to the carbonyl carbon, was proposed. Entry 2 of Table 45 provides an example of a highly regioselective reduction by $NaBH(OAc)_3$. More recently it has been demonstrated that a γ-hydroxyl group can deliver hydride onto a carbonyl site as well (entry 3).

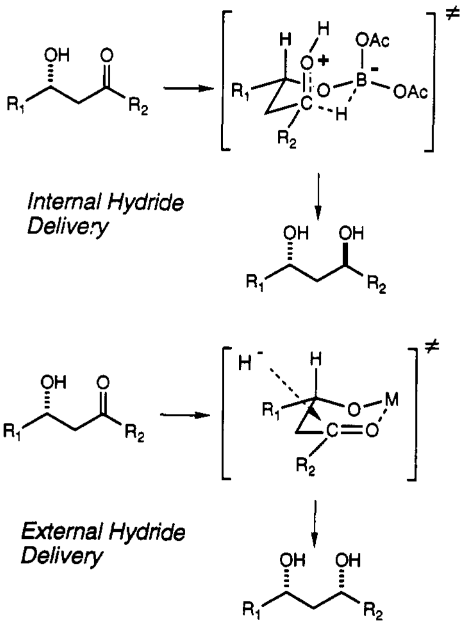
Table 45. Directed Ketone Reduction by Triacetoxyborohydride

Entry	Substrate	Product	Selectivity
1			one isomer
2			one isomer
3			"stereospecific"
4			50 : 1
5			50 : 1
6	 R = $(CH_2)_3Ph$		6 : 1[a]
7			>30 : 1

[a] Ratio of *anti,anti*-triol to all other diastereomers.

A study of the mechanism and diastereoselectivity of the directed reduction of acyclic β-hydroxy ketones by $Me_4NBH(OAc)_3$ has appeared recently; ketones, β-keto esters, and simple β-diketones which lack a suitably disposed hydroxyl group are not reduced under the standard conditions.[214e] Entries 4 and 5 (Table 45) illustrate the high anti selectivity of the reaction, regardless of the substitution at the α-carbon.[215] Consideration of chairlike transition structures provides a plausible rationale for the observed diastereoselection (Scheme 26).[216] It is noteworthy that the weak response of the stereoselectivity to the substitution at the α-carbon is well accommodated by this model. Entry 6 provides an example of sequential diastereoselective directed reductions. The potential utility of this directed reduction in the synthesis of polyketide-derived natural products is clear.

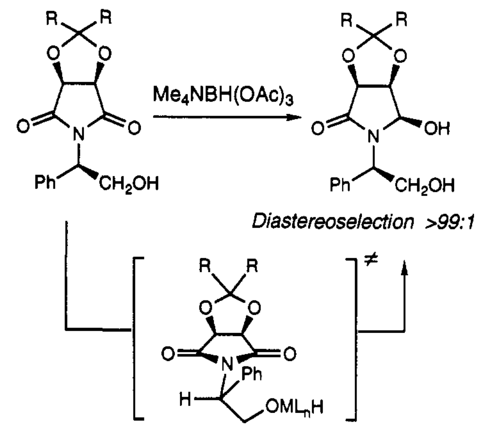
Scheme 26



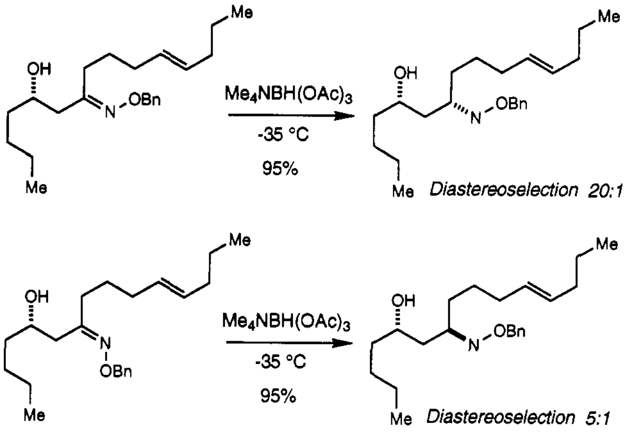
Intramolecular delivery of hydride in $Me_4NBH(OAc)_3$ reductions is supported not only by the stereochemical outcome of the reaction of cyclic substrates, but of acyclic systems as well. A general pattern holds with regard to stereoselectivity in the reduction of acyclic β-hydroxy ketones: Chelate-controlled additions of hydride reagents (external delivery) to α-unsubstituted substrates preferentially generate the *syn*-1,3-diol (Scheme 26),[217] whereas reductions proceeding through intramolecular delivery selectively produce the *anti*-1,3-diol.[218]

Imides (Scheme 27) and oximino ethers (Scheme 28) can also serve as substrates for hydroxyl-directed triacetoxyborohydride reduction.[219] The tartaric acid derivative shown below undergoes highly selective addition to one of the diastereotopic carbonyl groups when treated with $Me_4NBH(OAc)_3$, whereas the corresponding TBS ether is inert to the same conditions. Reduction through the reactive conformer shown is plausible; nucleophilic attack occurs from the convex face of the bicyclic system, where A(1,3) strain[22] is minimized leading to the positioning of the hydrogen in the amide plane.

Scheme 27

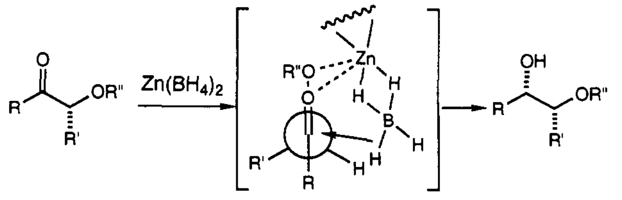


Scheme 28



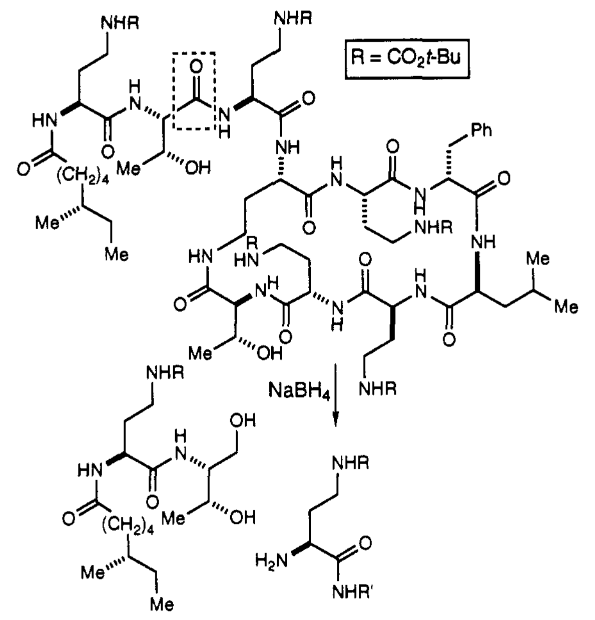
Most recently, it has been reported that a β-hydroxy group may effectively control the reduction of an oxime.[219] As is illustrated in Scheme 28, reduction by $Me_4NBH(OAc)_3$ affords either the syn or the anti product with stereocontrol. The rationale behind such reversal of stereochemistry will undoubtedly be the subject of future reports.

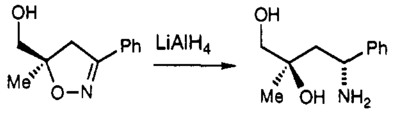
A number of reports have implicated internal delivery when rationalizing stereoselective reactions which involve other borohydrides.[220] For example, intramolecular reduction has been invoked in $Zn(BH_4)_2$ reactions of ketones bearing α- or β-heteroatoms,[221] although metal ion chelation followed by intermolecular attack by hydride would also rationalize the sense of stereoselection obtained. Scheme 29 illustrates a remarkable reductive cleavage by $NaBH_4$ of one of two threonine peptide bonds of a polymyxin antibiotic; the alcohol and amine shown were the principal isolated products.[222] A reaction directed by the less encumbered hydroxyl group is postulated; when the threonine hydroxyls are protected (OTHP), no transformation takes place.



Aluminum hydrides may also participate in directed reduction processes.[223] As eqs 73 and 74 demonstrate, hydroxyl groups direct the addition of $LiAlH_4$ to isoxazolines.[224]

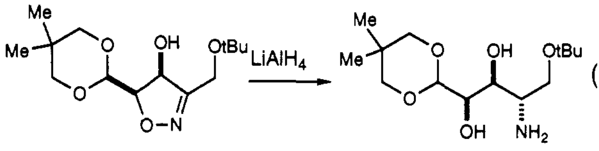
Scheme 29





(73)

Diastereoselection 7:1

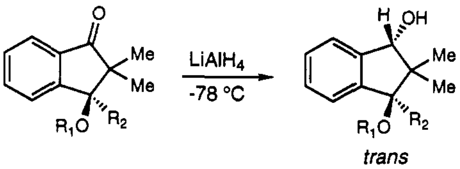


(74)

Diastereoselection >20:1

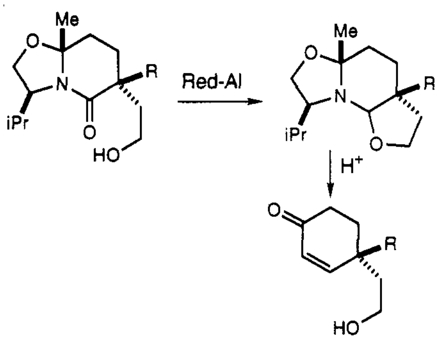
Cawley and Petrocine have reported the reduction of a series of cyclic hydroxy and alkoxy ketones with $LiAlH_4$ (Table 46).[225] The overall stereoselectivity of the reaction is proposed to depend on a competition between oxygen-delivered reduction, which provides the trans isomer exclusively, and intermolecular reduction, which yields a mixture of products. The trends observed with variation in the ratio of substrate to hydride are consistent with this postulate, if the undirected reaction involves a kinetic scheme which is higher order in $LiAlH_4$ than the directed process. Comparison of entry 2 with entry 4 indicates that the presence of an alkyl group α to the methyl ether may hinder dative complexation of the oxygen to the aluminum, thereby retarding the rate of intramolecular reduction. It is not clear a priori why ethers afford higher trans selectivity than do the corresponding alcohols (entry 1 vs 2 and 3 vs 4).

Table 46. Stereoselective Reduction of Cyclic Ketones by $LiAlH_4$



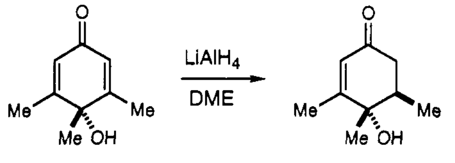
Entry	R_1	R_2	Substrate : Hydride		
			0.5	1.0	2.0
1	H	H	3	12	56
2	Me	H	100	100	100
3	H	Me	20	22	31
4	Me	Me	19	52	83

The ability of an internal hydroxyl group to facilitate reduction by $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al) has been exploited in the design of a chiral auxiliary for the synthesis of 4,4-disubstituted cyclohexenones (eq 75).[226] Whereas attempted cleavage of a valine-derived auxiliary with this reagent furnishes a host of undesired products, in the presence of an appropriately situated hydroxyethyl or aminoethyl substituent, smooth reduction of the lactam occurs. The precise mechanism by which the hydroxyl group accelerates the reduction (internal delivery of hydride versus metal ion binding site for carbonyl activation) has not yet been established.



(75)

Recent reports demonstrate that a γ-hydroxyl group can deliver hydride from $LiAlH_4$ to the β-carbon of a cyclic enone (eq 76).[227] The regio- and stereochemical outcome of the reaction are consistent with intramolecular transfer of hydride from an alkoxyaluminum hydride complex.

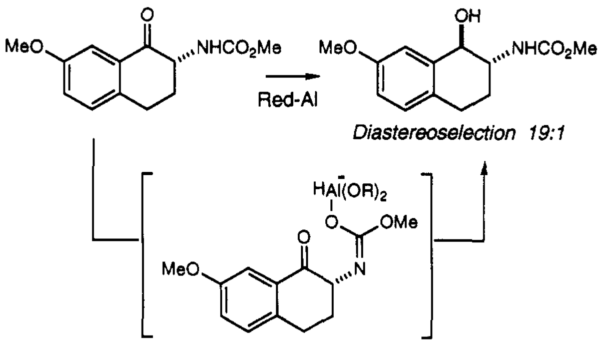


(76)

Diastereoselection >95%

In the course of studies directed toward the synthesis of a nonracemic dopamine agonist, an example of an amide-directed Red-Al reduction was realized (Scheme 30).[228] If the hydride reagent is added to the tetralone, racemization and incomplete reduction result. These data are consistent with the reaction proceeding through rapid formation of the monohydric aluminate intermediate, followed by intramolecular ketone reduction, which occurs in preference to both ketone deprotonation and intermolecular reduction. With excess tetralone, a tetrakisalkoxyaluminate may form. This species is

Scheme 30

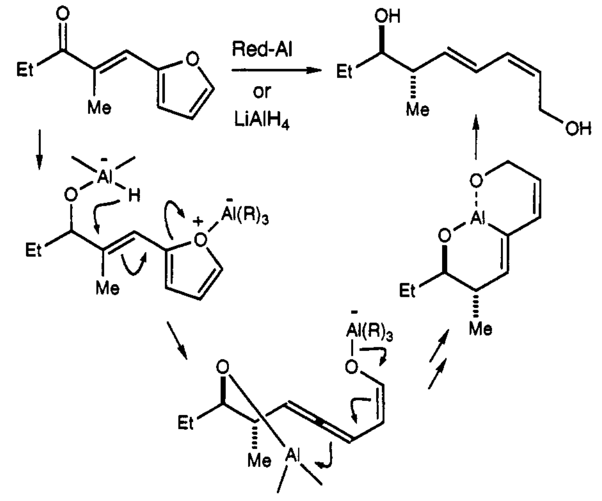


Diastereoselection 19:1

unable to undergo intramolecular reduction without prior disproportionation with aluminum hydride, a process which is apparently sluggish.

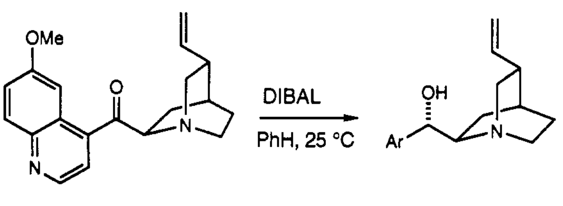
More recently, it has been shown that $LiAlH_4$ or Red-Al can effect the reductive fragmentation of a number of β-furanyl systems.[229] As is shown in Scheme 31, it is suggested that the hydroxyl group, formed from initial reduction of the corresponding ketone, directs delivery of the hydride.

Scheme 31

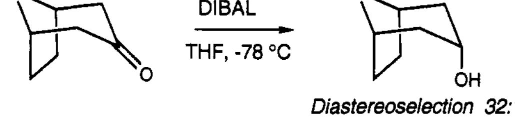


2. Reduction by Trivalent Hydride Reagents

The stereochemical outcome of a variety of carbonyl reductions by DIBAL (diisobutylaluminum hydride) has been rationalized on the basis of a directed reaction.[230] DIBAL stereoselectively reduces quinidinone to quinidine (eq 77), whereas $NaBH_4$ affords the opposite (Felkin–Anh) sense of stereoselection. Amine complexation to DIBAL, followed by intramolecular delivery, has been proposed.[231] The sense of stereoselection observed in the reduction of tropinone is dependent on the nature of the reducing agent; whereas DIBAL preferentially furnishes tropine (eq 78),[232] tetravalent metal hydride reagents such as lithium aluminum hydride and sodium borohydride preferentially produce the diastereomeric alcohol.



(77)

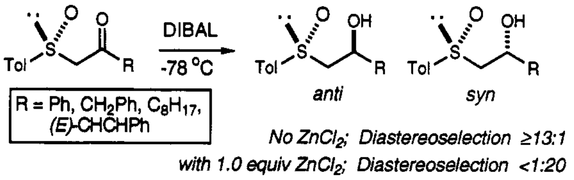


(78)

Diastereoselection 32:1

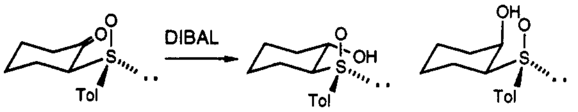
In the reduction of β-keto sulfoxides, the presence or absence of a Lewis acid plays a decisive role in determining the sense of diastereoselection (eq 79).[233] It was subsequently reported that similar results can be obtained with cyclic substrates (eq 80).[234]

It has been postulated that in the presence of $ZnCl_2$, chelate i undergoes reduction, whereas in its absence, conformer ii is the reactive species "because of dipolar



(79)

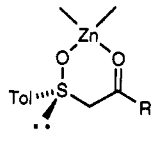
No $ZnCl_2$; Diastereoselection ≥13:1
with 1.0 equiv $ZnCl_2$; Diastereoselection <1:20



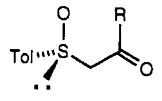
(80)

No $ZnCl_2$; Diastereoselection >20:1
with $ZnCl_2$; Diastereoselection 1:9

interactions"; in both cases, attack of external hydride occurs on the less hindered (β) face.[235]



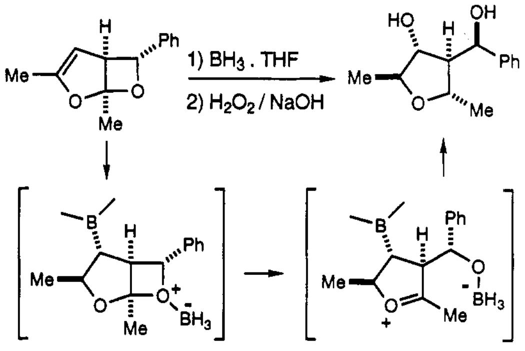
i



ii

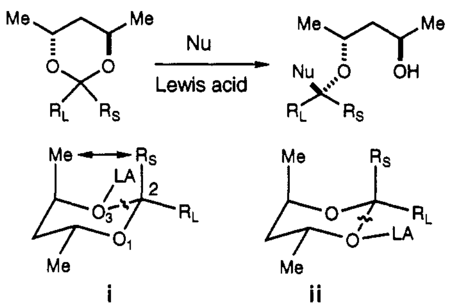
Another class of directed reductions by trivalent metal hydrides includes the cleavage of cyclic ketals by boranes and alanes. The proposed mechanism for this reaction involves (1) coordination by the Lewis acidic metal to a ketal oxygen (2) cleavage of the ring into an oxonium ion and an alkoxy metal hydride, and (3) intramolecular delivery of hydride to the oxonium ion. The reduction of the carbon–oxygen bond in the bicyclic ketal shown in Scheme 32 proceeds stereoselectively with retention of configuration, consistent with the postulate of intramolecular delivery.[236] The choice of which ketal C–O bond is cleaved in these reactions may be rationalized by consideration of steric inhibition to complexation to the metal, chelation by substrate heteroatoms to the metal, and relief of strain.

Scheme 32



Chiral ketals derived from 2,4-pentanediol have been cleaved by a wide range of nucleophiles with high diastereoselectivity (Scheme 33).[237] A preference for relieving the more severe 1,3-diaxial interaction ($M \leftrightarrow R_S$) offers a plausible rationale for the sense of induction observed in these reactions. Thus, binding of the Lewis acid to O_3 (i) should be preferred to O_1 (ii), since this complexation simultaneously increases the strength of the $n_{O1} \rightarrow \sigma^*_{C2-O3}$ stabilization and decreases the ability of O3 to donate to σ^*_{C2-O1}. Both effects serve to lengthen the O3–C2 (and shorten the O1–C2) bond relative to the uncomplexed ketal, thereby relieving the more

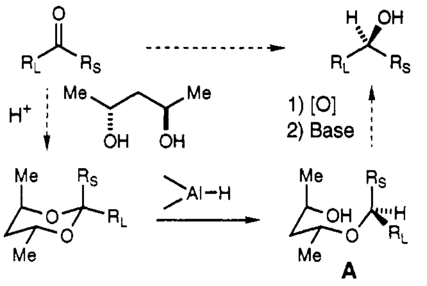
Scheme 33



destabilizing diaxial interaction (Me ↔ R_S); similarly, complexation of O1 (ii) would worsen this interaction by shortening the O3–C2 bond.[238] Identical stereoelectronic and steric effects are also expressed along the pathway to formation of the oxonium ion.

For most nucleophiles, acetal cleavage occurs with inversion of configuration at the carbon undergoing substitution, consistent with either nucleophilic attack on a tightly ion-paired oxonium intermediate or direct S_N2 displacement. However, it has been established that trivalent aluminum hydrides diverge from this stereochemical regularity by providing the product with retention of configuration.[239] This observation is consistent with the notion of rapid intramolecular hydride delivery within the ion-paired intermediate. A sequence which involves this reaction as a key step affords the equivalent of an enantioselective ketone reduction (Table 47). Low temperatures, high concentrations of aluminum hydride, and solvents of low to moderate Lewis basicity are required for high selectivity. The stereochemistry of the products of reduction by binary hydride–Lewis acid reagents suggests attack by external hydride (entry 1).[240]

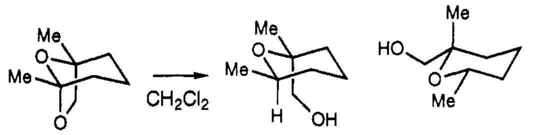
Table 47. Reduction of Acetals by DIBAL



Entry	R_L	R_S	Reagent (equiv)	% de of **A**
1	C_6H_{11}	Me	DIBAL (5.0)	88
			Cl_2AlH (6.0)	92
			Br_2AlH (6.0)	95
			Et_3SiH (1.0) /$BF_3·OEt_2$ (1.0)	14[a]
			Et_3SiH (1.2) /$TiCl_4$ (1.2)	4[b]
2	Hex	Me	Br_2AlH (20.0)	78
3	Ph	Me	Br_2AlH (6.0)	96
4	Me	C≡CBu	Br_2AlH (2.0)	0
			Br_2AlH (4.0)	36
			Br_2AlH (6.0)	86

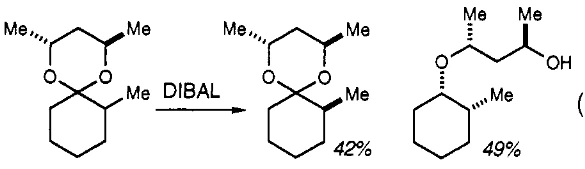
[a] Other isomer formed with 86% selectivity. [b] Other isomer formed with 96% selectivity.

Recently, the stereoselective reduction of a series of bicyclic ketals has been reported (eq 81).[241] Most noteworthy is that in selected instances satisfactory levels of kinetic resolution of diastereomeric ketals has been achieved (eq 82).[242]



(81)

with DIBAL (25°C) ; Diastereoselection 32:1
with Et_3SiH, $TiCl_4$ (-78 °C) ; Diastereoselection 1:99

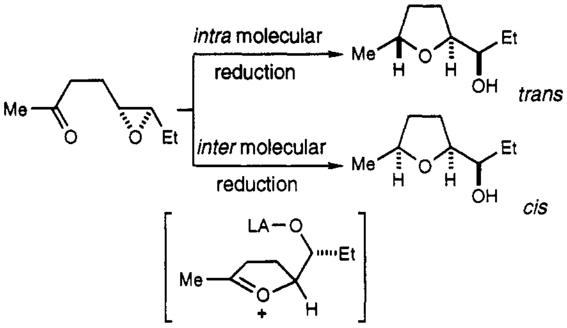


(82)

Diastereoselection >99:1 *Diastereoselection 19:1*

A related cyclization, directed reduction sequence has been utilized for the synthesis of a trans-2,5-disubstituted tetrahydrofuran from an epoxy ketone.[243] Nucleophilic attack by the carbonyl oxygen on the epoxide, induced by a Lewis or Brönsted acid, generates the oxonium ion. Intramolecular delivery of hydride to this intermediate furnishes the trans isomer, whereas intermolecular reaction should favor the cis. Silane–acid reagents provide the cis tetrahydrofuran, albeit with low selectivity, whereas $BH_3·SMe_2$ and thexylborane afford the trans isomer predominantly (Table 48). The concentration effect observed with $BH_3·SMe_2$ is consistent with the postulate that the overall reaction diastereoselectivity reflects competition between internal and external hydride for the oxonium ion. Cyclization–reduction of the corresponding cis epoxide proceeds with comparable levels of stereocontrol.

Table 48. Reduction of Oxonium Ions by Boranes

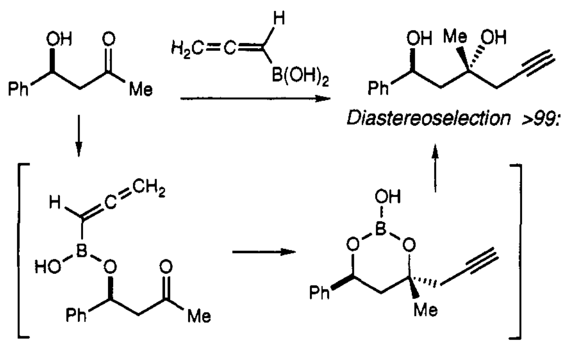


Conditions	*Cis : Trans*
Et_3SiH, TFA	2 : 1
Ph_3SiH, $BF_3·OEt_2$	5 : 1
$BH_3·SMe_2$ (0.005 M)	1 : 24
$BH_3·SMe_2$ (0.012 M)	1 : 11
thexylborane (0.030 M)	1 : 9

B. Nucleophilic Addition to C=O and C=N

Several reports suggest that directed addition of main group organometallics to polarized double bonds is possible.[244,245] As illustrated in Scheme 34, treatment of β-hydroxy ketones with allenylboronic acid furnishes homopropargylic alcohols with high diastereoselectivity (>99:1).[246] The reaction is proposed to proceed in-

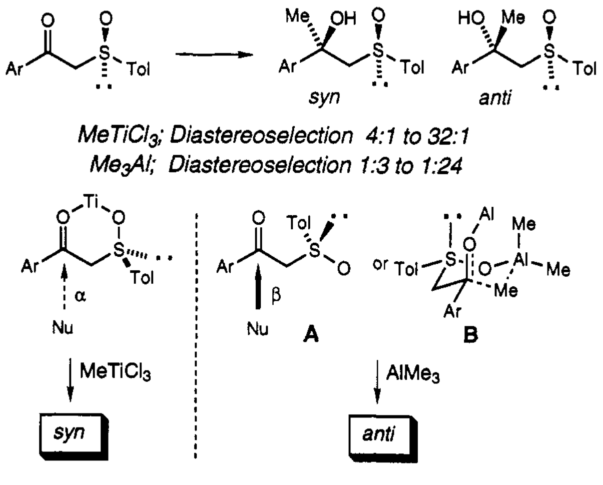
Scheme 34



tramolecularly, as indicated. Control experiments establish that a hydroxyl group accelerates the addition, but the precise mechanism by which this is effected (internal delivery versus chelation–activation) is unclear. It has been suggested that the diastereoselectivity of the allenylboronic acid reaction (>99:1) in comparison with that of propargylmagnesium bromide (<3:1) provides support for a highly organized transition state involving delivery rather than a less rigid transition state involving chelation.

The sense of stereoselection observed in the addition of methyl organometallics to β-keto sulfoxides is reagent dependent:[247] external attack at the less hindered face of a chelated intermediate rationalizes the syn selectivity of the $MeTiCl_3$ reaction (Scheme 35). It has been suggested that the intermolecular alkylation of the less encumbered face of a dipole-minimized β-keto sulfoxide conformer (A) leads to the complementary diastereoselection obtained upon reaction with $AlMe_3$. In analogy to tetravalent borohydride reduction of β-hydroxy ketones, we suggest an alternate transition-state model which invokes intramolecular delivery of the nucleophile by the sulfoxide oxygen (B; see Scheme 26 for comparison).

Scheme 35

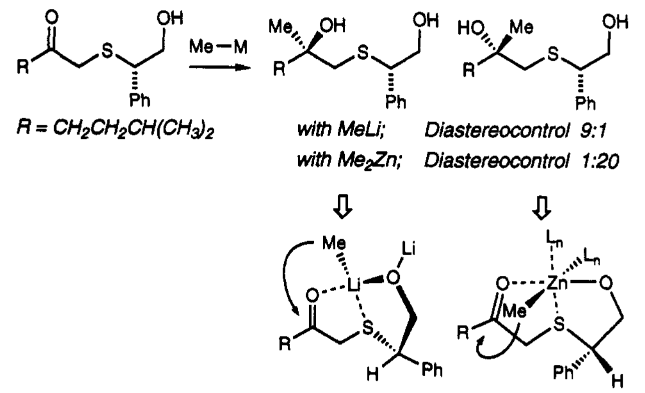


syn
anti
MeTiCl3; Diastereoselection 4:1 to 32:1
Me3Al; Diastereoselection 1:3 to 1:24
A
B
MeTiCl3
AlMe3
syn
anti

Nucleophilic addition of alkylmetals to chiral thiomethyl ketones has been shown to be diastereoselective and stereochemically complementary, depending on the alkylmetal employed.[248] Two examples are shown in Scheme 36; the opposite stereochemical outcomes with alkyllithium and alkylzinc reagents have been rationalized by the transition structures shown.

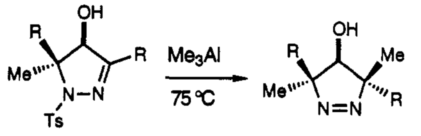
With $AlMe_3$, hydroxypyrazolines undergo addition exclusively syn to the hydroxyl group (eq 83).[249]

Scheme 36



Me—M
R = CH2CH2CH(CH3)2
with MeLi; Diastereocontrol 9:1
with Me2Zn; Diastereocontrol 1:20

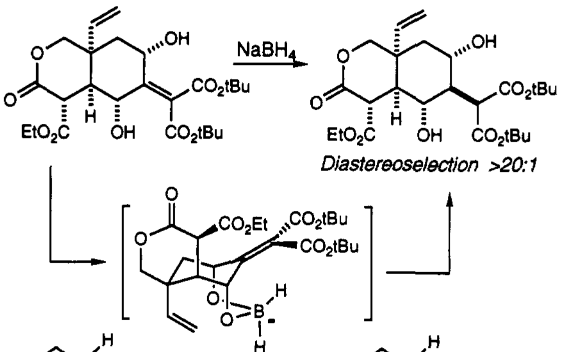
The corresponding methyl ethers are unreactive toward trimethylaluminum even at higher temperatures (110 °C).



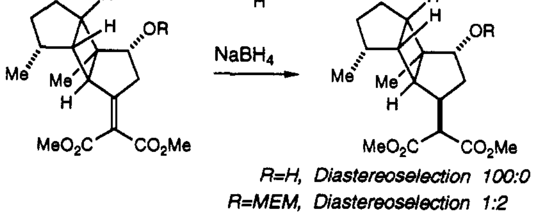
(83)

C. Conjugate Addition Reactions

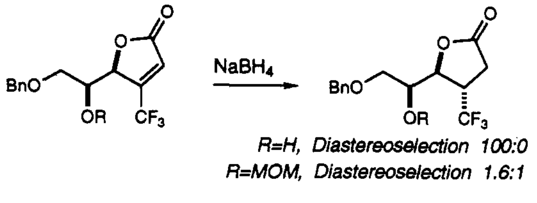
A range of nucleophiles (hydrides, organometallics, and peroxides) can be delivered in a 1,4-fashion to conjugated alkenes. There have been several reports of diastereoselective reductions of α,β-unsaturated carbonyl systems by $NaBH_4$ where the sense of addition is consistent with internal delivery by a hydroxyl group (eqs 84–86).[250] The reaction shown in eq 84 is believed to proceed via the chelated dialkoxyborohydride. Hydride delivery by the homoallylic alcohols in eqs 85–86 is effective; protection of these directing groups, however, leads to a diminution in stereoselectivity.



(84)



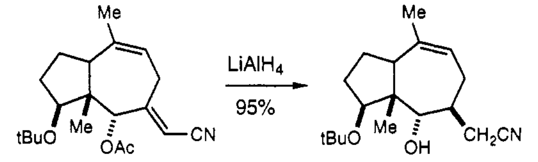
(85)



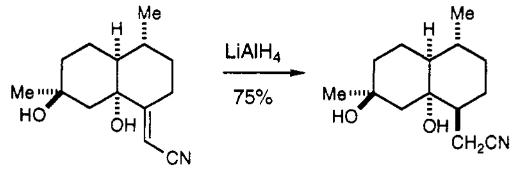
NaBH4
R=H, Diastereoselection 100:0
R=MOM, Diastereoselection 1.6:1

(86)

Lansbury has developed a general route to *trans*-γ-lactones through a sequence involving highly diastereoselective hydroxyl-directed reduction of α,β-unsaturated nitriles with $LiBH_4$ or $LiAlH_4$, followed by hydrolysis. Isolated α,β-unsaturated nitriles are unreactive toward $LiBH_4$ under the same conditions, whereas $LiAlH_4$ preferentially reduces the C–N π-system. Two examples are illustrated in eqs 87 and 88.[251]

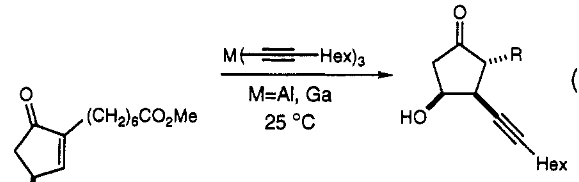


(87)

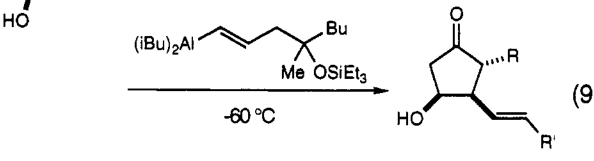


(88)

Although alanes do not generally add in a 1,4-fashion to enones that are constrained to lie in an s-trans conformation,[252] treatment of the hydroxycyclopentenone shown below with alkynyl- and alkenylalanes results in conjugate addition exclusively syn to the hydroxyl group (eqs 89 and 90).[253] The corresponding THP ether and the des(hydroxy) enone are unreactive; these data indicate delivery of the alane by the hydroxyl group.

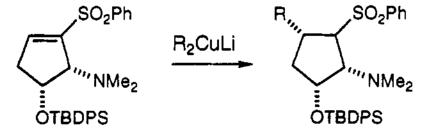


(89)



(90)

It appears that amines can direct the conjugate addition of dialkylcuprates to a cyclopentenyl sulfone.[254] In contrast to alkyllithiums, which add only to the less hindered face of the olefin, cuprates add exclusively to the more sterically encumbered face (eq 91).

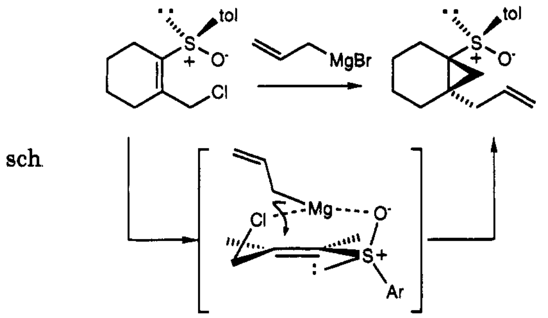


(91)

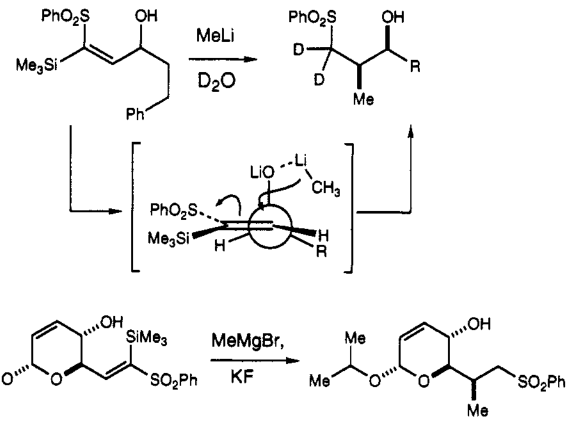
R = Me, Ph, $CHCH_2$

Recently, it was reported that reaction of allylmagnesium chloride with the unsaturated sulfoxide shown in Scheme 37 results in the stereoselective formation of the corresponding cyclopropane.[255] The proposed transition structure, where unfavorable allylic interactions (A(1,3)) are minimized,[202] is illustrated; association of the alkylmagnesium with the pendant chloride and sulfoxide groups is believed to lead to high levels of diastereocontrol.

Scheme 37

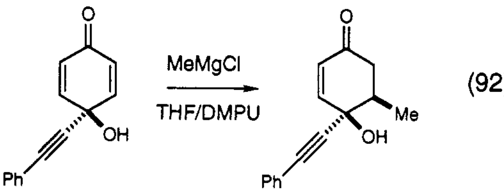


Scheme 38



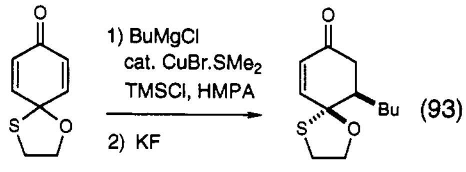
An interesting case of directed conjugate addition is shown in Scheme 38.[256] Association of the alkyllithium with the Lewis basic lithium alkoxide results in the stereoselective formation of the carbon–carbon bond. Also presented in Scheme 38 is a step in the synthesis of okadaic acid where this type of addition process is employed.[256e]

Addition of MeMgCl to quinol alkoxides proceeds with high levels of diastereocontrol; these reactions are believed to be directed ("ligand-assisted") by the internal hydroxyl group.[257] The example shown in eq 92 is illustrative. The transformation shown in eq 93 indicates that the directing ability of the alkoxy group is superior to that of the sulfide.[258]



(92)

Diastereoselection 13:1

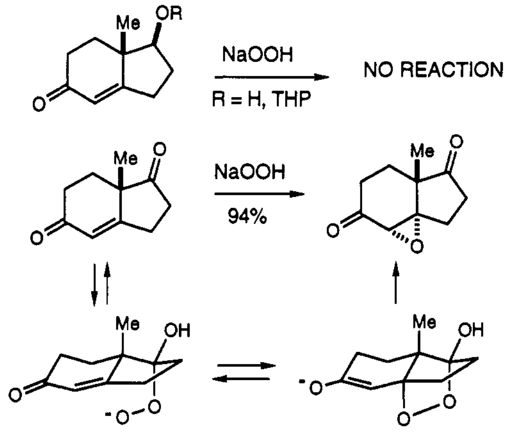


(93)

Diastereoselection 13:1

A remote carbonyl group has been reported to deliver an oxygen nucleophile, a peroxide, in an enone epoxidation reaction.[259] Whereas treatment of the alcohol or ether with NaOOH leads to no reaction, the derived ketone affords the α-epoxide as a single diastereomer in 94% yield (Scheme 39). It was proposed that initial

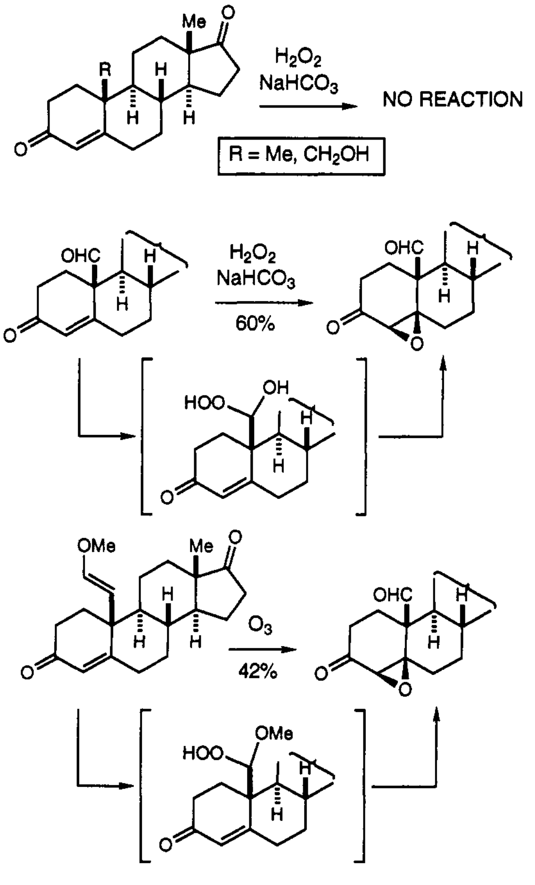
Scheme 39



addition of hydrogen peroxide to the nonconjugated ketone results in the formation of an alkyl hydroperoxide adduct, which then effects epoxidation intramolecularly. The Wieland–Miescher ketone also affords exclusively the trans-fused ring system under these conditions.

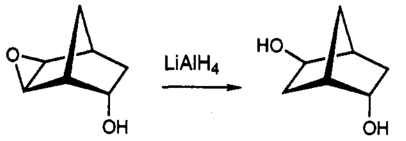
Similar observations were subsequently reported in connection to an androgen system (Scheme 40):[260] *tert*-butyl hydroperoxide does not effect epoxidation under these conditions, consistent with the mechanism illustrated in Scheme 39. Generation of the alkyl hydroperoxide intermediate through other pathways can also result in stereoselective epoxidation.[261] Thus, treatment of the illustrated enol ether with ozone furnishes only the *syn*-epoxy aldehyde.

Scheme 40

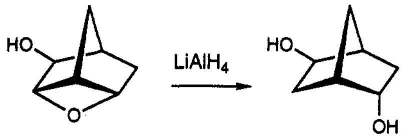


D. Nucleophilic Substitution Reactions

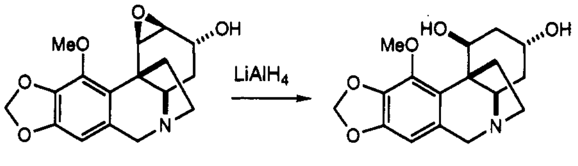
The hydroxyl-directed, regioselective ring cleavage of epoxy alcohols and related compounds by a variety of nucleophiles (hydride, alkoxide, and organometallic) has been achieved.[262] The first example of directed cleavage involved opening with hydride, and this reaction remains the most widely used in this class. Early work in this area involved $LiAlH_4$ as the reducing agent; examples shown in eqs 94–96 are illustrative.[263] The reaction is believed to proceed through ligation of the hydroxyl group to the reagent, followed by intramolecular hydride delivery from the resulting aluminate complex. Lithium aluminum hydride reduction of the methyl or THP ether of the alcohol in eq 94 preferentially affords the 1,2-diol (>10:1).



(94)



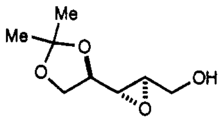
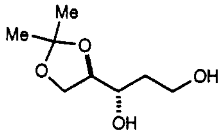
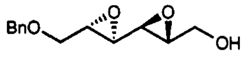
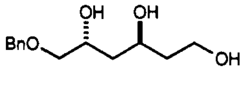
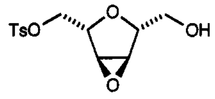
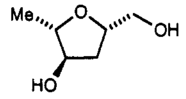
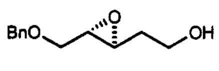
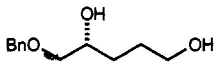
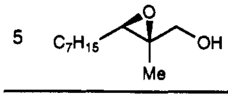
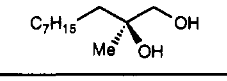
(95)



(96)

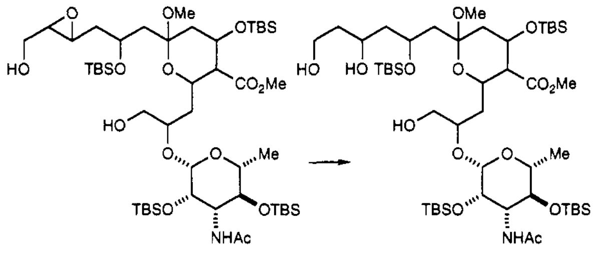
Recently, $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al) has supplanted $LiAlH_4$ as the reagent of choice for hydroxyl-directed epoxide opening.[264] In 1982, several reports indicated that this reagent regioselectively reduces acyclic 2,3-epoxy alcohols to 1,3-diols at or below ambient temperature (Table 49, entries 1 and 2).[265] Under identical conditions, no reaction is observed if the alcohol is protected. Propagating reductive cleavage of bis-epoxides (entry 2),[266] available from asymmetric epoxidation, furnishes access to the *syn*- and the *anti*-1,3-diol pattern found in many polyacetate-derived

Table 49. Cleavage of Epoxy Alcohols by $NaAlH_2(OCH_2CH_2OMe)_2$

Entry	Substrate	Product	Selectivity
1			only
2			only
3			12 : 1
4			only
5			100 : 1

natural products. Entry 3 illustrates a successful cleavage of a cyclic homoallylic epoxy alcohol.[267] Intramolecular delivery of hydride can be effected from the homoallylic position (entry 4), but not when opposed by strong steric hindrance to attack at C2 (entry 5).[268]

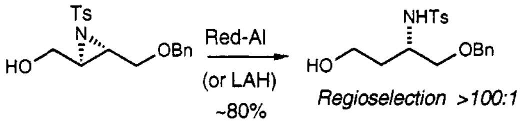
In the short interval since its discovery, the hydroxyl-delivered cleavage of epoxy alcohols by Red-Al has found widespread application in synthesis.[269] Equation 97 provides an application of regioselective reductive opening to a highly functionalized molecule.[270]



(97)

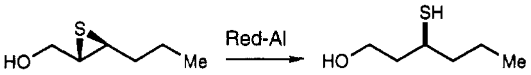
Regioselection 8:1

The available data suggest that the corresponding sulfur and nitrogen heterocycles react analogously. Reduction of the aziridino alcohol shown in eq 98 with either Red-Al or $LiAlH_4$ proceeds with high regioselectivity; reaction with DIBAL (THF) is equally selective, although the yield is 30%.[271] Exposure of a hydroxy thiirane to Red-Al also affords a product consistent with internal delivery of hydride (eq 99).[272]



(98)

Regioselection >100:1

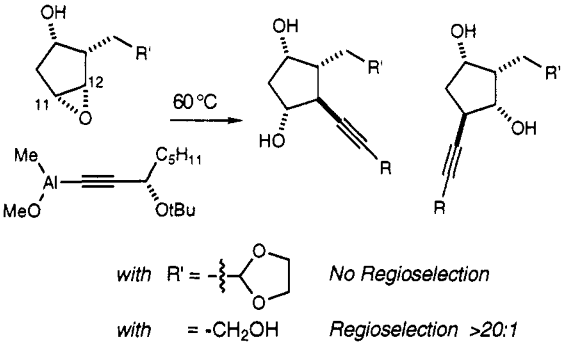


(99)

Regioselection 13:1

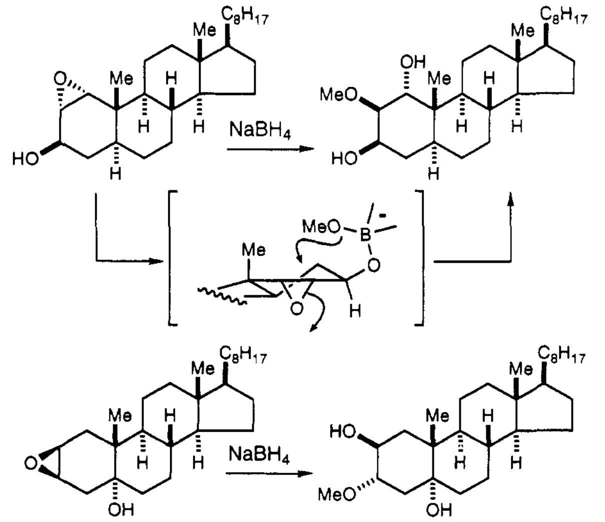
Treatment of a variety of steroidal *anti*-2,3-epoxy alcohols with $NaBH_4$/methanol results in the efficient cleavage of the epoxide (Scheme 41).[273] The corresponding α-alcohol is unreactive toward these conditions, as were all *syn*-epoxy alcohols examined. As is shown in Scheme 41, an *anti*-3,4-epoxy alcohol can undergo directed cleavage as well; under identical conditions the corresponding α-epoxide is recovered untouched.

The hydroxyl-directed cleavage of an epoxy alcohol by an organometallic has also been reported; whereas treatment of the acetal illustrated below with the alkynylalane provides the opening products with poor selectivity, reaction of the derived alcohol results in epoxide cleavage exclusively at the position proximal to the primary hydroxyl group (eq 100).[274] The corresponding dimethylalkynylalane affords the product of attack at C12 with much lower selectivity (1–4:1), indicating that the reaction is highly sensitive to the nature of the alkylating reagent.[275] Other workers have demonstrated that additions of alkyl- and alkynylaluminum species to cyclic and acyclic 2,3-epoxy alcohols[276,277] typically are not subject to internal delivery.[278]



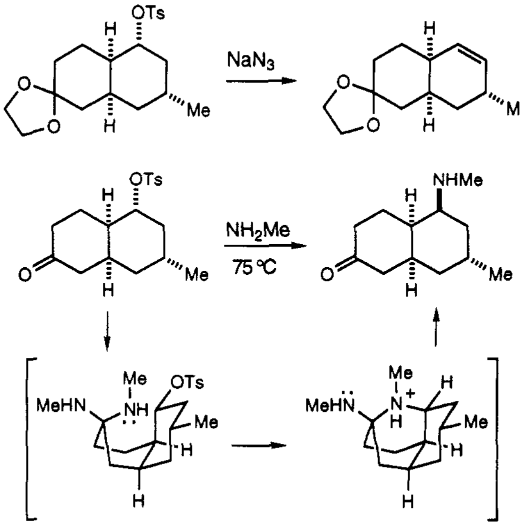
(100)

Scheme 41



Carbonyl groups have been reported to direct the displacement reaction of a secondary tosylate from the concave face of a *cis*-decalin system.[279] Treatment of the acetal shown in Scheme 42 with sodium azide results in elimination primarily (70%), as well as some substitution (30%).[280] However, reaction of the corresponding ketone with NH_2Me furnishes the desired secondary amine in excellent yield as the only product. To explain the difference in reactivity, it was postulated that the latter transformation proceeds in an intramolecular fashion through a transient aminal.

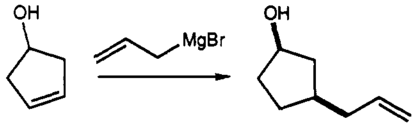
Scheme 42



VIII. Directed Carbometalation and Hydrometalation Reactions

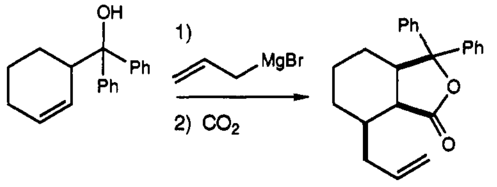
A. Alkylmagnesium Additions

Although alkylmagnesium halides normally do not react with unactivated alkenes, in certain instances the presence of a hydroxyl group can lead to the addition of the alkylmagnesium halide to the alkene. For example, treatment of allylmagnesium bromide to alkenes shown below (eqs 101 and 102, in refluxing ether) results in the stereoselective formation of carbon–carbon bonds.[281],[282]



(101)

Diastereoselection 4:1



(102)

Diastereoselection >20:1

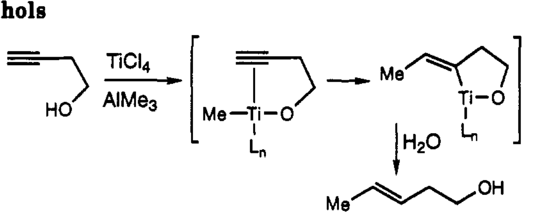
B. Alkyltitanium Additions

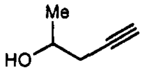
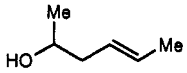
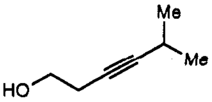
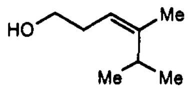
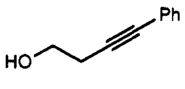
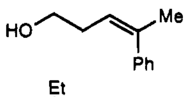
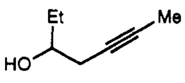
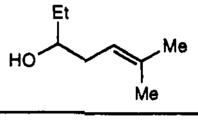
A number of transition metal-mediated, hydroxyl-delivered carbometalations of multiple bonds have been reported. Whereas 1-octyne forms dimers and higher oligomers upon treatment with $TiCl_4/AlMe_3$, under the same conditions homopropargylic alcohols undergo regioselective methylmetalation (Table 50).[283] Quenching with D_2O results in deuterium incorporation cis to the newly introduced methyl group. The mechanism shown below, involving delivery by the hydroxyl, accommodates these results. Ethylmetalation of terminal homopropargylic alcohols can be effected with $TiCl_4/ClAlEt_2$; however, reaction of the corresponding internal alkynes affords none of the desired addition product.[284] Hydroxyl-delivered carbometalation of bishomopropargylic alcohols is also possible.

Carbometalation of homoallylic alcohols with Ti/Al reagents provides a number of products (Scheme 43).[285] Although this reduces the reaction's utility in synthesis, the presence of only one olefin product suggests that delivery of the metalalkyl by the hydroxyl group is occurring. Addition to the alkene can furnish either of two alkyltitanium species (B or C). These intermediates may react further by β-hydride elimination. β-Elimination of exocyclic hydrogens is known to be favored relative to endocyclic.[286] Therefore, if chelation is operative, it would be reasonable that formation of only one of the three possible β-hydride elimination products (E) is observed. In the absence of chelation, one would expect to see production of A and D as well.

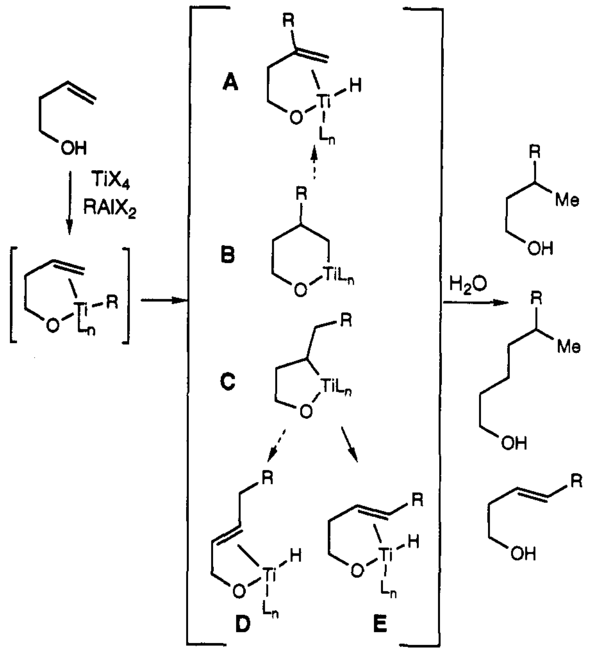
The facility with which these β-hydride eliminations occur is highly solvent dependent, pentane/Me_2O being the medium of choice for a more rapid reaction.[287] Homoallylic alcohols react site selectively and regio- and stereoselectively with $AlMe_3/TiCl_4$ in pentane/Me_2O to afford the methylated olefins (Scheme 44). The hydroxyl-delivered olefin carbometalation–β-hy-

Table 50. Methyltitanium Addition to Homopropargylic Alcohols

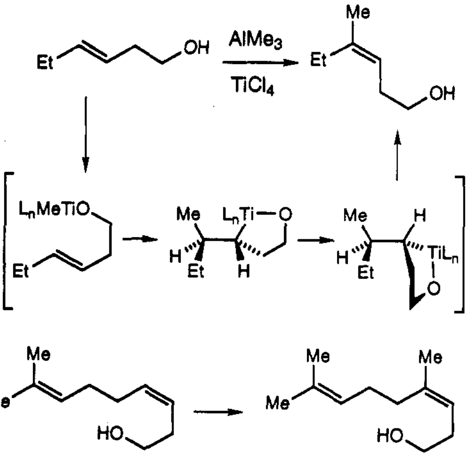


Entry	Substrate	Product	Yield (%)
1			80
2			67
3			76
4			66

Scheme 43

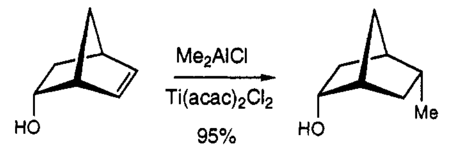


Scheme 44



dride elimination mechanism shown in Scheme 44 has been proposed to account for these observations.

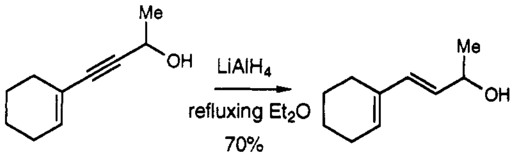
Recent studies indicate that treatment of rigid bicyclic alkenes bearing a heteroatom with $AlMe_2Cl$ and $AlEt_2Cl$ in the presence of small amounts of Ti(IV) complexes (e.g., Cp_2TiCl_2 or $Ti(acac)_2Cl_2$) results in the attachment of the alkyl group to the face of the alkene syn to the directing group.[288] The example shown in eq 103 is illustrative; the corresponding exo isomer affords no product.



(103)

C. Hydroaluminations of Alkynes

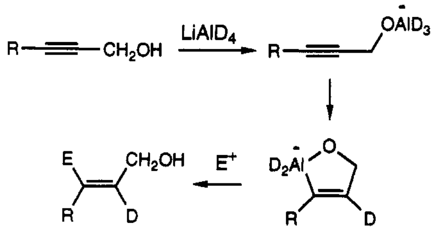
The hydroalumination of isolated alkynes by $LiAlH_4$ can be directed by properly situated heteroatoms, but requires vigorous conditions.[289] Reduction of the enynol shown in eq 104 with lithium aluminum hydride proceeds under mild conditions.[290] This reaction has been shown to be general for propargylic alcohols.[291]



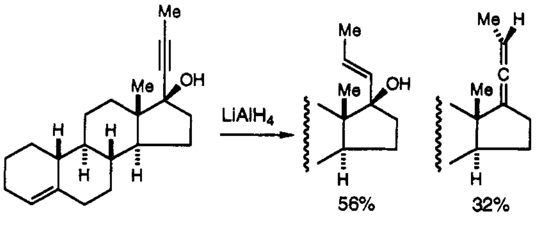
(104)

The reaction mechanism most probably involves coordination of the substrate hydroxyl to aluminum, then intramolecular delivery of hydride to the proximal carbon of the acetylene (Scheme 45).[292,293] The intermediate vinyl alanates can be derivatized with I_2 stereoselectivity to afford trisubstituted alkenes.[294]

Scheme 45

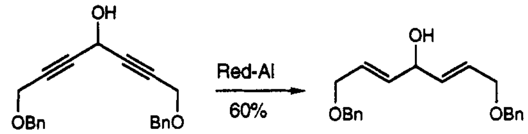


Formation of allenes, presumably a result of delivery of hydride to the distal carbon, can be a significant reaction pathway in these reductions (eq 105).[295] Other common side products are the cis allylic alcohol and the fully saturated alcohol.

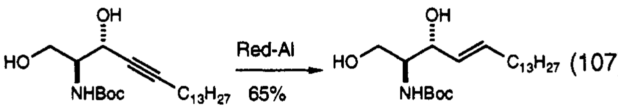


(105)

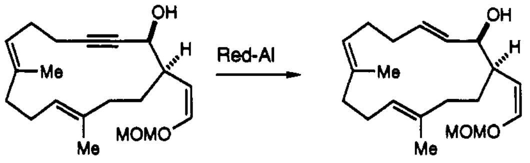
Recent reports indicate that $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al) effects trans hydroalumination of propargylic alcohols more selectively than does $LiAlH_4$.[296] This complex, which provides the fastest, highest yielding, and most stereoselective reduction among the metal hydrides examined, is the reagent of choice for accomplishing this transformation (eqs 106–108).[297]



(106)

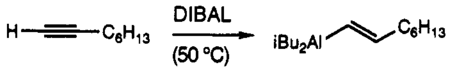


(107)

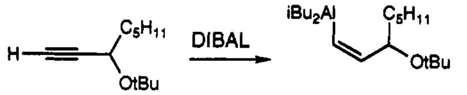


(108)

Ether oxygens are capable of delivering hydride to alkynes. Whereas treatment of unfunctionalized acetylenes with DIBAL furnishes the product of cis addition, a propargylic *tert*-butyl ether undergoes selective trans hydroalumination (eqs 109 and 110).[298] Since the derived trityl ether reacts in a normal fashion, it was suggested that dative coordination of oxygen to the trivalent metal might be responsible for the altered mode of addition.

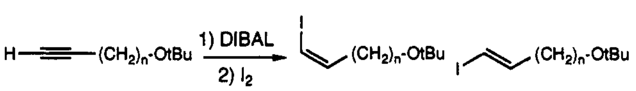


(109)



(110)

Hydroalumination of ω-*tert*-butoxyalkynes by DIBAL demonstrates that trans addition only prevails for acetylenes in which a chelate is favored (*n* = 1, 2, eq 111).[299] These data are consistent with oxygen-delivered hydroalumination of propargylic and homopropargylic *tert*-butyl ethers.

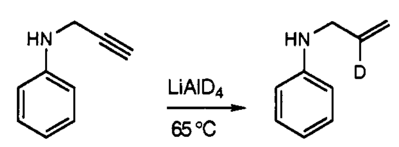


with n=1, 2	*>99:1*
with n=3	*1:24*
with n=4, 6, 8, 10	*<1:99*

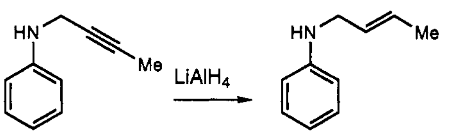
(111)

As with alcohols, propargylic amines may be reduced to the corresponding alkene upon treatment with lithium aluminum hydride.[300] Thus, exposure of *N*-(2-propynyl)aniline to $LiAlD_4$ in refluxing THF, followed by aqueous workup, affords the allylic amine shown in eq 112 in 84% yield. Hydroalumination of an internal acetylene selectively provides the *trans*-olefin product (eq 113). The observation that *N*-methyl-*N*-(2-propynyl)aniline does not react under these conditions suggests that internal delivery of hydride proceeds by way of an aluminum amide (eq 114).[301]

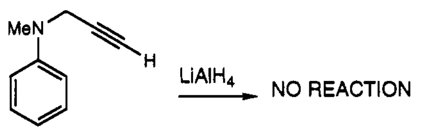
Treatment of 4-hydroxy-,[302] 4-halo-,[303] 4-(trialkylammonio)-,[304] and 4-alkoxy-2-butyn-1-ols[305] with Li-



(112)

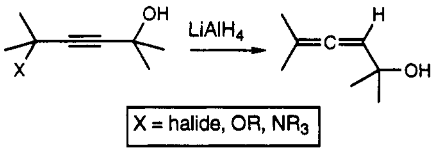


(113)



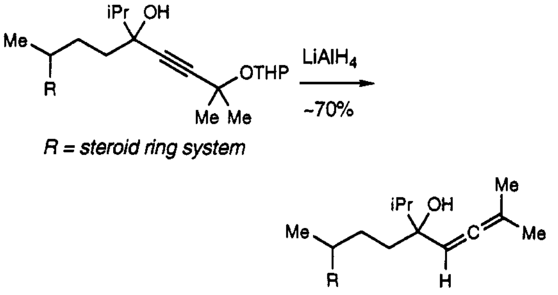
(114)

AlH_4 efficiently affords α-allenic alcohols (eq 115).[306] Reduction of the corresponding homopropargylic substrates furnishes β-allenic alcohols.[307] Again, the available data are consistent with intramolecular delivery of hydride to the alkyne.



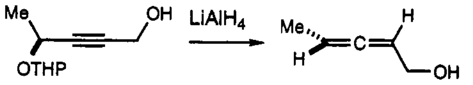
(115)

This type of reduction has been used in a synthesis of an allenic analogue of desmosterol, an intermediate in sterol biosynthesis (eq 116). A related compound lacking a hydroxyl substituent is unreactive toward $LiAlH_4$.[295d]



(116)

As is illustrated in eq 117, reduction of optically active substrates can provide a route to nonracemic α- and β-allenic alcohols.[308]



(117)

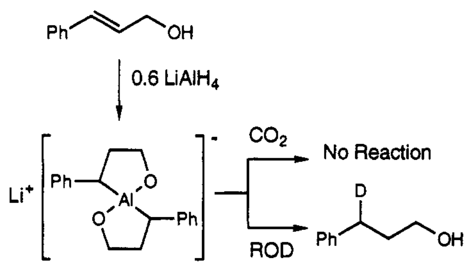
Enantiomeric Excess 90%

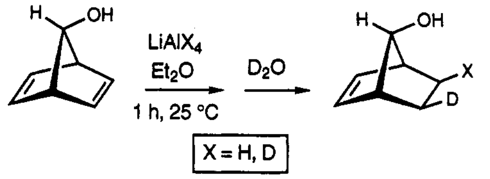
D. Hydroaluminations of Olefins

A variety of olefinic alcohols and amines are converted to their saturated derivatives when treated with lithium aluminum hydride; generally the alkene is activated toward hydroalumination either by ring strain or by an anion-stabilizing group. Reduction of cinnamyl alcohol to 3-phenyl-1-propanol serves as an example (Scheme 46).[309] On the basis of reactivity and deuterium labeling studies, it was surmised that the product of the reaction (prior to hydrolysis) is a chelated alkylaluminum species.[310]

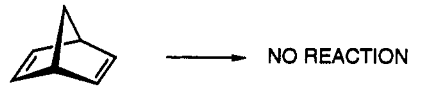
7-Hydroxynorbornadiene selectively undergoes exo,-cis addition to the alkene syn to the homoallylic hydroxyl under conditions toward which norbornadiene and 7-*tert*-butoxynorbornadiene are unreactive (eqs 118 and 119).[311,312] This observation supports the postulate of intramolecular delivery in these alkene hydroaluminations. *syn*-7-Norbornenol is reduced by $LiAlH_4$ to 7-norbornanol, whereas the olefins of the anti isomer and of *syn*-7-formylnorbornene are unreactive under the same conditions (eq 120). Together, these results demonstrate the viability of directed hydroalumination of olefins which bear appropriately situated directing groups.[313]

Scheme 46

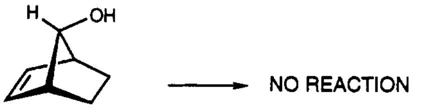




(118)

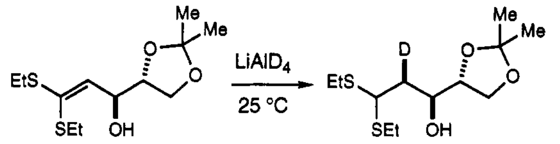


(119)



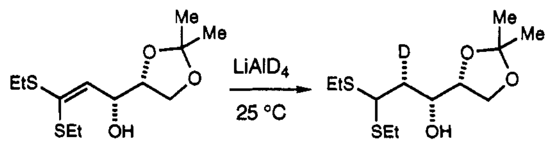
(120)

Reduction of ketene dithioacetals with $LiAlH_4$ can be directed by an internal hydroxyl group (eqs 121 and 122);[314] in contrast, the corresponding methyl ether is unreactive. Labeling studies demonstrate that hydride addition occurs at the alkene carbon proximal to the hydroxyl group and that the reaction is stereospecific. The sense of induction is consistent with intramolecular hydroalumination occurring out of a conformer which minimizes A(1,3) strain.[202]



(121)

Diastereoselection >20:1

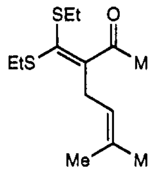
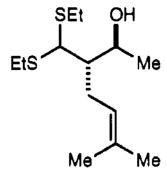
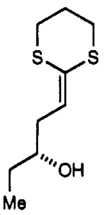
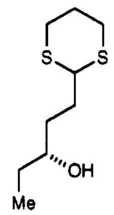
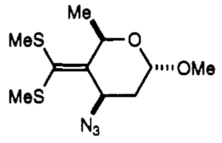
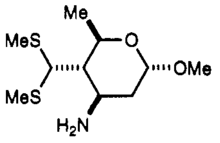


(122)

Diastereoselection >20:1

Similarly, the reduction of α-oxo ketene dithioacetals is subject to delivery by a resident heteroatom.[315] Hydride addition to the carbonyl precedes alkene hydroalumination, which occurs at 25 °C for trisubstituted olefins and at 50–65 °C for tetrasubstituted alkenes. Reduction affords a single diastereomer for

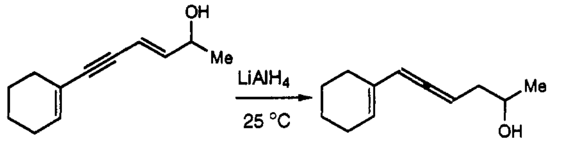
Table 51. Hydroalumination of Ketene Dithioacetals with $LiAlH_4$

Entry	Substrate	Product	Yield
1			71
2			..
3			84

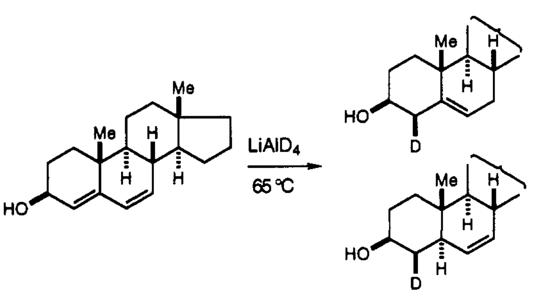
a range of substrates, providing the same sense of stereoselection regardless of the nature of the C_2 substituent (Table 51).[316]

Delivery of hydride to an alkene in an S_N2' fashion is possible under specified conditions. For example, $LiAlH_4$ effects the reductive rearrangement of 2,3-unsaturated methyl pyranosides to 3-deoxyglycals (Scheme 47).[317] The reactivity and stereochemical data are consistent with a requirement of syn S_N2' delivery of hydride.

An yne–diene may be converted to the corresponding β-allenic alcohol upon treatment with $LiAlH_4$ (eq 123).[318] Chiral lithium aluminum hydride complexes afford nonracemic β-allenic alcohols, albeit in low optical purity.[319] The directed reduction of dienols to olefinic alcohols can also be effected (eq 124).[320]



(123)



(124)

Scheme 47

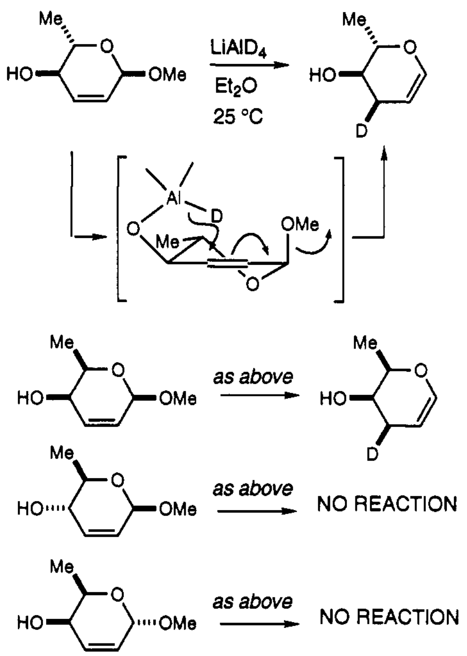
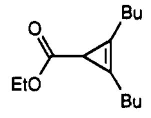
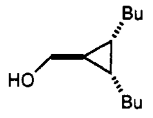
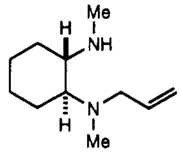
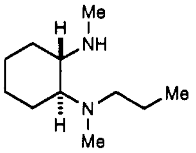
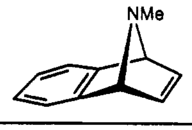
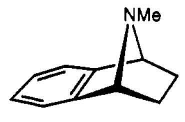


Table 52. Hydroalumination of Alkenes with $LiAlH_4$

Entry	Substrate	Product
1		
2		
3		

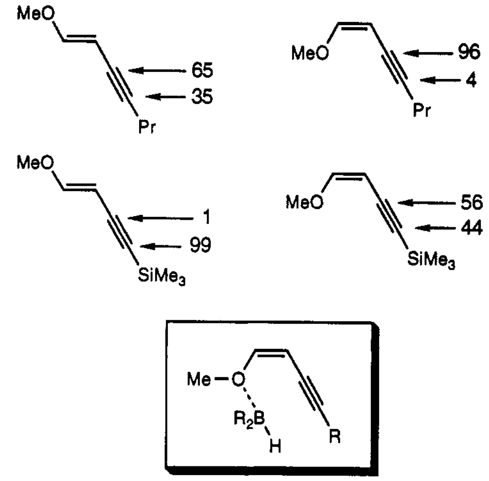
A number of other olefinic alcohols and amines, some of which are shown in Table 52,[321] are also reduced to their saturated derivatives by lithium aluminum hydride. Cyclopropenes undergo stereospecific hydroxyl-directed hydroalumination when treated with $LiAlH_4$ (entry 1);[322] the product stereochemistry and deuterium labeling studies are consistent with a delivered reaction.[323] In connection to the example provided in entry 2, the observation that *N*-allyl-*N*,*N*-dimethylamine does not react under identical conditions suggests a role for the remote amine in directing this process. The alkene of *N*-methyl-7-aza-2,3-benzobicyclo[2.2.1]heptadiene is reduced by $LiAlH_4$ at room temperature (entry 3); the unexpected reactivity has been attributed to intramolecular delivery of alane, presumed to be accessible under the reaction conditions, by the amine to the strained olefin.[324]

Although a few synthetically useful delivered $LiAlH_4$ hydroaluminations of alkenes have been discovered, as yet there are no broadly applicable methods for effecting this reaction.

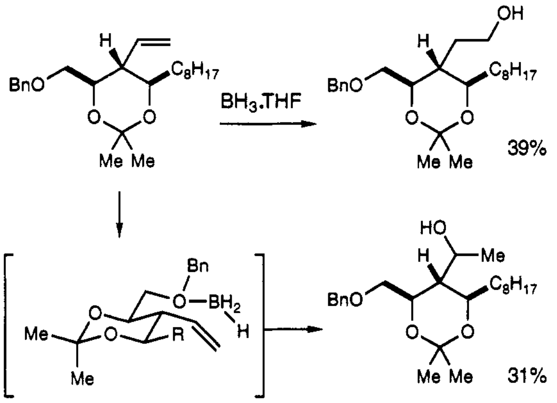
E. Hydroborations

Alkyne addition reactions of dialkylboranes to cis and trans 4-substituted-1-methoxybut-1-en-3-ynes afford different regioselectivities (Scheme 48), the cis isomer displaying a greater preference for placement of boron at the internal acetylenic carbon of the enyne.[325] Coordination of the cis ether oxygen to the borane prior to hydroboration is proposed as a rationale (see below), since the two isomers are electronically similar and steric considerations would predict the opposite trend. It is

Scheme 48



Scheme 49

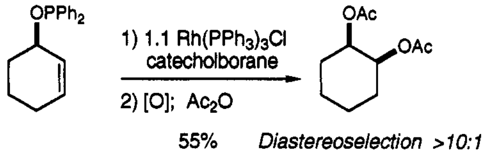


worthy of note that backside displacement of the Lewis base by the multiple bond, a step postulated to occur in hydroboration with borane–Lewis base complexes, is not possible in this geometry.[326]

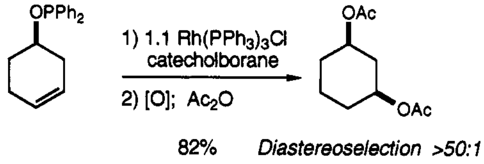
The directed hydroboration of alkenes has been the subject of several recent reports.[327] Intramolecular delivery by an ether has been suggested as an explanation for the surprisingly poor regioselectivity observed in the BH_3·THF hydroboration of the terminal olefin illustrated in Scheme 49.[328] Reaction with dicyclohexylborane, a bulkier reagent for which complexation to the ether oxygen is less favorable, provides the desired primary alcohol in 86% yield.

More recently, phosphinites have proved to be effective directing groups in rhodium-mediated alkene hydroboration (eq 125).[329] Reaction of the phosphinite derived from 2-cyclohexen-1-ol provides the syn-1,2 product, in contrast to hydroboration of the corresponding silyl ether, which affords the anti-1,3 isomer preferentially. A homoallylic phosphinite effectively directs hydroboration to the syn face (eq 126), in contrast to the TBS ether, which affords an approximately statistical mixture of products.

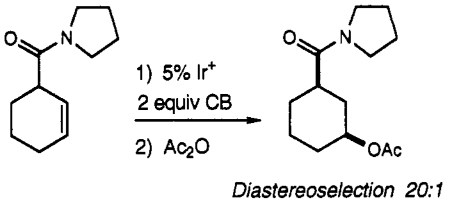
Directed, transition metal-catalyzed hydroboration reactions may be performed in a catalytic manner. Hydroxyl groups are not suitable directing groups, as the derived boronic ester, formed before the hydroboration process begins, is a poor ligand for both rhodium and iridium complexes.[330] However, amides efficiently direct the hydroboration process, with catecholborane (CB) and 5 mol % of [Ir(cod)(PCy_3)(py)]PF_6 (Ir^+). The examples in eqs 127 and 128 are illustrative; as shown, solvent effects provide further evidence that association of the Lewis basic amide group and the transition metal is responsible for the regio- and stereochemical outcome of these reactions.



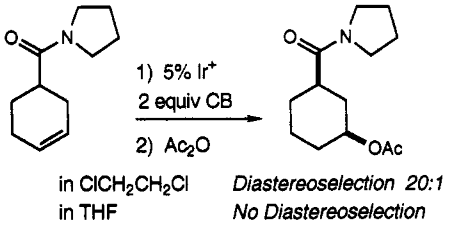
(125)



(126)



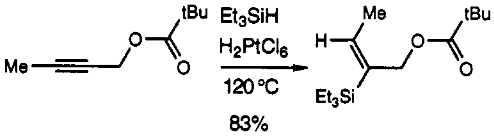
(127)



(128)

F. Hydrosilylations

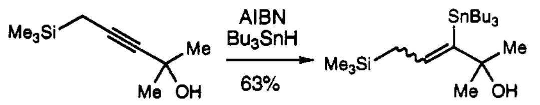
Hydrosilylation of the alkyne shown in eq 129 provides a single vinylsilane, whereas reaction of the corresponding propargylic alcohol preferentially furnishes the regioisomeric product.[331] Chelation of the ester group to platinum is proposed as an explanation for the selectivity.



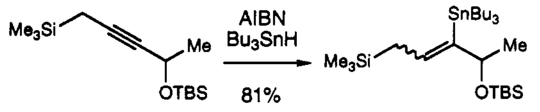
(129)

G. Hydrostannylations

Hydrostannylation reactions of propargylic alcohol derivatives proceed with high levels of regiocontrol; internal delivery by the oxygen functionality has been suggested as an explanation for these observations.[332] Addition of Bu_3SnH to alkynes typically affords a mixture of isomers, but for propargylic alcohols, acetates, and ethers only the regioisomer derived from addition of the tributyltin radical to the carbon proximal to the oxygen is produced (eqs 130–131). Homopro



(130)

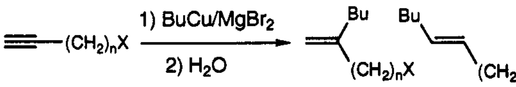


(131)

pargylic hydroxyl groups are not effective in these processes. Coordination of oxygen to the tin radical prior to its addition to the π-system is proposed as a rationale for the selectivity obtained. The issue of the possible role played by the inductive effect of the oxygen substituent has not been addressed.

H. Organocopper Additions

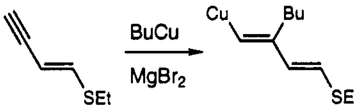
Internal delivery of the organometallic reagent is the suggested explanation for the anomalous regioselectivities observed in the addition of butyl copper to certain functionalized alkynes.[333] Whereas simple terminal acetylenes afford the 1,1-disubstituted olefin with high selectivity, homopropargylic amines and sulfides produce substantial quantities of the regioisomer (eq 132).



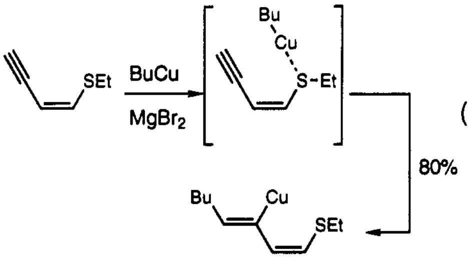
(132)

with X = NEt$_2$ n=2 No Regioselection
with X = SEt n=2 No Regioselection
with X = SEt n=3 Regioselection 20:1

Reaction of a bishomopropargylic sulfide furnishes the product of "normal" addition, consistent with the postulate that the diminished regioselectivity in the homoallylic cases is attributable to intramolecular delivery. The transformations of trans and cis enynes (eqs 133 and 134) provide additional support for this hypothesis. Thus, the trans isomer undergoes addition with the "normal" sense of regioselectivity, whereas the cis isomer affords the product of a directed reaction. A sulfide–organocopper complex is proposed to be an intermediate in the latter case.



(133)



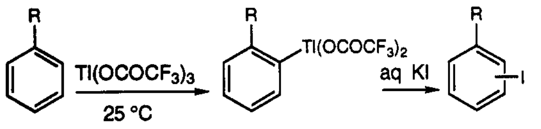
(134)

IX. Other Directed Reactions

A. Thallium Addition Reactions

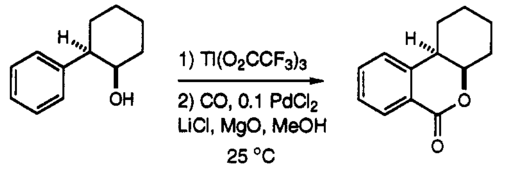
Table 53 provides evidence that electrophilic aromatic substitution reactions with thallium reagents are subject to heteroatom delivery.[334] Whereas propylbenzene preferentially affords the product of para addition (entry 1), arenes bearing oxygen-containing substituents can provide the ortho isomer predominantly (entries 2–9). When the reaction is performed under conditions leading to thermodynamic control of product distribution (for example, at elevated temperature), meta substitution is the main pathway. The following generalizations hold for arenes which bear acids, esters, alcohols, and ethers: (1) An oxygen bound to a carbon either α or β to the ring can deliver thallium to the ortho position (entries 2–9), but this ability is diminished beyond the β-position (entry 3). (2) Delivery of thallium is sensitive to steric effects (entries 3 and 4).

Table 53. Oxygen-Directed Thalium Addition Reactions

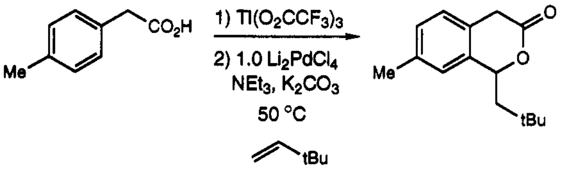


Entry	R	*ortho*	*meta*	*para*
1	$CH_2CH_2CH_3$	3	6	91
2	CO_2H	95	5	0
3	CH_2CO_2H	92	3	5
4	$CHMeCO_2H$	65	11	24
5	CO_2Me	95	5	0
6	CH_2CO_2Me	92	3	5
7	CH_2OH	>99	--	--
8	CH_2CH_2OH	83	6	11
9	CH_2OMe	>99	--	--

Palladium-mediated carbonylation or olefination of the arylthallium intermediate can provide a variety of aromatic compounds.[335] Equations 135 and 136 provide two examples.



(135)

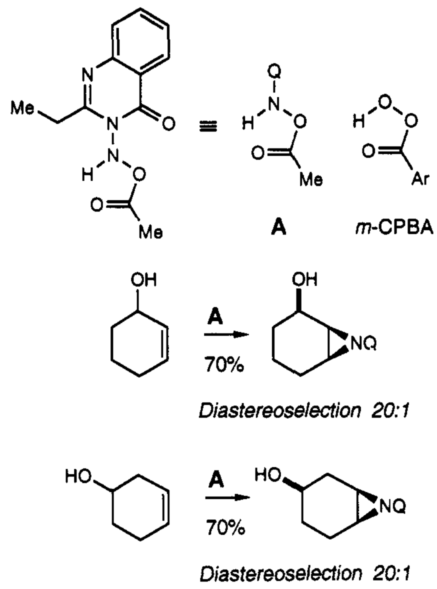


(136)

B. Aziridinations

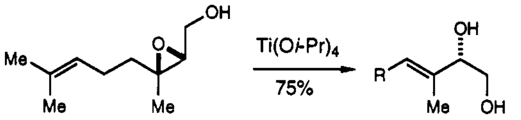
There are several reports on the hydroxyl-directed aziridination by 3-(acetoxyamino)-2-ethylquinazolone (A, Scheme 50; compare A and *m*-CPBA).[336] Treatment of 2-cyclohexen-1-ol with this reagent furnishes the syn isomer with high stereoselectivity. Under identical conditions, the derived acetate and methyl ether undergo aziridination more slowly and provide only the anti compound. The corresponding homoallylic alcohol undergoes reaction with high levels of stereocontrol as well; the derived homoallylic acetate provides a nearly equal mixture of the possible diastereomers. Reaction of geraniol occurs preferentially at the double bond proximal to the hydroxyl group (11:1), whereas that of geranyl chloride proceeds predominantly at the site distal from the heteroatom (6:1). Thus, A appears to be subject to stronger directivity effects than is *m*-CPBA, which affords 9:1 (syn:anti) face selectivity with 2-cyclohexen-1-ol and 1:2 site selectivity (preference for alkene α to alcohol) with geraniol. Since it seems reasonable that the transition structures for aziridination and epoxidation are similar (see section III), we may postulate that this difference arises from the greater basicity of the nitrogen in A vs the oxygen in *m*-CPBA.

Scheme 50

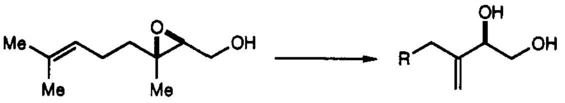


C. Cleavage of Epoxides

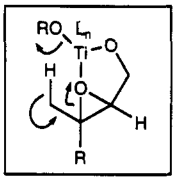
As exemplified in eqs 137 and 138, stoichiometric quantities of $Ti(Oi\text{-}Pr)_4$ mediate the regioselective opening of epoxy alcohols to allylic alcohols at 25 °C.[337] It is noteworthy that the reaction of 2,3-epoxynerol provides only the *trans*-olefin stereochemistry and that deprotonation occurs exclusively at the position cis to the hydroxymethyl group. The methyl ether of 2,3-epoxygeraniol is stable to the reaction conditions. On the basis of these observations, a transition structure involving a syn elimination within an epoxy alcohol–titanium alkoxide complex has been proposed.



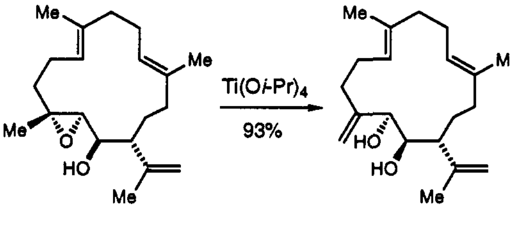
(137)



(138)

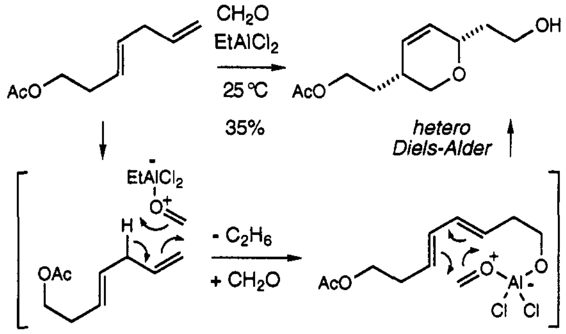


This directed epoxide cleavage reaction has found application in total synthesis.[338] For example, as shown in eq 139, in the course of studies directed toward the synthesis of (±)-asperdiol, exclusive formation of the depicted macrocyclic allylic alcohol was observed; interestingly, the compound epimeric at the hydroxyl-bearing carbon is converted into a complex mixture of products under the same conditions. On the basis of ^1H NMR and X-ray crystallographic analyses, it was suggested that the latter substrate has no low-energy conformation with a geometry appropriate for elimination.



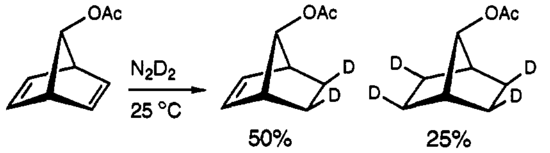
(139)

Scheme 51

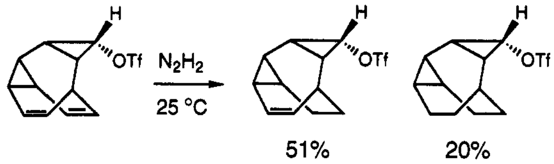


D. Diimide Reductions

Diimide reduction of 7-acetoxynorbornadiene preferentially affords the syn reduction product (eq 140), a result consistent with delivery by the ester.[339] The corresponding alcohol and *tert*-butyl ether react in a similar fashion. Other reports support the feasibility of oxygen delivery of diimide; the regioselective reduction of the depicted bullvalene derivative in eq 141 serves as an example.[340]

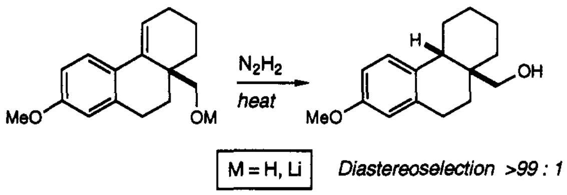


(140)



(141)

In the phenanthrene-derived system shown in eq 142, either the alcohol or the lithium alkoxide, but not the sodium or the potassium salt, is capable of directing reduction by diimide.[341] The nature of the interaction between oxygen and diimide that leads to delivery remains to be clarified.

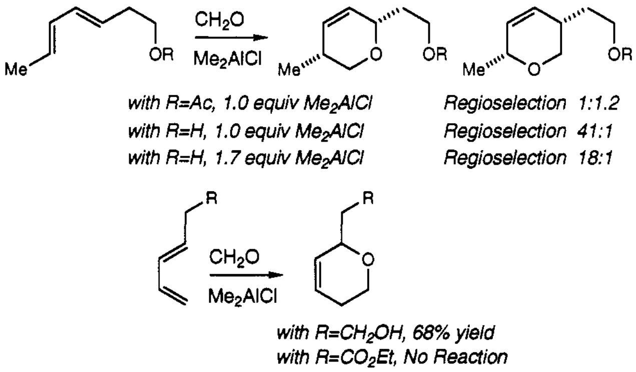


(142)

E. Electrocyclic Reactions

The regioselectivity observed in several electrocyclic reactions has been attributed to delivery of the reagent by a substrate functional group. In the course of a formal total synthesis of pseudomonoic acids A and C, the directed hetero-Diels–Alder reaction illustrated in Scheme 51 was realized.[342] The first step of the sequence is a Lewis acid-catalyzed ene reaction, the product of which is an aluminum alkoxide complex. Evolution of ethane, coordination of formaldehyde, and cyclization

Scheme 52



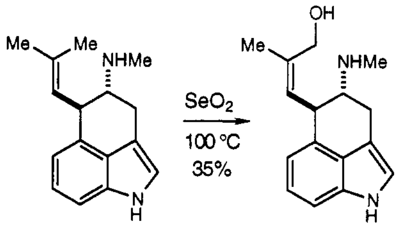
with R=Ac, 1.0 equiv Me_2AlCl *Regioselection 1:1.2*
with R=H, 1.0 equiv Me_2AlCl *Regioselection 41:1*
with R=H, 1.7 equiv Me_2AlCl *Regioselection 18:1*

with R=CH_2OH, 68% yield
with R=CO_2Et, No Reaction

then afford the desired trans-1,4-disubstituted pyran with high regioselectivity (16:1).

As illustrated in Scheme 52 subsequent study has provided support for the proposed intramolecular nature of the hetero-Diels–Alder reaction.[343] Cyclization of the diene acetate proceeds with poor regioselectivity, whereas the free alcohol undergoes a highly selective reaction. The decreased regioselectivity obtained in the presence of excess (1.7 equiv) Lewis acid is consistent with competitive intermolecular ring formation. The relative reactivities of the diene alcohol and ester shown below indicate that a substantial rate enhancement is associated with internal delivery of the dienophile.[344]

During the course of a synthesis of an ergot alkaloid, a selective oxidation by SeO_2 of the *cis*-methyl group of a trisubstituted olefin was observed (eq 143).[345] Since selenium dioxide generally displays a marked preference for oxidation of the *trans*-methyl substituent with this family of alkenes, coordination of the amino group to selenium has been invoked to explain the anomalous regioselectivity. Reaction of the derived tertiary amine might furnish insight into the nature of this interaction (for example, hydrogen-bond donation to the oxygen of SeO_2 vs nitrogen complexation to selenium).



(143)

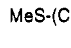
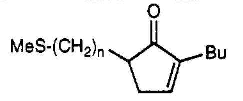
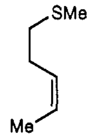
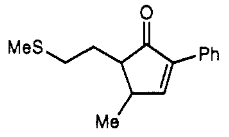
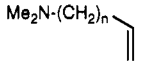
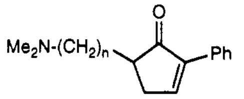
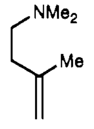
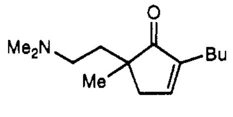
F. Cycloadditions

The intermolecular Pauson–Khand reaction of simple olefins typically provides cyclopentenones in low yield and with poor regioselectivity.[346] Incorporation of a Lewis basic sulfur or nitrogen ligand within the alkene results in moderate to high regioselectivity (Table 54) and improved yields (~65%).[347] The diminution in selectivity that occurs upon homologation is consistent with the directivity postulate (entries 1 vs 2 and 4 vs 5). Oxygen substituents such as alcohols and ethers afford equal mixtures of regioisomers.[348]

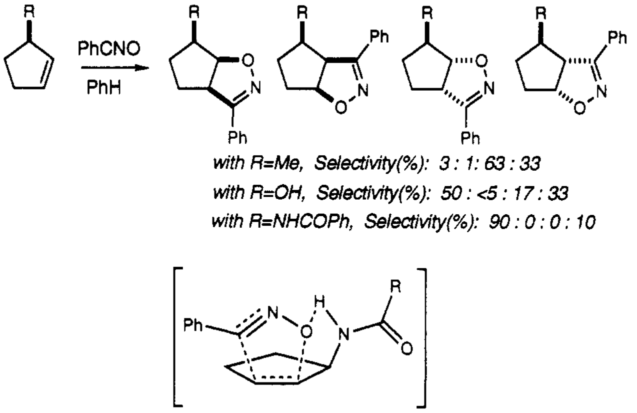
Olefin–nitrile oxide cycloaddition reactions have been reported to be subject to heteroatom delivery. Whereas reaction of the methylcyclopentene shown in Scheme 53 affords predominantly the cycloaddition product anti to the allylic substituent with poor regioselectivity, with the carbamate functionality at the allylic site, both high levels of stereo- and regiocontrol are attained. As the data below indicate, the hydroxyl group appears to be a weaker directing functionality. Solvent effects (e.g., CH_2Cl_2 vs DME) and alteration of the Lewis basicity of the allylic substituent [e.g., (p-OMe)C_6H_4NH vs (p-CF_3)C_6H_4NH] further support the contention that these transformations are directed by a bridging hydrogen atom (between the nitrile oxide and the directing group, as shown in Scheme 53).[349]

Table 54. Directed Pauson–Khand Cyclization

Substrate + R—≡ $\xrightarrow[\text{Co}_2(\text{CO})_8]{90\,°\text{C}}$ Cyclopentenone product

Entry	Substrate	Product		Selectivity
1			n = 2	8 : 1
2			3	3 : 1
3		 *anti* : *syn* = 19 : 1		40 : 1
4			n = 2	5 : 1
5			3	3 : 1
6				18 : 1

Scheme 53



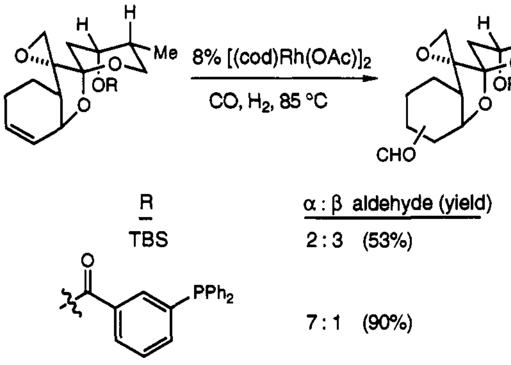
with R=Me, Selectivity(%): 3 : 1: 63 : 33
with R=OH, Selectivity(%): 50 : <5 : 17 : 33
with R=NHCOPh, Selectivity(%): 90 : 0 : 0 : 10

G. Hydrocarbonylations

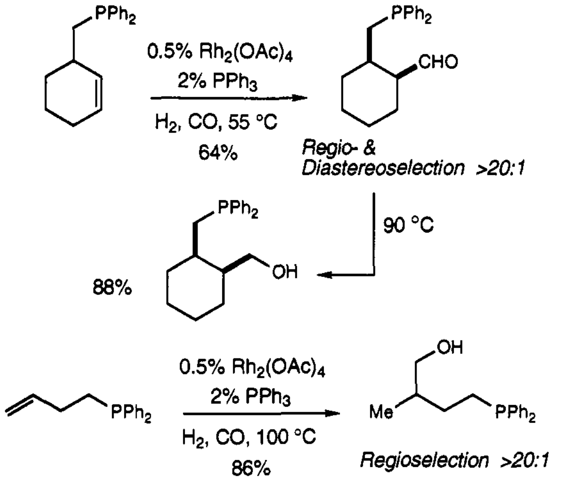
Several recent reports have established the feasibility of directing transition metal-catalyzed alkene hydrocarbonylation reactions. During the course of studies directed toward the synthesis of phyllanthocin, it was established that replacement of a silyl group with a m-(diphenylphosphino)benzoate reverses the face selectivity of a hydroformylation reaction (Scheme 54).[350] The observation that the para isomer reacts much more slowly than does the meta compound is consistent with the postulate that the role of the phosphine is to effect intramolecular delivery.

Recent reports indicate that phosphine delivery in the hydroformylation of cyclic and acyclic olefins is feasible (Scheme 55).[351] Reaction of 4-(diphenylphosphino)-1-butene affords the product derived from carbonylation of the internal position, whereas hydro-

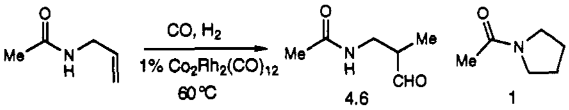
Scheme 54



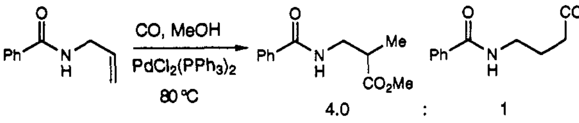
Scheme 55



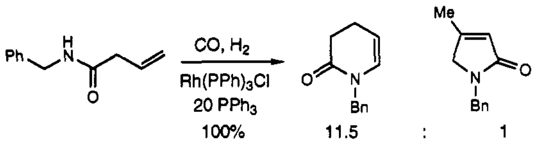
formylation of the corresponding phopshine oxide or of 1-hexene furnishes the unbranched aldehyde preferentially. Lower regioselectivity is observed in the reaction of the homoallylic phosphine in the presence of 50 equiv of PPh_3, as well as with the homologous olefinic phosphines. These data are consistent with the proposal that these transformations are directed by the Lewis basic phosphine group.



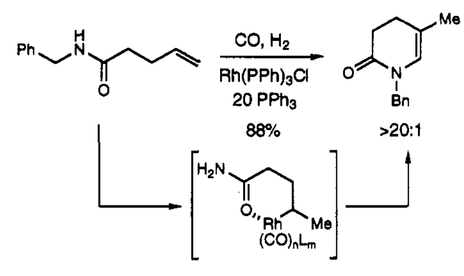
(144)



(145)



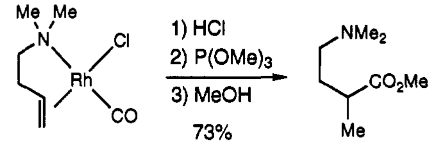
(146)



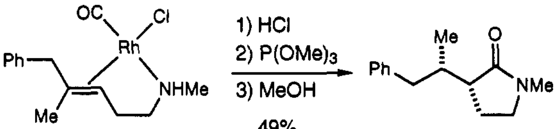
(147)

Amides can direct the hydrocarbonylation of alkenes.[352] *N*-Allylamides undergo hydroformylation with a modest preference for formation of the branched aldehyde (eqs 144 and 145),[353] in contrast to unfunctionalized alkenes, which yield the linear aldehyde preferentially. Reactions of unsautrated benzylamides result in high levels of regiocontrol (eqs 146 and 147). These reactions are thought to proceed through chelated transition structures, as illustrated in eq 147.[354]

As illustrated in eqs 148–150, amines[355] and phosphites[356] are suitable directing functionalities for the carbonylation reaction. Reactions with amines are preformed with stoichiometric amounts of Rh complexes, whereas those of phosphites are catalytic. Treatment of a homoallylic amine with $[(CO)_2RhCl]_2$ provides a chelated substrate–metal complex. Addition of HCl furnishes a Rh(III) hydride intermediate, which then undergoes sequential insertions to form an alkyl and then an acyl–rhodium complex. Cyclic and acyclicsubstrates can be employed, and high levels of regio- and diastereoselection are achieved.

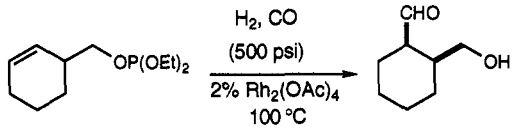


(148)



(149)

Regio- & Diastereoselection >20:1

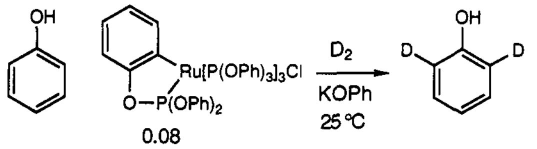


(150)

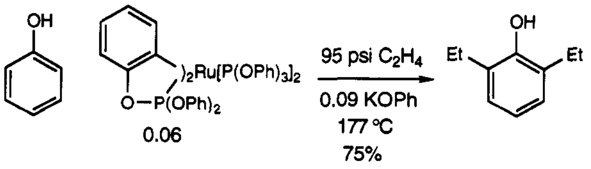
Regio- & Diastereoselection >20:1

H. Orthometalations

Equations 151 and 152 depict regiospecific ruthenium-catalyzed ortho deuteration[357] and ortho ethylation[358] of phenol. Both reactions appear to involve transesterification and orthometalation of the triphenylphosphite.



(151)

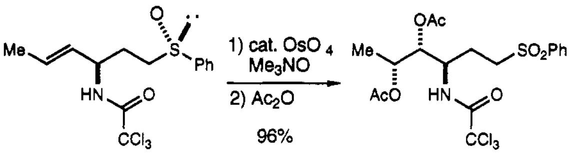


(152)

I. Oxidations

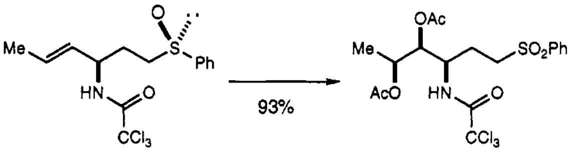
1. Osmium-Mediated Oxidations

There are no general methods available for effecting a delivered osmylation, but several groups have made important findings, albeit limited in scope.[359] Several reports indicate that osmylation reactions can be directed by sulfoxides[360] and sulfoximines.[361] Osmylation of either of the two bishomoallylic sulfoxides shown below (eqs 153–154) is highly stereoselective; product stereochemistry is dictated by the sulfur center. Reactions of the corresponding olefinic sulfide and sulfone proceed with low stereoselection (2:1). The relative rate of osmylation of these olefins is reported to be sulfone > sulfoxide ≫ sulfide.[362] In the presence of excess alkene, only the diol sulfone and the starting material are recovered, indicating that once complexation to osmium occurs, complete conversion to products follows. On the basis of a hard–soft acid–base argument, it has been suggested that binding takes place through the sulfoxide oxygen. It is worthy of note that this type of process may not be performed stereoselectivity with all homoallylic sulfoxides (eqs 155 and 156).[363]



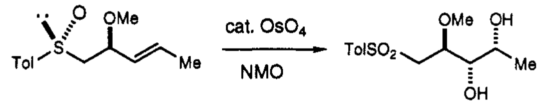
(153)

Diastereoselection >20:1



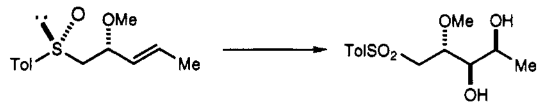
(154)

Diastereoselection >20:1



(155)

Diastereoselection 2:1



(156)

Diastereoselection 2:1

Sulfoximines can direct bis-hydroxylation in cyclic systems, thereby providing a route to enantiomerically pure dihydroxycycloalkanones.[362] As shown in Scheme 56, after introduction of the chiral auxiliary to an olefinic ketone, osmylation of either of the resulting diastereomers affords a single triol product. Since reaction of the corresponding sulfone proceeds with poor stereoselection (2:1), it was concluded that the high level of facial selectivity may be ascribed to the presence of the methylimino group.[364] The resulting diol can be desulfurized with Raney nickel or thermolyzed, producing enantiomerically pure triols or diols, respectively. Two additional examples involving cyclic substrates are shown in Scheme 56; extension of this strategy to acyclic systems has been unsuccessful.

A number of reports indicate that nitro groups can direct dihydroxylation processes.[365] Osmylation of the substrate shown in entry 1 of Table 55 furnishes the product arising from reaction on the more hindered olefin face, whereas oxidation with $KMnO_4$ produces the corresponding diastereomer. Control experiments implicate the nitrosulfonylmethane substituent as the directing group (entries 2 and 3). On the basis of previous reports,[361,362] which provide no evidence for sulfone direction, it is postulated that stereocontrol in this reaction arises from interaction of the nitro group with osmium.

Scheme 56

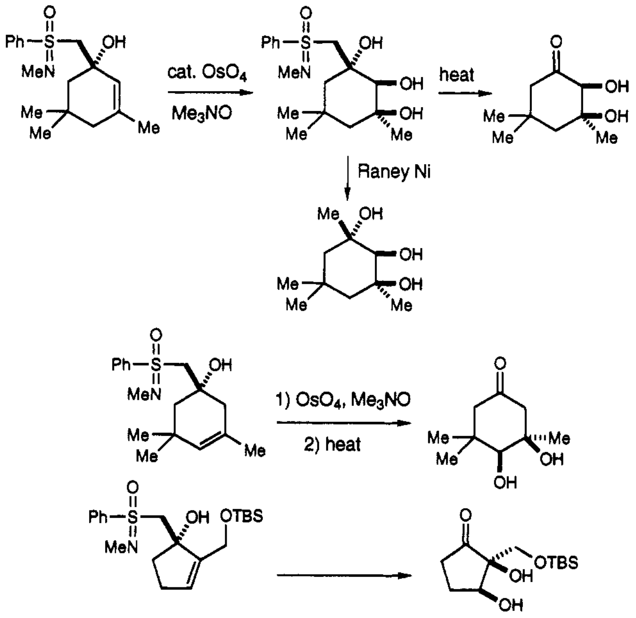
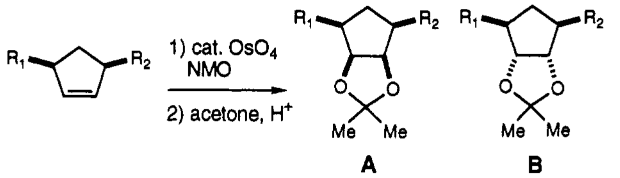
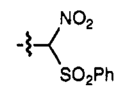
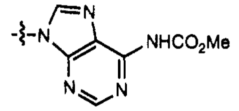
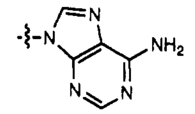
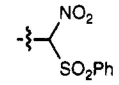
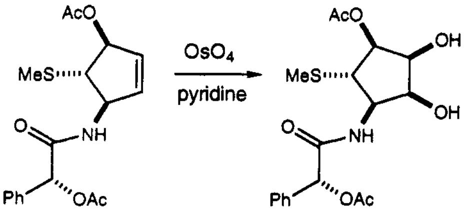


Table 55. Nitro-Directed Dihydroxylation Reactions



Entry	R₁	R₂	Product
1			A
2	-ξ-OH		B
3		-ξ-OR	A

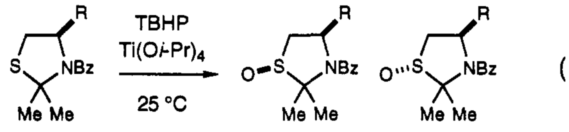
The highly stereoselective osmylation shown in eq 157 is presumably a directed process, as the dihydroxylation occurs at the more hindered diastereotopic face of the alkene.[366] Whether the carbamate or the acetate groups (or both, cooperatively) serve to deliver the oxidant is not clear and has not been addressed.



(157)

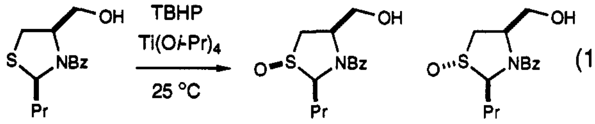
2. Titanium-Mediated Oxidations

Several examples of directed oxidation have been described.[367] There are a number of examples of hydroxyl-delivered oxidation of sulfides to sulfoxides by *tert*-butyl hydroperoxide/Ti(O*i*-Pr)$_4$.[368,369] Whereas reaction of the ester-substituted thiazolidine affords a roughly equal mixture of sulfoxide diastereomers, oxidation of the corresponding hydroxymethyl compound results in highly selective oxo transfer to the face syn to the hydroxyl group (eqs 158 and 159). A mechanism involving complexation of the substrate to titanium, followed by oxidation of the sulfide, has been proposed.



(158)

with R=CO$_2$Me *No Diastereoselection*
with R=CH$_2$OH *Diastereoselection >20:1*

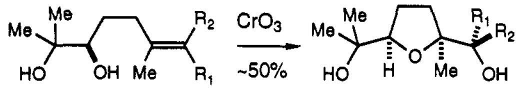


(159)

Diastereoselection 3:1

3. Chromium-Mediated Oxidations

Upon treatment with Collins reagent or pyridinium chlorochromate, 5,6-dihydroxyalkenes undergo oxidative cyclization to provide syn 2,5-disubstituted tetrahydrofurans with > 99% selectivity (eq 160).[370] The addition to the alkene proceeds in a cis fashion stereospecifically. If the hydroxyl remote from the olefin is protected, the γ–δ enone is formed in high yield, indicating a role for this OH group in facilitating the cyclization reaction.



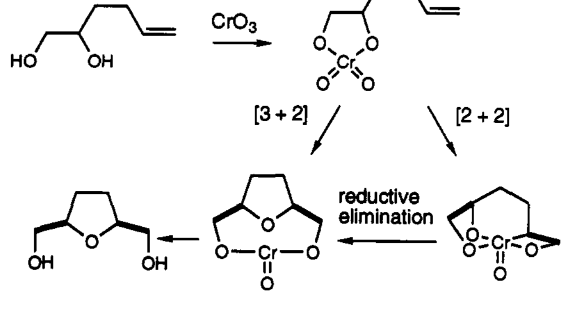
(160)

R$_1$ = CH$_2$OAc, R$_2$ = H
R$_1$ = H, R$_2$ = CH$_2$OAc

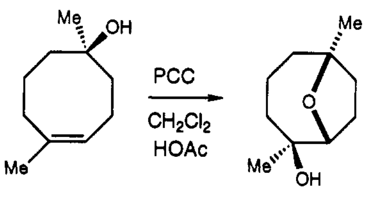
Diastereoselection >25:1

The two mechanisms proposed for this oxidative cyclization are shown in Scheme 57. Rapid formation of the chromium(VI) diester is followed by a concerted [3 + 2] cycloaddition, or by a sequence involving [2 + 2] cycloaddition–reductive elimination, to furnish the complexed product, the tetrahydrofuran diol. Molecular models indicate that syn ring stereochemistry should be preferred with either mechanism.

Scheme 57



Addition of high-valent oxonium reagents to alkenes is also subject to heteroatom delivery. Treatment of the unsaturated alcohol shown in eq 161 with pyridinium chlorochromate (PCC) affords the bicyclic alcohol with high regio- and stereoselectivity. Coordination of the hydroxyl group with the chromium oxidant has been proposed to account for the selective outcome of this class of oxidative ring-forming reactions.[371]



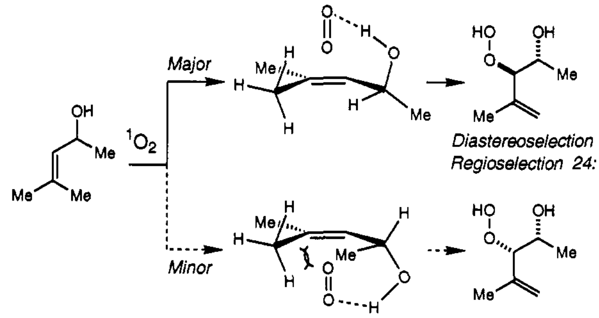
(161)

Regio- &
Diastereoselection >20:1

4. Oxidations with Singlet Oxygen

Recently, it has been demonstrated that the directing ability of a hydroxyl functional group may be extended to the singlet oxygen-mediated oxidations of some allylic alcohols; formation of the C–O bond, as is shown in Scheme 58, occurs with excellent levels of regio- and diastereocontrol.[372] Arguments based on hydrogen bonding of oxygen molecule with the hydroxyl group though the lowest energy transition structure (minimization of unfavorable allylic interactions) readily accounts for the observed trends and levels of stereochemical control.

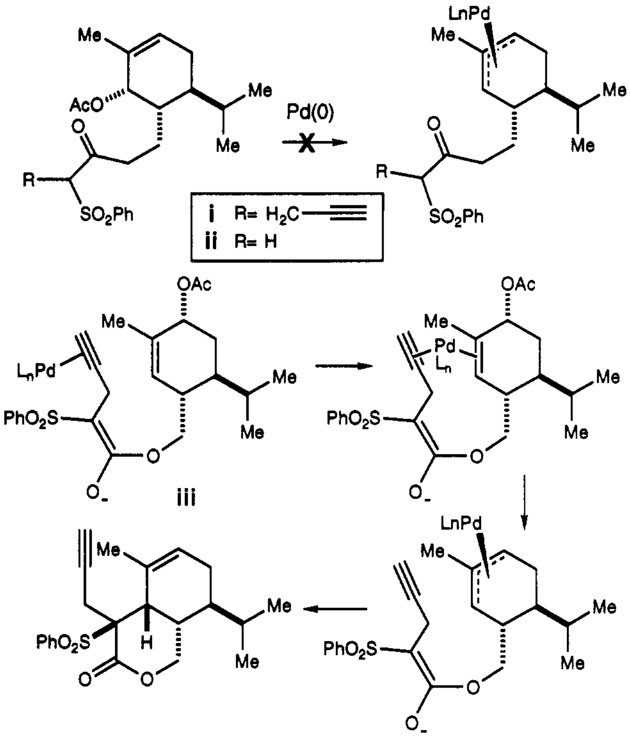
Scheme 58



J. Metal–Olefin Complexation

When allylic acetate i (Scheme 59) is treated with Pd(0) catalysts, no π-allyl complex formation occurs; starting material is recovered unreacted. In contrast, the isomeric acetate iii affords the π-complex, leading to the cyclization product in 65% yield and > 20:1 diastereocontrol.[373] Since ii did not show any reaction as well, it was suggested that the difference in reactivity between i and iii may be due to the initial association of the transition metal with the alkyne group. The metal complex would thus be delivered to the allylic acetate site. In i, the acetylene group cannot deliver the transition metal to the alkene because of geometric constraints.

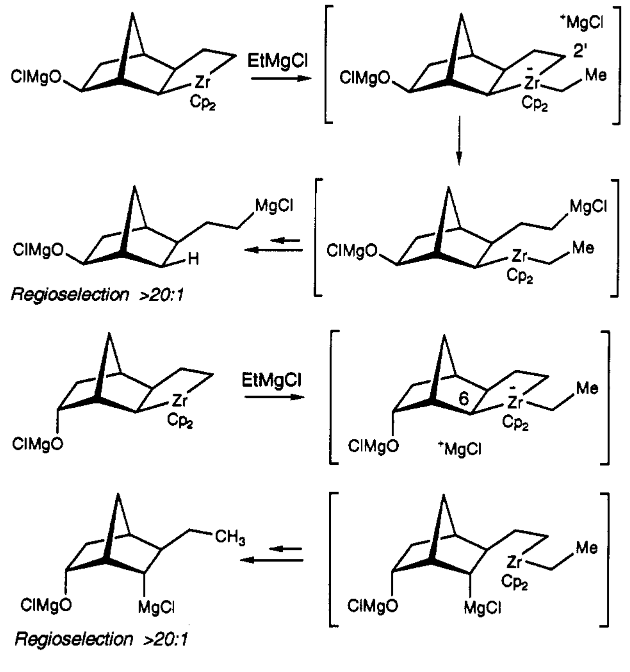
Scheme 59



K. Cleavage of Metallacycles

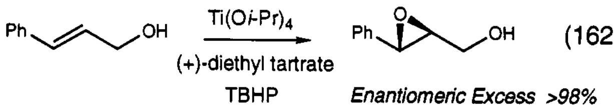
Cleavage of zirconacyclopentanes, formed by the regioselective addition of a zirconacyclopropane to an alkene, is effected by alkylmagnesium chlorides and can be directed by a neighboring heteroatom functionality.[374] Whereas the bicyclic system with the exo oxygen substituent (Scheme 60) affords cleavage at the sterically less hindered C2′–Zr bond, with the endo derivative, exclusive rupture at the C6–Zr bond is observed. Association of the magnesium metal with the endo heteroatom accounts for this complete reversal of regioselectivity.

Scheme 60



X. Summary of Advances in Asymmetric Directed Reactions

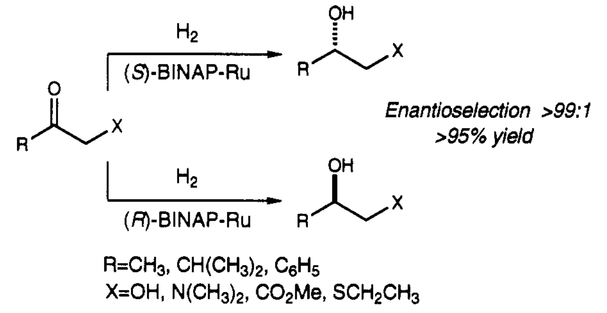
The discussions that were presented above clearly illustrate that directed transformations are of wide ranging utility in organic chemistry. Reduced degrees of freedom resulting from association of a heteroatom with the reagent renders these reactions excellent candidates for affording systems that are stereoselective in both the relative and the absolute sense. As has been demonstrated in the metal-catalyzed epoxidation reaction, introduction of asymmetry into the transition-metal catalyst by a C_2-symmetric chiral ligand (tartrate-based) results in high levels of enantiotopic face selectivity in reactions of achiral alkenes; an example of this widely used process is illustrated in eq 162.[375]



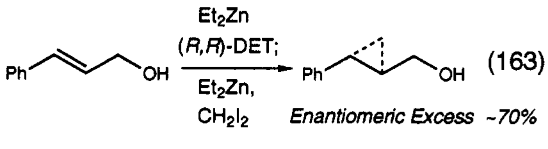
(162)

A transition metal-catalyzed reaction that is effectively influenced by an internal heteroatom can be developed to reach regio- and stereoselectivity levels often attained with natural enzymes, but with the added bonus that the man-made catalyst enjoys much wider substrate compatibility. The metal-catalyzed epoxidation reaction (section IV) is not an exception and the underlying principles that have emerged from the study of this process can be employed for the development of other transformations. Progress in the area of asymmetric hydrogenation (see section V), as represented in Scheme 61, bears testimony to this claim.[376]

Scheme 61



A recent report indicates that asymmetric versions of the directed cyclopropanation reaction (section II) may be forthcoming. As is shown in eq 163, treatment of an allylic alcohol with Et_2Zn and (*R*,*R*)-diethyl tartrate, followed by a sequential addition of Et_2Zn and CH_2I_2 leads to the formation of the cyclopropylcarbinol with ~70% enantiomeric excess.[377]



(163)

XI. Acknowledgments

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(36) A molecular orbital treatment of the reaction of (iodomethyl)zinc iodide with alkenes has been reported. Second-order perturbation calculations on the interaction of the σ and σ^* orbitals of the carbon–zinc bond with the π and π^* orbitals of the olefin indicate that the zinc reagent behaves as an electrophile. (Hida, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2497–2501.)

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(84) Sheng and Zajacek did not determine the sense of diastereoselection in these reactions.

(85) Sharpless later discovered that the vanadium-catalyzed epoxidation may be run conveniently at or below room temperature; see refs 57 and 374c.

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(103) A mechanism analogous to the well-studied chromic acid oxidation of alcohols is likely. See: *Oxidation in Organic Chemistry*; Wiberg, K. B., Ed.; Academic: New York, 1965; Part A.

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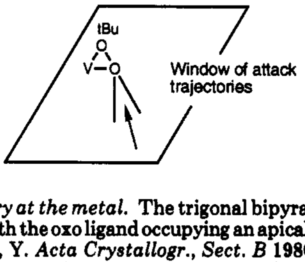
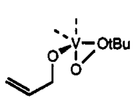
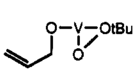


(*2*) *Geometry at the metal.* The trigonal bipyramid and the square pyramid, with the oxo ligand occupying an apical position (Gourdon, A.; Jeannin, Y. *Acta Crystallogr., Sect. B* **1980**, *36*, 304–309), are probably energy minima for the postulated five-coordinate intermediate (Figure 6, ii). The bidentate alkyl peroxide should prefer to occupy idealized coordination sites which require the oxygens to span as small an angle as possible, i.e., 90°. To simplify the analysis, we have assumed that for the square pyramid geometry, the vanadium lies nearly in the basal plane. We therefore consider two geometries for the three participating oxygen ligands:

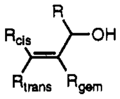




(*3*) *Conformation of the carbon backbone.* This is only relevant for homoallylic and bishomoallylic alcohols. We assume that a staggered conformation is preferred. (*4*) *Other aspects of the transition state model.* Spiro geometry. Bond distances (see: ref 78b): V—O (covalent) = 1.9 Å; V—O (dative) = 1.95 Å; V═O = 1.6 Å; C—O (epoxide) = 2.0 Å; O—O = 2.2 Å. (A similar analysis of molybdenum-catalyzed epoxidation was inconclusive.) The structure of the active catalyst is less well understood than in the case of vanadium. For leading references on epoxidation transition states, see: (a) ref 78a. (b) Jorgensen, K. A.; Wheeler, R. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1987**, *109*, 3240–3246. (c) Jorgensen, K. A.; Hoffmann, R. *Acta Chem. Scand., Ser. A* **1986**, *40*, 411–419. (d) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410–1415. (e) Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6098–6099. (f) Plesnicar, B.; Tasevski, M.; Azman, A. *J. Am. Chem. Soc.* **1978**, *100*, 743–746.

(115) There is a modest degree of flexibility in this angle (±10°). Sharpless has estimated a dihedral angle of 50° (ref 57).

(116) In the following discussion, the substituents of the allylic alcohol by the indicated labels are referred to as follows:



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(119) For an earlier application of this strategy to *m*-CPBA epoxidation, see: Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229–4232.

(120) Protiodesilylation at an epoxide carbon proceeds with retention of configuration: Chan, T. H.; Lau, P. W. K.; Li, M. P. *Tetrahedron Lett.* **1976**, 2667–2670.

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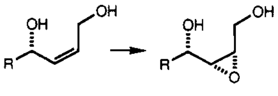

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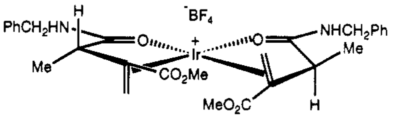

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Jacobsen Asymmetric Epoxidation Reaction

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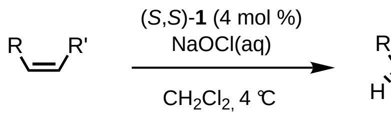
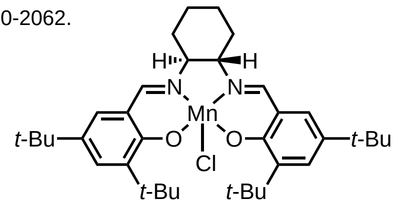
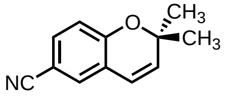
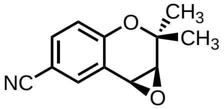
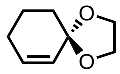
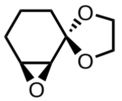
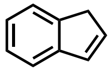
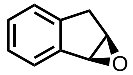




(*S*,*S*)-**1**

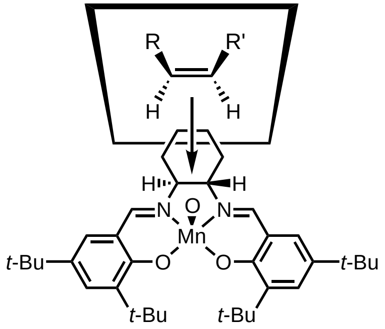
- Selectivity is determined through nonbonded interactions.
- In general, R is aryl, alkenyl or alkynyl and R' is a bulky group.
- *cis*-Disubstituted conjugated olefins are epoxidized with high levels of enantioselectivity.
- *trans*-Disubstituted olefins react more slowly and with diminished selectivity.

olefin	epoxide	yield, %	ee, %	equiv (*S*,*S*)-**1**
		96	97	0.03
		63	94	0.15
		79	84	0.006[a]

[a]Reaction carried out in the presence of 4-phenylpyridine *N*-oxide.

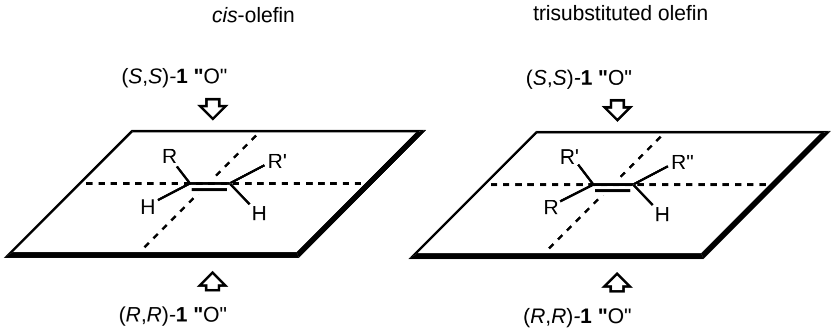
From: Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064.

- The observed selectivities have been explained by a side-on approach of olefin:



- Terminal olefins are poor substrates.
- Addition of substoichiometric amounts of 4-phenylpyridine *N*-oxide improves both catalyst selectivity and turnover numbers.

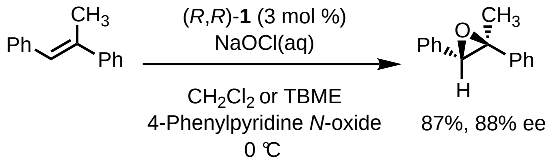
Mnemonics for the observed selectivities:

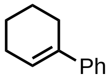
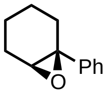
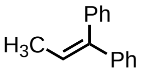
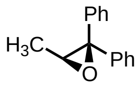
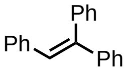
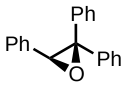


- *cis*-Olefins: Place Aryl, alkenyl or alkynyl substituent in upper-left quadrant (R) and the corresponding trans hydrogen atom in the lower-right quadrant.
- *trans*-Olefins are poor substrates.
- Trisubstituted olefins: Place the hydrogen atom in the lower-right quadrant.

Trisubstituted olefins:

- The following trisubstituted alkenes are epoxidized with high levels of enantioselectivity:

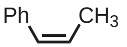
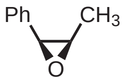
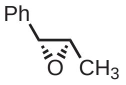
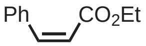
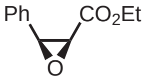
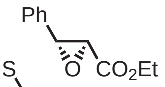
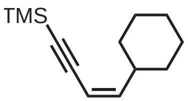
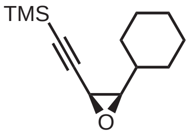
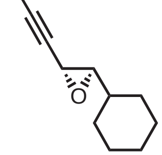


olefin	epoxide[a]	yield, %	ee, %
		69	93
		91	95
		97	92

From: Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378-4380.

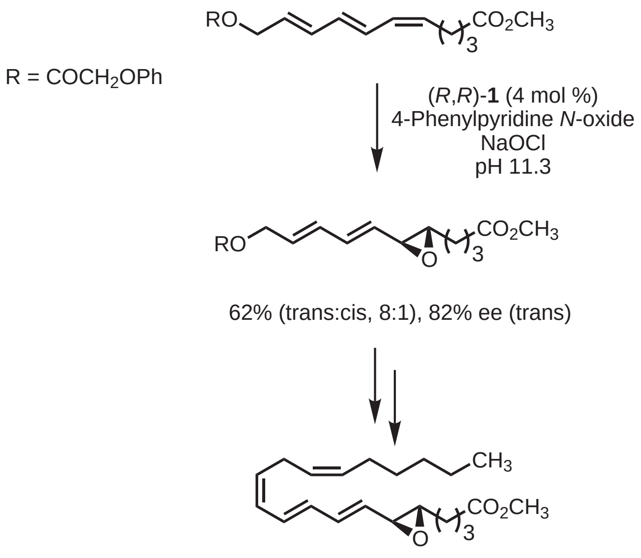
M. Movassaghi

- *cis*-β-Substituted styrene derivatives afford *cis*-epoxides as major products while *cis*-enynes and *cis*-dienes produce *trans*-epoxides.

olefin	equiv (*S*,*S*)-**1**	*cis*-epoxide	yield (%), ee (%)	*trans*-epoxide	yield (%), ee (%)
	0.04		77, 92		6.7, 83
	0.08		52, 97		15, 78
	0.04		10, 64		55, 98

From: Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**; pp. 159-202 and Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064.

- Rotation of a radical intermediate is proposed to account for the cis→ trans isomerization.

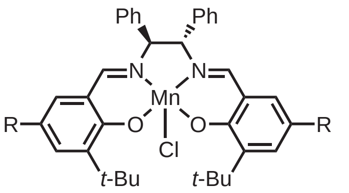


Leukotriene A_4 methyl ester

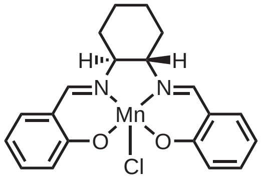
Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939-6941.

Tetrasubstituted Olefins:

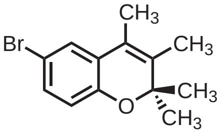
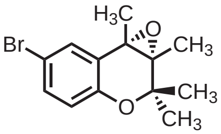
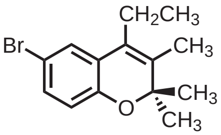
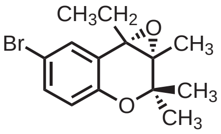
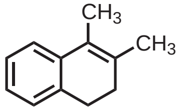
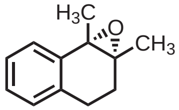
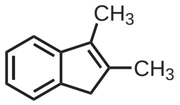
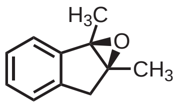
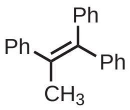
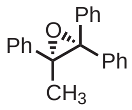
- High enantioselectivities are not yet general but may be attained in certain cases with catalysts shown.
- Chromene derivatives undergo epoxidation with higher enantioselectivity as compared to inden derivatives.



R = CH_3, (*S*,*S*)-**2**
R = OCH_3, (*S*,*S*)-**3**



(*S*,*S*)-**4**

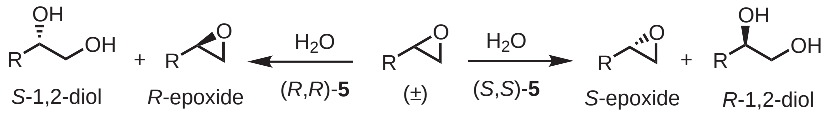
olefin	catalyst	epoxide	epoxide yield, %	ee, %
	(*S*,*S*)-**2**		84	96
	(*S*,*S*)-**2**		81	97
	(*S*,*S*)-**3**		45	65
	(*R*,*R*)-**3**		37	35
	(*S*,*S*)-**4**		12	46

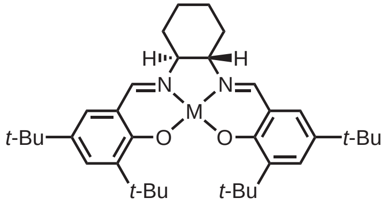
From: Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123-5126.

M. Movassaghi

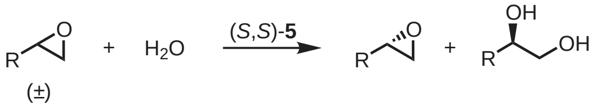
Jacobsen Catalytic Asymmetric Epoxide-Opening Reactions

Hydrolytic Kinetic Resolution (HKR):





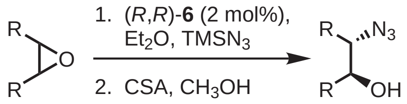
M = $Co(O_2CCH_3)(H_2O)$
(*S*,*S*)-**5**

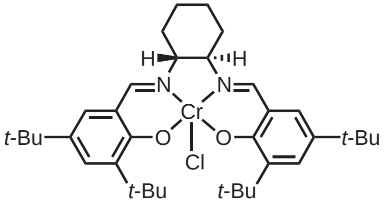


R	**5** (mol %)	water (equiv)	time (hours)	Epoxide ee (%)	Epoxide isolated yield (%)	Diol ee (%)	Diol isolated yield (%)	k_{rel}
CH_3	0.2	0.55	12	>98	44	98	50	>400
CH_2Cl	0.3	0.55	8	98	44	86	38	50
$(CH_2)_3CH_3$	0.42	0.55	5	98	46	98	48	290
Ph	0.8	0.70	44	98	38	98	39	20
$CH{=}CH_2$	0.64	0.50	20	84	44	94	49	30

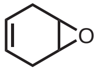
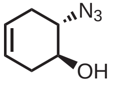
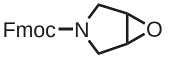
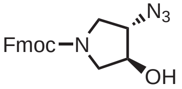
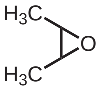
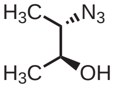
From: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938.

Enantioselective Opening of Meso Epoxides:





(*R*,*R*)-**6**

substrate	product	yield (%)	ee (%)
		72	81
		80	95
		65*	82

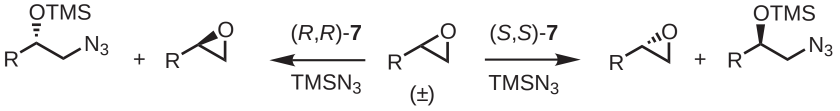
*Isolated yield of silyl ether.

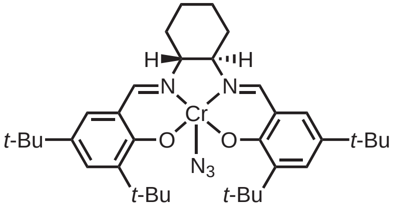
- Epoxides fused to 5-membered rings show higher enantioselectivity than 6-membered-ring and acyclic substrates.

Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897-5898.

M. Movassaghi

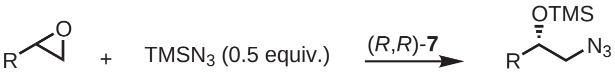
Kinetic Resolution of Terminal Epoxides with Trimethylsilyl Azide:





(*R*,*R*)-**7**

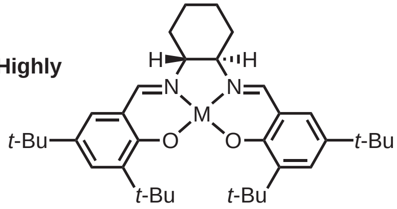
- High yields and ee's with a variety of substituents.



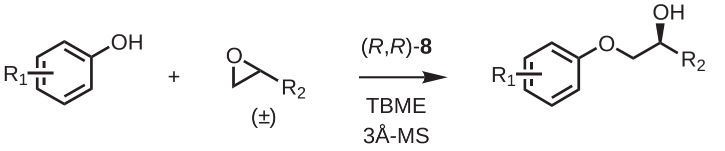
R	**7** (mol %)	yield (%)	ee (%)	k_{rel}
CH_2Cl	2.0	94	95	100
CH_2CN	2.0	80	92	45
$CH(OEt)_2$	2.0	96	89	44
CH_2Ph	2.0	94	93	71

Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420-7421.

Kinetic Resolution of Terminal Epoxides via Highly Enantioselective Ring-Opening with Phenols



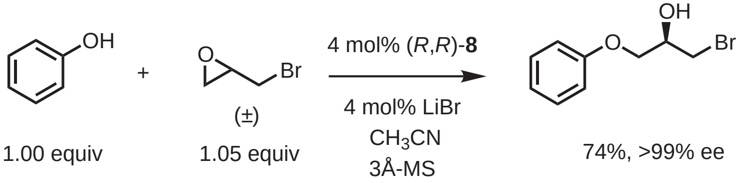
M = $Co[OC(CF_3)_3](H_2O)$
(*R*,*R*)-**8**



R_1	R_2	**8** (mol %)	temp. (℃)	yield (%)[a]	ee (%)
H	CH_2Cl	4.4	–15	97	99
H	$CH_2OCH_2CH{=}CH_2$	4.4	4	93	97
H	$COCH_2CH_3$	8.8	–20	96	96
H	CO_2CH_3	4.4	–20	98	96
p-CH_3	C_4H_9	4.4	25	95	97
m-CH_3	C_4H_9	4.4	25	99	99
o-CH_3	C_4H_9	4.4	25	<5	NA
o-Br	C_4H_9	8.8	–30	98	92
p-NO_2	C_4H_9	8.8	–20	93	91

[a] 2.2 equivalents of epoxide was used.

- With the exception of styrene oxide and ortho-substituted alkyl phenols, excellent yields and ee's are obtained with a wide range of substrates.



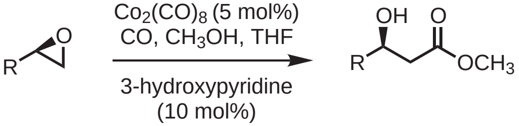
- A remarkable dynamic kinetic resolution was achieved using epibromohydrin.

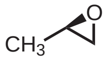
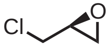
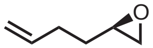
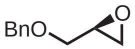
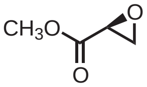
Ready, J. M.; Jacobsen E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086-6087.

M. Movassaghi

Carbomethoxylation of Chiral Terminal Epoxides

- The coupling of Jacobsen's HKR of terminal epoxides with Drent's protocol (Drent, E.; Kragtwijk, E. Eur. Pat. Appl. 577206, 30 Mar. 1994; *Chem Abstr.* **1994**, *120*, 191517c) for catalytic carbonylation of aliphatic epoxides provides a route to enantiomerically enriched acetate aldol products.



substrate	temperature (°C)	yield (%) [a]	ee (%)
	65	92	>99
	55	96	>99
	60	95	>99
	55	86	>99
	60	91[b]	>99

[a] Reactions conducted in CH_3OH-THF (1:1) at $[\text{epoxide}]_0 = 0.5$ M and a final CO pressure of 600 psi for 9 h. [b] CO pressure of 670 psi.

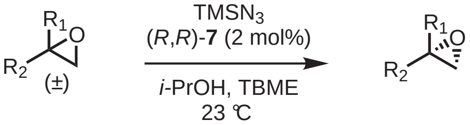
- Terminal epoxides bearing sp^2 substituents (e.g., styrene oxide and 1,3-butadiene monoepoxide) undergo carbomethoxylation in low yield (10-15%) and with poor regioselectivity (linear/branched ~1:1).

- The stereochemical integrity of the epoxide substrates is retained in the β-hydroxy ester products, even when the stereogenic center is enolizable.

- Preliminary experiments indicate that addition of *N*,*O*-dimethylhydroxylamine to the reaction mixture results in the direct formation of β-hydroxy Weinreb amides in 70-90% yield.

Hinterding, K.; Jacobsen, E. N. *J. Org. Chem.* **1999**, *64*, 2164-2165.

Chromium-Catalyzed Kinetic Resolution of 2,2-Disubstituted Epoxides:



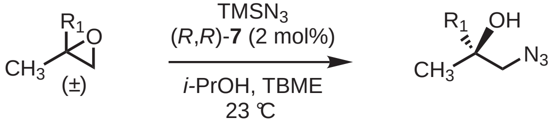
R_1	R_2	HN_3 (equiv)[a]	yield of epoxide (%)	ee (%)
$TBSOCH_2CH_2$	CH_3	0.55	42	99
$PhCH_2CH_2$	CH_3	0.60	44	97
n-C_5H_{11}	CH_3	0.55	42	99
c-C_6H_{11}	CH_3	0.50	46	98
t-BuO_2C[b]	CH_3	0.55	46	85
c-C_6H_{11}[b,c]	TMSC≡C	0.70	48	80

[a] Generated by combining equimolar amounts of $TMSN_3$ and *i*-PrOH. [b] Reaction conducted neat. [c] Used 5 mol% of (*R*,*R*)-**7**.

- Catalyst **7** can efficiently differentiate between methyl groups and alkyl chains but fails to distinguish between an ethyl and a phenethyl side chain.

- Sterically hindered epoxides (i.e. R_1=*i*-Pr, R_2=*n*-Bu) are not reactive.

- This kinetic resolution may be used to prepare enantiomerically enriched azido alcohols as well.



R_1	yield of azido alcohols (%)[a]	ee (%)
$TBSOCH_2CH_2$	47	90
$PhCH_2CH_2$	45	92
n-C_5H_{11}	44	95
c-C_6H_{11}	40	99

[a] 0.50 equivalents of HN_3 was used.

Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **2000**, *40*, 7303-7306.

M. Movassaghi

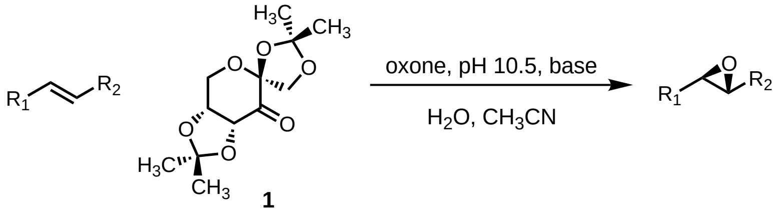
Shi Asymmetric Epoxidation Reaction

Reviews:

Wang, Z.-X.; Tu, W; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

Frohn, M.; Shi, Y. *Synthesis* **2000**, *14*, 1979-2000.

General Transformation:



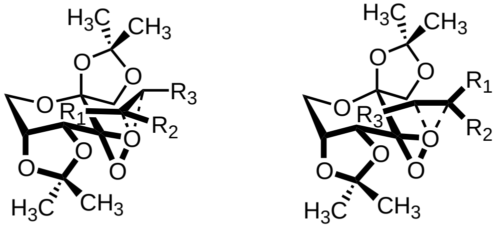
1

- Useful for epoxidation of *trans*-disubstituted olefins (ketone **1**), trisubstituted olefins (ketone **1**), conjugated *cis*-disubstituted olefins (ketone **2**, see p. 3), and styrenes (ketone **2**, see p. 3).

Catalyst Conditions:

- Ketone **1** can be readily prepared from *D*-fructose ($15/kg) by ketalization (acetone, $HClO_4$, 0 ℃, 53%) and oxidation (PCC, 23 ℃, 93%). *L*-Fructose can be prepared in 3 steps from readily available *L*-sorbose.
- Ketone **1** can be used catalytically (20–30 mol %).
- Oxone (a commercial mixture of 2:1:1 $KHSO_5$:$KHSO_4$:K_2SO_4) is used as the stoichiometric oxidant but H_2O_2/CH_3CN can also be used (peroxyimidic acid is the proposed oxidant).
- Generally, the optimum pH for dioxirane epoxidation is 7–8. At higher pH, Oxone tends to decompose. However, at pH 7–8 the Shi catalyst decomposes due to to competing Baeyer-Villiger reaction. By increasing the pH to 10.5 (by addition of K_2CO_3), the amount of ketone used can be reduced to a catalytic amount (30 mol %) and the amount of Oxone can be reduced to a stoichiometric amount (1.5 equiv), suggesting that at this pH the ketone is sufficiently reactive to compete with Oxone decomposition.
- Dimethoxymethane (DMM) and CH_3CN (2:1 v/v) solvent mixtures generally provide higher ee's.
- Reaction temperatures range from –10 to 20 ℃.

- It is proposed that the Shi epoxidation proceeds through a dioxirane intermediate and a spiro transition state and that a so-called planar transition state is a main competing pathway. The spiro transition state is believed to be electronically favored as a result of a stabilizing interaction between an oxygen lone pair of the dioxirane with the π* orbital of the olefin.



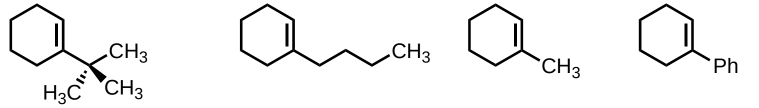
Spiro

Planar

Higher ee's are observed with smaller R_1 and larger R_3 substituents.

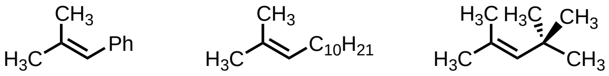
Examples:

1. Effect of smaller R_1 (also: "T-branch"; phenyl groups can be considered smaller than methyl).



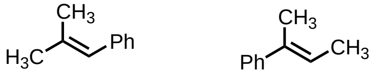
26% ee | 79% ee | 81% ee | 98% ee

2. Effect of larger R_3 (also: "L-branch").



76% ee | 86% ee | 91% ee

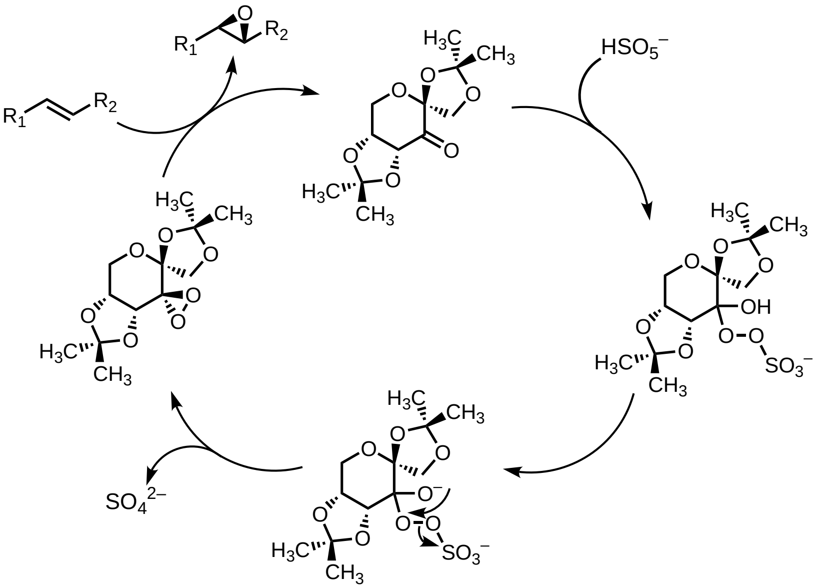
3. Comparing the size of R_1 and R_3.



76% ee | 97% ee

Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *19*, 11224-11235.

Proposed Catalytic Cycle:



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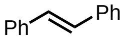
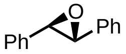
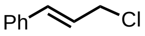
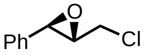
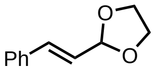
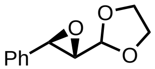
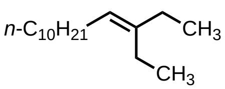
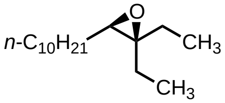
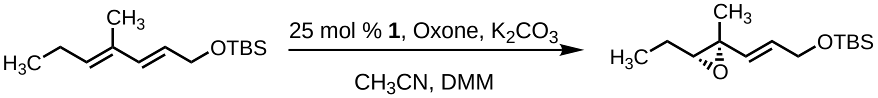
Examples of Shi Epoxidations:

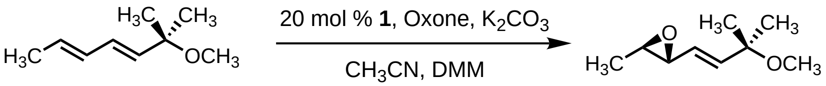
Substrate	Product	Yield	ee (%)
		73%	95%
		61%	93%
		41%	93%
		94%	89%

From: Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996***, 118*, 9806-9807
and Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

- Monoepoxidation of conjugated dienes favors the more electron-rich or less sterically hindered olefin. The amount of catalyst used must be properly controlled (0.2–0.3 equiv) to prevent bis-epoxidation. Vinyl silanes and allylic silyl ethers are deactivated towards epoxidation (attributed to sterics and inductive deactivation, respectively).

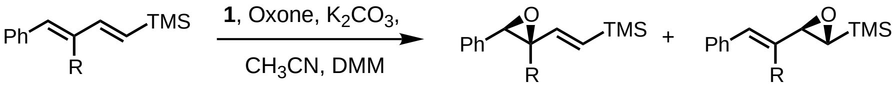


81% y, 96% ee



65% y, 89% ee

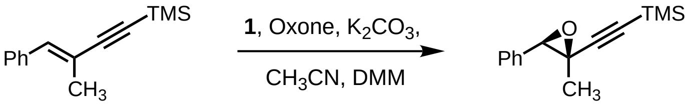
- Regioselectivity increases when either olefin of a 1,3-diene is trisubstituted. It is proposed that the trisubstituted olefin prevents full conjugation of the diene due to $A_{1,2}$ strain, thereby isolating the olefins toward their individual steric or electronic environments.



	Yield	ee	Ratio
R = H	31%	95%	1:1
R = CH_3	77%	92%	14:1

Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948-2953.

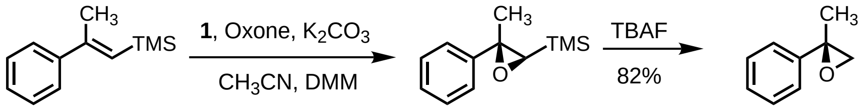
- Epoxidation of enynes occurs selectively at the C-C double bond.



64% y, 94% ee

Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425-4428.
Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646-7650.

- 1,1-Disubstituted epoxides can be synthesized enantioselectively by Shi epoxidation of trisubstituted vinyl silanes followed by TBAF-mediated desilyation.



74% y, 94% ee

94% ee

Warren, J.D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675-7677.

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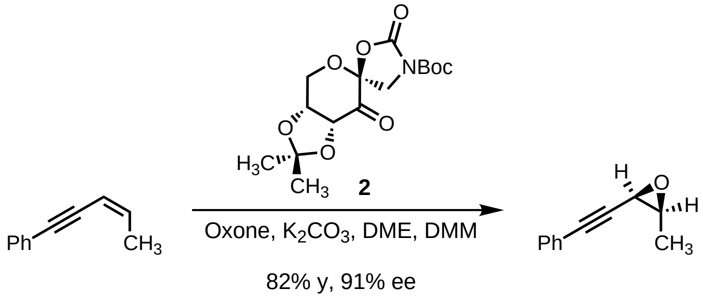
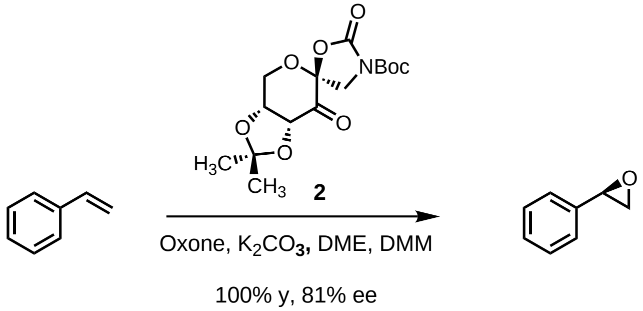
- A modified catalyst is useful for epoxidation of *cis*-disubstituted olefins and styrenes.



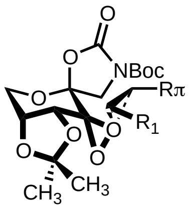
The enantiomeric excess is generally high for cyclic olefins and acyclic olefins conjugated with an alkynyl or aromatic group.

Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551-11552.

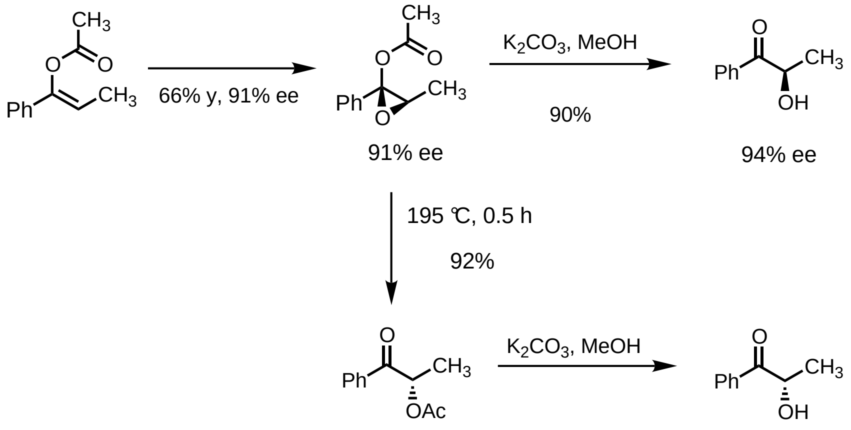


Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929-1931.
Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435-2446.

In both cases, it is proposed that the π-substituent of the substituent prefers to be proximal to the spiro oxazolidinone.

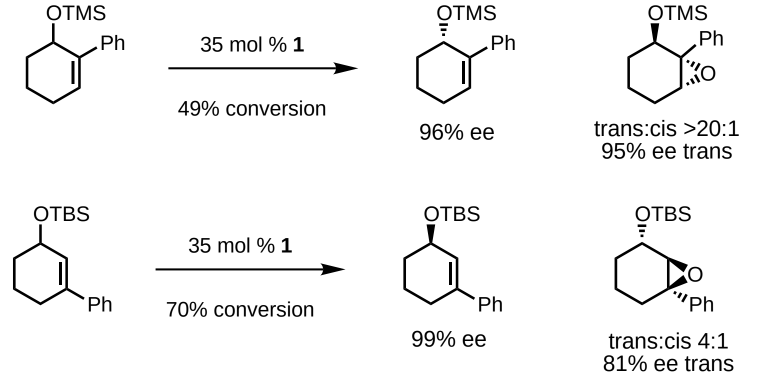


- Enol esters can be used as substrates for the preparation of α-hydroxyketones in either enantiomeric form.



Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819-7822.

- Kinetic resolution of racemic 1,3- and 1,6-disubstituted cyclohexenes can provide optically enriched allylic silyl ethers.



Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718-7719.

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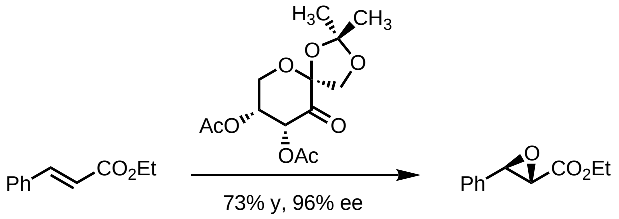
- The original Shi catalyst decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient α,β-unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the Baeyer-Villiger decomposition.

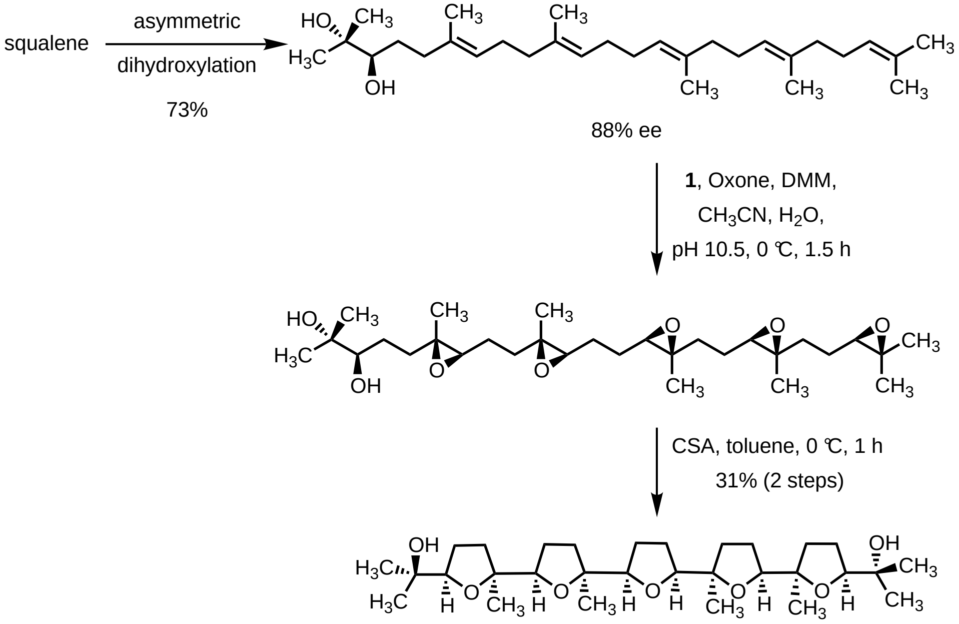


73% y, 96% ee

Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792-8793.

Applications in Synthesis:

Glabrescol:



asymmetric dihydroxylation

73%

1, Oxone, DMM, CH_3CN, H_2O, pH 10.5, 0 ℃, 1.5 h

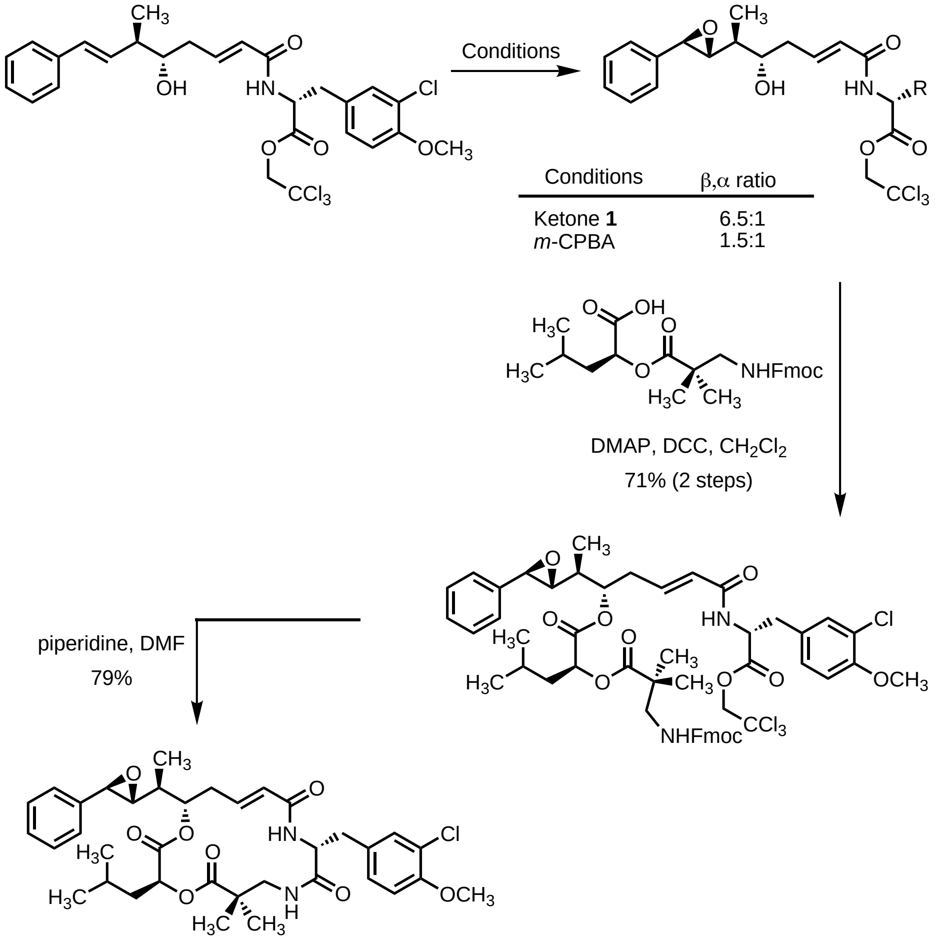
CSA, toluene, 0 ℃, 1 h
31% (2 steps)

originally proposed structure of Glabrescol

Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831-4832.

Cryptophycin 52:

The Shi epoxidation system provided the desired epoxide in a 6:1 diastereomeric ratio, while other epoxidation methods never exceeded a 2:1 ratio.



Conditions

Conditions	β,α ratio
Ketone **1**	6.5:1
m-CPBA	1.5:1

DMAP, DCC, CH_2Cl_2
71% (2 steps)

piperidine, DMF
79%

Cryptophycin 52

Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813-1815.

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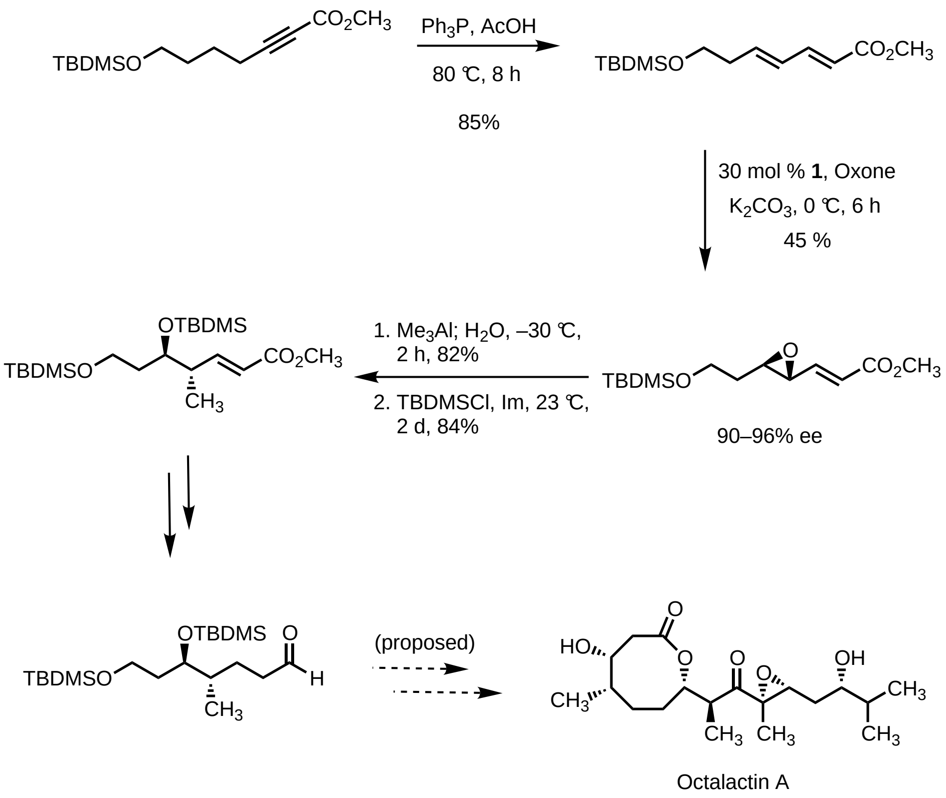
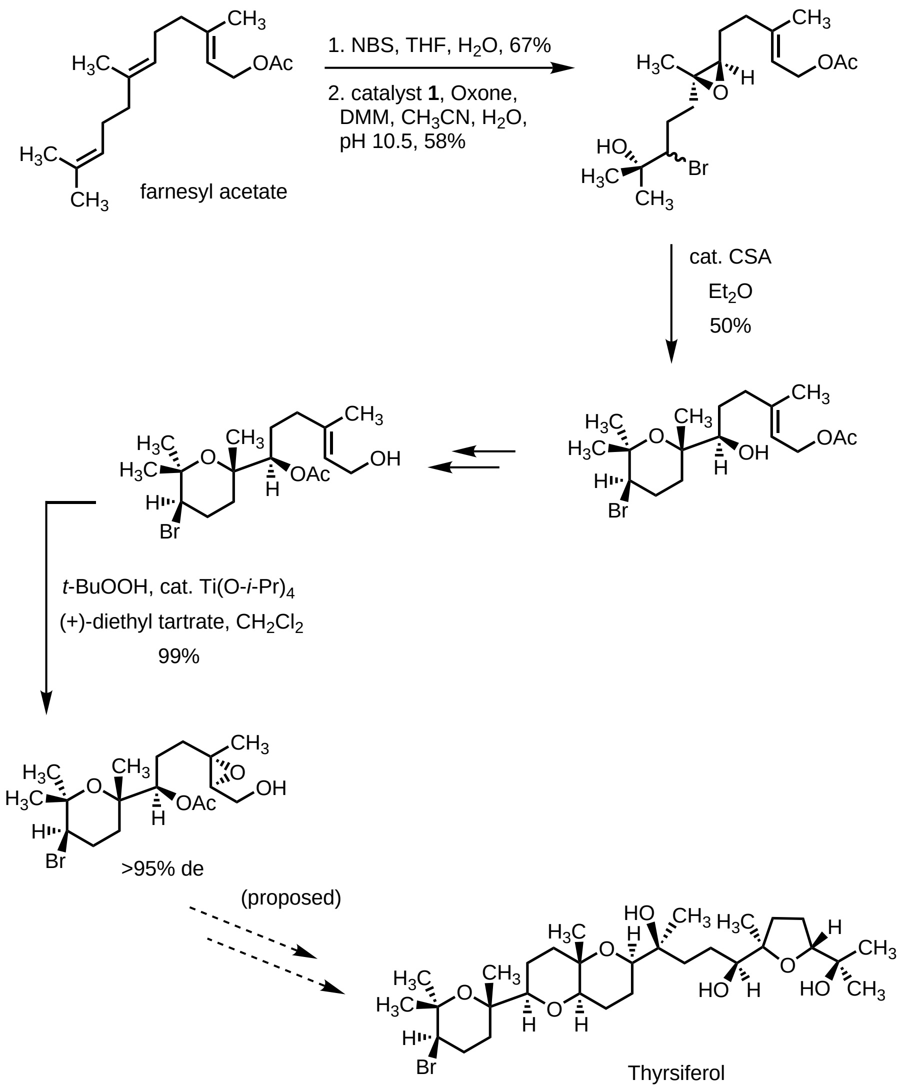
Octalactin A:



Bluet, G.; Campagne, J.-M. *Synlett* **2000**, *1*, 221-222.

Thyrsiferol:

Effective kinetic resolution could be achieved in which only one bromotetrahydropyran diastereomer was formed in quantitative yield. The unreactive diastereomer was separated from the cyclization product and isolated in 30% yield.



McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593-595.

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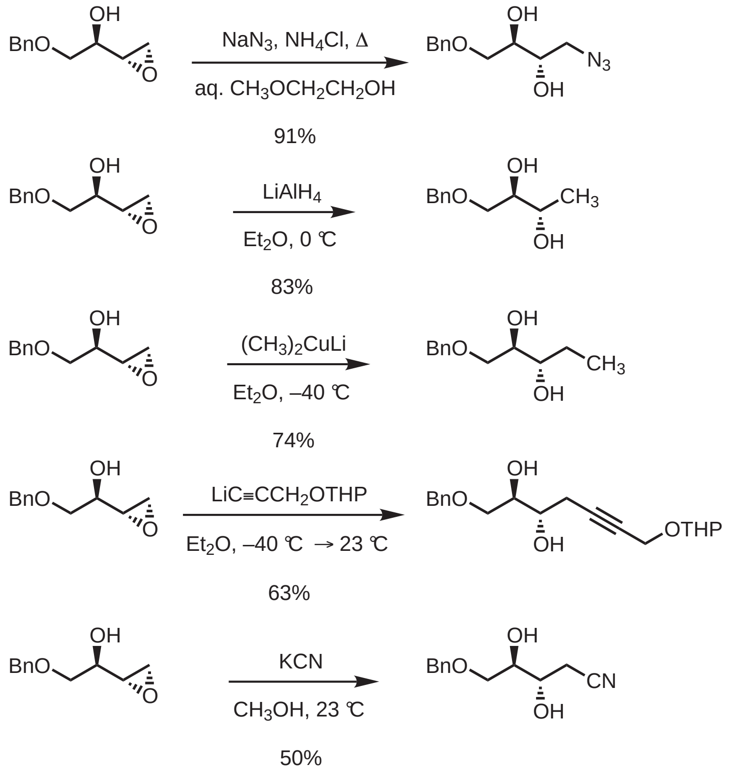
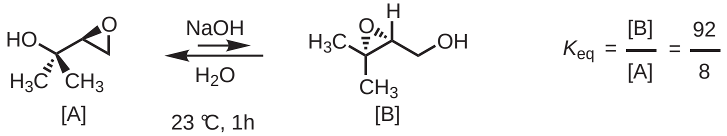
Opening of Terminal Epoxides:

- Nucleophilic opening of terminal epoxides is often highly regioselective.



Behrens, C. H.; Sharpless, K. B.; *Aldrichimica Acta*, **1983**, *16*, 67-80.

Payne Rearrangement:

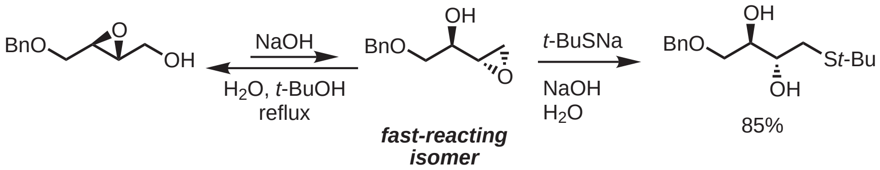


$$K_{eq} = \frac{[B]}{[A]} = \frac{92}{8}$$

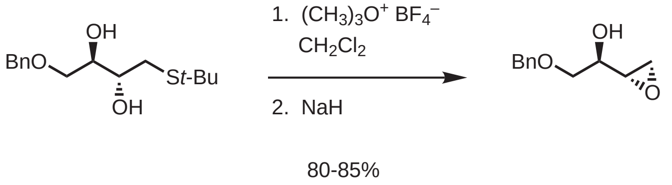
- Steric factors permitting, equilibrium generally favors the more substituted epoxide.

Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819-3822.

Payne Rearrangement-Opening Sequence:



- β-Hydroxy sulfides are readily converted into terminal epoxides.

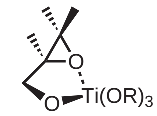


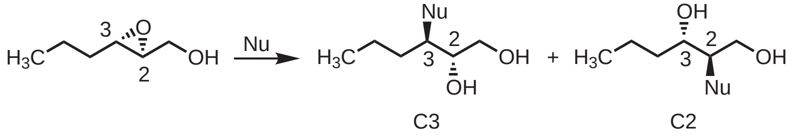
Behrens, C. H.; Sharpless, K. B.; *Aldrichimica Acta*, **1983**, *16*, 67-80.

2,3-Epoxy alcohols:

- $Ti(O\textit{i}\text{-}Pr)_4$ can catalyze the addition of nucleophiles to C3 of 2,3-epoxy alcohols:

Proposed:



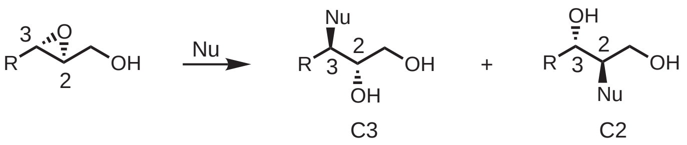


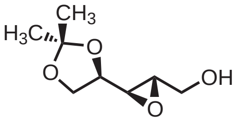
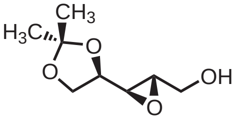
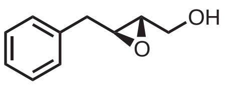
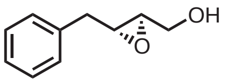
Nucleophile	$Ti(O\textit{i}Pr)_4$	C3 : C2	yield
Et_2NH	0	3.7 : 1	4
Et_2NH	1.5	20 : 1	90
i-PrOH	0	-	0
i-PrOH	1.5	100 : 1	88
$(allyl)_2NH$	1.5	100 : 1	96
allyl alcohol	1.5	100 : 1	90
NH_4OBz	1.5	100 : 1	74
NH_4OAc	1.5	65 : 1	73
KCN	1.7	2.4 : 1	76

From: Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557-1560.

M. Movassaghi

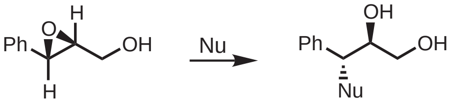
- Regioselectivity of uncatalyzed nucleophilic opening of 2,3-epoxy alcohols varies with the substrate and reaction conditions.



substrate	nucleophile	regioselectivity C3 : C2	combined yield (%)
	NaN_3	1 : 10	90
	NaSPh	1 : >10	76
	NaN_3	1.4 : 1	71
	NaSPh	1 : 1.4	72

Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696-5704.

- Phenyl substitution at C3 of 2,3-epoxy alcohols can lead to high C3-regioselectivity.

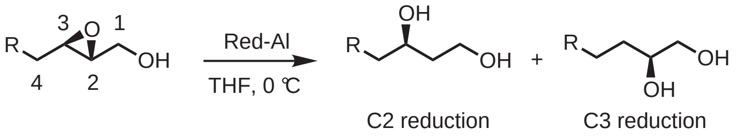


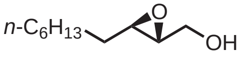
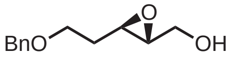
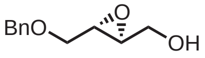
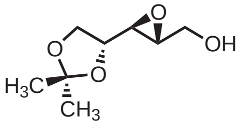
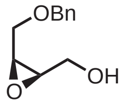
reagent	Nu	yield
allyl magnesium bromide	allyl	96
R_2CuLi or $R_2(CN)CuLi_2$	R	78-88
NaN_3/NH_4Cl	N_3	>95
R_2NH/KOH	R_2N	84
ArONa	ArO	83
PhSH/NaOH	PhS	81

From: Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437-475, and references therein.

- C2 reduction of 2,3-epoxy alcohols using Red-Al is highly selective when C4 is oxygenated.

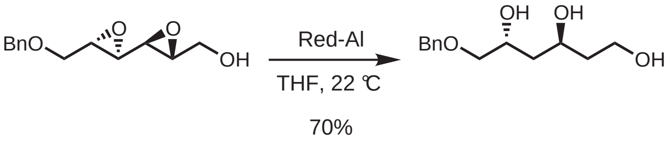
Red-Al = $[(CH_3OCH_2CH_2O)_2AlH_2]^- Na^+$



epoxy alcohol	C2 : C3	yield (%)
	1 : 1	94
	5 : 1	89
	40 : 1	98
	>100 : 1	78
	100 : 1	95

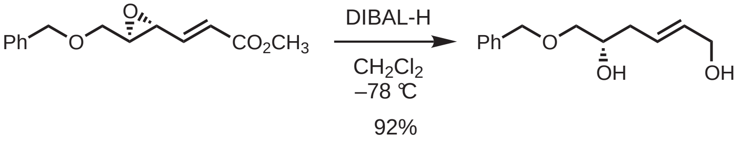
Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378-1380 and Finan, J.; Kishi Y. *Tetrahedron Lett.* **1982**, *23*, 2719-2722.

- 1,3-Bis-epoxides:



Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378-1380.

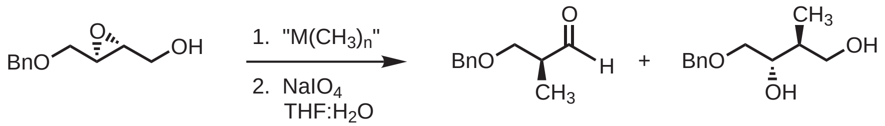
- Allylic epoxides:



Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292-1293.

M. Movassaghi

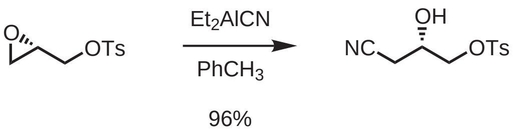
- The regioselectivity of epoxide opening can vary with the organometallic reagent.

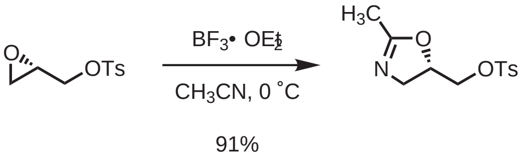


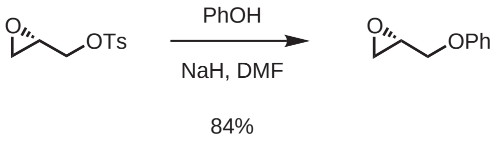
$(CH_3)_2CuLi$ Et_2O, –20 °C	10-12%	74-79%
$(CH_3)_3Al$, CH_2Cl_2 0 → 23 °C	69-73%	13-14%

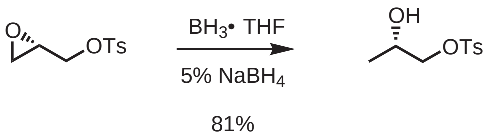
Johnson, M. R.; Nakata T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343-4346.
Roush, W. R.; Adam, M. H.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, 1377-1380.

- AE of allyl alcohol followed by in situ derivatization affords versatile chiral building blocks, such as glycidol tosylate (now commercially available).
- Reactions of glycidol tosylate:



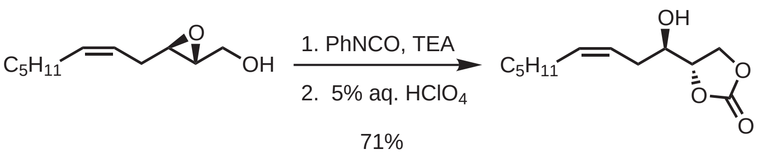




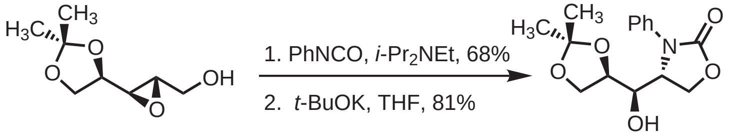


Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295-1304.
Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437-475.

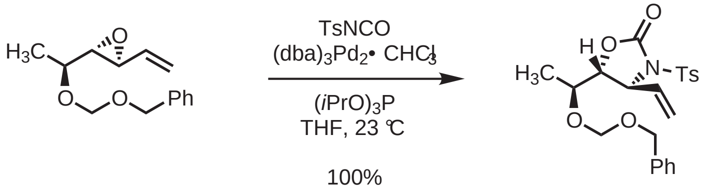
- Internal nucleophiles may be used to open 2,3-epoxy alcohols:



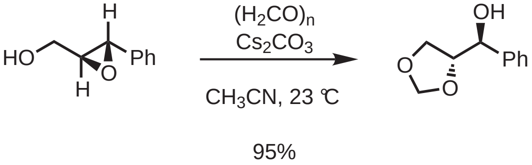
Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1980**, *102*, 7986-7987.



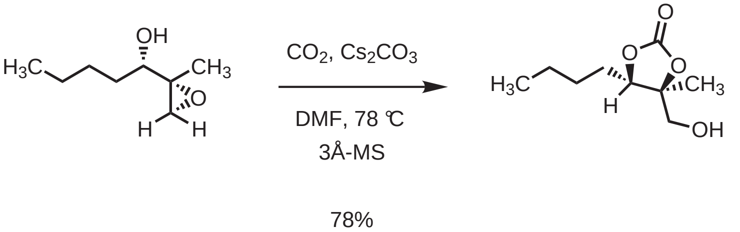
Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109-1111.



Trost B. M., Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792-3794.



McCombie, S. W.; Metz, W. A. *Tetrahedron Lett.* **1987**, *28*, 383-386.



Myers, A. G.; Widdowson, K. L. *Tetrahedron Lett.* **1988**, *29*, 6389-6392.

The Noyori Asymmetric Hydrogenation Reaction

Reviews:

Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327–3355.

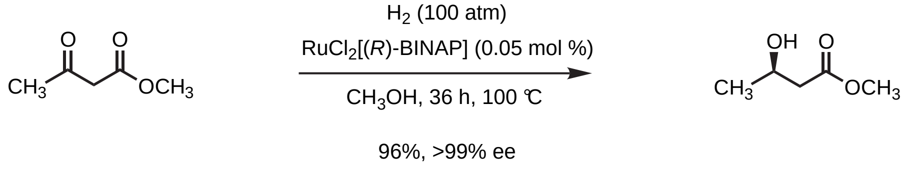
Noyori, R. *Acta. Chem. Scand.* **1996**, *50*, 380–390.

Genet, J. P. In *Reductions in Organic Synthesis*, Abdel-Magid, A. F., Ed.; ACS Symposium Series, 641; American Chemical Society: Washington, D.C., **1996**, pp. 31–51.

Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, **1993**, pp. 56–82.

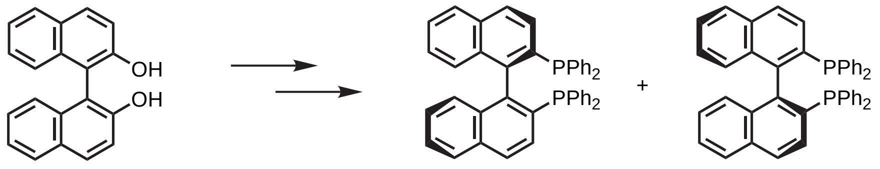
Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56.

Original Report:



Noyori, R., Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akuragawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858.

- Both enantiomers of BINAP are commercially available. Alternatively, both enantiomers can be prepared from the relatively inexpensive (±)-1,1'-bi-2-naphthol.



(±)-1,1'-Bi-2-naphthol

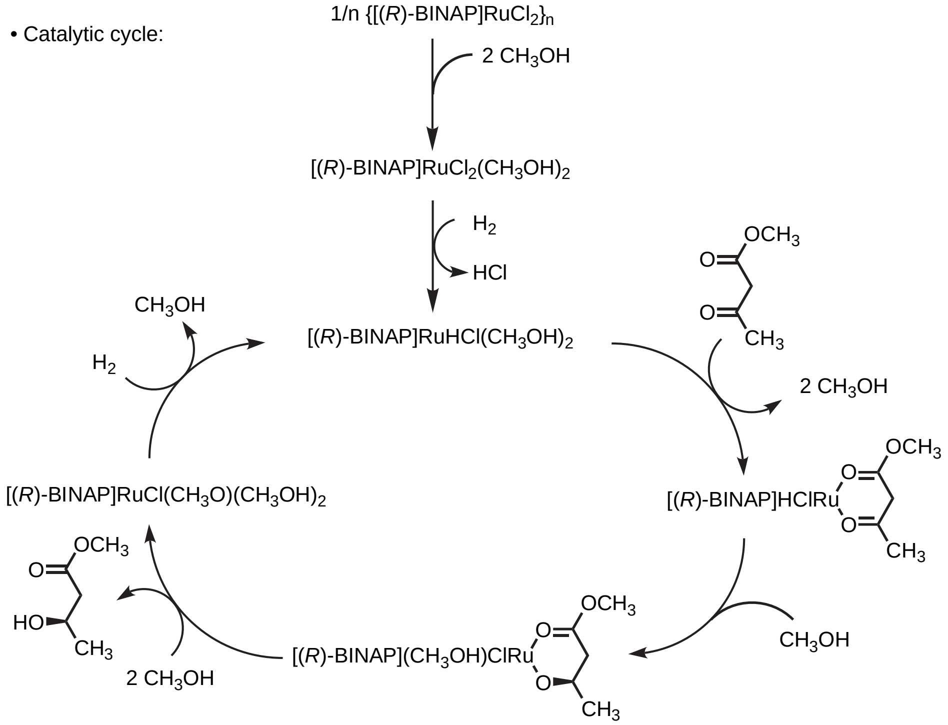
(*R*)-(+)-BINAP
20%

(*S*)-(–)-BINAP
20%

Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20–32.

Mechanism:

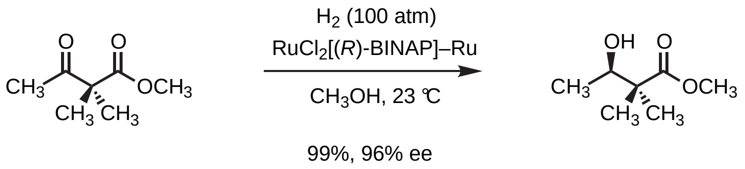
- Catalytic cycle:



1/n {[(*R*)-BINAP]$RuCl_2$}$_n$
2 CH_3OH
[(*R*)-BINAP]$RuCl_2(CH_3OH)_2$
H_2
HCl
[(*R*)-BINAP]$RuHCl(CH_3OH)_2$
2 CH_3OH
[(*R*)-BINAP]HClRu
CH_3OH
[(*R*)-BINAP](CH_3OH)ClRu
2 CH_3OH
[(*R*)-BINAP]$RuCl(CH_3O)(CH_3OH)_2$
H_2
CH_3OH

Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, **1993**, pp. 56–82.

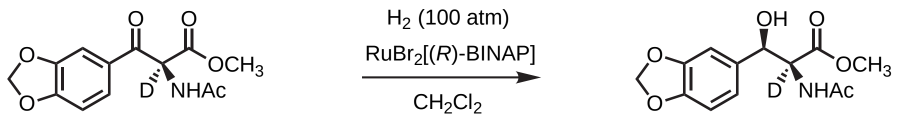
- Evidence that the reduction proceeds through the keto form of the β-keto ester is the fact that the reduction of methyl 2,2-dimethyl-3-oxobutanoate occurs with high yield and high enantioselectivity. However, pathways that involve hydrogenation of the enol form of other β-keto esters cannot be ruled out.



Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350.

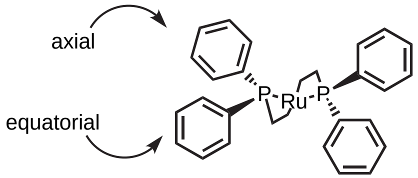
Andrew Haidle

- The use of a deuterated substrate provides further evidence that the reduction proceeds through the keto tautomer. Enolization is rapid, so the deuterium is lost quickly. However, when the reaction was stopped at 1.3% conversion, the hydroxy ester product retained 80% of the deuterium at C-2, and no deuterium was incorporated at C-3.

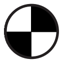


Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

- A crystal structure of $Ru(OCOCH_3)_2$[(*S*)-BINAP] revealed that the rigid BINAP backbone forces the phenyl rings attached to phosphorous to adopt the conformation depicted here (the napthyl rings are omitted for clarity).



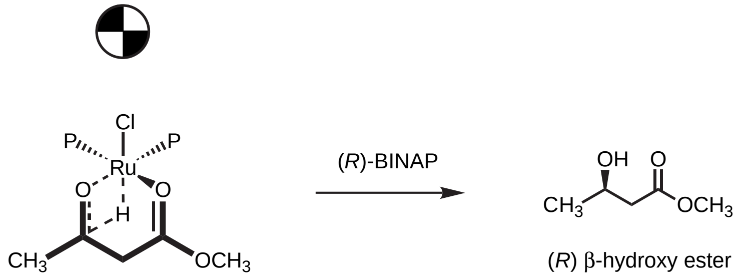
$Ru(OCOCH_3)_2$[(*S*)-BINAP]

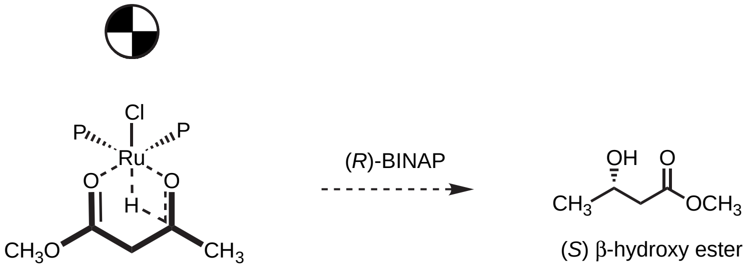


- The two protruding equatorial *P*-phenyl groups allow a coordinating ligand access to only two quadrants on the accessible face of Ru (the other face is blocked by BINAP's napthyl rings). This situation is represented by a circle with two black quadrants where no coordination can occur.

Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566–569.

- Of the two possible diastereomeric transition states for complexes with (*R*)-BINAP shown below, the one leading to the (*R*) β-hydroxy ester allows the approach of the ketone at an unhindered quadrant (as represented by the light lower left quadrant of the circle).





Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56.

Reaction Conditions:

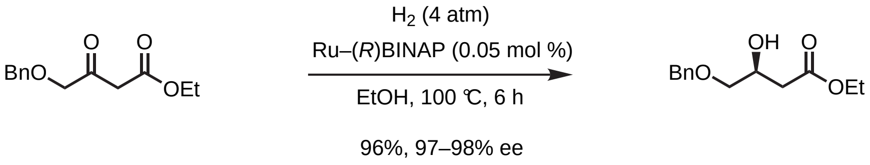
- Noyori has published conditions to prepare the active Ru-BINAP catalyst in one step from commercially available $[RuCl_2(benzene)]_2$, and it can be used without a purification step. Also, the reaction can be run at 4 atm/100 ℃ or 100 atm/23 ℃.

Note: 1 atm = 14.7 psi

Kitamura, M.; Tokunaga, M.; Okhuma, T; Noyori, R. *Org. Synth.* **1993**, *71*, 1–13.

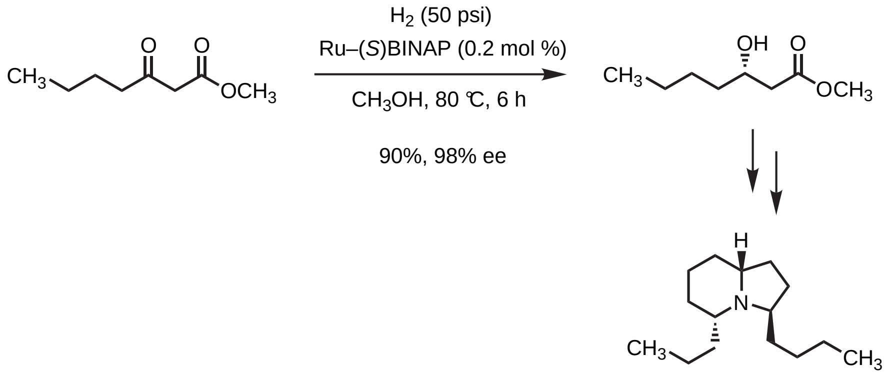
Andrew Haidle

- This in situ procedure of catalyst generation was found to be much more reliable. Also, reactions with this catalyst were more enantioselective and required less catalyst. The following reaction was done on a 10 kg scale. Note the benzyl group is not removed.



Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014–1018.

- A simplified, milder set of conditions that also features a catalyst available in one step from commercially available BINAP and $RuCl_2$•cyclooctadiene has been published. The reaction proceeds at a sufficiently low H_2 pressure (50 psi) to avoid reduction of trisubstituted olefins, but not terminal olefins.

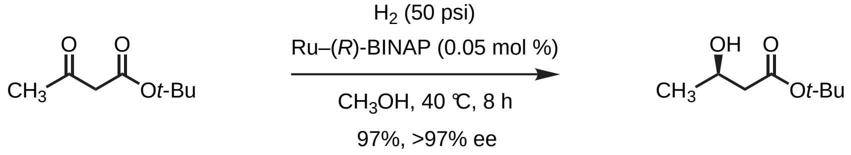


(–)-Indolizidine 223AB

Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227–4230.

Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990–5994.

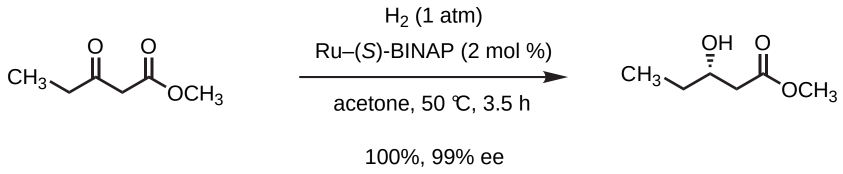
- These conditions have been improved on even further, with milder reaction conditions and lower catalyst loadings.



- The authors present kinetic data to show the dramatic increase in reaction rate that occurs in the presence of a catalytic amount of strong acid, and they suggest that failed reactions may result from low levels of basic impurities. Note that the acid-sensitive *t*-Bu ester is not cleaved under these conditions.

King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689–6691.

- Reduction of β-keto esters has been achieved at 1 atm of hydrogen using a catalyst prepared in situ from BINAP, (COD)Ru(2-methylallyl)$_2$, and HBr, all of which are commercially available. No special reaction apparatus is necessary for this procedure; however, the catalyst loading is unusually high.



Genet, J. P.; Ratovelomanana-Vidal, V.; Caño de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801–4804.

Andrew Haidle

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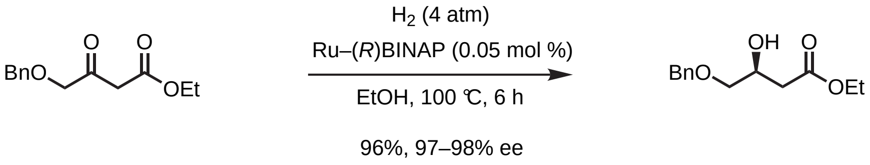

Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014–1018.

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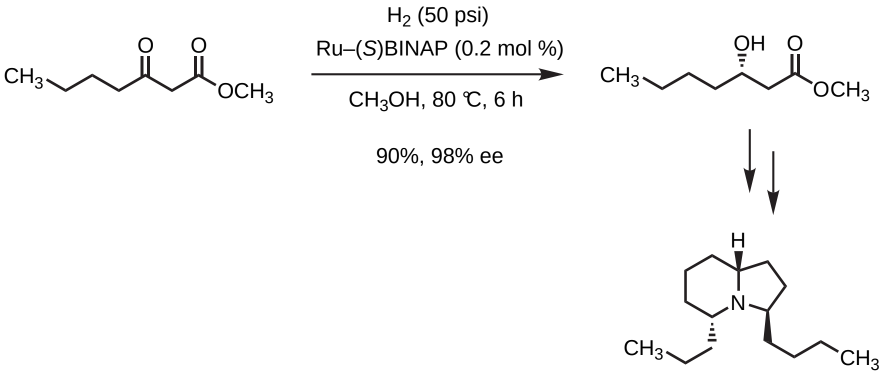

(–)-Indolizidine 223AB

Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227–4230.

Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990–5994.

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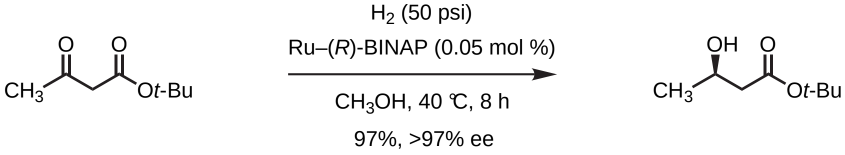

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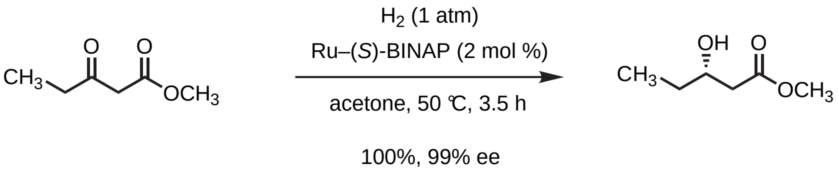
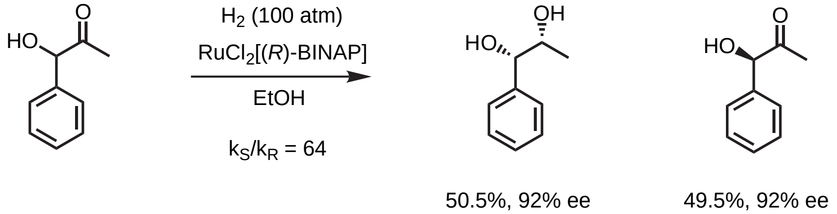


Genet, J. P.; Ratovelomanana-Vidal, V.; Caño de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801–4804.

Dynamic Kinetic Resolution:

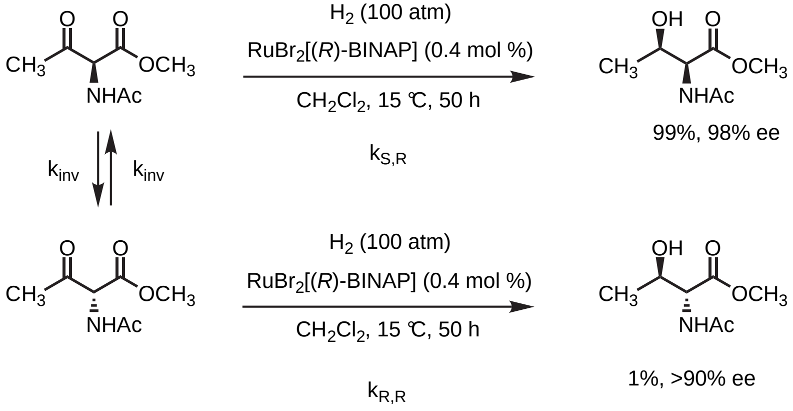
- Kinetic resolution of enantiomers occurs when the chiral catalyst reacts with one enantiomer much more rapidly than the other.



- An inherent drawback to kinetic resolution is the fact that the maximum yield is 50% of enantiopure material.

Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, **1993**, pp. 56–82.

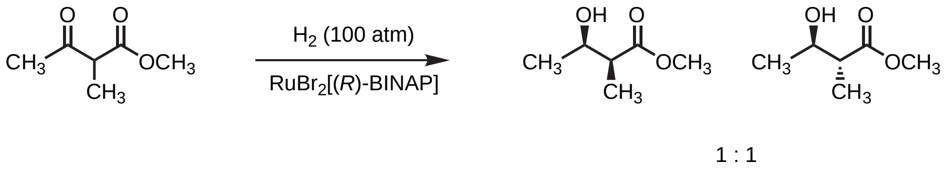
- If the initially present stereocenter can be epimerized under the reaction conditions, i.e., the enantiomer that does not react can be transformed into the one that does react, then the theoretical yield is 100%. This is a dynamic kinetic resolution.

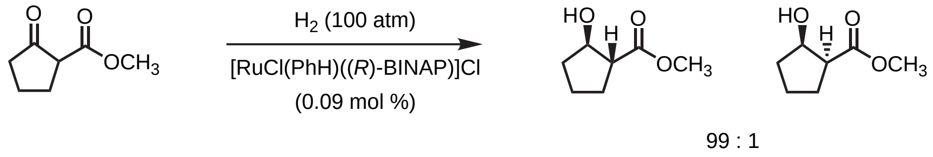


- For yields approaching 100% of the desired enantiomer, rapid isomerization between the two enantiomeric β-keto esters must occur ($k_{inv} > k_{S,R}$ and $k_{R,R}$).

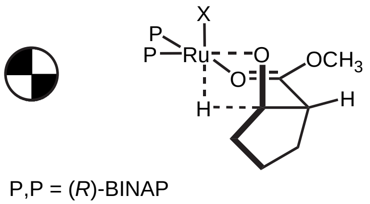
Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

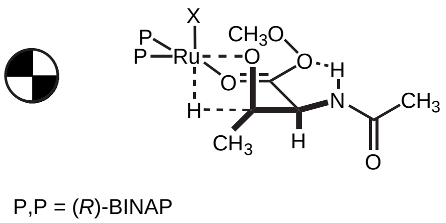
- The stereochemistry of the secondary alcohol is determined by the choice of catalyst, but the stereochemistry at the α-position is substrate dependent.





- The preference for one diastereomer over the other can be rationalized by examining the likely transition states for carbonyl reduction. If the reduction of the α-amino compound is carried out in methanol instead of dichloromethane, the diastereoselectivity drops from 99 : 1 to 82 : 18.





Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

- A detailed mathematical model of the dynamic kinetic resolution process has been published.

Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144–152.

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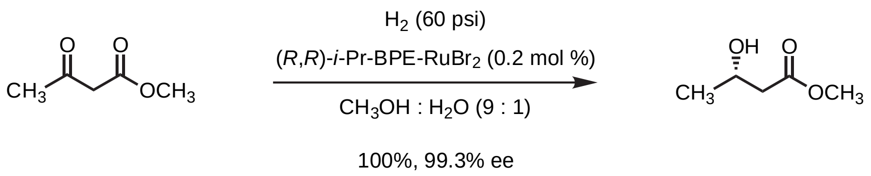
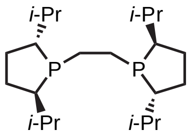
Other Ligands:

- Burk's 1,2-bis(*trans*-2,5-diisopropylphospholano)ethane (*i*-Pr-BPE) is a useful ligand for the reduction of many β-keto esters, and the reaction conditions are milder than those originally reported by Noyori.

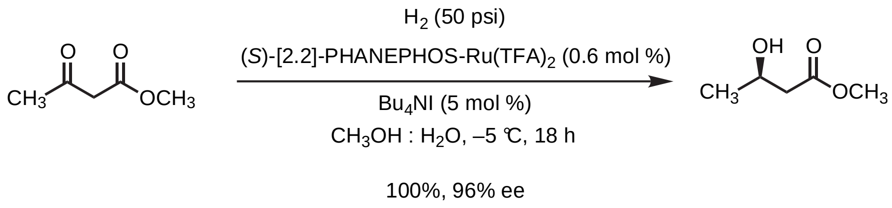


(*R*,*R*)-*i*-Pr-BPE =



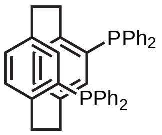
Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423–4424.

- Using the novel [2.2]-PHANEPHOS ligand, extremely mild, neutral conditions for the reduction of β-keto esters have been developed.



H_2 (50 psi)
(*S*)-[2.2]-PHANEPHOS-Ru$(TFA)_2$ (0.6 mol %)
Bu_4NI (5 mol %)
$CH_3OH : H_2O$, –5 ℃, 18 h
100%, 96% ee
CH_3
OCH_3
OH
O

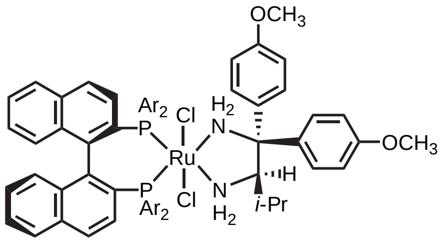
(*S*)-[2.2]-PHANEPHOS =

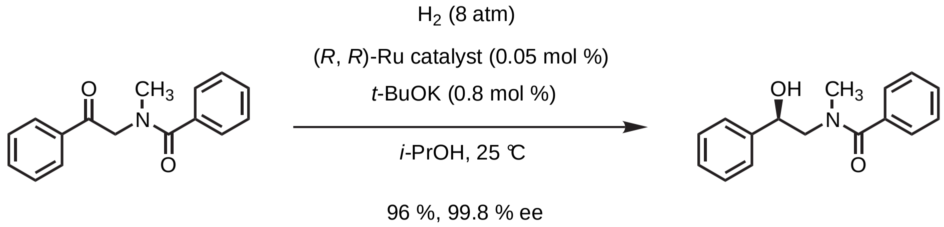


Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441–4444.

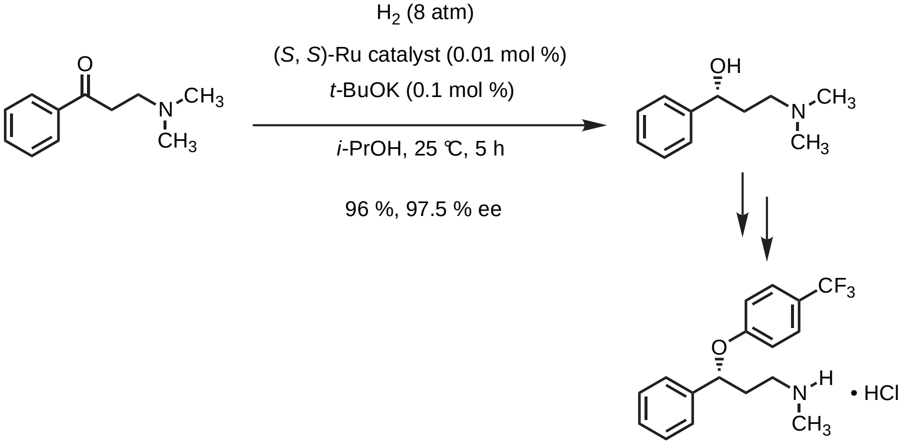
- Noyori has discovered a Ru–based catalyst, *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-diapen], that efficiently reduces α-, β-, and γ-amino ketones in a highly enantioselective fashion under mild conditions.

trans-$RuCl_2$[(*R*)-xylbinap][(*R*)-diapen] =





- The mechanism of this reduction differs from the Ru-BINAP catalyst in that the adjacent nitrogen is believed not to ligate to the Ru center.
- This method allows for a practical synthesis of the antidepressent (*R*)-fluoxetine without the need for any chromatographic separations.

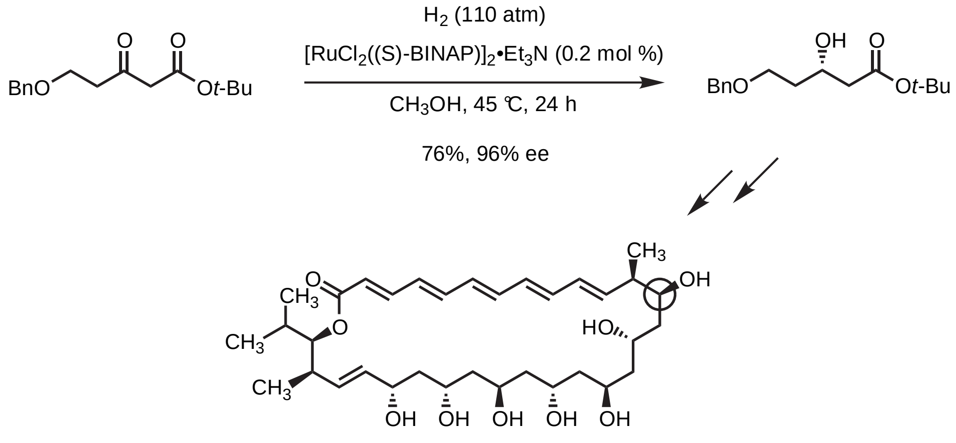


Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511.

Andrew Haidle

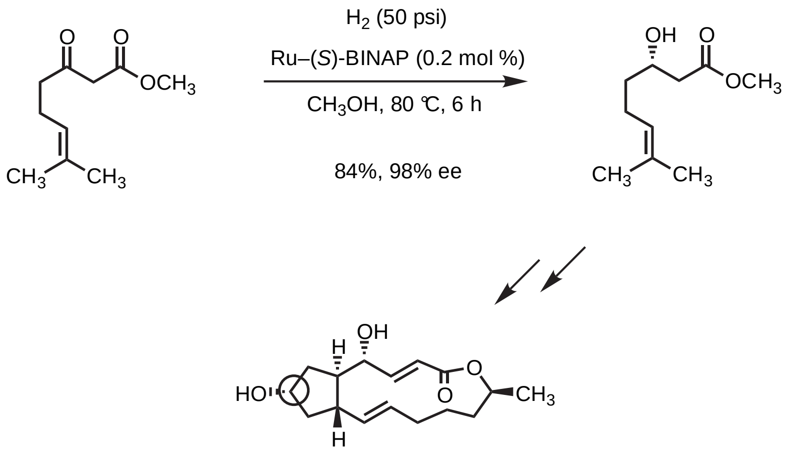
Examples in Total Synthesis:

- In all of the examples, the carbonyl carbon that is initally reduced is circled in the final product.



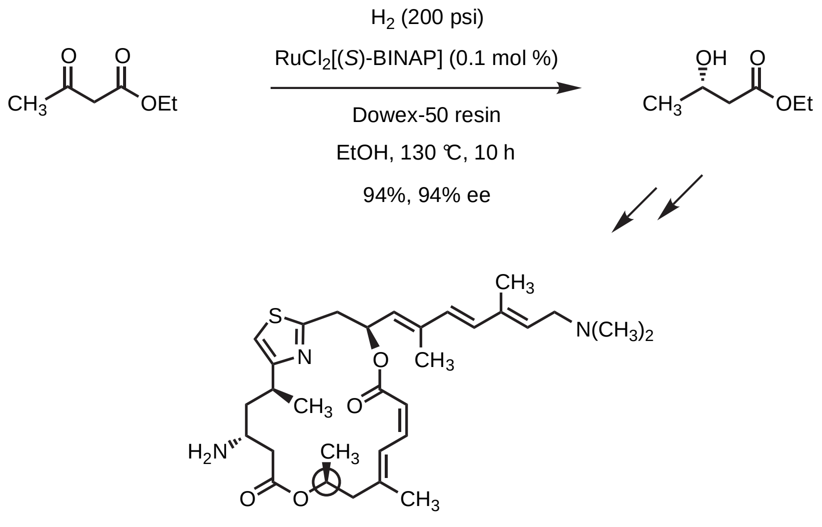
(–)-Roxaticin

Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.



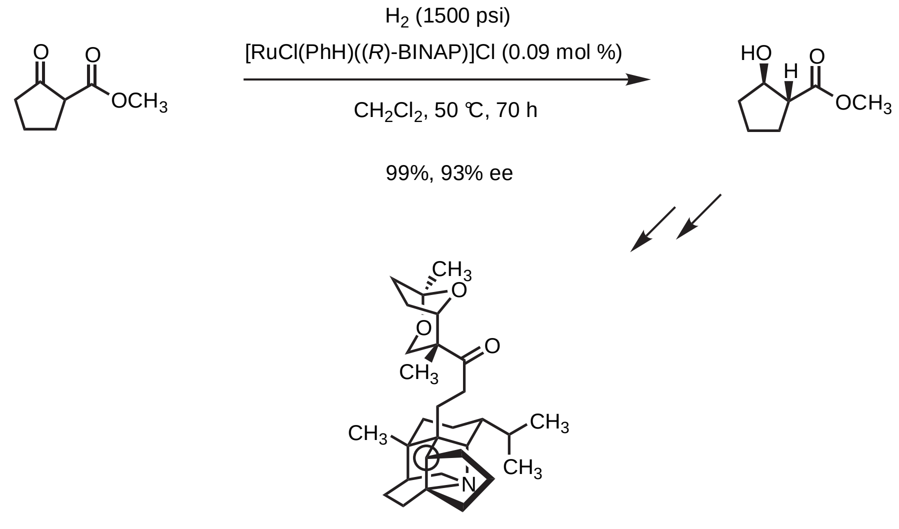
(+)-Brefeldin A

Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639–6645.



Pateamine A

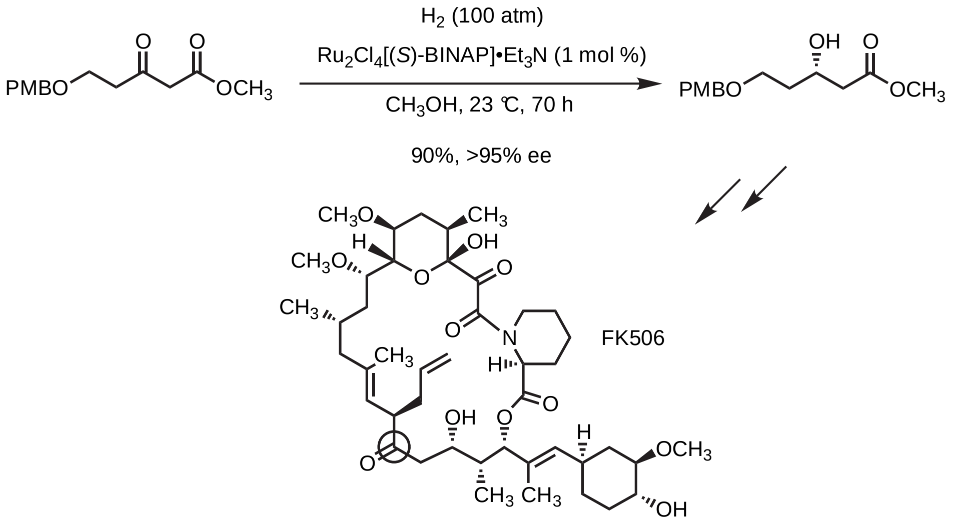
Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.



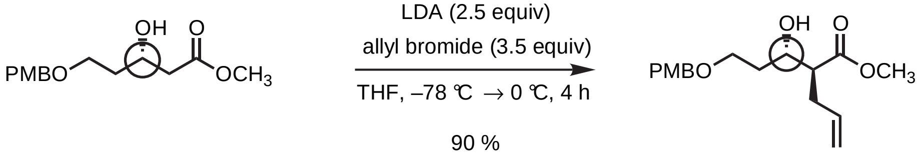
(+)-Codaphniphylline

Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120–1130.

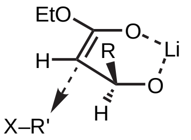
Andrew Haidle



- Although the chirality of the β-hydroxy ester is lost in the final product, it is used to set two other stereocenters.



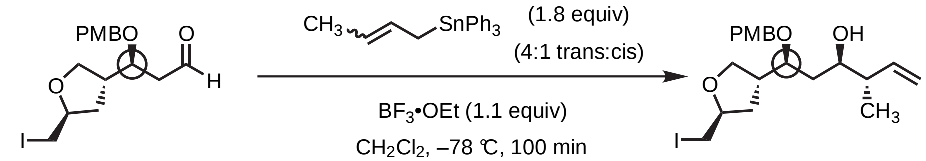
- Chelation control and steric shielding explain the high diastereoselectivity of the allylation reaction.



(from the work of Fráter and Seebach)

Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277.

Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109–120.



(5:1 diastereomeric mixture)

54%, >97% dr

(67% maximum yield for major diastereomer)

Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601.

Reviews:

Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4490–4527.

Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

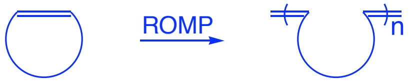
Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900–1923.

Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3013–3043.

Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.

Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.

Ring-Opening Metathesis Polymerization (ROMP):

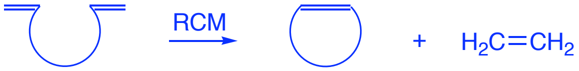


- ROMP is thermodynamically favored for strained ring systems, such as 3-, 4-, 8- and larger-membered compounds.

- When bridging groups are present (bicyclic olefins) the ΔG of polymerization is typically more negative as a result of increased strain energy in the monomer.

- Block copolymers can be made by sequential addition of different monomers (a consequence of the "living" nature of the polymerization).

Ring-Closing Metathesis (RCM):

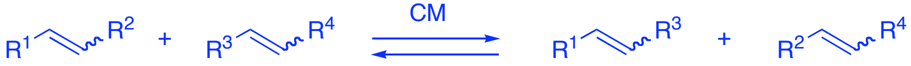


- The reaction can be driven to the right by the loss of ethylene.

- The development of well-defined metathesis catalysts that are tolerant of many functional groups yet reactive toward a diverse array of olefinic substrates has led to the rapid acceptance of the RCM reaction as a powerful method for forming carbon-carbon double bonds and for macrocyclizations.

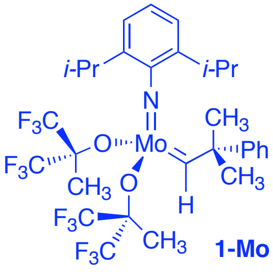
- Where the thermodynamics of the closure reaction are unfavorable, polymerization of the substrate can occur. This partitioning is sensitive to substrate, catalyst, and reaction conditions.

Cross Metathesis (CM):

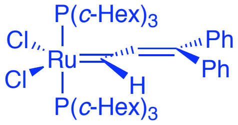


- Self-dimerization reactions of the more valuable alkene may be minimized by the use of an excess of the more readily available alkene.

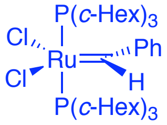
Catalysts



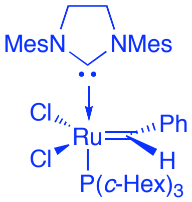
1-Mo



2-Ru



3-Ru (Grubbs' 1st Generation Catalyst)



4-Ru (Grubbs' 2nd Generation Catalyst)

- The well-defined catalysts shown above have been used widely for the olefin metathesis reaction. Titanium- and tungsten-based catalysts have also been developed but are less used.

- Schrock's alkoxy imidomolybdenum complex **1-Mo** is highly reactive toward a broad range of substrates; however, this Mo-based catalyst has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents, and exhibits thermal instability.

- Grubbs' Ru-based catalysts exhibit high reactivity in a variety of ROMP, RCM, and CM processes and show remarkable tolerance toward many different organic functional groups.

- The electron-rich tricyclohexyl phosphine ligands of the d^6 Ru(II) metal center in alkylidenes **2-Ru** and **3-Ru** leads to increased metathesis activity. The NHC ligand in **4-Ru** is a strong σ-donor and a poor π-acceptor and stabilizes a 14 e^- Ru intermediate in the catalytic cycle, making this catalyst more effective than **2-Ru** or **3-Ru**.

- Ru-based catalysts show little sensitivity to air, moisture or minor impurities in solvents. These catalysts can be conveniently stored in the air for several weeks without decomposition. All of the catalysts above are commerically available, but **1-Mo** is significantly more expensive.

Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed Engl.* **1995**, *34*, 2039–2041.
Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.

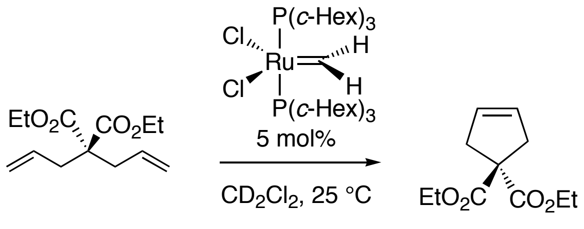
M. Movassaghi and L. Blasdel

Mechanism:

- The olefin metathesis reaction was reported as early as 1955 in a Ti(II)-catalyzed polymerization of norbornene: Anderson, A. W.; Merckling, M. G. *Chem. Abstr.* **1955**, *50*, 3008i.

- 15 years later, Chauvin first proposed that olefin metathesis proceeds via metallacyclobutanes: Herisson, P. J.-L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161–176.

- It is now generally accepted that both cyclic and acyclic olefin metathesis reactions proceed via metallacyclobutane and metal-carbene intermediates: Grubbs, R. H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, *97*, 3265–3266.



- A kinetic study of the RCM of diethyl diallylmalonate using a Ru-methylidene describes two possible mechanisms for olefin metathesis:

- The "dissociative" mechanism assumes that upon binding of the olefin a phosphine is diplaced from the metal center to form a 16-electron olefin complex, which undergoes metathesis to form the cyclized product, regenerating the catalyst upon recoordination of the phosphine.

- The "associative" mechanism assumes that an 18-electron olefin complex is formed which undergoes metathesis to form the cyclized product.

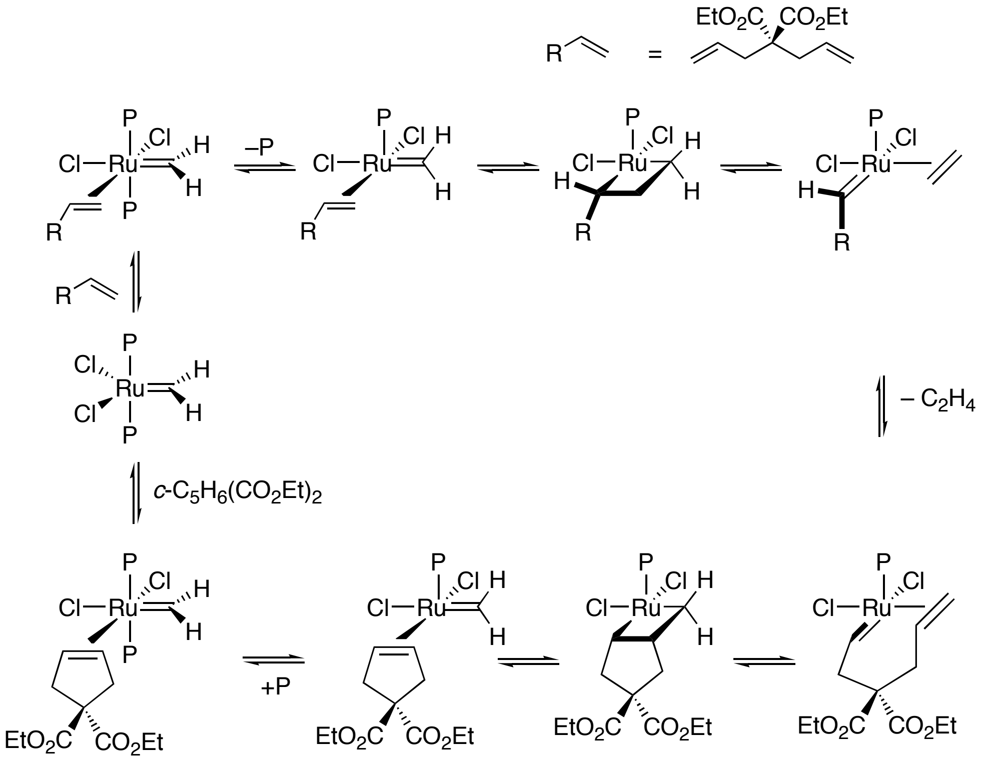
- Addition of 1 equivalent of phosphine (with respect to catalyst) decreases the rate of the reaction by as much 20 times, supporting the dissociative mechanism.

- It was concluded in this study that the "dissociative" pathway is the dominant reaction manifold (>95%).

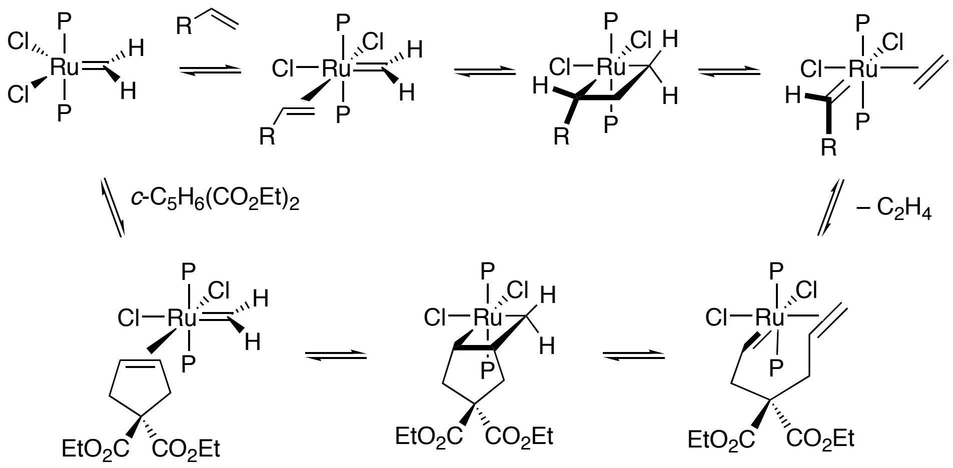
Dias, E. L.; Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.

Dissociative:

P = P(c-Hex)$_3$

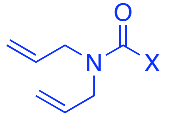
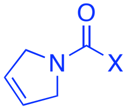
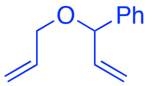
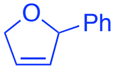
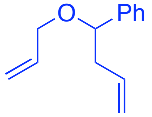
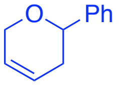
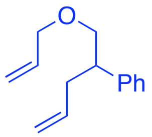
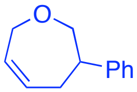
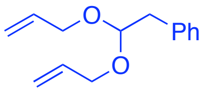
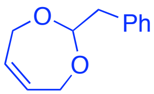
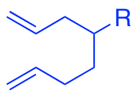
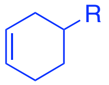


Associative:



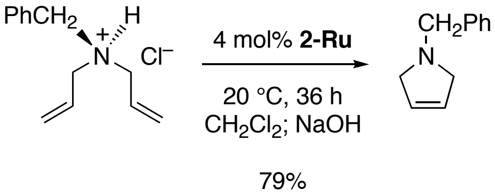
M. Movassaghi

Catalytic RCM of Dienes:

substrate		product	time (h)	yield (%)[a]
	X = CF_3 X = O*t*-Bu		1 1	93 91
			2	84
			5	86
			8	72
			1	87
	R = CO_2H CH_2OH CHO		1 1 1	87 88 82

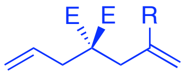
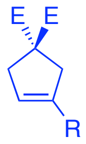
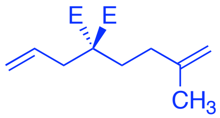
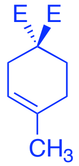
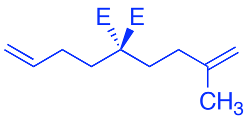
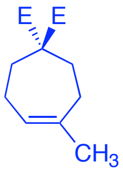
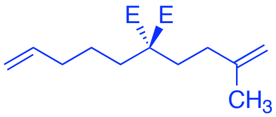
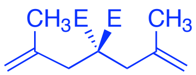
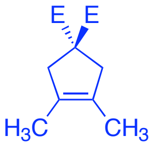
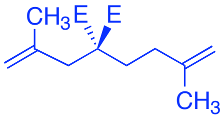
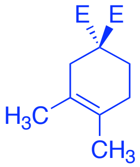
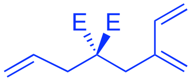
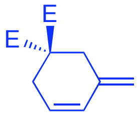
[a] 2-4 mol% **2-Ru**, C_6H_6, 20 °C.

- Five-, six-, and seven-membered oxygen and nitrogen heterocycles and cycloalkanes are formed efficiently.
- Catalyst **2-Ru** can be used in the air, in reagent-grade solvents (C_6H_6, CH_2Cl_2, THF, *t*-BuOH).
- In contrast to the molybdenum catalyst **1-Mo**, which is known to react with acids, alcohols, and aldehydes, the ruthenium catalyst **2-Ru** is stable to these functional groups.
- Free amines are not tolerated by the ruthenium catalyst; the corresponding hydrochloride salts undergo efficient RCM with catalyst **2-Ru**.



Fu, G. C.; Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.

Synthesis of Tri- and Tetrasubstituted Cyclic Olefins via RCM

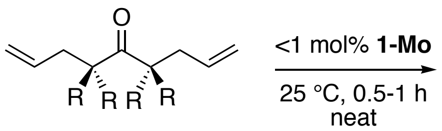
substrate[a]		product	yield with **3-Ru** (%)[b]	yield with **1-Mo** (%)[c]
	R = CH_3 *i*-Pr *t*-Bu Ph Br CH_2OH		93 98 NR 25 NR 98	100 100 96 97 NR decomp
			97	100
			96	100
		–	No RCM[d]	No RCM[d]
			NR	93
			NR	61
			96[e]	100[e]

[a] E = CO_2Et. [b] 0.01 M, CH_2Cl_2, 5 mol%. [c] 0.1 M, C_6H_6, 5 mol%. [d] Only recovered starting material and an acyclic dimer were observed. [e] The isomeric cyclopentene product is not observed.

- Functional group compatibility permitting, the Mo-alkylidene catalyst is typically more effective for RCM of substituted olefins.

Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318.

Geminal Substitution



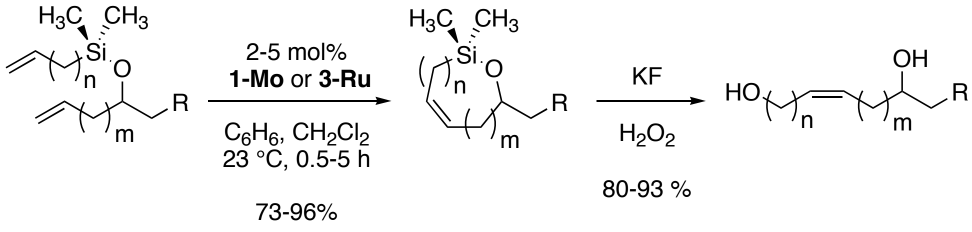
R = H 0%; (polymerization)

CH_3 95%

- "Thorpe-Ingold" effects favor cyclization with gem-disubstituted substrates.

Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R., Jr.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978–10980.

RCM of Temporarily Connected Dienes

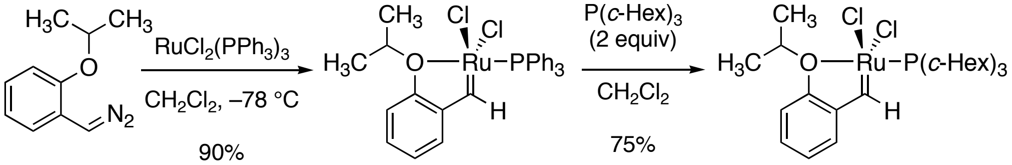


m = 1-3, n = 0-2

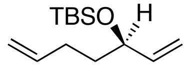
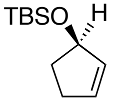
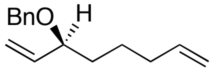
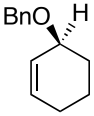
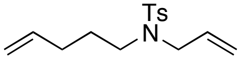
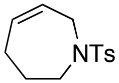
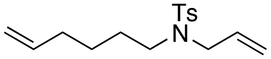
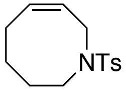
- RCM of allyl- or 3-butenylsilyloxy dienes (n≥1) proceeded efficiently with alkylidene **3-Ru**, while the more sterically hindered vinylsilyl substrates (n=0) required the use of alkylidene **1-Mo**.
- RCM of silicon-tethered alkenes is very efficient even at higher concentrations (0.15 M with catalyst **3-Ru**).

Chang. S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757–4760.

A Recyclable Ru-Based Metathesis Catalyst



5-Ru

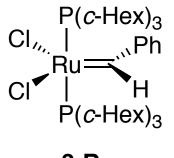
substrate	product[a]	time (h)	temp. (°C)	yield (%)[b]	recovered catalyst (%)[b]
		0.5	22	90	75
		2.0	22	95	89
		1.0	40	99	88
		1.0	40	72	88

[a]5 mol% **5-Ru**, CH_2Cl_2, Ar Atm. [b]Isolated yield after chromatography on silica gel.

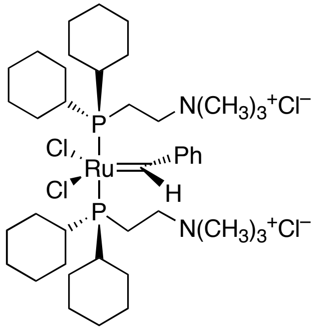
- Catalyst **5-Ru** exhibitsexcellent stability toward air and moisture and can be recycled in high yield by chromatography on silica gel.

Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

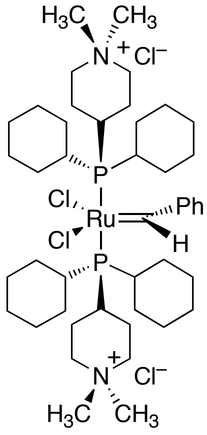
RCM in Methanol and Water



3-Ru



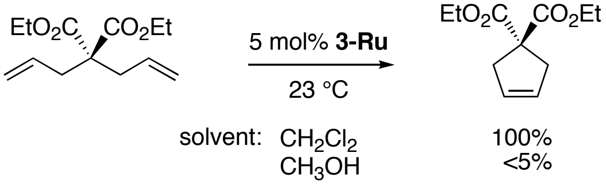
6-Ru



7-Ru

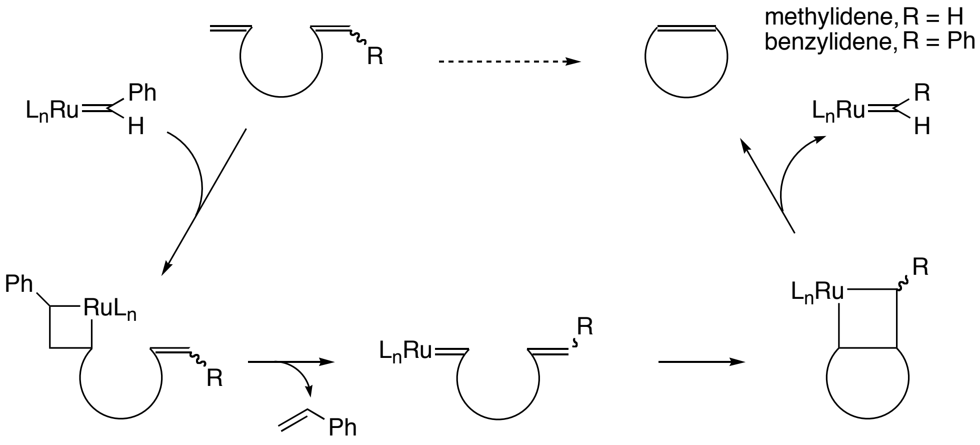
- Alkylidenes **6-Ru** and **7-Ru** are well-defined, water-soluble Ru-based metathesis catalysts that are stable for days in methanol or water at 45 °C.

- Although benzylidene **3-Ru** is highly active in RCM of dienes in organic solvents, it has no catalytic acitivity in protic media.

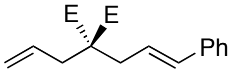
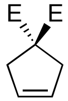
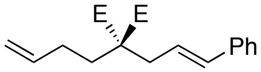
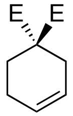
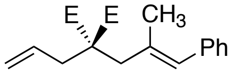
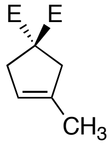
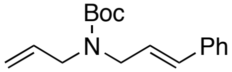
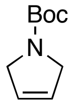
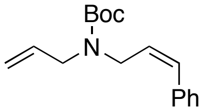
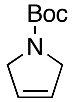
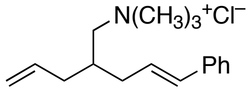
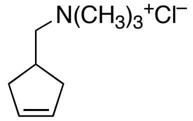


Stabilization of Ru-Carbene Intermediates by Phenyl Substitution

- first turnover step of RCM:



- Substitution of one of the two terminal olefins of the substrate with a phenyl group leads to regeneration of benzylidene catalyst, which is far more stable than the corresponding methylidene catalyst in methanol.

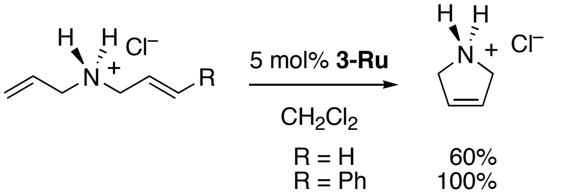
substrate[a]	product[b]	solvent	catalyst	conversion[c]
		methanol	**6-Ru** **7-Ru**	80 95
		methanol	**6-Ru** **7-Ru**	45[d] 55[d]
		methanol	**7-Ru**	>95
		methanol	**6-Ru** **7-Ru**	40 90[e]
		methanol	**6-Ru** **7-Ru**	30 >95[f]
		methanol water water	**7-Ru** **7-Ru** **7-Ru**	90 60 90[g]

[a] E = CO_2Et. [b] 5 mol% catalyst (**6-** or **7-Ru**), 0.37 M substrate, 45 °C. [c] Conversions were determined by ^1H NMR. [d] Substrate conc. = 0.1 M. [e] 30 h. [f] 2 h. [g] 10 mol% **7-Ru** used.

- Alkylidene **7-Ru** is a significantly more active catalyst than alkylidene **6-Ru** in these cyclizations; this higher reactivity is attributed to the more electron-rich phosphines in **7-Ru**.

- *Cis*-olefins are more reactive in RCM than the corresponding *trans*-olefins.

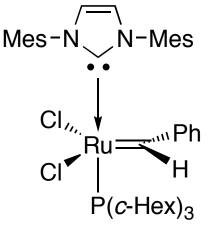
- Phenyl substitution within the starting material can also greatly increase the yield of RCM in organic solvents.



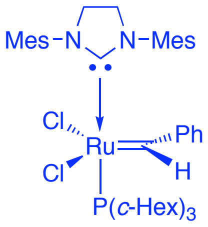
Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904–9909.

M. Movassaghi

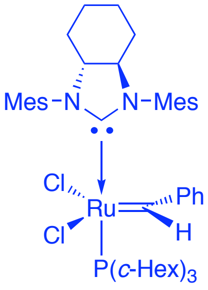
NHC Ruthenium Catalysts:



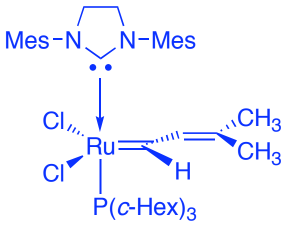
8-Ru



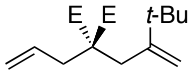
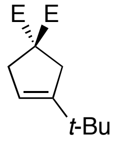
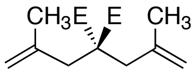
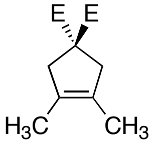
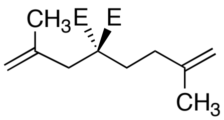
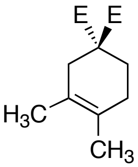
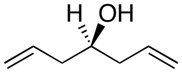
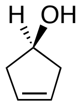
4-Ru



9-Ru



10-Ru

substrate[a]	product	time (h)	yield of product (%) using catalyst:[b]				
			1-Mo	**3-Ru**	**8-Ru**	**4-Ru**	**9-Ru**
		1	37	0	100	100	100
		24	93	0	40[c]	31	55
		1.5	52	0	95	90	87
		0.2	0	0	NA	100	100

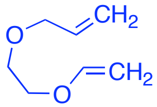
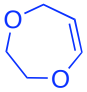
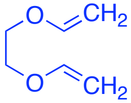
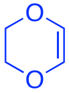
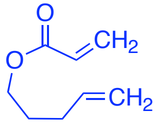
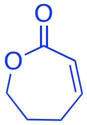
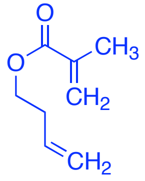
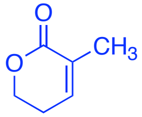
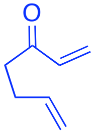
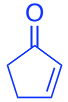
[a]E = CO_2Et. [b]5 mol% of catalyst, CD_2Cl_2, reflux. [c]1.5 h.

- Alkylidenes **4-** and **9-Ru** are the most reactive Ru-based catalysts.
- In the case of **4-** and **9-Ru** as little as 0.05 mol% is sufficient for efficient RCM.

Scholl, M.; Ding, S.; Lee, C.-W.; Grubbs, R. H. *Org. Lett.* **1999**,1, 953-956.
Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.

For the first Ru-based metathesis catalyst employing the Arduengo carbene ligand, see:
Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490–2493.

RCM of functionalized dienes

diene	product	yield (%)
		49
		0
		97
		86
		93

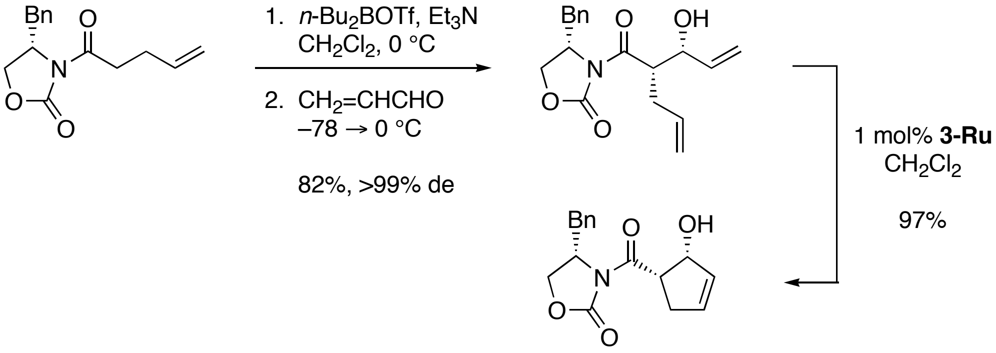
[a]Reactions conducted with 5 mol% **10-Ru**.

- Substrates containing both allyl and vinyl ethers provide RCM products while no RCM products are observed if vinyl ethers alone are present.
- α,β-Unsaturated lactones and enones of various ring sizes are produced in good to excellent yields.

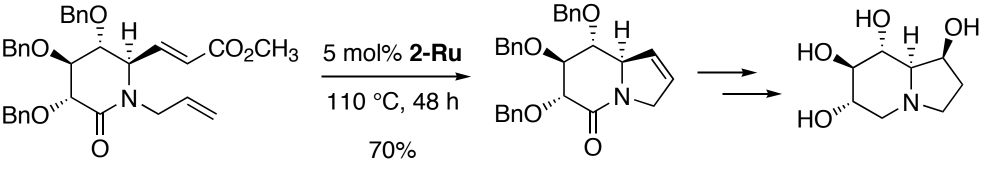
Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

M. Movassaghi

RCM Applications in Synthesis:



Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192–4193.

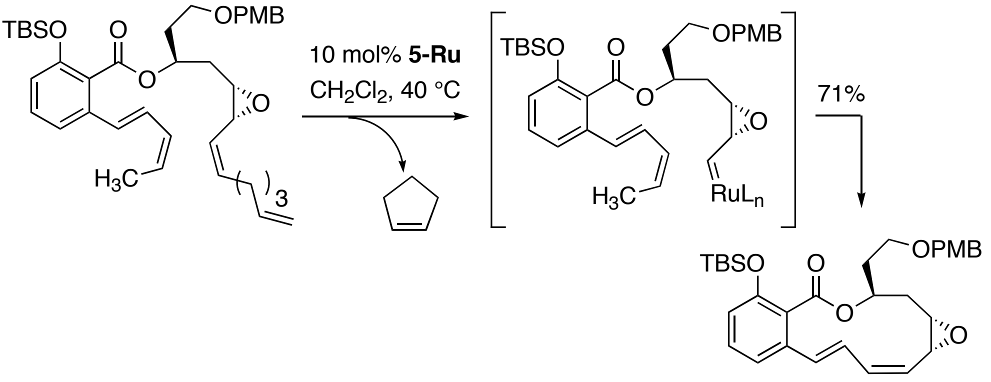


Castanospermine

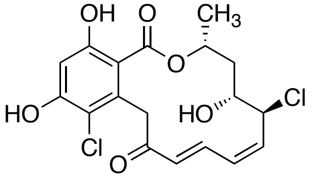
Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547–550.

- Particularly difficult cyclizations (due to steric congestion or electronic deactivation) can be achieved by **relay ring closing metathesis**, which initiates catalysis at an isolated terminal olefin. The reaction is driven by release of cyclopentene.

Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.

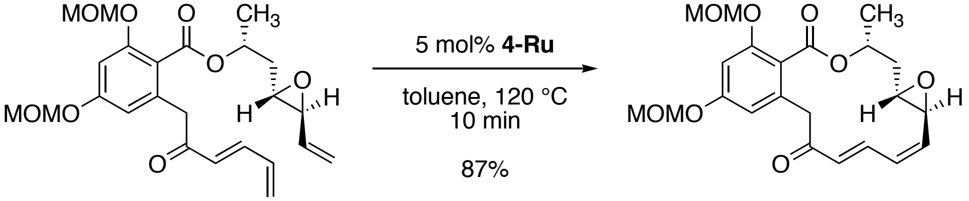


Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem. Int. Ed.* **2004**, *43*, 3601–3605.

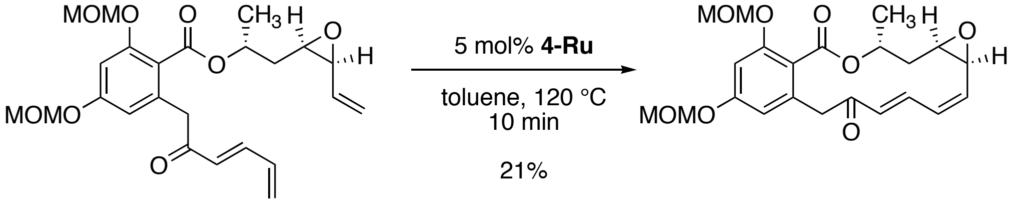


Pochonin C

trans epoxide

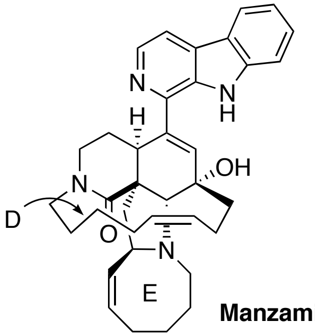


cis epoxide



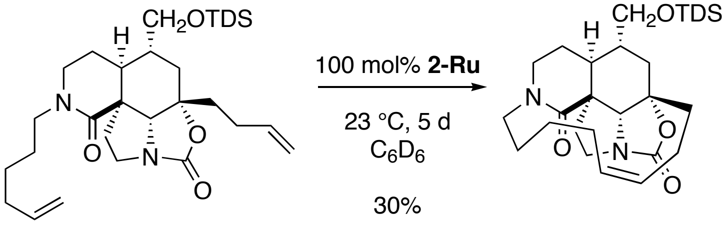
- Pre-organization of the substrate can have a dramatic effect upon the reaction efficiency.
- Both epoxide substrates produce macrocycles with good regioselectivity (i.e., the 14-membered ring rather than the 12-membered ring) and *E*/*Z* selectivity. However, the *trans* epoxide macrocycle is formed in a much higher yield.

Barluenga, S.; Lopez, P.; Moulin, E.; Winssinger, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 2367–2370.

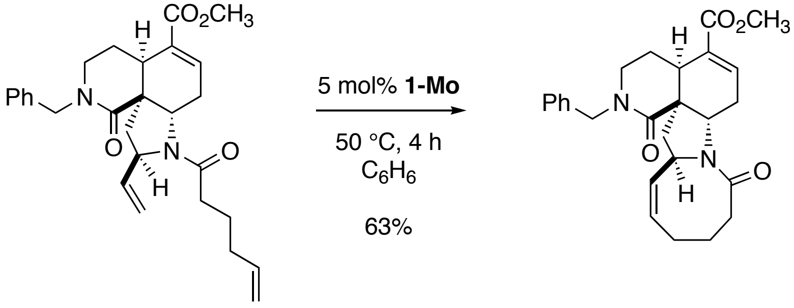


Manzamine A

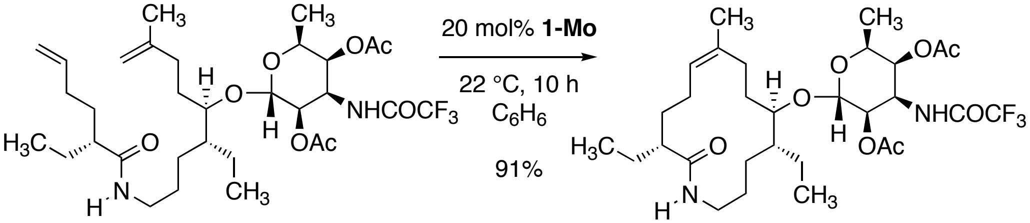
- The use of RCM in construction of both the D and the E rings of Manzamine A has been reported:



Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191–3194.



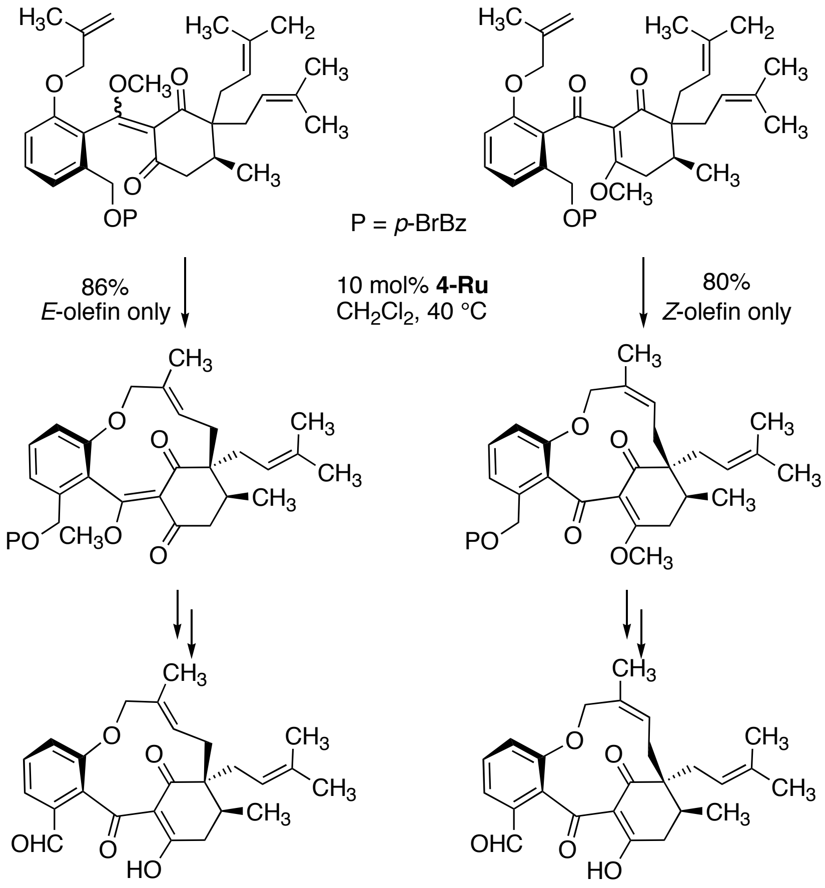
Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691–694.



- Before the advent of NHC ligands, **1-Mo** was used more frequently than the Ru catalysts for macrocyclization of trisubstituted olefins. The latter catalysts are typically less reactive with sterically hindered substrates.

Zhongmin, X.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.

Slight changes in substrate structure can control whether the *E*- or *Z*-olefin is formed:



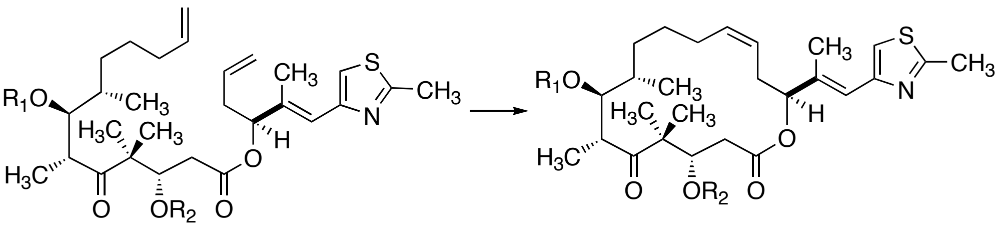
Coleophomone B

Coleophomone C

Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888.

Synthesis of Epothilone C:

- Small changes can drastically affect reaction outcome. In the example below, TBS protective groups changes the E/Z selectivity.



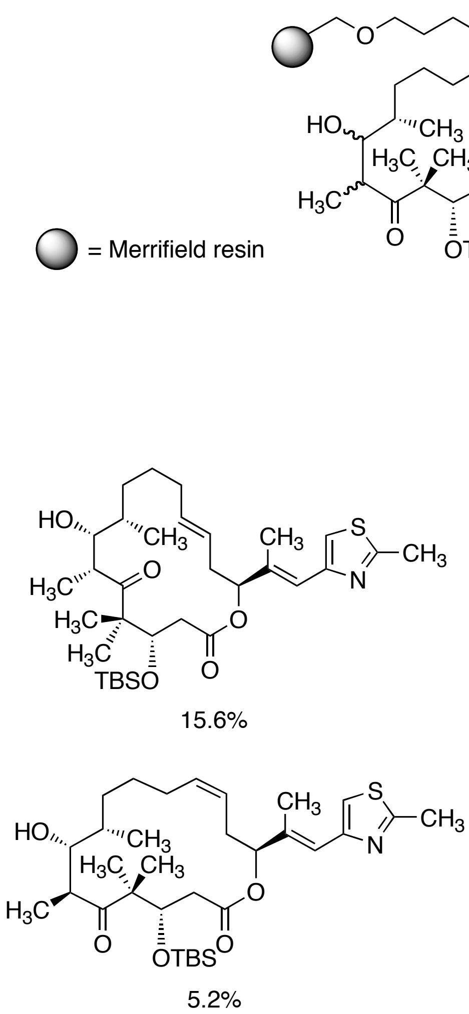
R$_1$	R$_2$	Catalyst	Conditions	Yield	*E/Z*
H	H	**1-Mo**	50 mol%, PhH, 55 °C	65 %	2 : 1
H	TBS	**3-Ru**	10 mol%, CH_2Cl_2, 25 °C	85%	1 : 1.2
TBS	TBS	**3-Ru**	6 mol%, CH_2Cl_2, 25 °C	94%	1 : 1.7
TBS	TBS	**1-Mo**	50 mol%, PhH, 55 °C	86%	1 : 1.7

Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973.

Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 11073–11092.

Schinzer, D.; Bauer, A.; Bohm, O. M.; Limberg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483–2491.

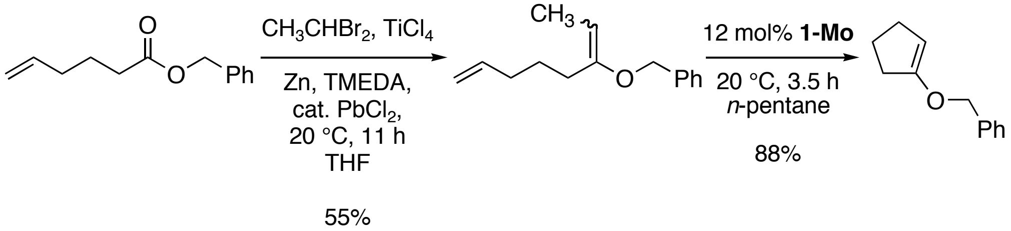
Solid-Phase Synthesis of Epothilone A:

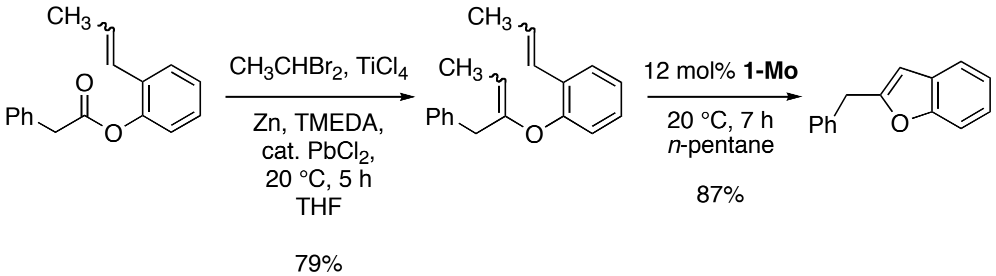


- The amount of alkylidene **3-Ru** (75%) used was greater than the total yield of product (52%), perhaps reflecting the generation of a resin-bound Ru intermediate.
- Addition of *n*-octene or ethylene has been documented to provide a catalytic cycle; see: Maarseveen, J. H.; Hartog, J. A. J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249.

Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268–272.

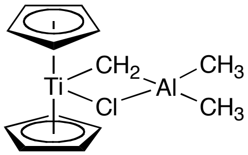
Catalytic RCM of Olefinic Enol Ethers:





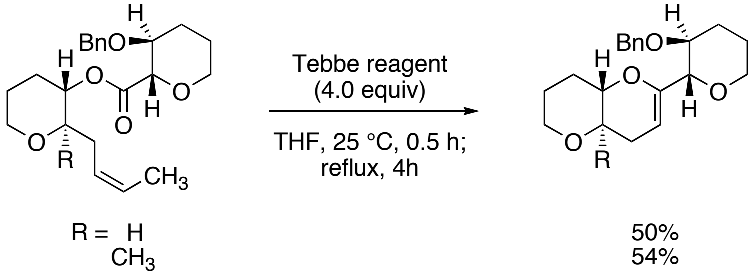
- Only catalyst **1-Mo** is effective for RCM of these substrates.

Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029–4031.



Tebbe reagent

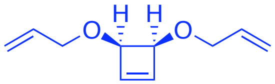
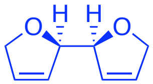
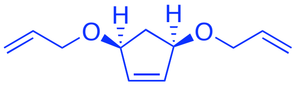
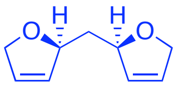
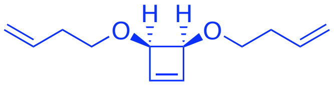
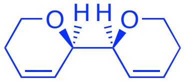
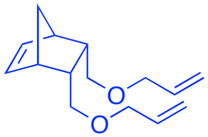
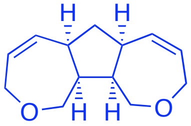
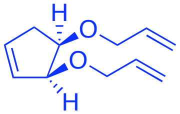
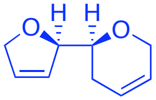
Tandem Olefination-Metathesis



- Here, a Ti-alkylidene is used in RCM.

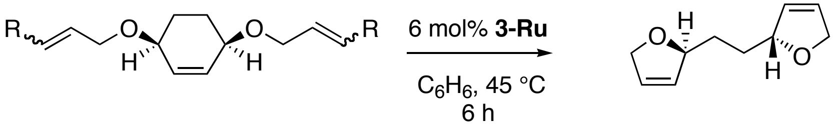
Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335-10336.

Tandem Ring Opening-Ring Closing Metathesis of Cyclic Olefins

substrate	product	yield (%)	catalyst **3-Ru** (mol %)	conc. (M)	time (h)	temp. (°C)
		82	3	0.1	1.5	45
		90	5	0.1	2	60
		70	3	0.07	6	45
		68	6	0.04	2	45
		92	5	0.04	3	60

- Without sufficient ring strain in the starting cyclic olefin, competing oligomerization (via CM) can occur.

- Higher dilution favors intramolecular reaction:

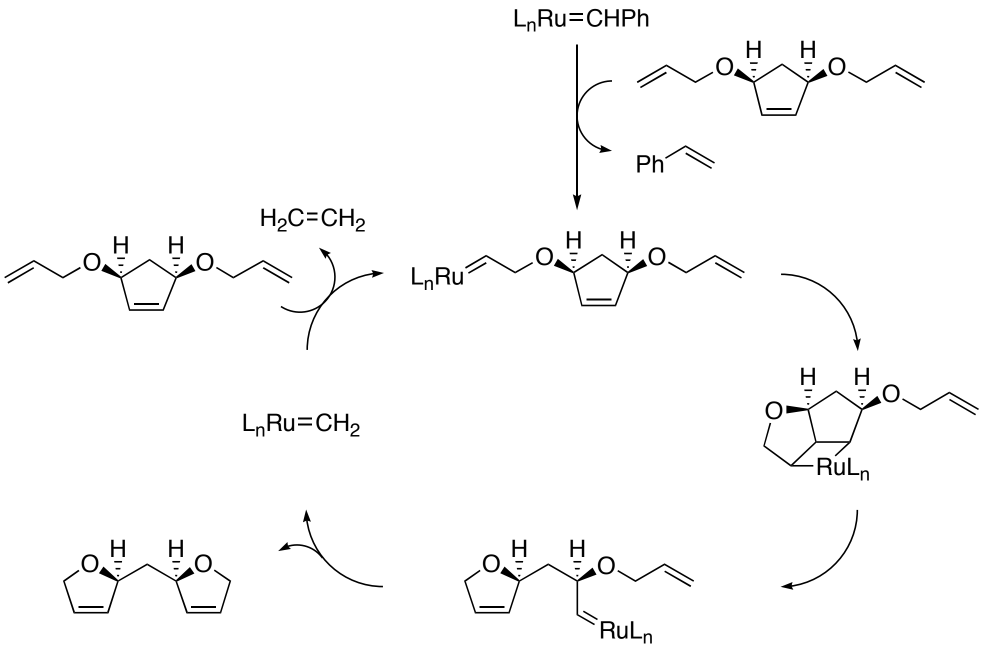


R = H	0.12 M	16%
H	0.008 M	73%
CH_3	0.2 M	42%

- The relative rate of intramolecular metathesis versus CM may be further increased by substitution of the acyclic olefin.

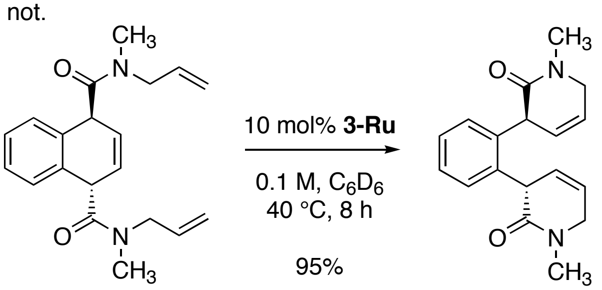
M. Movassaghi

Proposed Mechanism for Ring Opening-Ring Closing Metathesis:

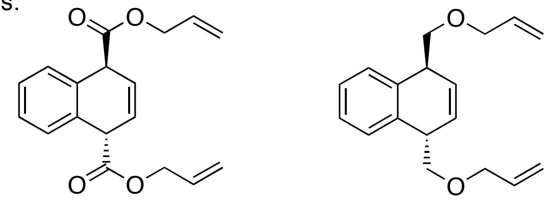


- Initial metathesis of the acyclic olefin is supported by the fact that substitution of this olefin decreases the rate of metathesis and by the beneficial effects of dilution upon the intramolecular manifold.

- Subtle conformational preferences within the substrate are key to the success of these transformations; as shown, *trans*-1,4-dihydronaphthalene diamide undergoes efficient ring opening-ring closing metathesis while the corresponding diester and diether derivatives do not.

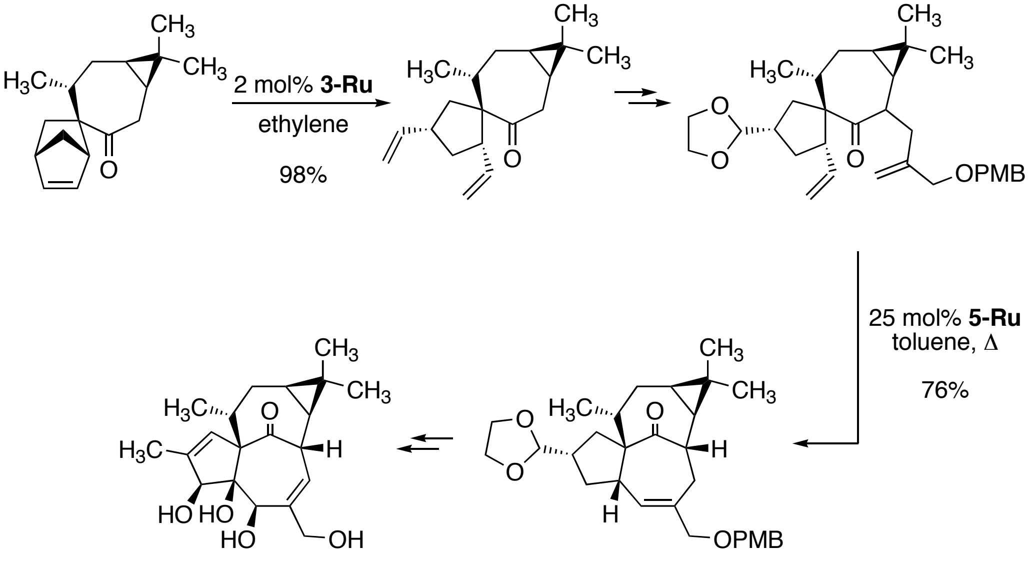


unreactive substrates:



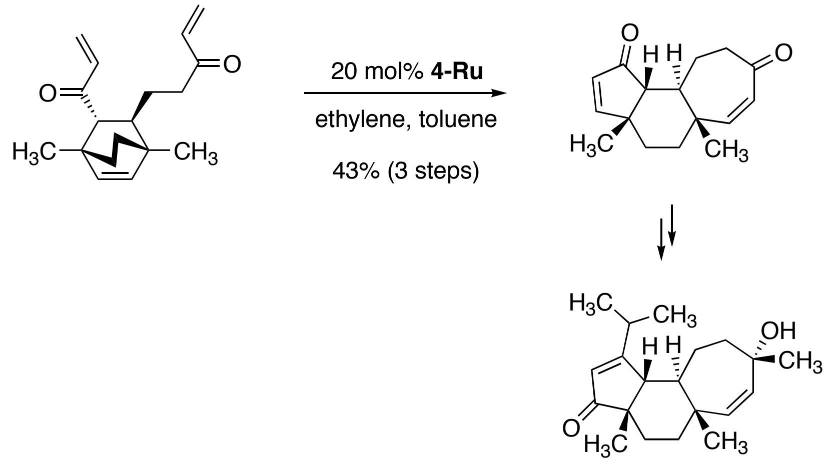
Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640.

Examples in Complex Synthesis:



Ingenol

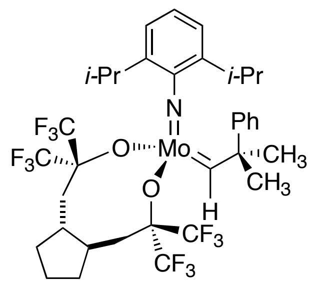
Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300–16301.



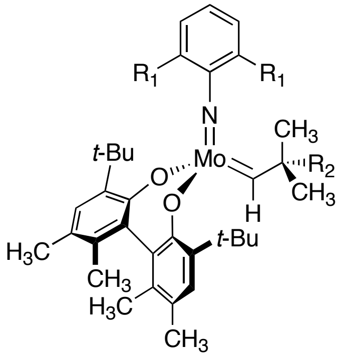
Cyanthiwigin U

Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334–5335.

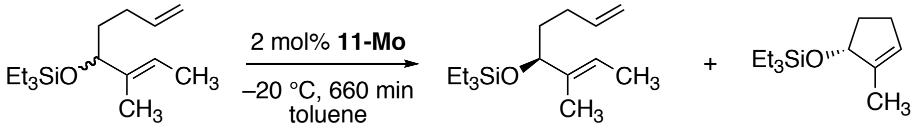
Kinetic Resolution via Asymmetric RCM



11-Mo



12-Mo: R_1 = *i*-Pr R_2 = Ph
13-Mo: R_1 = CH_3 R_2 = Ph
14-Mo: R_1 = Cl R_2 = Ph
15-Mo: R_1 = Cl R_2 = CH_3

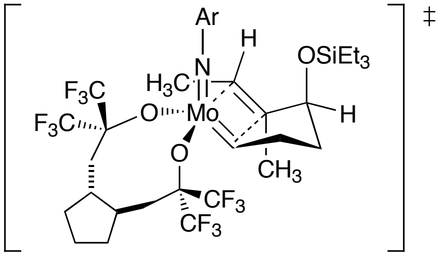


38%, 48% ee

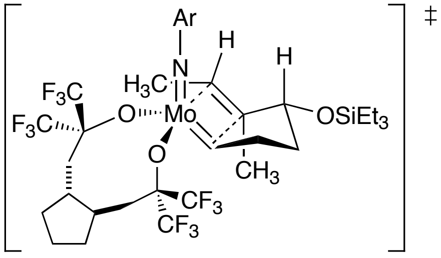
62%

- The first catalytic, asymmetric kinetic resolution via RCM was achieved, with low selectivity, using the chiral alkylidene **11-Mo**.

Proposed Transition State Models for the Observed Selectivity



DISFAVORED

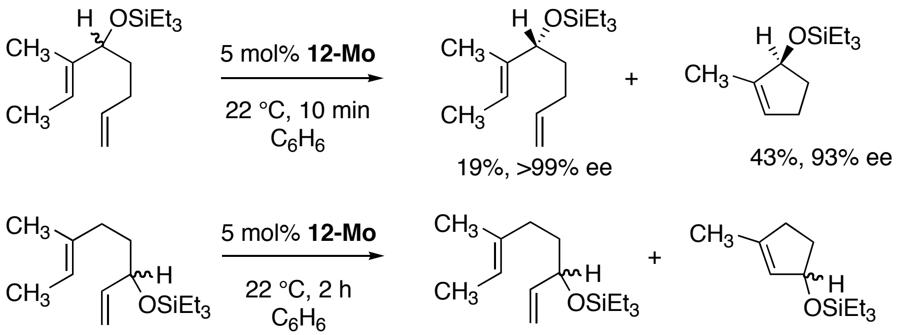


FAVORED

Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$

Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824–832.
Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499–2500.

Catalytic, Enantioselective RCM



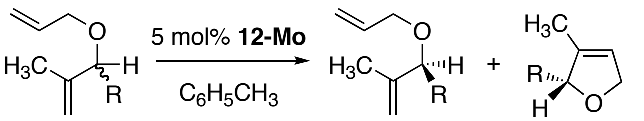
50%, <5% ee

40%, <5% ee

- Diastereodifferentiation occurs during formation or breakdown of the metallabicyclobutane intermediates and not during the initial metathesis step.

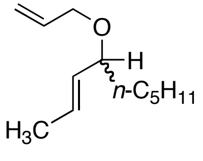
Alexander, J. B.; La, D. S.; Cefalo, D. R. Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.

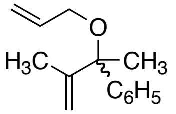
Mo-alkylidene Catalyzed Kinetic Resolution and Enantioselective Desymmetrization via RCM



R	temp. (°C)	time (h)	conv. (%)	recovered SM ee (%)	k_{rel}
n-C_5H_{11}	–25	6	63	92	10
i-C_4H_9	–25	10	56	95	23
c-C_6H_{11}	–25	7	62	98	17
c-C_6H_{11}	22	0.1	64	97	13
C_6H_5	–25	6	56	75	8

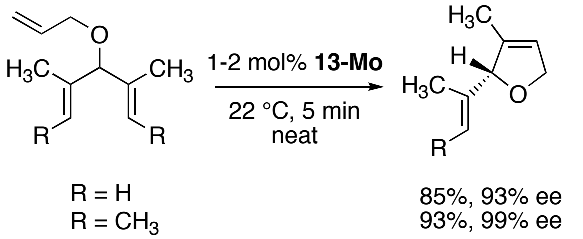
- Increasing the size of the α-substituent can lead to greater selectivity.
- 1,2-disubstituted alkenes and tertiary ethers are not effectively resolved by either alkylidene **12-Mo** or **13-Mo**.





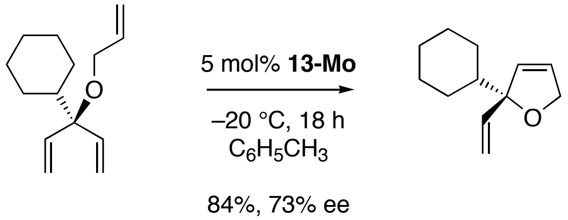
M. Movassaghi

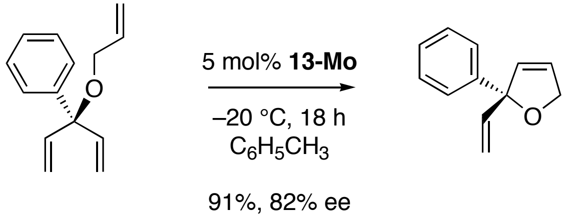
- The alkylidene catalysts **12-Mo** and **13-Mo** are very effective in catalytic, enantioselective desymmetrization processes, especially in the case of secondary allylic ethers.



- Remarkably, this catalytic, asymmetric RCM can be carried out in the absence of solvent, with <5% dimer formation.

- The catalytic, enantioselective desymmetrization of tertiary allylic ethers requires the use of alkylidene **13-Mo**.

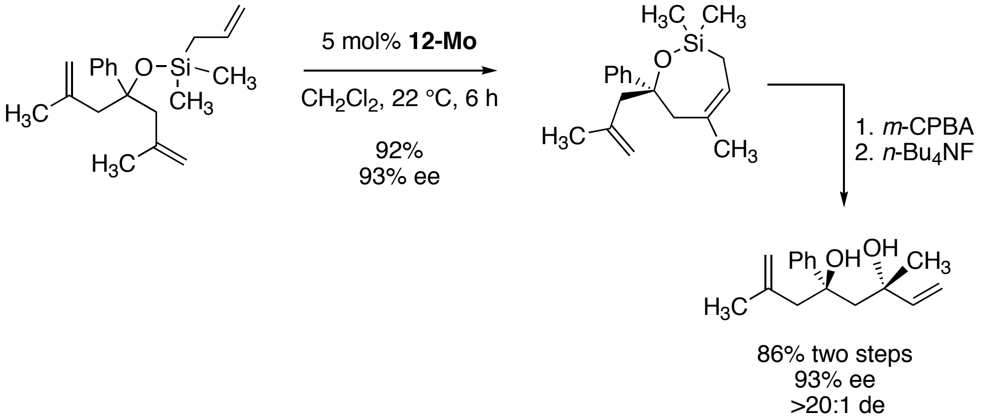




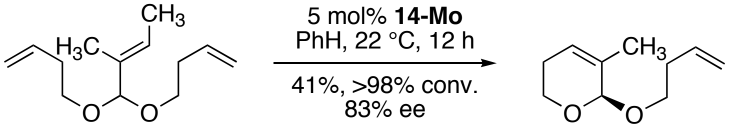
- It is believed that the stereodifferentiating step is the formation of the metallabicyclobutane intermediate; see: Alexander, J. B.; La, D. S.; Cefalo, D. R. Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.***1998**, *120*, 4041–4042.

La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720–9721.

- Desymmetrization metathesis reactions have been used to make a variety of heteroatom-containing products:

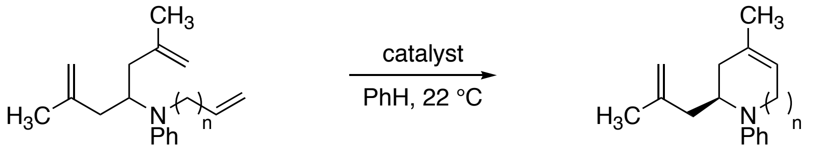


Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868.



- Only 29% ee was observed using **12-Mo**. **14-Mo** is the catalyst of choice for synthesizing non-racemic acetals.

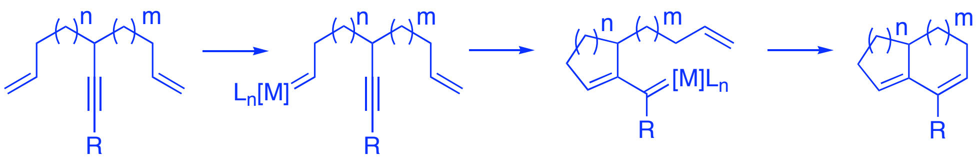
Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553-9559.



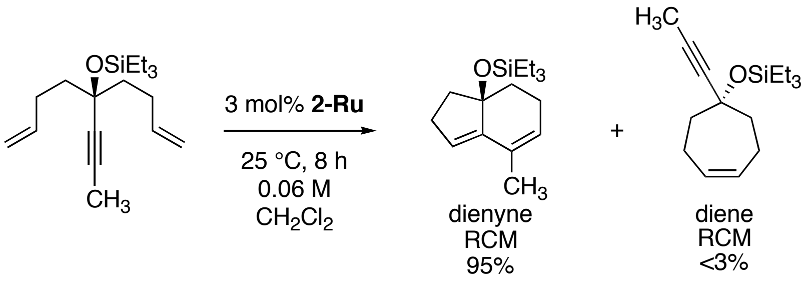
n	catalyst	%mol catalyst	time	yield	ee
1	**12-Mo**	5	20 min	78%	98%
2	**12-Mo**	2	7 h	90%	95%
3	**15-Mo**	5	20 min	93%	>98%

Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J Am. Chem. Soc.* **2002**, *124*, 6991–6997.

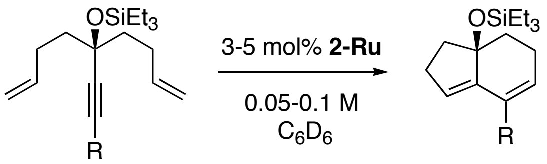
Catalytic RCM of Dienynes: Construction of Fused Bicyclic Rings



- Fused [5.6.0], [5.7.0], [6.6.0], and [6.7.0] bicyclic rings have been successfully constructed by RCM of dienynes.

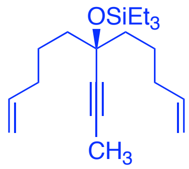
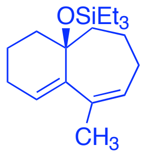
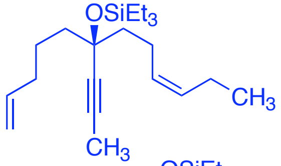
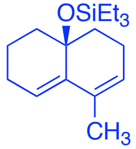
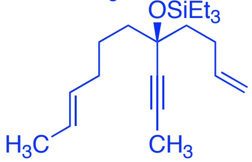
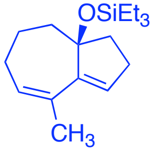
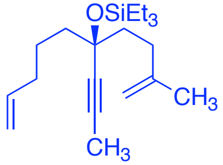
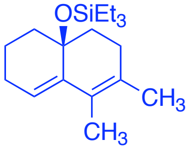
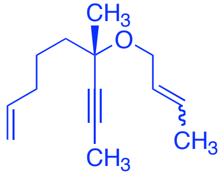
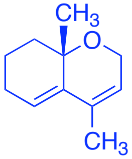


- The dienyne RCM is largely favored over the competing diene RCM.

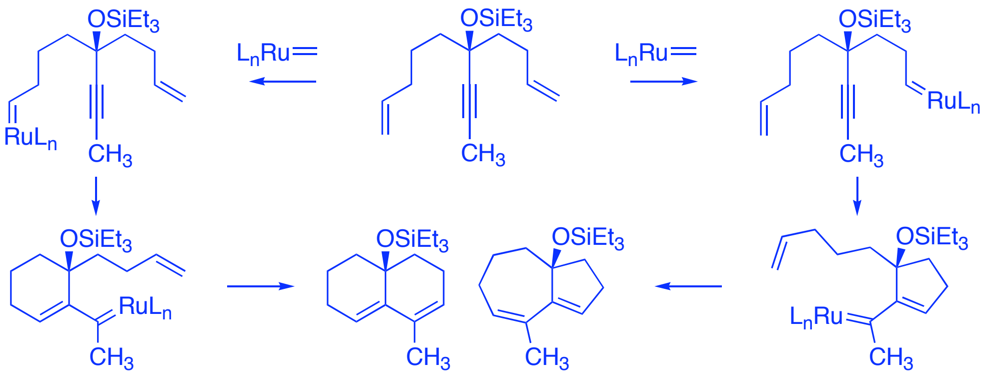


R	yield (%)	conditions
H	>98	23 °C, 15 min
CH_3	95	23 °C, 8 h
i-Pr	78	60 °C, 4 h
t-Bu	NR	
Ph	96	60 °C, 3 h
CO_2CH_3	82	60 °C, 4 h
$Si(CH_3)_3$	NR	
$Sn(n\text{-}Bu)_3$	NR	
Cl, Br, I	NR	

- Mo-, W- or Ti-based catalysts are not effective for the above transformations.
- Reaction rates decrease as the size of the acetylene substituent increases.
- Substrates containing heteroatoms directly attached to the acetylene do not cyclize.

substrate	product	yield (%)	mol% **2-Ru**	time (h)	conc. (M)	temp. (°C)
		88	6	8	0.06	65
		83	3	6	0.03	65
		78	15	1.5	0.01	100
		89	15	12	0.05	65
		88	3	6	0.05	65

- Regiochemical control within unsymmetrical substrates is achieved by substitution of the olefin required to undergo metathesis last.
- Unsymmetrical substrates containing equally reactive olefins produce a mixture of bicyclic products:

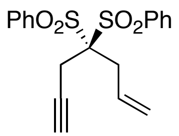
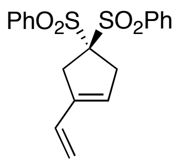
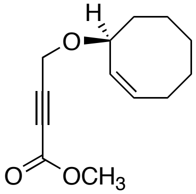
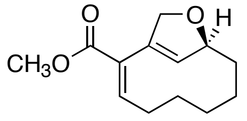
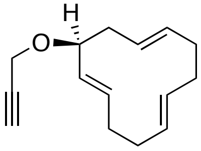
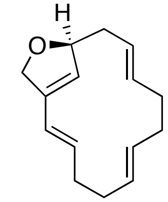
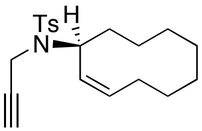
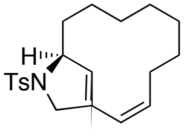


86%, 1:1

Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081.

M. Movassaghi

Enyne Metathesis Reactions Catalyzed by $PtCl_2$

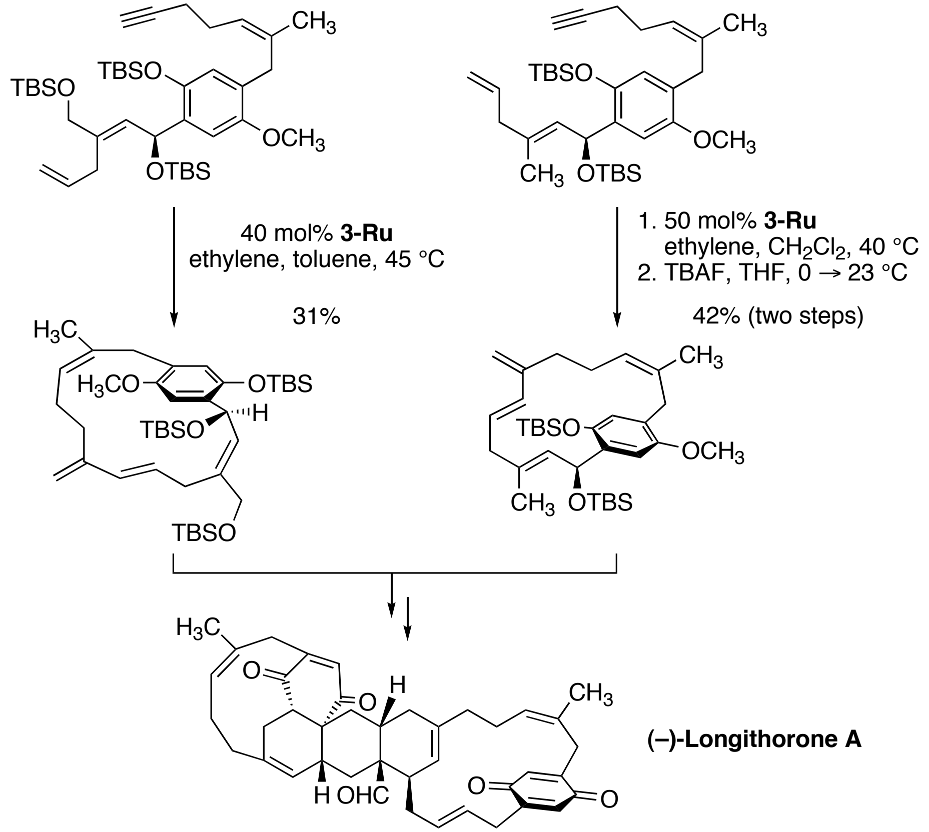
substrate	product	yield
		96%
		70%
		54%
		80%

[a]Reactions conducted in toluene at 80 °C using 4-10 mol% of $PtCl_2$

- In most cases commercial $PtCl_2$ was used as received.
- A cationic reaction pathway, involving the complexation of cationic Pt(II) with the alkyne, has been proposed.
- Remote alkenes are unaffected.

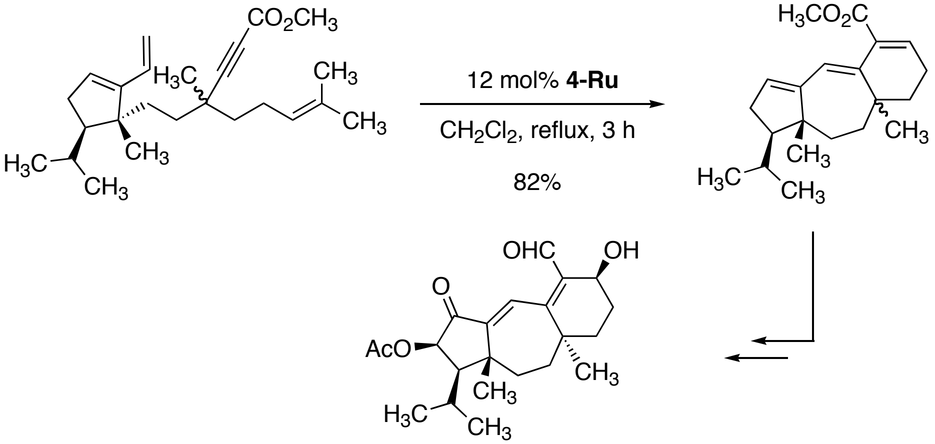
Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786.

Enyne Metathesis in Synthesis



(–)-Longithorone A

Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.



Guanacastepene A

Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817–1820.

Cross Metathesis

Olefin categorization and rules for selectivity

Type I – Rapid homodimerization, homodimers consumable

Type II – Slow homodimerization, homodimers sparingly consumable

Type III – No homodimerization

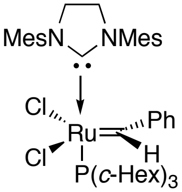
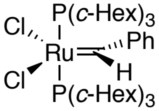
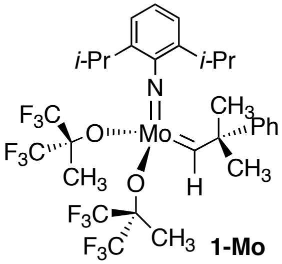
Type IV – Olefins inert to CM, but do not deactivate catalyst (spectator)

Reaction between two olefins of Type I.................................... Statistical CM

Reaction between two olefins of same type (non-Type I)........ Non-selective CM

Reaction beween olefins of two different types........................ Selective CM

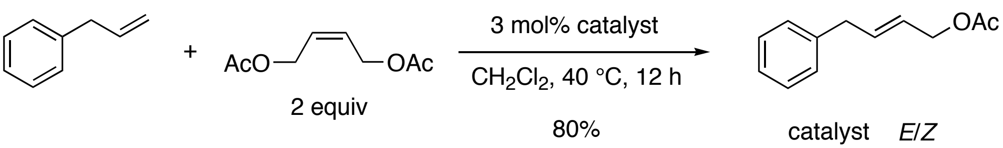
Selective Cross-Metathesis Reactions as a Function of Catalyst Structure:

Olefin type	 **4-Ru**	 **3-Ru**	 **1-Mo**
Type I (fast homodimerization)	terminal olefins, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (no large ortho substit.), allyl phosphonates, allyl silanes, allyl phosphine oxides, allyl sulfides, protected allyl amines	terminal olefins, allyl silanes, 1° allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	terminal olefins, allyl silanes
Type II (slow homodimerization)	styrenes (large ortho substit.), acrylates, acrylamides, acrylic acid, acrolein, vinyl keones, unprotected 3° allylic alcohols, vinyl epoxides, 2° allylic alcohols, perfluoalkyl substituted olefins	styrene, 2° allylic alcohols, vinyl dioxolanes, vinyl boronates	styrene, allyl stannanes
Type III (no homodimerization)	1,1-disubstituted olefins, non-bulky trisub. olefins, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes	3° allyl amines, acrylonitrile
Type IV (spectators to CM)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)	1,1-disubstituted olefins, disub a,b-unsaturated carbonyls, 4° allylic carbon-containing olefins, perfluorinated alkane olefins, 3° allyl amines (protected)	1,1-disubstituted olefins

Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

L. Blasdel

Non-selective Cross Metathesis: Two Type I Olefins

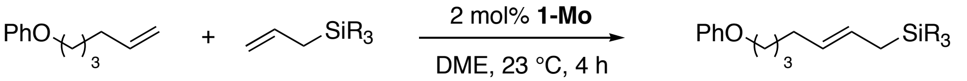


catalyst	*E*/*Z*
3-Ru	3.2 : 1
4-Ru	7 : 1

- The difference in *E*/*Z* ratios reflects the enhanced activity of **4-Ru** relative to **3-Ru**. Because it is more active, **4-Ru** can catalyze secondary metathesis of the product, allowing equilibration of the olefin to the more thermodynamically stable *trans* isomer.

Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

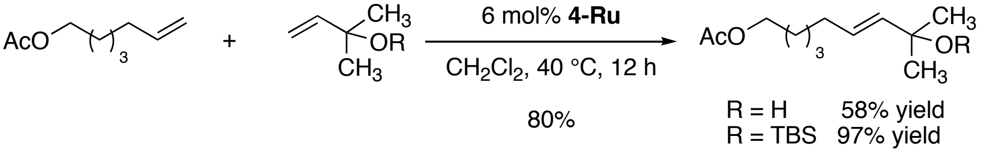
- Selectivity for the *trans* olefin can also be enhanced using sterically hindered substrates:



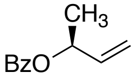
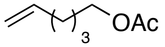
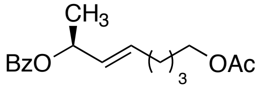
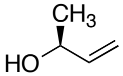
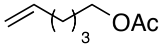
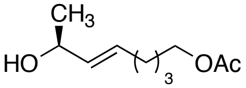
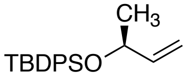
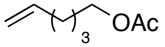
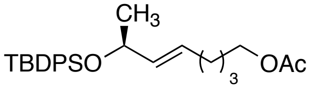
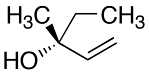
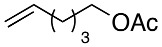
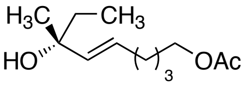
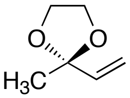
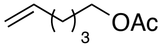
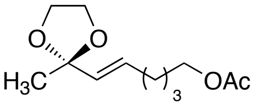
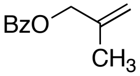
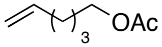
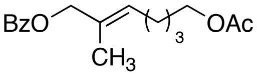
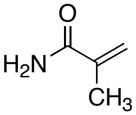
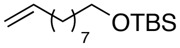
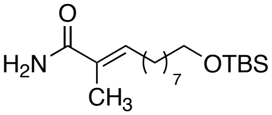
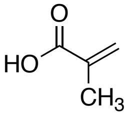
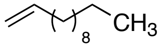
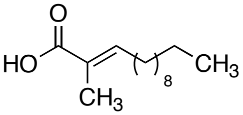
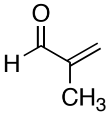
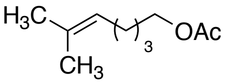
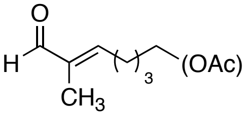
R	Yield	*E*/*Z*
CH_3	72%	2.6 : 1
Ph	77%	7.6 : 1

Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117–2120.

- In addition, steric bulk can assist in favoring the cross metathesis reaction over homodimerization pathways.
- The lower yield obtained with the unprotected alcohol is a result of homodimerization of the tertiary allylic alcohol. Subjecting this dimer to the reaction conditions results in no CM product, indicating that the dimer cannot undergo a secondary metathesis reaction.



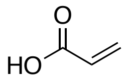
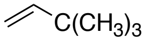
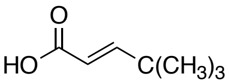
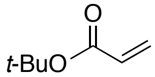
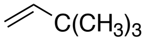
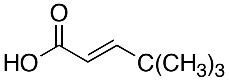
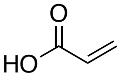
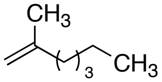
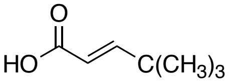
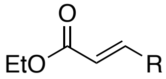
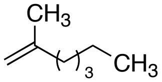
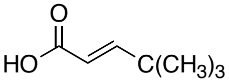
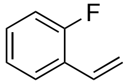
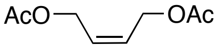
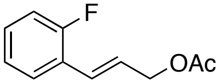
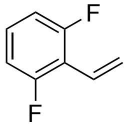
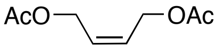
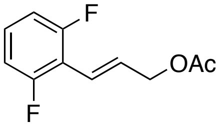
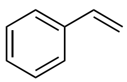
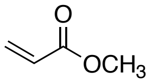
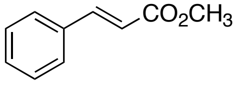
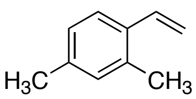
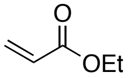
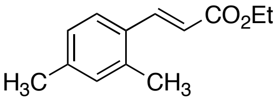
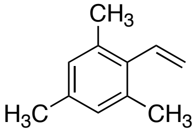
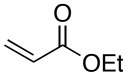
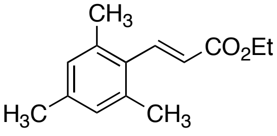
Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Olefin 1	Olefin 2	product[a,b]	Isolated Yield (%)	*E*/*Z*
Secondary allylic alcohols (Type I with Type II)				
	 2.0 equiv		82	10 : 1
	 1.0 equiv		50[c] (62)[d]	14 : 1
	 2.0 equiv		53	6.7 : 1
Quaternary allylic olefins (Type I with Type III)				
 2.0 equiv			93	>20 : 1
 1.0 equiv			91	>20 : 1
1,1-Disubstituted olefins (Type I with Type III)				
	 2.0 equiv		80	4 : 1
	 1.2 equiv		71	> 20 : 1
	 1.1 equiv		23	4 : 1
	 1.0 equiv		97	> 20 : 1

[a] 3–5 mol% **4-Ru**, CH_2Cl_2, 40 °C. [b] See last reference on left half of this page.

[c] With 2 equiv Olefin 2, the yield was 92%. [d] Reaction was performed at 23 °C.

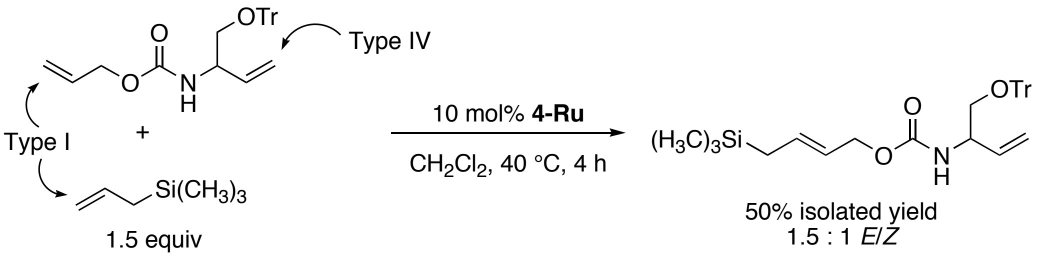
L. Blasdel

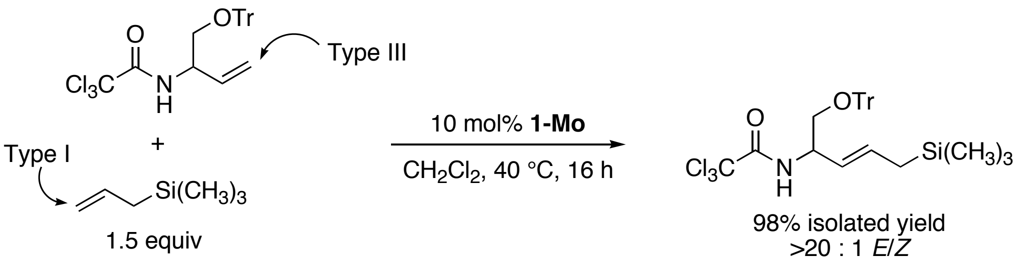
Olefin 1	Olefin 2	product[a]	Isolated Yield (%)	*E*/*Z*
Type II and Type III				
	 neat		73	
	 neat		73	
	 4.0 equiv		83	2 : 1
	 4.0 equiv		55 R = H 83 R = CH_3	2 : 1 2 : 1
	 2.0 equiv		98	>20 : 1
	 2.0 equiv		50	>20 : 1
	 1.5–2.0 equiv		92	>20 : 1
	 1.5–2.0 equiv		87	>20 : 1
	 1.5–2.0 equiv		5	>20 : 1

[a] 1–5 mol% **4-Ru**, CH_2Cl_2, 40 °C.

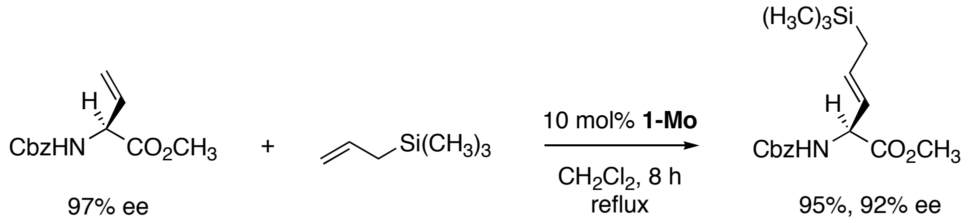
Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Selective Cross-Metathesis Reactions:

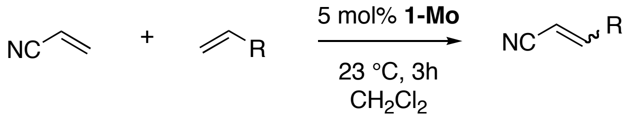




Brümmer, O; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441–446.



Brümmer, O; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441–446.



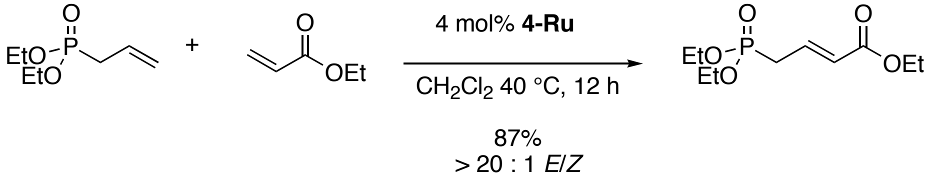
R	yield (%)	*E*:*Z*
$CH_2Si(CH_3)_3$	76	1:3
$(CH_2)_3OBn$	60	1:7.6
$(CH_2)_2CO_2Bn$	44	1:5.6

- The basis for the high *cis*-selectivity with acrylonitrile as substrate is not known.

Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162–5163.

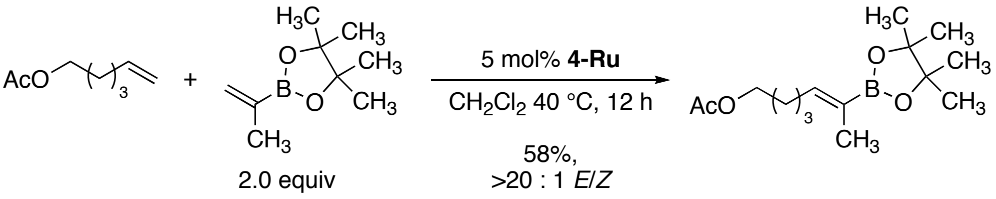
Reagent preparation

A Horner–Wadsworth–Emmons reagent:



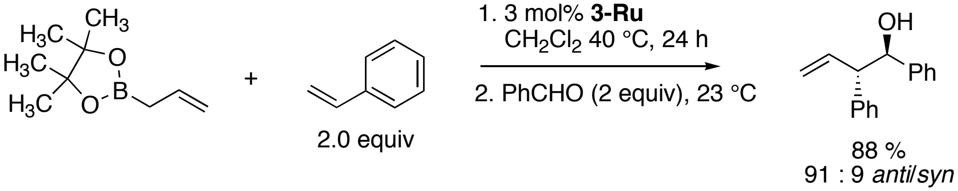
Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7–10.

A Suzuki reagent:



Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733–7736.

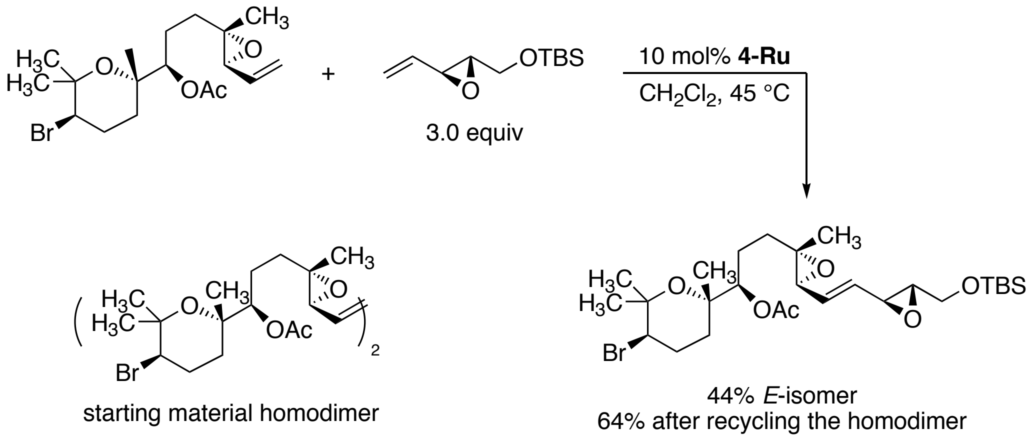
One-pot CM and allylboration reactions:



Yamamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128–130.

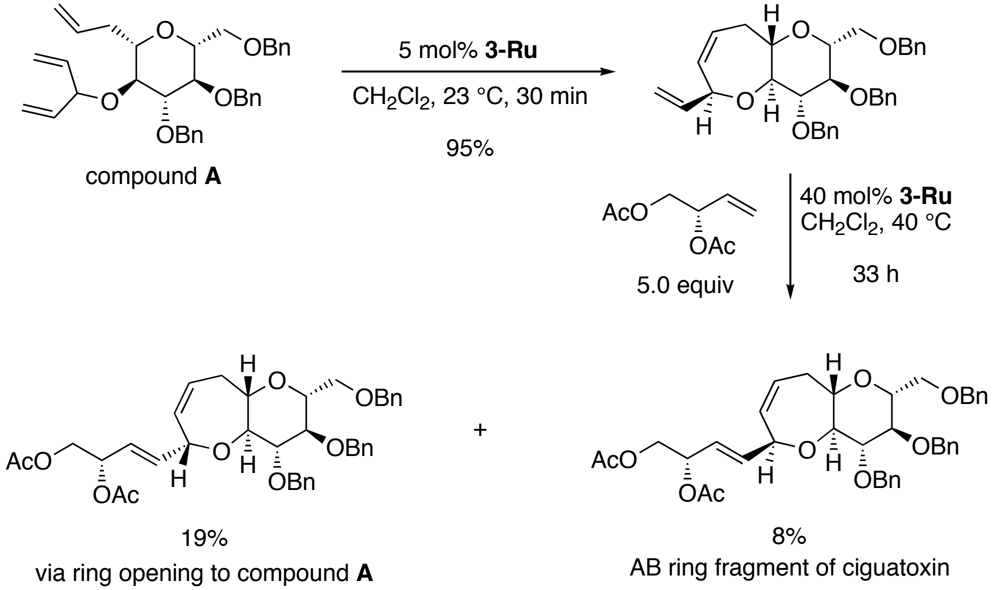
Examples in synthesis

- En route to the ABS ring fragment of thyrsiferol:



McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593–595.

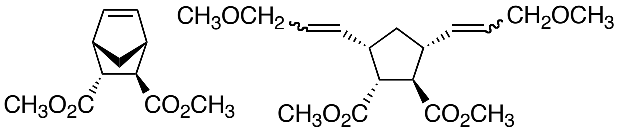
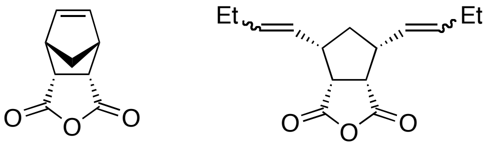
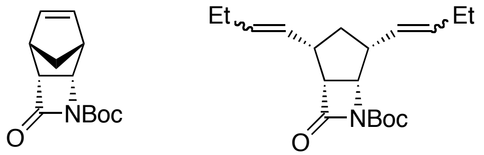
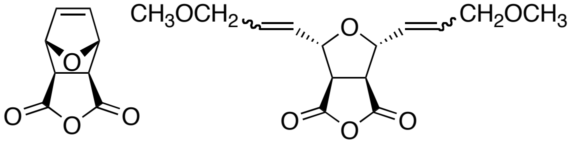
- CM can be difficult in the presence of strained olefins, as was found in the preparation of the AB ring fragment of ciguatoxin:



Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405–5408.

L. Blasdel

Ring Opening Cross-Metathesis:

substrate	product	alkene[a]	mol % cat.[b]	time	yield	*E*,*E*:*E*,*Z*
		A	6	96	94	2:1
		B	2	14	85	2:1
		C	8[c]	3	73	1.5:1
		A	2	89	15	NA

[a] 25 °C; 1.5 Equivalents of alkene used: A = *trans*-1,4-dimethoxybut-2-ene; B = *trans*-hex-3-ene; C = *cis*-hex-3-ene. Solvent: C_6H_6 (entries 1 and 2) or CH_2Cl_2 (entries 3 and 4). [b]Cat. = **2-Ru**. [c] Cat. = **3-Ru**.

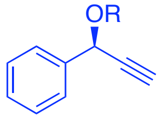
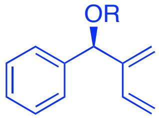
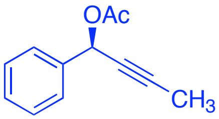
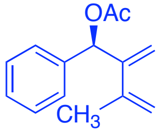
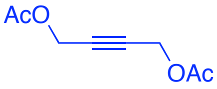
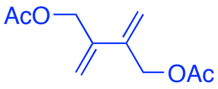
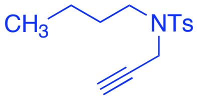
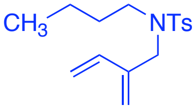
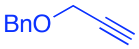
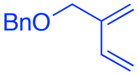
- In these cases a preference for the *E*-olefin geometry is observed in ring opening metathesis.
- Higher yields were achieved by the slow addition of the cyclic alkene to a solution of the 1,2-disubstituted alkene.
- Faster and more efficient ring opening cross metathesis was observed using *cis*-hex-3-ene vs. *trans*-hex-3-ene.

Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411-412.

Enantioselective ROM–CM reactions have been described: La, D. S.; Ford, J. F.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603–11604.

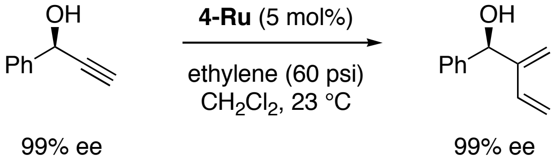
Enyne Cross-Metathesis

- **4-Ru** outperforms **3-Ru** in both rate and overall conversion in the cross-metathesis of ethylene and alkynes.

substrate	product		time (h)	yield (%)
		R = H R = Ac R = TBS	2.0 2.0 8.5	73 92 91
			16	77
			4.0	69
			4.0	91
			6.0	72

[a]Reactions conducted in CH_2Cl_2 at 23 °C using 5 mol% of **4-Ru** at 60 psi of ethylene pressure.

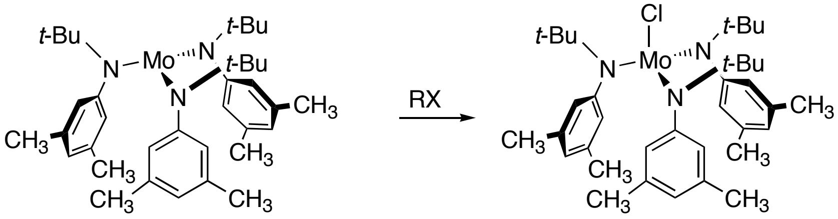
- Reactions conducted at 1 atm of ethylene pressure typically gave low conversions even after extended reaction times.
- The more reactive imidazolylidene **4-Ru** can tolerate free hydroxyl groups and coordinatingfunctionality at the propargylic and homopropargylic positions.
- Chiral propargylic alcohols afford chiral diene products without loss of optical purity:



Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271–2274.

Metathesis of Alkynes and Diynes

- Inspired by the activation of the triple bond of molecular nitrogen with molybdenum complexes of the general type Mo[N(t-Bu)Ar]$_3$ (see: Laplaza, C. E.; Cummins, C. C. *Science*, **1995**, *268*, 861), the reactivity of this class of molybdenum catalysts toward alkynes was explored.

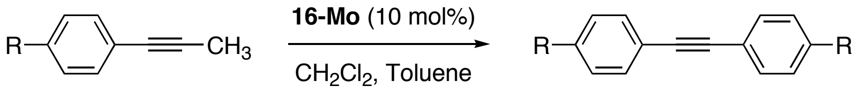


16-Mo

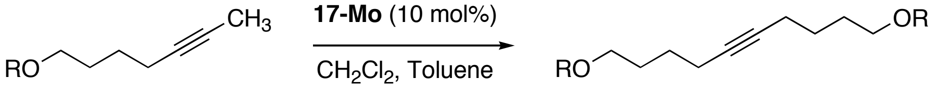
17-Mo, X = Cl
18-Mo, X = Br

- Oxidation of the Mo(III)-precatalyst **16-Mo** occurs in situ upon addition of ~25 equivalents of additives such as CH_2Cl_2, CH_2Br_2, CH_2I_2, and BnCl.

- Alkyne metathesis may be achieved with equal efficiency either by in situ oxidation of precatalyst **16-Mo** or by use of pure Mo(IV)-catalysts **17-Mo** and **18-Mo**.



R = H, 60%
R = CN, 58%



R = CH_3, 59%
R = THP, 55%

- Catalyst **17-Mo** is sensitive to acidic protons such as those of secondary amides.

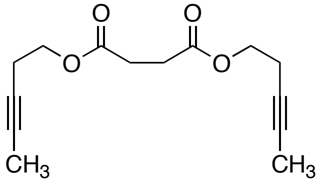
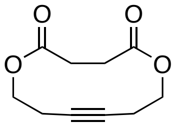
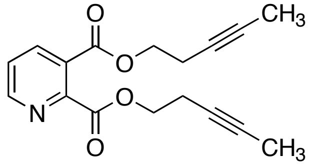
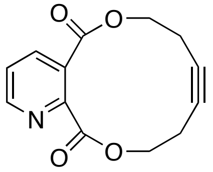
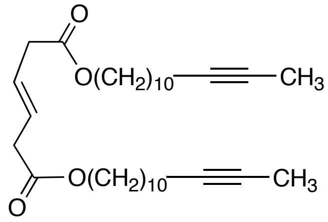
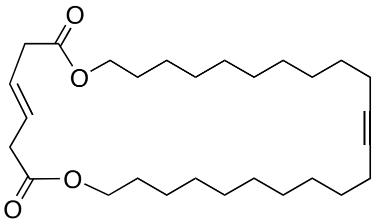
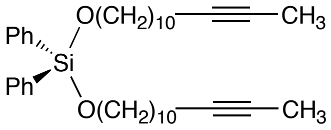
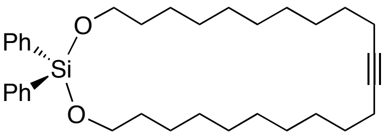
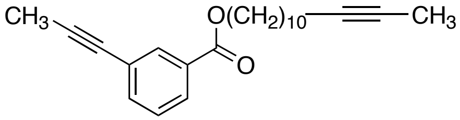
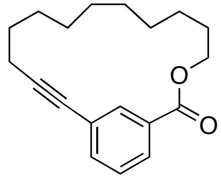
- Terminal alkynes are incompatible with the catalysts.

- Use of CH_2Cl_2 as the reaction solvent or the addition of ~25 equivalents of CH_2Cl_2 per mol of **16-Mo** in toluene are equally effective.

- Catalysts **17-Mo** and **18-Mo** tolerate functional groups such as esters, amides, thioethers, basic nitrogen atoms, and polyether chains, many of which are incompatible with the tungsten alkylidyne catalysts previously used.

RCM of Diynes

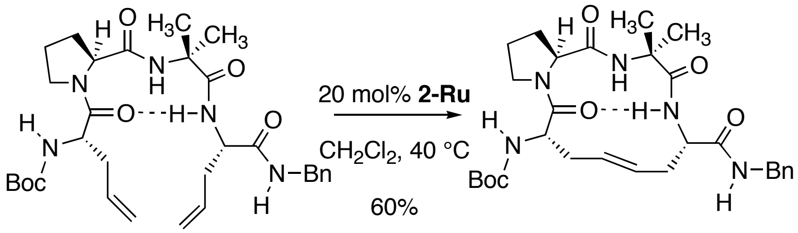
- Efficient synthesis of ≥12-membered rings containing internal alkynes can be achieved with **17-Mo**.

substrate	product[a]	yield (%)
		91
		88
		82
		74
		83

[a] Reactions conducted in toluene at 80 °C for 20-48h; **17-Mo** was generated in situ from **16-Mo** and CH_2Cl_2 (~25 equiv).

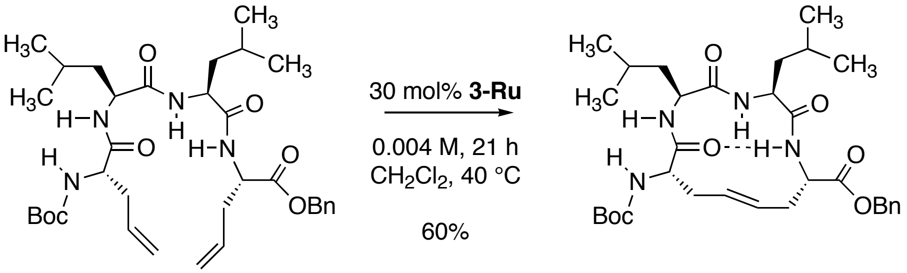
Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453–9454.

Synthesis of Cyclic β-Turn Analogs by RCM



- The presence of the Pro-Aib sequence in the tetrapeptide induces a β-turn conformation which was covalently captured by RCM, yielding a 14-membered macrocycle.

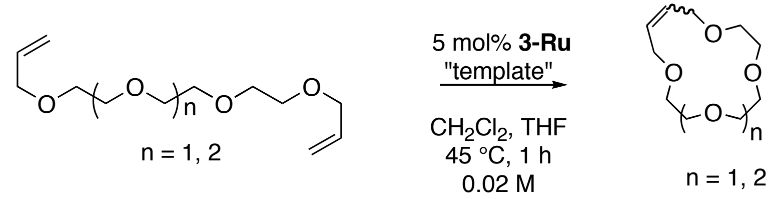
Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855-5856.



- Although interactions that increase the rigidity of the substrate and reduce the entropic cost of cyclization can be beneficial in RCM, it is not a strict requirement for macrocyclization byRCM.

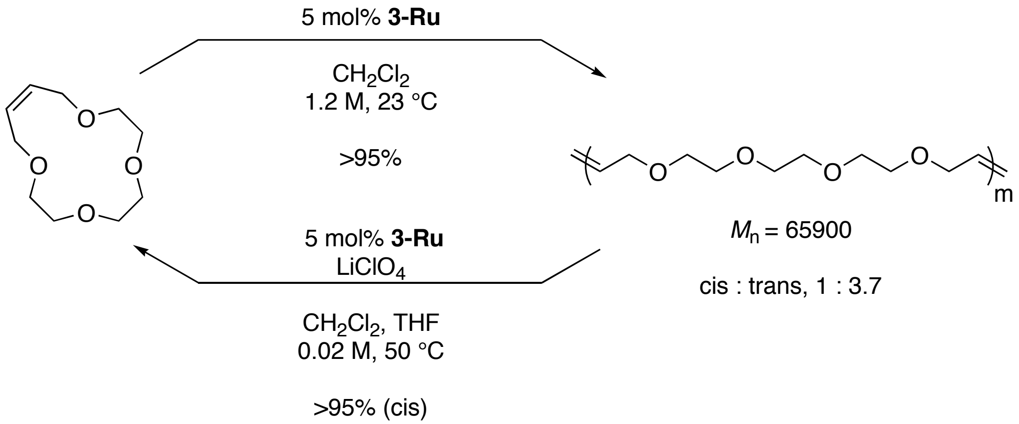
Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614.

Template-Directed RCM



substrate (n)	"template" (equiv)	yield (%)	cis:trans
1	none	39	38:62
1	$LiClO_4$ (5)	>95	100:0
1	$NaClO_4$ (5)	42	62:38
2	none	57	26:74
2	$LiClO_4$ (5)	89	61:39

- Preorganization of the linear polyether about a complementary metal ion can enhance RCM.
- In general, ions that function best as templates also favor the formation of the cis isomer.

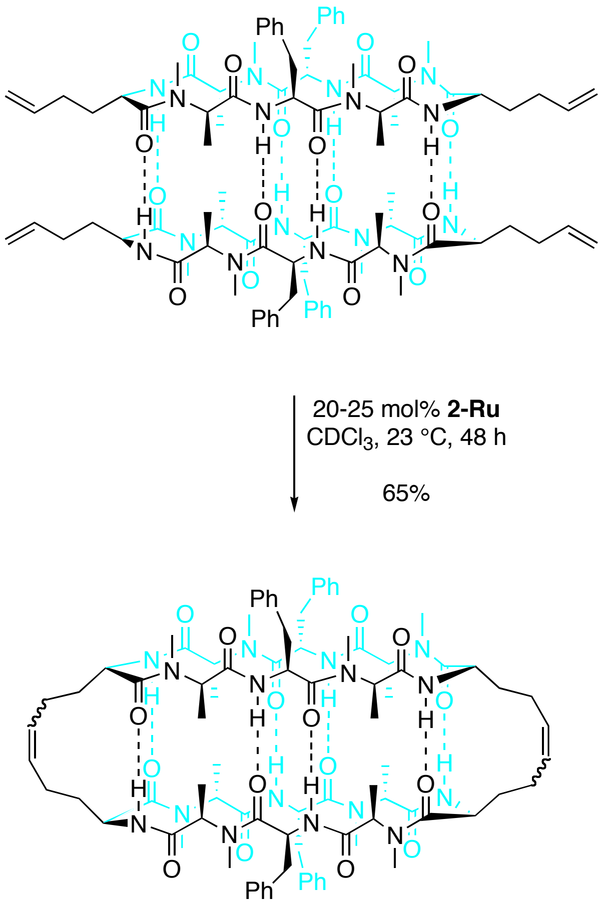


- Polymer degradation in the absence of a Li^+ template produced the corresponding crown ether as a mixture of *cis*- and *trans*-olefins (20% combined yield) along with other low molecular weight polymers.

Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101–1103.

RCM-Mediated Covalent Capture

- The eight-residue cyclic peptide cyclo[-(L-Phe-D-^{Me}N-Ala-L-HomoallylGly-D-^{Me}N-Ala)$_2$-] self-assembles to form two slow-exchanging antiparallel β-sheet-like hydrogen bonded cylinders (K_a(CDCl$_3$) = 99 M^{-1}, only the reactive isomer is shown).



20-25 mol% **2-Ru**
CDCl$_3$, 23 °C, 48 h

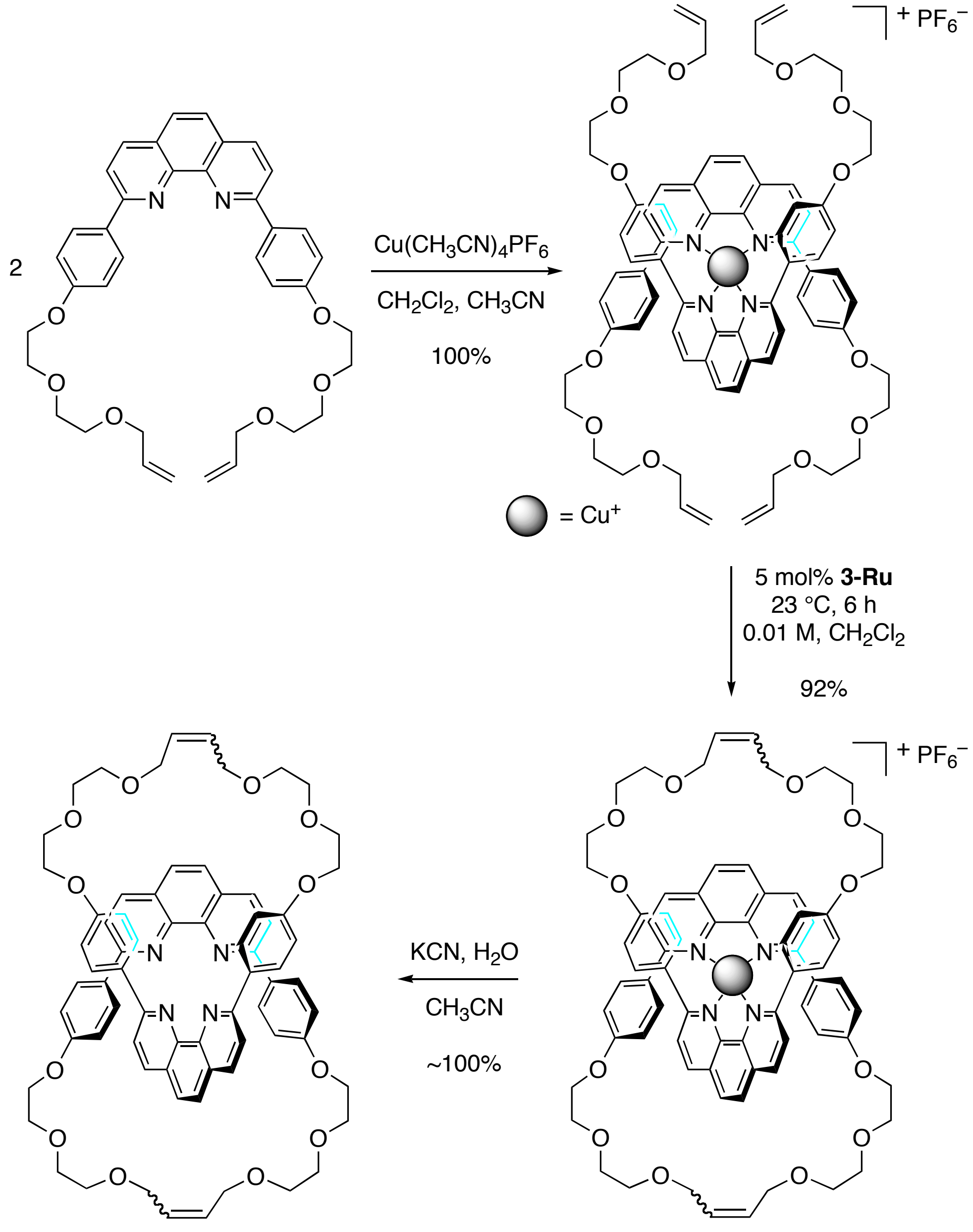
65%

- The hydrogen-bonded ensemble positions the terminal olefins of the four L-homoallylglycine residues in sufficiently close proximity that each pair undergoes RCM in the presence of alkylidene **2-Ru** to give a tricyclic cylindrical product containing a 38-membered ring as a mixture of three (cis-cis, cis-trans, trans-trans) olefin isomers.

- This covalent capture strategy may be useful in stabilizing kinetically labile α-helical and β-sheet peptide secondary structures.

Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364–12365.

Synthesis of Catenanes



Cu(CH$_3$CN)$_4$PF$_6$
CH$_2$Cl$_2$, CH$_3$CN
100%

5 mol% **3-Ru**
23 °C, 6 h
0.01 M, CH$_2$Cl$_2$
92%

KCN, H$_2$O
CH$_3$CN
~100%

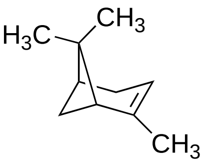
32-membered catenane

trans:cis, 98:2

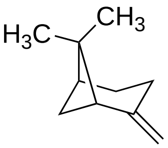
- The remarkable efficiency of this RCM is proposed to be due to preorganization of the substrate.

Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308–1310.

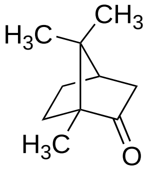
Common Terpenes and Chiral Pool Molecules



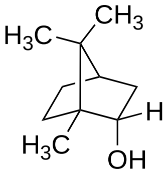
(+)-α-pinene



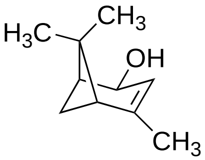
(–)-β-pinene



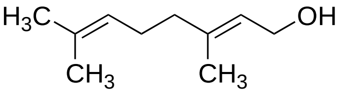
(1*R*)-(+)-camphor



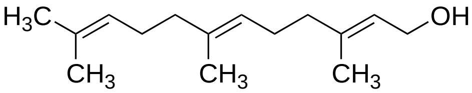
(+)-borneol



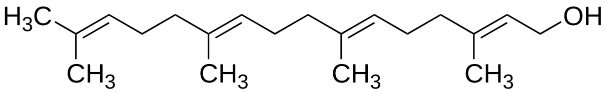
(*S*)-*cis*-verbenol



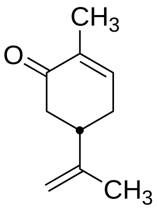
geraniol



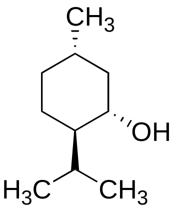
farnesol



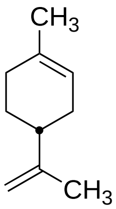
geranylgeraniol



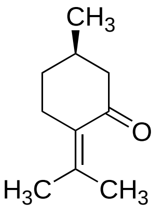
(+)-carvone



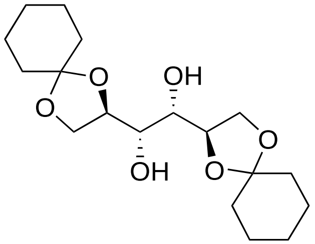
(+)-menthol



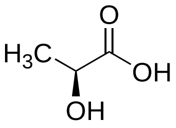
(*R*)-(+)-limonene



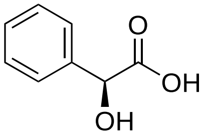
(+)-pulegone



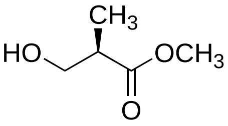
1,2:5,6-di-*O*-cyclohexylidene-
D-mannitol



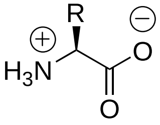
(L)-(+)-lactic acid



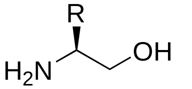
(S)-(+)-mandelic acid



Roche ester

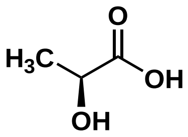


amino acids

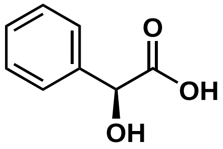


amino alcohols

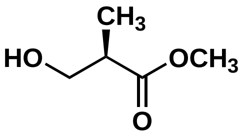
And a Few Others Useful Ones...



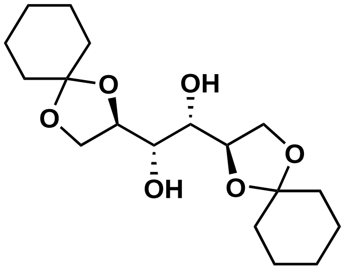
(L)-(+)-lactic acid



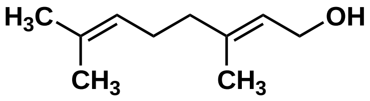
(S)-(+)-mandelic acid



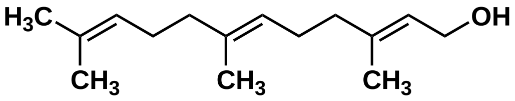
Roche ester



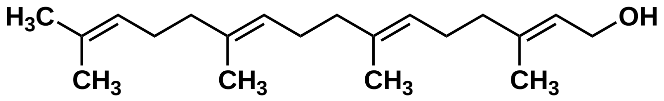
1,2:5,6-di-*O*-cyclohexylidene-D-mannitol



geraniol

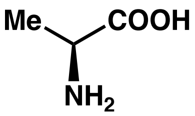


farnesol

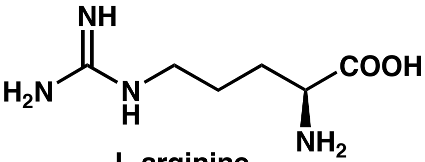


geranylgeraniol

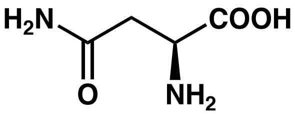
Inexpensive Chiral Starting Materials and Resolving Agents: Amino Acids



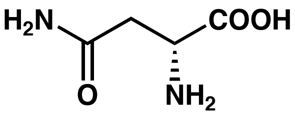
L-alanine



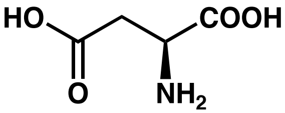
L-arginine



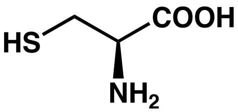
L-asparagine



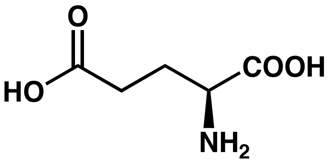
D-asparagine



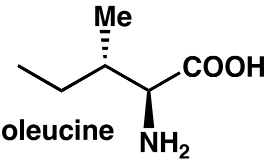
L-aspartic acid



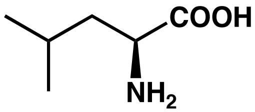
L-cysteine



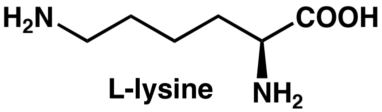
L-glutamic acid



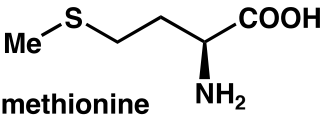
L-isoleucine



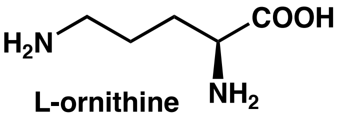
L-leucine



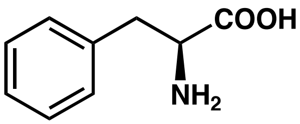
L-lysine



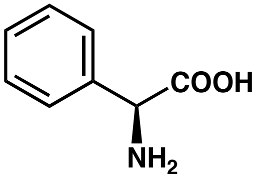
L-methionine



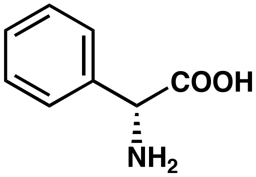
L-ornithine



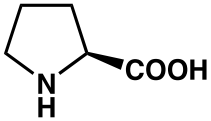
L-phenylalanine



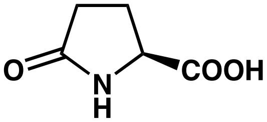
L-phenylglycine



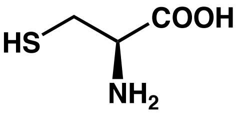
D-phenylglycine



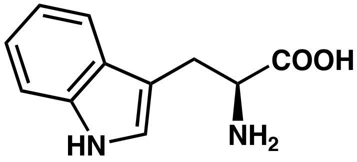
L-proline



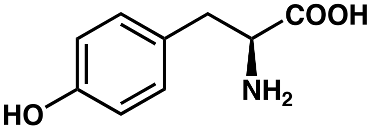
L-pyroglutamic acid



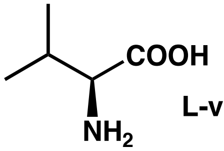
L-serine



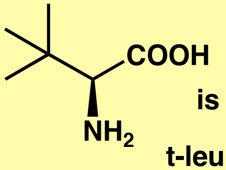
L-tryptophan



L-tyrosine



L-valine



is very expensive!

t-leucine

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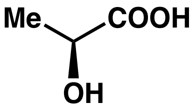
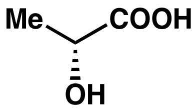
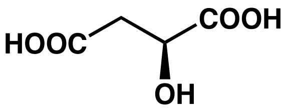
Inexpensive Chiral Starting Materials and Resolving Agents: Hydroxyacids



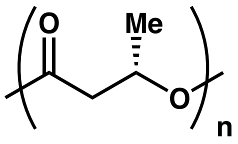
L-lactic acid



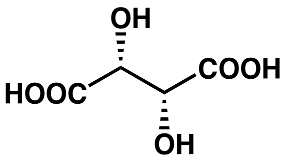
D-lactic acid



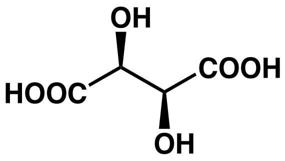
(*S*)-Malic acid



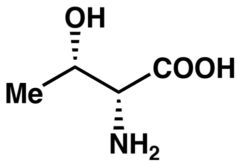
(Poly)-3-(*R*)-hydroxybutyrate



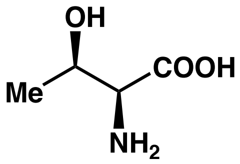
L-Tartaric acid



D-Tartaric acid

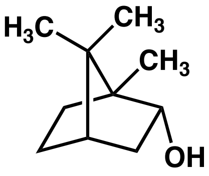


D-Threonine

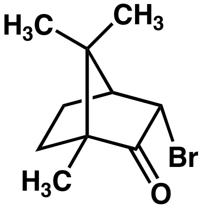


L-Threonine

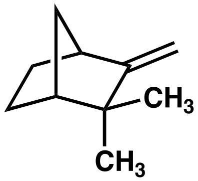
Inexpensive Chiral Starting Materials and Resolving Agents: Terpenes



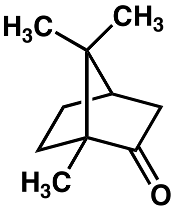
l-(-)-Borneol



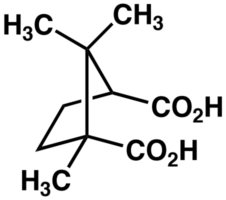
endo-3-Bromo-*d*-camphor



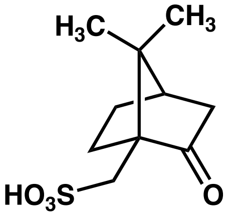
(+)-Camphene



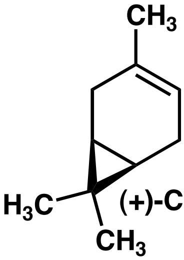
d-(+)-Camphor



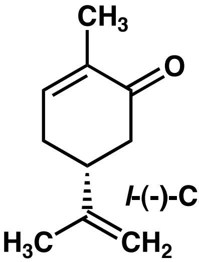
D-(+)-Camphoric acid



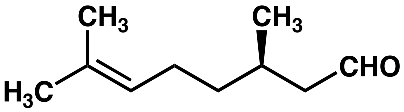
d-10-Camphorsulfonic acid



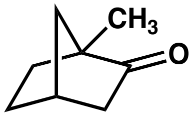
(+)-Carene



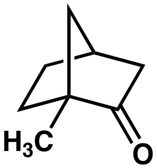
l-(-)-Carvone



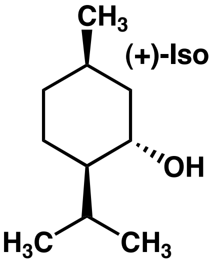
(+)-Citronellal



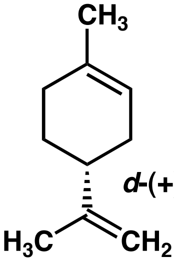
l-(+)-Fenchone



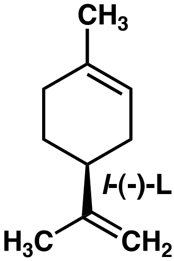
d-(-)-Fenchone



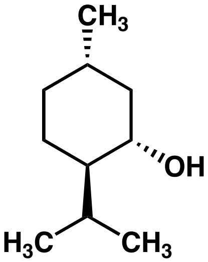
(+)-Isomenthol



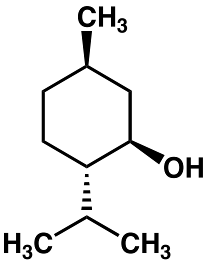
d-(+)-Limonene



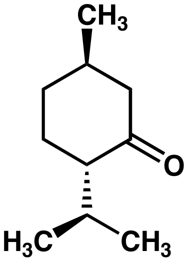
l-(-)-Limonene



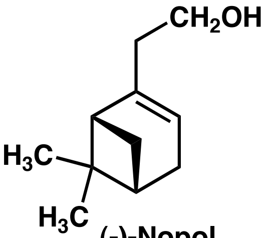
d-(+)-Menthol



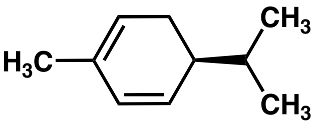
l-(-)-Menthol



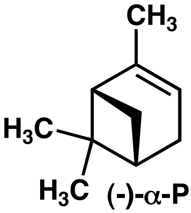
l-(-)-Menthone



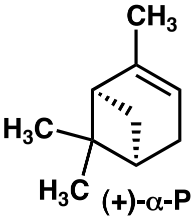
(-)-Nopol



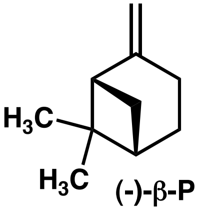
(-)-α-Phellandrene



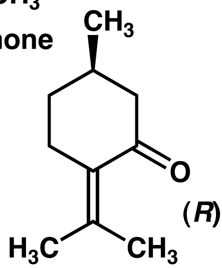
(-)-α-Pinene



(+)-α-Pinene



(-)-β-Pinene



(*R*)-(+)-Pulegone

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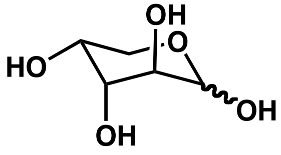
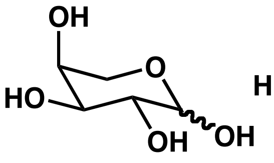
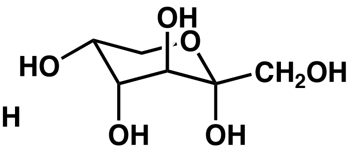
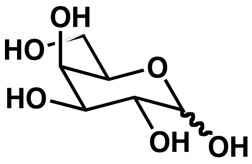
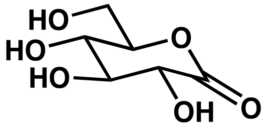
Inexpensive Chiral Starting Materials and Resolving Agents: Carbohydrates

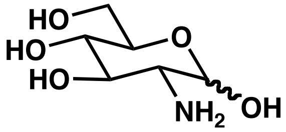

D-Arabinose

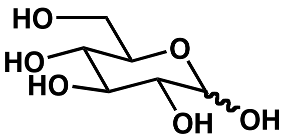

L-Arabinose

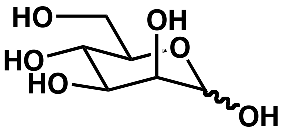

D-Fructose

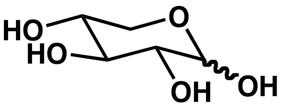

D-Galactose

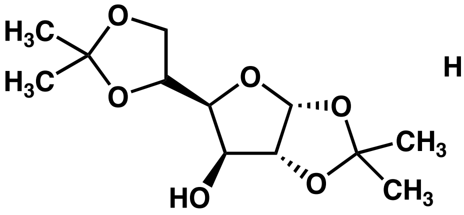

D-Gluconic acid, δ-lactone

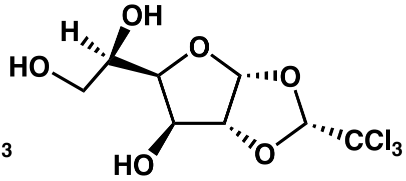

D-Glucosamine

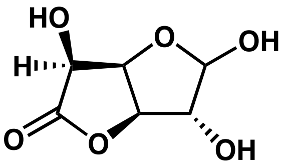

D-Glucose

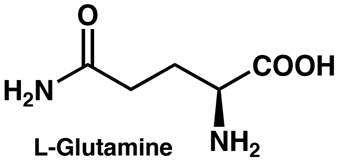

D-Mannose

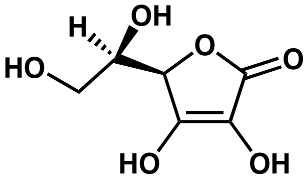

D-Xylose

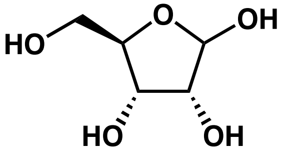

Diacetone-D-glucose

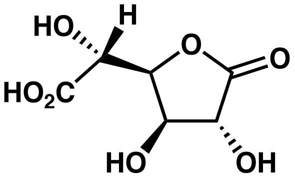

α-Chloralose

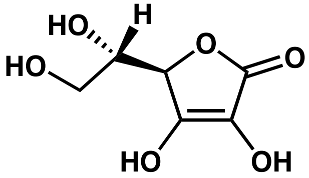

D-Glucurone

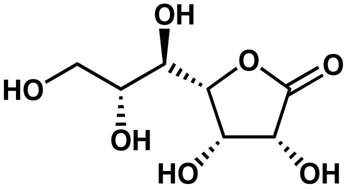

L-Glutamine

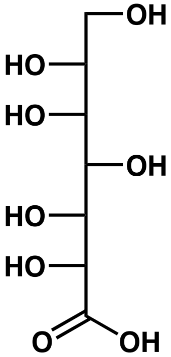

D-Isoascorbic acid

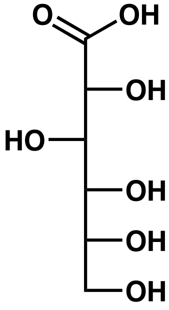

D-Ribose

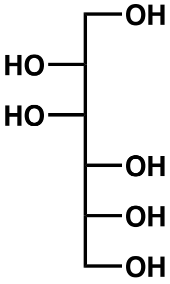

D-Saccharic 1,4-lactone

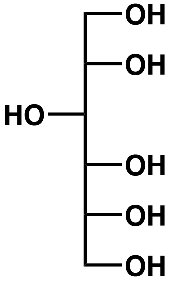

L-Ascorbic acid

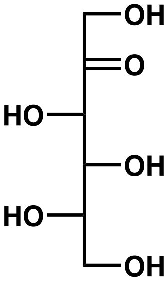

D-Glucoheptonic acid γ-lactone

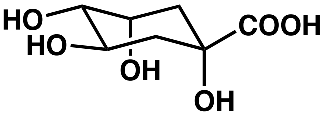

D-Glucoheptonic acid


D-Gluconic acid


D-Mannitol


D-Sorbitol


L-Sorbose


D-Quinic acid

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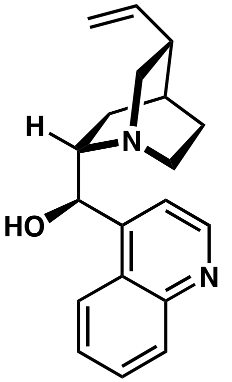
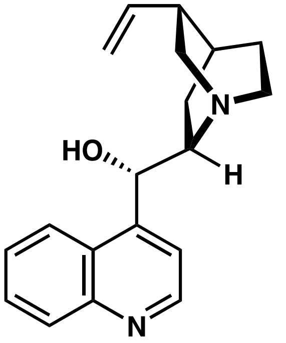
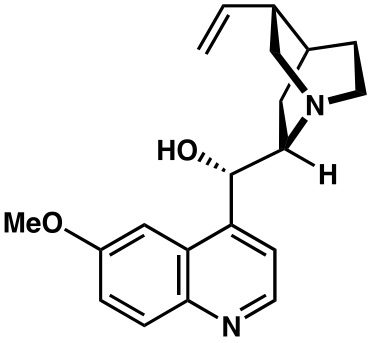
Inexpensive Chiral Starting Materials and Resolving Agents: Alkaloids



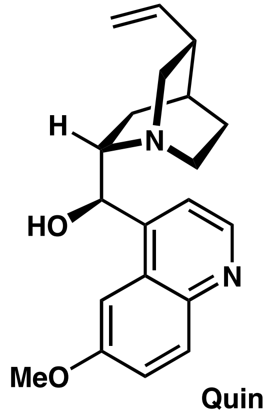
(-)-Cinchonidine



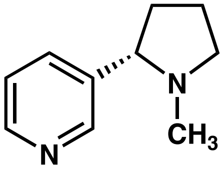
(+)-Cinchonine



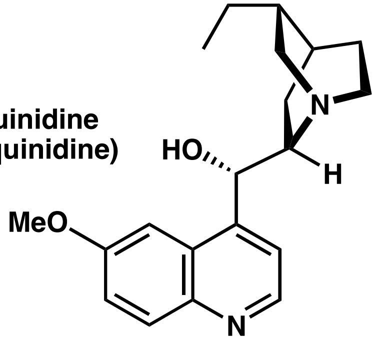
Quinidine



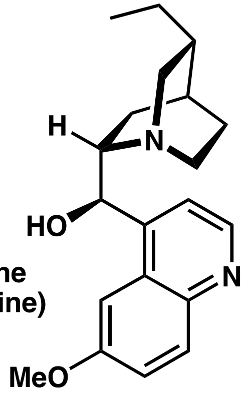
Quinine



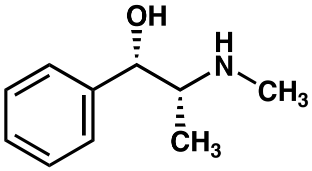
***l*-(-)-Nicotine**



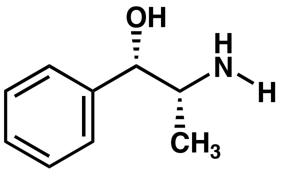
Hydroquinidine (dihydroquinidine)



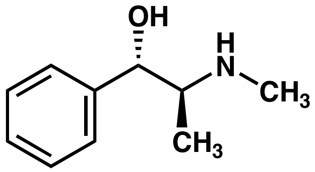
Hydroquinine (dihydroquinine)



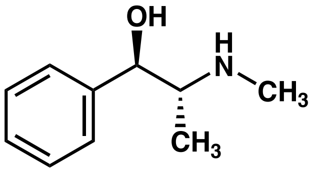
D-(+)-Ephedrine



(+)-Norephedrine

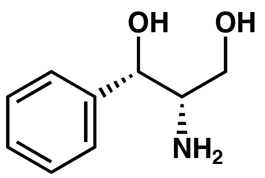


D-(+)-Pseudoephedrine

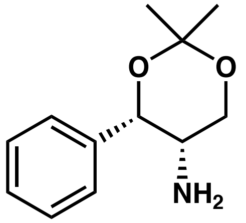


L-(-)-Pseudoephedrine

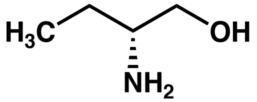
Inexpensive Chiral Starting Materials and Resolving Agents: Other Ligands



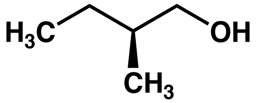
L-(+)-2-Amino-1-phenyl-1,3-propanediol



(4S,5S)-(+)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane



L-(-)-2-Amino-1-butanol



(-)-2-Methyl-1-butanol

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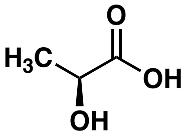
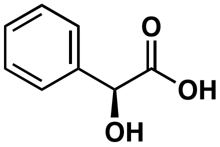
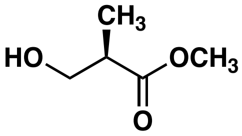
And a Few Others Useful Ones...



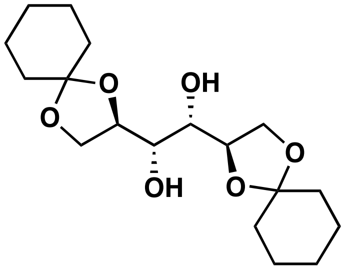
(L)-(+)-lactic acid



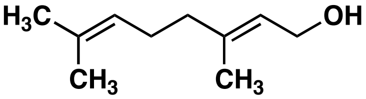
(S)-(+)-mandelic acid



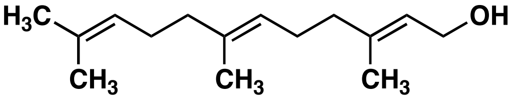
Roche ester



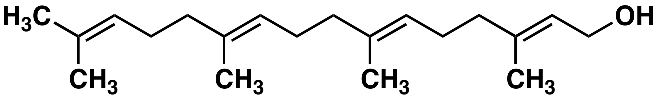
1,2:5,6-di-*O*-cyclohexylidene-D-mannitol



geraniol



farnesol



geranylgeraniol

http://www.courses.fas.harvard.edu/colgsas/1063

http://evans.harvard.edu/problems/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 1

Introduction to FMO Theory

- General Bonding Considerations
- The H_2 Molecule Revisited (Again!)
- Donor & Acceptor Properties of Bonding & Antibonding States
- Hyperconjugation

Reading Assignment for week:

Kirby, Stereoelectronic Effects

Carey & Sundberg: **Part A**; Chapter 1

Fukui,*Acc. Chem. Res.* **1971**, *4*, 57. (pdf)

Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)

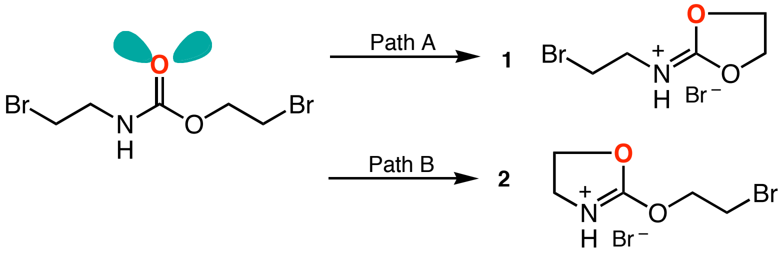
Robertson, *Org. Letters* **2005**, *7*, 5007 (pdf)

D. A. Evans

Monday,
September 18, 2006

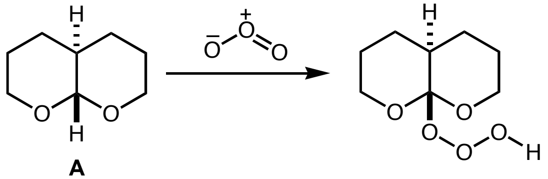
Problems of the Day

The molecule illustrated below can react through either Path A or Path B to form salt **1** or salt **2**. In both instances the carbonyl oxygen functions as the nucleophile in an intramolecular alkylation. What is the preferred reaction path for the transformation in question?

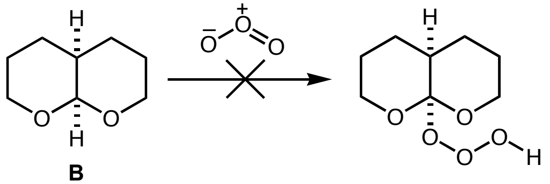


This is a "thought" question posed to me by Prof. Duilo Arigoni at the ETH in Zuerich some years ago

FIRST HOUR EXAM, 2005. The oxidation of acetals by electrophilic ozone is known to be sensitive to structure. Two striking examples of different reactivity are detailed in the questions below. Using clear three-dimensional drawings provide a rationale for the observation that rigid glycoside **A** readily undergoes oxidation but glycoside **B** does not. Be sure to indicate all relevant stereoelectronic interactions.



A



B

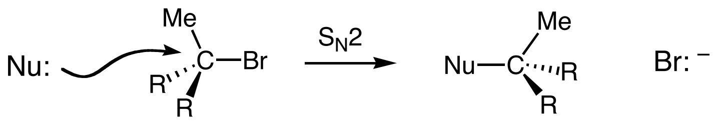
Deslongchamps, *Can. J. Chem.* **1974**, 3651-3664.

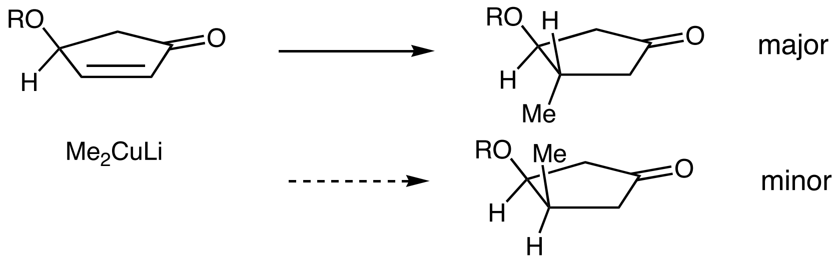
An Introduction to Frontier Molecular Orbital Theory-1

Universal Effects Governing Chemical Reactions
There are three:

■ Steric Effects

Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules

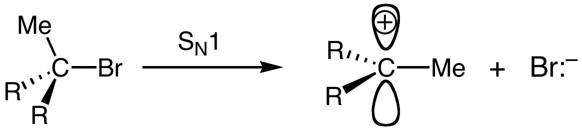




■ Electronic Effects (Inductive Effects):

The effect of bond and through-space polarization by heteroatom substituents on reaction rates and selectivities

Inductive Effects: Through-bond polarization
Field Effects: Through-space polarization



rate decreases as R becomes more electronegative

■ Stereoelectronic Effects

Geometrical constraints placed upon ground and transition states by orbital overlap considerations.

Fukui Postulate for reactions:

"During the course of chemical reactions, the interaction of the highest filled (HOMO) and lowest unfilled (antibonding) molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition structure."

■ General Reaction Types

Radical Reactions (~10%): $A\bullet + B\bullet \longrightarrow A—B$

Polar Reactions (~90%): $A(:) + B(+) \longrightarrow A—B$

Lewis Base ↑ (A) Lewis Acid ↑ (B)

FMO concepts extend the donor-acceptor paradigm to non-obvious families of reactions

■ Examples to consider

$H_2 + 2\,Li(0) \longrightarrow 2\,LiH$

$CH_3–I + Mg(0) \longrightarrow CH_3–MgBr$

"Organic chemists are generally unaware of the impact of electronic effects on the stereochemical outcome of reactions."

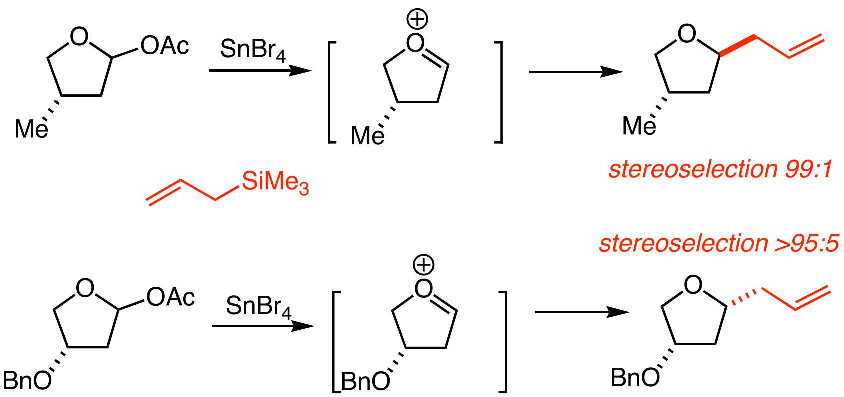
"The distinction between electronic and stereoelectronic effects is not clear-cut."

Steric Versus Electronic Effects; A time to be careful!!

Steric Versus electronic Effects: Some Case Studies

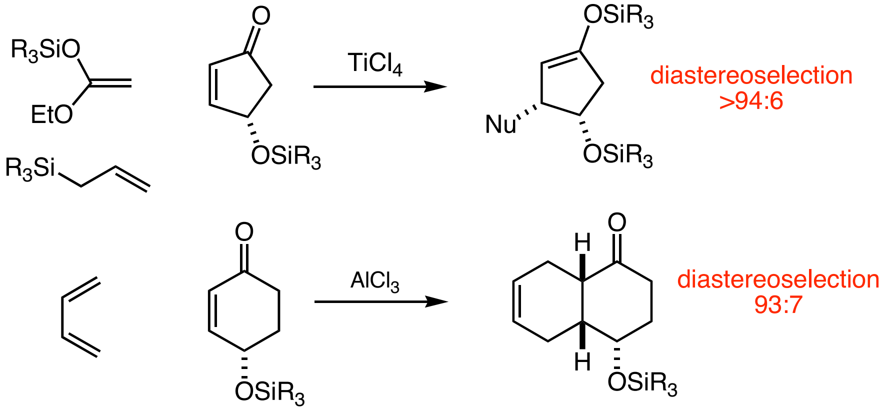
When steric and electronic (stereoelectronic) effects lead to differing stereochemical consequences

Woerpel etal. *JACS* **1999**, 121, 12208.



stereoselection 99:1

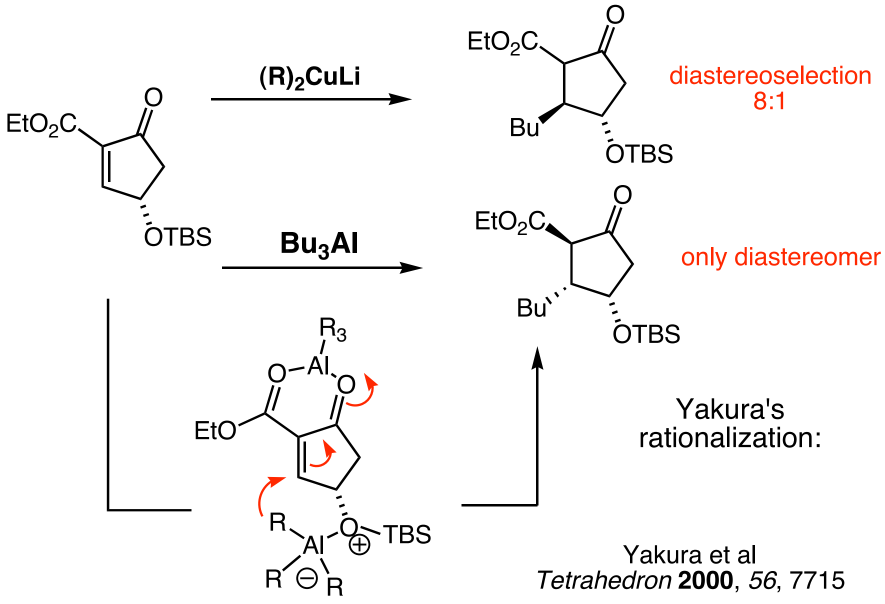
stereoselection >95:5



diastereoselection >94:6

diastereoselection 93:7

Danishefsky et al *JOC* **1991**, *56*, 387

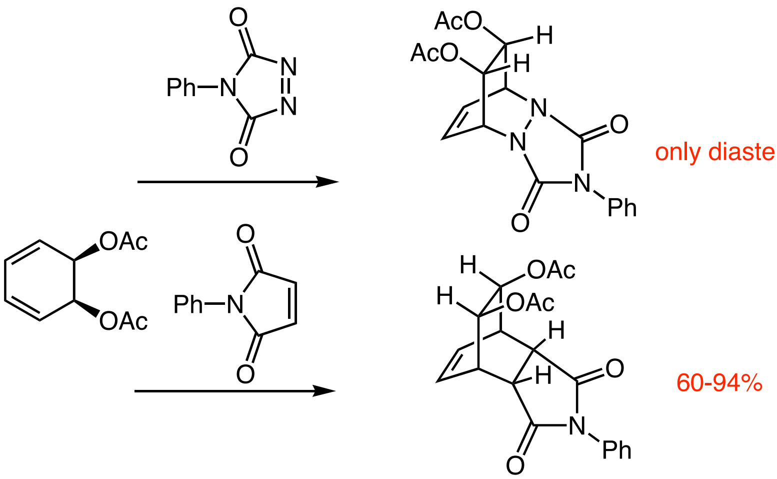


diastereoselection 8:1

only diastereomer

Yakura's rationalization:

Yakura et al
Tetrahedron **2000**, *56*, 7715



only diastereomer

60-94%

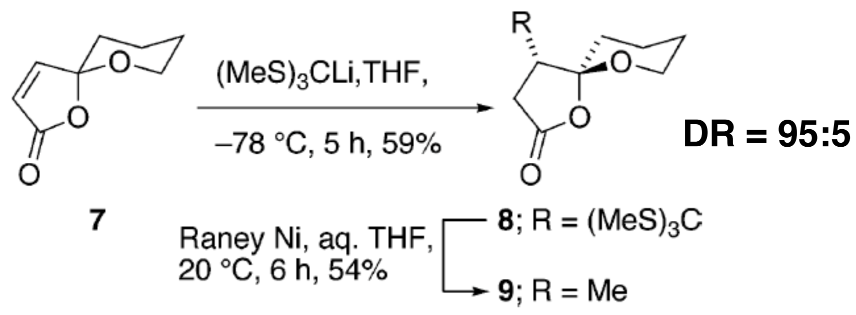
Mehta et al, *Acc Chem. Res.* **2000**, *33*, 278-286

Progress in the Synthesis of the Lituarines: Stereocontrol in Sequential C–C Bond Formation on a Spirobutenolide Template

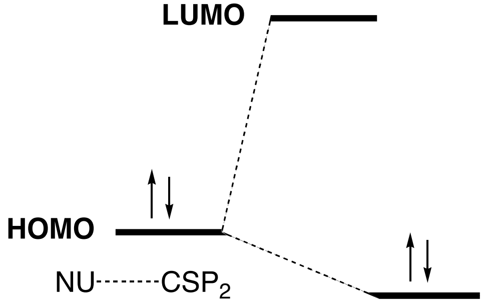
ORGANIC LETTERS
2005
Vol. 7, No. 22
5007–5010

Jeremy Robertson* and Jonathan W. P. Dallimore

Scheme 2. Conjugate Addition Model Study[1b]



TRANSITION STATE
HYPERCONJUGATION



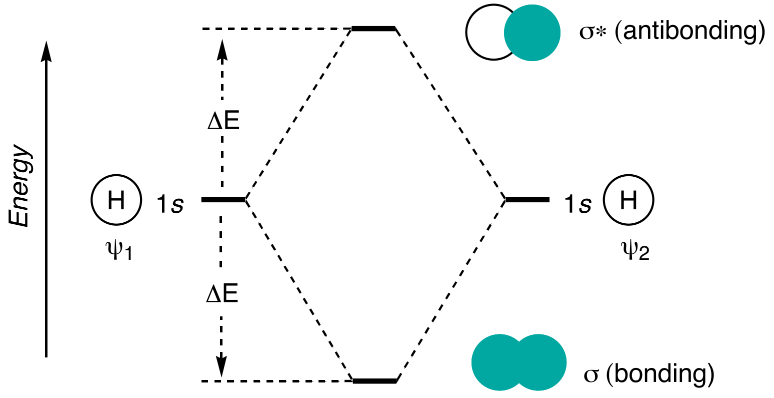
(5) Our working hypothesis is that a stabilizing interaction of the incoming nucleophile, and then the forming C−C bond, with the tetrahydropyran [C(15)−O]σ^* acts cooperatively with electrostatic and solvation effects to favor attack *anti* to the six-membered ring oxygen. Cf. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

The H_2 Molecular Orbitals & Antibonds

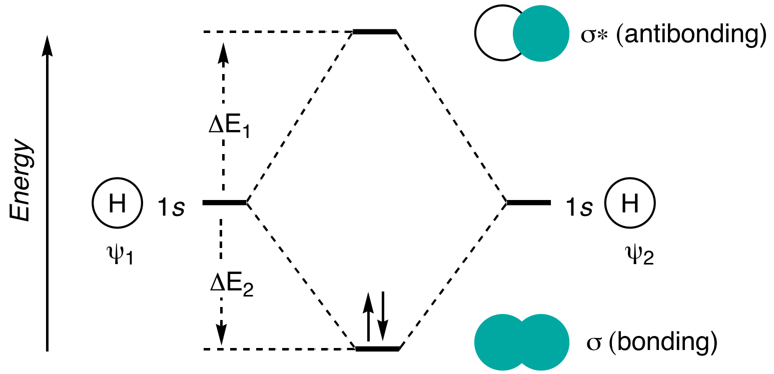
The H_2 Molecule (again!!)

Let's combine two hydrogen atoms to form the hydrogen molecule. Mathematically, linear combinations of the 2 atomic 1s states create two new orbitals, one is bonding, and one antibonding:

- **Rule one**: A linear combination of n atomic states will create n MOs.



Let's now add the two electrons to the new MO, one from each H atom:



Note that ΔE_1 is greater than ΔE_2. Why?

Linear Combination of Atomic Orbitals (LCAO): Orbital Coefficients

- **Rule Two**:

Each MO is constructed by taking a linear combination of the individual atomic orbitals (AO):

Bonding MO $\sigma = C_1\psi_1 + C_2\psi_2$

Antibonding MO $\sigma* = C^*_1\psi_1 - C^*_2\psi_2$

The coefficients, C_1 and C_2, represent the contribution of each AO.

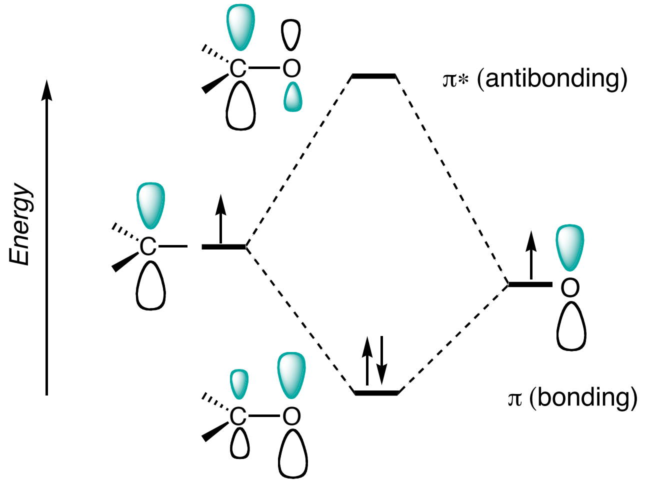
- **Rule Three**: $(C_1)^2 + (C_2)^2 = 1$

The squares of the C-values are a measure of the electron population in neighborhood of atoms in question

- **Rule Four**: bonding$(C_1)^2$+ antibonding$(C^*_1)^2$= 1

In LCAO method, both wave functions must each contribute one net orbital

Consider the pi–bond of a C=O function: In the ground state pi-C–O is polarized toward Oxygen. Note (Rule 4) that the antibonding MO is polarized in the opposite direction.



Bonding Generalizations

■ *Bond strengths (Bond dissociation energies) are composed of a covalent contribution (δ E_{cov}) and an ionic contribution (δ E_{ionic}).*

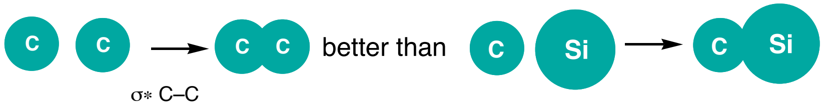
$$\text{Bond Energy (BDE)} = \delta\, E_{covalent} + \delta\, E_{ionic}$$

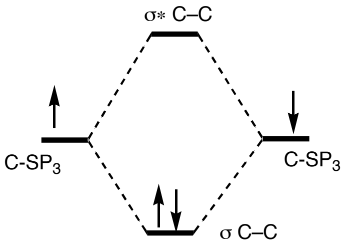
When one compares bond strengths between C–C and C–X, where X is some other element such as O, N, F, Si, or S, keep in mind that covalent and ionic contributions vary independently. Hence, the mapping of trends is not a trivial exercise.

Useful generalizations on covalent bonding

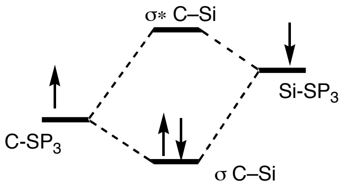
■ *Overlap between orbitals of comparable energy is more effective than overlap between orbitals of differing energy.*

For example, consider elements in Group IV, Carbon and Silicon. We know that C-C bonds are considerably stronger by Ca. 20 kcal mol^{-1} than C-Si bonds.





$H_3C–CH_3$ BDE = 88 kcal/mol
Bond length = 1.534 Å



$H_3C–SiH_3$ BDE ~ 70 kcal/mol
Bond length = 1.87 Å

This trend is even more dramatic with pi-bonds:

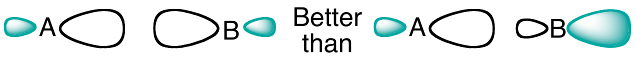
π C–C = 65 kcal/mol π C–Si = 36 kcal/mol π Si–Si = 23 kcal/mol

■ *Weak bonds will have corresponding low-lying antibonds.*

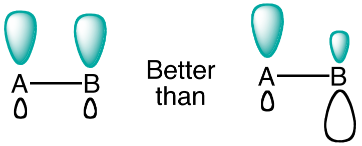
Formation of a weak bond will lead to a corresponding low-lying antibonding orbital. Such structures are reactive as both nucleophiles & electrophiles

■ *Orbital orientation strongly affects the strength of the resulting bond.*

For σ Bonds:



For π Bonds:

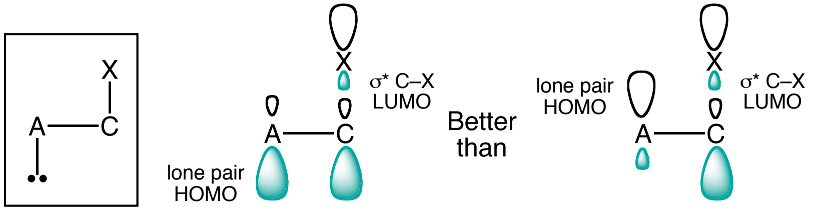


This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

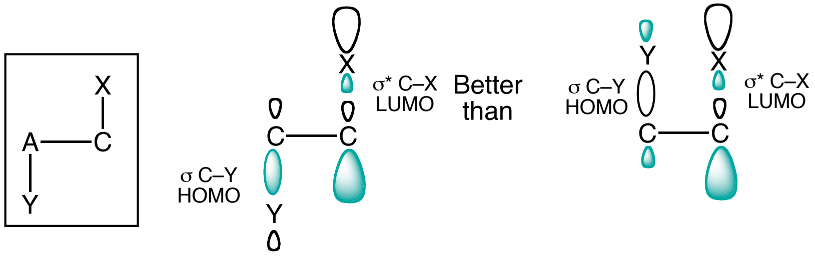
■ *Anti orientation of filled and unfilled orbitals leads to better overlap.*

This is a corrollary to the preceding generalization. There are two common situations.

Case-1: Anti Nonbonding electron pair & C–X bond



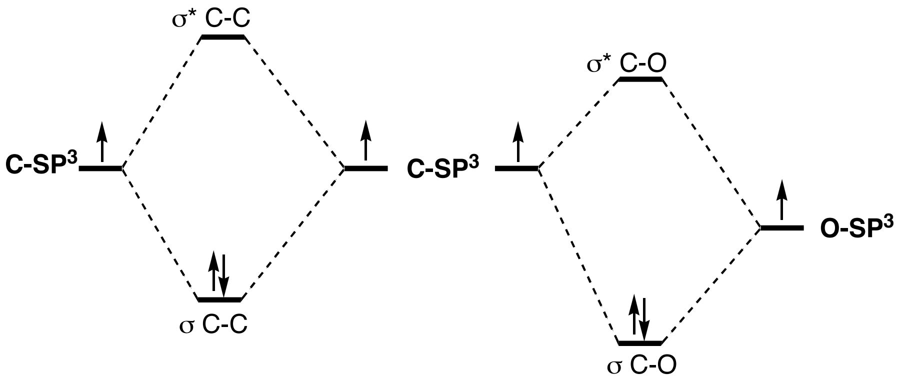
Case-2: Two anti sigma bonds



Donor-Acceptor Properties of Bonding and Antibonding States

Donor Acceptor Properties of C-C & C-O Bonds

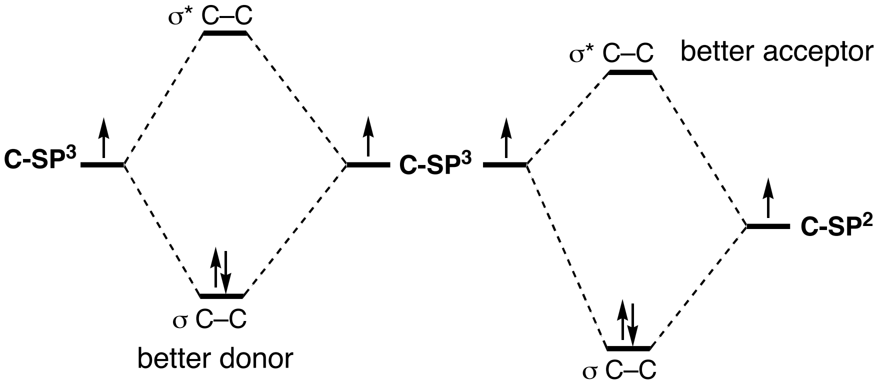
Consider the energy level diagrams for both bonding & antibonding orbitals for C–C and C–O bonds.



■ The greater electronegativity of oxygen lowers both the bonding & antibonding C-O states. Hence:

- ■ σ C–C is a better donor orbital than σ C–O
- ■ σ*C–O is a better acceptor orbital than σ*C–C

Donor Acceptor Properties of C_{SP3}-C_{SP3} & C_{SP3}-C_{SP2} Bonds

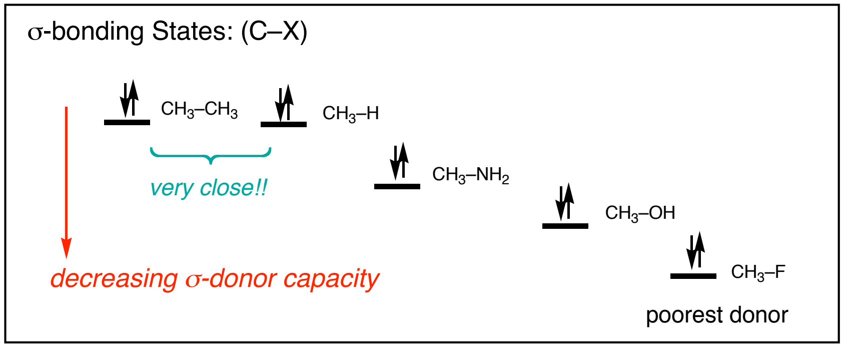


■ The greater electronegativity of C_{SP2} lowers both the bonding & antibonding C–C states. Hence:

- ■ σ C_{SP3}-C_{SP3} is a better donor orbital than σ C_{SP3}-C_{SP2}
- ■ σ*C_{SP3}-C_{SP2} is a better acceptor orbital than σ*C_{SP3}-C_{SP3}

Hierarchy of Donor & Acceptor States

Following trends are made on the basis of comparing the bonding and antibonding states for the molecule CH_3–X where X = C, N, O, F, & H.



σ-bonding States: (C–X)

CH_3–CH_3

CH_3–H

very close!!

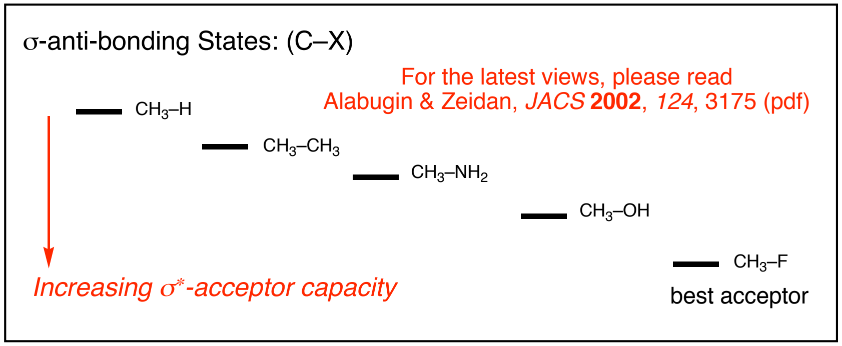
CH_3–NH_2

CH_3–OH

CH_3–F

decreasing σ-donor capacity

poorest donor



σ-anti-bonding States: (C–X)

For the latest views, please read Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)

CH_3–H

CH_3–CH_3

CH_3–NH_2

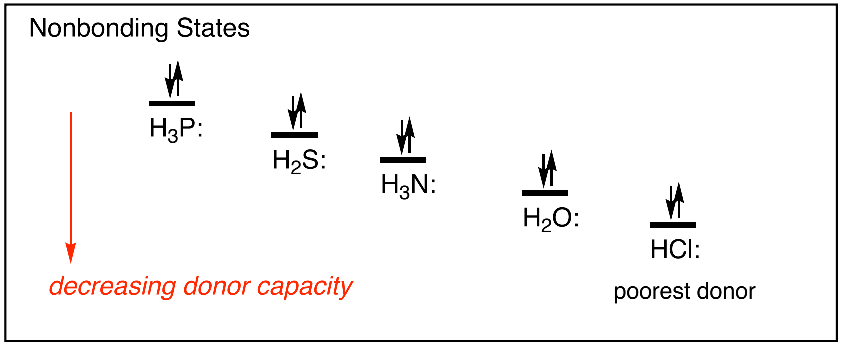
CH_3–OH

CH_3–F

Increasing σ-acceptor capacity*

best acceptor

The following are trends for the energy levels of *nonbonding states* of several common molecules. Trend was established by photoelectron spectroscopy.



Nonbonding States

H_3P:

H_2S:

H_3N:

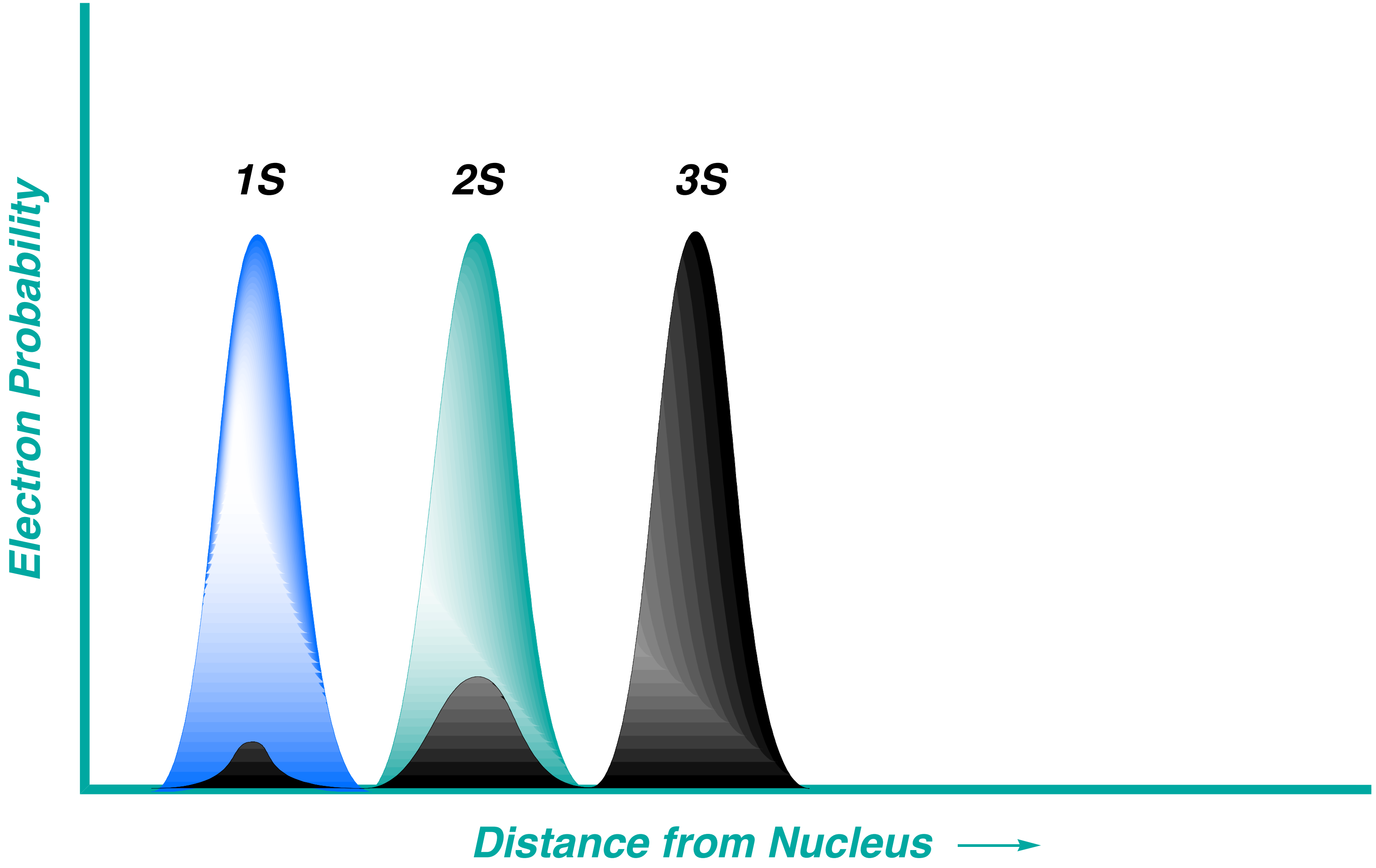
H_2O:

HCl:

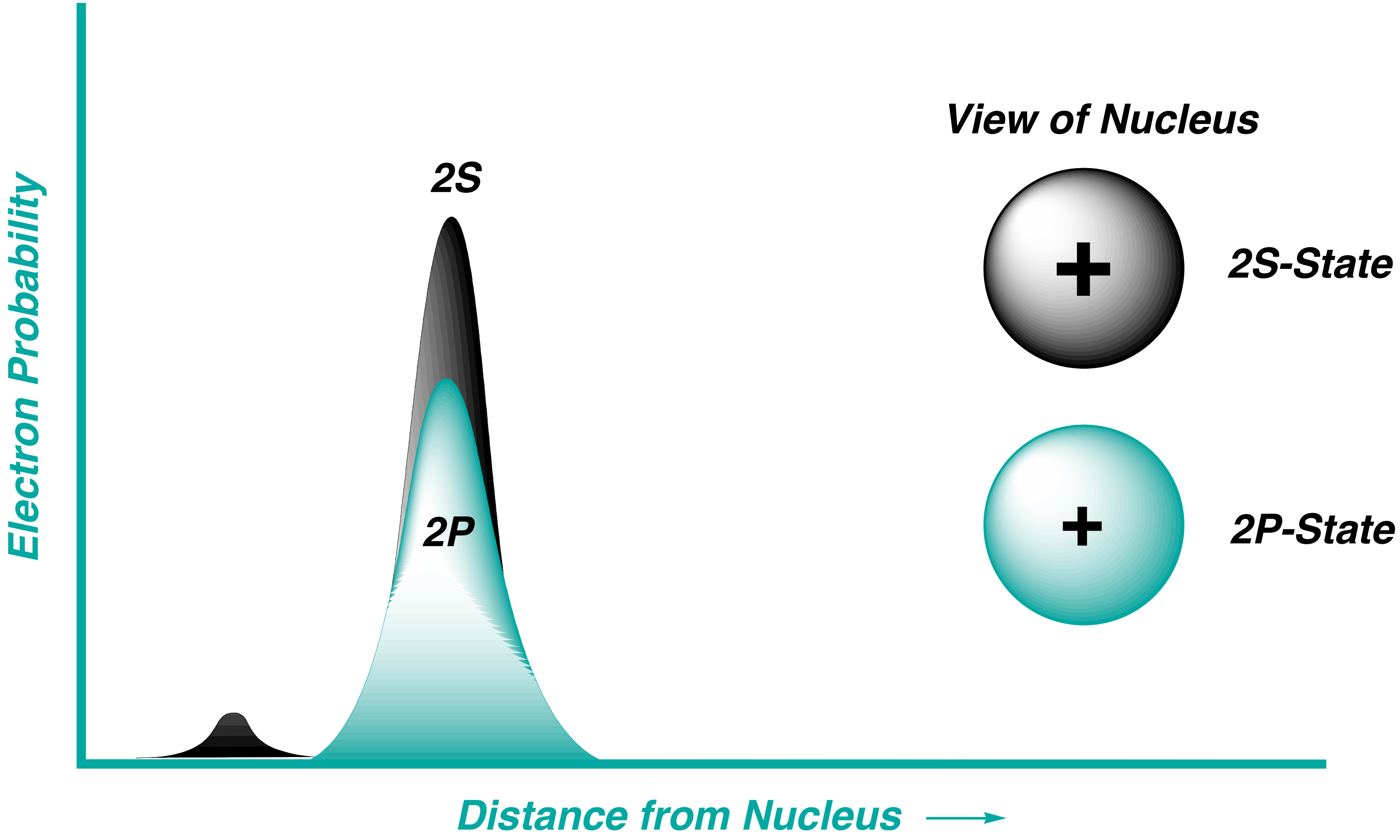
decreasing donor capacity

poorest donor

Radial Electron Density of S-States



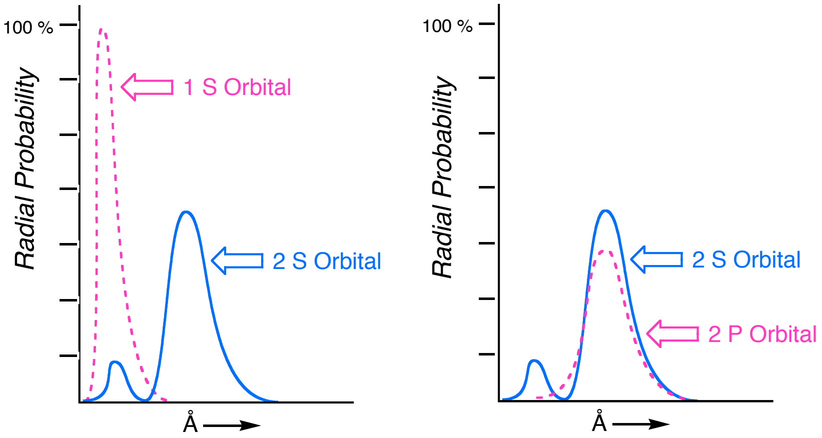
Radial Electron Density of S- & P-States

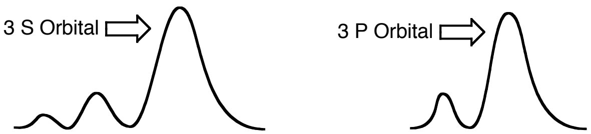


Hybridization vs Electronegativity

Electrons in 2S states "see" a greater effective nuclear charge than electrons in 2P states.

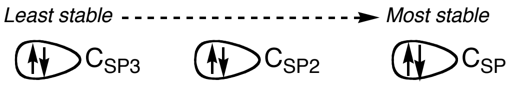
This becomes apparent when the radial probability functions for S and P-states are examined: The radial probability functions for the hydrogen atom S & P states are shown below.





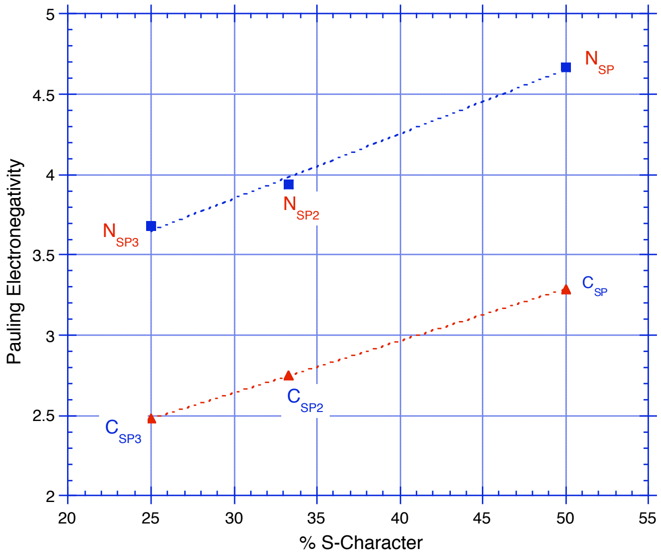
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in S-states "see" a higher nuclear charge.

Above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital

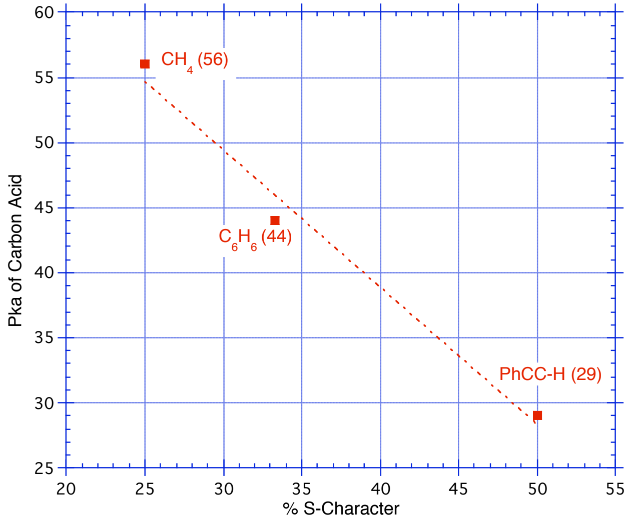


The above trend indicates that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

There is a linear relationship between %S character & Pauling electronegativity



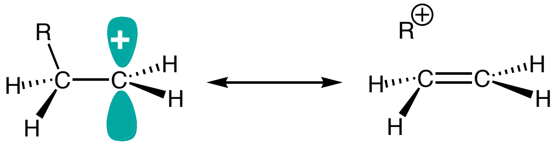
There is a direct relationship between %S character & hydrocarbon acidity



Hyperconjugation: Carbocation Stabilization

- The interaction of a vicinal bonding orbital with a p-orbital is referred to as hyperconjugation.

This is a traditional vehicle for using valence bond to denote charge delocalization.



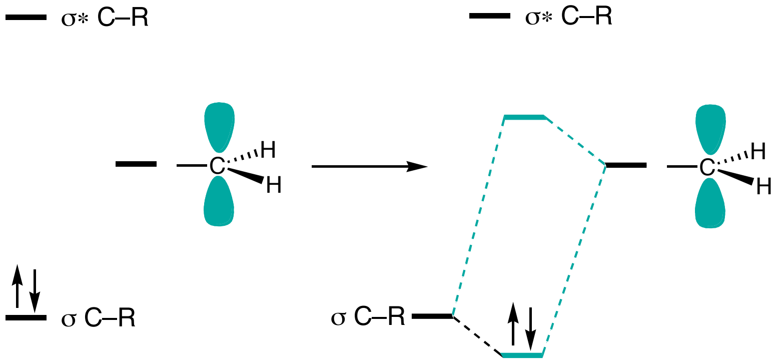
The graphic illustrates the fact that the C-R bonding electrons can "delocalize" to stabilize the electron deficient carbocationic center.

Note that the general rules of drawing resonance structures still hold: the positions of all atoms must not be changed.

Stereoelectronic Requirement for Hyperconjugation:

Syn-planar orientation between interacting orbitals

The Molecular Orbital Description



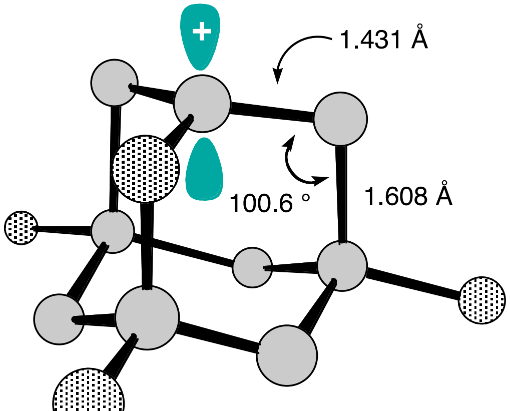
- Take a linear combination of σ C–R and CSP$_2$ p-orbital:

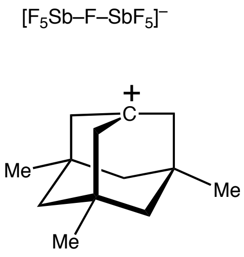
"The new occupied bonding orbital is lower in energy. When you stabilize the electrons is a system you stabilize the system itself."

Physical Evidence for Hyperconjugation

- Bonds participating in the hyperconjugative interaction, e.g. C–R, will be lengthened while the C(+)–C bond will be shortened.

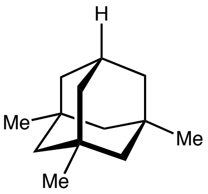
First X-ray Structure of an Aliphatic Carbocation

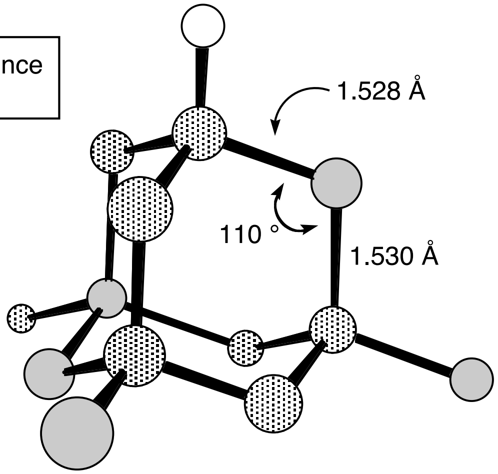




T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

The Adamantane Reference (MM-2)





Hyperconjugation, The Anomeric Effect, and More

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 2

Stereoelectronic Effects-2

- "Positive" and "Negative" Hyperconjugation
- Anomeric and Related Effects
- Peracid & Dioxirane Epoxidation (Stereoelectronics)

Kirby, Stereoelectronic Effects   Chapters 1-5

Carey & Sundberg: **Part A**; Chapter 1, Chapter 3

Fukui, *Acc. Chem. Res.* **1971**, *4*, 57. (pdf)

Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)

D. A. Evans

Wednesday,
September 20, 2006

Useful LIterature Reviews

Kirby, A. J. (**1982**). The Anomeric Effect and Related Stereoelectronic Effects at Oxygen. New York, Springer Verlag.

Box, V. G. S. (**1990**). "The role of lone pair interactions in the chemistry of the monosaccharides. The anomeric effect." *Heterocycles* **31**: 1157.

Box, V. G. S. (**1998**). "The anomeric effect of monosaccharides and their derivatives. Insights from the new QVBMM molecular mechanics force field." *Heterocycles* **48**(11): 2389-2417.

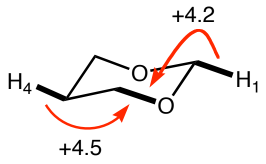
Graczyk, P. P. and M. Mikolajczyk (**1994**). "Anomeric effect: origin and consequences." *Top. Stereochem*. **21**: 159-349.

Juaristi, E. and G. Cuevas (**1992**). "Recent studies on the anomeric effect." *Tetrahedron* **48**: 5019 **(PDF)**

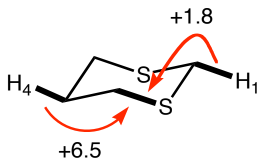
Carey & Sundberg: **Part A**; Chapter 3 pp 151-156

Database problem 307

Natural bond order (NBO) analysis is a powerful computational tool that allows one to quantitatively estimate the energy of hyperconjugative effects (Alabugin & Zeiden, *JACS* **2002**, *124*, 3175). The stabilizing interactions for the H_1 and H_4 equatorial hydrogens for 1,3-dioxane and 1,3-dithiane are provided below. It is interesting that the two indicated hyperconjugative interactions in dioxane are approximately the same (4.5 vs 4.2) but that the same interactions in dithiane are quite different (6.5 vs 1.8). In fact, the authors refer to C–S bonds as "one directional" acceptor orbitals.



σC–H → σ^*C–O



σC–H → σ^*C–S

numbers refer to interaction energies in kcal/mol at the B3LYP/6-31+G*** level

There is one quite reasonable qualitative argument that can rationalize the "one directional" character of σ^*C–S. Please provide your argument in the space provided below.

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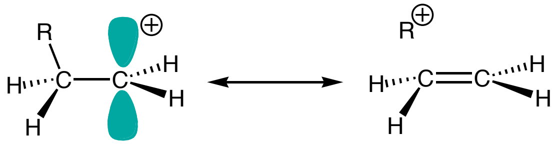

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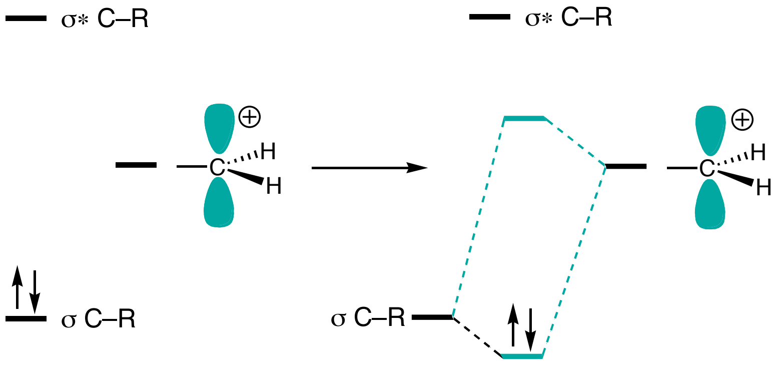

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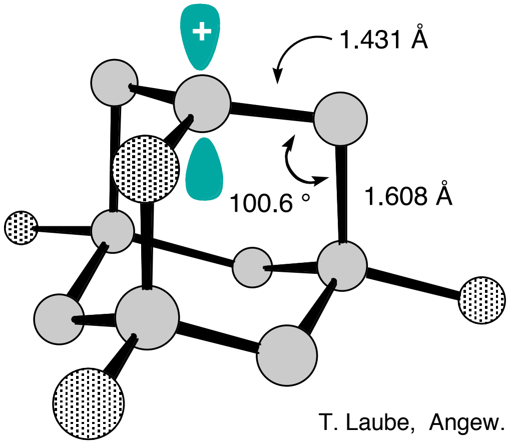
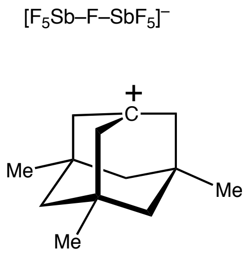
"The new occupied bonding orbital is lower in energy. When you stabilize the electrons is a system you stabilize the system itself."

Physical Evidence for Hyperconjugation

- Bonds participating in the hyperconjugative interaction, e.g. C–R, will be lengthened while the C(+)–C bond will be shortened.

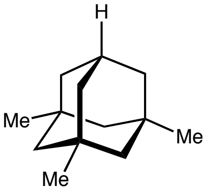
First X-ray Structure of an Aliphatic Carbocation

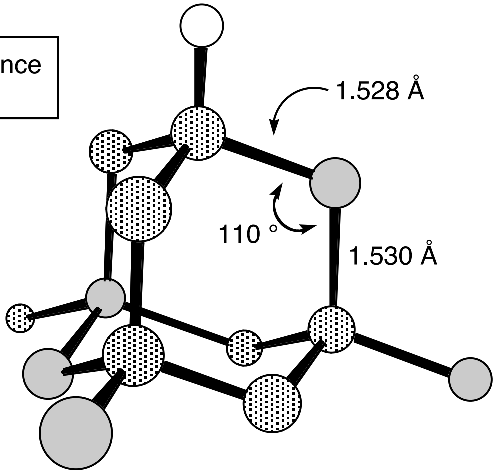




T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

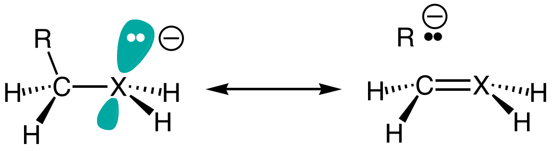
The Adamantane Reference (MM-2)





"Negative" Hyperconjugation

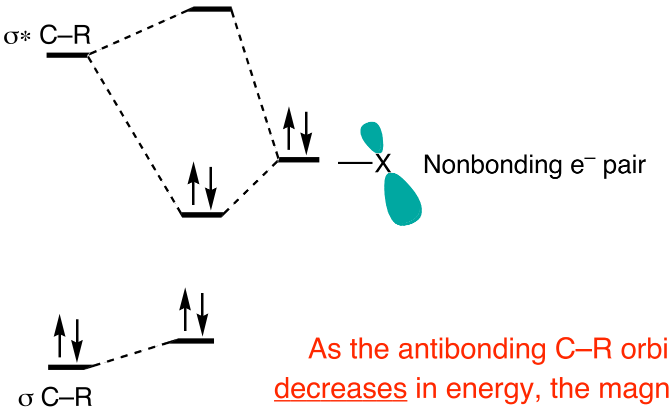
- Delocalization of nonbonding electron pairs into vicinal antibonding orbitals is also possible



This decloalization is referred to as "Negative" hyperconjugation

Since nonbonding electrons prefer hybrid orbitals rather that P orbitals, this orbital can adopt either a syn or anti relationship to the vicinal C–R bond.

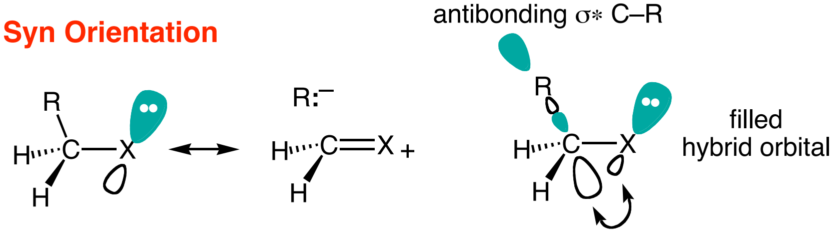
The Molecular Orbital Description



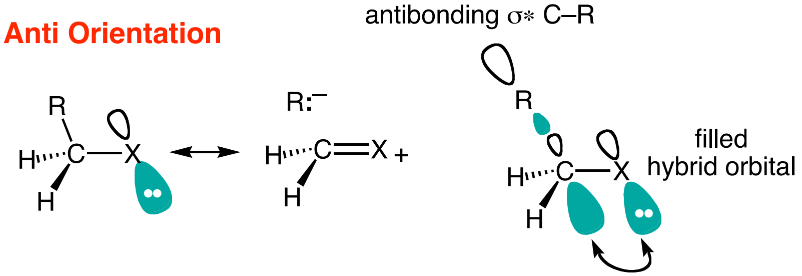
As the antibonding C–R orbital decreases in energy, the magnitude of this interaction will increase

Note that σ C–R is slightly destabilized

Syn Orientation



Anti Orientation



- Overlap between two orbitals is better in the anti orientation as stated in "Bonding Generalizations" handout.

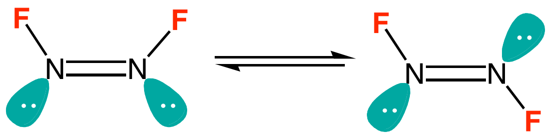
The Expected Structural Perturbations

Change in Structure	Spectroscopic Probe
■ Shorter C–X bond	X-ray crystallography
■ Longer C–R bond	X-ray crystallography
■ Stronger C–X bond	Infrared Spectroscopy
■ Weaker C–R bond	Infrared Spectroscopy
■ Greater e-density at R	NMR Spectroscopy
■ Less e-density at X	NMR Spectroscopy

The interaction of filled orbitals with adjacent antibonding orbitals can have an ordering effect on the structure which will stabilize a particular geometry. Here are several examples:

Case 1: N_2F_2

This molecule can exist as either cis or trans isomers



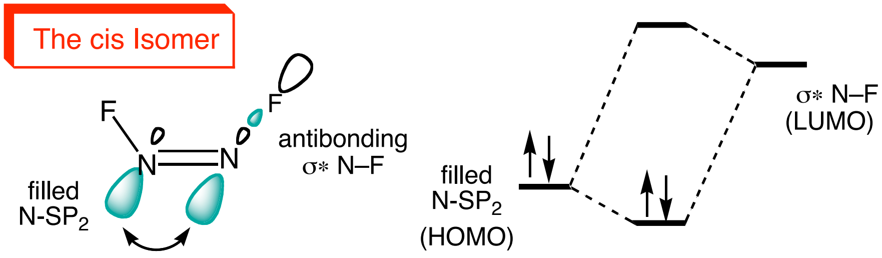
There are two logical reasons why the trans isomer should be more stable than the cis isomer.

- ■ The nonbonding lone pair orbitals in the cis isomer will be destabilizing due to electron-electron repulsion.
- ■ The individual C–F dipoles are mutually repulsive (pointing in same direction) in the cis isomer.

In fact the cis isomer is favored by 3 kcal/ mol at 25 °C.

Let's look at the interaction with the lone pairs with the adjacent C–F antibonding orbitals.

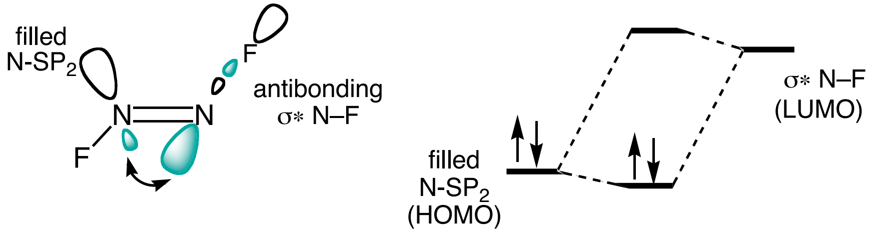
The cis Isomer



- ■ Note that by taking a linear combination of the nonbonding and antibonding orbitals you generate a more stable bonding situation.
- ■ Note that two such interactions occur in the molecule even though only one has been illustrated.

The trans Isomer

Now carry out the same analysis with the same 2 orbitals present in the trans isomer.



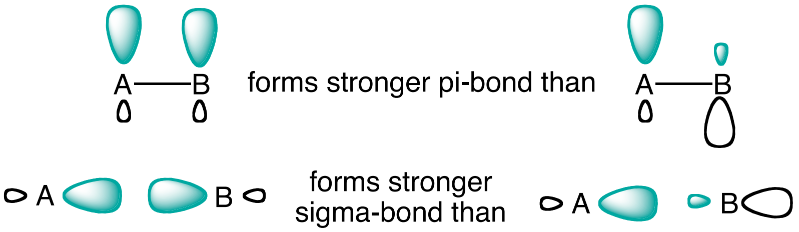
- ■ In this geometry the "small lobe" of the filled N-SP$_2$ is required to overlap with the large lobe of the antibonding C–F orbital. Hence, when the new MO's are generated the new bonding orbital is not as stabilizing as for the cis isomer.

Conclusions

- ■ Lone pair delocalization appears to override electron-electron and dipole-dipole repulsion in the stabilization of the cis isomer.
- ■ This HOMO-LUMO delocalization is stronger in the cis isomer due to better orbital overlap.

Important Take-home Lesson

Orbital orientation is important for optimal orbital overlap.



forms stronger pi-bond than

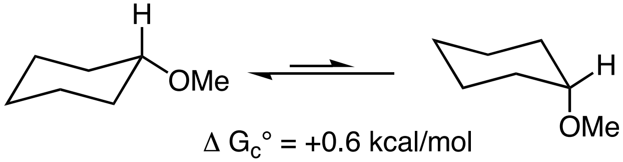
forms stronger sigma-bond than

This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

The Anomeric Effect: Negative Hyperconjugation

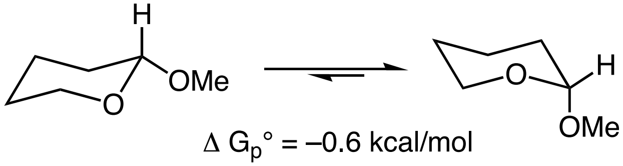
The Anomeric Effect

It is not unexpected that the methoxyl substituent on a cyclohexane ring prefers to adopt the equatorial conformation.



$\Delta G_c^\circ = +0.6$ kcal/mol

What is unexpected is that the closely related 2-methoxytetrahydropyran prefers the axial conformation:



$\Delta G_p^\circ = -0.6$ kcal/mol

That effect which provides the stabilization of the axial OR conformer which overrides the inherent steric bias of the substituent is referred to as the anomeric effect.

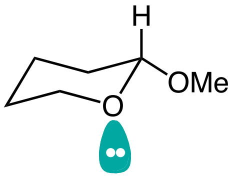
Let anomeric effect = A

$$\Delta G_p^\circ = \Delta G_c^\circ + A$$

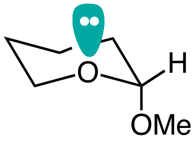
$$A = \Delta G_p^\circ - \Delta G_c^\circ$$

$$A = -0.6 \text{ kcal/mol} - 0.6 \text{ kcal/mol} = -1.2 \text{ kcal/mol}$$

Principal HOMO-LUMO interaction from each conformation is illustrated below:



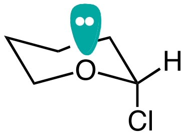
axial O lone pair↔σ∗ C–H



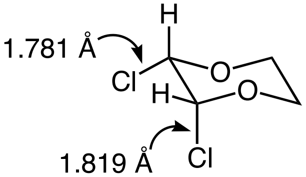
axial O lone pair↔σ∗ C–O

■ Since the antibonding C–O orbital is a better acceptor orbital than the antibonding C–H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

Other electronegative substituents such as Cl, SR etc also participate in anomeric stabilization.

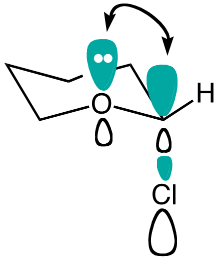


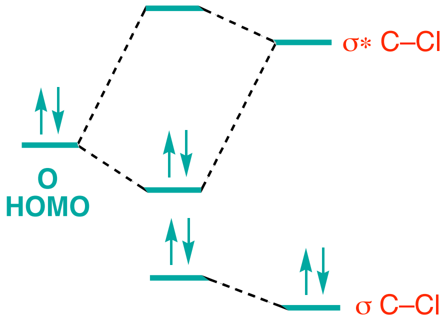
This conformer preferred by 1.8 kcal/mol



Why is axial C–Cl bond longer ?

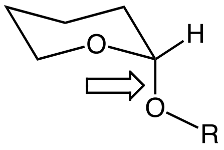
axial O lone pair↔σ∗ C–Cl

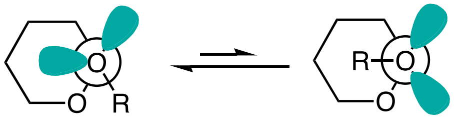




The Exo-Anomeric Effect

■ There is also a rotational bias that is imposed on the exocyclic C–OR bond where one of the oxygen lone pairs prevers to be anti to the ring sigma C–O bond

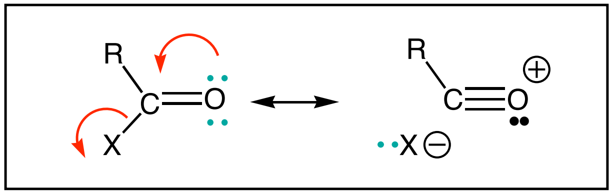




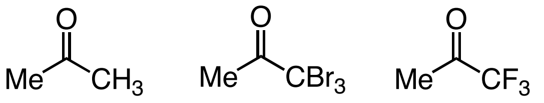
favored

A. J. Kirby, *The Anomeric and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, 1983
E. Jurasti, G. Cuevas, *The Anomeric Effect, CRC Press*, 1995

Do the following valence bond resonance structures have meaning?

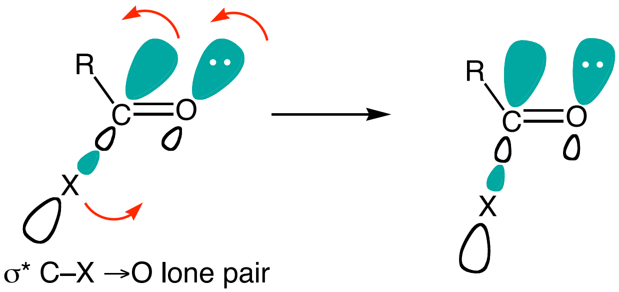


Prediction: As X becomes more electronegative, the IR frequency should increase



$\upsilon_{C=O}$ (cm^{-1}) 1720 1750 1780

Prediction: As the indicated pi-bonding increases, the X–C–O bond angle should decrease. This distortion improves overlap.



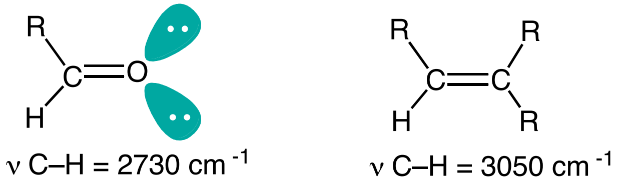
σ* C–X →O lone pair

Evidence for this distortion has been obtained by X-ray crystallography

Corey, *Tetrahedron Lett.* **1992**, *33*, 7103-7106

Aldehyde C–H Infrared Stretching Frequencies

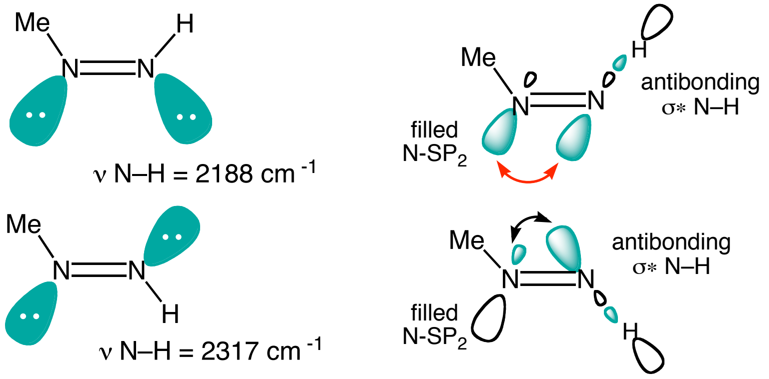
Prediction: The IR C–H stretching frequency for aldehydes is lower than the closely related olefin C–H stretching frequency. For years this observation has gone unexplained.



Sigma conjugation of the lone pair anti to the H will weaken the bond. This will result in a low frequency shift.

Infrared evidence for lone pair delocalization into vicinal antibonding orbitals.

The N–H stretching frequency of cis-methyl diazene is 200 cm^{-1} lower than the trans isomer.

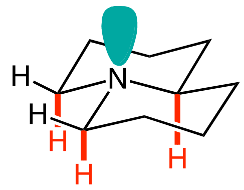


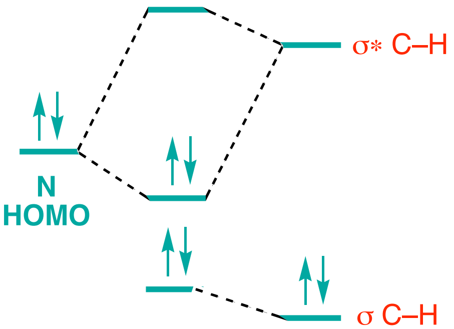
■ The low-frequency shift of the cis isomer is a result of N–H bond weakening due to the anti lone pair on the adjacent (vicinal) nitrogen which is interacting with the N–H antibonding orbital. Note that the orbital overlap is not nearly as good from the trans isomer.

N. C. Craig & co-workers *JACS* **1979**, *101*, 2480.

The Anomeric Effect: Nitrogen-Based Systems

Observation: C–H bonds anti-periplanar to nitrogen lone pairs are spectroscopically distinct from their equatorial C–H bond counterparts





Spectroscopic Evidence for Conjugation

Infrared Bohlmann Bands

Characteristic bands in the IR between 2700 and 2800 cm^{-1} for C-H_4, C-H_6 , & C-H_{10} stretch

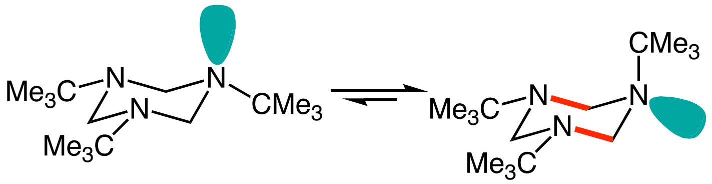
Bohlmann, *Ber.* **1958** *91* 2157

Reviews: McKean, *Chem Soc. Rev.* **1978** *7* 399
L. J. Bellamy, D. W. Mayo, *J. Phys. Chem.* **1976** *80* 1271

NMR : Shielding of H antiperiplanar to N lone pair

H_{10} (axial): shifted furthest upfield
H_6, H_4: $\Delta\delta = \delta\ H_{axial} - \delta\ H_{equatorial}$ = -0.93 ppm
Protonation on nitrogen reduces $\Delta\delta$ to -0.5ppm

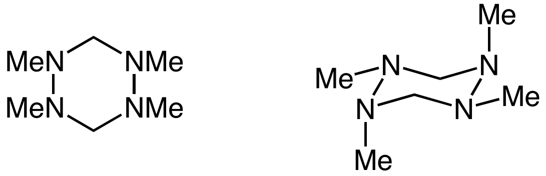
H. P. Hamlow et. al., *Tet. Lett.* **1964** 2553
J. B. Lambert et. al., *JACS* **1967** *89* 3761



$\Delta G°$ = – 0.35kcal/mol

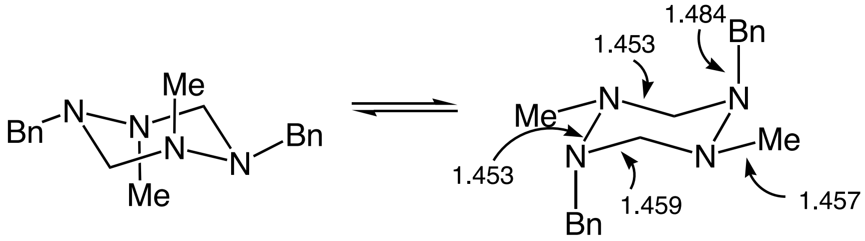
A. R. Katritzky et. al., *J. Chemm. Soc. B* **1970** 135

Favored Solution Structure (NMR)



J. E. Anderson, J. D. Roberts, *JACS* **1967** *96* 4186

B Favored Solid State Structure (X-ray crystallography)



A **B**

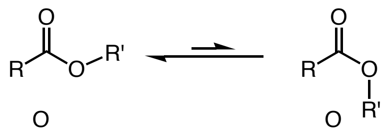
Rationalize why **B** might be more stable than **A**.

A. R. Katrizky et. al., *J. C. S. Perkin II* **1980** 1733

Carboxylic Acids (& Esters): Anomeric Effects Again?

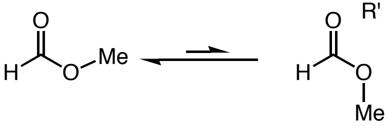
■ **Conformations:** There are 2 planar conformations.

(Z) Conformer



(E) Conformer

Specific Case:
Methyl Formate

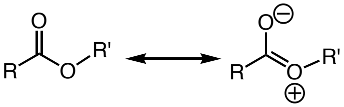


ΔG° = +4.8 kcal/mol

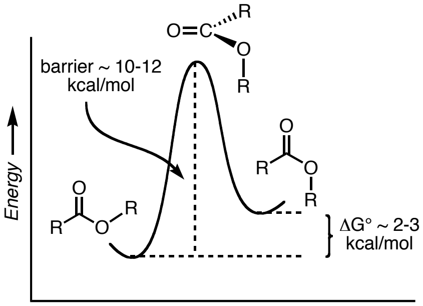
The (E) conformation of both acids and esters is less stable by 3-5 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must also be considered. These effects will be introduced shortly.

■ **Rotational Barriers:** There is hindered rotation about the =C–OR bond.

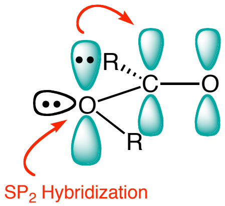
These resonance structures suggest hindered rotation about =C–OR bond. This is indeed observed:



Rotational barriers are ~ 10-12 kcal/mol. This is a measure of the strength of the pi bond.



■ **Lone Pair Conjugation:** The oxygen lone pairs conjugate with the C=O.

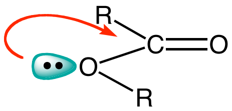


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

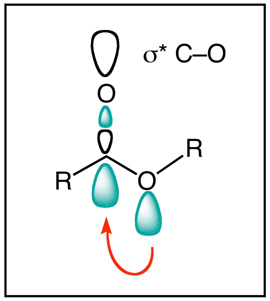
■ **Oxygen Hybridization:** Note that the alkyl oxygen is Sp2. Rehybridization is driven by system to optimize pi-bonding.

■ **Hyperconjugation:** Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

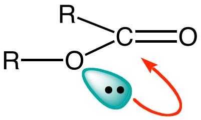
(Z) Conformer



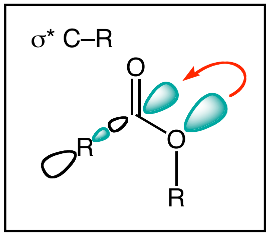
In the (Z) conformation this lone pair is aligned to overlap with σ* C–O.



(E) Conformer



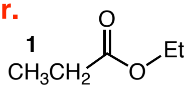
In the (E) conformation this lone pair is aligned to overlap with σ* C–R.



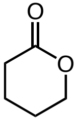
Since σ* C–O is a better acceptor than σ* C–R (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

Esters versus Lactones: Questions to Ponder.

1



2



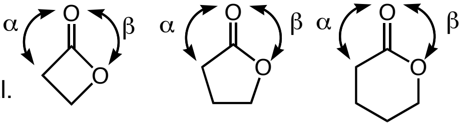
versus

Esters strongly prefer to adopt the (Z) conformation while small-ring lactones such as **2** are constrained to exist in the (Z) conformation. From the preceding discussion explain the following:

1) Lactone **2** is significantly more susceptible to nucleophilic attack at the carbonyl carbon than **1**? Explain.

2) Lactone **2** is significantly more prone to enolization than **1**? In fact the pKa of **2** is ~25 while ester **1** is ~30 (DMSO). Explain.

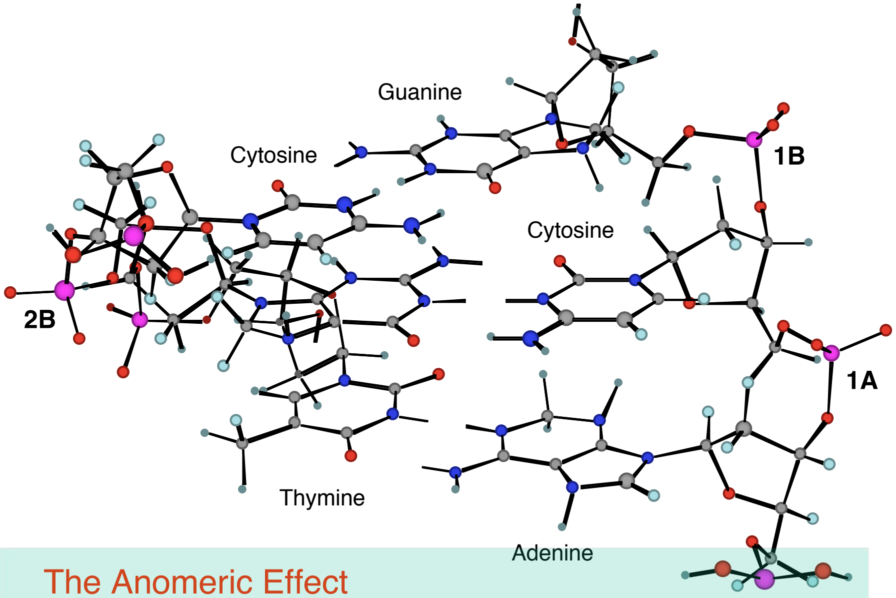
3) In 1985 Burgi, on carefully studying the X-ray structures of a number of lactones, noted that the O-C-C (α) & O-C-O (β) bond angles were not equal. Explain the indicated trend in bond angle changes.



α–β = 12.3 ° α–β = 6.9 ° α–β = 4.5 °

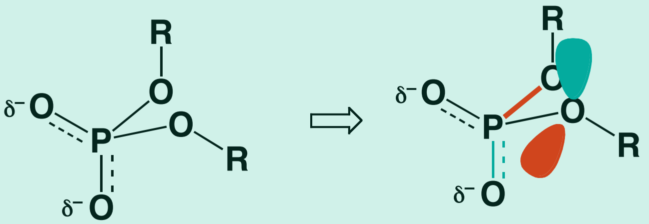
Anomeric Effects in DNA Phosphodiesters

Calculated Structure of ACG–TGC Duplex

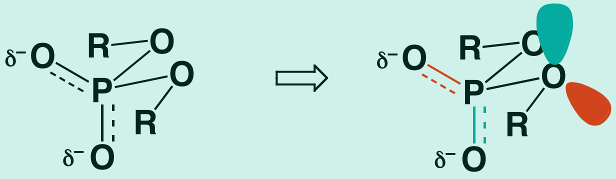


The Anomeric Effect

Acceptor orbital hierarchy: δ* P–OR * > δ* P–O$^-$



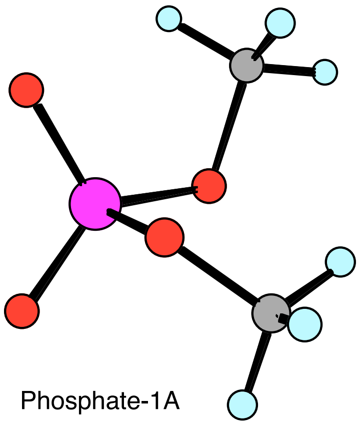
Gauche-Gauche conformation



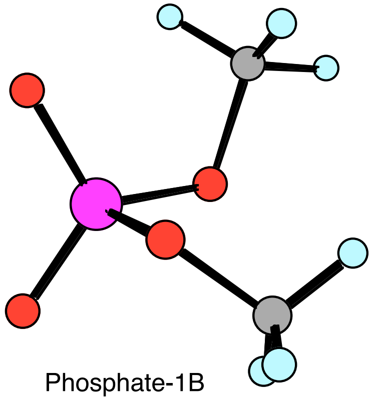
Anti-Anti conformation

Gauche-Gauche conformation affords a better donor-acceptor relationship

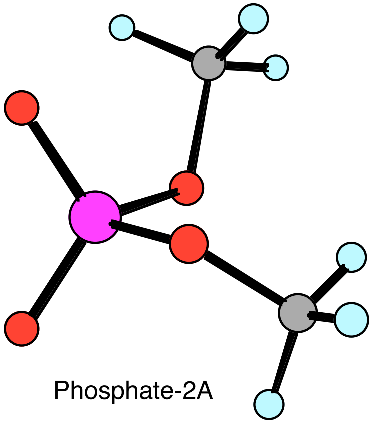
The Phospho-Diesters Excised from Crystal Structure



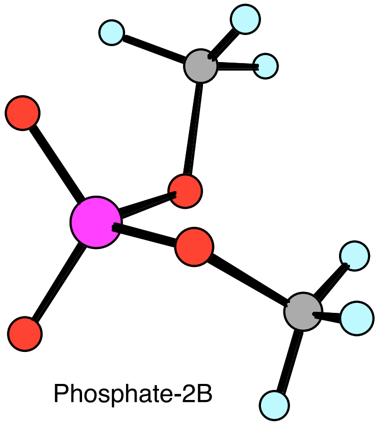
Phosphate-1A



Phosphate-1B



Phosphate-2A



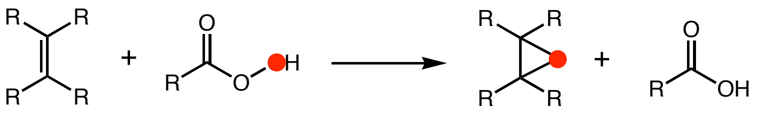
Phosphate-2B

Oxygen lone pairs may establish a simultaneous hyperconjugative relationship with both acceptor orbitals only in the illustrated conformation.

Plavec, et al. (**1996**). “How do the Energetics of the Stereoelectronic Gauche & Anomeric Effects Modulate the Conformation of Nucleos(t)ides? ” Pure Appl. Chem. **68**: 2137-44.

Olefin Epoxidation via Peracids: An Introduction

■ The General Reaction:



HOMO
πC–C

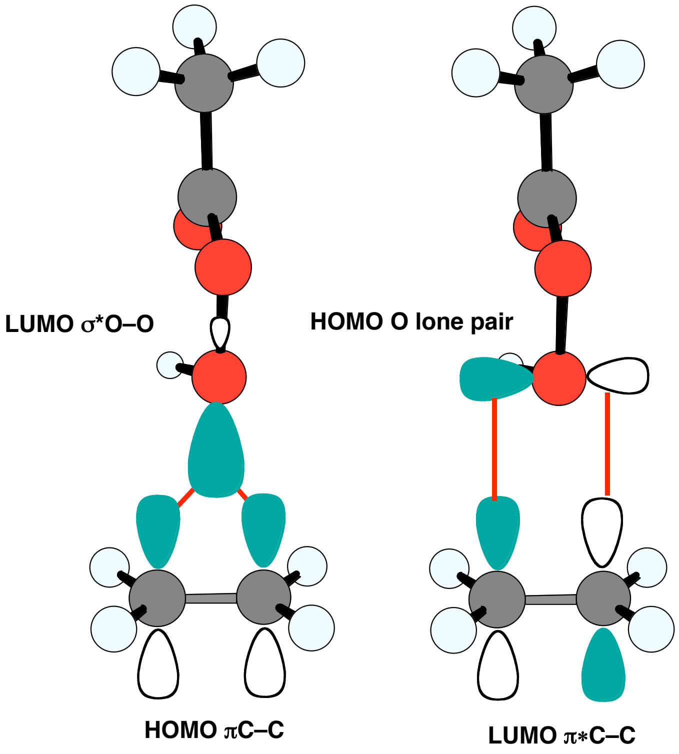
LUMO
σ*O–O

note labeled oxygen is transferfed

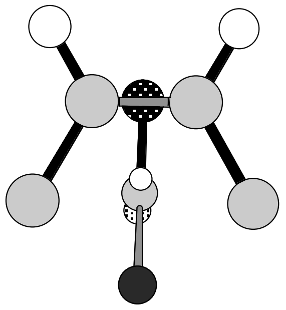
O-O bond energy: ~35 kcal/mol

HOMO–LUMO Interactions for Peracid Epoxidation

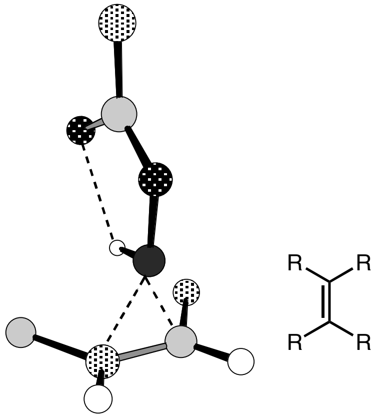
Since 2 C–O bonds are formed in the epoxidation reaction, there are two HOMO–LUMO pairs that should be considered. They are illustrated below.



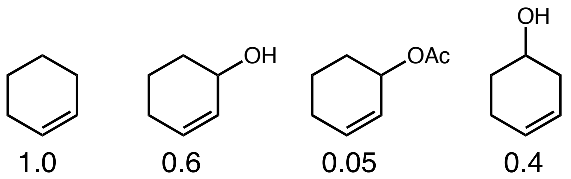
■ The transition state:



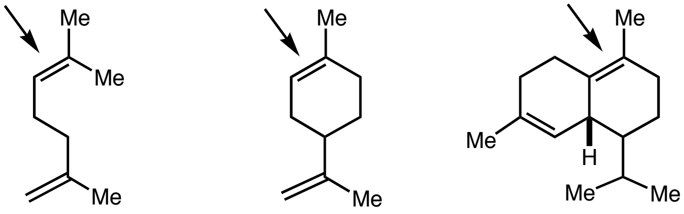
View from below olefin



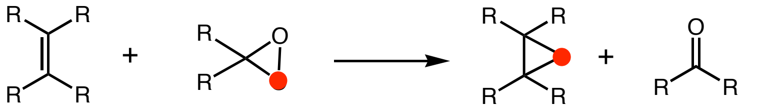
■ Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:



■ The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



Olefin Epoxidation with Dioxiranes



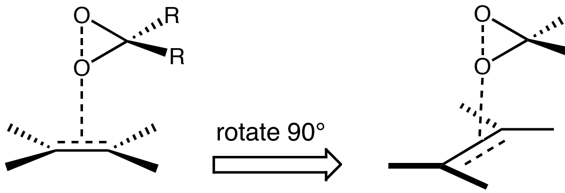
HOMO1
πC–C
LUMO2
π∗C–C

LUMO1
σ*O–O
HOMO2
O lone pr

note labeled oxygen is transferfed

O-O bond energy: ~35 kcal/mol

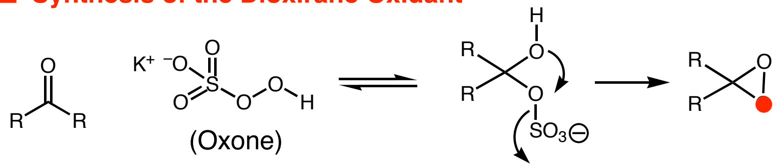
Transition State for the Dioxirane Mediated Olefin Epoxidation



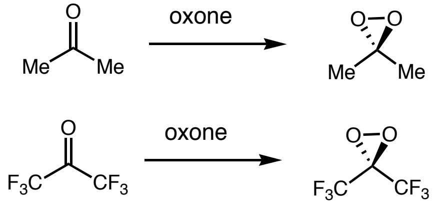
stabilizing $O_{lp} \rightarrow \pi^*$ C=C
cis olefins react ~10 times faster than *trans*

Houk, *JACS*, **1997**, 12982.

■ Synthesis of the Dioxirane Oxidant



Synthetically Useful Dioxirane Synthesis

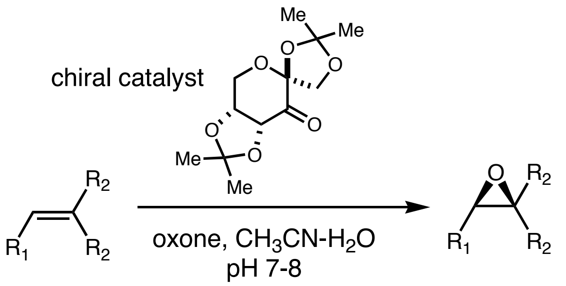


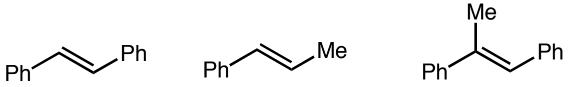
co-distill to give ~0.1 M soln of dioxirane in acetone

co-distill to give ~0.6 M soln of dioxirane in hexafluoroacetone

Asymmetric Epoxidation with Chiral Ketones

Review: Frohn & Shi, *Syn Lett* **2000**, 1979-2000 **(PDF)**

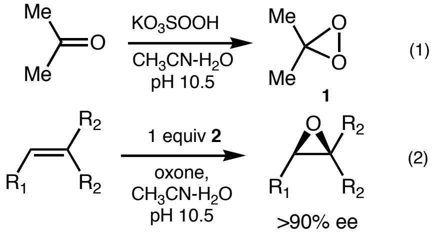




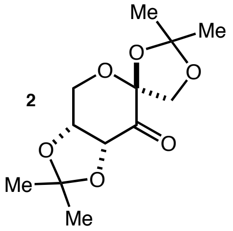
>95% ee 84% ee 92% ee

Question: First hour Exam 2000 (Database Problem 34)

Question 4. (15 points). The useful epoxidation reagent dimethyldioxirane (**1**) may be prepared from "oxone" (KO_3SOOH) and acetone (eq 1). In an extension of this epoxidation concept, Shi has described a family of chiral fructose-derived ketones such as **2** that, in the presence of "oxone", mediate the asymmetric epoxidation of di- and tri-substituted olefins with excellent enantioselectivities (>90% ee) (*JACS* **1997**, *119*, 11224).



2

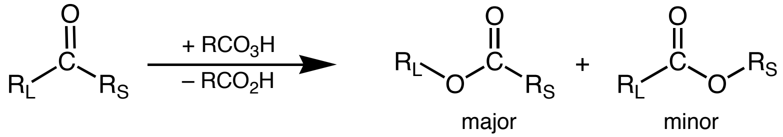


Part A (8 points). Provide a mechanism for the epoxidation of ethylene with dimethyldioxirane (**1**). Use three-dimensional representations, where relevant, to illustrate the ***relative*** stereochemical aspects of the oxygen transfer step. Clearly identify the frontier orbitals involved in the epoxidation.

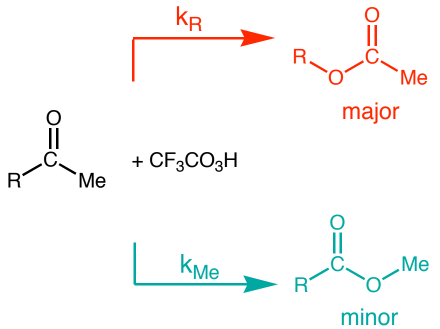
Part B (7 points). Now superimpose chiral ketone **2** on to your mechanism proposed above and rationalize the sense of asymmetric induction of the epoxidation of trisubstituted olefins (eq 2). Use three-dimensional representations, where relevant, to illustrate the ***absolute*** stereochemical aspects of the oxygen transfer step.

The Baeyer-Villiger Reaction: Stereoelectronic Effects

Let R_L and R_S be Sterically large and small substituents.

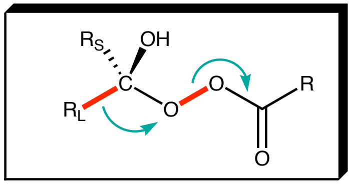


The major product is that wherein oxygen has been inserted into the R_L–C=O bond.



R	k_R / K_{Me}
CH_3CH_2	72
$CH_3(CH_2)_2$	150
$(CH_3)_3C$	830
$PhCH_2$	>2000

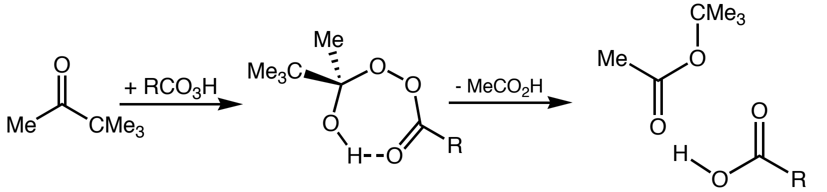
The Intermediate



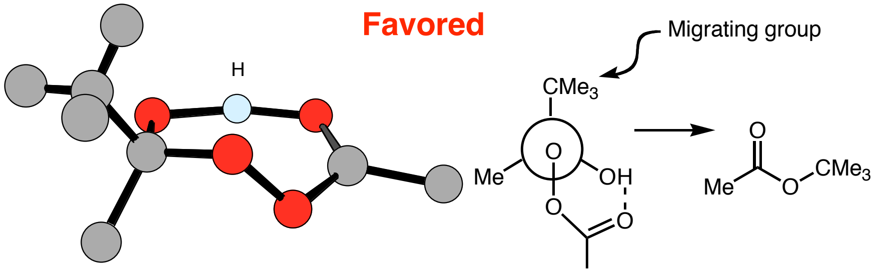
The important stereoelectronic components to this rearrangement:

1. The R_L–C–O–O dihedral angle must be180° due to the HOMO LUMO interaction σ-R_L–C with σ*–O–O.
2. The C–O–O–C' dihedral angle will be ca. 60° due to the gauche effect (O-lone pairsσ*–C–O).

This gauche geometry is probably reinforced by intramolecular hydrogen bonding as illustrated on the opposite page:

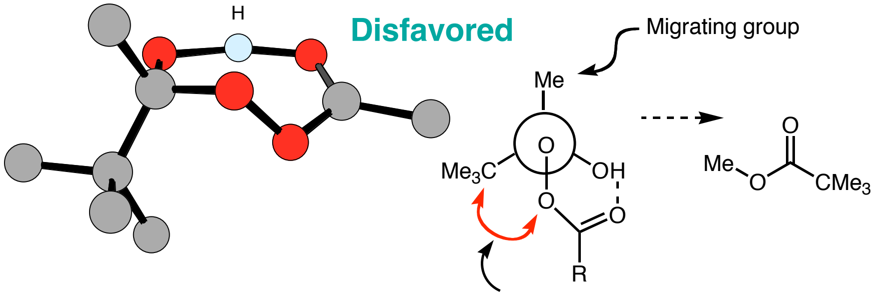


Favored



Conformer A

Disfavored



Conformer B

The destabilizing gauche interaction

Steric effects destabilize Conformer B relative to Conformer A; hence, the reaction is thought to proceed via a transition state similar to A.

For relevant papers see:
Crudden, *Angew. Chem. Int. Ed* **2000**, *39*, 2852-2855 **(pdf)**
Kishi, *JACS* **1998**, *120*, 9392 **(pdf)**

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 3

Stereoelectronic Effects-3

- The S_N2 Reaction: Stereoelectronic Effects
- Baldwin's Rules for Ring Closure

Read Kirby, Chapter 5, Cary & Sundberg, Chapter 5

Useful LIterature Reviews

Johnson, C. D. (**1993**). “Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules.” *Acc. Chem. Res.* **26**: 476-82. **(Pdf)**

Beak, P. (**1992**). “Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms.” *Acc. Chem. Res.* **25**: 215. **(Pdf)**

D. A. Evans

Friday,
September 22, 2006

"Rules for Ring Closure: Baldwin's Rules"

Sir Jack Baldwin

The Primary Literature

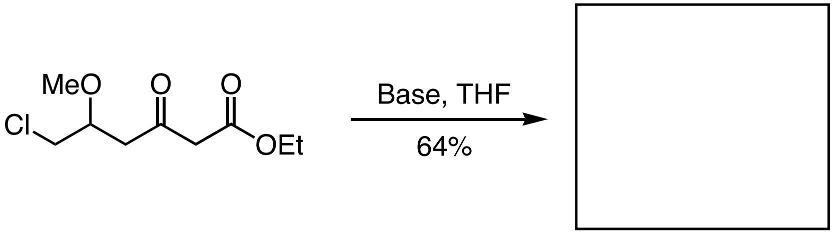
Baldwin, *J. Chem. Soc., Chem. Comm.* **1976**, 734, 736.

Baldwin, *J. Chem. Soc., Chem. Comm.* **1977** 233.

Baldwin, *J. Org. Chem.* **1977**, *42*, 3846.

Baldwin, *Tetrahedron* **1982**, *38*, 2939.

Problem 689. Predict the product of the reaction below. Include a rationalization based on a detailed analysis of competing transition state geometries.



Distinguished Members of the ETH

Eidgenössische Technische Hochschule Zürich

Prof. Dr. Jack D. Dunitz
Laboratory of Organic Chemistry
ETH Hoenggerberg, HCI
CH-8093 Zürich, Switzerland

Jack Dunitz (1923) studied chemistry at Glasgow University, (Ph.D. 1947) and held research fellowship at Oxford University (1946-1948, 1951-1953), the California Institute of Technology (1948-1951, 1953-1954), the U.S. National Institute of Health, Bethesda MD (1954-1955), and the Royal Institution, London (1956-1957), before taking up a professorship at the ETH-Zürich, a post that he held until his retirement in 1990. He has held Visiting Professorships in the United States, Israel, Japan and the United Kingdom, has been elected to membership of several learned societies, and has received several awards for his work. He has written more than 300 scientific papers.

Prof. Erick Carreira

Erick M. Carreira was born in Havana, Cuba in 1963. He obtained a B.S. degree in 1984 from the Univ. of Illinois at Urbana–Champaign under the supervision of Scott E. Denmark and a Ph.D. degree in 1990 from Harvard University under the supervision of David A. Evans. After carrying out postdoctoral work with Peter Dervan at the California Institute of Technology through late 1992, he joined the faculty at the same institution as an assistant professor of chemistry and subsequently was promoted to the rank of associate professor of chemistry in the Spring of 1996, and full professor in Spring 1997. Since September 1998, he has been full professor of Organic Chemistry at the ETH Zürich.

Eidgenössische Technische Hochschule Zürich

Prof. Dr. Albert Eschenmoser
Laboratory of Organic Chemistry
ETH Hoenggerberg, HCI
CH-8093 Zürich, Switzerland

Albert Eschenmoser has been Professor Emeritus at ETH Zurich since 1992.

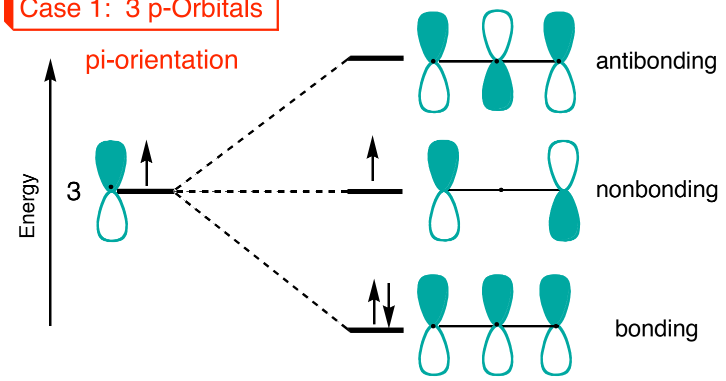
He was born in Erstfeld (Uri), Switzerland, on August 5, 1925 and received his Dipl.sc.nat. in 1949 and his D.Sci. in 1951 from the Swiss Federal Institute of Technology (ETH), where he became private lecturer in Organic Chemistry in 1956, associate professor in 1960, and full professor for General Organic Chemistry in 1965. In his research in organic and bioorganic chemistry, Eschenmoser has made contributions to theory of terpene biosynthesis, structure elucidation of natural products, stereochemistry and mechanism of organochemical and biochemical reactions, development of new methods for organic synthesis, total synthesis of complex natural products and chemical etiology of nucleic acid structure. Eschenmoser is a member of the German Academy Leopoldina (Halle), Academia Europaea (UK) and the Pontifical Academy (Vatican), a foreign member of the American Academy of Arts and Sciences (Boston), the National Academy of Sciences (Washington), the Royal Society (UK), the Academy of Science in Göttingen, the Croatian Academy of Sciences and Arts (Zagreb), the orden Pour le mérite für Wissenschaften und Künste (Berlin), and the Österreichisches Ehrenzeichen für Wissenschaft und Kunst (Wien), he is a honorary member of the Royal Society of Chemistry (London), Gesellschaft Österreichischer Chemiker (Wien), and the Pharmaceutical Society of Japan. He holds honorary degrees from the Universities of Fribourg, Chicago, Edinburgh, Bologna, Frankfurt, Strasbourg, Harvard, and from The Scripps Research Institute.

Three-Center Bonds: A Review

Consider the linear combination of three atomic orbitals. The resulting molecular orbitals (MOs) usually consist of one bonding, one nonbonding and one antibonding MO.

Case 1: 3 p-Orbitals

pi-orientation



Note that the more nodes there are in the wave function, the higher its energy.

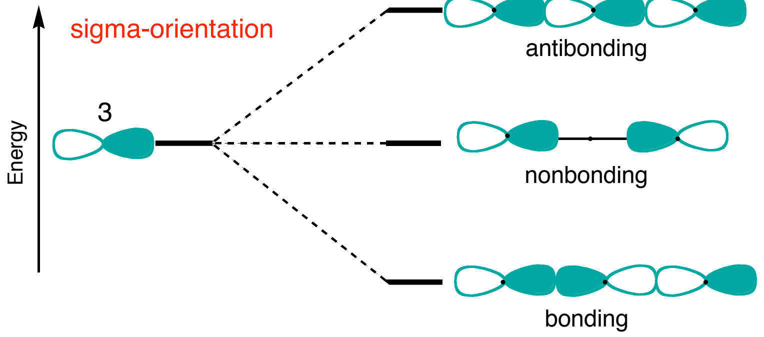
$H_2C{=}CH{-}\overset{+}{C}H_2$ **Allyl carbonium ion:** both pi-electrons in bonding state

$H_2C{=}CH{-}\overset{\bullet}{C}H_2$ **Allyl Radical:** 2 electrons in bonding obital plus one in nonbonding MO.

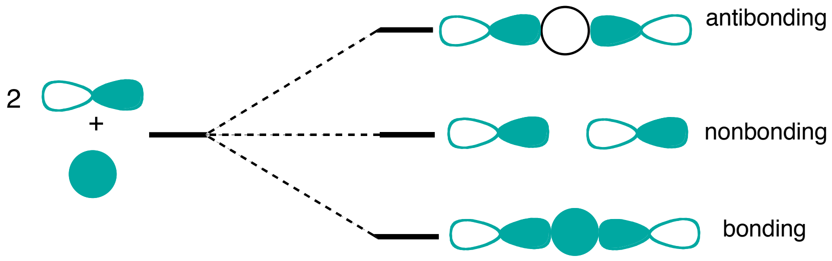
$H_2C{=}CH{-}\overset{-}{C}H_2$ **Allyl Carbanion:** 2 electrons in bonding obital plus 2 in nonbonding MO.

Case 2: 3 p-Orbitals

sigma-orientation



Case 3: 2 p-Orbitals; 1 s-orbital

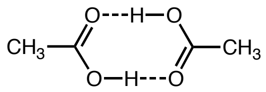


Case 4: 2 s-Orbitals; 1 p-orbital

Do this as an exercise

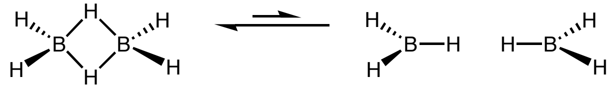
Examples of three-center bonds in organic chemistry

A. H-bonds: (3–center, 4–electron)



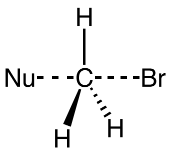
The acetic acid dimer is stabilized by ca 15 kcal/mol

B. H-B-H bonds: (3-center, 2 electron)



diborane stabilized by 35 kcal/mol

C. The S_N2 Transition state: (3–center, 4–electron)

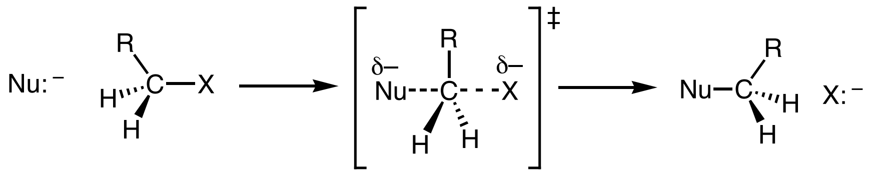


The S_N2 transition state approximates a case 2 situation with a central carbon p-orbital

The three orbitals in reactant molecules used are:
1 nonbonding MO from Nucleophile (2 electrons)
1 bonding MO σ C–Br (2 electrons)
1 antibonding MO σ* C–Br

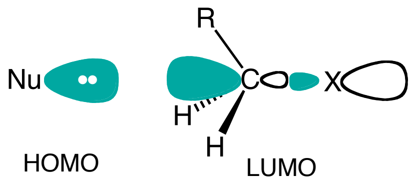
Substitution Reactions: General Considerations

Why do S_N2 Rxns proceed with backside displacement?



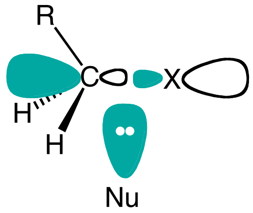
Given the fact that the LUMO on the electrophile is the C–X antibonding orblital, Nucleophilic attack could occur with either inversion or retention.

Inversion



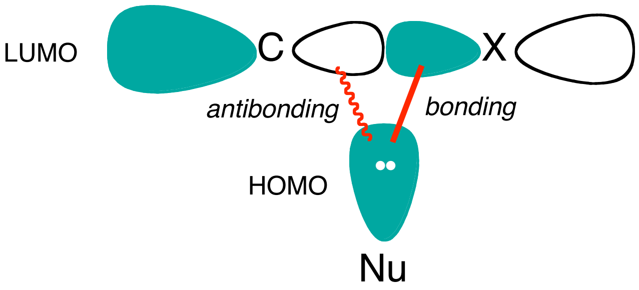
Constructive overlap between Nu & σ*C–X

Retention



Overlap from this geometry results in no net bonding interaction

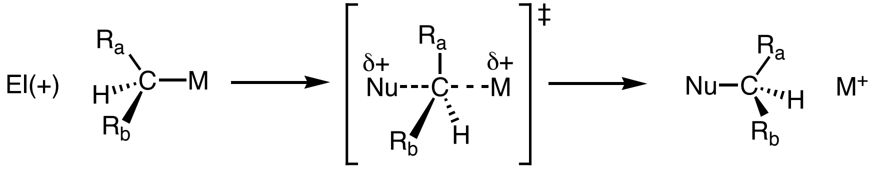
Expanded view of σ*C–X



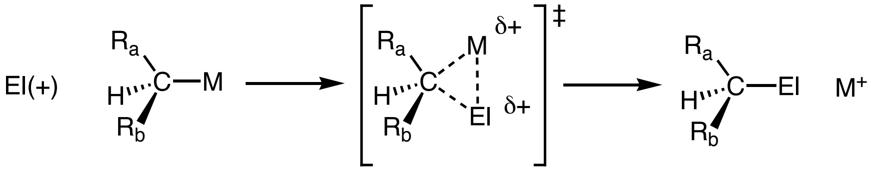
Fleming, page 75-76

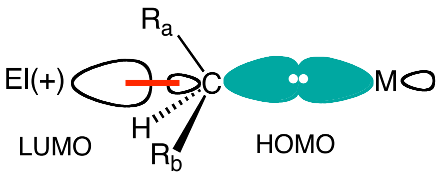
Electrophilic substitution at saturated carbon may occur with either inversion of retention

Inversion

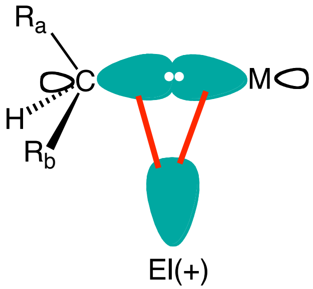


Retention



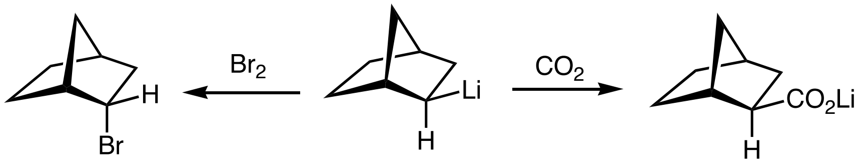


Inversion



Retention

Examples



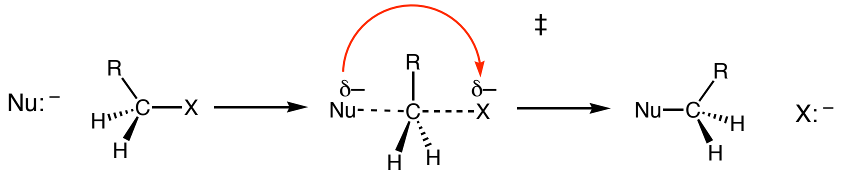
predominant inversion

predominant retention

Stereochemistry frequently determined by electrophile structure

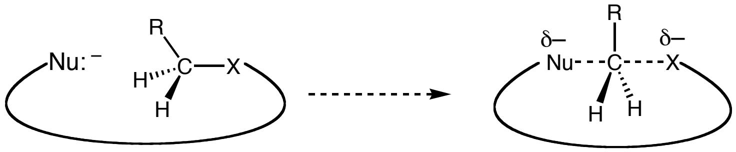
See A. Basu, *Angew. Chem. Int. Ed.* **2002**, *41*, 717-738 **(PDF)**

S_N2 Reaction: Stereoelectronic Effects



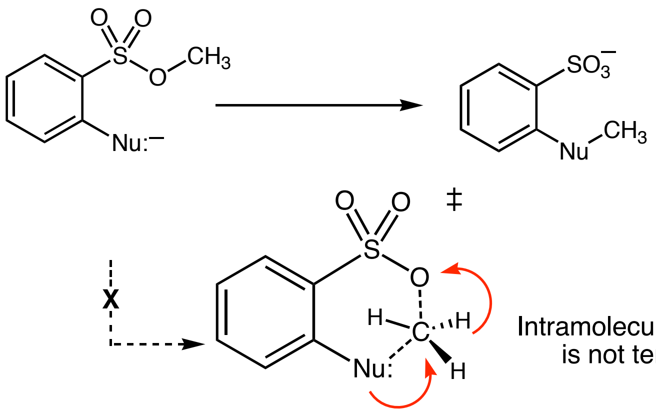
What is the absolute requirement for the Nu–C–X bond angle??
180° +/– ??

Eschenmoser: Tether Nu and X



"tethered reactants" "constrained transition state"

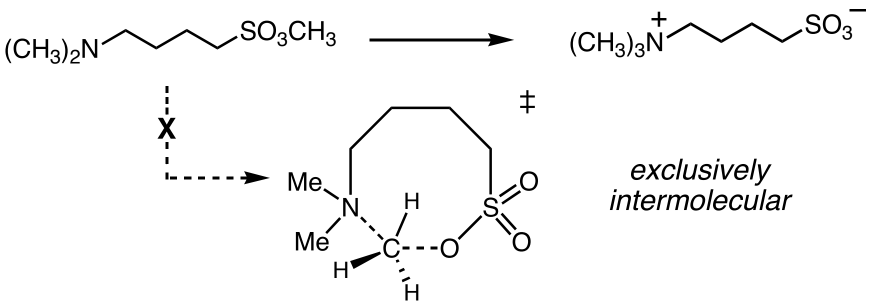
Eschenmoser, *Helv. Chim Acta* **1970**, *53*, 2059 **(PDF)**



Intramolecular option is not tenable

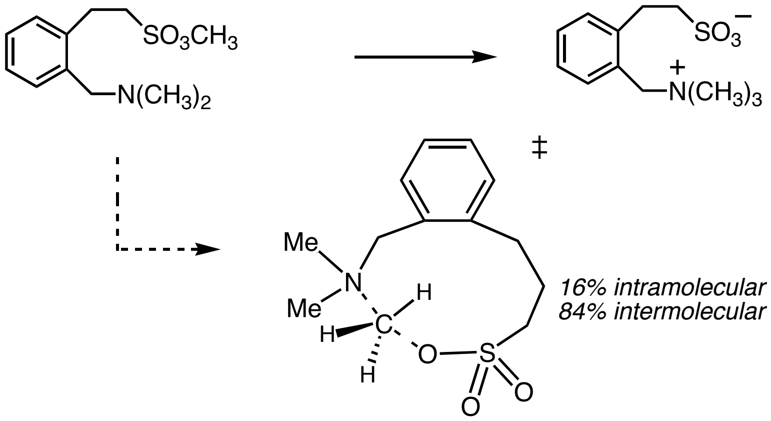
The reaction illustrated above proceeds exclusively through bimolecular pathway in contrast to the apparent availability of the intramolecular path.

Related Cases: " The Endocyclic Restriction Test"



exclusively intermolecular

King, et al. **1982** *Chem Commun*. 175
King, et al. **1982** *Tetrahedron Lett. 23, 4465*



16% intramolecular
84% intermolecular

10-membered transition structure

Hence, the Nu–C–X 180 ° transition state bond angle must be rigidly maintained for the reaction to take place.

"Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms",
Peter Beak,
Acc. Chem. Res.; **1992** *25*, 215-222 **(PDF)**

Ring Closure and Stereoelectronic Considerations An Examination of Baldwin's Rules

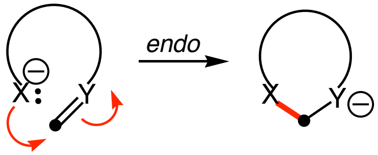
"Baldwin's Rules" provides a qualitative set of generalizations on the probability of a given ring closure.

There are circumstances where the "rules" don't apply.

- They do not apply to non-first-row elements participating in the cyclization event. The longer bond lengths and larger atomic radii of 2nd row elements result in relaxed geometrical constraints.

For example, a change in a heteroatom from O to S could result in relaxation of a given geometric constraint.

X = O vs S

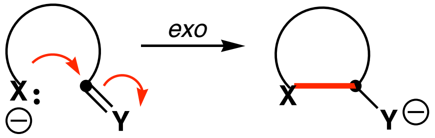


- The "rules" do not apply to electrocyclic processes.

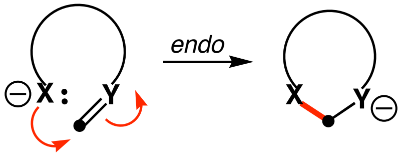
Nomenclature

Classes of Ring Closing Processes

A. Exo-cyclization modes identified by the breaking bond being positioned exocyclic to the forming cycle.



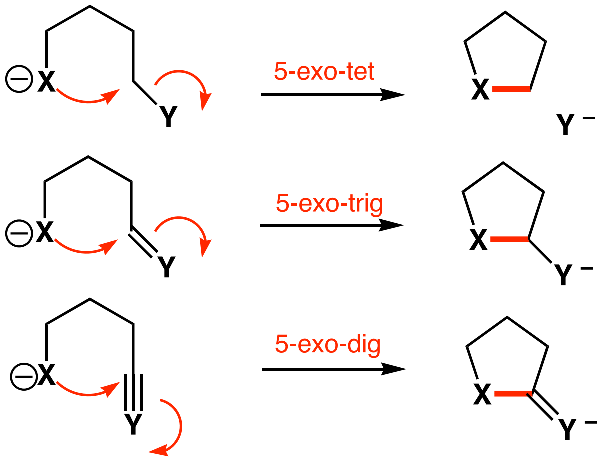
B. Endo-cyclization modes identified by the breaking bond being positioned endocyclic to the forming cycle.



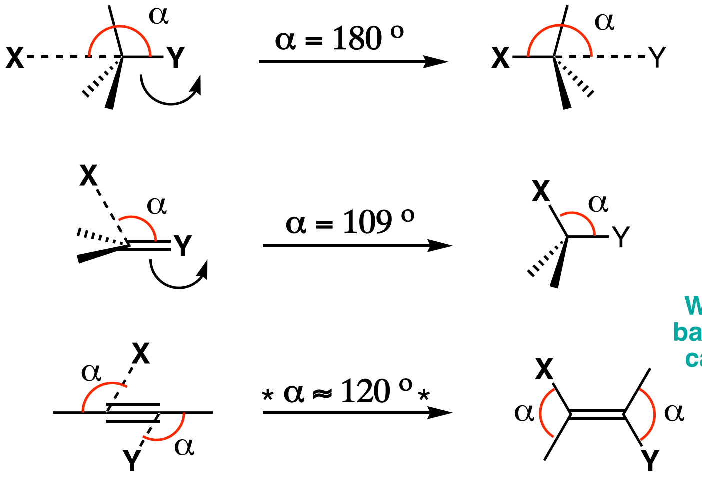
X = first-row element N, O

C. Nucleophilic ring closures sub-classified according to hybridization state of **electrophilic** component: (tetrahedral = tet; trigonal = trig; digonal = dig)

D. Nucleophilic ring closures further subclassified according to size of the fomed ring. For example:



Required trajectories (Baldwin):



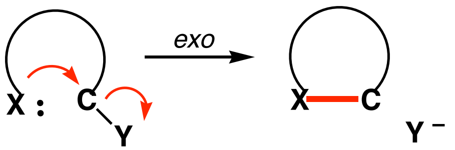
Will come back to this case later

Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

Rules for Ring Closure: SP^3 Carbon & Related Systems

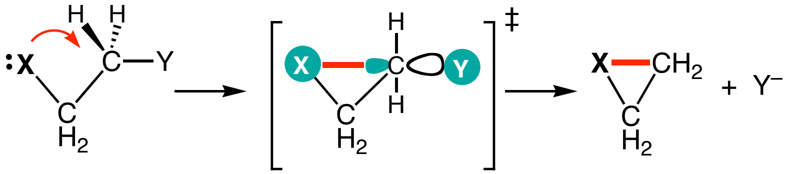
Tetrahedral Carbon

All exo cyclization modes are allowed: (n-exo-tet, n = 3→)



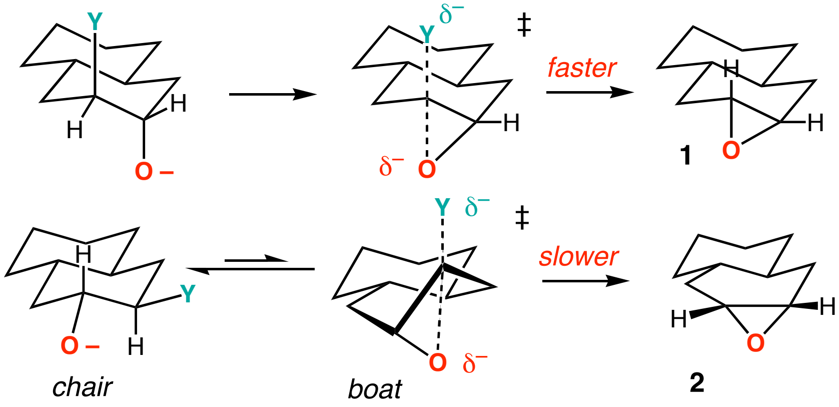
There are stereoelectronic issues to consider for **n-exo-tet** cyclizations

Formation of 3-Membered Rings (3-exo-tet)



Conformational Effects in Epoxide Ring Formation/cleavage

Those stereoelectronic effects that operate in ring cleavage also influence ring formation. Consider a rigid cyclohexene oxide system:



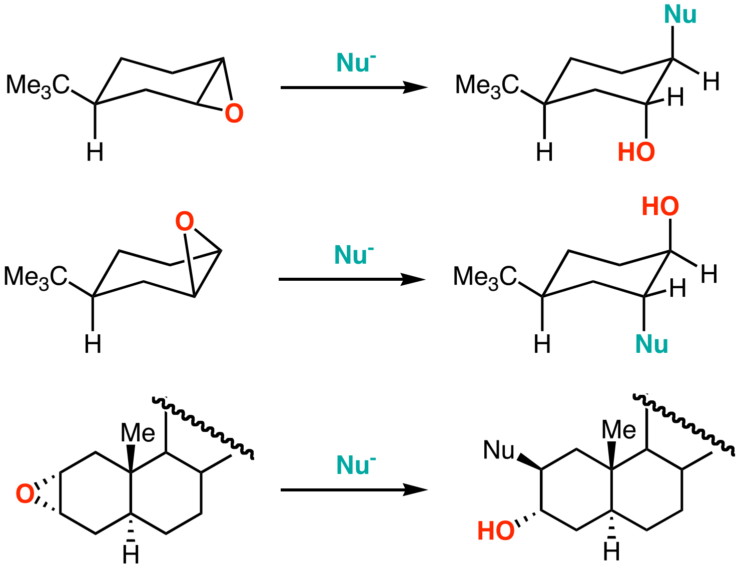
FÜRST-PLATTNER RULE

In this simple model, the transition-state leading to **1** involves the diaxial orientation of nucleophile and leaving group. This orientation affords the best overlap of the anti-bonding C–Y orbital and the nonbonding electron pairs on the nucleophile O^-.

In the formation of the diastereomeric epoxide **2**, the proper alignment of orbitals may only be achieved by cyclization through the less-favored boat conformer. Accordingly, while both cyclizations are "allowed", there are large rate differences the the rates of ring closure.

While the FÜRST-PLATTNER RULE deals wilth the microscopic reverse, in the opening of epoxides by nucleophiles, the stereoelectronic arguments are the same.

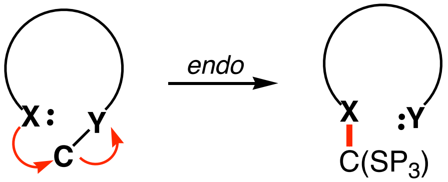
Stereoelectronic Effects in Epoxide Ring Cleavage



Rules for Ring Closure: SP3 Carbon & Related Systems

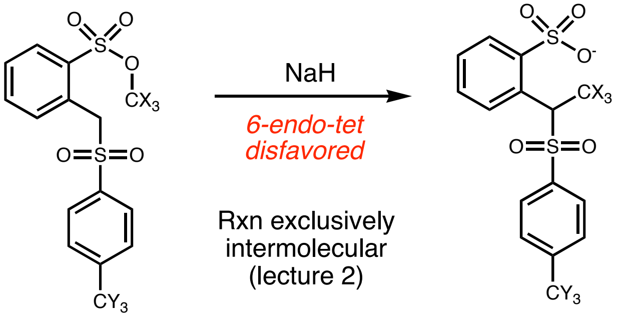
Tetrahedral Carbon

Endo cyclization modes that are disallowed (n-endo-tet, n = 3→~9)



The stereoelectronic requirement for a 180° X–C–Y bond angle is only met when the endo cyclization ring size reaches 9 or 10 members.

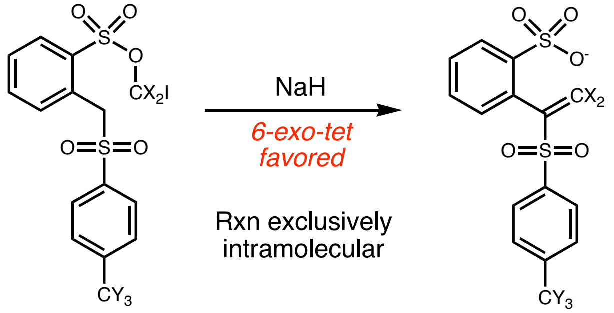
Case 1: Eschenmoser, *Helvetica Chim. Acta* **1970**, *53*, 2059.



6-endo-tet disfavored

Rxn exclusively intermolecular (lecture 2)

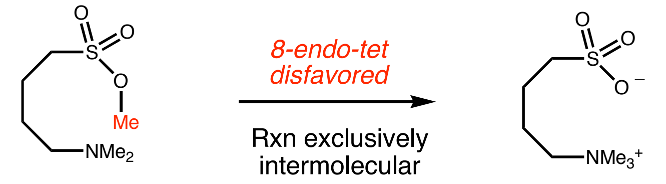
Cyclization exclusively intermolecular. However the exocyclic analog is exclusively intramolecular



6-exo-tet favored

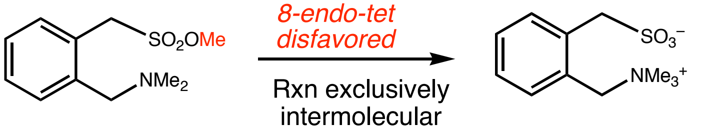
Rxn exclusively intramolecular

Case 2: King, *J.C.S. Chem. Comm.*, **1979**, 1140.



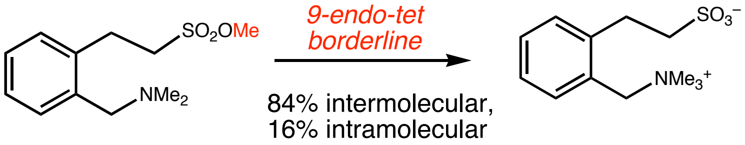
8-endo-tet disfavored

Rxn exclusively intermolecular



8-endo-tet disfavored

Rxn exclusively intermolecular



9-endo-tet borderline

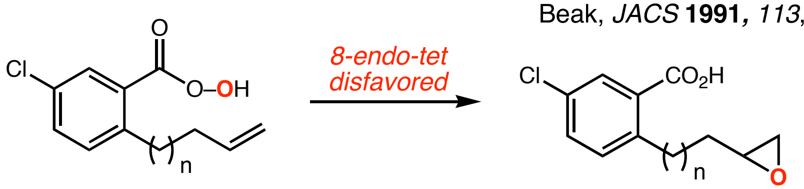
84% intermolecular, 16% intramolecular

Conclusions

Allowed endo cyclization modes will require transition state ring sizes of at least nine members.

Intramolecular epoxidation has also been evaluated

Beak, *JACS* **1991**, *113*, 6281.



8-endo-tet disfavored

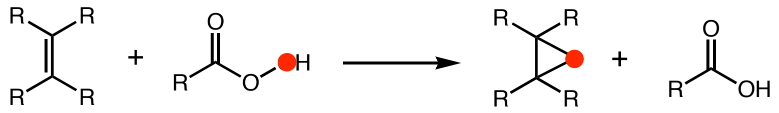
n = 1: rxn exclusively intermolecular
n = 9: rxn is intramolecular

Beak states that the conclusions made with carbon substitution also hold for oxygen atom transfer.

Beak, P. (**1992**). “Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms.” *Acc. Chem. Res.* **25**: 215.

Olefin Epoxidation via Peracids: An Intramolecular Case

■ The General Reaction:



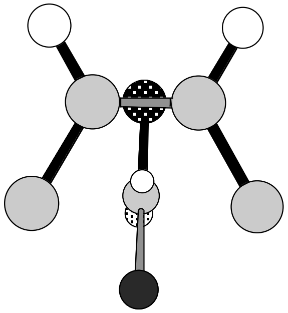
HOMO
πC–C

LUMO
σ^*O–O

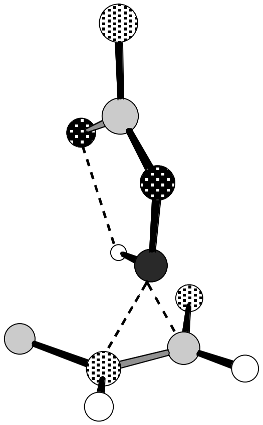
note labeled oxygen is transferfed

O-O bond energy: ~35 kcal/mol

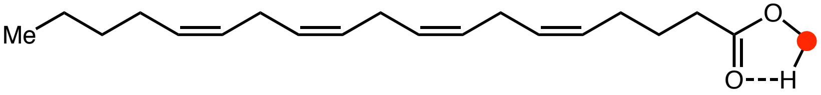
■ The transition state:



View from below olefin

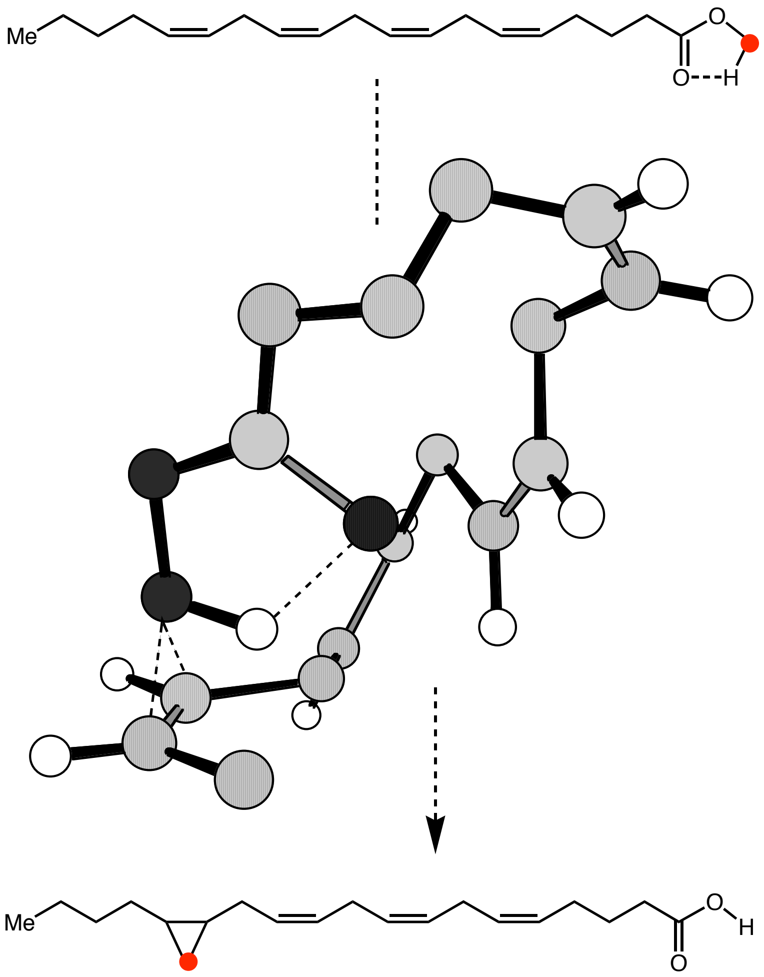


Per-arachidonic acid Epoxidation



Which olefin is selectively epoxidized??

Per-arachidonic acid Epoxidation



E. J. Corey, *JACS* **101**, 1586 (1979)

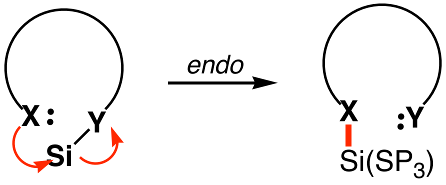
For a more detailed study see P. Beak, *JACS* **113**, 6281 (1991)

For theoretical studies of TS see R. D. Bach, *JACS* **1991**, *113*, 2338
R. D. Bach, *J. Org. Chem* **2000**, *65*, 6715

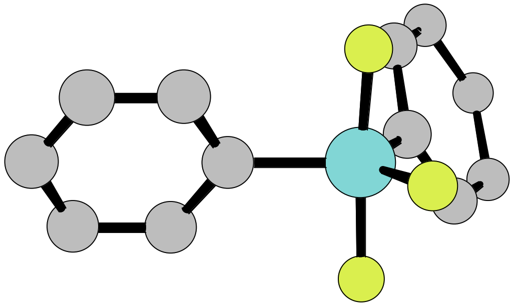
Rules for Ring Closure: SP3 Carbon Versus Silicon

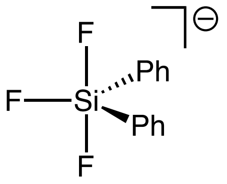
Tetrahedral Silicon

All Endo-Tet cyclization modes are allowed

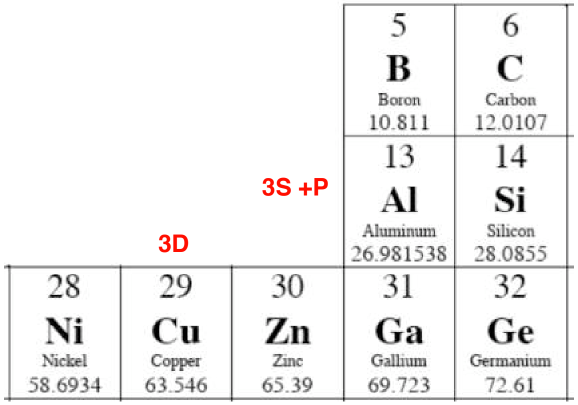


Silicon may readily proceed through a hypervalent intermediate.





Inorg. Chem. **1984**, *23*, 1378

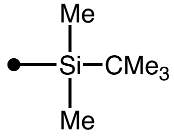


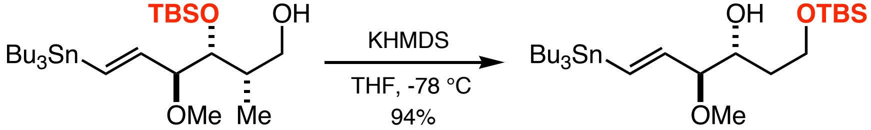
			5 **B** Boron 10.811	6 **C** Carbon 12.0107
			13 **Al** Aluminum 26.981538	14 **Si** Silicon 28.0855
28 **Ni** Nickel 58.6934	29 **Cu** Copper 63.546	30 **Zn** Zinc 65.39	31 **Ga** Gallium 69.723	32 **Ge** Germanium 72.61

Brook Rearrangements

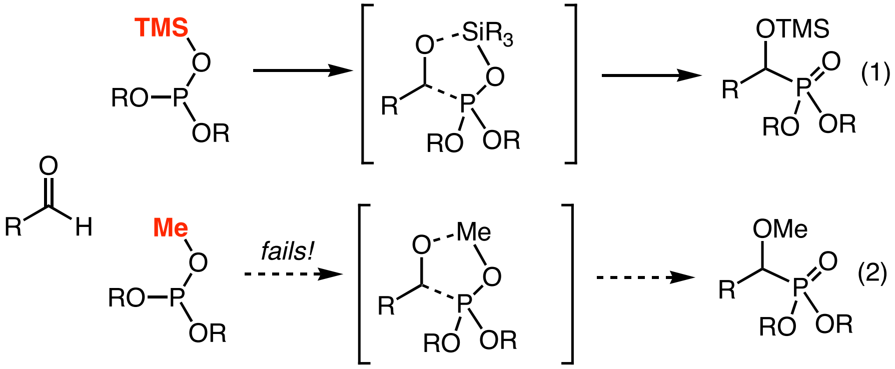
Explain what drives this rearrangement.

TBS =

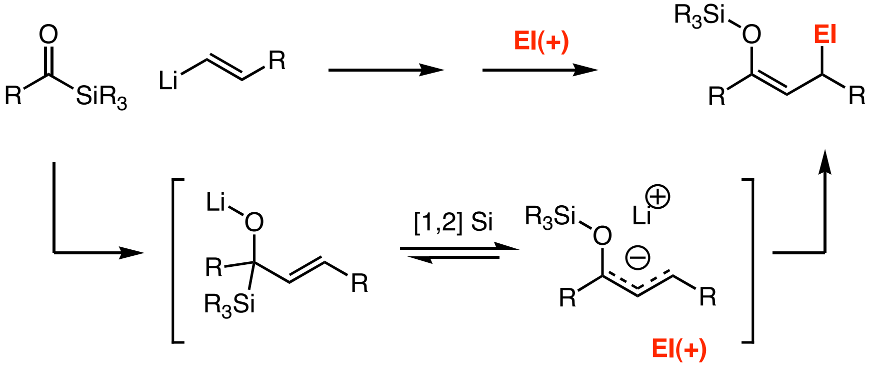




Calter, M. A. Ph. D. Thesis, Harvard University, 1993.



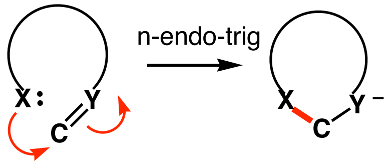
Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084



Rules for Ring Closure: SP2 Carbon & Related Systems

Trigonal Carbon

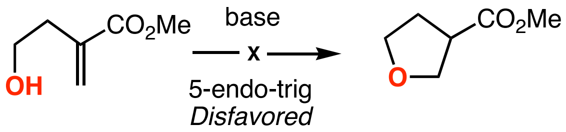
Endo cyclization modes that are disallowed (3 to 5-endo-trig)



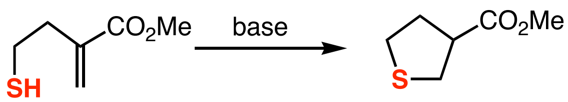
X = first-row element

The 5-endo-trig cyclization is a watershed case

Case 1: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

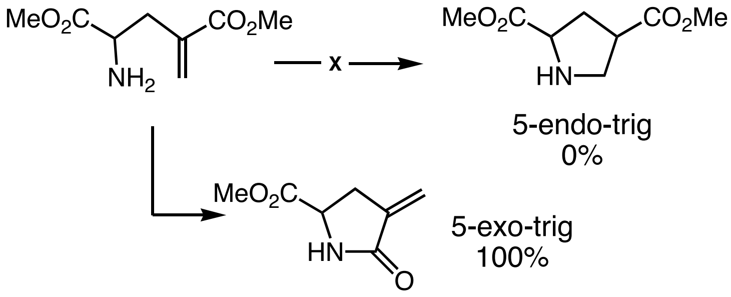


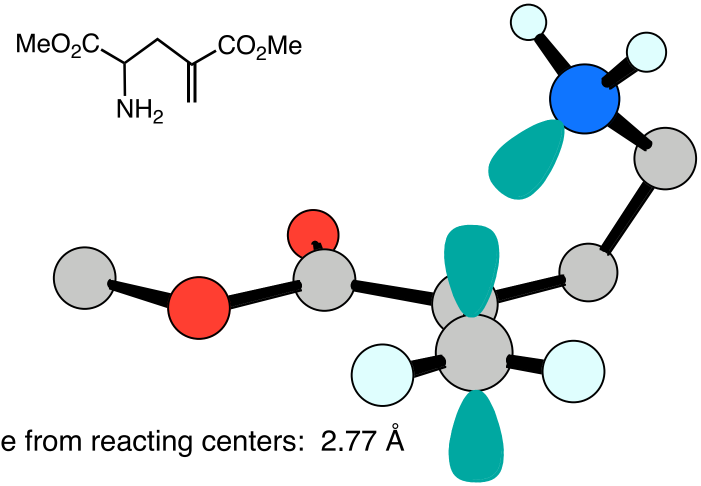
however



Second row atom relaxes the cyclization geometrical requirement

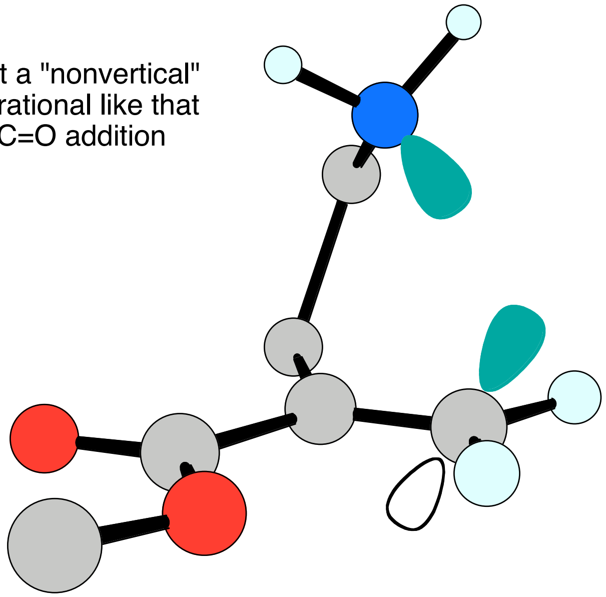
Case 2: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.





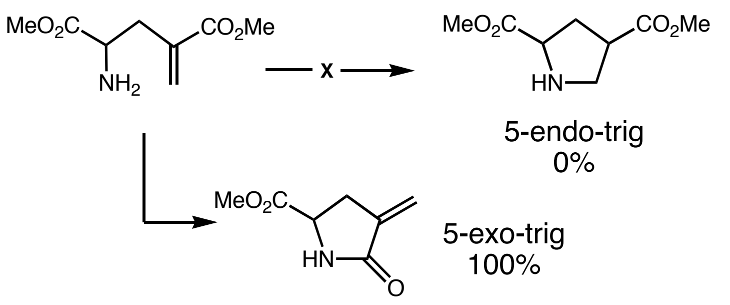
distance from reacting centers: 2.77 Å

It is possible that a "nonvertical" trajectory is operational like that suspected in C=O addition

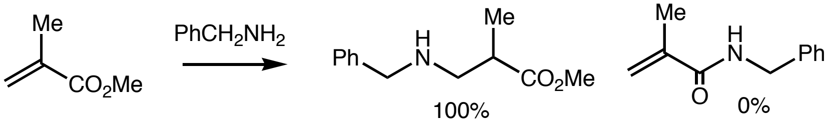


Rules for Ring Closure: SP^2 Carbon & Related Systems

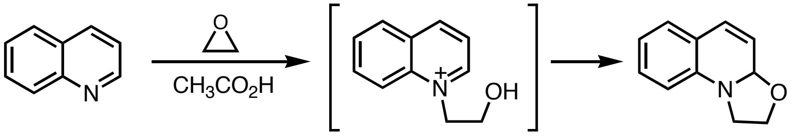
Case 2: continued...



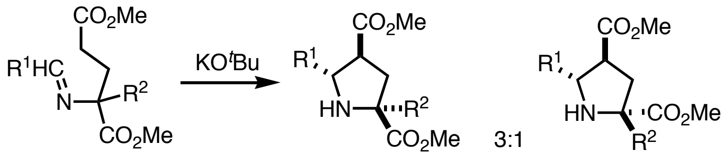
Control experiment: Intermolecular reaction favors conjugate addtion;



Apparent exceptions to disallowed 5-endo-trig cyclization process



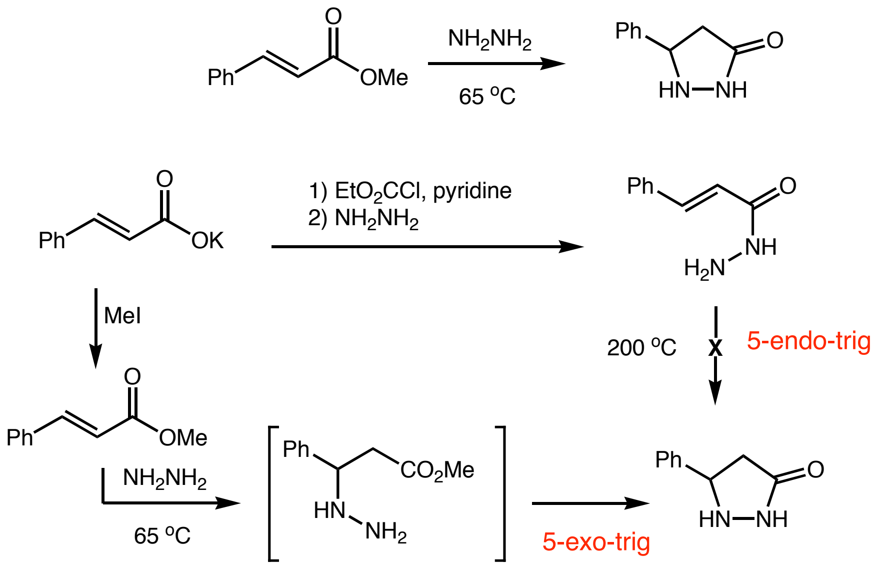
Filer, *J. Am. Chem. Soc.* **1979**, *44*, 285.



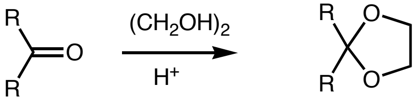
R^1 = aryl, R^2 = aryl, alkyl

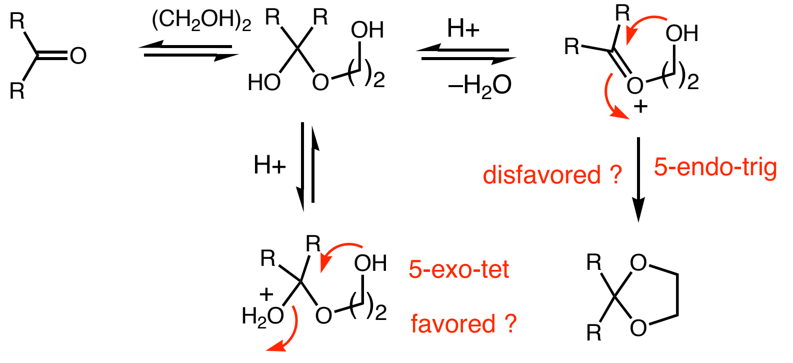
Grigg, *J. Chem. Soc., Chem. Commun.* **1980**, 648.

Case 3:



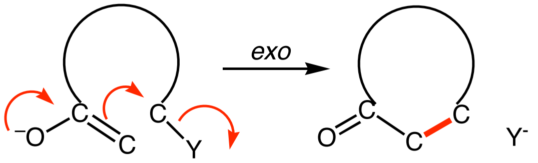
Does the illustrated ketalization process necessarily violate "the rules"?



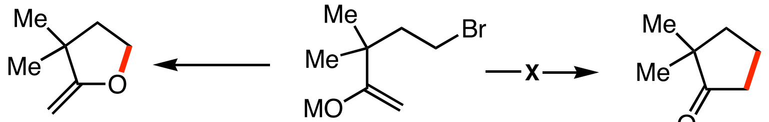


Johnson, C. D. (**1993**). “Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules.” *Acc. Chem. Res.* **26**: 476-82.

Trigonal Carbon: Exocyclic Enolate Alkylation



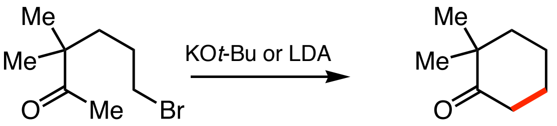
- By definition, an exo-tet cyclization, but stereoelectronically behaves as an endo trig.



(1)

only observed product

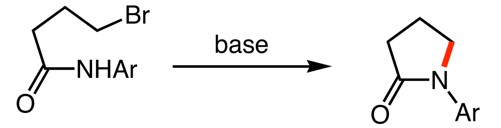
However:

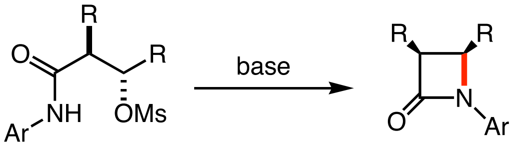


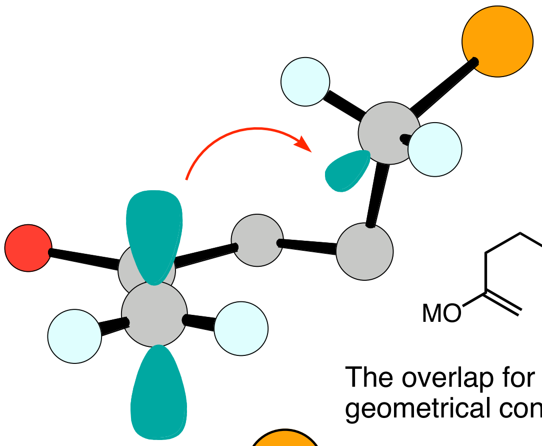
> 95% by NMR

Baldwin, *J. Chem. Soc., Chem. Commun.* **1977**, 233.

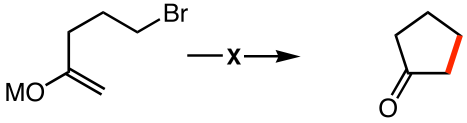
- Given the failure of the enolate alkylation shown above (eq 1), explain why these two cyclizations are successful.



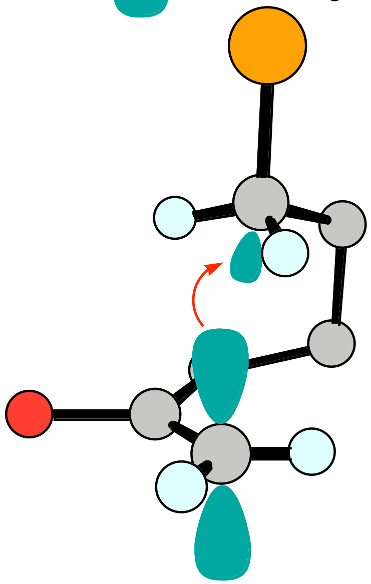




distance between reacting centers: 3.37Å

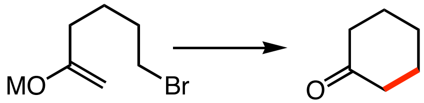


The overlap for C-alkylation is poor due to geometrical constraints of 5-membered ring

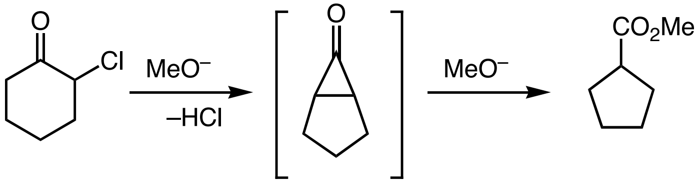


distance between reacting centers: 3.04Å

The relaxed geometrical constraint provided by the added CH_2 group now renders the 6-membered cyclization possible



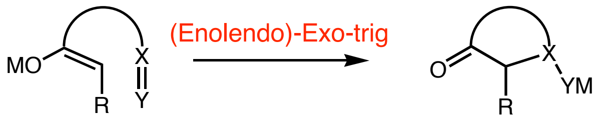
Favorskii Rearrangement (Carey, Pt B, pp 609-610)
Your thoughts on the mechanism



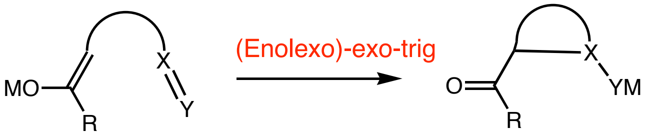
Rules for Ring Closure: SP2 & SP Carbon & Related Systems

Trigonal Carbon: *Intramolecular Aldol Condensations*

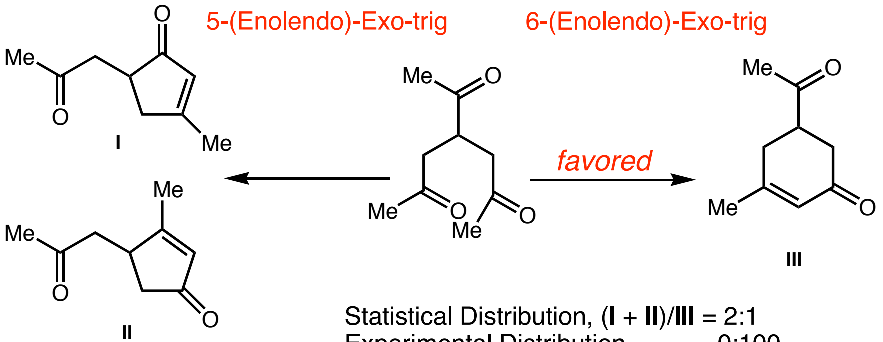
Baldwin, *Tetrahedron* **1982**, *38*, 2939



Favored: 6-7-(enolendo)-exo-trig
Disfavored: 3-5-(enolendo)-exo-trig



Favored: 3-7-(enolexo)-exo-trig



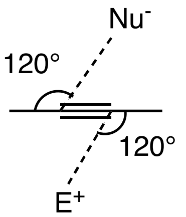
Statistical Distribution, (**I** + **II**)/**III** = 2:1
Experimental Distribution, = 0:100

(KOH, MeOH, r.t., 5 min, 77% y.)

Caution: Baldwin's conclusions assume that the **RDS** is ring closure; however, it is well known (by some!) that the rate determining step is dehydration in a base-catalyzed aldol condensation.

Digonal Carbon: Cyclizations on to Acetylenes

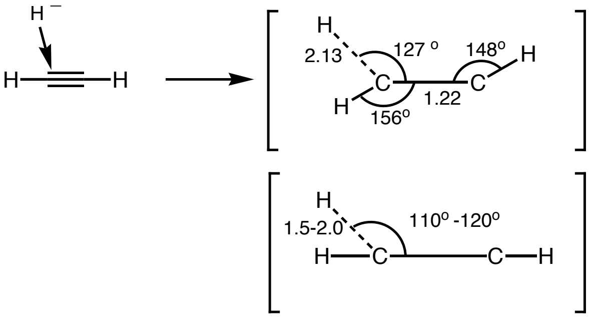
DIGONAL: Angle of approach for attack on triple bonds



Baldwin:

- 3 and 4-Exo-dig are disfavored
- 5 to 7-Exo-dig are favored
- 3 to 7-Endo-dig are favored

Ab initio SCF 4-31G calculations for the interaction of hydride with acetylene:



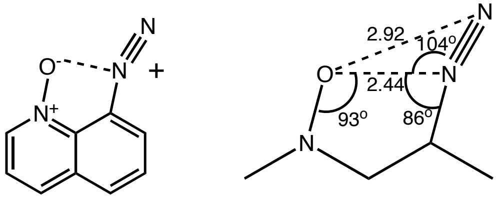
4-31G basis set

Houk, *J.ACS.* **1979**, *101*, 1340.

STO-3G minimal basis set

Dunitz, *Helv Chim. Acta* **1978**, *61*, 2538.

Crystal Structures do not support Baldwin

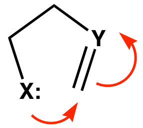


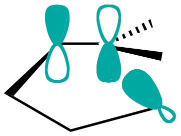
J. Dunitz and J. Wallis *J. C. S. Chem. Comm.* **1984**, 671.

Rules for Ring Closure: SP Carbon & Related Systems

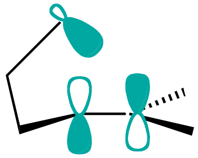
Endo Digonal versus Endo Trigonal Cyclizations

5-endo-trig



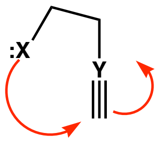


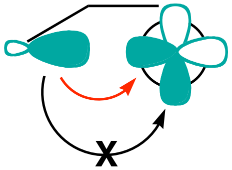
In-plane approach; nucleophile lone pair is orthogonal to π*



Out-of-plane approach; nucleophile lone pair can't achieve Bürgi-Dunitz angle

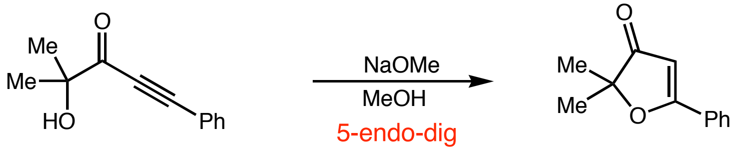
5-endo-dig

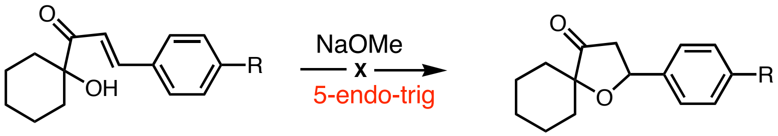




Allowed due to in-plane pi orbitals

For an opposing viewpoint to Baldwin's view of nucleophile trajectories, see Menger's article on directionality in solution organic chemistry: *Tetrahedron* **1983**, *39*, 1013.





R = H, OMe

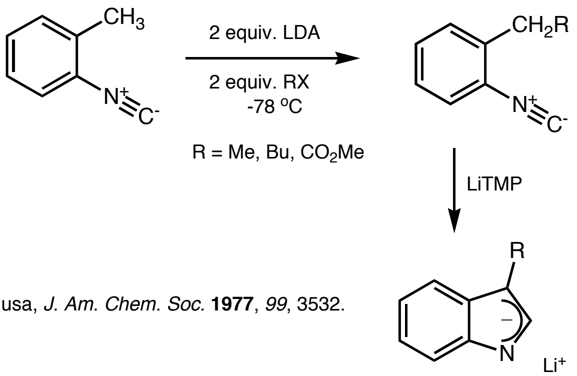
however, the acid catalyzed version does cyclize

Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.

Johnson, *Can. J. Chem.* **1990**, *68*, 1780

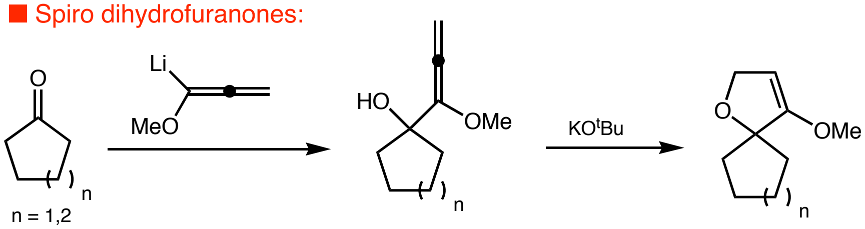
J. Am. Chem. Soc. **1983**, *105*, 5090
J. Chem. Soc., Chem. Commun. **1982**, 36.

■ Indole synthesis:



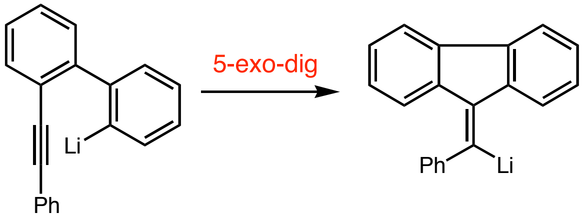
Saegusa, *J. Am. Chem. Soc.* **1977**, *99*, 3532.

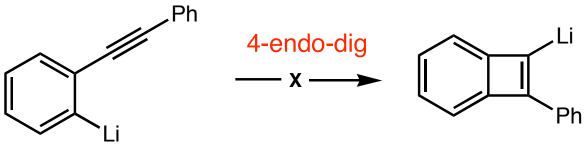
■ Spiro dihydrofuranones:



Developing negative charge on the central allenic carbon is in the same plane as the OMe group

Magnus, *J. Am. Chem. Soc.* **1978**, *100*, 7746.





Rules for Ring Closure: SP Carbon & Related Systems

Conclusions and Caveats

- Baldwin's Rules are an effective first line of analysis in evaluating the stereoelectronics of a given ring closure

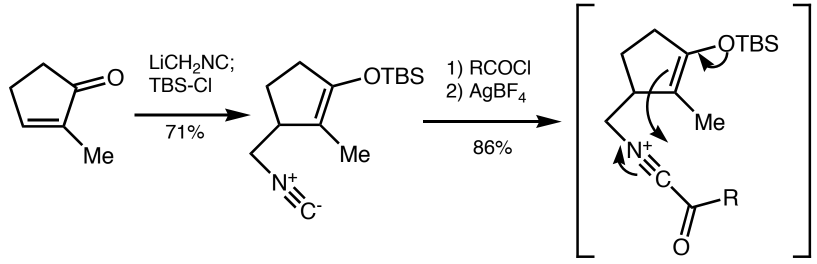
- Baldwin's Rules have provided an important foundation for the study of reaction mechanism

- Competition studies between different modes of cyclization only give information about relative rates, and are not an absolute indicator of whether a process is "favored" or "disfavored"

- Structural modifications can dramatically affect the cyclization mode; beware of imines and epoxides

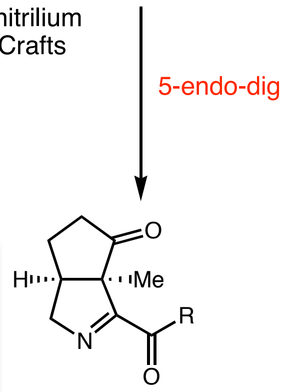
	EXO			**ENDO**		
	Tet	**Trig**	**Dig**	**Tet**	**Trig**	**Dig**
3	√	√	X		X	X
4	√	√	X		X	X
5	√	√	√	X	X	√
6	√	√	√	X	√	√
7	√	√	√	X	√	√

Digonal Cyclizations: Interesting Examples

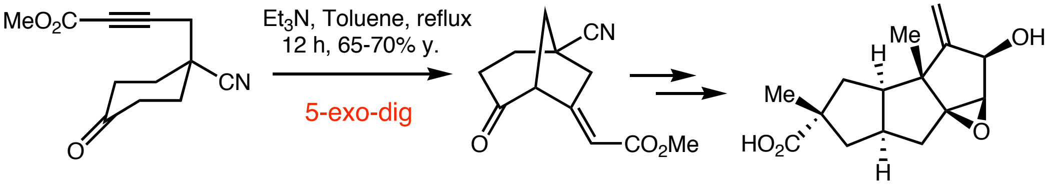


Works for varying ring sizes and R groups; acylnitrilium ion can also work as an electophile in a Friedel-Crafts type of reaction

- Livinghouse, *Tetrahedron* **1992**, *48*, 2209.



DAE undergraduate, UCLA, 1972



- Trost, *JACS* **1979**, *101*, 1284

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 4

Conformational Analysis-1

- Ethane, Propane, Butane & Pentane Conformations
- Simple Alkene Conformations

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapters 2 & 3

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds **(handout)**

The Ethane Barrier Problem

F. Weinhold, *Nature* ***2001***, *411*, 539-541
"A New Twist on Molecular Shape" **(handout)**

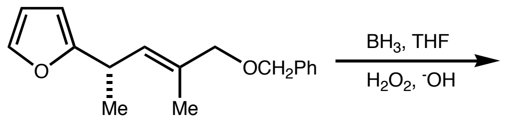
F. M. Bickemhaupt & E. J. Baerends, *Angew. Chem. Int. Ed.* ***2003***, *42*, 4183-4188, *"The Case for Steric Repulsion Causing the Staggered Conformation in Ethane"* **(handout)**

F. Weinhold,, *Angew. Chem. Int. Ed.* ***2003***, *42*, 4188-4194, *"Rebuttal of the Bikelhaupt–Baerends Case for Steric Repulsion Causing the staggered Connformation of Ethane"* **(handout)**

D. A. Evans

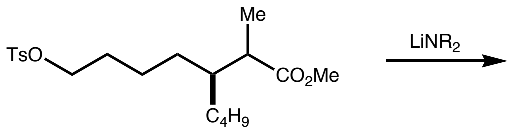
Monday,
September 25, 2006

Problem 61. The following stereoselective hydroboration has been reported by Kishi in his synthesis of monensin (*JACS* **1979**, *101*, 259). Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



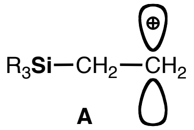
The product ?
Stereoselection: 8/1

Problem 68. The following stereoselective enolate alkylation has been reported by Kim (*Tetrahedron Lett.* **1986**, *27*, 943). Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



The product ?
Stereoselection: >40:1

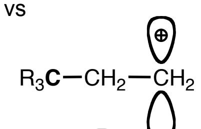
Problem 722. Carbonium ion **A** has been calculated to be 38 kcal/mol more stable than carbonium ion **B** (Jorgensen *JACS* **1985**, *107*, 1496). The profound stabilization of carbonium ions by silicon in this fashion is referred to as the "beta-silicon effect". For example, the S_N1 solvolysis reaction of **1** is 10^{+12} times as fast as the corresponding reaction of **2**. The solvolysis of **2** leads to the olefin. For a good review see: Lambert *Acc. Chem. Res.* **1999**, *32*, 183-190



$R_3\mathbf{Si}{-}CH_2{-}\overset{\oplus}{C}H_2$

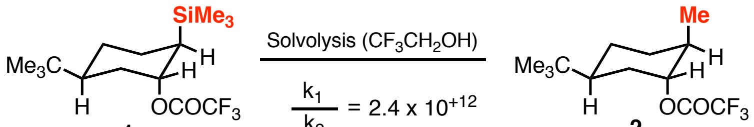
A

vs



$R_3\mathbf{C}{-}CH_2{-}\overset{\oplus}{C}H_2$

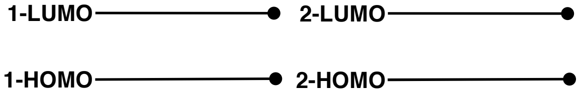
B



1 **2**

$$\frac{k_1}{k_2} = 2.4 \times 10^{+12}$$

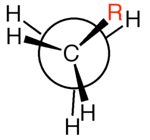
Part A: Identify the HOMO–LUMO interactions in the S_N1 reactions of **1** and **2**.



The following discussion is intended to provide a general overview of acyclic conformational analysis

Ethane & Propane

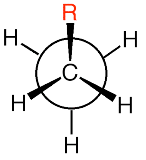
The conformational isomerism in these 2 structures reveals a gratifying level of internal consistency.



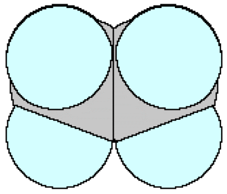
eclipsed conformation

$\Delta E = +3.0\ \text{kcal mol}^{-1}$ (R = H)

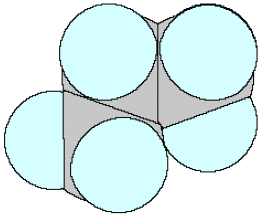
$\Delta E = +3.4\ \text{kcal mol}^{-1}$ (R = Me)



staggered conformation



Van derWaals radii of vicinal hydrogens do not overlap in ethane



In propane there is a discernable interaction

For purposes of analysis, each eclipsed conformer may be broken up into its component destabilizing interactions.

Incremental Contributions to the Barrier.

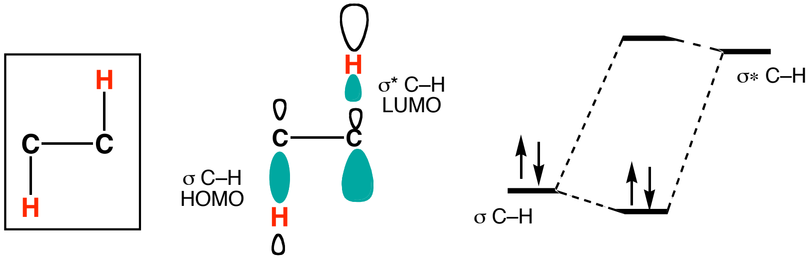
Structure	Eclipsed atoms	δ E (kcal mol $^{-1}$)
ethane	3 (H↔H)	+1.0 kcal mol $^{-1}$
propane	2 (H↔H)	+1.0 kcal mol $^{-1}$
	1 (H↔Me)	+1.4 kcal mol $^{-1}$

Ethane Rotational Barrier: The FMO View

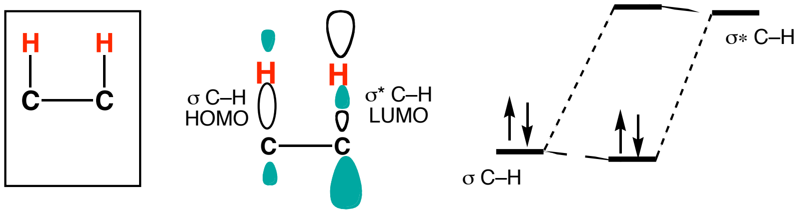
F. Weinhold, *Angew. nature* ***2001***, *411*, 539-541 *"A New Twist on Molecular Shape"*

One explanation for the rotational barrier in ethane is that better overlap is possible in the staggered conformation than in the eclipsed conformation as shown below.

In the staggered conformation there are 3 anti-periplanar C–H Bonds



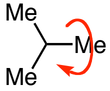
In the eclipsed conformation there are 3 syn-periplanar C–H Bonds



Following this argument one might conclude that:

- ■ **The staggered conformer has a better orbital match between bonding and antibonding states.**
- ■ **The staggered conformer can form more delocalized molecular orbitals.**

J. P. Lowe was the first to propose this explanation
"A Simple Molecuar Orbital Explanation for the Barrier to Internal Rotation in Ethane and Other Molecules"
J. P. Lowe, *JACS* **1970**, *92*, 3799



Estimate the rotational barrier about the C1-C2 bond in isobutane

Relationship between ΔG and Keq and pKa

Recall that:

$$\Delta G^\circ = -RT \ln K$$

or

$$\Delta G^\circ = -2.3RT \log_{10}K$$

At 298 K: $2.3RT = 1.4$ (ΔG in kcal Mol^{-1})

$$\Delta G^\circ_{298} = -1.4 \log_{10}Keq$$

Since $pKeq = -\log_{10}Keq$

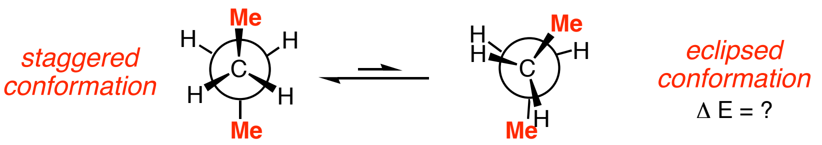
$$\boxed{\Delta G^\circ_{298} = 1.4\ pKeq}$$

Hence, pK is proportional to the free energy change

Keq	pKeq	ΔG°
1.0	0	0
10	–1	–1.4
100	–2	–2.8 kcal /mol

Butane

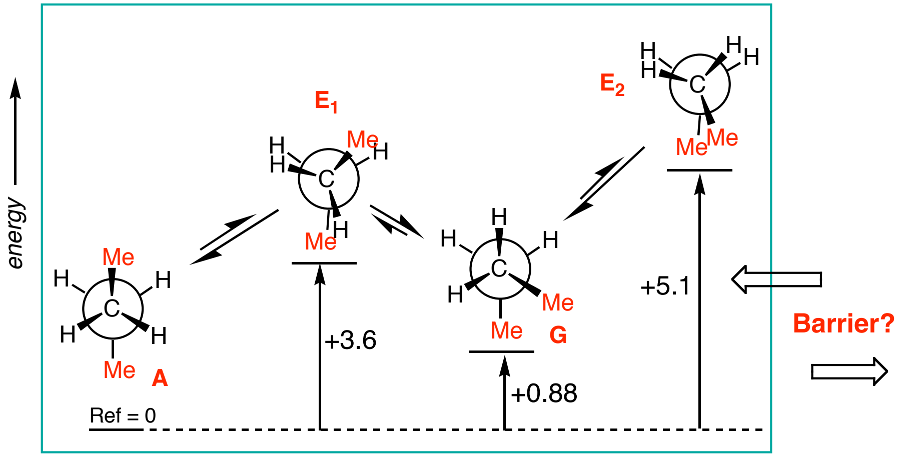
Using the eclipsing interactions extracted from propane & ethane we should be able to estimate all but one of the eclipsed butane conformations



Eclipsed atoms	δ E (kcal mol^{-1})
1 (H↔H)	+1.0 kcal mol^{-1}
2 (H↔Me)	+2.8 kcal mol^{-1}
Δ E est = 3.8 kcal mol^{-1}	

The estimated value of +3.8 agrees quite well with the value of +3.6 reported by Allinger (*J. Comp. Chem.* **1980**, *1*, 181-184)

n-Butane Torsional Energy Profile

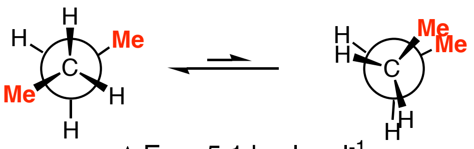


Acyclic Conformational Analysis: Butane

Butane continued

From the torsional energy profile established by Allinger, we should be able to extract the contribution of the Me↔Me eclipsing interaction to the barrier:

staggered conformation



eclipsed conformation

Δ E = +5.1 kcal mol^{-1}

Let's extract out the magnitide of the Me–Me interaction

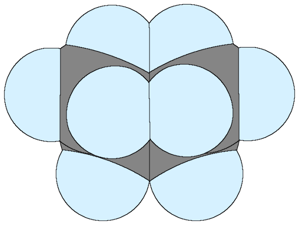
$$2\,(H\leftrightarrow H) \;+\; 1\,(Me\leftrightarrow Me) \;=\; +5.1$$

$$1\,(Me\leftrightarrow Me) \;=\; +5.1 \;-\; 2\,(H\leftrightarrow H)$$

$$\mathbf{1\,(Me\leftrightarrow Me) \;=\; +3.1}$$

Incremental Contributions to the Barrier.

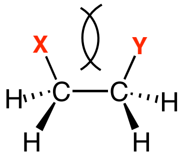
Eclipsed atoms	δ E (kcal mol^{-1})
2 (H↔H)	+2.0
1 (Me↔Me)	+3.1



Eclipsed Butane conformation

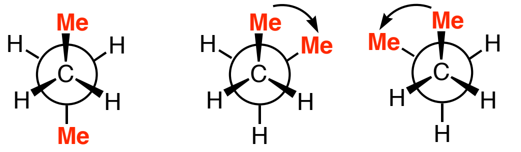
From the energy profiles of ethane, propane, and n-butane, one may extract the useful eclipsing interactions summarized below:

Hierarchy of Eclipsing Interactions



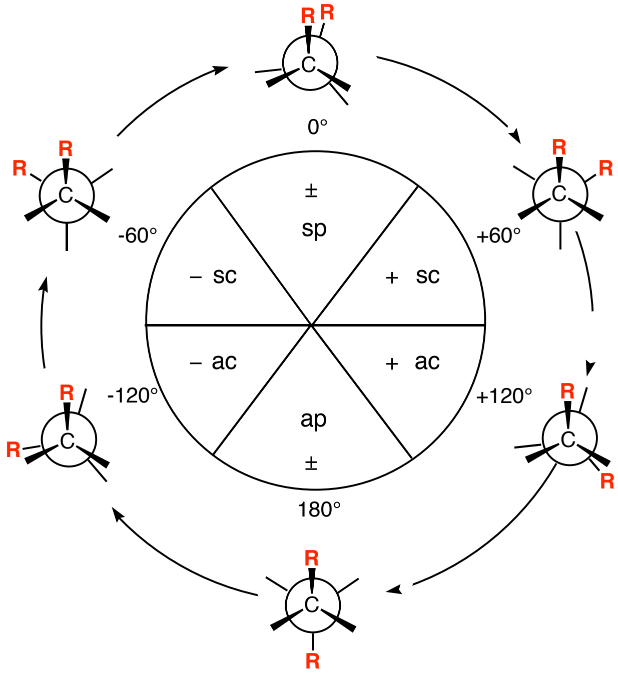
X—Y	δ E kcal mol^{-1}
H—H	+1.0
H—Me	+1.4
Me—Me	**+3.1**

Nomenclature for staggered conformers:



	trans or t or (anti)	gauche(+) or g^{+}	gauche(-) or g^{-}
Conformer population at 298 K:	70%	15%	15%

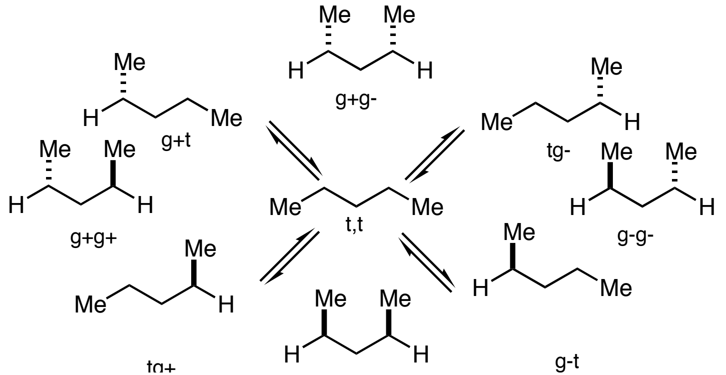
(Klyne, Prelog, *Experientia* **1960**, *16*, 521.)

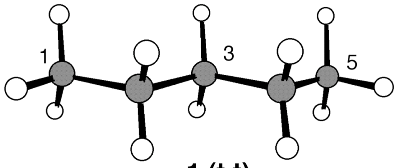


	Torsion angle	Designation	Symbol	*n*-Butane Conformer
Energy Maxima →	0 ± 30°	± syn periplanar	± sp	E_2
Energy Minima ⇢	+60 ± 30°	+ syn-clinal	+ sc (g+)	G
→	+120 ± 30°	+ anti-clinal	+ ac	E_1
⇢	180 ± 30°	antiperiplanar	ap (anti or t)	A
→	-120 ± 30°	- anti-clinal	- ac	E_1
⇢	-60 ± 30°	- syn-clinal	- sc (g-)	G

n-Pentane

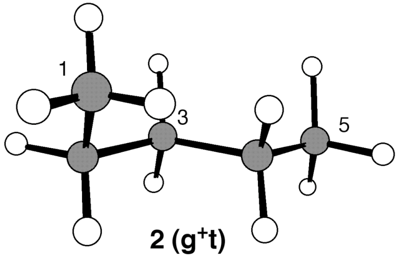
Rotation about both the C_2-C_3 and C_3-C_4 bonds in either direction (+ or -):





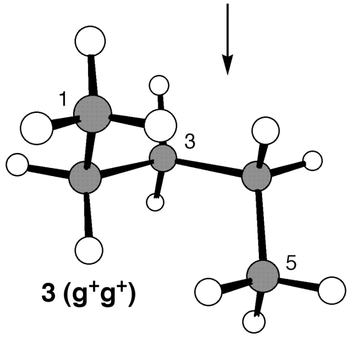
1 (t,t)

Anti(2,3)-Anti(3,4) →



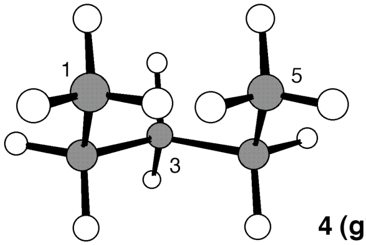
2 (g$^+$t)

Gauche(2,3)-Anti(3,4)



3 (g$^+$g$^+$)

Gauche(2,3)-Gauche(3,4)

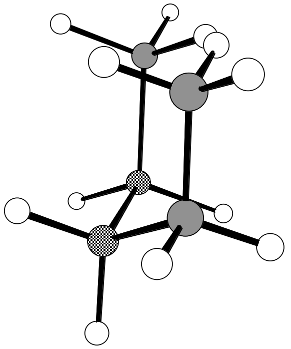


4 (g$^+$g$^-$)

← Gauche(2,3)-Gauche'(3,4)
double gauche pentane

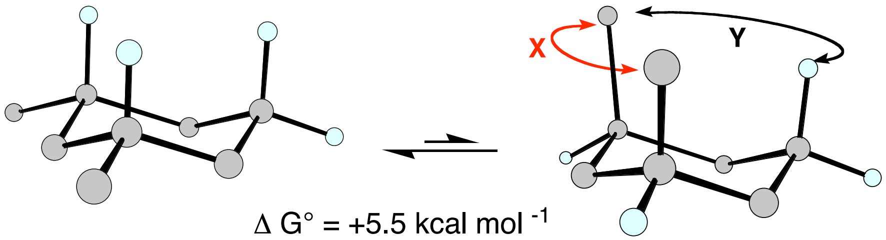
From prior discussion, you should be able to estimate energies of **2** & **3** (relative to **1**). On the other hand, the least stable conformer **4** requires additional data before is relative energy can be evaluated.

The double-gauche pentane conformation



The new high-energy conformation: **(g$^+$g$^-$)**

Estimate of 1,3-Dimethyl Eclipsing Interaction



$\Delta G° = +5.5$ kcal mol $^{-1}$

$\Delta G = X + 2Y$ where:

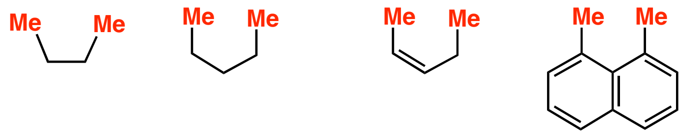
X = 1,3(Me–Me) & Y = 1,3(Me–H)

1,3(Me–H) = Skew-butane = 0.88 kcal mol-1

1,3(Me-Me) = $\Delta G - 2Y = 5.5 - 1.76 = + 3.7$ kcal mol-1

$\boxed{\text{1,3(Me}\leftrightarrow\text{Me) = + 3.7 kcal mol}^{-1}}$

Estimates of In-Plane 1,2 &1,3-Dimethyl Eclipsing Interactions

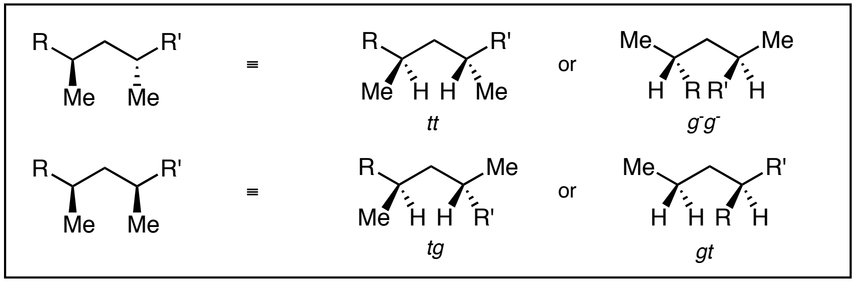


3.1 ~ 3.7 ~3.9 ~ 7.6

It may be concluded that in-plane 1,3(Me↔Me) interactions are Ca +4 kcal/mol while 1,2(Me↔Me) interactions are destabliizing by Ca 3 kcal/mol.

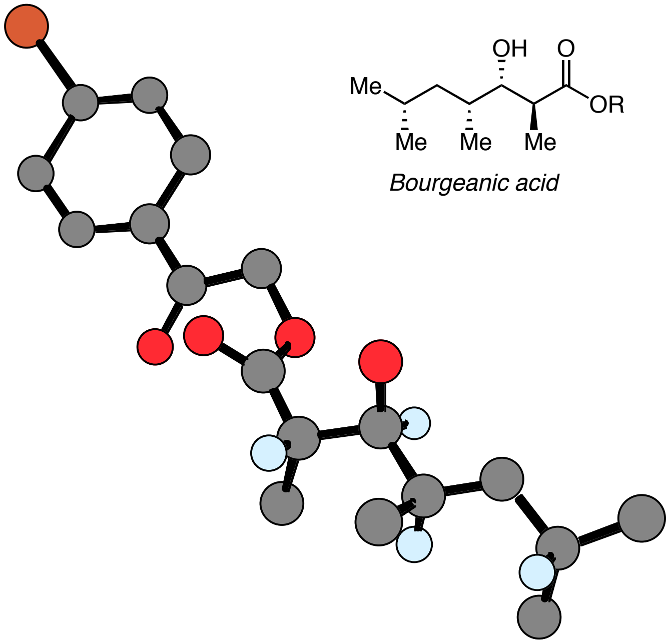
The syn-Pentane Interaction - Consequences

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds **(handout)**



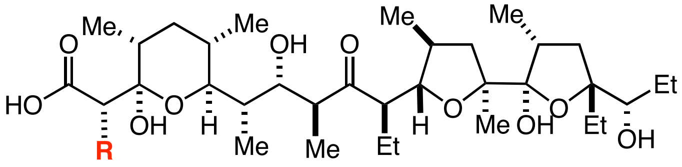
Consequences for the preferred conformation of polyketide natural products

Analyze the conformation found in the crystal state of a bourgeanic acid derivative!



Bourgeanic acid

Lactol & Ketol Polyether Antibioitics

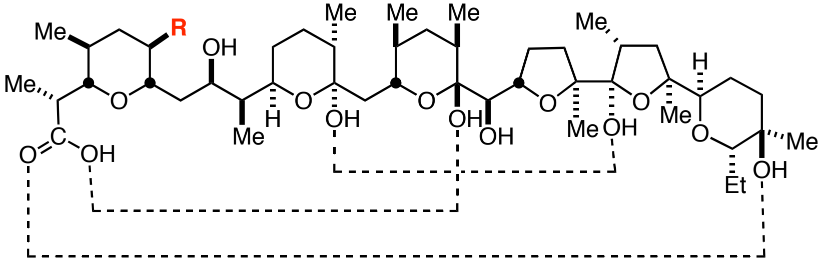


Ferensimycin B, R = Me
Lysocellin, R = H

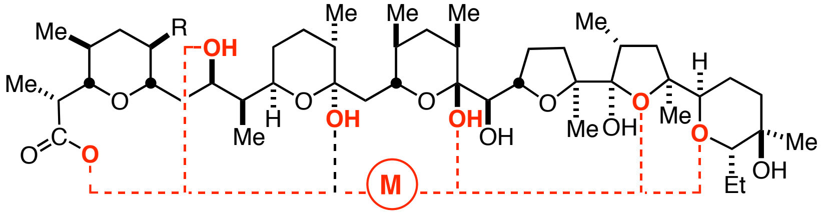
The conformation of these structures are strongly influenced by the acyclic stereocenters and internal H-bonding

Alborixin R = Me; X-206 R = H

Internal H-Bonding



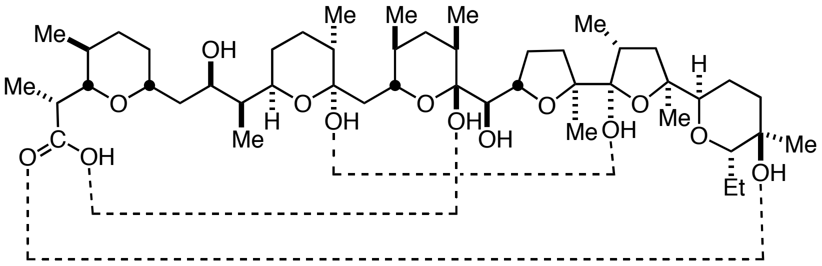
Metal ion ligation sites (M = Ag, K)

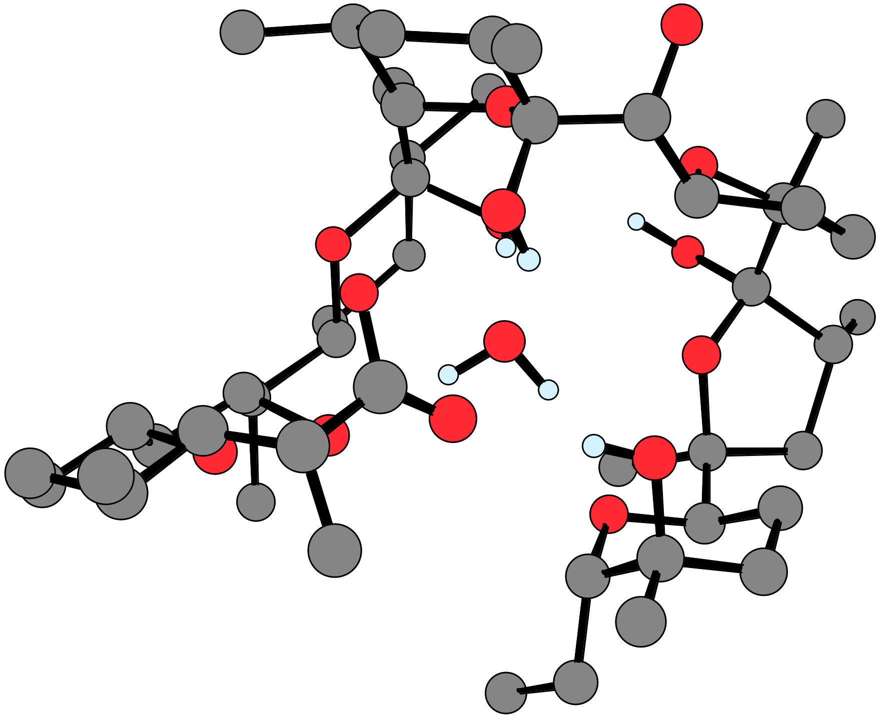


Conformational Analysis: Ionophore X-206/X-rays

X-ray of Ionophore X-206 · H_2O

Internal H-Bonding

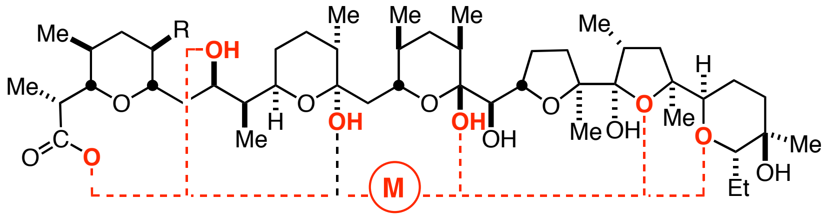


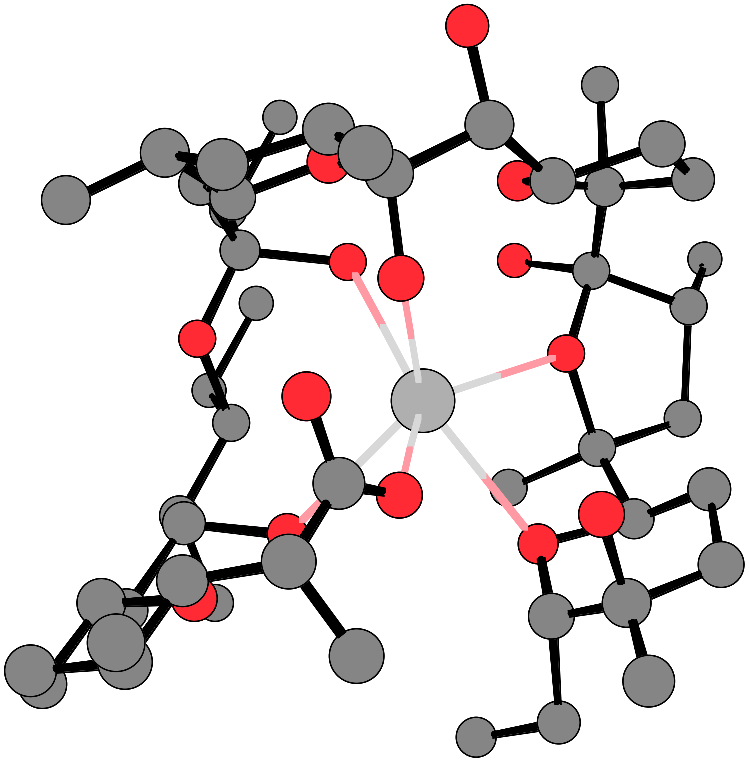


"The Total Synthesis of the Polyether Antibiotic X-206". Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

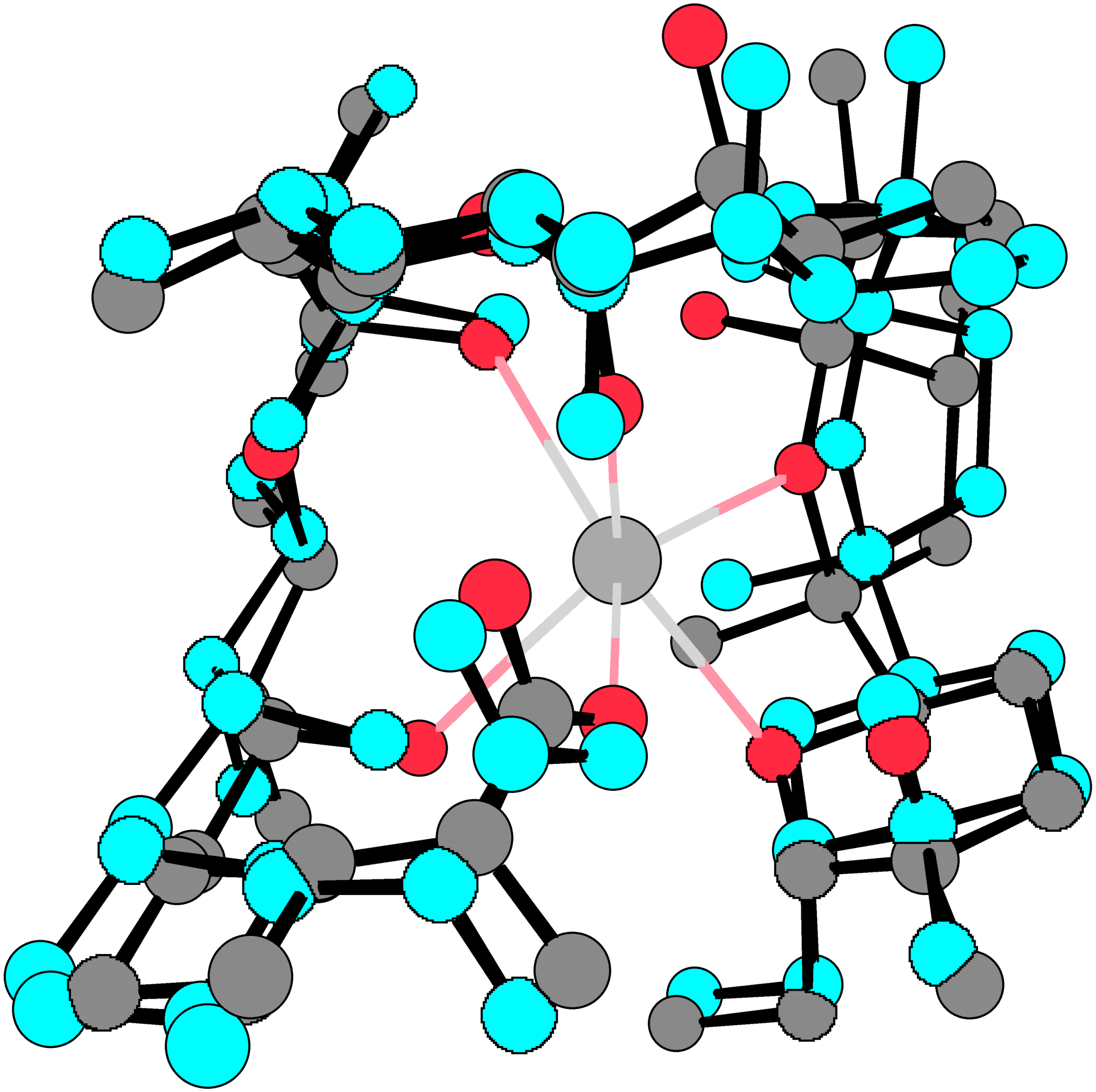
X-ray of Ionophore X-206 - Ag^+ - Complex

Metal ion ligation sites (M = Ag, K)

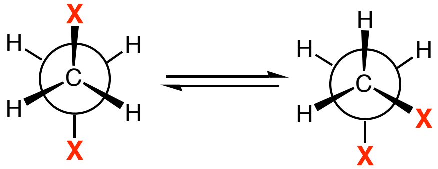




Conformational Analysis: Ionophore X-206/X-ray overlay



The 1,2-Dihaloethanes



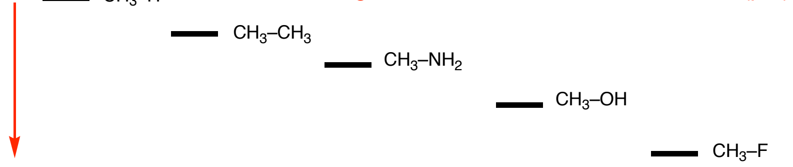
X = Cl; ΔH° = + 0.9–1.3 kcal/mol
X = Br; ΔH° = + 1.4–1.8 kcal/mol
X = F; ΔH° = – 0.6-0.9 kcal/mol

Observation: While the anti conformers are favored for X = Cl, Br, the gauche conformation is prefered for 1,2-difluroethane. Explain.

Relevant Article: *Chem. Commun* **2002**, 1226-1227 **(pdf)**

σ-anti-bonding States: (C–X)

For the latest views, read
Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)



CH_3–H

CH_3–CH_3

CH_3–NH_2

CH_3–OH

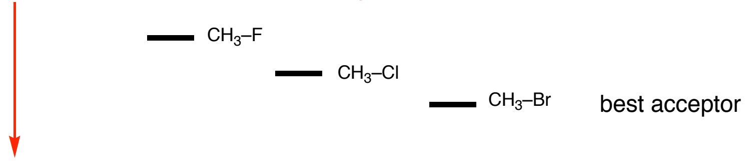
CH_3–F

Increasing σ-acceptor capacity*

best acceptor

σ-anti-bonding States: (C–X)

For the latest views, read
Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)



CH_3–F

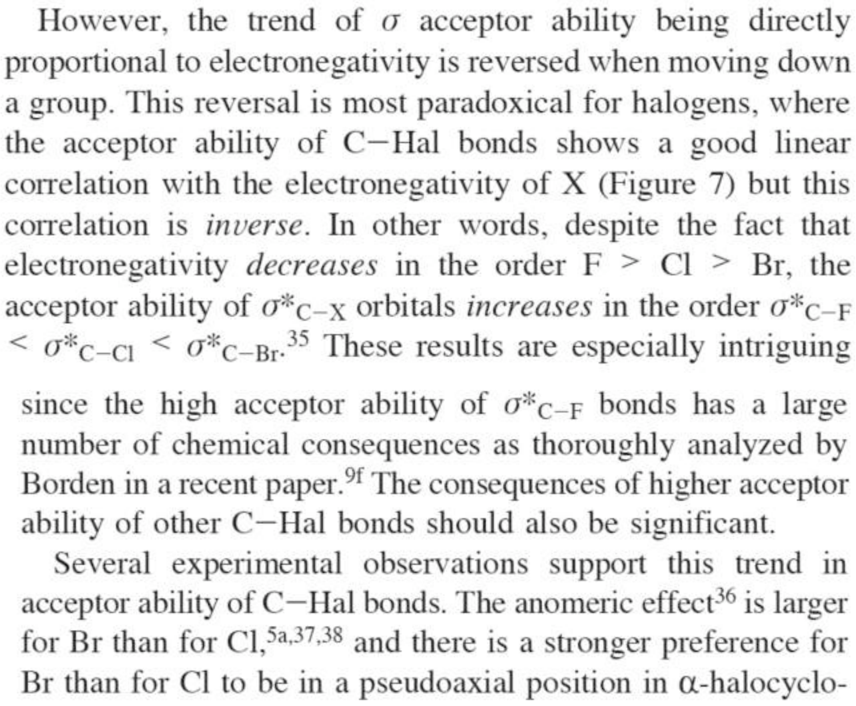
CH_3–Cl

CH_3–Br

best acceptor

Increasing σ-acceptor capacity*

Alabugin & Zeidan, *JACS* **2002**, *124*, 3175 (pdf)

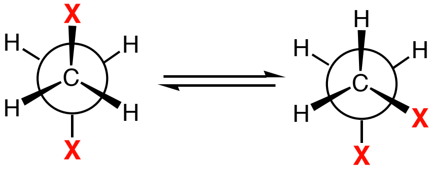


However, the trend of σ acceptor ability being directly proportional to electronegativity is reversed when moving down a group. This reversal is most paradoxical for halogens, where the acceptor ability of C−Hal bonds shows a good linear correlation with the electronegativity of X (Figure 7) but this correlation is *inverse*. In other words, despite the fact that electronegativity *decreases* in the order F > Cl > Br, the acceptor ability of σ^*_{C-X} orbitals *increases* in the order $\sigma^*_{C-F} < \sigma^*_{C-Cl} < \sigma^*_{C-Br}$.[35] These results are especially intriguing since the high acceptor ability of σ^*_{C-F} bonds has a large number of chemical consequences as thoroughly analyzed by Borden in a recent paper.[9f] The consequences of higher acceptor ability of other C−Hal bonds should also be significant.

Several experimental observations support this trend in acceptor ability of C−Hal bonds. The anomeric effect[36] is larger for Br than for Cl,[5a,37,38] and there is a stronger preference for Br than for Cl to be in a pseudoaxial position in α-halocyclo-

Your Thoughts on the trend shown below:

The 1,2-Dihaloethanes

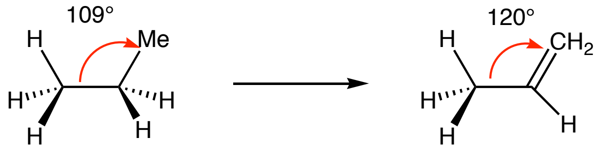


X = Cl; ΔH° = + 0.9–1.3 kcal/mol
X = Br; ΔH° = + 1.4–1.8 kcal/mol
X = F; ΔH° = – 0.6-0.9 kcal/mol

Stabilized Eclipsed Conformations in Simple Olefins

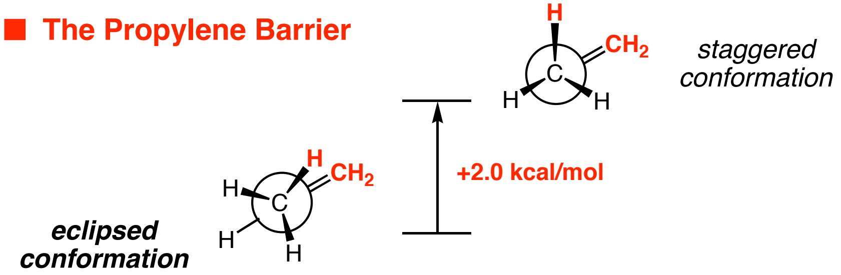
Simple olefins exhibit unusal conformational properties relative to their saturated counterparts

Propane versus Propene

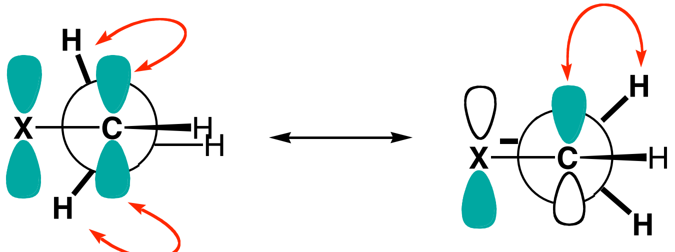


Hybridization change opens up the C–C–C bond angle

■ The Propylene Barrier



New (de)stabilizing effect

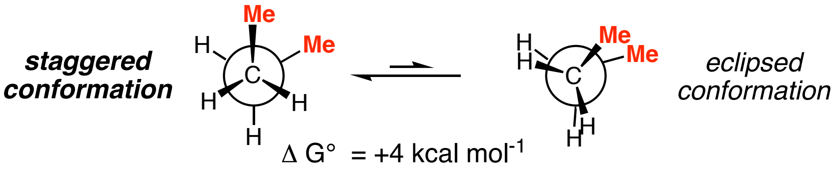


stabilizing conjugation between π*–C–X & σ–C–H

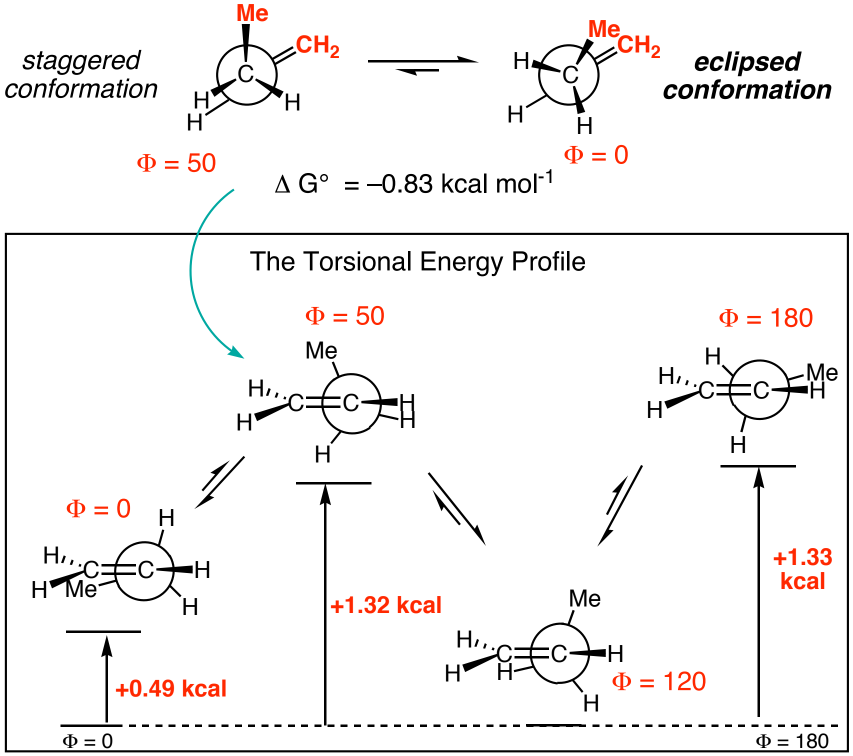
K. Wiberg, *JACS* **1985**, *107*, 5035-5041

K. Houk, *JACS* **1987**, *109*, 6591-6600

Butane versus 1-Butene



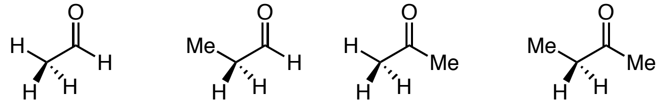
Δ G° = +4 kcal mol^{-1}



Δ G° = –0.83 kcal mol^{-1}

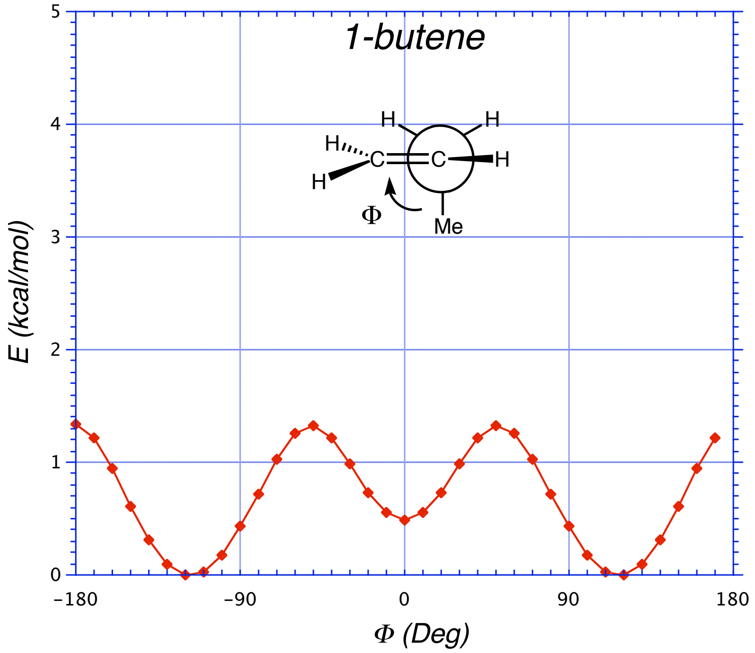
Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.

■ Acetaldehyde exhibits a similar conformational bias

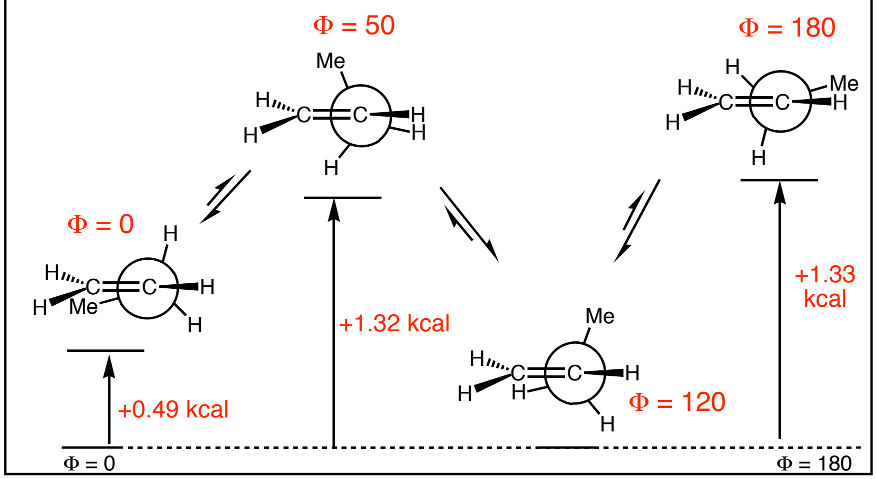


The low-energy conformation in each of above cases is eclipsed

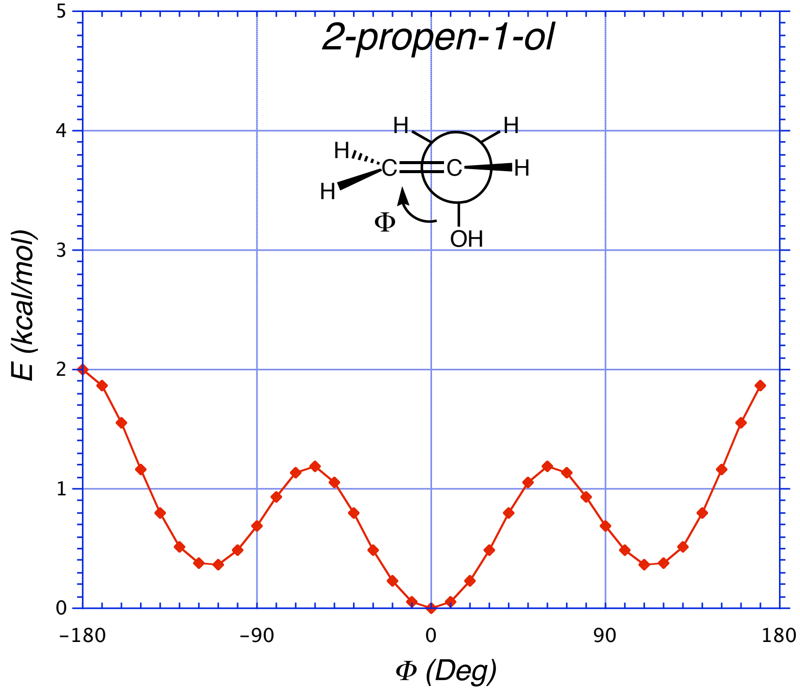
Conformational Barriers to Rotation: Olefin A-1,2 Interactions



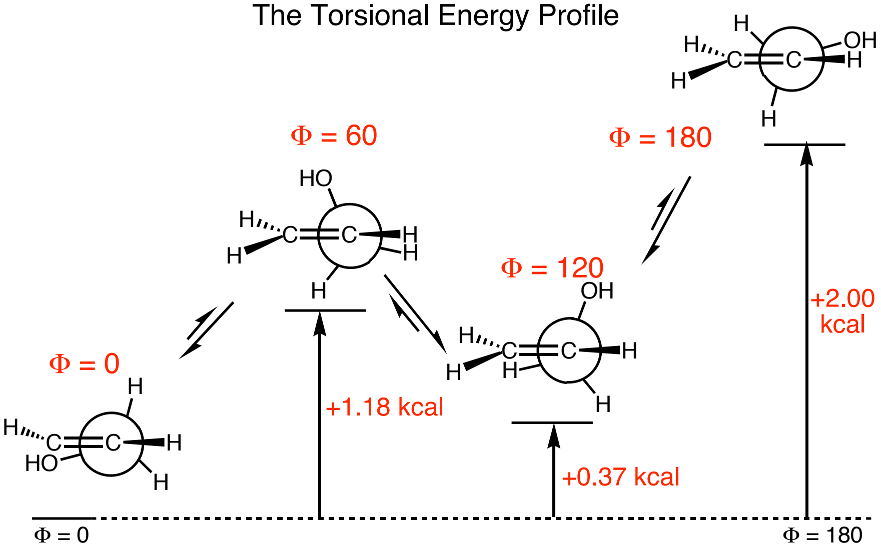
The Torsional Energy Profile

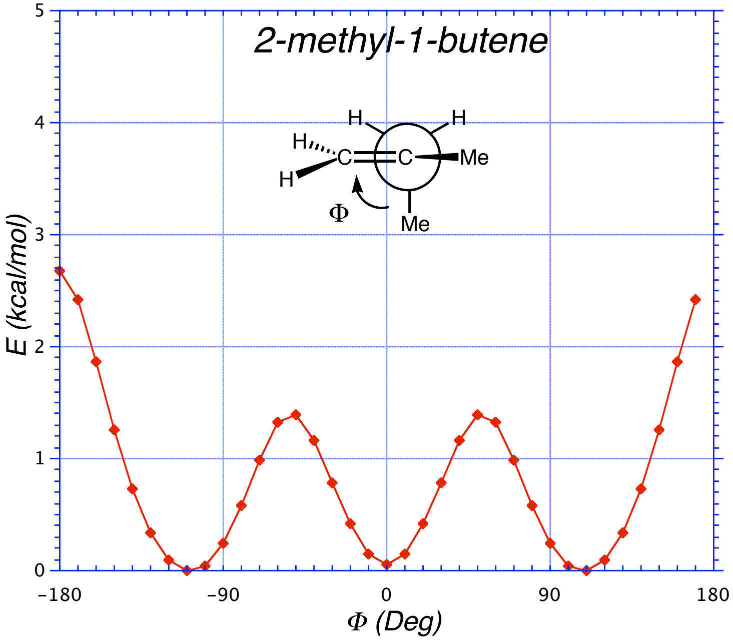


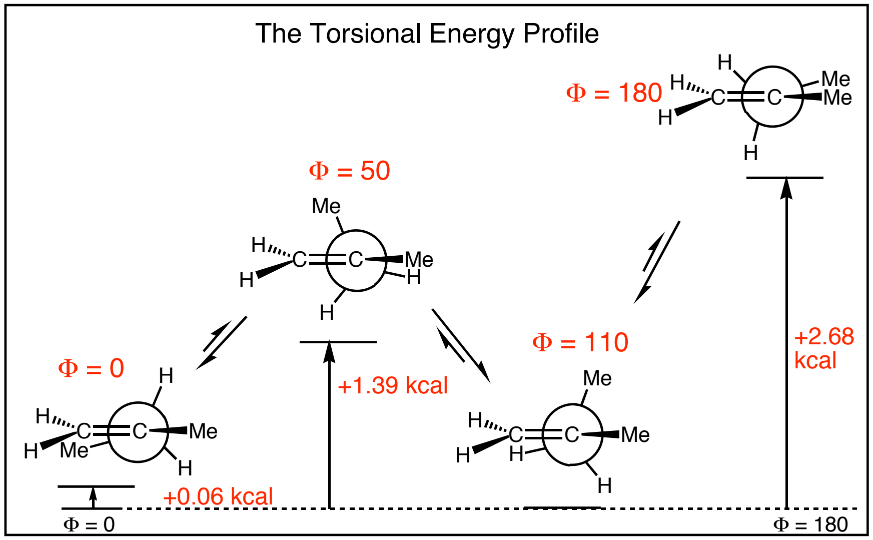
Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.

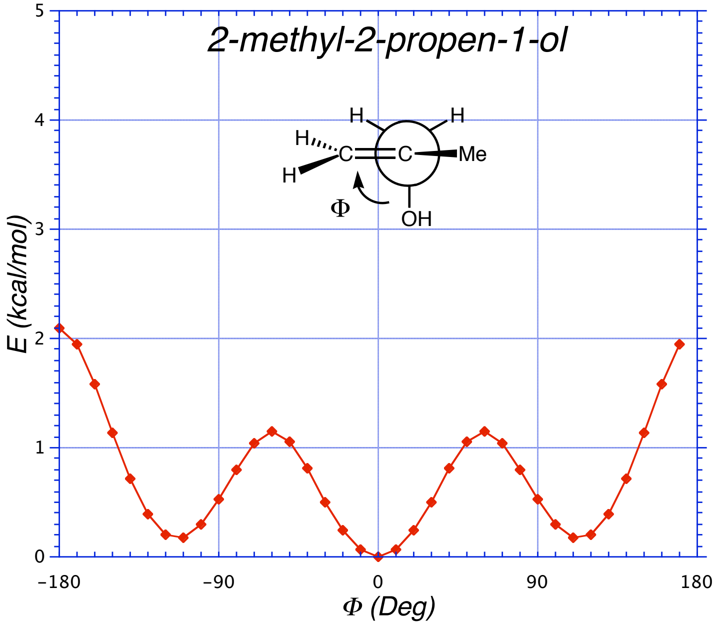


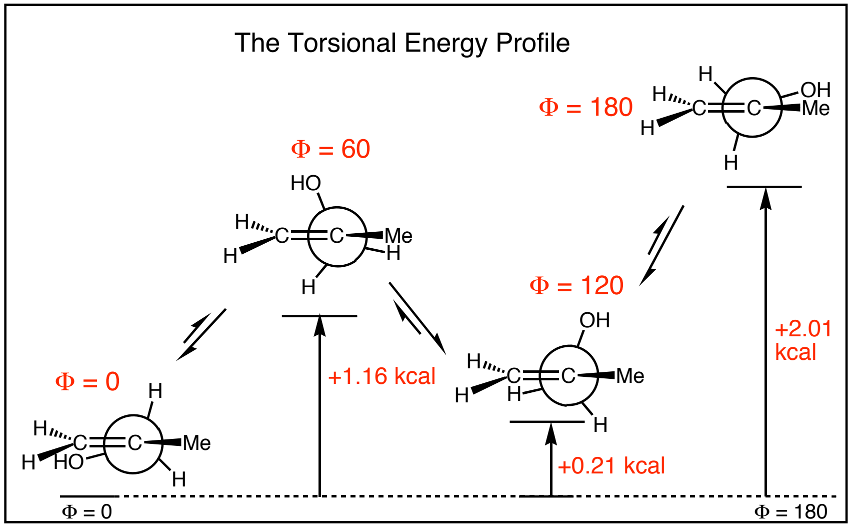
The Torsional Energy Profile



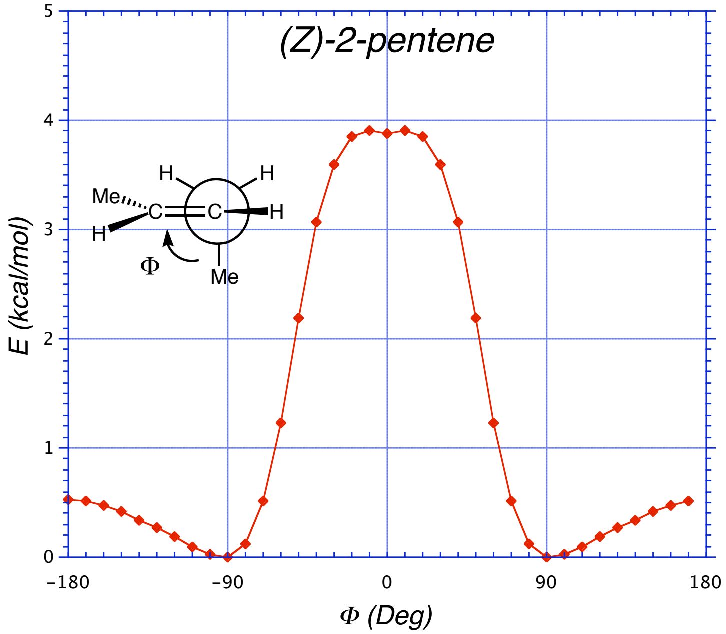

2-methyl-1-butene
H
H
H
C
C
Me
H
Φ
Me
E (kcal/mol)
5
4
3
2
1
0
−180
−90
0
90
180
Φ (Deg)

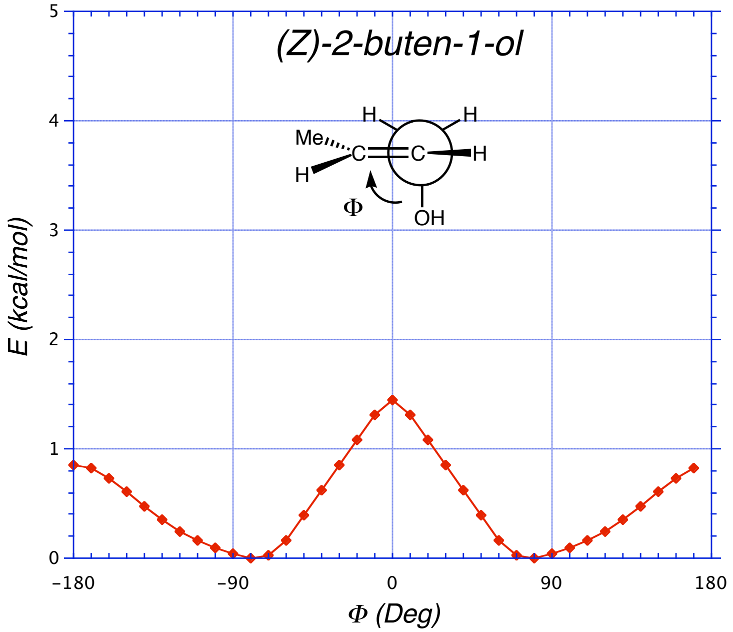

The Torsional Energy Profile
Φ = 180
Φ = 50
Φ = 110
Φ = 0
Me
Me
H
H
H
H
+2.68 kcal
+1.39 kcal
+0.06 kcal
Φ = 0
Φ = 180

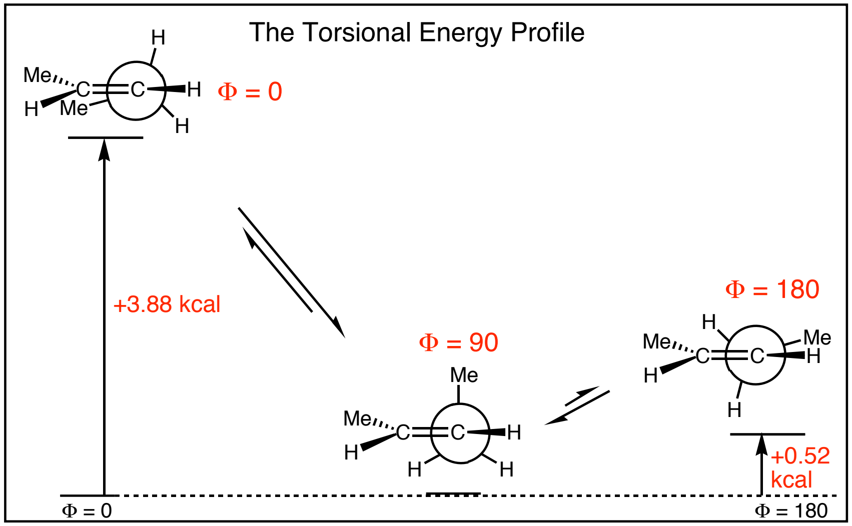

2-methyl-2-propen-1-ol
H
H
H
C
C
Me
H
Φ
OH
E (kcal/mol)
5
4
3
2
1
0
−180
−90
0
90
180
Φ (Deg)


The Torsional Energy Profile
Φ = 180
Φ = 60
Φ = 120
Φ = 0
OH
HO
Me
H
+2.01 kcal
+1.16 kcal
+0.21 kcal
Φ = 0
Φ = 180

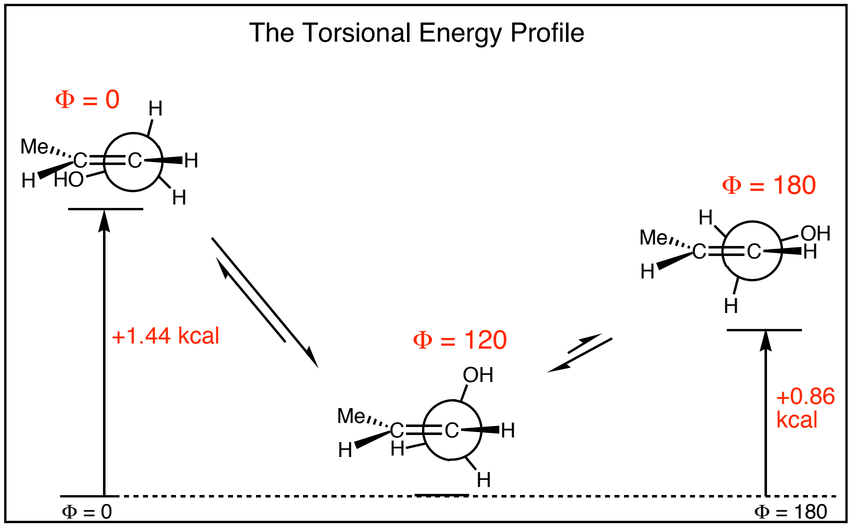
Conformational Barriers to Rotation: Olefin A-1,3 Interactions







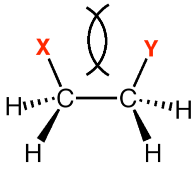
Values calculated using MM2 (molecular mechanics) force fields via the Macromodel multiconformation search.



Review: Hoffman, R. W. *Chem. Rev.* **1989,** *89,* 1841.

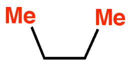
Useful Destabilizing Interactions to Remember

Hierarchy of Vicinal Eclipsing Interactions

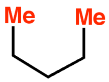


X—Y	δ E kcal mol $^{-1}$
H—H	+1.0
H—Me	+1.4
Me—Me	**+3.1**

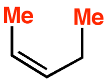
Estimates of In-Plane 1,2 &1,3-Dimethyl Eclipsing Interactions



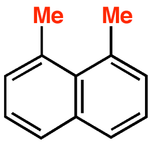
~ 3.1



~ 3.7

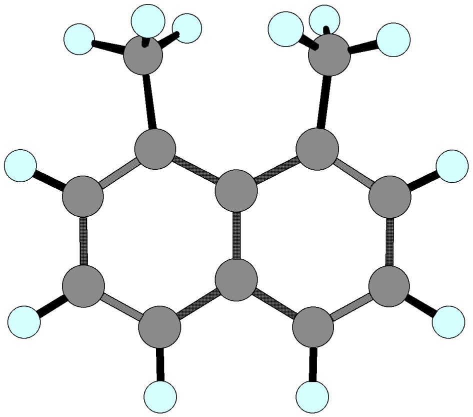


~3.9



~ 7.6

It may be concluded that in-plane 1,3(Me↔Me) interactions are Ca +4 kcal/mol while 1,2(Me↔Me) interactions are destabliizing by Ca +3 kcal/mol.



minimized structure

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 5

Acyclic Conformational Analysis-2

- Introduction to Allylic Strain

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapters 2 & 3

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds **(handout)**

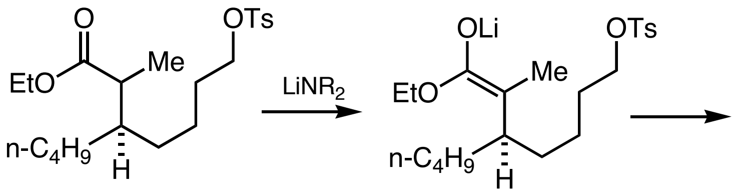
R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841-1860
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations
(handout)

D. A. Evans

Wednesday,
September 27, 2006

Problems of the Day:

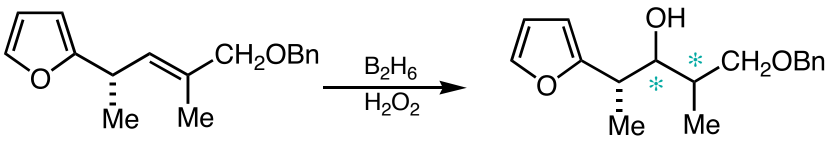
Can you predict the stereochemical outcome of this reaction?



1 + **2**

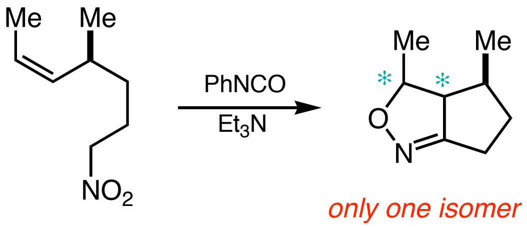
98:2

D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, *27*, 943.



diastereoselection 8:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1979**, *101*, 259.



only one isomer

A. Kozikowski & Co-workers, *Tetrahedron Lett.* **1982**, *23*, 2081.

7.46 (d, J = 8 Hz, 2 H). **12:** NMR δ 0.92 (d, J = 7 Hz, 6 H), 1.16–164 (m, 9 H), 1.80 (s, 3 H), 1.87 (s, 3 H), 2.40 (s, 3 H), 3.42 (s, 3 H), 4.04 (dd, J = 11, 4 Hz, 1 H), 5.72 (m, 1 H), 5.88 (t, J = 3 Hz, 1 H), 6.44 (t, J = 2 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H). **13:** NMR δ 0.98 (d, J = 8 Hz, 6 H), 1.64 (m, 3 H), 2.89 (br t, J = 8 Hz, 2 H), 3.80 (s, 3 H), 6.43 (d, J = 3 Hz, 1 H), 6.83 (apparent, t, J = 4 Hz, 1 H), 6.93 (d, J = 3 Hz, 1 H), 7.06 (apparent d, J = 4 Hz, 2 H). **15:** NMR δ 1.76 (s, 6 H), 3.52 (d, J = 8 Hz, 2 H), 3.76 (s, 3 H), 5.37 (t, J = 8 Hz, 1 H), 6.36 (d, J = 3 Hz, 1 H), 6.76 (apparent t, J = 4 Hz, 1 H), 6.86 (d, J = 3 Hz, 1 H), 7.00 (apparent d, J = 4 Hz, 2 H). New compounds have been fully characterized by spectral means and have satisfactory elemental composition.

(4) To our knowledge, the directive effect of a benzylic alkylthio group on aromatic ring metalation has not been previously examined. For a leading reference see Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976,** *41,* 3653.

(5) Gjos, N. J.; Gronowitz, S. *Acta Chem. Scand.* **1971,** *25,* 2596.

(6) Plieninger, H.; Hobel, M.; Liede, V. *Chem. Ber.* **1963,** *96,* 1618.

(7) Attempts to use less electron-rich aromatic rings or to cyclize to form five- or seven-membered rings has led to equivocal results.

(8) Brown, R. K. *Chem. Heterocycl. Compd.* **1972,** *25,* 227.

(9) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974,** *96,* 5495.

(10) For a recent approach to 4-substituted oxindoles, see Kozikowski, A. P.; Kuniak, M. P. *J. Org. Chem.* **1978,** *43,* 2083. Renewed interest in ergot alkaloids stems in part from their possible use as prolactin inhibitors or in treatment of Parkinson's disease. See the following. Floss, H. G.; Cassady, J. M.; Robbers, J. E. *J. Pharm. Sci.* **1973,** *62,* 699. Cassady, J. M.; Li, G. S.; Spitzner, E. B.; Floss, H. G.; Clemens, J. A. *J. Med. Chem.* **1974,** *17,* 300.

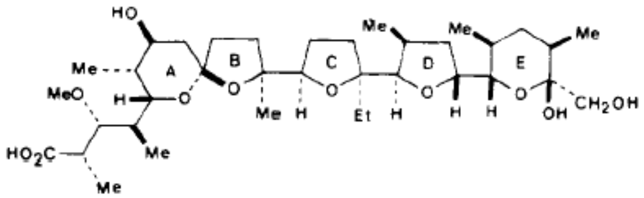
Barry M. Trost,* Manfred Reiffen, Michael Crimmin
Department of Chemistry, University of Wisconsin—Madison
Madison, Wisconsin 53706

Received August 30, 1978

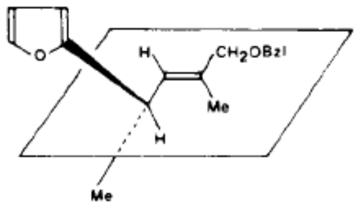
Total Synthesis of Monensin. 1. Stereocontrolled Synthesis of the Left Half of Monensin[1]

Sir:

Monensin (**1**),[2] produced by a strain of *Streptomyces cinnamonensis,* is perhaps the best known, most historical example from among a group of about 40 naturally occurring



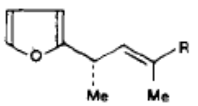
based on an example similar to this case.[8] The origin of the remarkable stereospecificity observed might be related to the conformational preference of **3**; based on the pioneering investigations by Wilson,[9] Herschbach,[10] Bothner-By,[11] and others,[12] the preferred conformation of **3** is assumed to be A. Therefore, hydroboration would take place preferentially from the sterically less hindered α face to yield **4**.



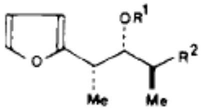
A

We call this Allylic Strain

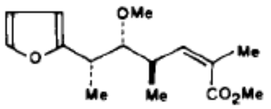
Methylation of **4** (CH_3I, KH, DMF–THF (1:4), 0 °C, followed by debenzylation (1 atm of H_2, 10% Pd/C, CH_3OH, RT), gave the alcohol **5**[7] (^1H NMR ($CDCl_3$) δ 0.96 (3 H, d, J = 7 Hz), 1.27 (3 H, d, J = 7 Hz), 3.21 (3 H, s)) in 88% overall yield. Optical resolution of **5** was achieved in a three-step sequence: (1) (−)-$C_6H_5CH(CH_3)N{=}C{=}O$, Et_3N at 50 °C; (2) separation of the resultant diastereomeric urethanes



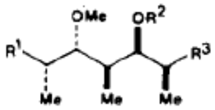
2 R=$CO_2C_2H_5$
3 R=$CH_2OCH_2C_6H_5$



4 R^1=H, R^2=$CH_2OCH_2C_6H_5$
5 R^1=CH_3, R^2=CH_2OH
6 R^1=CH_3, R^2=CHO



7



8 R^1=2-furyl, R^2=H, R^3=CH_2OH
9 R^1=2-furyl, R^2=$CH_2C_6H_5$, R^3=$CH_2OCH_2OCH_3$
10 R^1=CO_2CH_3, R^2=$CH_2C_6H_5$, R^3=$CH_2OCH_2OCH_3$
11 R^1=CO_2CH_3, R^2=$CH_2C_6H_5$, R^3=CH_2OH

Chem. Rev. **1989**, *89*, 1841–1860

Allylic 1,3-Strain as a Controlling Factor in Stereoselective Transformations

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Received May 24, 1988 (Revised Manuscript Received August 23, 1989)

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    10.2. 2-Oxoniaallyl Systems 1854

Prof. Reinhard W. Hoffmann was born in 1933 in Würzburg. He studied chemistry at the Universität Bonn from 1951 to 1958 and received his Dr. rer. nat. with a theses under the direction of Prof. B. Helferich, a former student of Emil Fischer. Prof. Hoffmann spent 2 years as a postdoctoral fellow at The Pennsylvania State University with Prof. G. W. Brindley in the Department of Ceramic Technology followed by another postdoctoral year with Prof. G. Wittig at the Universität Heidelberg working in benzyne chemistry. Subsequent independent studies on heterolytic fragmentation of azo compounds led to the habilitation in 1964. In 1967 Prof. Hoffmann moved as a dozent to the Technische Hochschule Darmstadt and in 1970 to his present position as Professor of Organic Chemistry at the Philipps-Universität Marburg. Over the years Prof. Hoffmann held visiting professorships at the Universität Bern, University of Wisconsin, Madison, and the University of California, Berkeley. His research interests developed from nucleophilic carbenes and electron-rich olefins to the investigation of stereoselective transformations.

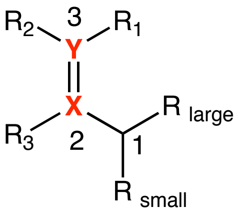
The Definition of Allylic Strain

F. Johnson, *Chem. Rev.* **1968**, *68*, 375; *Allylic Strain in Six-Membered Rings*

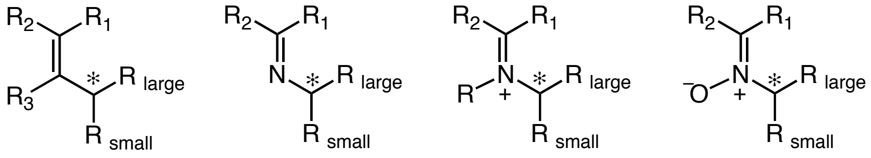
R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841-1860 **(handout)**
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations

Houk, Hoffmann *JACS* **1991**, *113*, 5006

Consider the illustrated general structure where X & Y are permutations of C, N, and O:



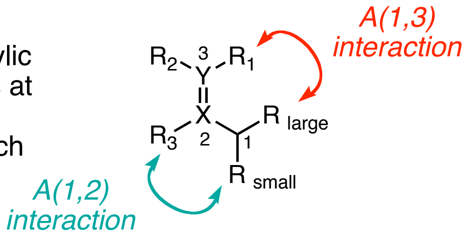
Typical examples:



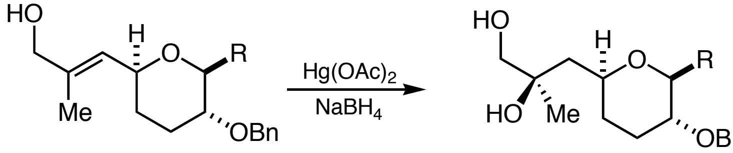
Olefin Imine Imonium ion Nitrone

In the above examples, the resident allylic stereocenter (⁎) and its associated substituents frequently impart a pronounced bias towards reactions occuring at the pi-bond.

Nonbonding interactions between the allylic substituents (R_{large}, R_{small}) & substituents at the 2- & 3-positions play a critical role in defining the stereochemical course of such reactions



Representative Reactions controlled by Allylic Strain Interactions

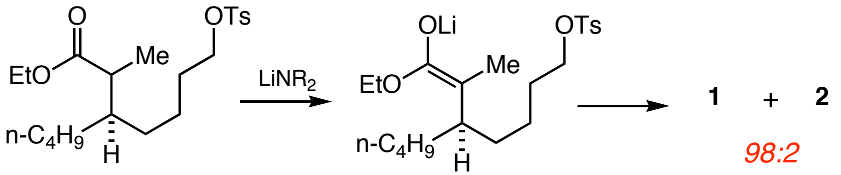


diastereoselection 10:1

M. Isobe & Co-workers, *Tetrahedron Lett.* **1985**, *26*, 5199.

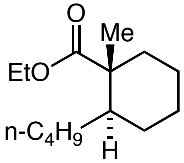
Can you predict the stereochemical outcome of this reaction?

D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, *27*, 943.

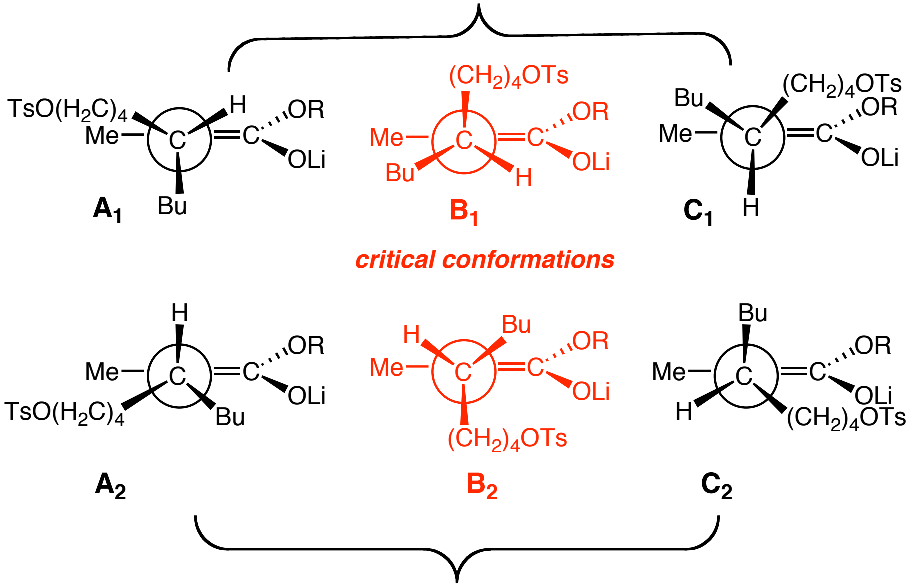


🟥 Relevant enolate conformations

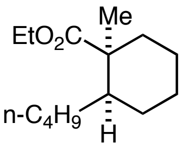
1



major

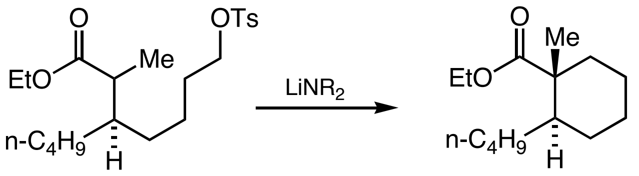


2

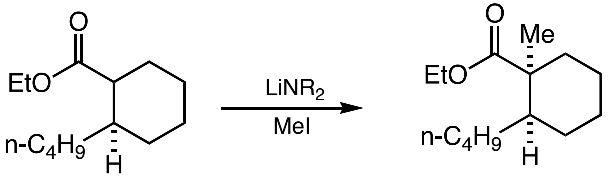


minor

Allylic Strain & Enolate Diastereoface Selection

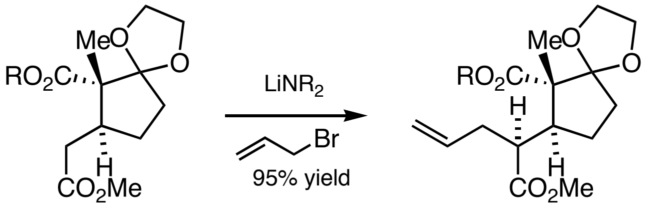


diastereoselection 98:2



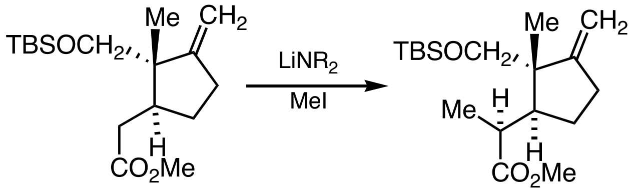
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.



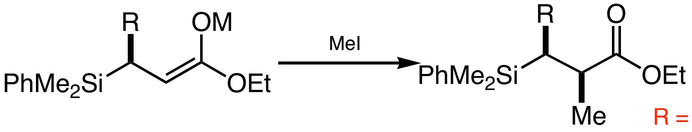
"one isomer"

G. Stork & Co-workers, *Tetrahedron Lett*. **1987**, *28*, 2088.



"one isomer"

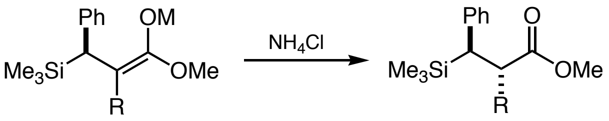
T. Money & Co-workers, *Chem. Commun*. **1986**, 288.



R = Me: *diastereoselection 99:1*

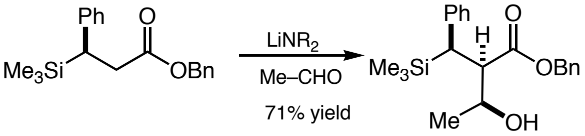
R = Ph: *diastereoselection 97:3*

I. Fleming & Co-workers, *Chem. Commun*. **1984**, 28.



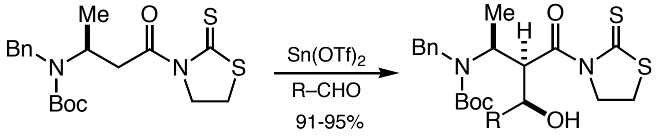
R-substituent	*diastereoselection*
R = Me	87:13
R = Et	80:20
R = CHMe$_2$	40:60 major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun*. **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun*. **1984**, 904.



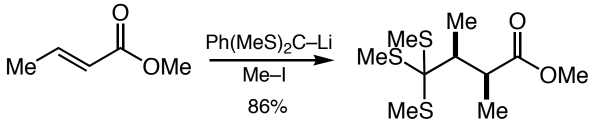
diastereoselection 90:10 at C_3
one isomer at C_2

I. Fleming & Co-workers, *Chem. Commun*. **1986**, 1198.



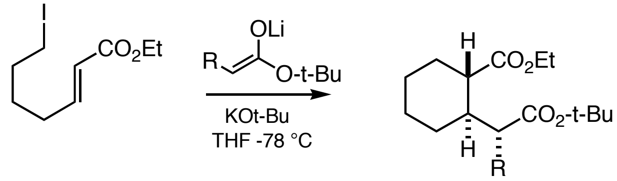
diastereoselection >95%

T. Mukaiyama & Co-workers, *Chem. Letters* **1986**, 637



diastereoselection 99:1

K. Koga & Co-workers, *Tetrahedron Letters* **1985**, *26*, 3031.

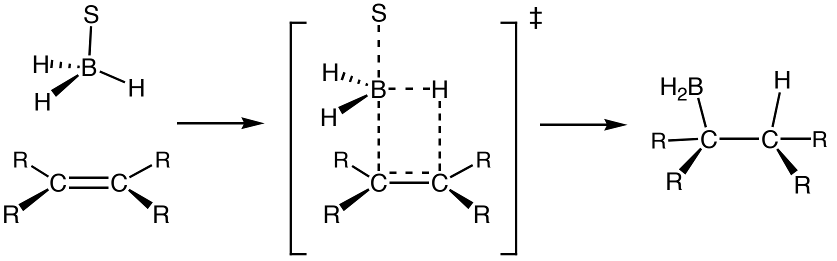


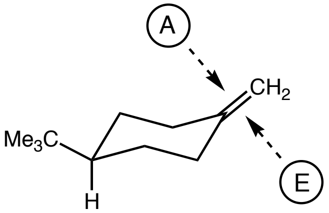
R = H: one isomer
R = Me: > 15 :1

Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, *26*,1723.

Allylic Strain & Olefin Hydroboration

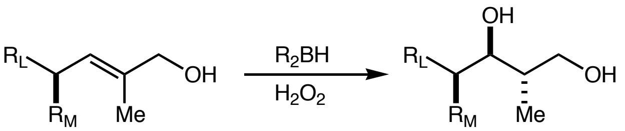
The basic process





Oxidant	Ratio, A:E	Reference
MCPBA	69:31	*JOC*, **1967**, *32*, 1363
BH_3, H_2O_2	34:66	*JOC*, **1970**, *35*, 2654

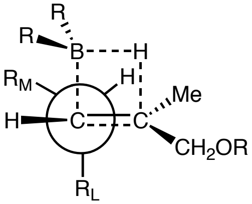
Acyclic hydroboration can be controlled by A(1,3) interactions:

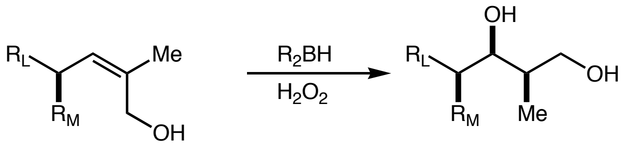


major diastereomer

control elements

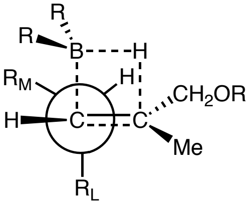
A(1,3) allylic strain
Steric effects; R_L vs R_M
Staggered transition states



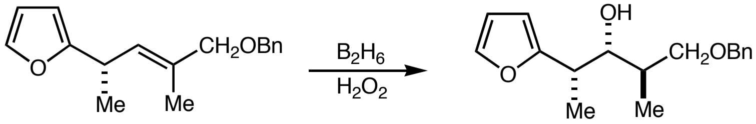


major diastereomer

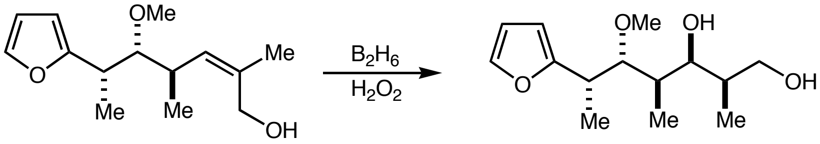
See Houk, *Tetrahedron* **1984**, *40*, 2257



Hydroborations dominated by A(1,3) Strain

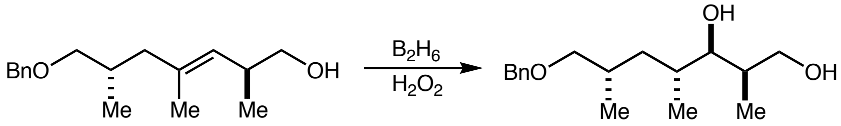


diastereoselection 8:1



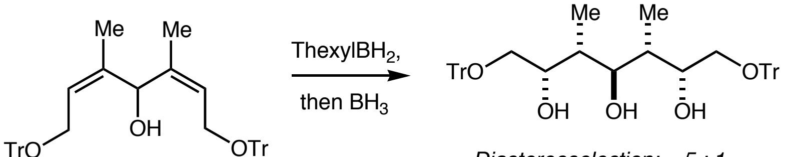
diastereoselection 12:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1979**, *101*, 259.

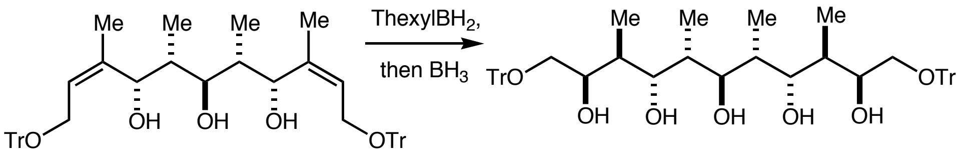


Diastereoselection = 3:1

C. H. Heathcock et. al. *Tetrahedron Lett* **1984** *25* 243.



Diastereoselection; 5 : 1

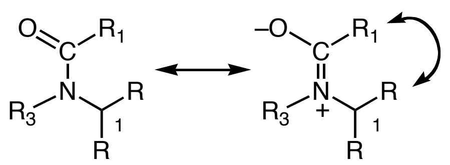


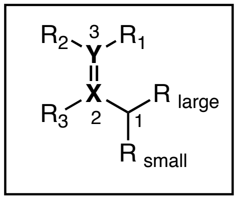
Diastereoselection; 4: 1

Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

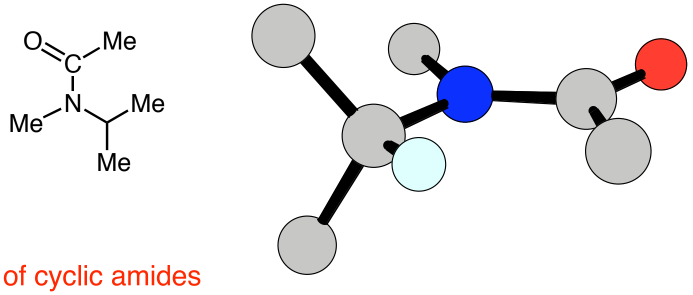
Allylic Strain & Amide Conformation

Consider the resonance structures of an amide:

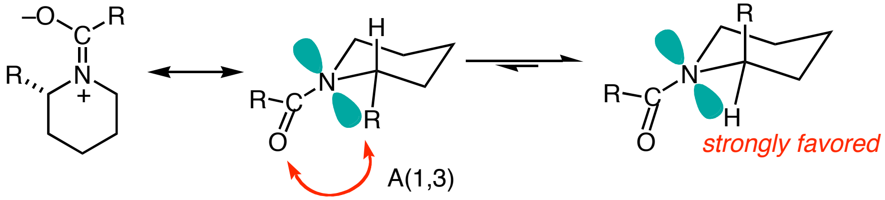




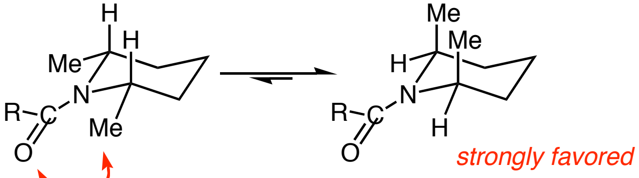
A(1,3) interactions between the "allylic substituent" and the R1 moiety will strongly influence the torsion angle between N & C1.

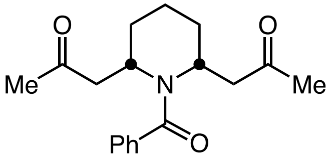


■ conformations of cyclic amides



Chow
Can. J. Chem. **1968**, *46*, 2821



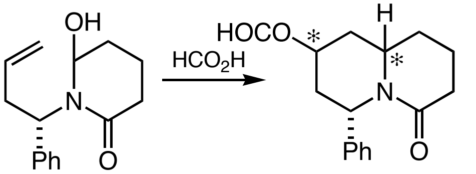


published X-ray structure of this amide shows chair diaxial conformation

Quick, *J. Org. Chem.* **1978**, *43*, 2705

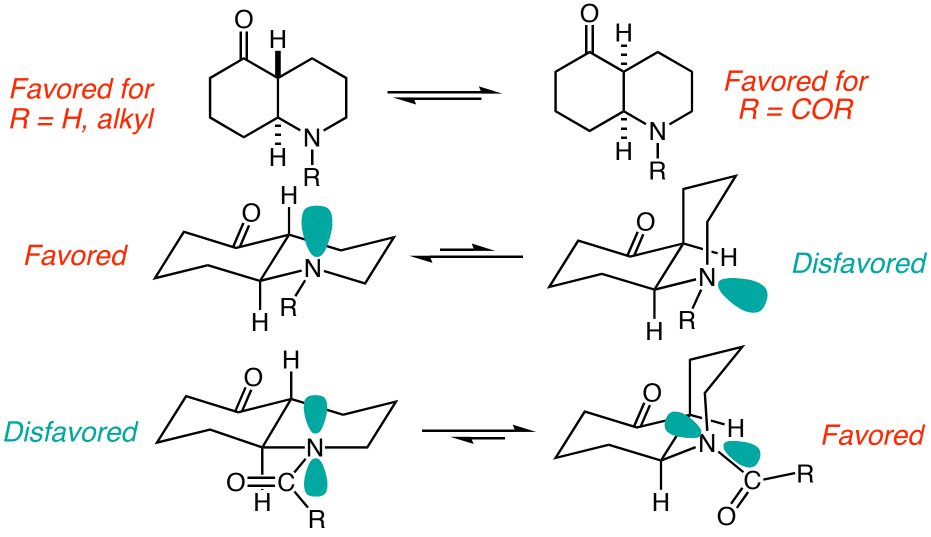
■ Problem: Predict the stereochemical outcome of this cyclization.

D. Hart, *JACS* **1980**, *102*, 397

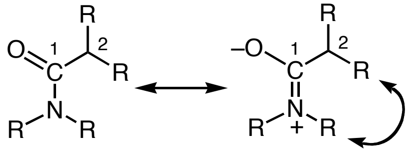


diastereoselection >95%

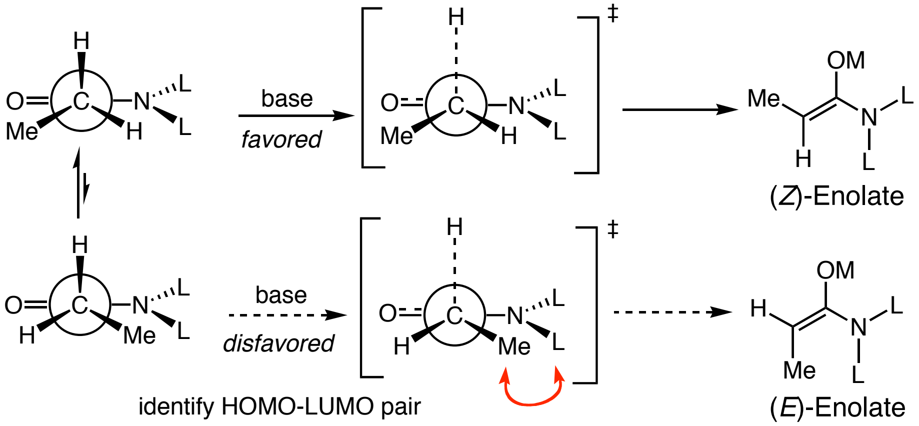
The selection of amide protecting group may be done with the knowledge that altered conformational preferences may result:



A(1,3) interaction between the C2 & amide substituents will strongly influence the torsion angle between C1 & C2.

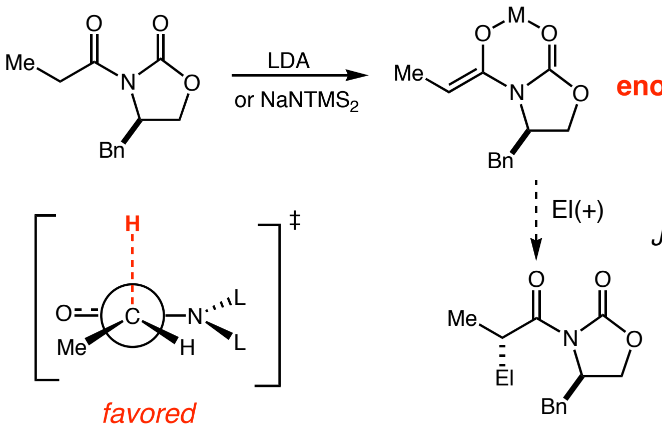


As a result, amides afford (Z) enolates under all conditions



identify HOMO-LUMO pair

A(1,3) Strain and Chiral Enolate Design

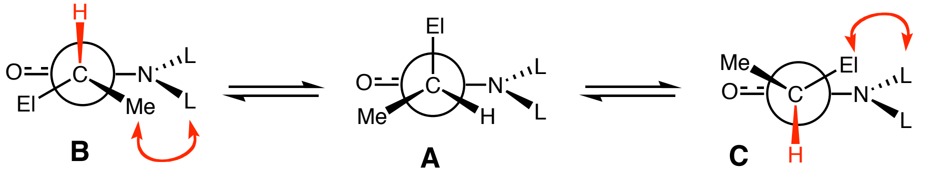


enolization selectivity >100:1

JACS. **1982**, *104*, 1737.

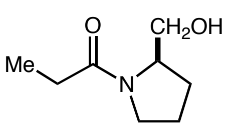
favored enolization geometry

- In the enolate alkylation process product epimerization is a serious problem. Allylic strain suppresses product enolization through the intervention of allylic strain

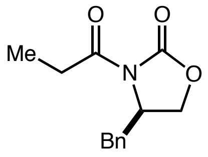


While conformers **B** and **C** meet the stereoelectronic requirement for enolization, they are much higher in energy than conformer **A**. Further, as deprotonation is initiated, A(1,3) destabilization contributes significantly to reducing the kinetic acidity of the system

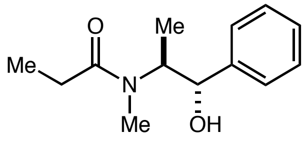
These allylic strain attributes are an integral part of the design criteria of chiral amide and imide-based enolate systems



Evans
Tetr Lett. **1977**, *29*, 2495

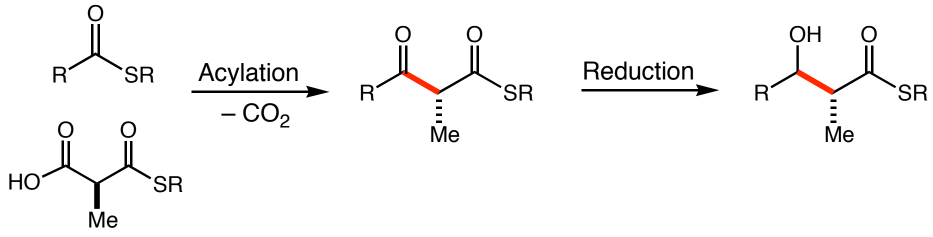


Evans
JACS **1982**, *104*, 1737.

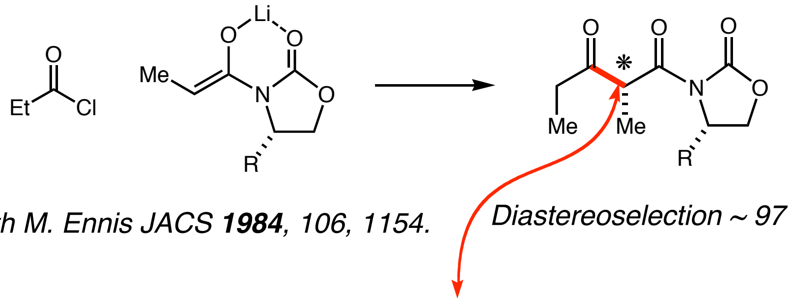


Myers
JACS **1997**, *119*, 6496

Polypropionate Biosynthesis: The Acylation Event



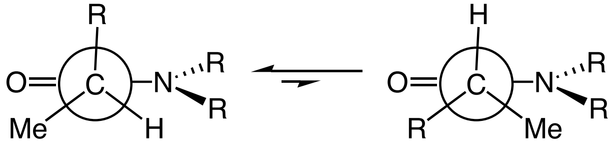
First laboratory analogue of the acylation event



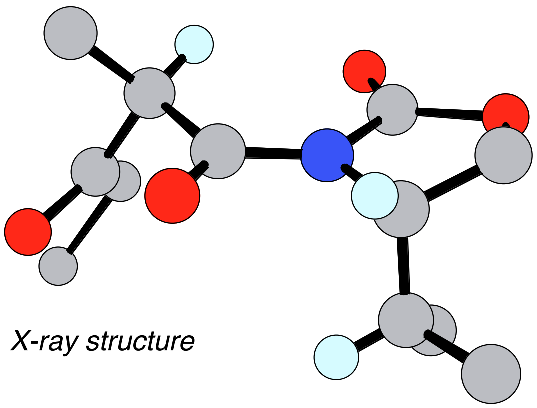
with M. Ennis JACS **1984**, *106, 1154.*

Diastereoselection ~ 97 : 3

Why does'nt the acylation product rapidy epimerize at the exocyclic stereocenter??

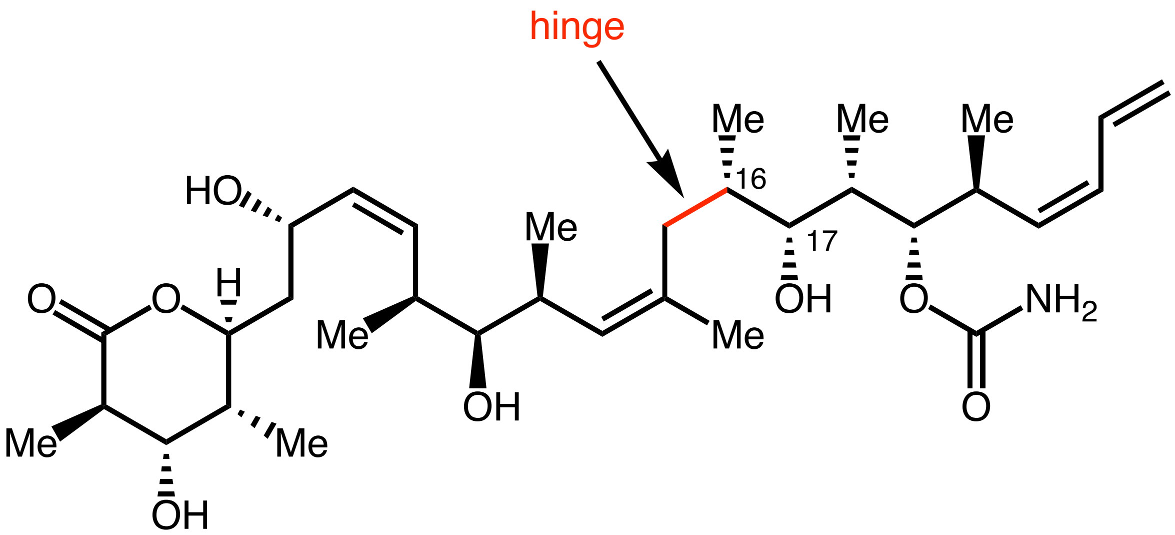


favored



X-ray structure

Discodermolide



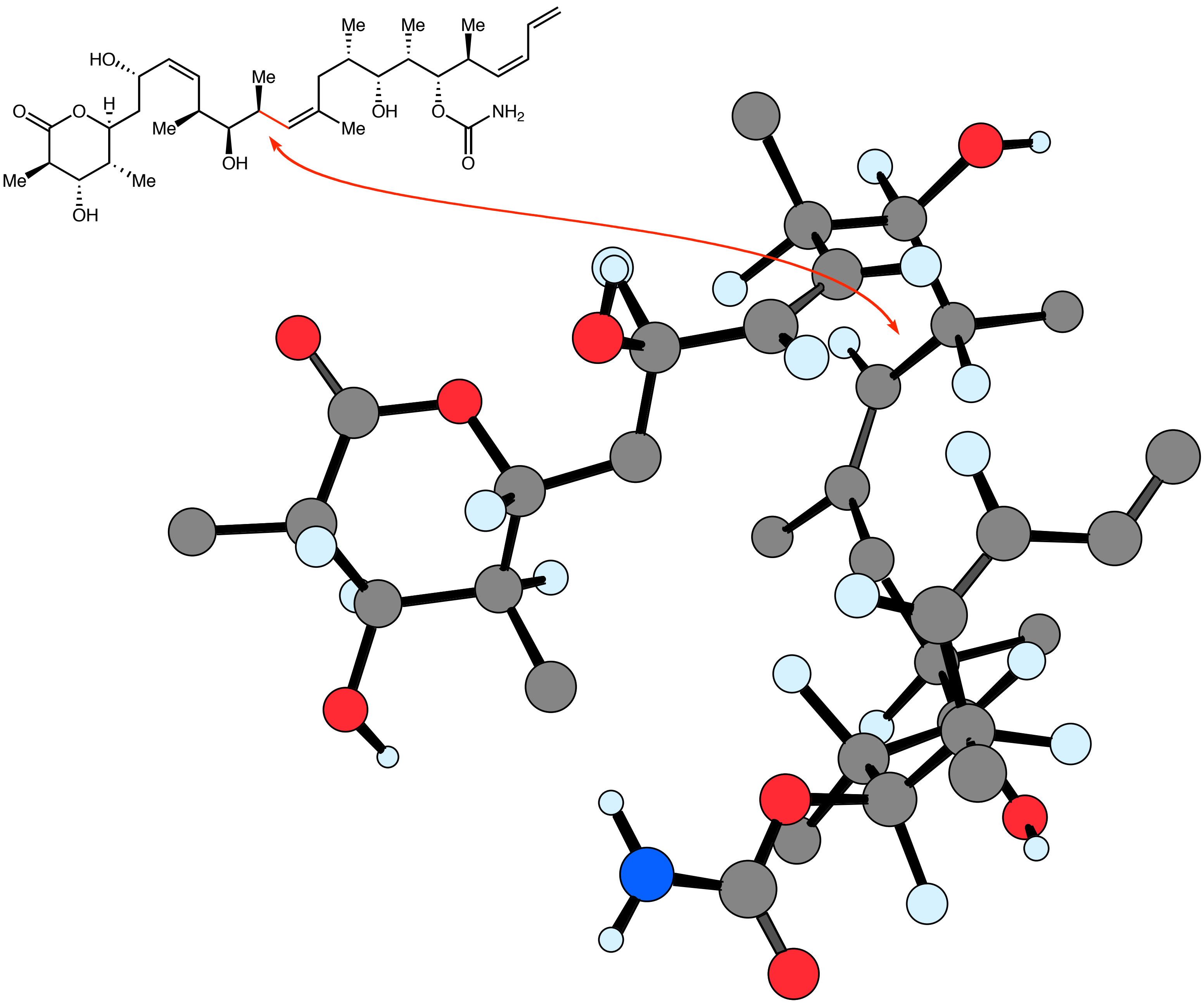
- immunosuppressive activity
- potent microtubule-stabilizing agent
(antitumor activity similar to that of taxol)

The epimers at C16 and C17 have no or almost no biological activity.

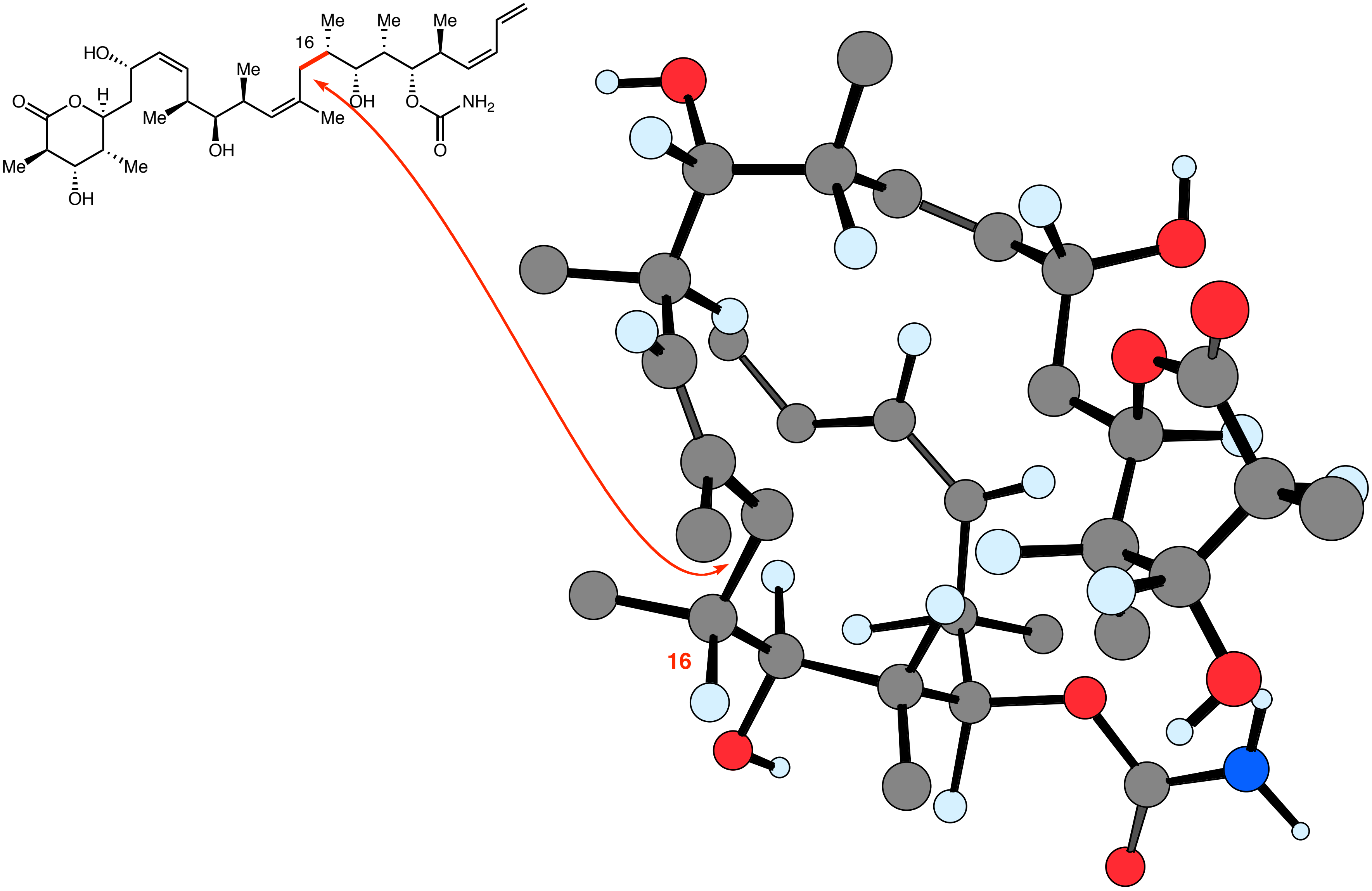
The conformation about C16 and C17 is critical to discodermolide's biological activity.

S. L. Schreiber et al. *JACS* **1996**, *118*, 11061.

Conformational Analysis - Discodermolide X-ray 1



Conformational Analysis - Discodermolide X-ray 2



http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 6

Conformational Analysis-3

- Conformational Analysis of $C_4 \rightarrow C_6$ Rings

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapter 3

Eliel & Wilen, "Stereochemistry of Organic Compounds, "Chapter 11, Configuration and Conformation of Cyclic Molecules, Wiley, 1994

Ribeiro & Rittner, "The Role of Hyperconjugation in the Conformational Analysis of Methylcyclohexane and Methylheterocyclohexanes"
J. Org. Chem., **2003**, *68*, 6780-6787 **(handout)**

Stability Relationships in Bicyclic Ketones,
Synlett **2005,** 2911-2914 **(handout)**

The Application of Cyclobutane Derivatives in Organic Synthesis
Chem Rev. 2003, 103, 1485-1537 **(pdf)**

de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics"
Angew Chem. Int. Ed. **1979**, *18*, 809-826 **(pdf)**

The Application of Cyclobutane Derivatives in Organic Synthesis
Chem. Rev. **2003,** *103,* 1485-1537 **(pdf)**

D. A. Evans

Friday,
September 29, 2006

Conformational Analysis of Cyclic Systems

Three Types of Strain:

Prelog Strain: van der Waals interactions

Baeyer Strain: bond angle distortion away from the ideal

Pitzer Strain: torsional rotation about a sigma bond

Baeyer Strain for selected ring sizes

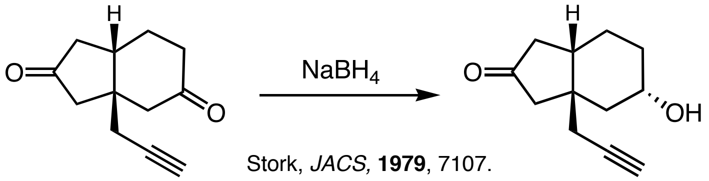
size of ring	Ht of Combustion (kcal/mol)	Total Strain (kcal/mol)	Strain per CH_2 (kcal.mol)	"angle strain" deviation from 109°28'
3	**499.8**	**27.5**	9.17	24°44'
4	656.1	26.3	6.58	9°44'
5	793.5	6.2	1.24	0°44'
6	**944.8**	**0.1**	0.02	-5°16'
7	1108.3	6.2	0.89	
8	1269.2	9.7	1.21	
9	**1429.6**	**12.6**	1.40	
10	**1586.8**	**12.4**	1.24	
11	**1743.1**	**11.3**	1.02	
12	1893.4	4.1	0.34	
13	2051.9	5.2	0.40	
14	2206.1	1.9	0.14	
15	2363.5	1.9	0.13	

Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds* Chapter 11, John Wiley & Sons, 1994.

- Baeyer "angle strain" is calculated from the deviation of the *planar* bond angles from the ideal tetrahedral bond angle.

- Discrepancies between calculated strain/CH_2 and the "angle strain" results from puckering to minimize van der Waals or eclipsing torsional strain between vicinal hydrogens.

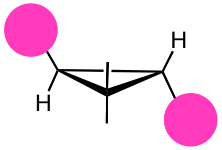
Problem: Rationalize the regioselectivity of the following reduction



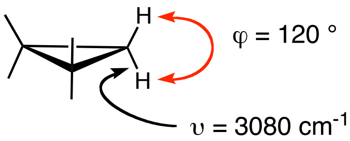
Stork, *JACS,* **1979**, 7107.

Cyclopropane: Bonding, Conformation, Carbonium Ion Stabilization

Cyclopropane



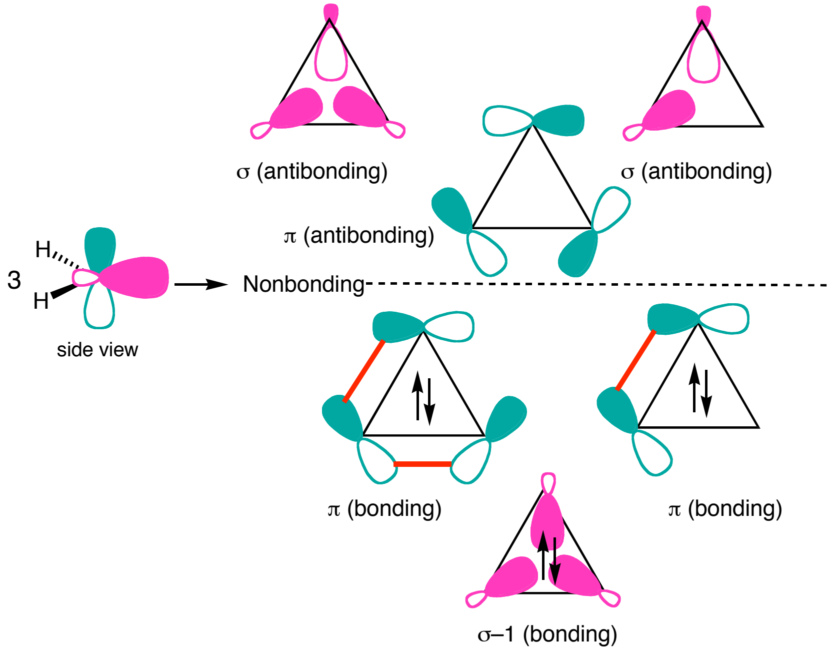
- ■ Necessarily *planar*.
- ■ Subtituents are therefore eclipsed.
- ■ Disubstitution prefers to be *trans.*



■ Almost sp^2, not sp^3

Walsh Model for Strained Rings:

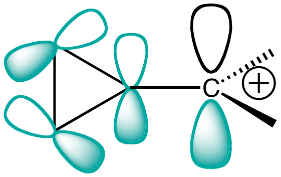
■ Rather than σ and σ* c-c bonds, cyclopropane has sp^2 and p-type orbitals instead.



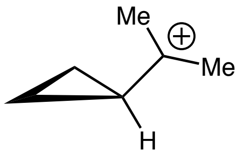
de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics" *Angew Chem. Int. Ed.* **1979**, *18*, 809-826 **(handout)**

de Meijere, A.; Wessjohann, L. "Tailoring the Reactivity of Small Ring Building Blocks for Organic Synthesis." *Synlett* 1990, 20. (pdf)

Carbocation Stabilization via Cyclopropylgroups

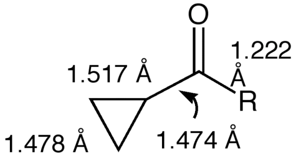


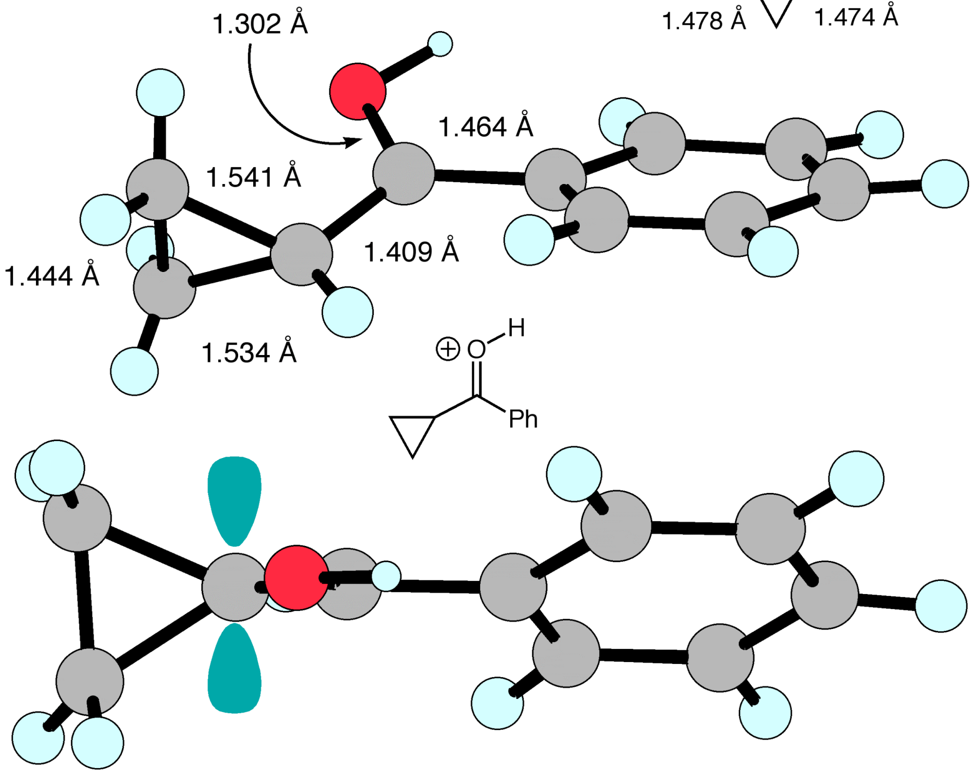
A rotational barrier of about 13.7 kcal/mol is observed in following example:



NMR in super acids
δ(CH$_3$) = 2.6 and 3.2 ppm

X-ray Structures support this orientation

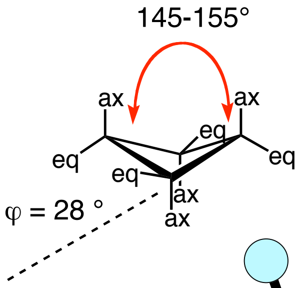




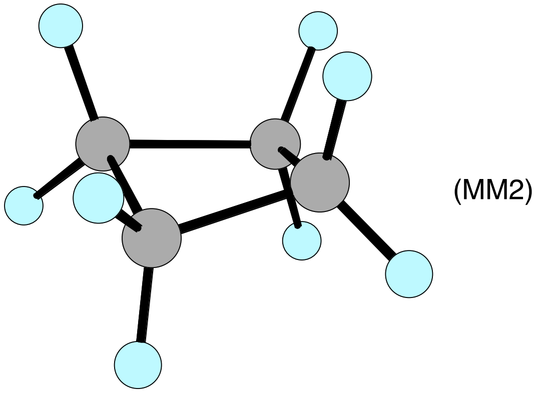
R. F. Childs, *JACS* **1986**, *108*, 1692

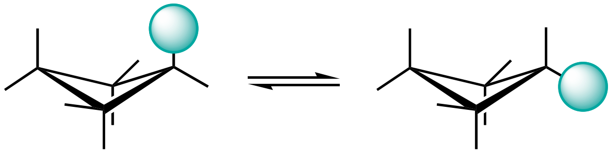
Conformational Analysis: Cyclic Systems-2

Cyclobutane

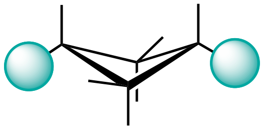


- ■ Eclipsing torsional strain overrides increased bond angle strain by puckering.
- ■ Ring barrier to inversion is 1.45 kcal/mol.

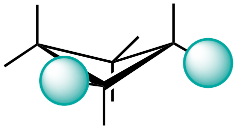




■ ΔG = 1 kcal/mol favoring R = Me equatorial

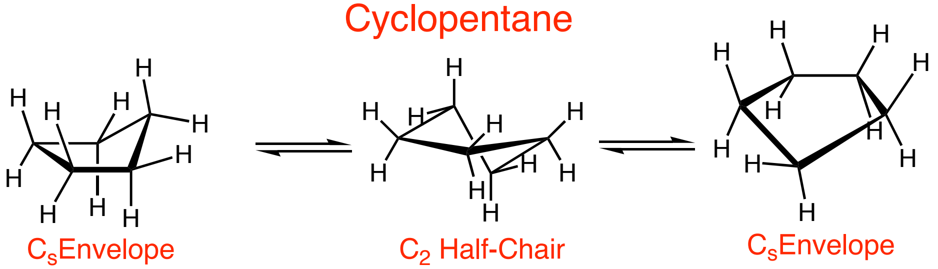


■ 1,3 Disubstitution prefers *cis* diequatorial to *trans* by 0.58 kcal/mol for di-bromo cmpd.



■ 1,2 Disubstitution prefers *trans* diequatorial to *cis* by 1.3 kcal/mol for diacid (roughly equivalent to the cyclohexyl analogue.)

Cyclopentane

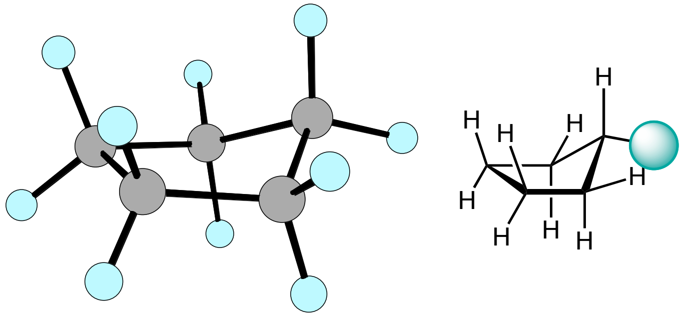


■ Two lowest energy conformations (10 envelope and 10 half chair conformations C_s favored by only 0.5 kcal/mol) in rapid conformational flux (pseudorotation) which causes the molecule to appear to have a single out-of-plane atom "bulge" which rotates about the ring.

■ Since there is no "natural" conformation of cyclopentane, the ring conforms to minimize interactions of any substituents present.

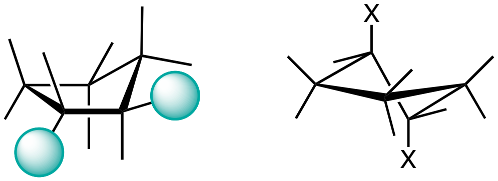
C_sEnvelope

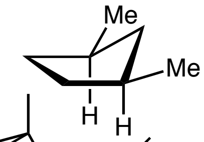
(MM2)



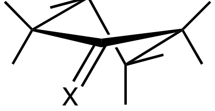
■ A single substituent prefers the equatorial position of the flap of the envelope (barrier ca. 3.4 kcal/mol, R = CH_3).

■ 1,2 Disubstitution prefers *trans* for steric/torsional reasons (alkyl groups) and dipole reasons (polar groups).





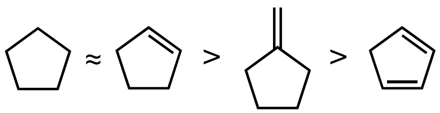
■ 1,3 Alkyl Disubstitution: **Cis**-1,3-dimethyl cyclopentane 0.5 kcal/mol **more stable** than trans.



■ A carbonyl or methylene prefers the planar position of the half-chair (barrier 1.15 kcal/mol for cyclopentanone).

Methylenecyclopentane and Cyclopentene

Strain trends:

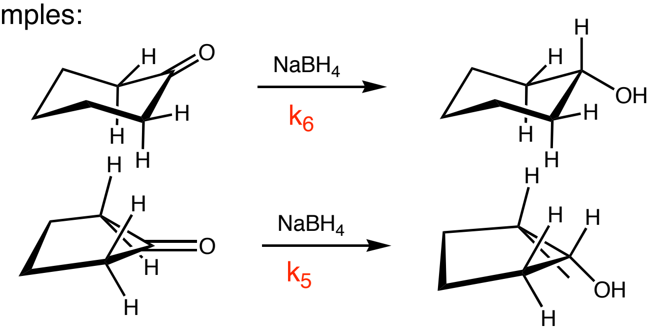


- Decrease in eclipsing strain more than compensates for the increase in angle strain.

Relative to cyclohexane derivatives, those of cyclopentane prefer an sp^2 center in the ring to minimize eclipsing interactions.

"Reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in the 5-ring and to avoid the formation or retention of the exo double bond in the 6-ring systems." Brown, H. C., Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.

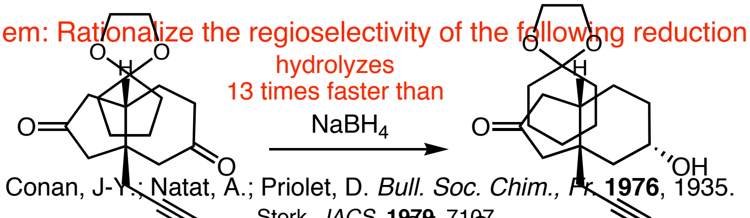
Examples:



$\frac{k_6}{k_5}$ = 23

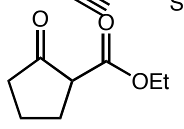
Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.

Problem: Rationalize the regioselectivity of the following reduction

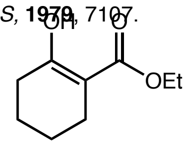


Conan, J-Y.; Natat, A.; Priolet, D. *Bull. Soc. Chim., Fr.* **1976**, 1935.

Stork, *JACS*, **1979**, 7107.



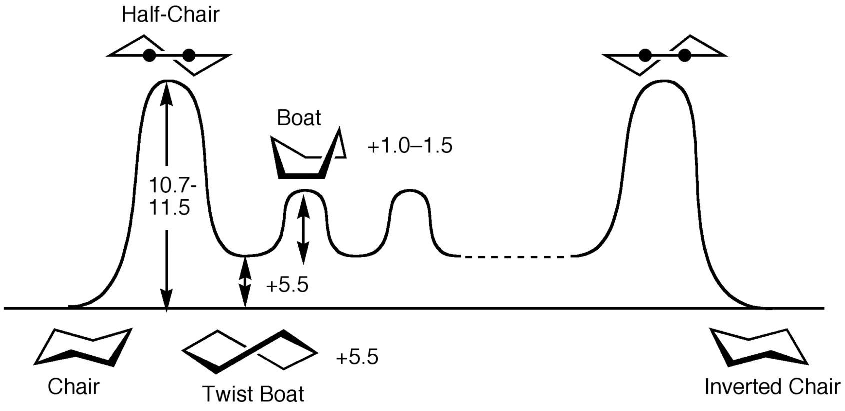
95.5:4.5 keto:enol

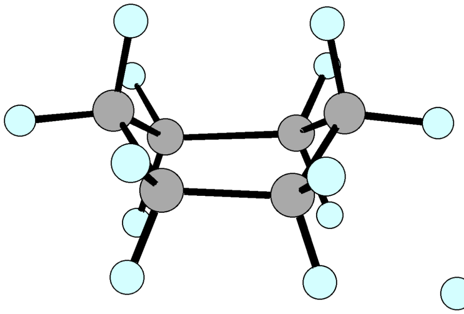


76:24 enol:keto

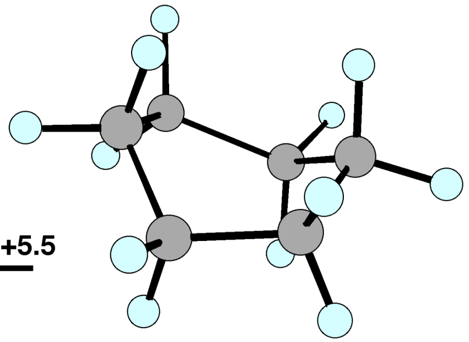
Brown, H. C., Brewster, J. H.; Shechter, H. *JACS* **1954**, *76*, 467.

Cyclohexane Energy Profile (kcal/mol)



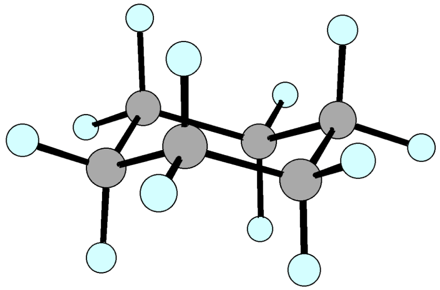


ΔE = +6.5-7.0



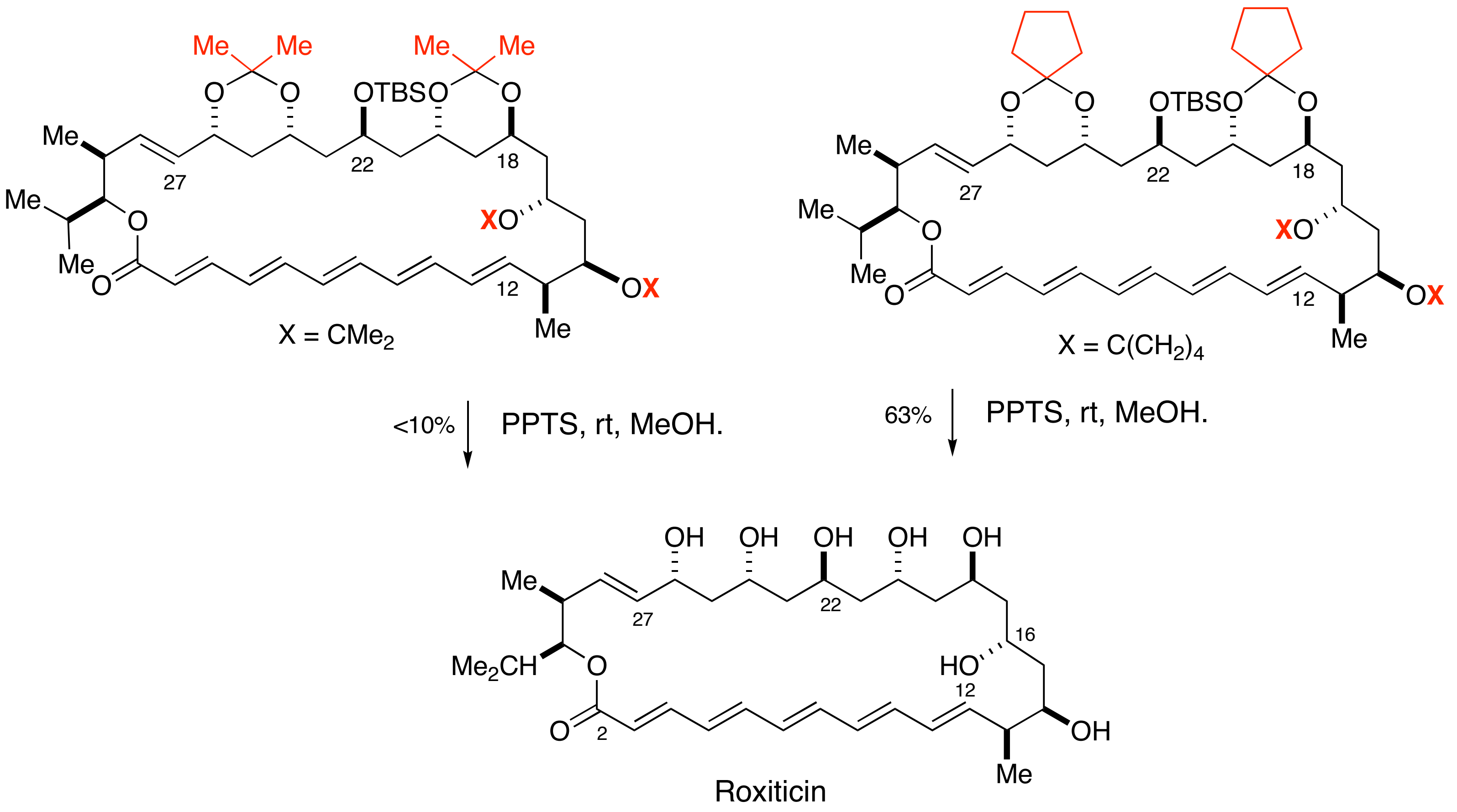
ΔE = +5.5

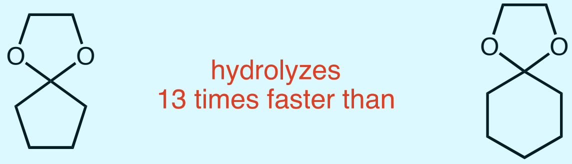
The barrier: +10.7-11.5



E = 0

"Total Synthesis of the Antifungal Macrolide Antibiotic (+)-Roxaticin," Evans, D. A.; Connell, B. T.
J. Am. Chem. Soc., **2003**, *125*, 10899-10905





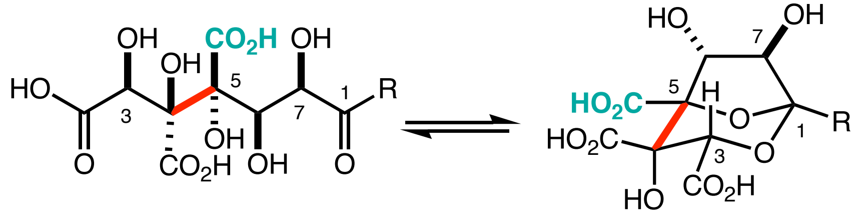
hydrolyzes
13 times faster than

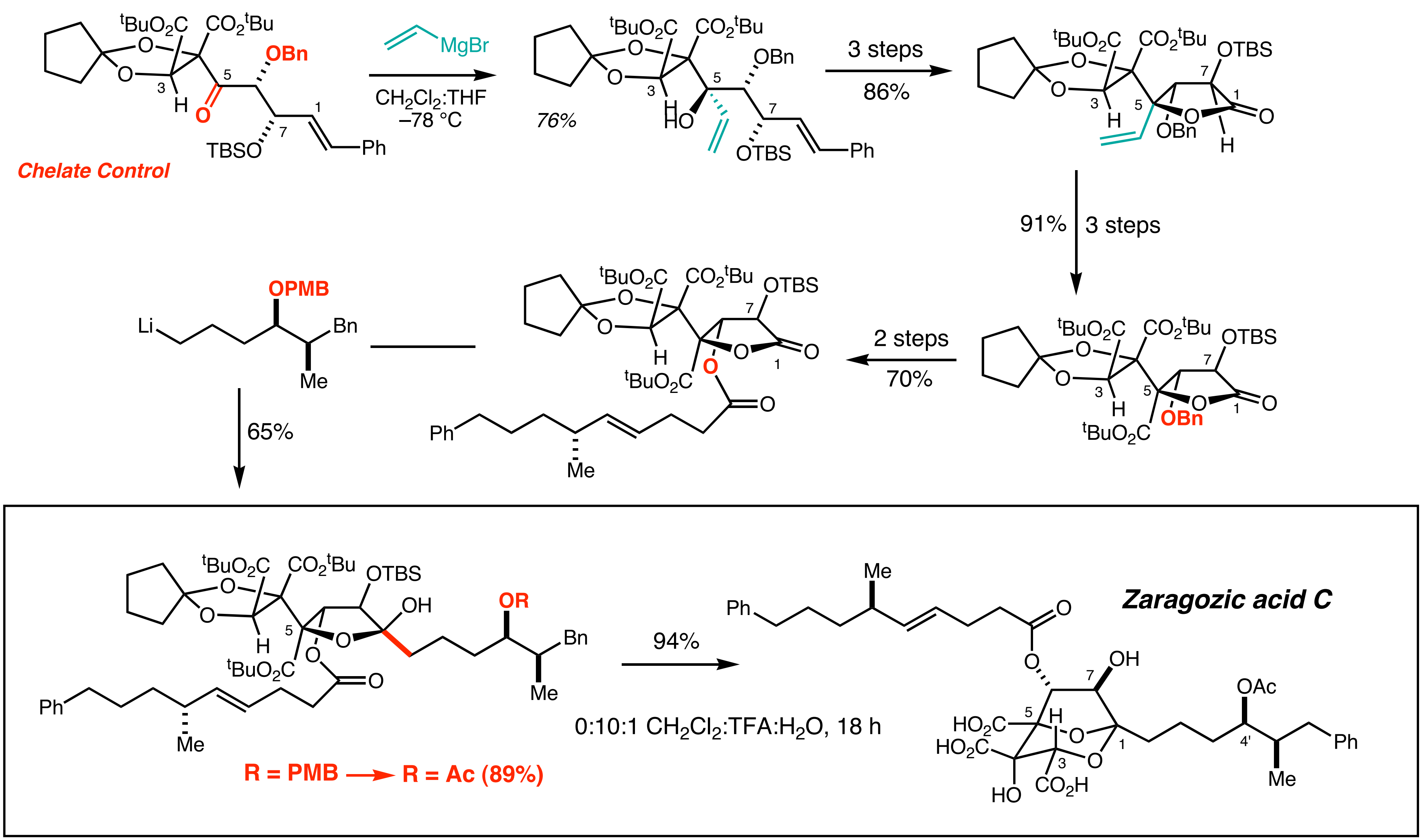
Conan, J-Y.; Natat, A.; Priolet, D. *Bull. Soc. Chim., Fr.* **1976**, 1935.

Zaragozic Acid C Synthesis

J. Leighton, J. Barrow

JACS **1994,** *116,* 12111-12112

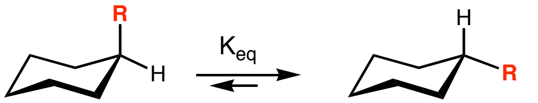




Zaragozic acid C

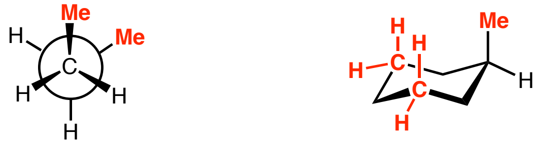
Conformational Analysis: Cyclic Systems-4

Monosubstituted Cyclohexanes: *A* Values



$\Delta G° = –RT\ln K_{eq}$

- Me–axial has **2 gauche butane interactions** more than Me–equatorial.
  Expected destabilization: ≈ 2(0.88) kcal/mol = ~1.8 kcal/mol;
  Observed: 1.74 kcal/mol



- The *A*– Value, or -ΔG°, is the preference of the substituent for the equatorial position.

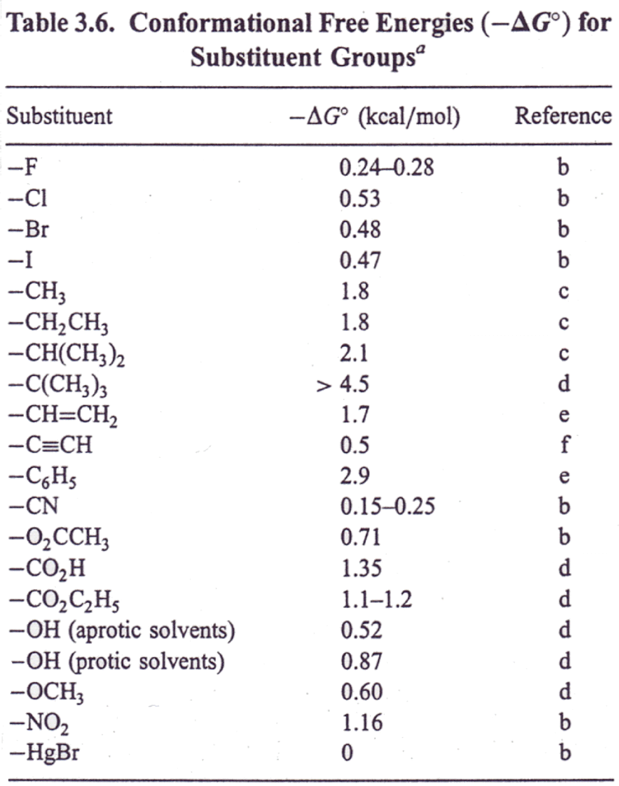
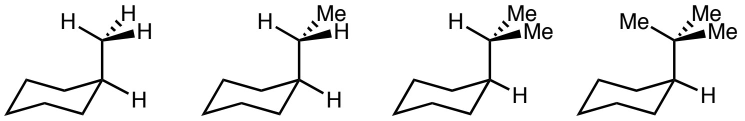


Table 3.6. Conformational Free Energies (–ΔG°) for Substituent Groups[a]

Substituent	–ΔG° (kcal/mol)	Reference
–F	0.24–0.28	b
–Cl	0.53	b
–Br	0.48	b
–I	0.47	b
$–CH_3$	1.8	c
$–CH_2CH_3$	1.8	c
$–CH(CH_3)_2$	2.1	c
$–C(CH_3)_3$	> 4.5	d
$–CH{=}CH_2$	1.7	e
–C≡CH	0.5	f
$–C_6H_5$	2.9	e
–CN	0.15–0.25	b
$–O_2CCH_3$	0.71	b
$–CO_2H$	1.35	d
$–CO_2C_2H_5$	1.1–1.2	d
–OH (aprotic solvents)	0.52	d
–OH (protic solvents)	0.87	d
$–OCH_3$	0.60	d
$–NO_2$	1.16	b
–HgBr	0	b

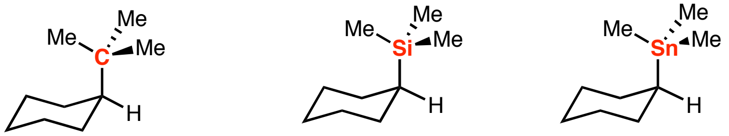
C & S, Part A, pg 140

A Values depend on the *relative size* of the particular substituent.



A–Value 1.74 1.80 2.15 5.0

The "relative size" of a substituent and the associated A-value may not correlate. For example, consider the $–CMe_3$ and $–SiMe_3$ substituents. While the $–SiMe_3$ substituent has a larger covalent radius, it has a smaller A-value:

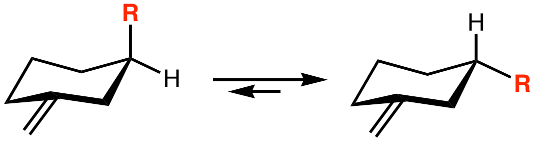


A–Value 4.5-5.0 2.5 1.1

Can you explain these observations?

- The impact of double bonds on A-values:

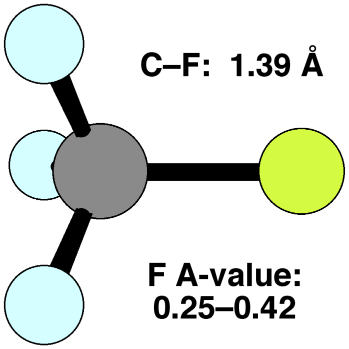
Lambert, *Accts. Chem. Res.* **1987**, *20*, 454



substituent	–ΔG°	A-value (cyclohexane)
R = Me	0.8	1.74
R = OMe	0.8	0.6
R = OAc	0.6	0.71

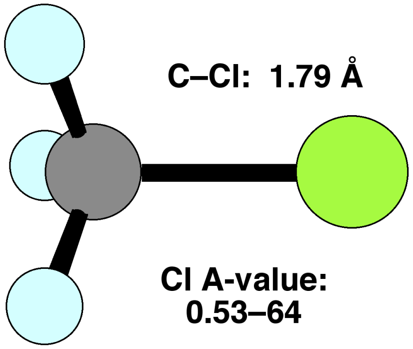
The Me substituent appears to respond strictly to the decrease in nonbonding interactions in axial conformer. With the more polar substituents, electrostatic effects due to the trigonal ring carbon offset the decreased steric environment.

Bond Lengths and A-Values of Methyl Halides



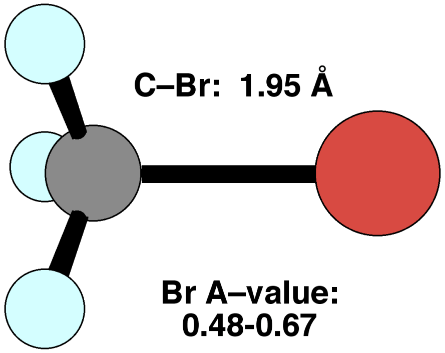
C–F: 1.39 Å

F A-value:
0.25–0.42



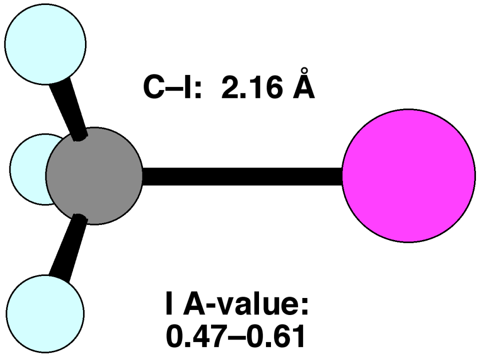
C–Cl: 1.79 Å

Cl A-value:
0.53–64



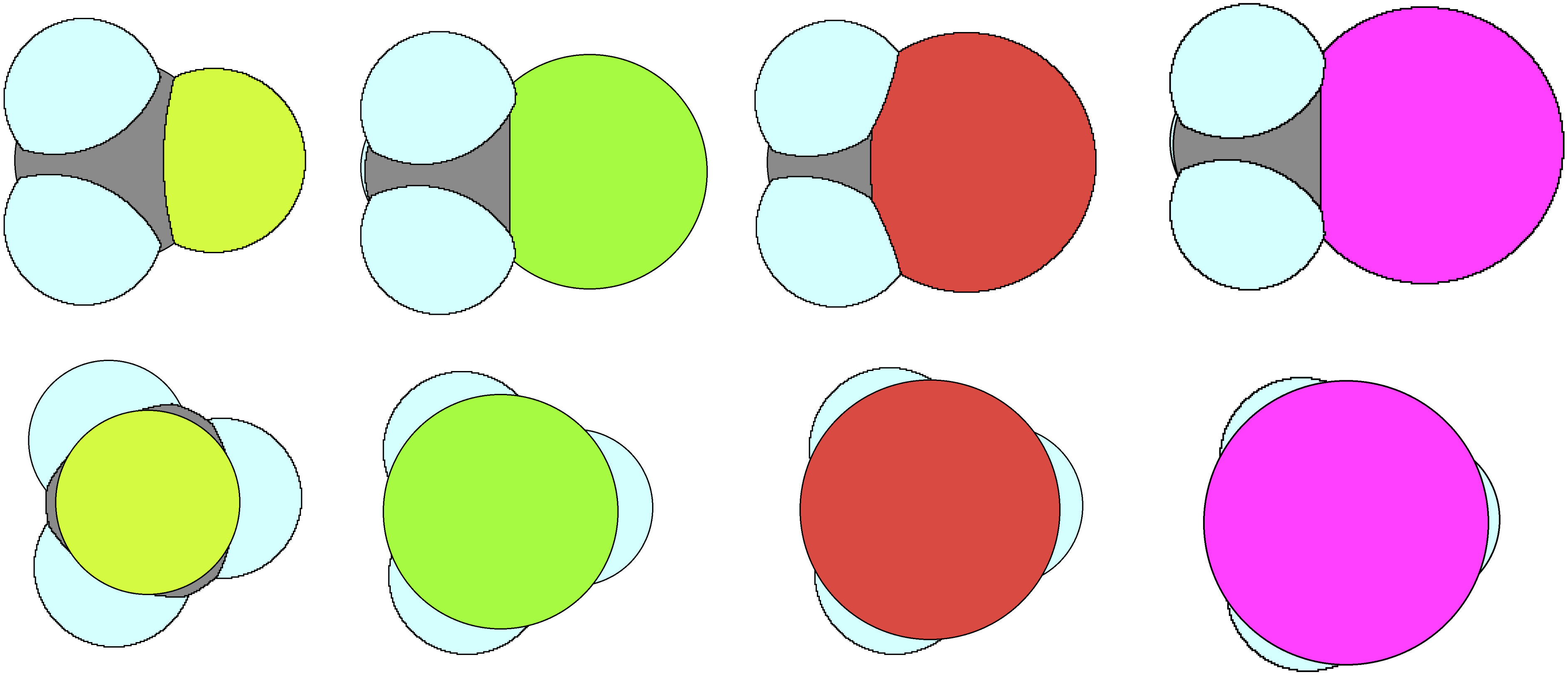
C–Br: 1.95 Å

Br A–value:
0.48-0.67



C–I: 2.16 Å

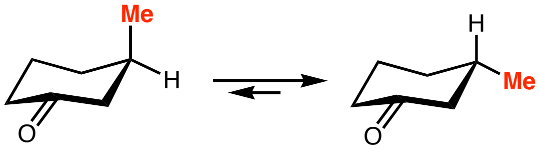
I A-value:
0.47–0.61



Chem 3D Pro (Verson 5.0)

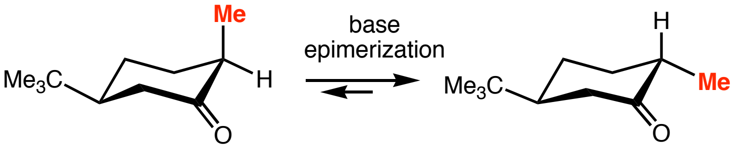
Impact of Trigonal Carbon

- Let's now compare look at the carbonyl analog in the 3-position



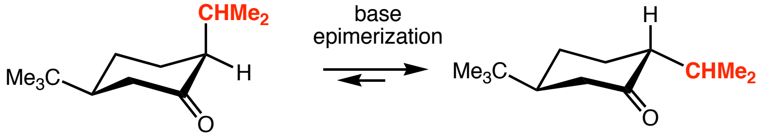
ΔG° = –1.36 kcal/mol
versus –1.74 for cyclohexane

- Let's now compare look at the carbonyl analog in the 2-position

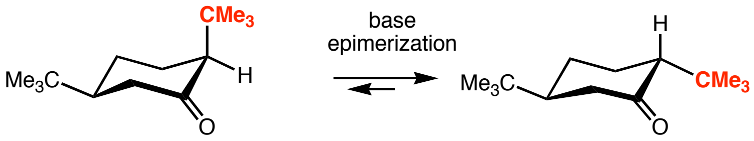


ΔG° = –1.56 kcal/mol
versus –1.74 for cyclohexane

However, the larger alkyl groups do not follow the expected trend.
Can you explain? (see Eliel, page 732)



ΔG° = –0.59 kcal/mol
versus –2.15 for cyclohexane

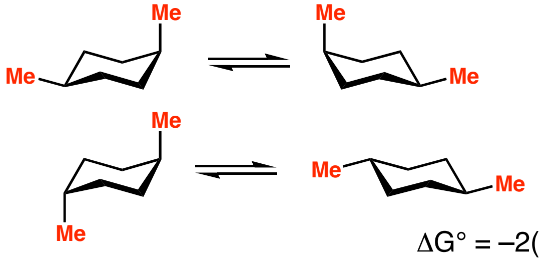


ΔG° = –1.62 kcal/mol
versus –5.0 for cyclohexane

Polysubstituted Cyclohexane *A* Values

- As long as the substituents on the ring do not interact in either conformation, their A-values are roughly additive

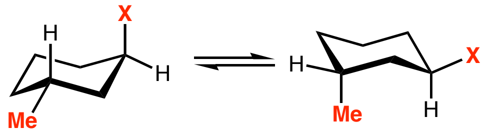
1,4 Disubstitution: *A* Values are roughly additive.



ΔG° = 0 kcal/mol

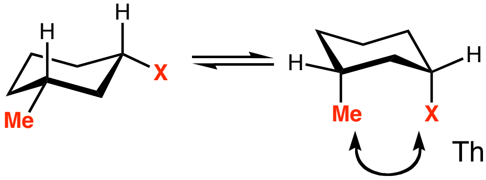
ΔG° = –2(1.74) = –3.48 kcal/mol

1,3 Disubstitution: *A* Values are only additive in the trans diastereomer



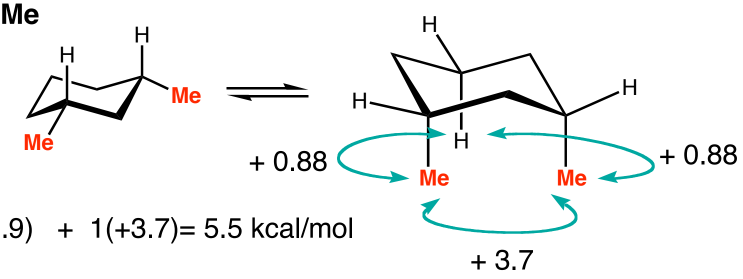
ΔG° = A(Me) – A(X)

The cis Isomer



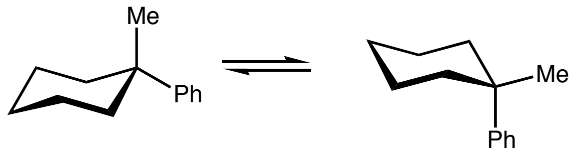
The new interaction!

For X = Me



ΔG° = 2(.9) + 1(+3.7)= 5.5 kcal/mol

Let's now consider geminal substitution



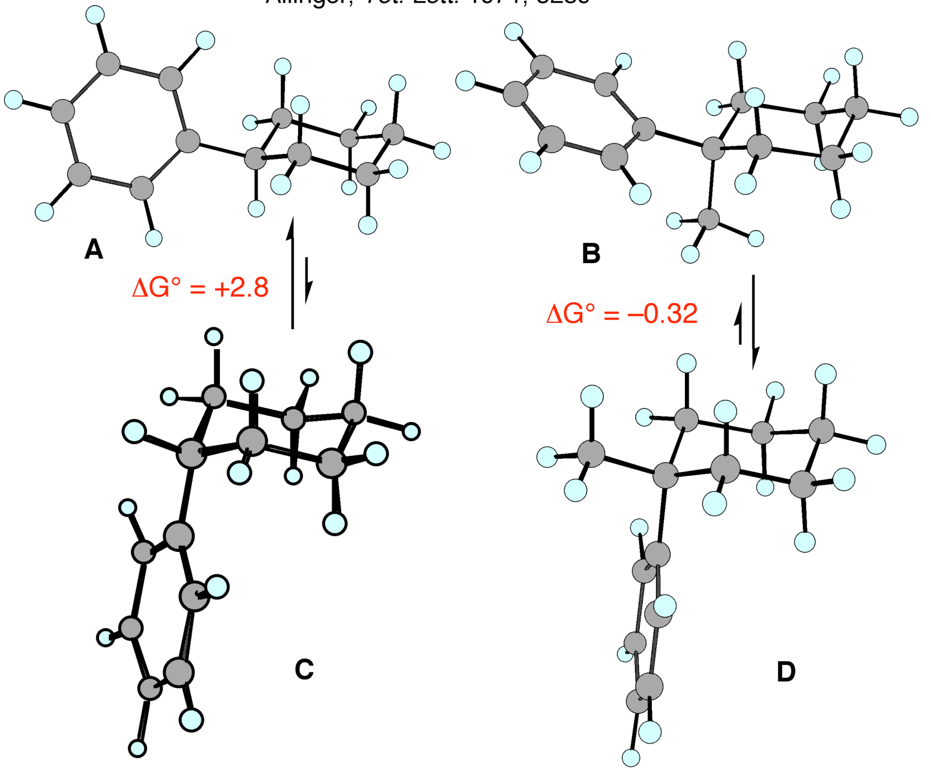
The prediction: ΔG° = A(Ph) – A(Me)

ΔG° = +2.8 – 1.7 = +1.1 kcal/mol

Observed: ΔG° = –0.32 kcal/mol

Hence, when the two substituents are mutually interacting you can predict neither the magnitude or the direction of the equilibrium. Let's analyze this case.

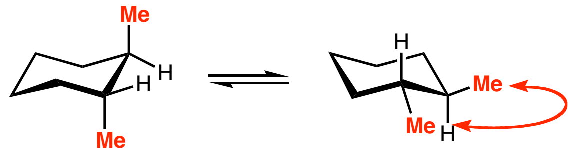
Allinger, *Tet. Lett.* 1971, 3259



Note the difference in the Ph substituent in **A** & **B**.

Let's now consider vicinal substitution

Case 1:



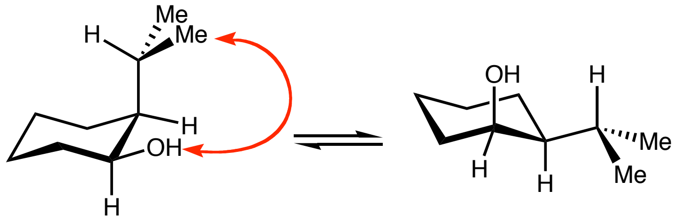
The prediction: ΔG° = 1 gauche butane – 2A(Me)

ΔG° = +0.88 – 2(1.74) = +2.6 kcal/mol

Observed: ΔG° = +2.74 kcal/mol

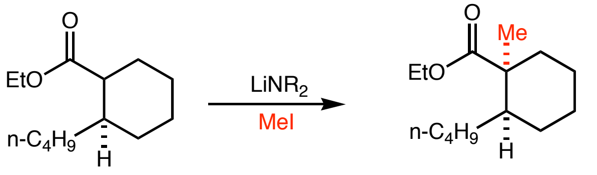
If the added gauche butane destabilization in the di-equatorial conformer had not been added, the estimate would have been off.

Case 2:



The conformer which places the isopropyl group equatorial is much more strongly preferred than would be suggested by *A*- Values. This is due to a syn pentane OH/Me interaction.

Problem:
Can you rationalize the stereochemical outcome of this reaction?



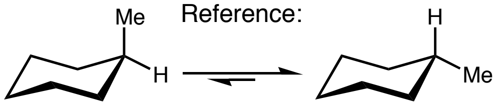
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, *27*, 943.

Heteroatom-Substituted 6-Membered Rings

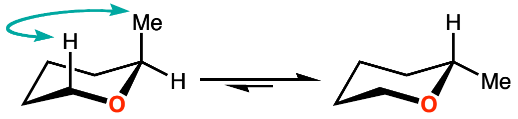
- A-values at the 2-position in both the O & N heterocycles are larger than expected. This is due to the shorter C–O (1.43 Å), and C–N (1.47 Å) bond lengths relative to carbon (C–C; 1.53 Å). The combination of bond length and bond angle change increases the indicated 1,3-diaxial interaction (see eq 1, 4).

Reference:



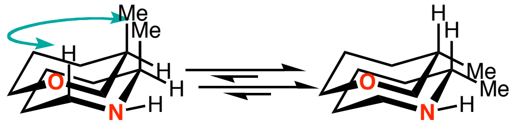
–ΔG° = 1.74 kcal/mol

(1)



–ΔG° = 2.86 kcal/mol

(2)

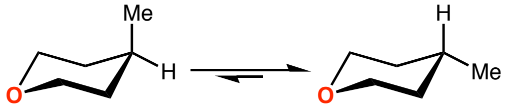


–ΔG° = 1.43 kcal/mol

(4)

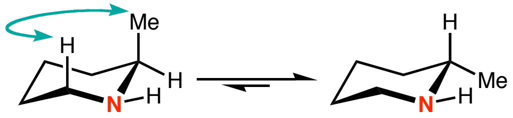
–ΔG° = 2.5 kcal/mol

(3)



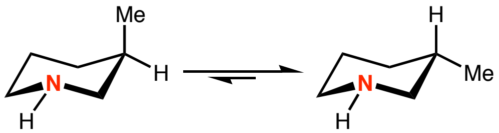
–ΔG° = 1.95 kcal/mol

(4)



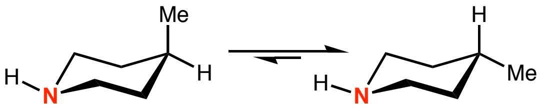
–ΔG° = 2.5 kcal/mol

(5)



–ΔG° = 1.6 kcal/mol

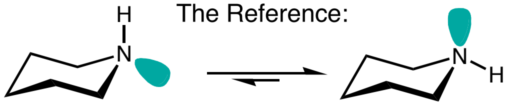
(6)



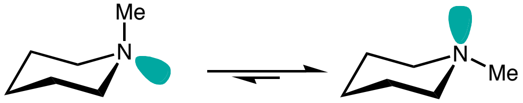
–ΔG° = 1.9 kcal/mol

A-Values for *N*-Substituents in Piperidine

The Reference:

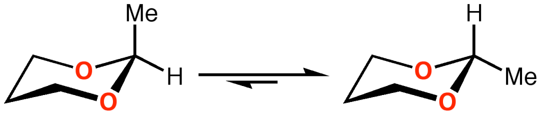


ΔG° = –0.36 kcal/mol

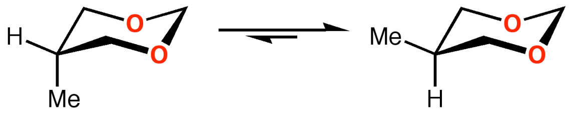


ΔG° = –3.0 kcal/mol

- Hydrogen is "bigger" than the N–lone Pair.
- The A-value of N–substituents is slightly larger than the corresponding cyclohexane value. Rationalize

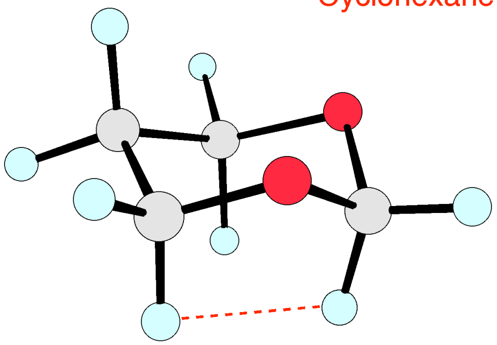


–ΔG° = 4.0 kcal/mol

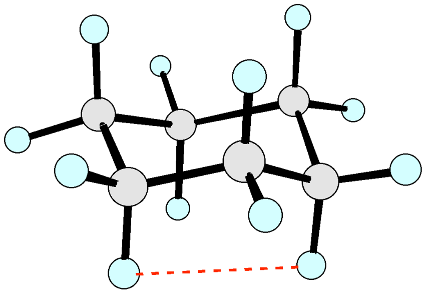


–ΔG° = 0.8 kcal/mol

- The indicated distance is 2.05 Å. The analogous H–H distance in Cyclohexane is 2.45 Å



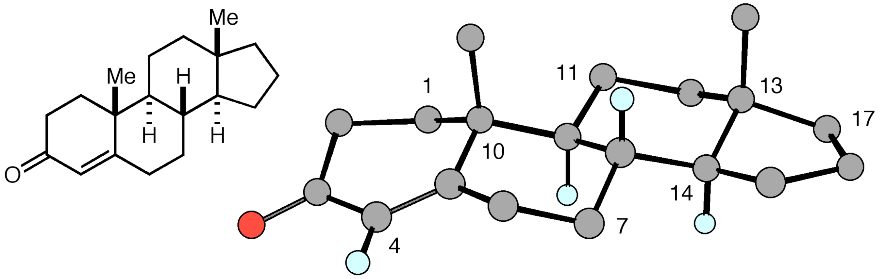
2.05 Å



2.45 Å

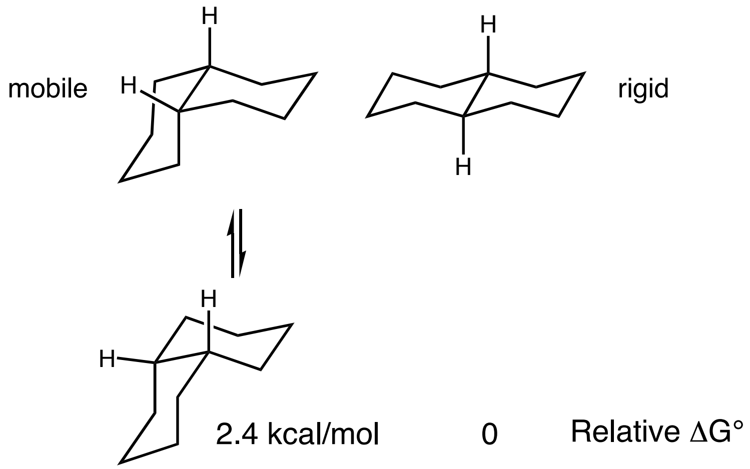
Conformational Analysis: Bicyclic Ring Systems

Conformations of Bicyclic Ring Systems

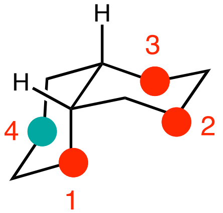


The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

Decalin Ring System (6/6)



Let's identify the destabilizing gauche butane interactions in the cis isomer

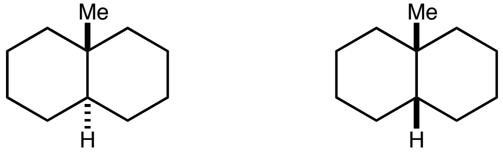


Gauche-butane interactions

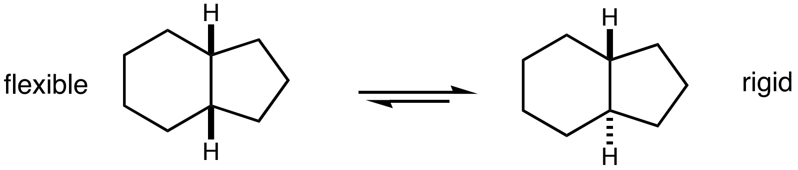
C1 → C2
C1 → C3
C4 → C3

$\Delta G°(est) = 3(0.88) = 2.64$ kcal/mol

Estimate the energy difference between the two methyl-decalins shown below.



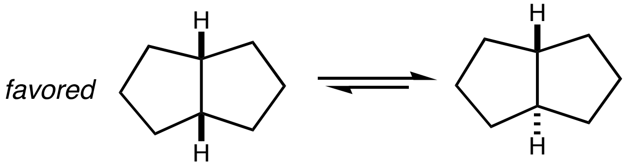
Hydrindane Ring System (6/5)



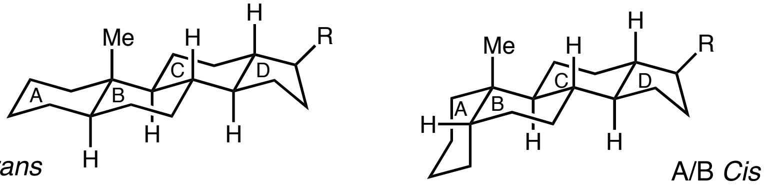
$\Delta G° = -0.5$ kcal/mol (at 23 °C)
$\Delta G° = 0.0$ kcal/mol (at ~200 °C)

■ The turnover to favor the *cis* fusion results from the entropic preference for the less ordered *cis* isomer.

The 5-5 Ring System



$\Delta G° = +6.4$ kcal/mol



A/B *Trans*

A/B *Cis*

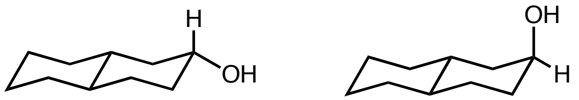
Rationalize the conformational flexibility of a *A/B Trans* vs. *A/B Cis* Steroid!

Conformational Analysis: Axial vs Equatorial Reactivity

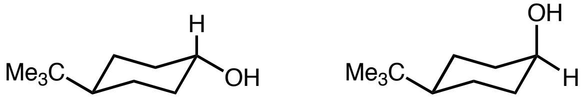
Different reactivity for axial and equatorial substituents

Axial substituents are more hindered, thus less reactive in many transformations

- Acetylation with Ac_2O/Py

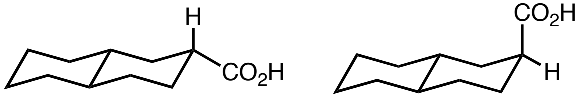


k_{rel} 1 0.13

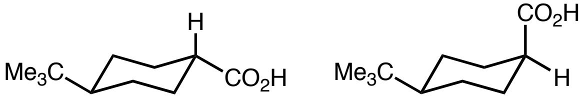


k_{rel} 1 0.27

- Acid-catalyzed esterification

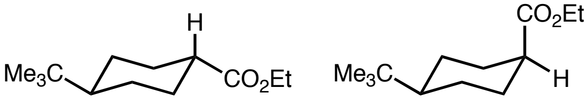


k_{rel} 1 0.04



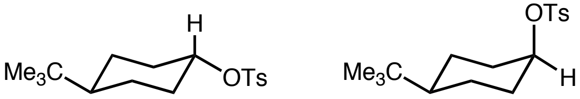
k_{rel} 1 0.05

- Ester Saponification



k_{rel} 20 1

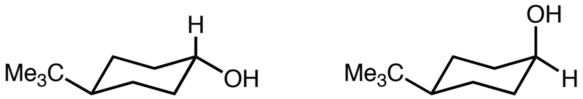
- S_N2 Reactions (Displacement with Ph–S^-)



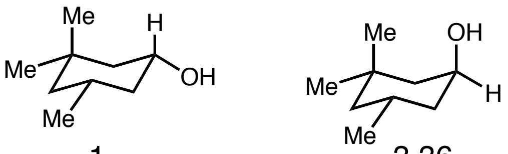
k_{rel} 1 31

The axial diastereomer is not always slower reacting:

- Alcohol Oxidation with Cr(6+)



k_{rel} 1 3.2



k_{rel} 1 3.36

The rate-determining step is breakdown of the chromate ester. This is an apparent case of strain acceleration

For a more detailed discussion of this topic see:
Eliel, E. L., S. H. Wilen, et al. (1994). *Stereochemistry of Organic Compounds pp 720-726*

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 7

Conformational Analysis-4

- Ground State Torsional Effects (Conformational Transmission)
- Conformational Analysis of $C_6 \rightarrow C_8$ Rings continued
- Transition State Torsional Effects

- Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapter 4
"Study & Descrption of Reaction Mechanisms"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions **(handout)**

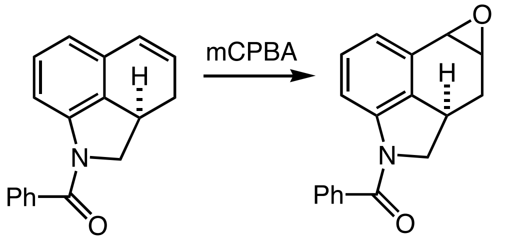
Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981**(handout)**

D. A. Evans

Monday,
October 2, 2006

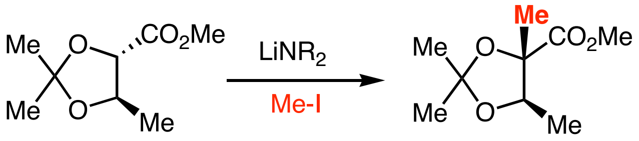
Problems of the Day:

Predict the stereochemical outcome of this reaction. The diastereoselection is 99:1



Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

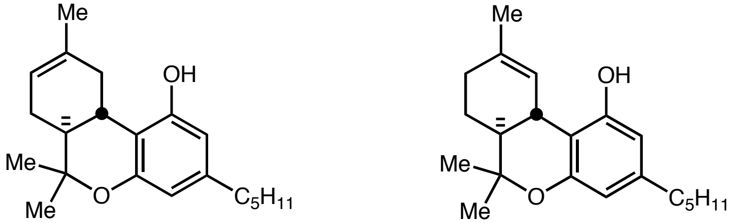
Rationalize the stereochemical outcome of this reaction.



diastereoselection is 8:1.

Ladner, et.al. *Angew. Chemie, Int. Ed* **1982**, *21*, 449-450

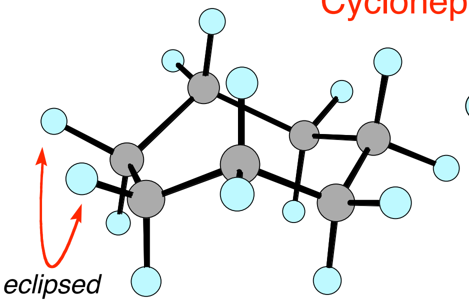
Which is the more stable C=C isomer in the two THC structures?



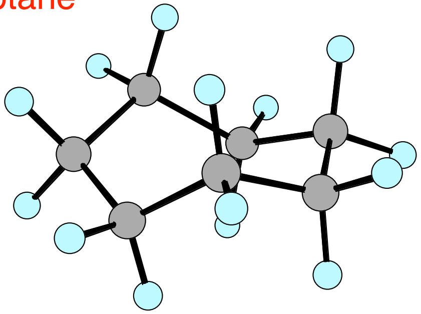
R. W. Kierstead, *JACS* **1967**, *89*, 5934

Conformational Analysis: Cylcoheptane

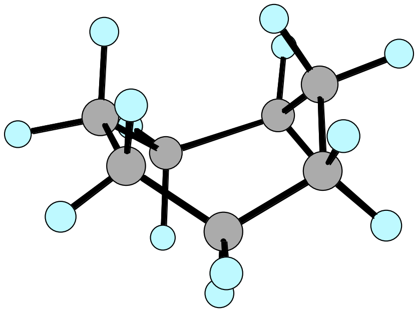
Cycloheptane



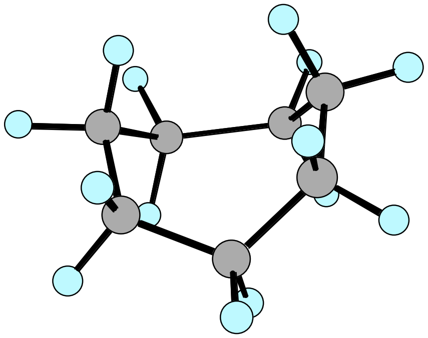
Chair (2.16 kcal/mol)



Twist-Chair (0 kcal/mol)



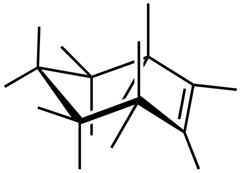
Boat (3.02 kcal/mol)

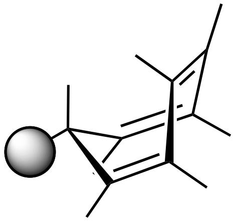


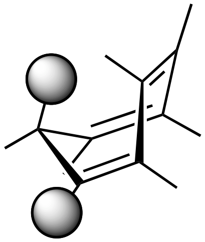
Twist-Boat (2.49 kcal/mol)

Hendrickson, J. B. *JACS* **1961**, *83*, 4537.
See Eliel, page 762+

Olefins preferentially oriented to eliminate eclipsing interactions.

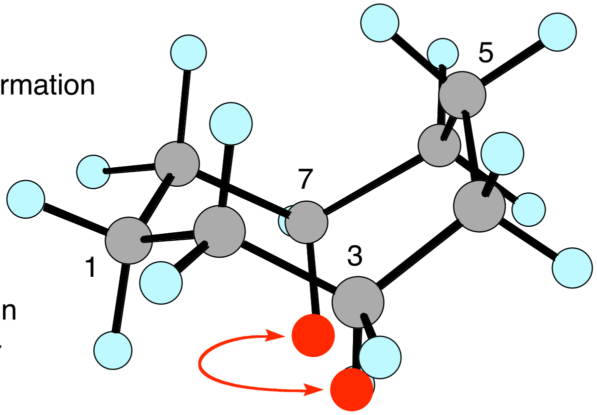






Cyclooctane

Chair-Boat
Lowest-energy conformation

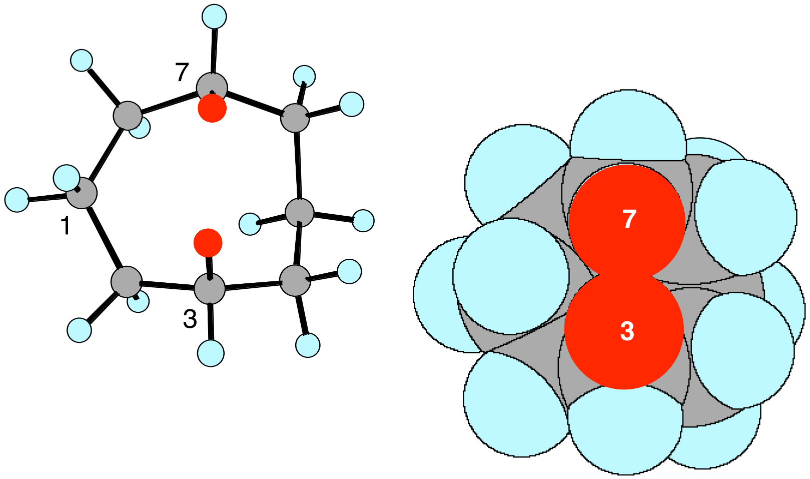


Transannular strain between C_3 & C_7

Ring strain originates in eclipsing interactions and transannular vanderWaals interactions

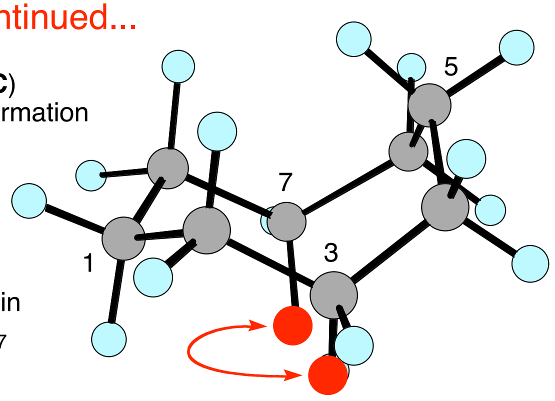
Methylene position	1	2	3	4	5
ΔG $\frac{\text{pseudoequatorial } \mathbf{Me}}{\text{pseudoaxial } \mathbf{Me} \text{ (kcal/mol)}}$	1.8	2.8	>4.5	-0.3	6.1

Underside view of boat-chair C3 & C7 eclipsing interactions



Cyclooctane continued...

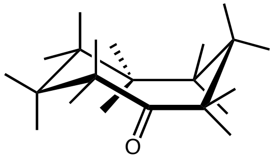
Chair-Boat (**BC**)
Lowest-energy conformation



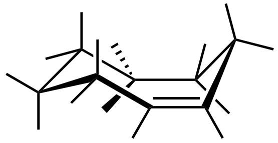
Transannular strain between C_3 & C_7

Methyl position	1	2	3	4	5
$\Delta G \dfrac{\text{(pseudoeqatorial)}}{\text{(pseudoaxial) (kcal/mol)}}$	1.8	2.8	>4.5	-0.3	6.1

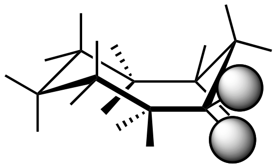
Cyclooctane derivatives



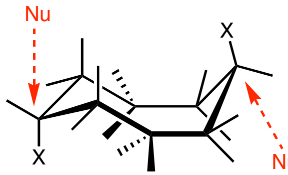
Carbonyl is positioned at C_3 or C_7



Olefin is positioned at C_3-C_4 or C_6-C_7

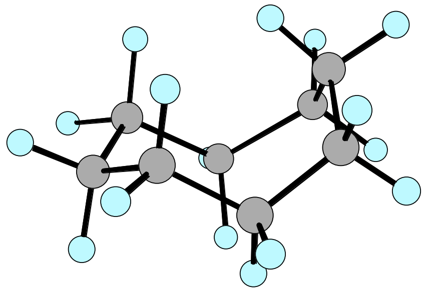


Disubstitution occurs at C_4 or C_6

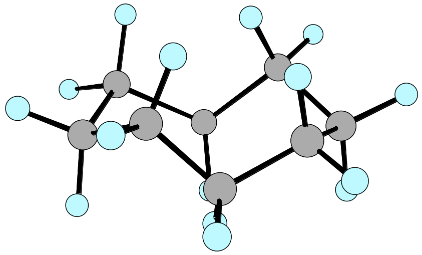


S_N2 occurs at C_1 and C_5

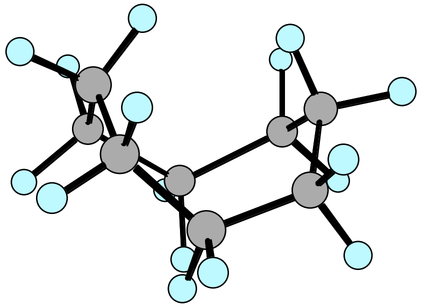
Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.



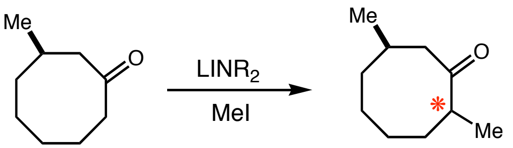
Chair-Boat (**CB**) conformation
reference structure



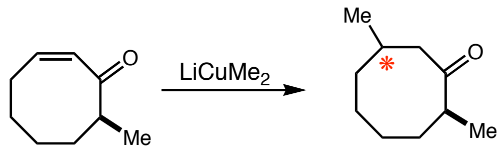
Chair-Chair (**CC**) conformation
(+1–1.6 kcal/mol)



Boat-Boat (**BB**) conformation
(>+ 8 kcal/mol)



Predict
stereochemistry



Predict
stereochemistry

Ground State Torsional Effects

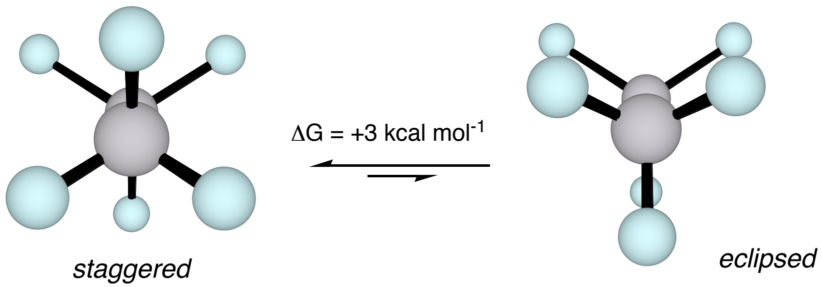
Torsional Effects

Torsional Strain: the resistance to rotation about a bond

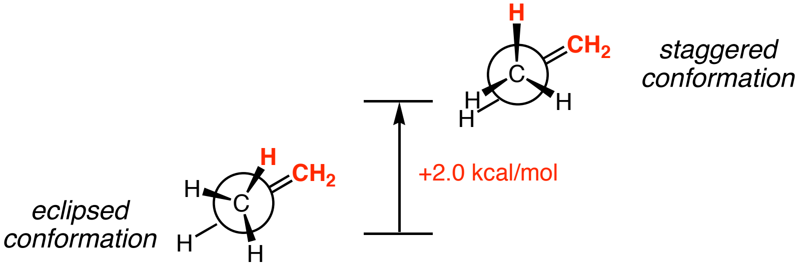
Torsional energy: the energy required to obtain rotation about a bond

Torsional Angle: also known as dihedral angle

Torsional steering: Stereoselectivity originating from transition state torsional energy considerations



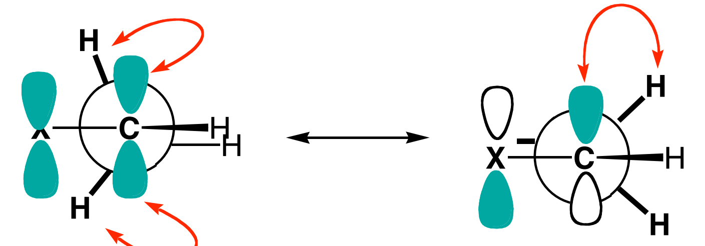
Torsional Strain (Pitzer Strain): Ethane



Wiberg K. B.; Martin, E. *J. Amer. Chem. Soc.* **1985**, *107*, 5035-5041.

See Lecture 5 for previous discussion

Relevant Orbital Interactions:

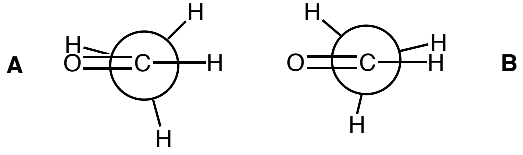


σ C–H & π electrons are destabilizing

stabilizing conjugation between π*–C–X & σ–C–H

Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *JACS* **1987**, *109*, 6591-6600.

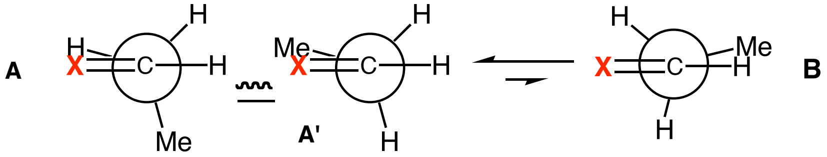
Conformational Preferences: Acetaldehyde



The eclipsed conformation (conformation **A**) is preferred.
Polarization of the carbonyl decreases the 4–electron destabilizing
Rotational barrier: 1.14 kcal/mol

Houk, *JACS* **1983**, *105*, 5980-5988.

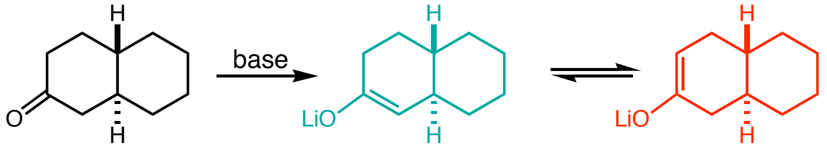
Conformational Preferences
1-Butene (X = CH_2); Propanal (X = O)



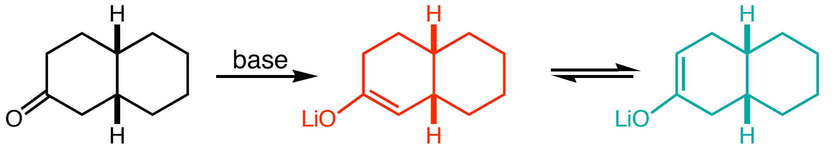
Conformation A is preferred. There is little steric repulsion between the methyl and the X-group in conformation A'.

Ground State Torsional Effects: Conformational Transmission

Observation:
Relative enolate stability correlates to ring junction stereochemistry



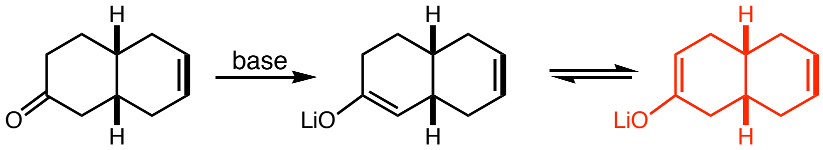
ratio: 13 : 87



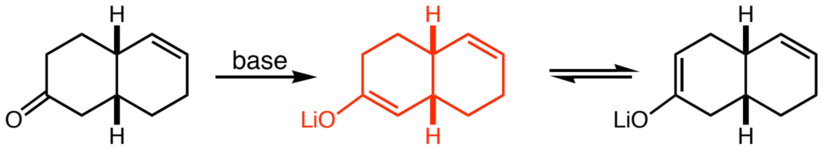
ratio: 70 : 30

House, *JOC* **1965**, *30*, 1341

Observation:
Relative enolate stability seems to be correlated to position of C=C



ratio: 10 : 90

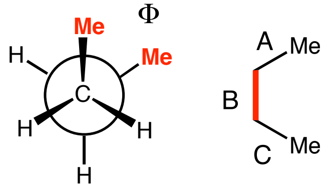


ratio: 92 : 8

How do we explain the experimental observations shown above?

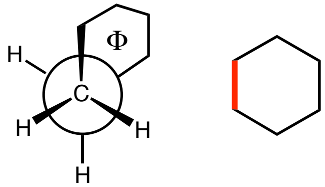
Readings: Velluz etal, *Angew. Chemie, Int Ed*. **1965**, *4*, 181-270 **(pdf)**

Let Φ be defined as the torsion or dihedral angle for butane



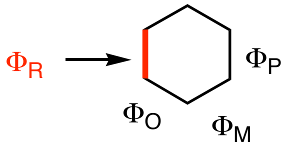
Φ = 60° for butane

Let's now consider cyclohexane



Perfect chair	**real chair**
Φ = 60°	**Φ = 56°**
CCC∠ 109° 28'	CCC∠ 111°

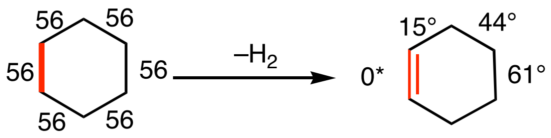
Given cyclohexane with an identified torsion angle ΦR, if ΦR either increases or decreases what effects in angle change are transmitted to ΦO, ΦM, and ΦP?



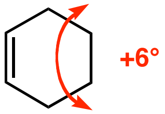
	$\Phi_R = 56°$	$\Phi_R = 0°$	[Δ]
Φ_O	56	15	–41°
Φ_M	56	44	–11°
Φ_P	56	61	+6°

$$[\Delta] = \Phi_R(0°) - \Phi_R(56°)$$

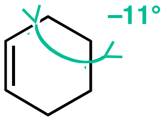
Operation:



Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:



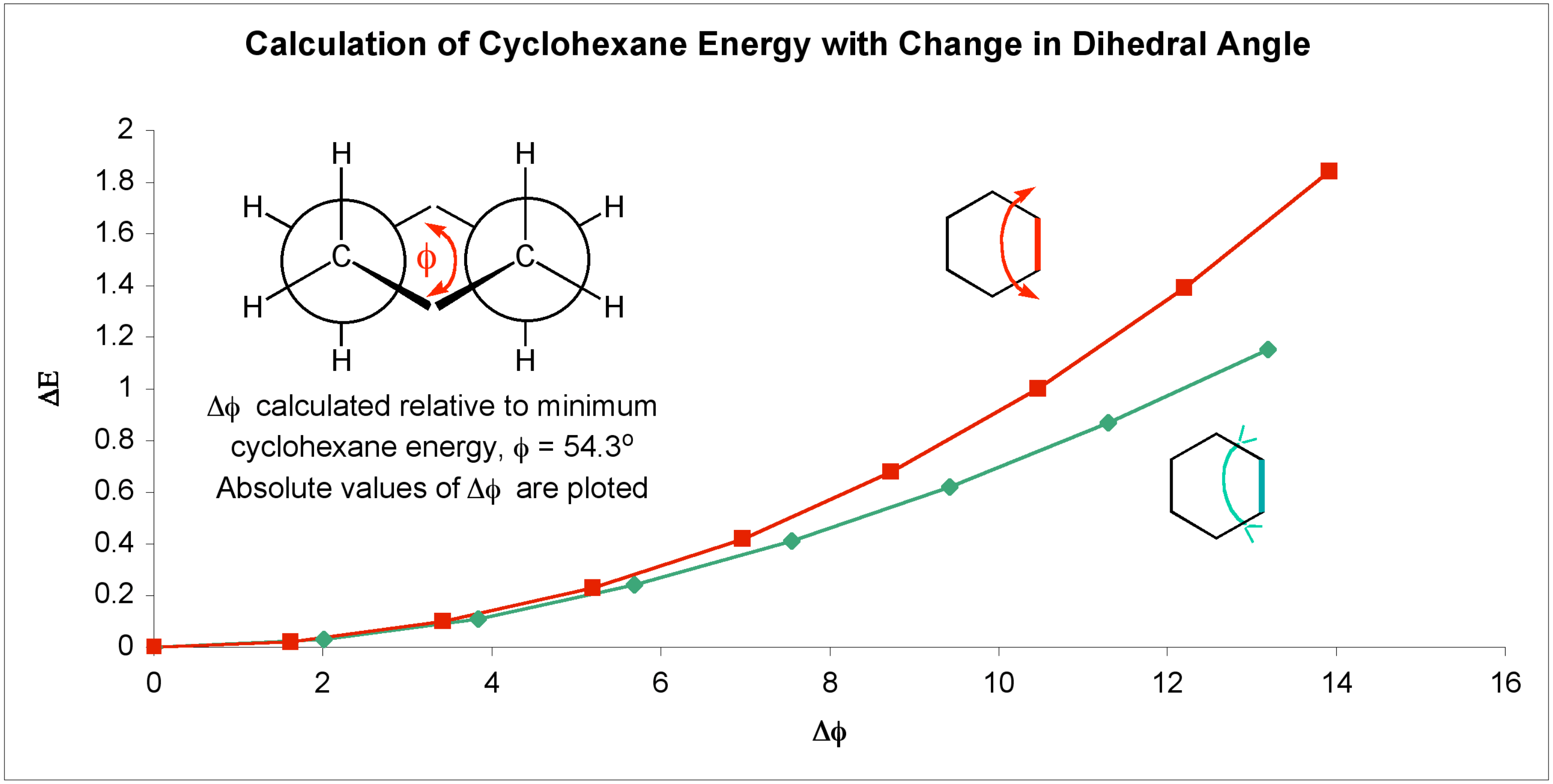
For Φ_P



For Φ_M

Conformational Analysis:
Cyclohexane Dihedral Angle Distortions

Dear Class:
During our discussions on "Conformational Transmission", it is assumed (by Velluz) that it is energetically preferable to **decrease** the C–C torsion angle in cyclohexane rather than to **open up** this angle. The plot provided below confirms this assumption.



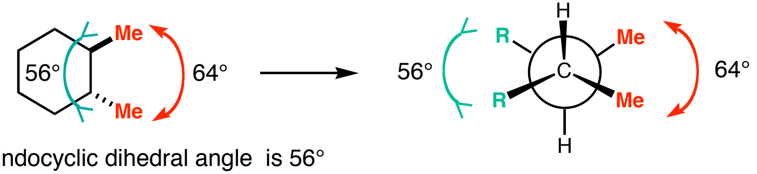
Calculation of Cyclohexane Energy with Change in Dihedral Angle

Δϕ calculated relative to minimum cyclohexane energy, ϕ = 54.3°
Absolute values of Δϕ are ploted

Single-point energy minimizations using molecular mechanics MMFF (Spartan `04)

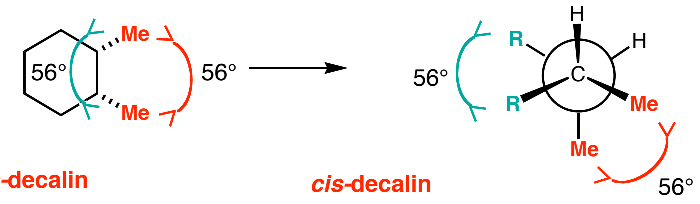
Ground State Torsional Effects: Conformational Transmission-2

Operation: *trans*-dimethylcyclohexane

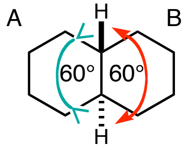


Endocyclic dihedral angle is 56°
Exocyclic dihedral expands correspondingly (+4°): 64°

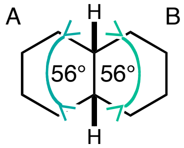
Operation: *cis*-dimethylcyclohexane



***trans*-decalin**

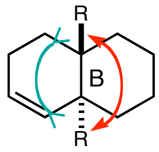


***cis*-decalin**

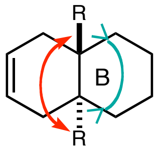


Simple Application: Reinforcing Torsional Effects

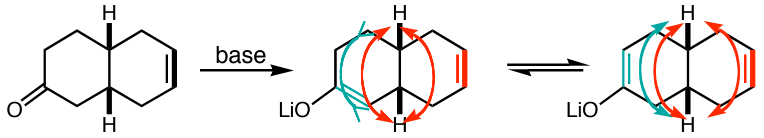
Which C=C bond isomer below is more stable?



1) C=C will open up ring=B torsion angle
2) Ring B will resist increase in its ring fusion torsion angle
3) Therefore torsion effects are opposed



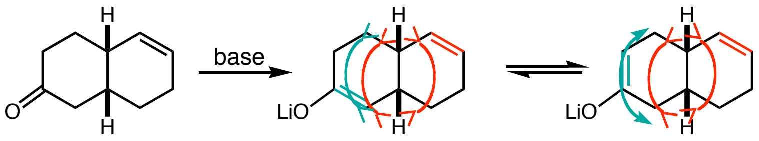
1) C=C will close down ring=B torsion angle
2) Ring B will accomodate decrease in its ring fusion torsion angle
3) Therefore torsion effects are reinforcing



ratio: 10 : 90

effects opposing

effects reinforcing

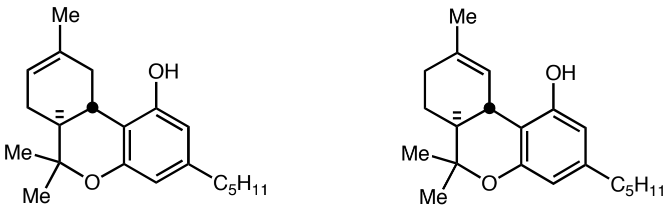


ratio: 92 : 8

effects reinforcing

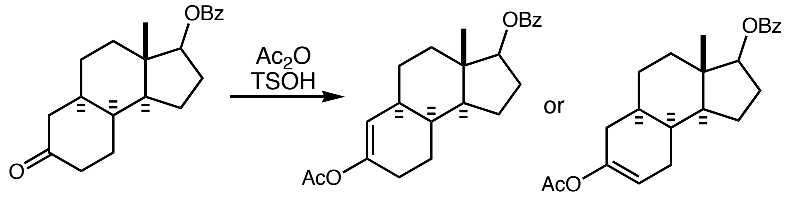
effects opposing

Question: Which is the more stable C=C isomer in the two THC structures?



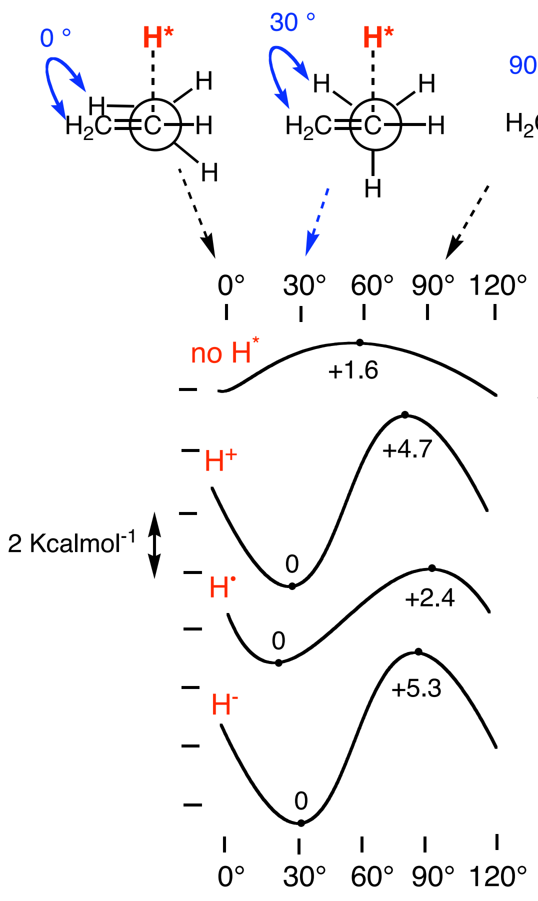
R. W. Kierstead, *JACS* **1967**, *89*, 5934

Question: Which enol acetate is more stable?



Transition State Torsional Effects According to Houk

Houk: "Torsional effects in transition states are more important than in ground states"



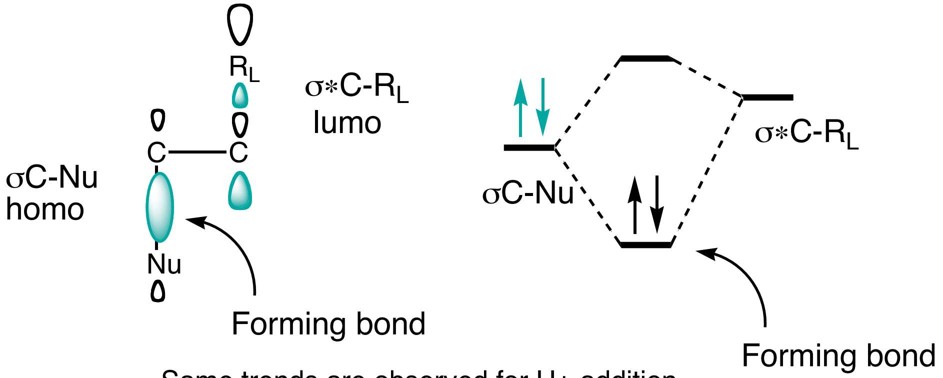
See lecture 5

Houk, *JACS* **1981**, *103*, 2438

Houk, *JACS* **1982**, *104*, 7162

Transition states

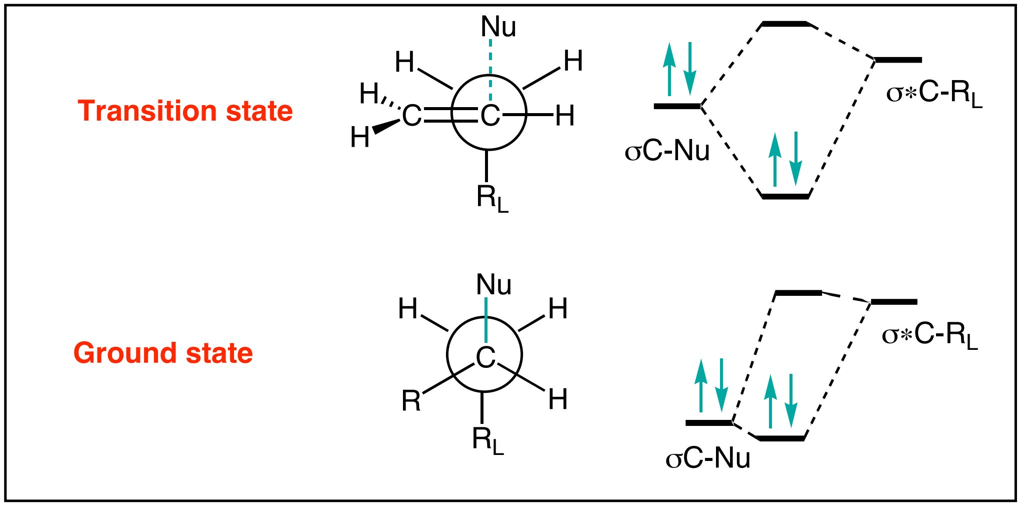
H-radical and H-anion: antiperiplanar σ∗C–R orbital stabilized the TS illustrated for Nu addition



Same trends are observed for H+ addition

Houk, *Science* **1981**, *231*, 1108-1117

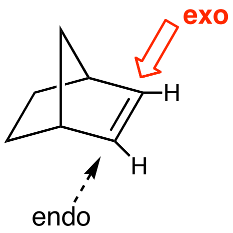
"The Theory and Modeling of Stereoselective Organic Reactions"



Transition State Torsional Effects: Olefin Additions

■ Olefin Addition Reactions: Case one

How do we account for the high exo selectivities in addition reactions to norbornene?



Highly exo selective for electrophilic, nucleophilic and cycloaddition reactions

Rate enhancement due to strain

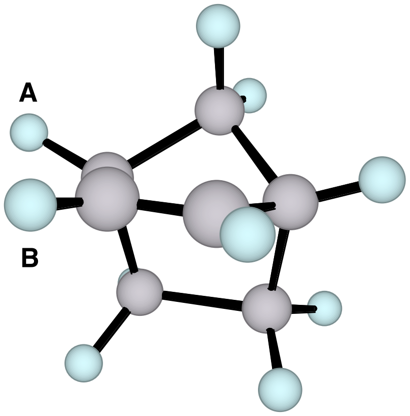
The Controversy over origin of high exoselectivities

Steric effects

Least nuclear motion

Orbital distortion

Schleyer: torsional steering



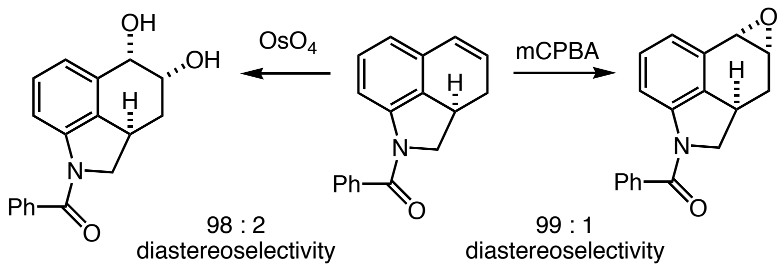
Schleyer, P. R. *J. Amer. Chem. Soc.* **1967**, *89*, 701.

Addition from exo face avoids eclipsing A & B hydrogens

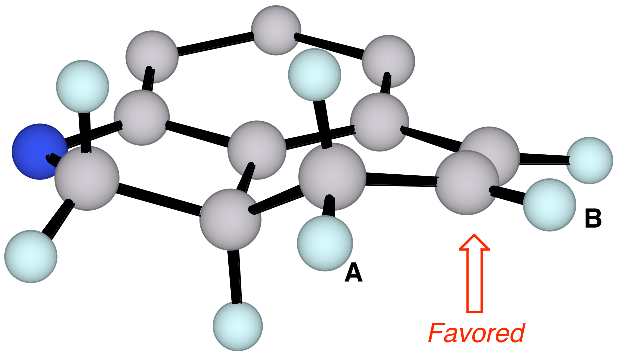
(better hyperconjugative stabilization of transition state)

■ Olefin Addition Reactions: Case two

How do we account for the high selectilvities in the oxidation of the indicated olefin?



Nitrogen protecting group does not affect selectivities



Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

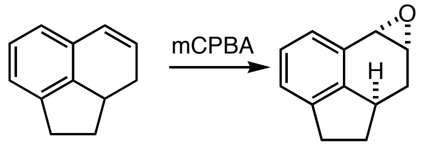
Addition from indicated olefin face avoids eclipsing A & B H's

(better hyperconjugative stabilization of transition state)

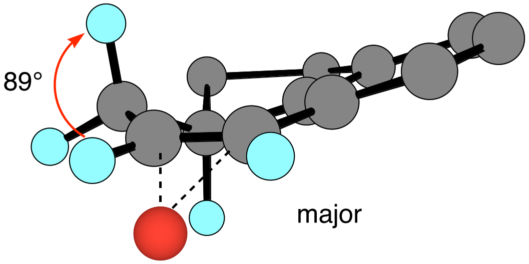
Martinelli has carried out further studies on related structures...........

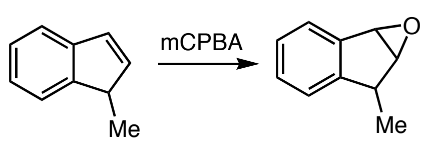
Transition State Torsional Effects: Olefin Additions

Martinelli: Torsional steering important in selectivity

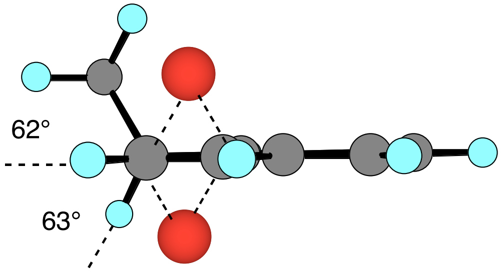


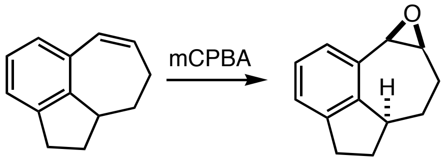
99 : 1 diastereoselectivity



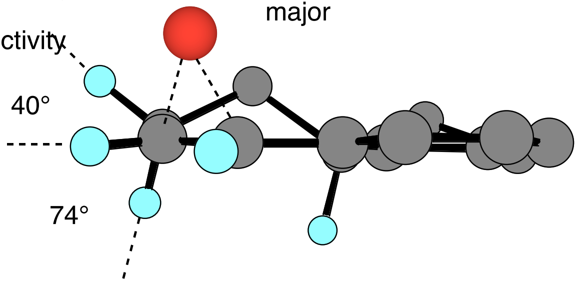


50 : 50 diastereoselectivity





99 : 1 diastereoselectivity



Authors propose that diastereoselection controlled by TS torsional effects

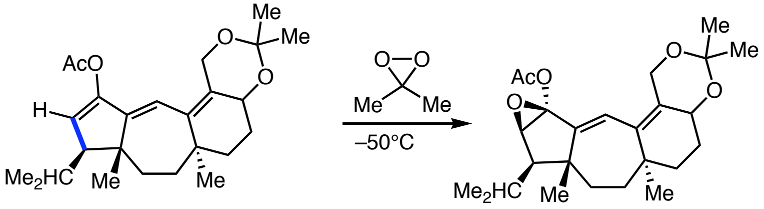
Martinelli & Houk, *J. Org. Chem.* **1994**, *59*, 2204.

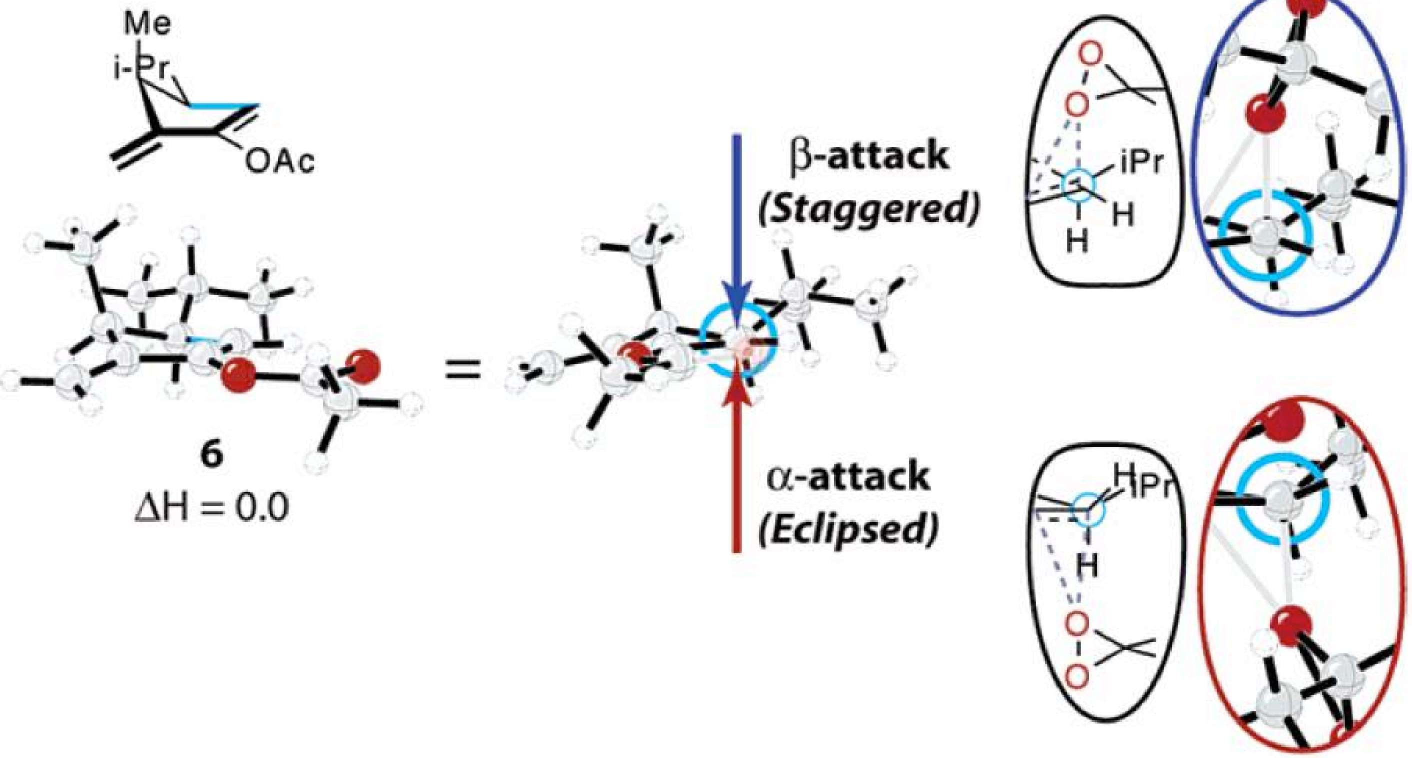
Transition State Torsional Effects: Olefin Additions

Torsional Steering Controls the Stereoselectivity of Epoxidation in the Guanacastepene A Synthesis

ORGANIC LETTERS
2006
Vol. 8, No. 8
1513–1516

Paul Ha-Yeon Cheong,[†] Heedong Yun,[‡] Samuel J. Danishefsky,[‡,§] and K. N. Houk*,[†]

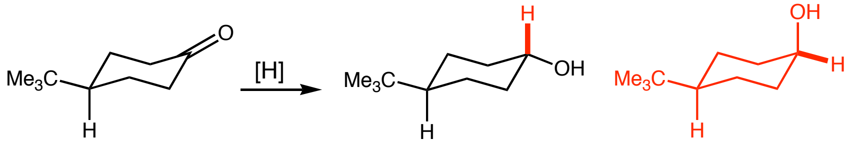


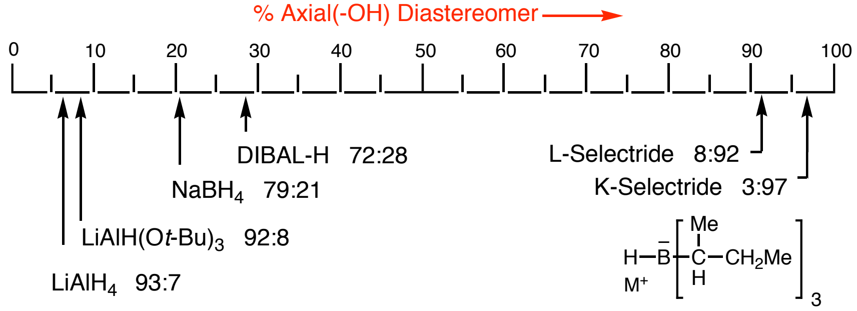


6
ΔH = 0.0

Cyclohexanone Addition Reactions: Hydride Reduction

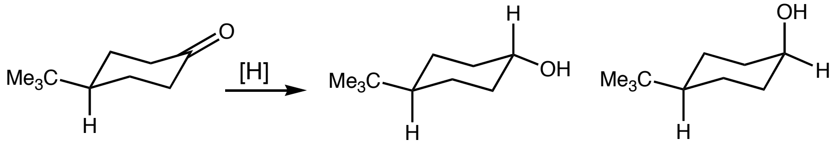
Stereoselective Reductions: Cyclic Systems



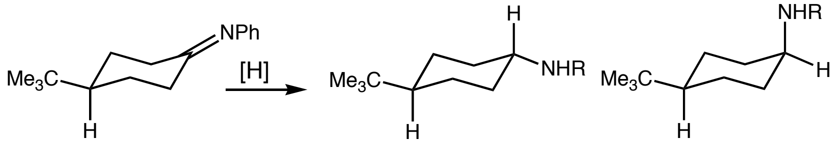


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

The most stereoselective Reductions



Reagent	Ratio
KBH(s-Bu)$_3$	03 :97
Li in NH$_3$	99 :01

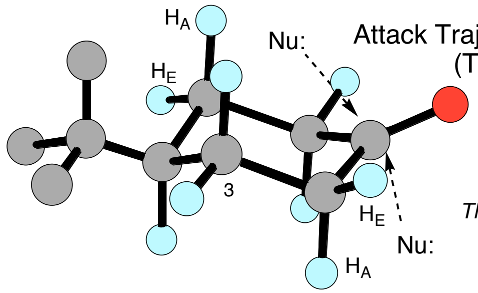


(R)	Reagent	Ratio
R = Bn	LiBH(s-Bu)$_3$	03 :97
R = Ph	LiBH(s-Bu)$_3$	01 :99
	Al/Hg/MeOH	~90 :10

Ganem, *Tet. Let* **1981**, *22*, 3447

Hutchins, *JOC* **1983**, *48*, 3412

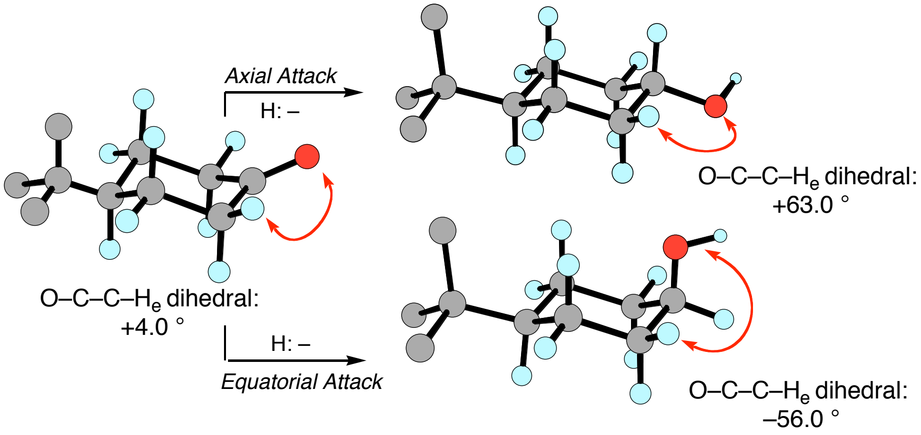
private communication



Attack Trajectories for Cyclohexanone
(Torsional Argument)

This approach favored sterically

The steric hindrance encountered by Nu-attack from the axial C=O face by the axial ring substituents (hydrogens in this case) at the 3-positions is more severe than the steric hinderance encountered from Nu-attack from the equatorial C=O face.


Axial Attack
H: –
O–C–C–H$_e$ dihedral: +63.0 °
O–C–C–H$_e$ dihedral: +4.0 °
H: –
Equatorial Attack
O–C–C–H$_e$ dihedral: –56.0 °

The Issues Associated with the Reduction Process

Steric Effects: Attack across equatorial C=O face sterically more favorable.

Torsional Effects: However, attack across the axial face of the C=O group avoids development of eclipsing interactions in the transition state. (Note the dihedral angle sign changes between reactants & products shown above). These "torsional effects" favor axial attack.

Prediction

For "small" hydride reagents such as LiAlH$_4$, torsional effects are felt to be dominant and this explains the predisposition for axial attack.

Prediction

For "large" hydride reagents such as H–BR$_4$, steric effects now are dominant and this explains the predisposition for equatorial attack.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 8

Olefin Addition Reactions–1

- Hydroboration
- Epoxidation & Directed Epoxidation

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions ***(Handout)***

K. Houk, *Tetrahedron.* **1984**, *40*, 2257-2274
Theoretical Studies of Stereoselective Hydroboration Reactions ***(Handout)***

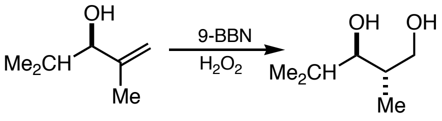
Hoveyda, Evans, Fu, *Chem Rev.* **1993**, *93*, 1307-1370
Substrate-Directable Chemical Reactions
(Electronic Handout)

D. A. Evans

Wednesday,
October 4, 2006

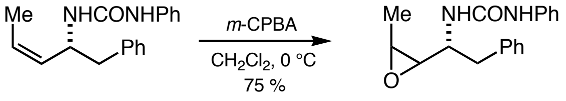
Problems of the Day: (To be discussed)

Rationalize the stereochemical outcome of these reactions.



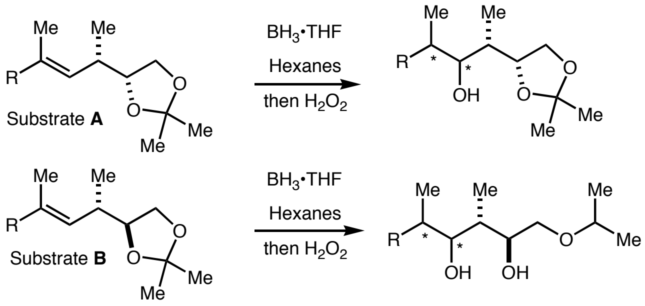
diastereoselection 24:1

W. C. Still & J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487.



Roush, *J. Org. Chem.* **1987**, *52*, 5127. *Diastereoselection =* 95 : 5

Problem 309. The indicated olefins were subjected to hydroboration/oxidation as shown (*Synlett,* **1993**, 696).



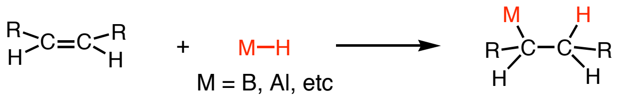
Part A. Please predict the major stereoisomer obtained from these reactions and illustrate your predictions with clear 3D drawings.

Part B. Please also explain the fact that **B** suffers reductive ring opening while **A** does not..

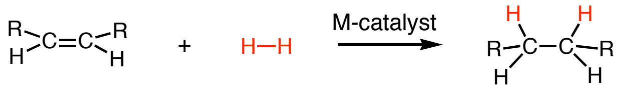
Olefin Addition Reactions: Introduction

Representative Cis-Addition Processes

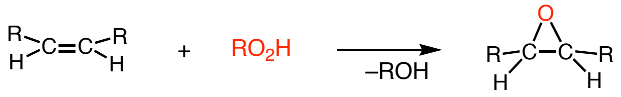
- Hydrometallation



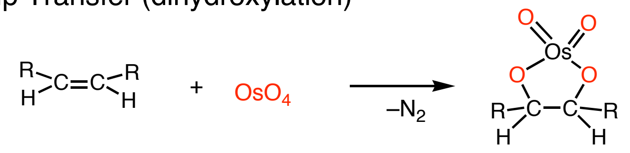
- Hydrogenation



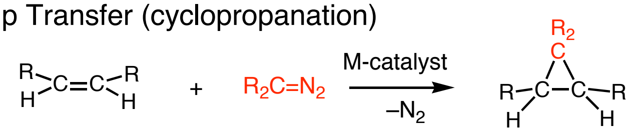
- Group Transfer (epoxidation)



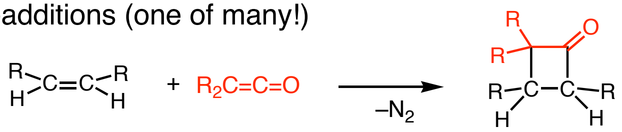
- Group Transfer (dihydroxylation)



- Group Transfer (cyclopropanation)



- Cycloadditions (one of many!)



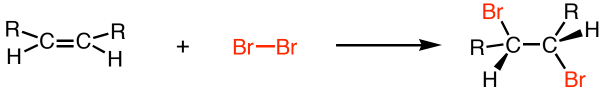
Attributes:

Each process adds to the C=C via a stereospecific process

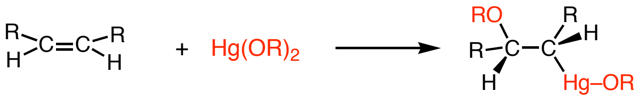
Intermediates *may* be involved in some of the indicated reactions

Representative Trans-Addition Processes

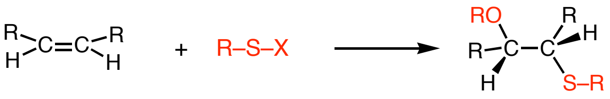
- Halogenation



- Oxy–metallation (M = Hg(II), Tl(III))



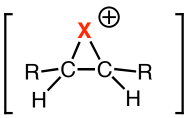
- Oxy–sulfenation (M = S(II), Se(II))



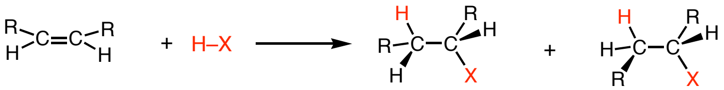
Attributes:

Each process may proceed via an bridged intermediate where X is the initiating electrophile

Olefin substitution may disrupt bridging



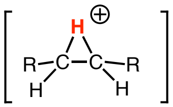
- Addition of hydrogen halides



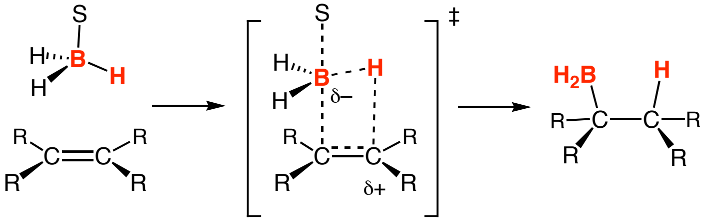
Attributes:

Process may proceed via an bridged intermediate where H+ is the initiating electrophile

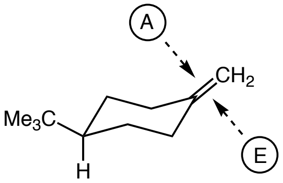
Olefin substitution, reaction conditions as well as halide type may disrupt bridging



The basic process

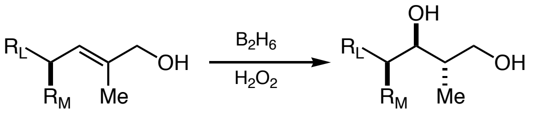


Response to steric effects: Here is a good calibration system:



Oxidant	Ratio, A:E	Reference
MCPBA	69:31	*JOC*, **1967**, *32*, 1363
BH_3, H_2O_2	34:66	*JOC*, **1970**, *35*, 2654

Acyclic hydroboration can be controlled by A(1,3) interactions:

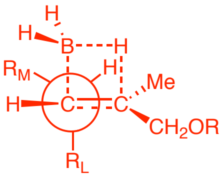


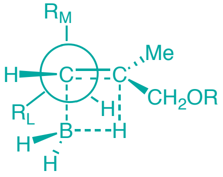
major diastereomer

control elements

A(1,3) allylic strain
Steric effects; R_L vs R_M
Staggered transition states

major

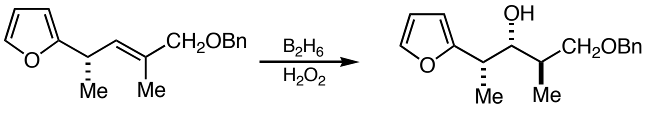




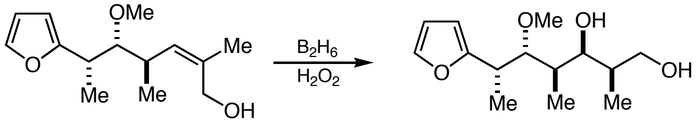
minor

Houk, "*Theoretical Studies of Stereoselective Hydroboration Reactions*"
Tetrahedron **1984**, *40*, 2257 **(Handout)**

Hydroborations dominated by A(1,3) Strain

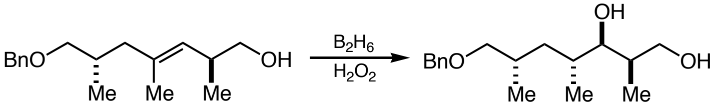


diastereoselection 8:1



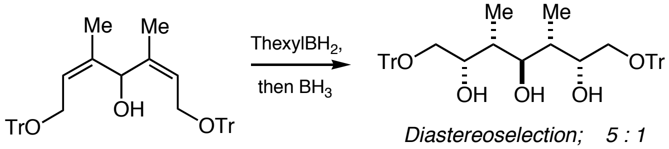
diastereoselection 12:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1979**, *101*, 259.

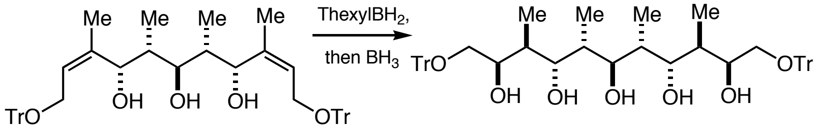


Diastereoselection = 3:1

C. H. Heathcock et. al. *Tetrahedron Lett* **1984** *25* 243.



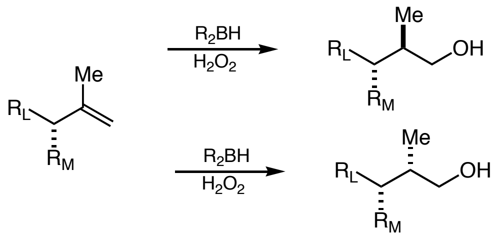
Diastereoselection; 5 : 1



Diastereoselection; 4: 1

Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

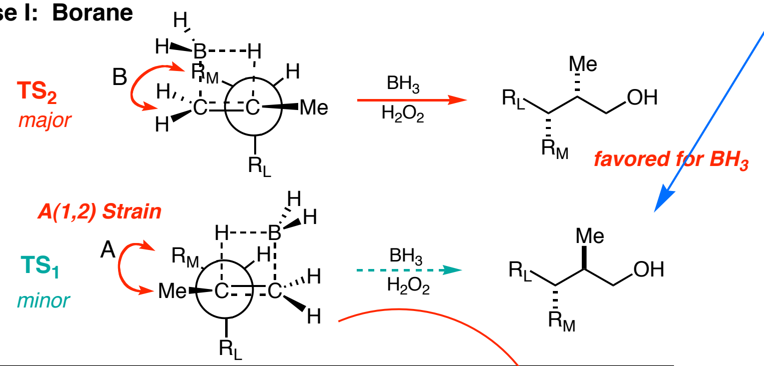
Hydroborations dominated by A(1,2) Strain



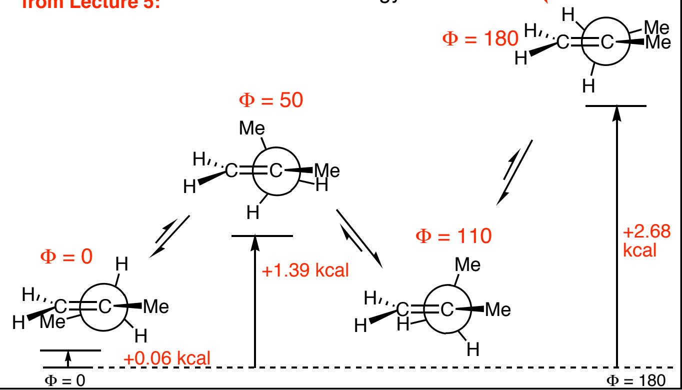
R_2BH structure is a potential variable

Houk's rules: Orient R_L anti-periplanar to incoming reagents to avoid TS eclipsing:

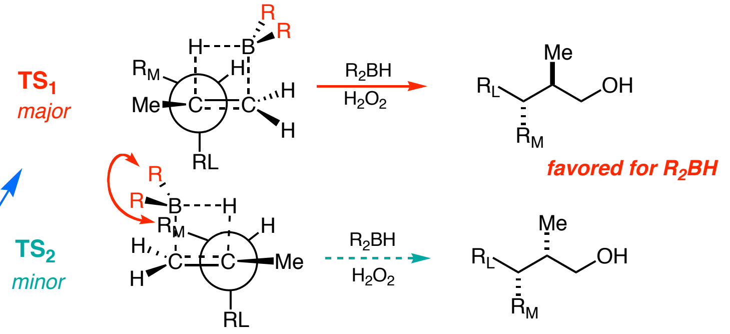
■ Case I: Borane



from Lecture 5: The Torsional Energy Profile



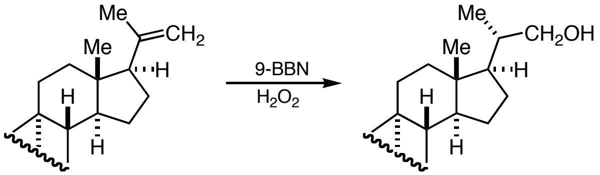
■ Case II: Dialkylboranes



Midland finds that TS_1 favored for R_2BH reagents, but TS_1 ~ TS_2 for BH_3

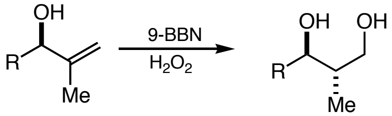
Others have found that TS_1 favored over TS_2 for BH_3

Representative Examples



M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725..

R_2BH	*diastereoselection*
borane methylsulfide	1 : 1
thexylborane	4 : 1
9-BBN	14 : 1
dicyclohexylborane	26 : 1

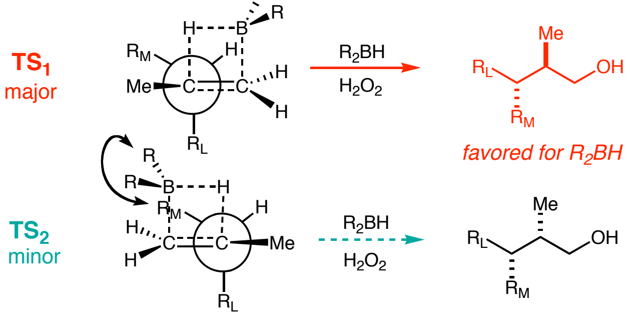


R = n-Bu: *diastereoselection 11:1*
R = $CHMe_2$: *diastereoselection 24:1*

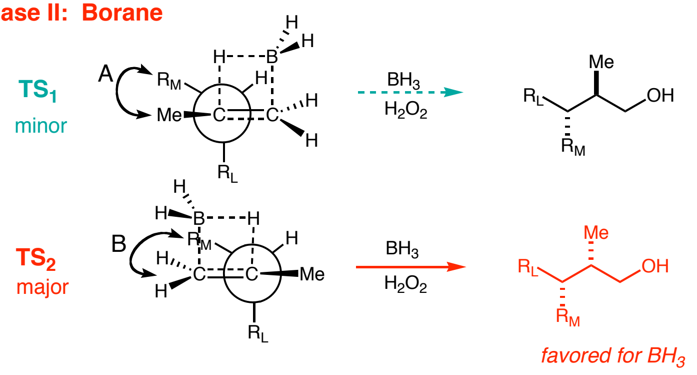
Model is consistent if you presume HO = R_M: R = R_L

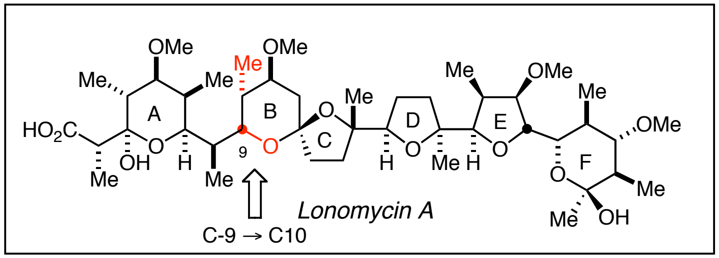
W. C. Still & J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487.

■ Case I: Dialkylboranes

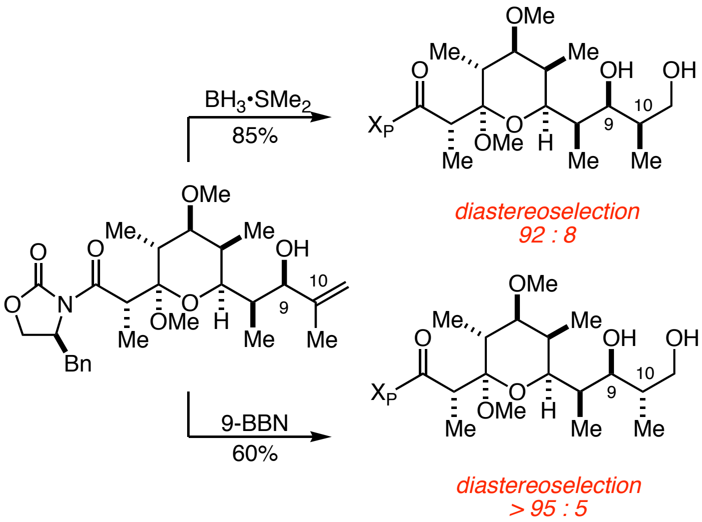


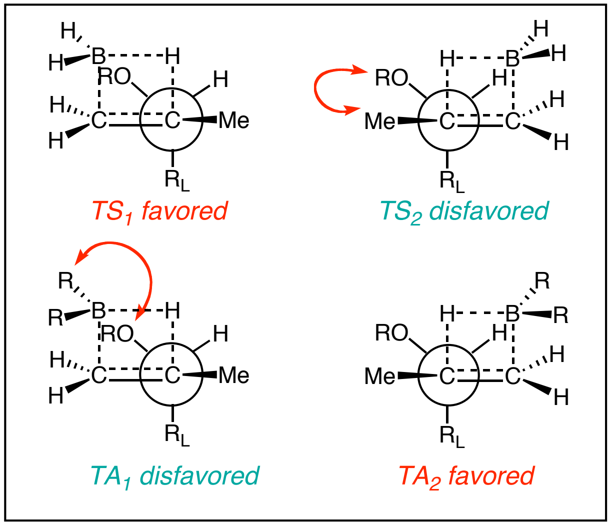
■ Case II: Borane





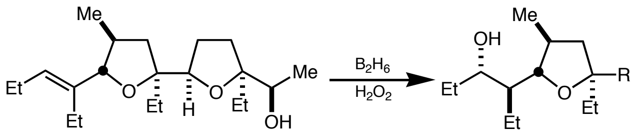
Evans, Ratz, Huff, Sheppard, *JACS* **1995**, *117*, 3448-3467.





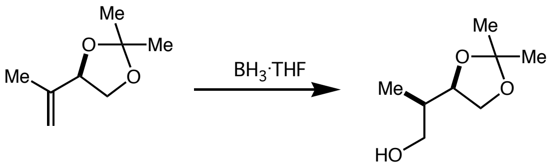
Represetative Hydroboration Examples: Acyclic Control

For each of the examples shown below, attempt to rationalize the stereochemical outcome of the reaction in terms of one of the models presented in the discussion.



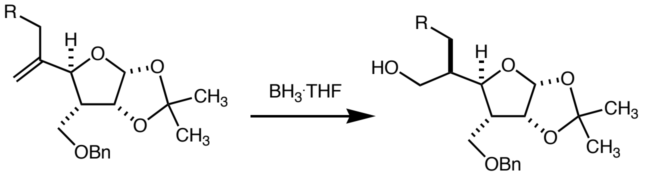
"one isomer"

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1978**, *100*, 2933.



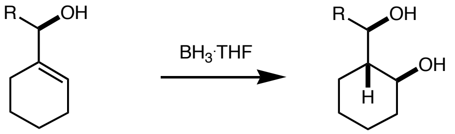
Mori, K.
Tetrahedron **1976**, *32*, 1979

diastereoselection 12:1



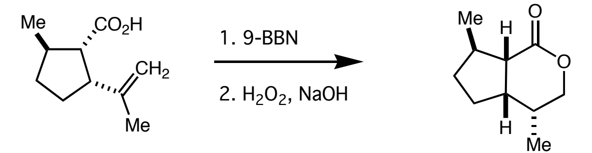
Oikawa et. al.
Tetrahedron Lett. **1983**, *19*, 1987.

R=H; Diastereoselection = 6.8:1
R=OBn Diastereoselection = 6.6:1



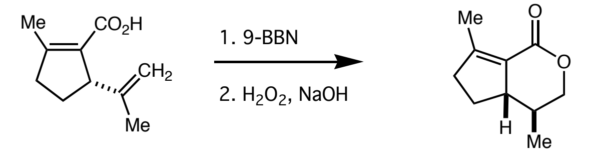
Birtwistle et. al.
Tetrahedron Lett. **1986**, *25*, 243.

R = CH$_3$; Diastereoselction = 6.7:1
R = isopropyl "One Compound"



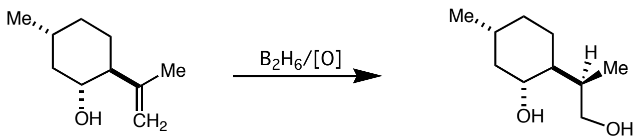
Wolinsky, J.; Eustace, E. J.
J. Org. Chem. **1972**, *37*, 3376.

Diastereoselection = 7:1

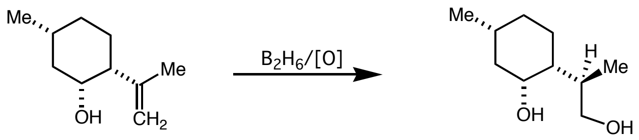


Wolinsky, J.; Nelson, D.
Tetrahedron. **1968**, *25*, 3767.

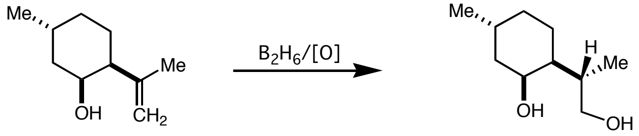
Diastereoselection = 10:1



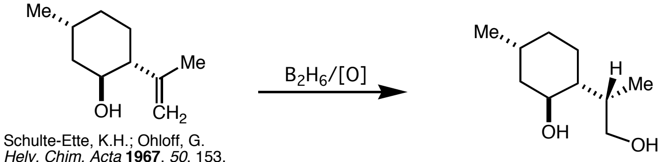
Diastereoselection = 19:1



Diastereoselection = 32:1



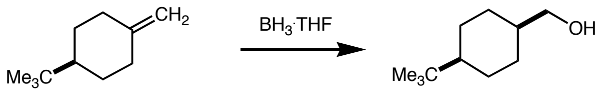
Diastereoselection = 10:1



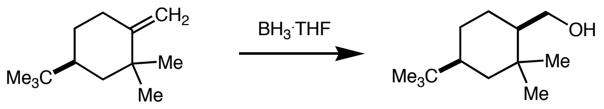
Schulte-Ette, K.H.; Ohloff, G.
Helv. Chim. Acta **1967**, *50*, 153.

Diastereoselection = 4.6:1

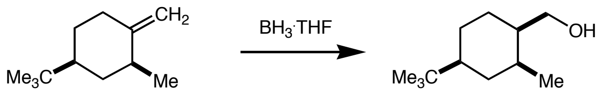
Representative Hydroboration Examples: Cyclic Systems



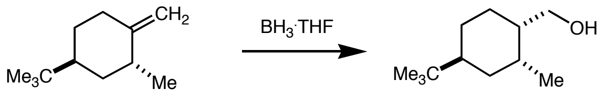
Diastereoselection = 2.1:1



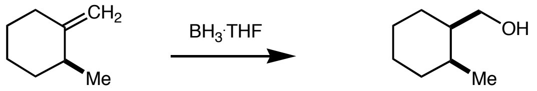
Diastereoselection = 1.2:1



Diastereoselection = 3.3:1

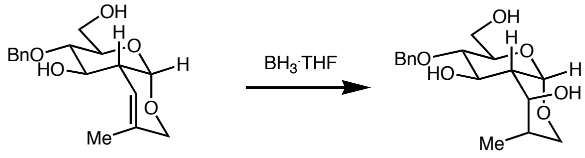


Diastereoselection = 2.4:1



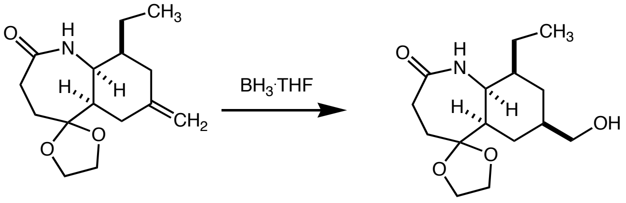
Y. Senda et. al.
Tetrahedron **1977**, *33*, 2933.

Diastereoselection = 4.9:1
(Compare with H.C. Brown's case, with 9-BBN; 1.5:1)



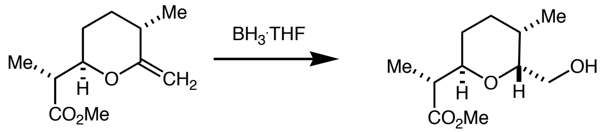
B. Fraser-Reid et. al.
J. Am. Chem. Soc. **1984**, *106*, 731.

Major isomer; no ratio given.



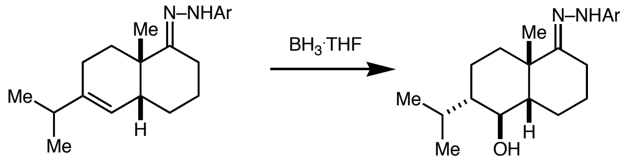
Sallay, S. I.
J. Am. Chem. Soc. **1967**, *89*, 6762.

90% yield, *no diastereoselection given*



Ley, S. et.al.
J. Chem. Soc. Chem. Commun. **1983** 630.

55% yield with the diastereomeric alcohol produced in an unspecified amount. Recycling of the minor isomer further provided 15% of the desired material



McMurry, J. E.
J. Am. Chem. Soc. **1968**, *90*, 6321.

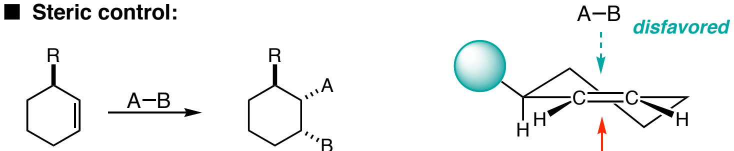
Minor diastereomer not detected

Directed Reactions: An Introduction

Stereochemical Control Elements for all reactions

- Steric & Electronic Factors
- Stereoelectronic Considerations
- Associative Substrate-Reagent Interactions

■ **Steric control:**



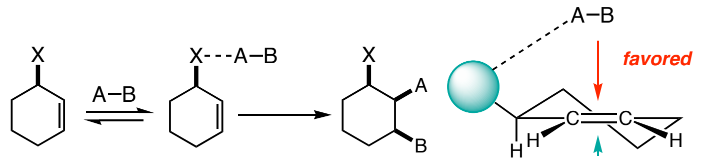
favored product

Nonbonding Interactions disfavor the syn diastereoface

Directed Reactions

Review: Hoveyda, Evans, Fu *Chem. Reviews* **1993**, *93*, 1307

■ **Associative Substrate-Reagent Interactions**



favored product

Noncovalent Interaction favors the syn diastereoface

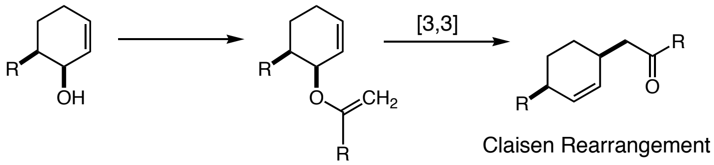
A–B

Agenda

- **Directed Oxidations**
  - Epoxidation
  - Hydroboration
- **Directed Reductions**
  - Hydrogenation
  - Hydride reduction
- **Directed C–C Bond Constructions**

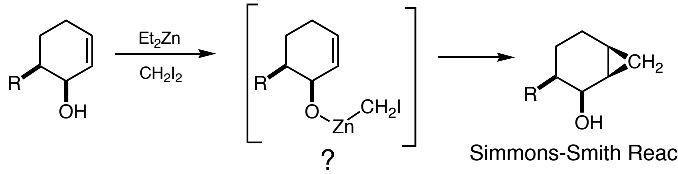
Heteroatom-directed Reactions

Mechanism-based: (HO & C=C must be allylic)



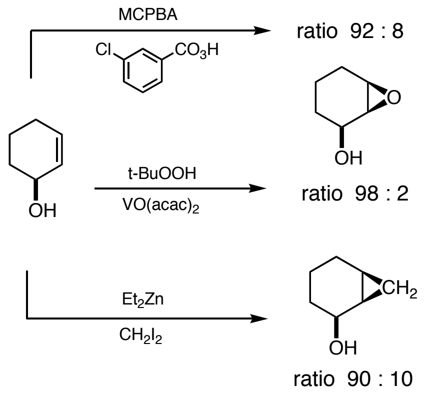
Claisen Rearrangement

via Reagent Ligation



Simmons-Smith Reaction

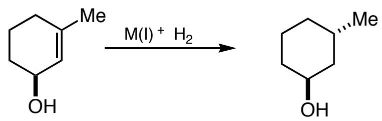
Hydroxyl-directed Reactions



Henbest
J. Chem. Soc. 1958, (1957)

Sharpless
JACS **95**, 6136, (1973)

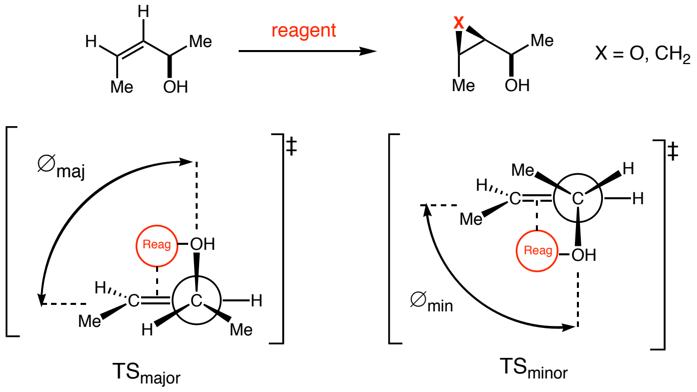
Winstein
JACS **91**, 6892, (1969)



(Ir^+) Stork
JACS **105**, 1072 (1983)
(Rh^+) Evans
JACS **106**, 3866 (1984)

Directed Reactions: An Introduction

Orientation of the Directing Group



Orientation of directing group is not the same for all reactions

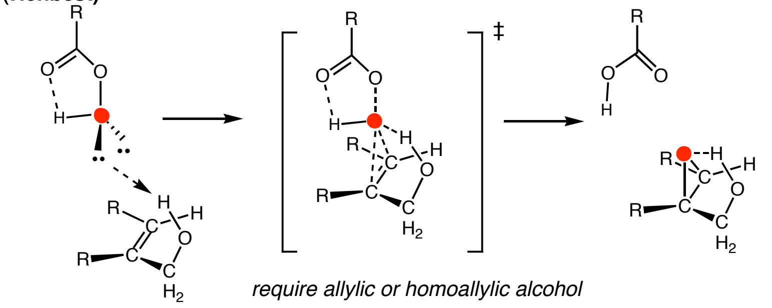
Reagent	Selectivity	Φ Estimate
t-BuO$_2$H, V^{+5}	71 : 29	~ 50 °
RCO$_3$H	95 : 5	~ 120 °
CH$_2$I$_2$, Zn–Cu	> 99 : 1	?

The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

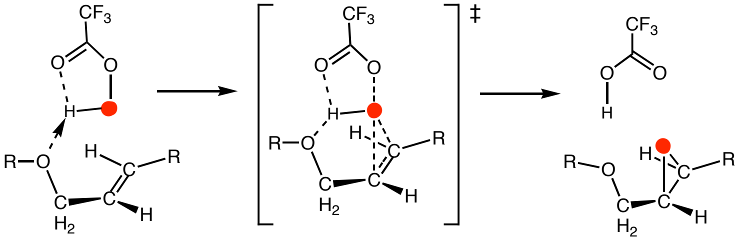
The Directed Peracid Epoxidation

■ Transition State Hydrogen Bonding: Substrate as H-bond donor (Henbest)

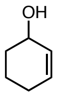
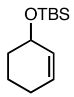
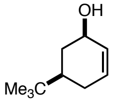
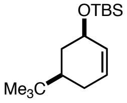
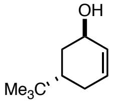
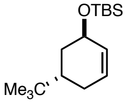


require allylic or homoallylic alcohol

■ Transition State Hydrogen Bonding: Peracid as H-bond donor (Ganem)



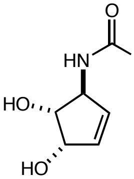
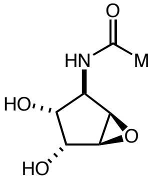
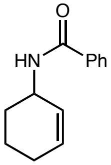
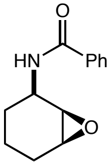
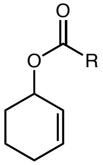
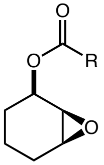
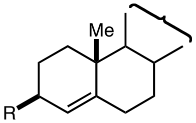
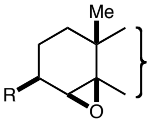
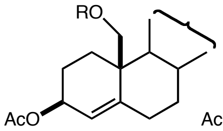
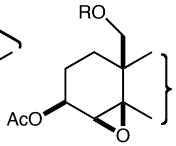
require more acidic peracid both allylic alcohols and ethers OK

	Syn : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF$_3$CO$_3$H)		*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF$_3$CO$_3$H)
	24 : 1	50 : 1		1 : 7	5 : 1
	24 : 1	100 : 1		1 : 8	12 : 1
	5 : 1	100 : 1		1 : 4	1 : 6

Ganem *Tet. Let.* **1985**, *26*, 4895

Diastereoselective Peracid Epoxidation

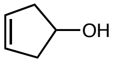
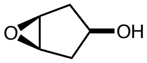
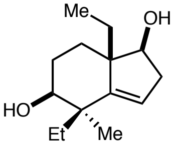
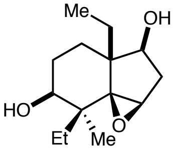
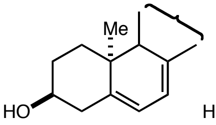
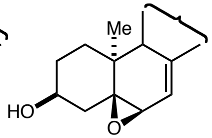
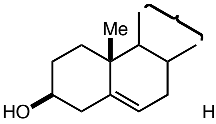
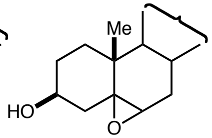
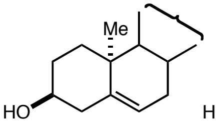
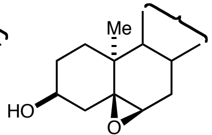
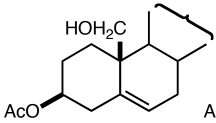
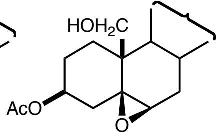
Epoxidation of Cyclic Olefins with Amide &Urethane Directing Groups

Substrate	Major Product	Selectivity
		"highly selective"
		"highly selective"
	 a. R = NH$_2$ b. R = NHBn c. R = NMe$_2$	3 : 1 5 : 1 10 : 1
	 a. R = OCONHBn b. R = OCONMe$_2$	>20 : 1 >20 : 1
	 a. R = CONH$_2$ b. R = CONHBn c. R = CONMe$_2$	6 : 1 >10 : 1 2 : 1

Conditions: Perbenzoic acid, or meta-chlorobenzoic acid in benzene.

(Table 11, p1316, from the Evans, Hoveyda, Fu review article)

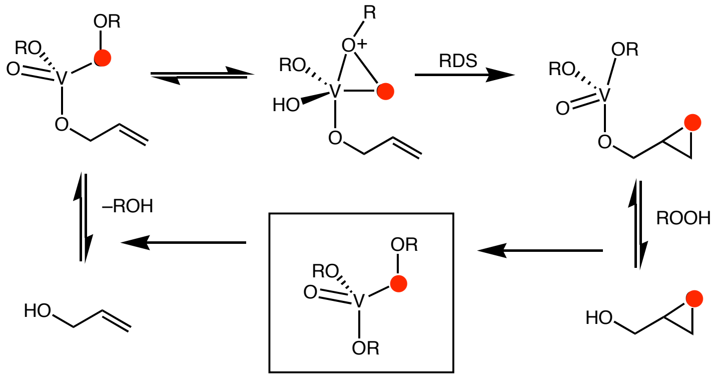
Epoxidation of Cyclic Homoallylic Alcohols

Substrate	Major Product	Selectivity
		9 : 1
		"highly selective"
		16 : 1
		1 : 1
		21 : 1
		5 : 1

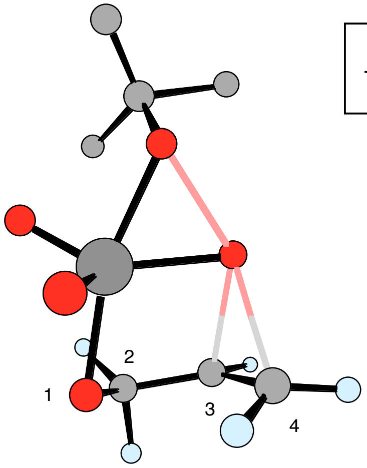
Conditions: Perbenzoic acid, or meta-chloroperbenzoic acid in benzene or cyclopentane.

(Table 14, p1318, from the Evans, Hoveyda, Fu review article)

The Sharpless Epoxidation

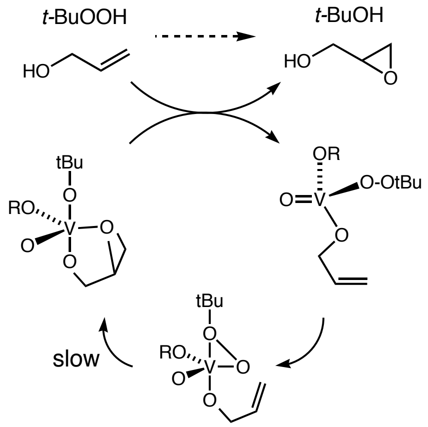


Aldrichimica Acta, **12**, 63 (1979)

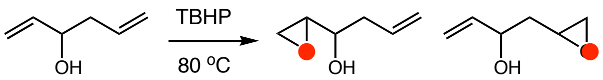


Chem 3D Transition State

$O–C_2–C_3–C_4$ = 41°
The Sharpless estimate: ~50°

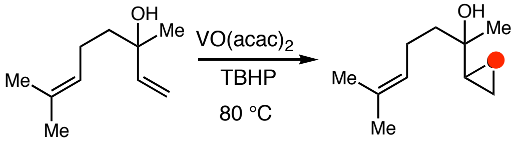


■ The literature precedent: Sheng, Zajecek, *J. Org. Chem.* **1970**, *35*, 1839

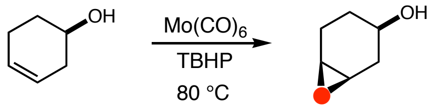


Catalyst VO(acac)$_2$ 4 : 1
Catalyst Mo(CO)$_6$ 1 : 1

■ Next step: Sharpless, Michaelson *JACS* **1973**, *95*, 6136

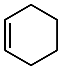
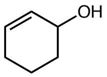
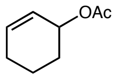
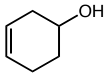


Regioselection 20:1



Stereoselection 98:2
(90 % yield)

Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives JACS **1973**, *95*, 6136

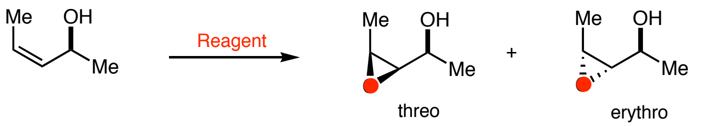
Substrate	peracid	Mo(CO)$_6$	VO(acac)$_2$
	1.00	1.00	1.00
 OH	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
 OAc	0.046 (37 : 63)	0.07 (40 : 60)	--
 OH	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

Column header: $k_{rel}^{a,b}$ (diastereoselectivity^c)

[a,b] The relative rate data apply only to a given column.
Values in parenthesis refer to the ratio of syn:anti epoxide.

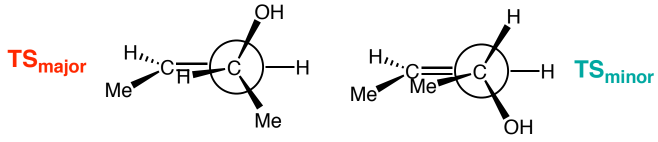
Epoxidation of Acyclic Alcohols

■ Allylic Alcohols:

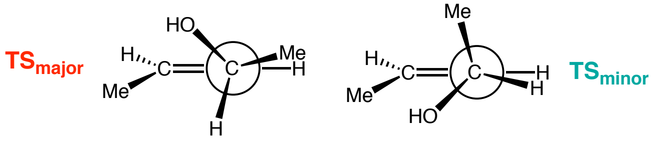


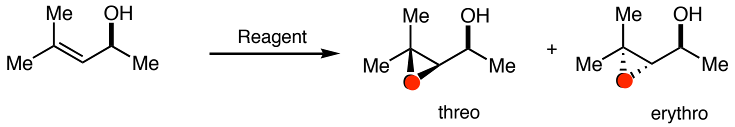
Φ Estimate	Reagent	Ratio
~ 120 °	*m*-CPBA	95 : 5
40-50 °	*t*-BuOOH / VO(acac)$_2$	71 : 29
	t-BuOOH / Mo(CO)$_6$	84 : 16

■ RCO$_3$H Transition States: Φ ~ 120 °



■ V(+) Transition States: Φ ~ 45 °

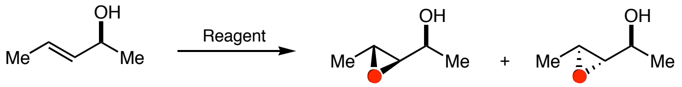




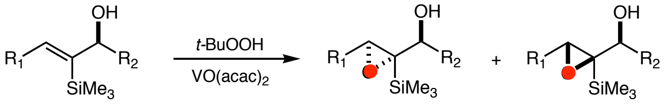
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, *21*, 1657, 4843.

K. B. Sharpless & Coworkers
Tetrahedron Lett. **1979**, *20,* 4733.

Reagent	Ratio
m-CPBA	95 : 5
t-BuOOH / VO(acac)$_2$	86 : 14
t-BuOOH / Mo(CO)$_6$	95 : 5
t-BuOOH / (*t*-BuO)$_3$Al	100 : 0

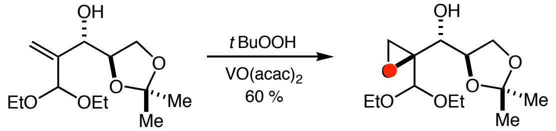


Reagent	Ratio
m-CPBA	64 : 36
t-BuOOH / VO(acac)$_2$	29 : 71
t-BuOOH / Mo(CO)$_6$	62 : 38
t-BuOOH / (*t*-BuO)$_3$Al	64 : 36

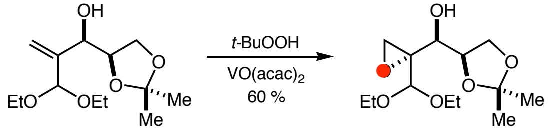


Oshima, *Tetrahedron Lett.* **1982**, *23*, 3387.

R$_1$	R$_2$	Yield	Ratio
H	Bu	84 %	99 : 1
C$_5$H$_{11}$	Me	70 %	99 : 1

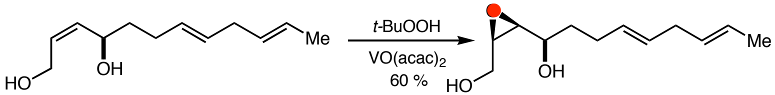


only isomer



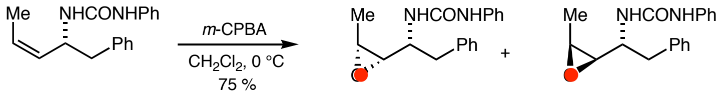
only isomer

Depezay, *Tetrahedron Lett.* **1978**, *19*, 2869.



Boeckman, *JACS* **1977**, *99*, 2805.

Diastereoselection = 7 : 1

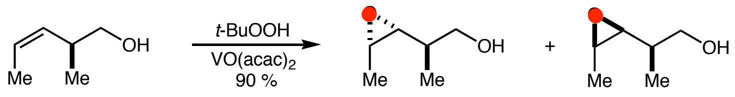


Roush, *J. Org. Chem.* **1987**, *52*, 5127.

Diastereoselection = 95 : 5

Epoxidation of Acyclic Homoallylic Alcohols

Homoallylic Alcohols (Mihelich, *JACS* **1981**, *103*, 7690)

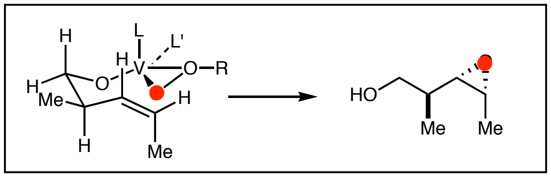


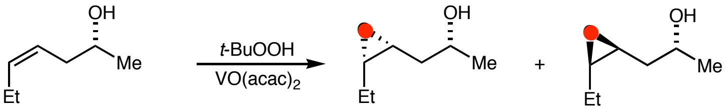
Diastereoselection > 400 : 1

Control Elements

A(1,3) Strain

Directed Rxn

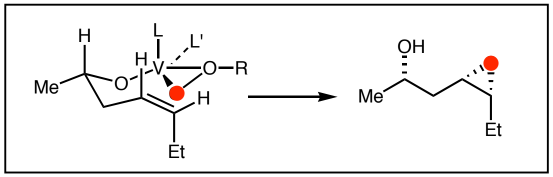




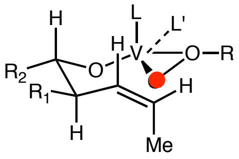
Diastereoselection 12 : 1

Control Elements

Directed Rxn

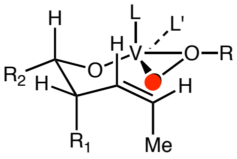


Prediction



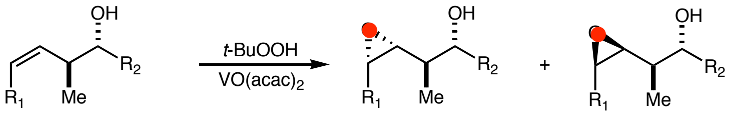
Anti diastereomer

Anti should be more diastereoselective than syn



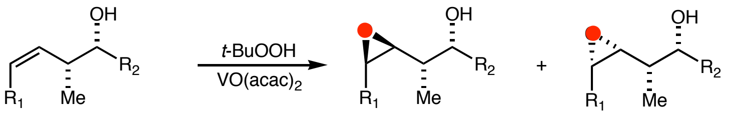
Syn diastereomer

Anti diastereomer

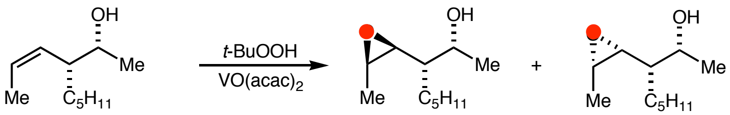


R$_1$	R$_2$	Yield	Ratio
C_6H_{13}	Me	92 %	104 : 1
Me	*i*-Pr	97 %	> 400 : 1

Syn diastereomer



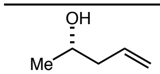
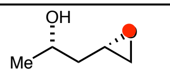
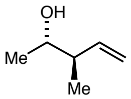
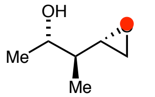
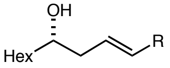
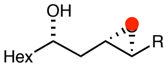
R$_1$	R$_2$	Yield	Ratio
C_6H_{13}	Me	73 %	70 : 1
Me	Me	70 %	85 : 1
Me	C_5H_{11}	81 %	16 :1



E. D. Mihelich & Coworkers
J. Am. Chem. Soc. **1981**, *103*, 7690.

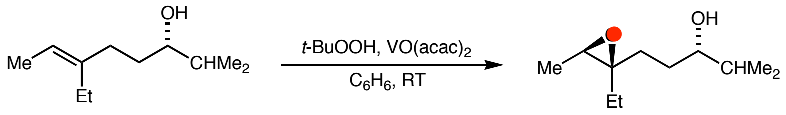
Diastereoselection = 211 : 1

Epoxidation of Homoallylic Alcohols with TBHP, VO(acac)$_2$

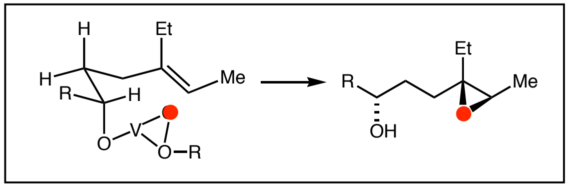
Substrate	Product	Selectivity
		2 : 1
		4.6 : 1
 R = $(CH_2)_7CO_2Me$		1.4 : 1

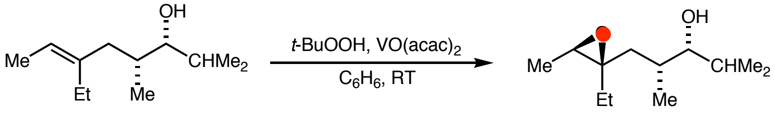
Epoxidation of Acyclic Homoallylic Alcohols

Bishomoallylic Alcohols (Kishi, *Tet. Lett.* **1978**, *19*, 2741)



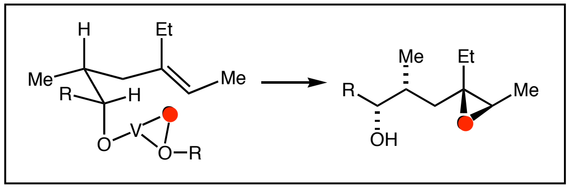
diastereoselection ~ 9 : 1

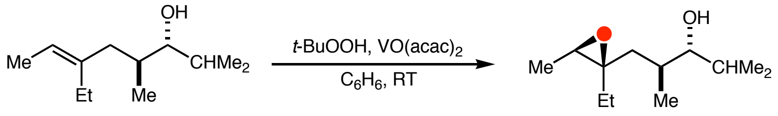




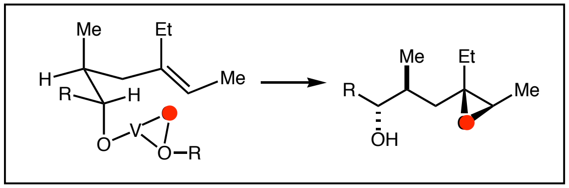
diastereoselection ~ 20 : 1

2nd stereocenter is reinforcing

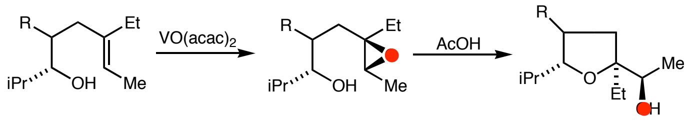




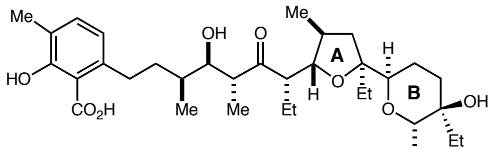
diastereoselection ~ 6 : 1

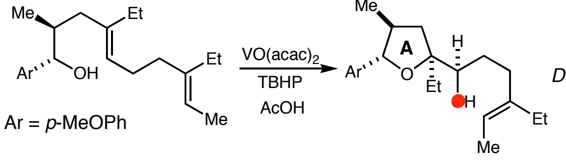


Epoxidation & Cyclization of Bishomoallylic Alcohols



The Kishi Lasalocid Synthesis (*JACS* **1978**, *100*, 2933)

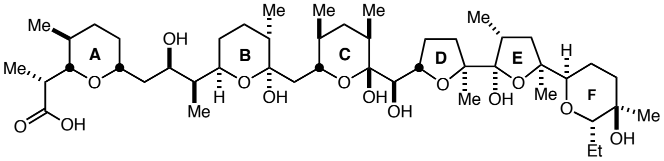


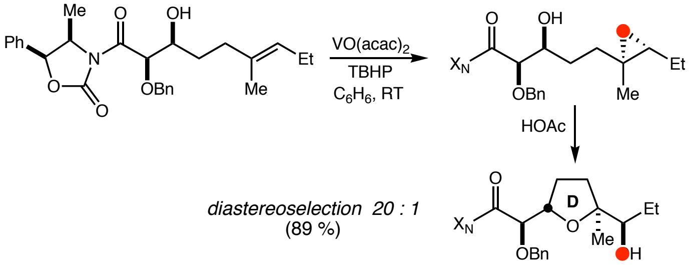


Ar = *p*-MeOPh

Diastereoselection 8:1

Evans X-206 Synthesis JACS **1988**, *110*, 2506.





diastereoselection 20 : 1
(89 %)

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 9

Olefin Addition Reactions–2

- Curtin-Hammett Principle
- Hydrogenation

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

Hoveyda, Evans, & Fu (**1993**). *Substrate-directable chemical reactions.* Chem. Rev. 93: 1307-70 ***(pdf)***

J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987) ***(Handout)***

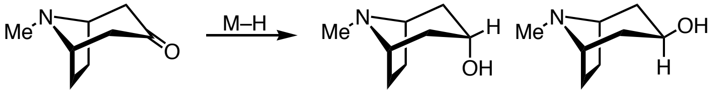
H. Yamamoto et.al, *Angew. Chem. Int. Ed.* **2005,** *44,* 4389-4391 **(pdf)**

D. A. Evans

Friday,
October 6, 2006

Problems of the Day:

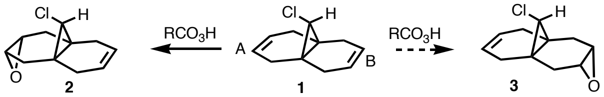
Rationalize the stereochemical outcome of the indicated reaction.



R. Noyori
Bull. Chem. Soc. Japan **47**, 2617, (1974)

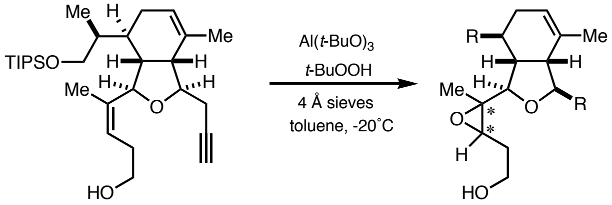
R_2AlH	97 : 3
$LiAlH_4$	28 : 72

Problem 579. The following publication (*J. Org. Chem.* **1991**, *56,* 5553) reported the surprisingly selective olefin epoxidation illustrated below. In this reaction, olefin B in **1** was found to be much less reactive than olefin A. Using your knowlege of stereoelectronic effects, provide an explanation for the reduced reactivity of olefin B in diene **1**.



2 *favored* **1** **3** *disfavored*

Problem 313. Overman and co-workers recently reported the indicated selective epoxidation in conjunction with a synthesis of briarellins A and E, a new family of diterpenes (*JACS* **2003**, *125*, 6650). It should be noted that the Al(t-BuO)$_3$/(t)-BuOOH reagent system is both highly diastereoselective and site selective. It is also relevant to the mechanism of the reaction that the ring-trisubstituted olefin lacking an allylic oxygen substituent would normally be more prone to epoxidation with a peracid than the acyclic trisubstituted olefin.



Part. Provide a general mechanism illustrating how the Al(t-BuO)$_3$/(t)-BuOOH reagent epoxidizes olefins. Three-dimensional drawings are recommended.
Part B. Provide a general mechanism illustrating how the above epoxidation proceeds and provide the stereochemistry (✻) of the product epoxide along with a stereochemical analysis of the noted face selectivity.

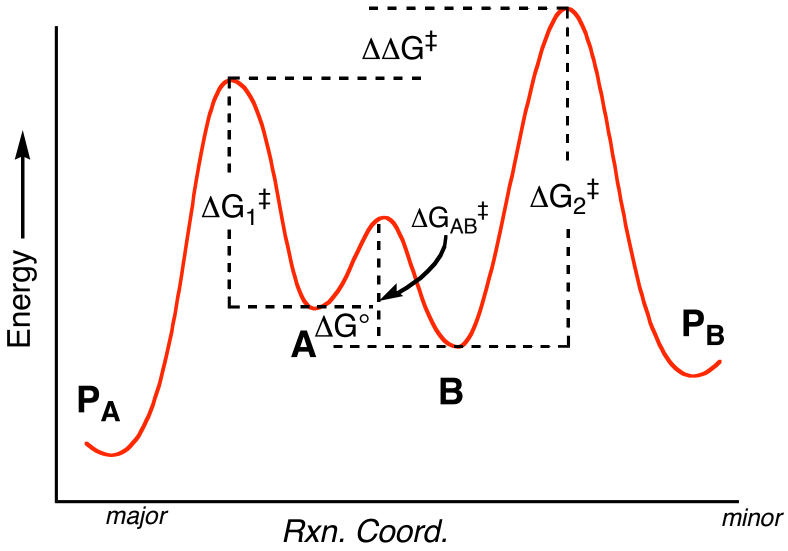
A Brief Introduction to the Curtin-Hammett Principle

J. I. Seeman, *J. Chem,Ed.* **1986,** *63,* 42-48 *The Curtin-Hammett Principle and the Winstein-Holness Equation*

J. I. Seeman, *Chem. Rev.* **1983**, *83*, 84-134. *Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammet-Winstein-Holness Kinetics*

Curtin–Hammett Conditions

$$P_A \xleftarrow[\text{slow}]{k_1} A \underset{\underset{\text{fast}}{k_B}}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow[\text{slow}]{k_2} P_B$$



Curtin–Hammett Principle

"The product composition, P_A vs P_B is not solely dependent on relative proportions of the conformational isomers in the substrate;

it is controlled by the difference in standard Gibbs energies (ΔΔG) of the respective transition states."*

The C-H principle may be extended to rapidly interconverting diastereomers, or constitutional isomers as well.

Curtin–Hammett Conditions: Conformer Populations vs Product Ratios

"Curtin–Hammett Conditions"

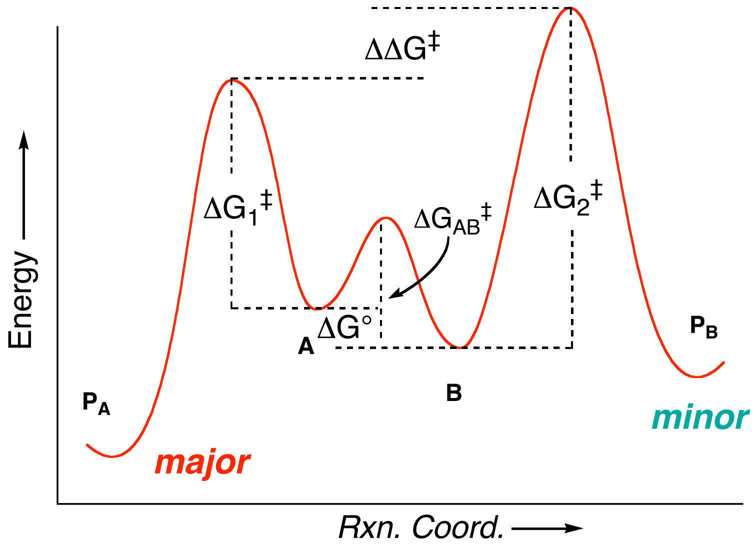
k_1, k_2 << k_A, k_B:

$$\mathbf{P_A} \xleftarrow[\textbf{slow}]{k_1} \mathbf{A} \underset{k_B}{\overset{k_A}{\rightleftharpoons}} \mathbf{B} \xrightarrow[\textbf{slow}]{k_2} \mathbf{P_B} \qquad (1)$$

fast

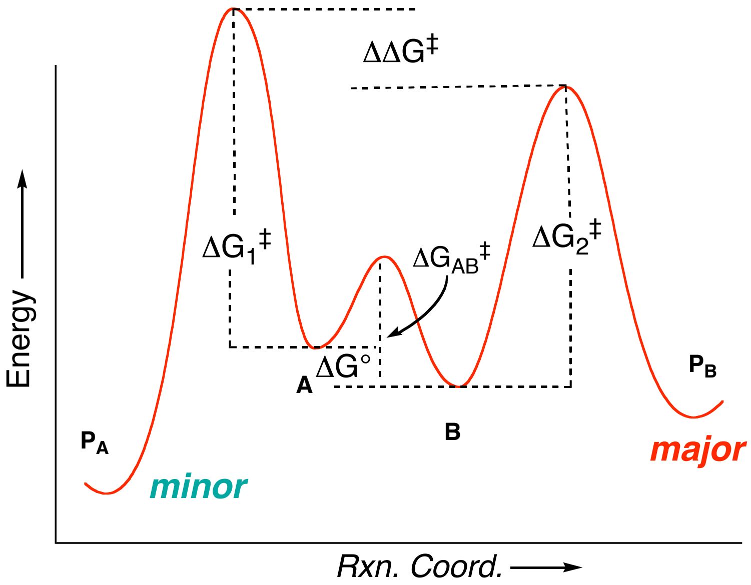
Case 1: Less stable conformer leads to the **major** product.

If reaction rates are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the A/B ratio is constant throughout the course of the rxn.



Case 2: Less stable conformer leads to the **minor** product.

If reaction rates are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the A/B ratio is constant throughout the course of the rxn.



Curtin - Hammett Principle

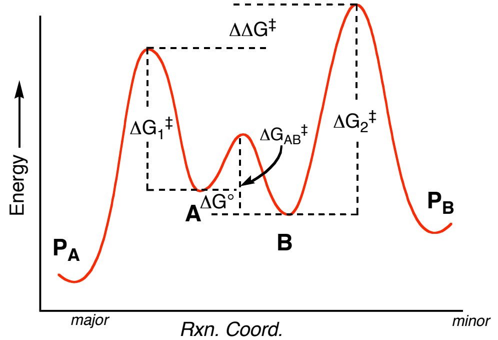
The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies ($\Delta\Delta G^{\ddagger}$) of the respective transition states.

Case 2: Curtin-Hammett Conditons

k_1, k_2 << k_A, k_B: If the rates of reaction are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the ratio of A to B is constant throughout the course of the reaction.

$$\mathbf{P_A} \xleftarrow[\text{slow}]{k_1} \mathbf{A} \underset{k_B}{\overset{k_A}{\rightleftharpoons}} \mathbf{B} \xrightarrow[\text{slow}]{k_2} \mathbf{P_B} \qquad (1)$$

fast



The Derivation:

Using the rate equations $\frac{d[P_A]}{dt} = k_1[A]$ and $\frac{d[P_B]}{dt} = k_2[B]$ we can write:

$$\frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]} \quad \text{or} \quad d[P_B] = \frac{k_2[B]}{k_1[A]} d[P_A] \qquad (2)$$

Since A and B are in equilibrium, we can substitute $K_{eq} = \frac{[B]}{[A]}$

$$\int d[P_B] = \frac{k_2}{k_1} K_{eq} \int d[P_A] \quad \text{Integrating, we get} \quad \frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} \qquad (3)$$

When A and B are in rapid equilibrium, we must consider the rates of reaction of the conformers as well as the equilibrium constant when analyzing the product ratio.

To relate this quantity to ΔG values, recall that $\Delta G^{o} = -RT \ln K_{eq}$ or $K_{eq} = e^{-\Delta G^\circ/RT}$, $k_1 = e^{-\Delta G_1^{\ddagger}/RT}$, and $k_2 = e^{-\Delta G_2^{\ddagger}/RT}$. Substituting this into the above equation:

$$\frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} = \frac{e^{-\Delta G_2^{\ddagger}/RT}}{e^{-\Delta G_1^{\ddagger}/RT}} (e^{-\Delta G^\circ/RT}) = e^{-\Delta G_2^{\ddagger}/RT} e^{-\Delta G^\circ/RT} e^{\Delta G_1^{\ddagger}/RT} \qquad (4)$$

Combining terms:

$$\boxed{\frac{[P_B]}{[P_A]} = e^{-(\Delta G_2^{\ddagger} + \Delta G^\circ - \Delta G_1^{\ddagger})/RT} \text{ or } \frac{[P_B]}{[P_A]} = e^{-\Delta\Delta G^{\ddagger}/RT}}$$

Where $\Delta\Delta G^{\ddagger} = \Delta G_2^{\ddagger} + \Delta G^\circ - \Delta G_1^{\ddagger}$

Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

Within these limits, we can envision three scenarios:

- If both conformers react at the **same rate**, the product distribution will be the same as the ratio of conformers at equilibrium.
- If the **major conformer** is also the faster reacting conformer, the product from the major conformer should prevail, and will not reflect the equilibrium distribution.
- If the **minor conformer** is the faster reacting conformer, the product ratio will depend on all three variables in eq (2), and the observed product distribution will not reflect the equilibrium distribution.

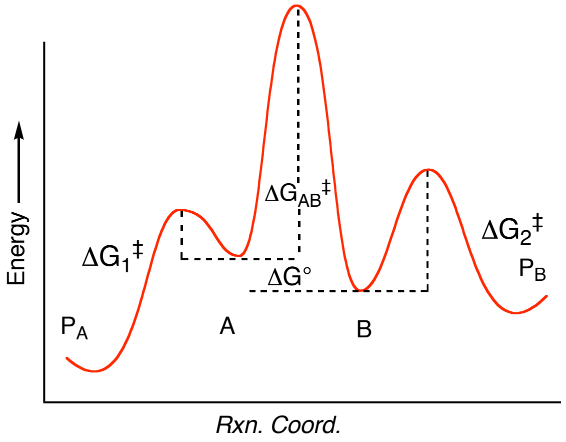
This derivation implies that you could potentially isolate a product which is derived from a conformer that you can't even observe in the ground state!

Non-Curtin-Hammett–Conditions

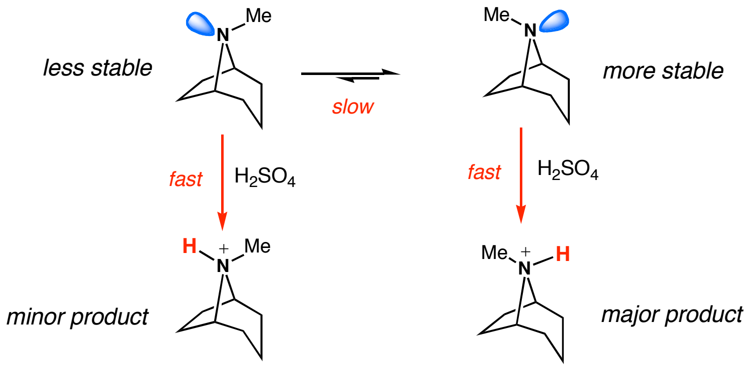
"Non-Equilibrating Conformers"

k_1, k_2 >> k_A, k_B: If the rates of reaction are **faster** than the rate of interconversion, A and B cannot equilibrate during the course of the reaction, and the product distribution (P_B/P_A) will simply reflect the initial equilibrium composition.

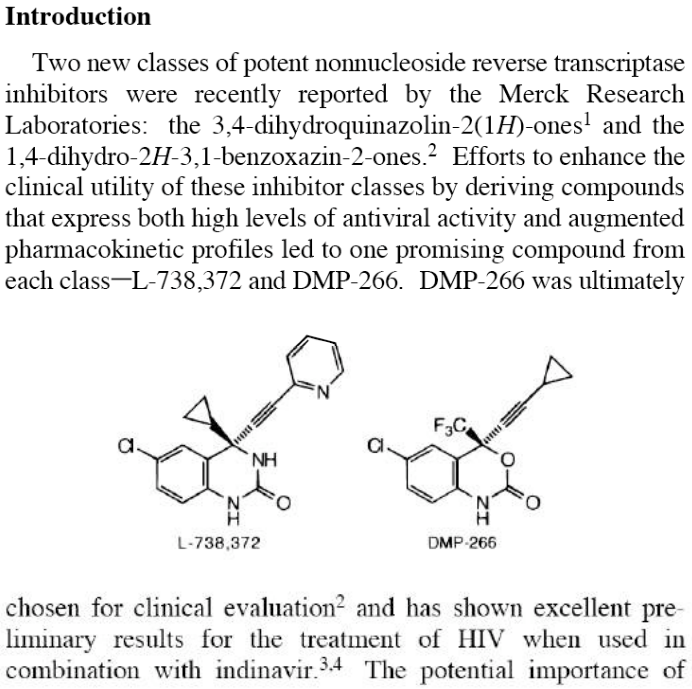
$$\frac{[P_B]}{[P_A]} = \frac{[B]_o}{[A]_o}$$



"Non-Equilibrating Conformers"



The rates of protonation are much faster than the rates of conformation interconversion



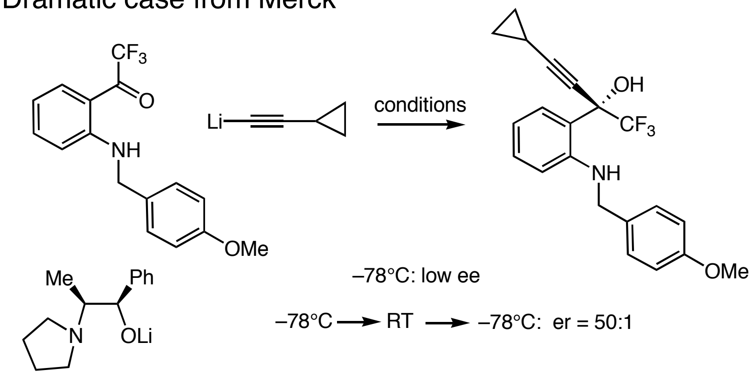
Introduction

Two new classes of potent nonnucleoside reverse transcriptase inhibitors were recently reported by the Merck Research Laboratories: the 3,4-dihydroquinazolin-2(1*H*)-ones[1] and the 1,4-dihydro-2*H*-3,1-benzoxazin-2-ones.[2] Efforts to enhance the clinical utility of these inhibitor classes by deriving compounds that express both high levels of antiviral activity and augmented pharmacokinetic profiles led to one promising compound from each class—L-738,372 and DMP-266. DMP-266 was ultimately chosen for clinical evaluation[2] and has shown excellent preliminary results for the treatment of HIV when used in combination with indinavir.[3,4] The potential importance of

L-738,372

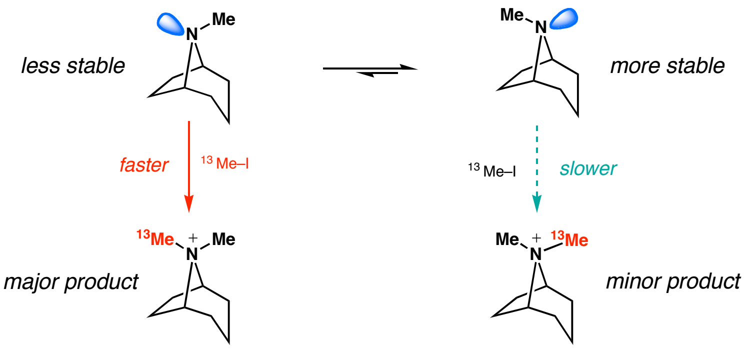
DMP-266

A Dramatic case from Merck



JACS **1998,** *120*, 2028-2038

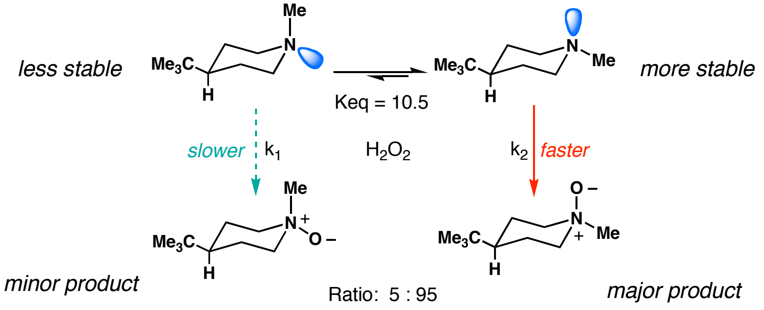
Tropane alkylation is a well-known example.



The less stable conformer reacts much faster than the more stable conformer, resulting in an unexpected major product!

JOC **1974** 319

Oxidation of piperidines:



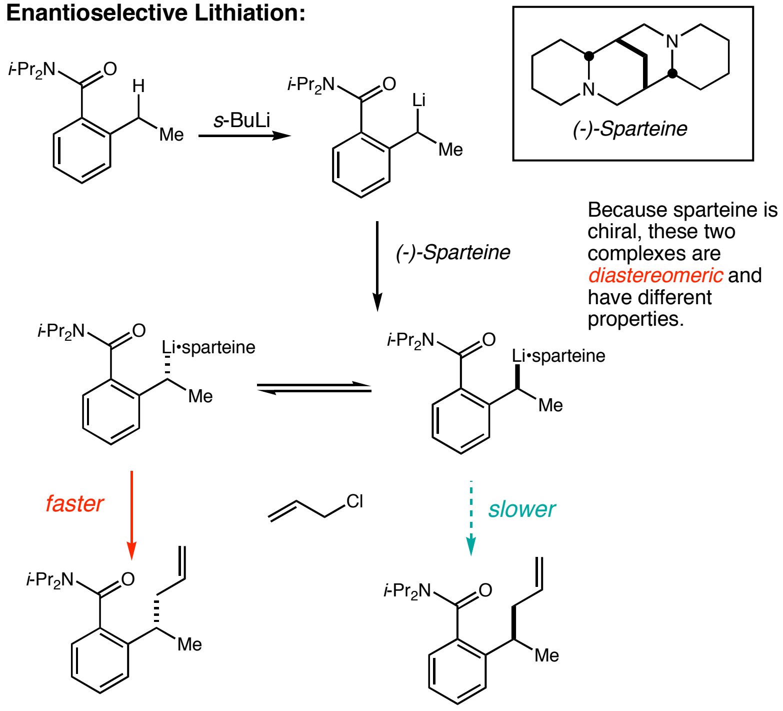
Ratio: 5 : 95

When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

Note that in this case, the more stable conformer is also the faster reacting conformer!

Tet. **1972** 573
Tet. **1977** 915

Enantioselective Lithiation:



Because sparteine is chiral, these two complexes are *diastereomeric* and have different properties.

82 - 87% ee

Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of (-)-sparteine results in racemic product.

Note that the two alkyllithium complexes MUST be in equilibrium, as the enantioselectivity is the same over the course of the reaction. If they were not equilibrating, the enantioselectivity should be higher at lower conversions.

This is a case of ***Dynamic Kinetic Resolution***: Two enantiomeric alkyl lithium complexes are equilibrating during the course of a reaction with an electrophile.

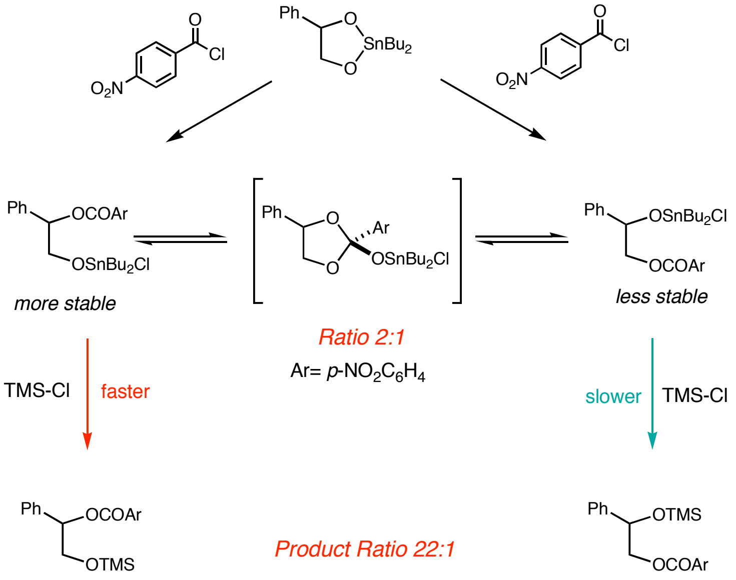
Beak, *Acc. Chem. Res*, **1996**, 552

Reactions Involving Interconverting Isomers

The Curtin-Hammett treatment can be extended to ANY case where different products are formed from two rapidly intereconverting starting materials, whether they are conformers, tautomers or isomers.

$$\underset{major}{P_A} \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} \underset{minor}{P_B}$$

Stannylene ketals provide an efficient way to acylate the more hindered site of 1,2-diols.



The two stannyl esters are in equilibrium at room temperature, and the more stable isomer is initially formed more slowly. The stannyl esters are allowed to equilibrate before quenching with TMS-Cl, which reacts more rapidly with the less hindered primary alkoxystannane.

JOC **1996**, 5257

"It was pointed out by Professor L. P. Hammett in 1950 (private communication) that ..."

David Y. Curtin, 1954

" Because Curtin is very generous in attributing credit, this is sometimes referrred to as the Curtin-Hammett principle rather than the Curtin principle."

Louis Plack Hammett, 1970

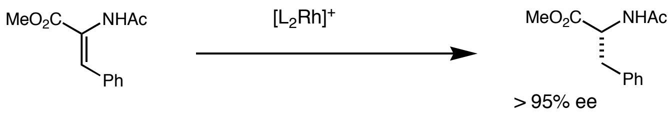
Curtin - Hammett Principle: *The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.*

THE TAKE-HOME LESSON:

Never assume that the most stable conformation of a compound is the most reactive. It may be, but then again, it may not.

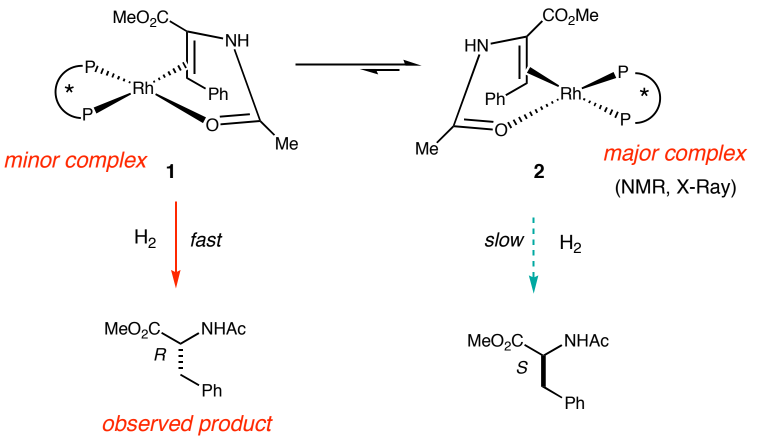
Mechanism of Asymmetric Hydrogenation

The asymmetric hydrogenation of prochiral olefins catalyzed by Rhodium is an important catalytic process.



Enantioselectivities are generally very high when the ligand is a chelating diphosphine. (ee's are given for S,S-CHIRAPHOS)

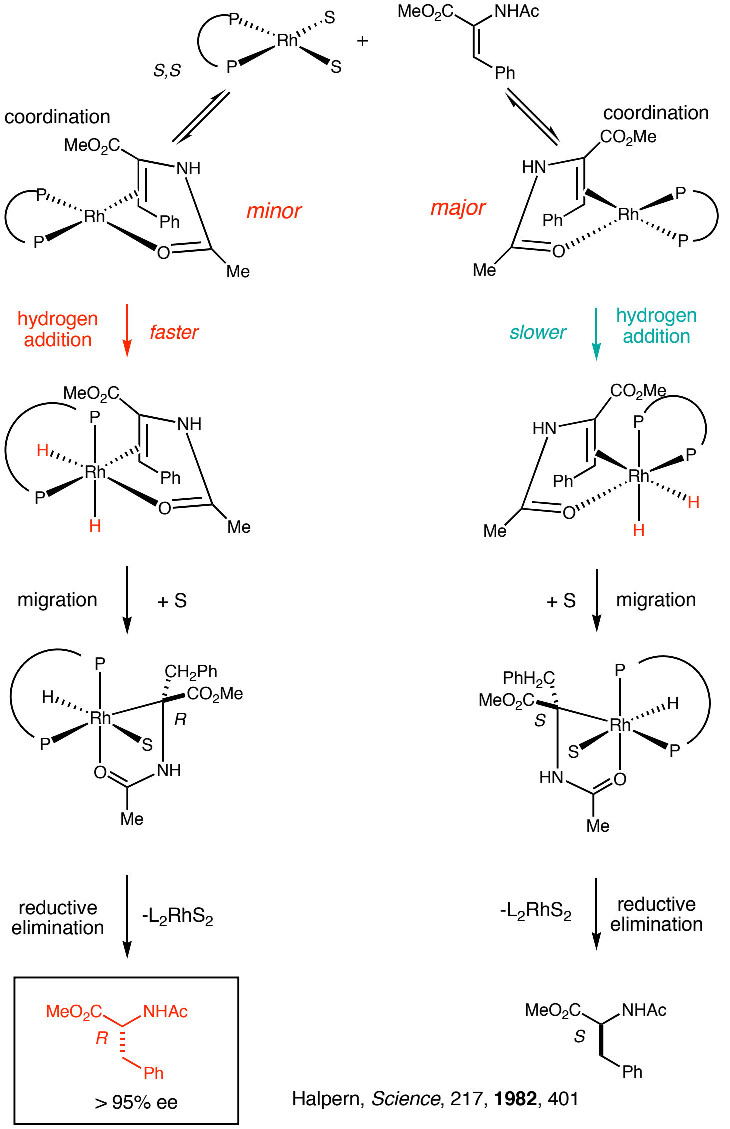
When a chiral ligand is used, there are two diastereomeric complexes which may be formed:



Observations:

- Complex 2 is the only diasteromer observed for the catalyst-substrate complex (1HNMR, X-Ray crystallography) in the absence of hydrogen
- The enantioselectivity is strongly dependant on the pressure of H_2, and degrades rapidly at higher hydrogen pressures
- The observed enantiomer is exclusively derived from the minor complex 2

These observations may be explained using the ***Curtin - Hammett Principle***



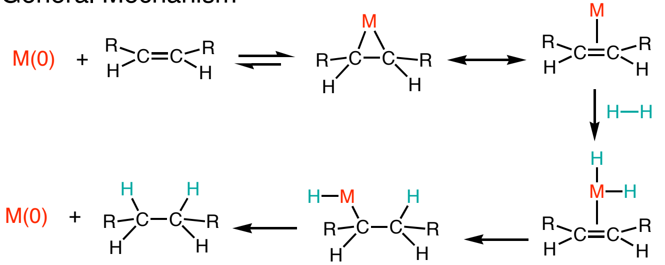
Halpern, *Science*, 217, **1982**, 401

Diastereoselective Hydrogenation: Introduction

The Hydrogenation Reaction

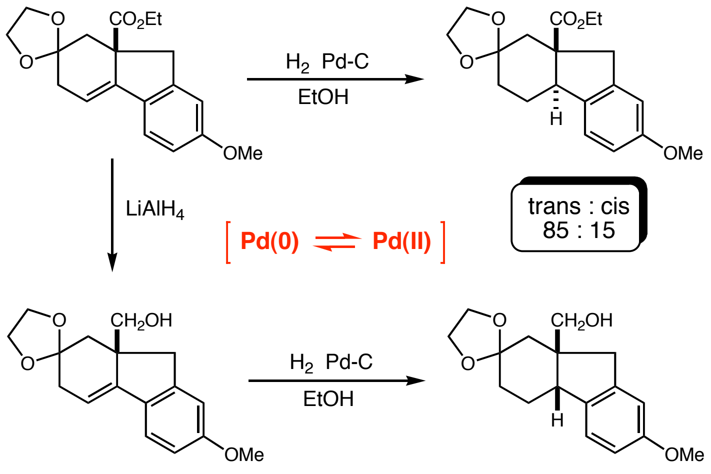
Review article: J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987) **(handout)**

■ General Mechanism



Historically, primary stereochemical control designed around analysis of steric environment in vicinity of C=C.

However, the influence of polar effects was documented



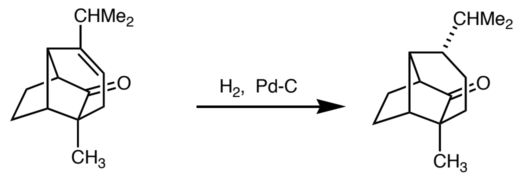
[**Pd(0) ⇌ Pd(II)**]

trans : cis
85 : 15

trans : cis
5 : 95

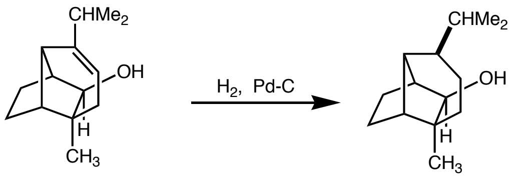
Thompson, *J.Org. Chem.* **36**, 2577 (1971)

Polar functional groups may play a role in controlling the diastereoselectivity of the hydrogenation process;
however, the control elements were not well-defined.



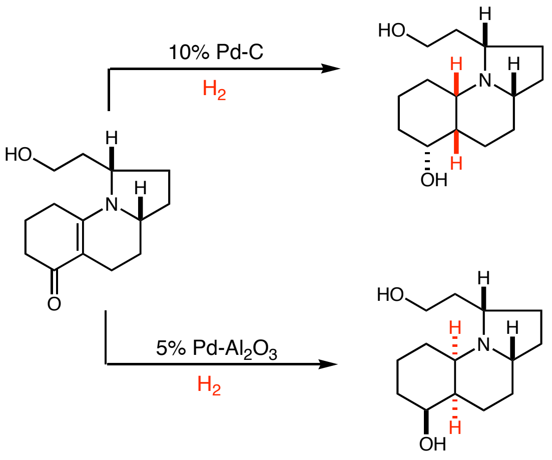
only isomer

however



trans:cis = 55:45

J. E. McMurry & Co-workers, *Tetrahedron Lett.*. 3731 (1970)



Steric Control

sole product

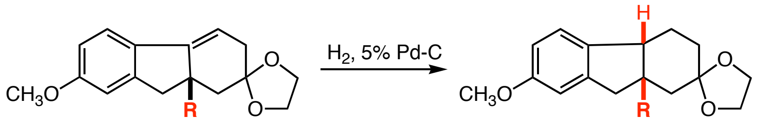
Directed ?

12 : 1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **102**, 7156 (1980)

Diastereoselective Hydrogenation: Introduction-2

The first rational attempt to identify those FGs which will direct the reaction

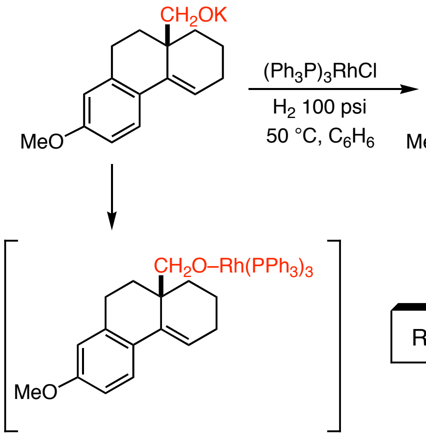


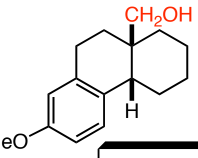
10

R	cis : trans
CH_2OH	95 : 5
CHO	93 : 7
CN	75 : 25
COONa	55 : 45
COOH	18 : 82
COOMe	15 : 85
COMe	14 : 86
$CONH_2$	10 : 90

H. Thompson & Co-workers, *J. Am. Chem. Soc.* **95**, 838 (1973)

The first rational attempt to associate catalyst with substrate:



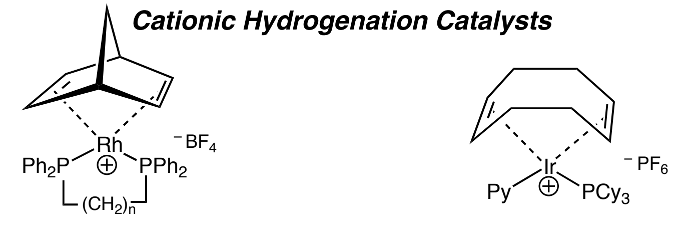


cis : trans
>98 : 2

Rxn Catalytic in Rh (4 mol%)

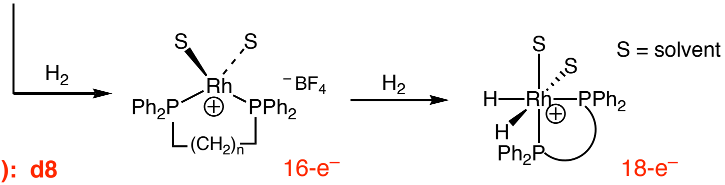
Thompson & Coworkers, *J. Am. Chem. Soc.* **97,** 6232 (1974)

Cationic Hydrogenation Catalysts



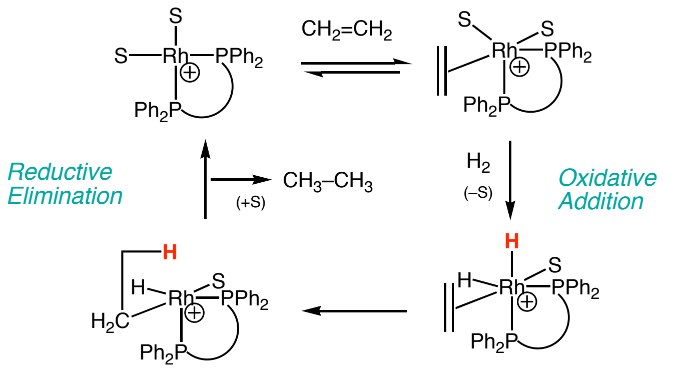
Schrock & Osborne,
J. Am. Chem. Soc. **91**, 2816 (1969)

R. Crabtree
J. Organomet. Chem. **168**, 183 (1979)



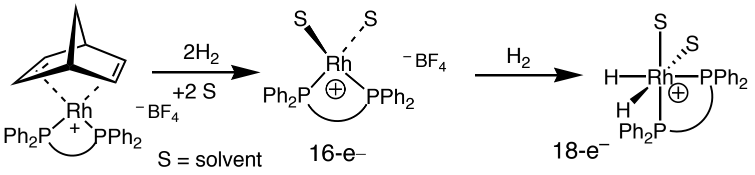
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.

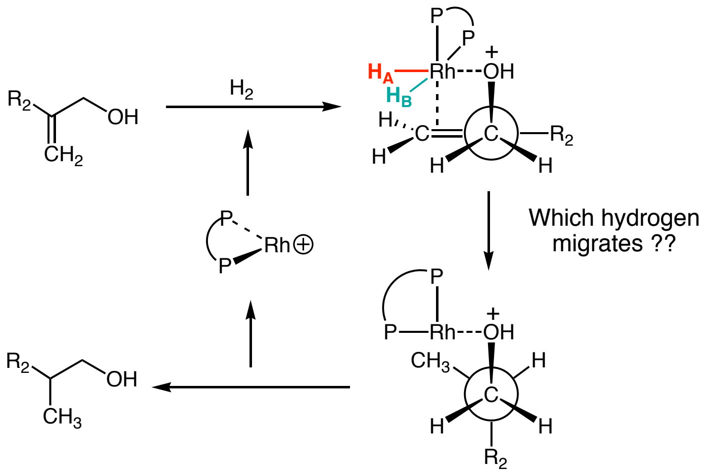
S = solvent



Diastereoaselective Hydrogenation: Cationic Catalysts

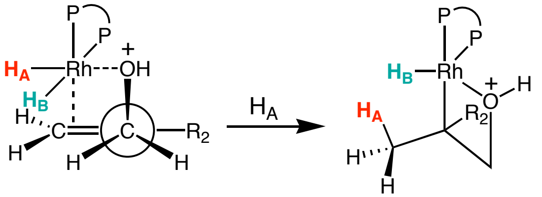
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.





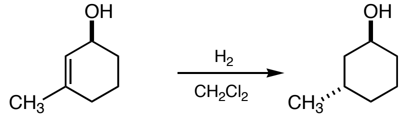
Which hydrogen migrates ??

A potential stereoelectronic effect

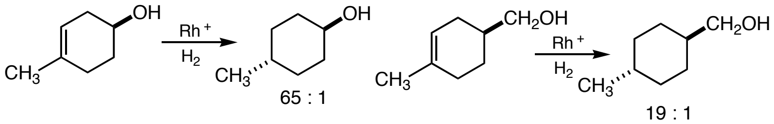


That H atom lying parallel to the pi-system (H_A) should migrate preferentiallyif the dihydride is an intermediate.

D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)

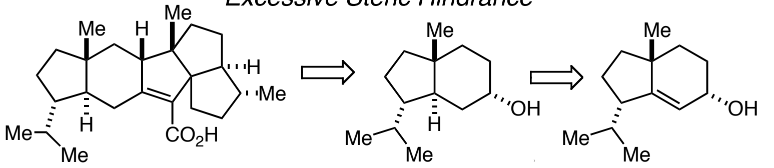


Catalyst	Mol% Catalyst	H_2 Pressure	trans:cis (Yield)
$Rh(DIPHOS\text{-}4)^+$	17.5	15 psi H_2	200 : 1 (89%)
	3.5	375 psi H_2	300 : 1 (95%)
$Ir(pyr)PCy_3$	20.0	15 psi H_2	50 : 1 (82%)
	2.5	15 psi H_2	150 : 1 (85%)

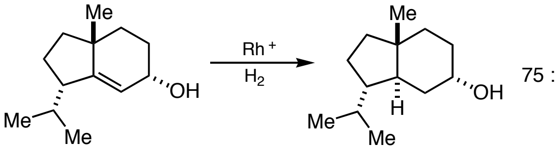


$Rh(DIPHOS\text{-}4)^+$ H_2 1000 psi CH_2Cl_2

Excessive Steric Hindrance



Retigeranic Acid



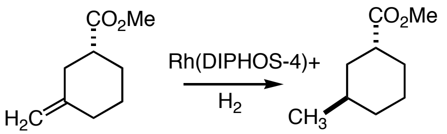
75 : 1 (95%)

$Rh(DIPHOS\text{-}4)^+$ H_2 800 psi THF

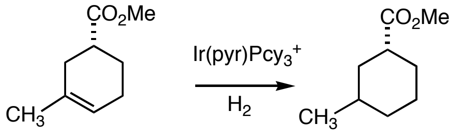
THF is important to success of rxn to buffer the Lewis acidity of the catalyst which causes elimination of ROH under normal conditions

Diastereoselective Hydrogenation: Cyclic Substrates

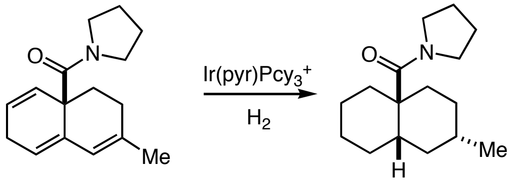
Polar functional groups other than OH may also direct the process



diastereoselection 91 : 9

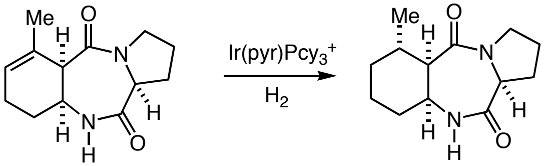


diastereoselection 89:11

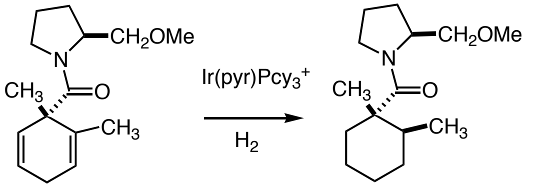


diastereoselection >99:1

J.M. Brown and S.A. Hall, *J. Organomet. Chem.*, **1985**, *285*, 333.

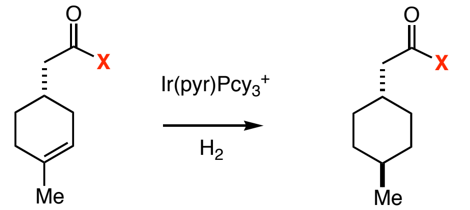


diastereoselection >99:1

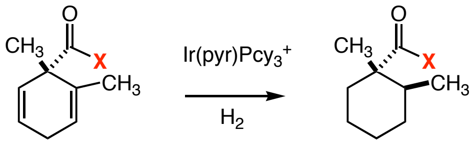


diastereoselection >99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.

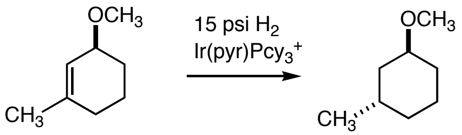


X	Diastereoselection
OMe	55:45
NC_4H_8	99:1



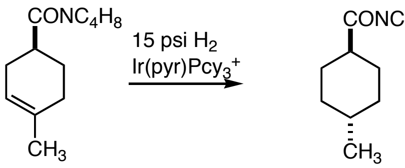
X	Diastereoselection
OMe	99:1
NC_4H_8	>99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.



diastereoselection >99:1

R.H. Crabtree and M.W. Davis, *J. Org. Chem.*, **1986**, *51*, 2655.

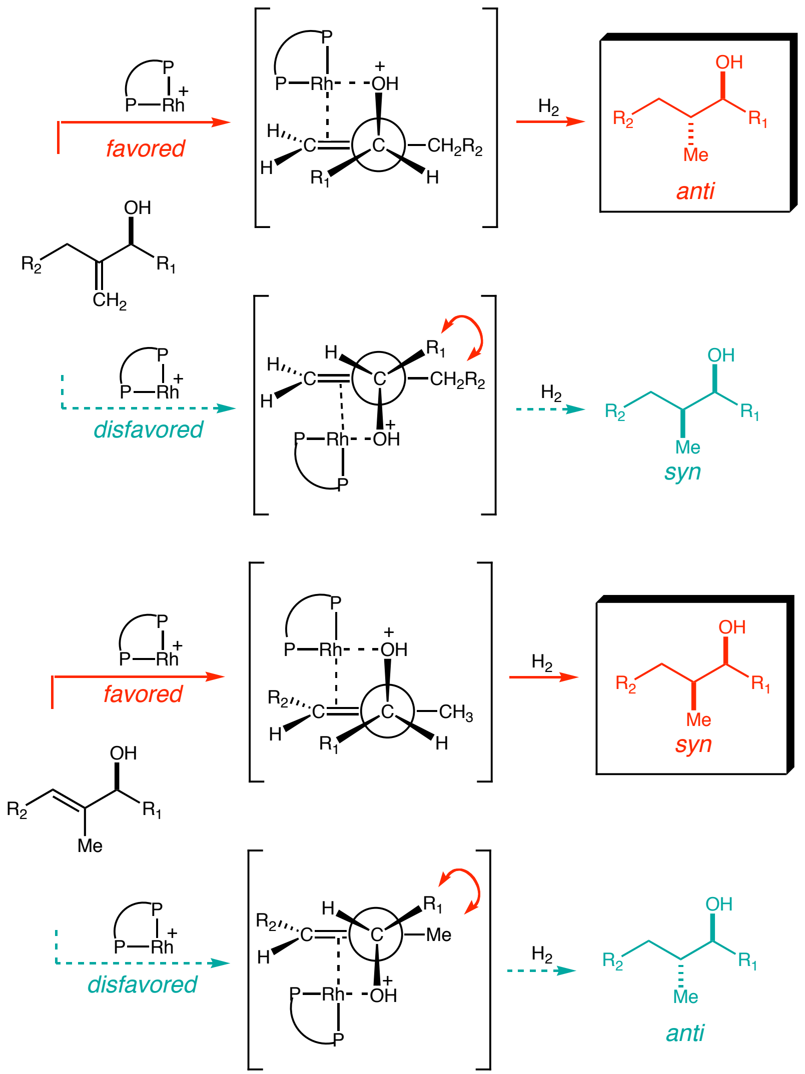


diastereoselection >99:1

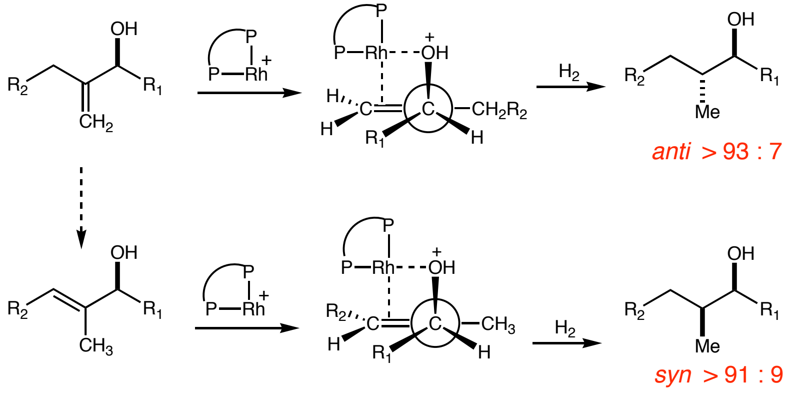
A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.

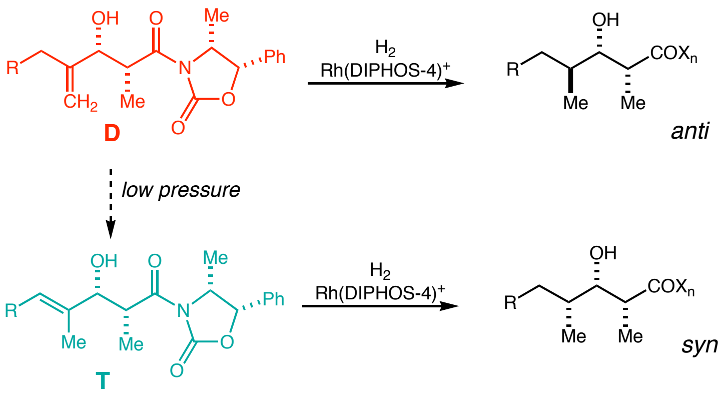
Diastereoselective Hydrogenation: Acyclic Substrates

Acyclic Allylic Alcohols



D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)

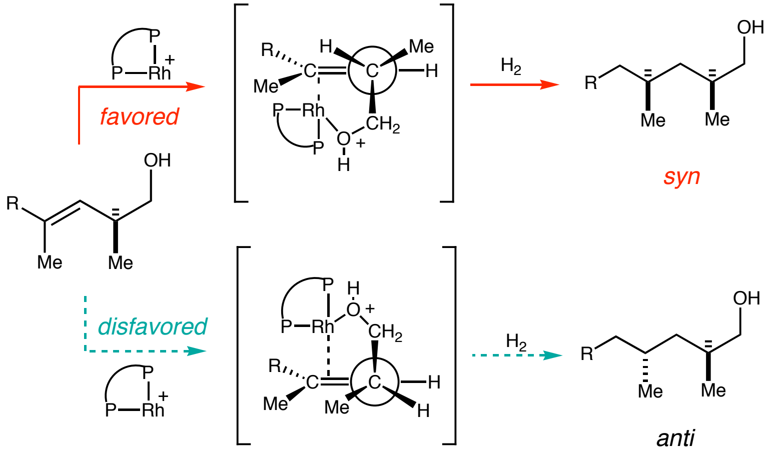




	Anti : Syn Ratio	
Hydroxy-Olefin	15 psi H_2	640 psi H_2
D R = CH_3	25 : 75 (23%)	93 : 7
R = $(CH_3)_2CH$	52 : 48 (35%)	94 : 6
R = Ph	71 : 29 (-)	93 : 7
T R = CH_3	13 : 87 (6%)	9 : 91
R = $(CH_3)_2CH$	12 : 88 (8%)	8 : 92
R = Ph	21 : 79 (-)	6 : 94

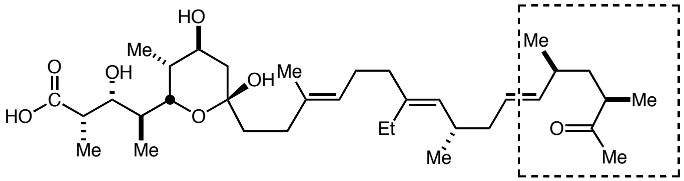
Diastereoselective Hydrogenation: Acyclic Substrates

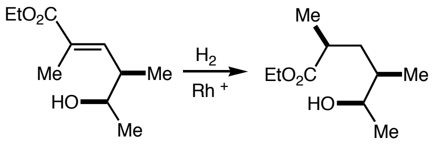
Homoallylic Alcohols Evans, Morrissey *Tetrahedron Lett.* **26** 6005 (1985)



A(1,3) destabilization

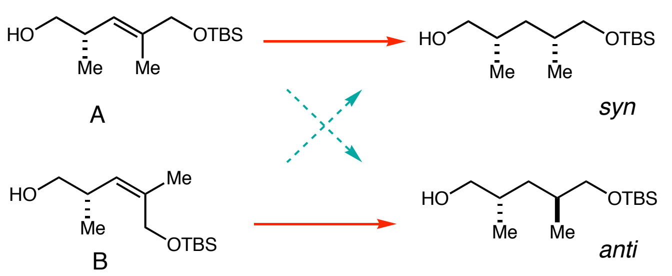
The Premonensin Synthesis





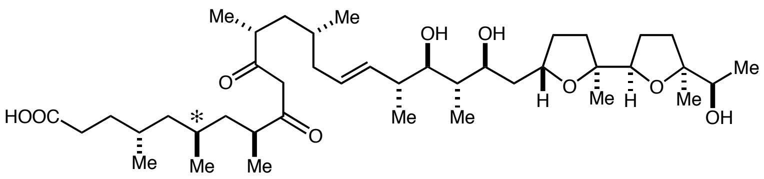
Catalyst	Ratio
Rh(DIPHOS-4) $^+$	85 : 15
Rh(–)(BINAP) $^+$	65 : 35
Rh(+)(BINAP) $^+$	98 : 2 (90%)

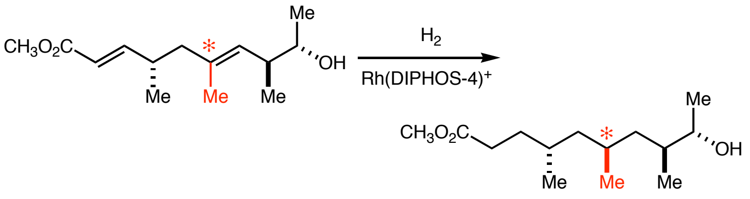
Evans, DiMare, *JACS*, **1986**, *108*, 2476)



Olefin	Catalyst (H_2 Pressure)	syn : anti
A	Rh(DIPHOS-4)$^+$ (1000 psi)	95 : 5
A	Ir(pyr)PCy$_3^+$ (15 psi, 2.5 mol%)	73 : 27
B	Rh(DIPHOS-4)$^+$ (1000 psi)	9 : 91

The Ionomycin Synthesis





Diastereoselection: 94 : 6 (93%)

with Dow, Shih, Zahler, Takacs, *JACS* **1990**, *112*, 5290

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 10

Olefin Addition Reactions–3

- Olefin Bromination
- Olefin Oxymercuration
- Halolactonization
- Simmons-Smith Reaction

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

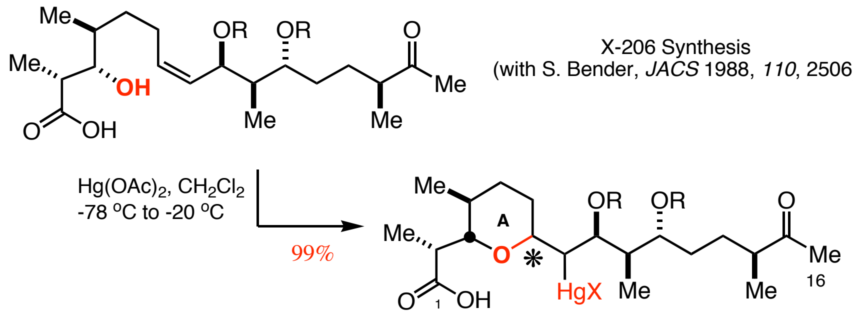
Investigation of the early Steps in Electrophilic Bromination through the Study of the Reaction of Sterically Encumbered Olefins
R. S. Brown, *Accts. Chem. Res.* **1997**, *30*, 131 **(handout)**

Bromoniun Ions or β-Bromocarbocations in Olefin Bromination. A Kinetic Approach to Product Selectivities
M-F. Ruasse, *Accts. Chem. Res.* **1990**, *23*, 87 **(handout)**

D. A. Evans

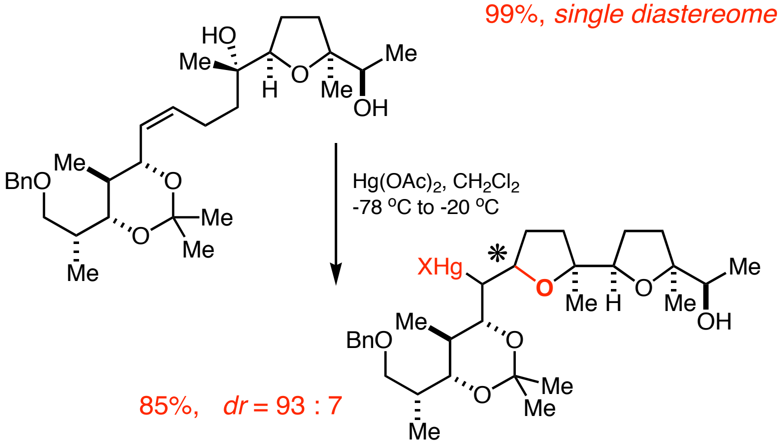
Monday,
October 9, 2006

Predict stereochemical outcome



X-206 Synthesis
(with S. Bender, *JACS* 1988, *110*, 2506)

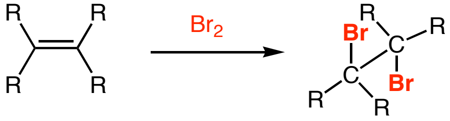
99%, *single diastereomer*



Ionomycin Synthesis
(with Dow & Shih, *JACS* 1990, *112*, 5290)

Olefin Bromination-1

Introduction



- Reaction is first order in alkene

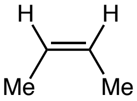
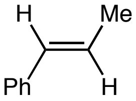
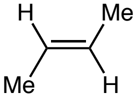
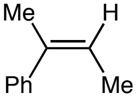
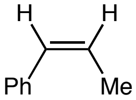
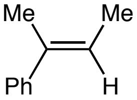
At low concentrations of Br_2, rxn is also **first order in Br_2**

At higher concentrations of Br_2 in nonpolar solvents rxn is **2nd order in Br_2**.

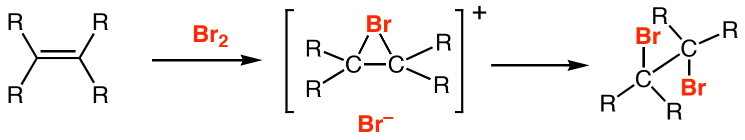
- Substituent Effects on Bromination Rates

Alkene	k_{rel}
$CH_2{=}CH_2$	1
$CH_3CH{=}CH_2$	61
n-$PrCH{=}CH_2$	70
i-$PrCH{=}CH_2$	57
t-$BuCH{=}CH_2$	27
$(CH_3)_2C{=}CH_2$	5470
cis-$CH_3CH{=}CHCH_3$	2620
trans-$CH_3CH{=}CHCH_3$	1700
$(CH_3)_2C{=}CHCH_3$	130,000
$(CH_3)_2C{=}C(CH_3)_2$	1,800,000

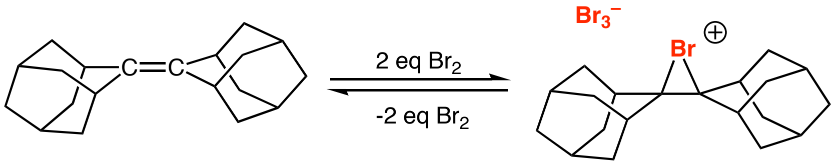
- Stereochemical outcome versus structure (Br_2 in HOAc @ 25°)

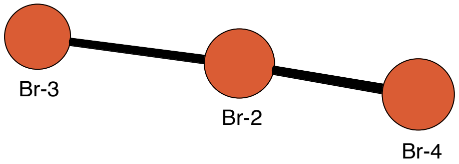
Alkene	% anti addition	Alkene	% anti addition
	100%		83%
	100%		63%
	73%		68%

- Bromonium ion origin of the anti (trans) selectivity first suggested by Roberts, *JACS* **1937**, *59*, 947

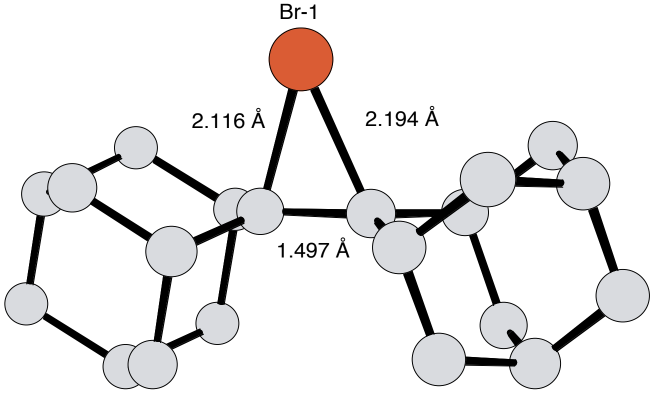


- First X-ray Structure of a bromonuium ion: Brown, *JACS* **1985**, *107*, 4504



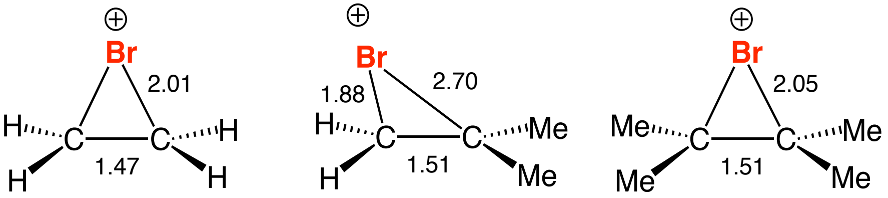


X-ray structure



Olefin Bromination-2

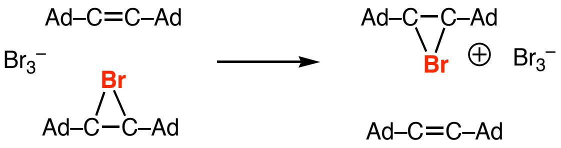
- Calculated Geometries of Substituted Bromonium Ions
Ruasse, *Chem Commun.* **1990**, 898
More recent calculations: Sigalas, *Tetrahedron* **2003**, *59*, 4749

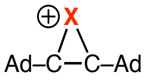


Note; the C–Br bond lengths in previous X-ray structure are 2.116 Å.

- Bromonium Ions undergo fast exchange with olefins
Brown, *Accts. Chem. Res.* **1997**, *30*, 131

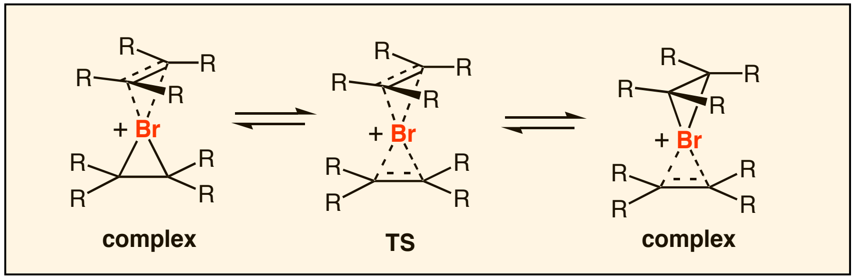
Unprecedented until 1991 (Bennet, JACS **1991**, *113*, 8532)



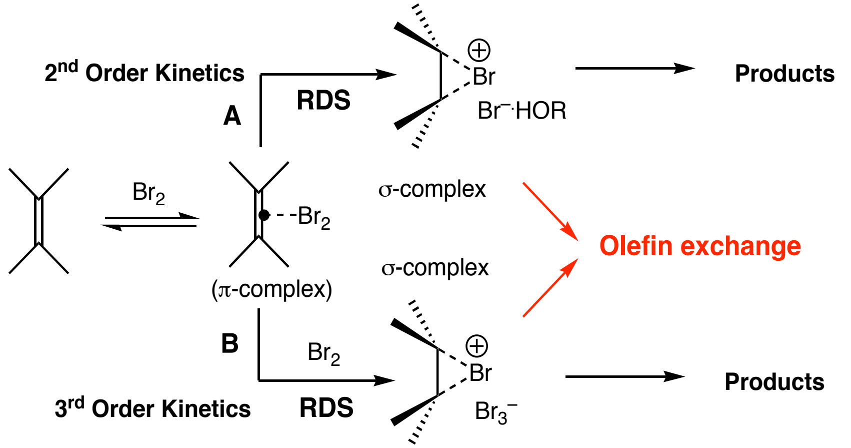


X = Br: exchange rate: 2 x 10^6 M^{-1} s^{-1}
X = I : exchange rate: 8 x 10^6 M^{-1} s^{-1}

There is an intermediate in the halogen transfer (ab initio calcs):

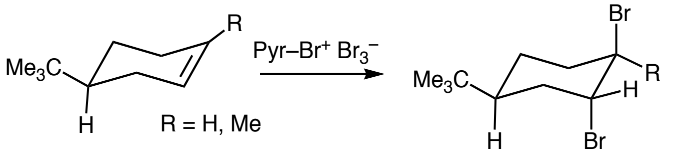


Overall Reaction Mechanism



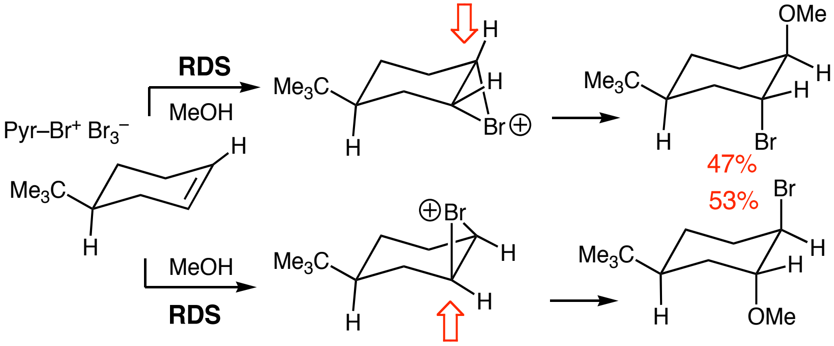
One is not committed to an addition product from the σ-complex

Bromination of Cyclohexene Derivatives **Pasto, *JACS* 1970, *92,* 7480**



exclusive product

Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening (**Lecture-3**).

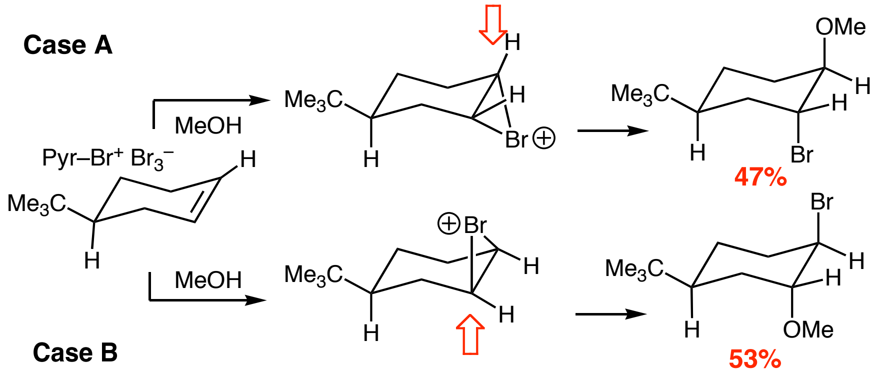


It appears that bromine attack from both olefin faces occurs with near equal probability.

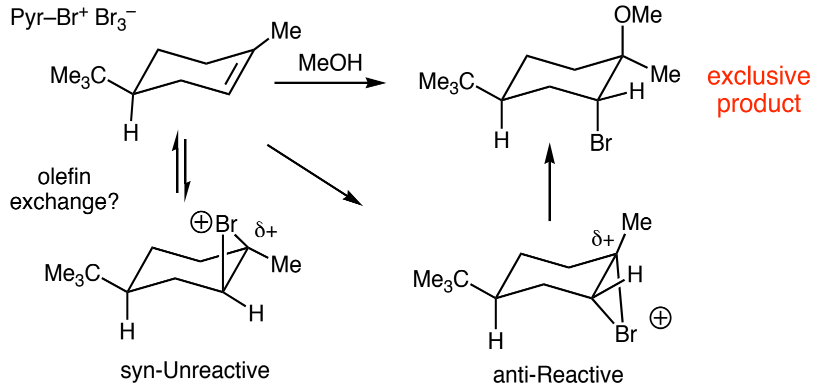
Bromination of Cyclohexene Derivatives **Pasto, *JACS* 1970, *92*, 7480**

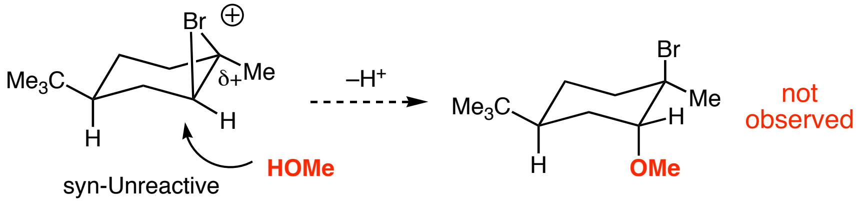
Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

Case A



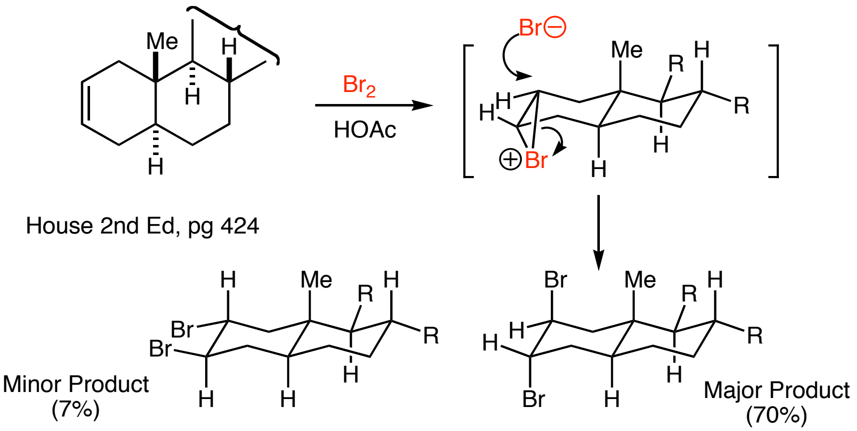
Case B



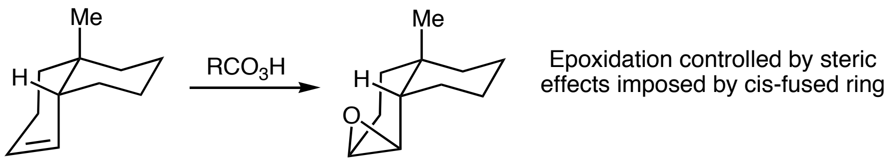


From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opening must proceed against the polarization due to Methyl substituent. Therefore it is reasonable that bromoniun ion exchange must be occuring.

Representative Examples of Diastereoselective Bromination

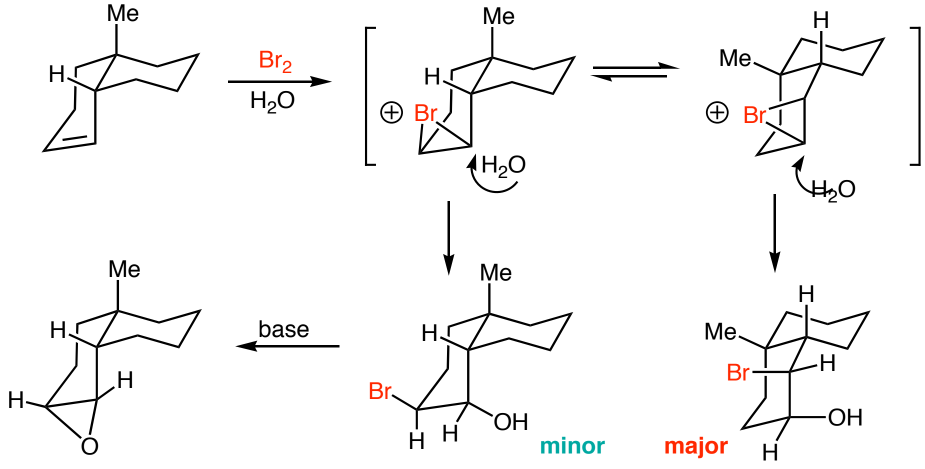


How to generate either epoxide from a conformationaly biased olefin



Epoxidation controlled by steric effects imposed by cis-fused ring

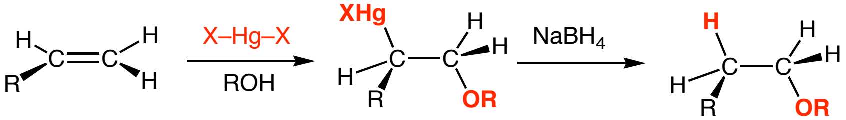
How do we construct the other epoxide diastereomer??



both bromohydrins afford same product

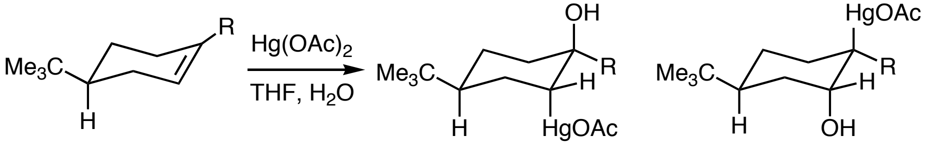
Oxymercuration **Pasto, *JACS* 1970, *92,* 7480**

The basic process:



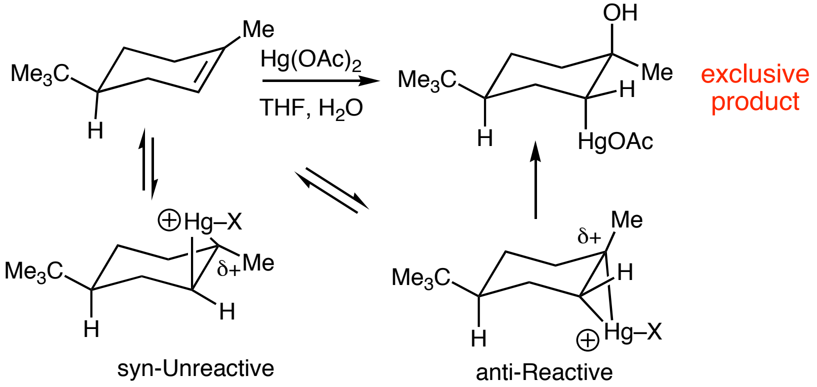
Kinetics: Halpern, *JACS* **1967**, *89*, 6427 Reduction: Pasto, *JACS* **199**, *91*, 719
Overview: B rown, *JOC* **1981**, *46*, 3810.

Oxy-Mercuration & bromination follow identical pathways (Pasto)

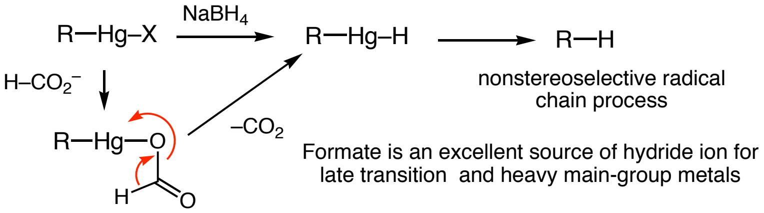


R = H 41% 48%

R = Me 100%



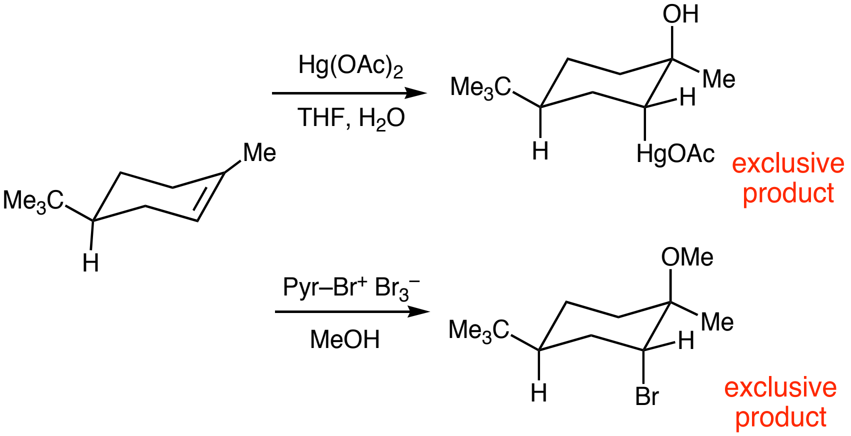
Reduction of the Hg–C bond



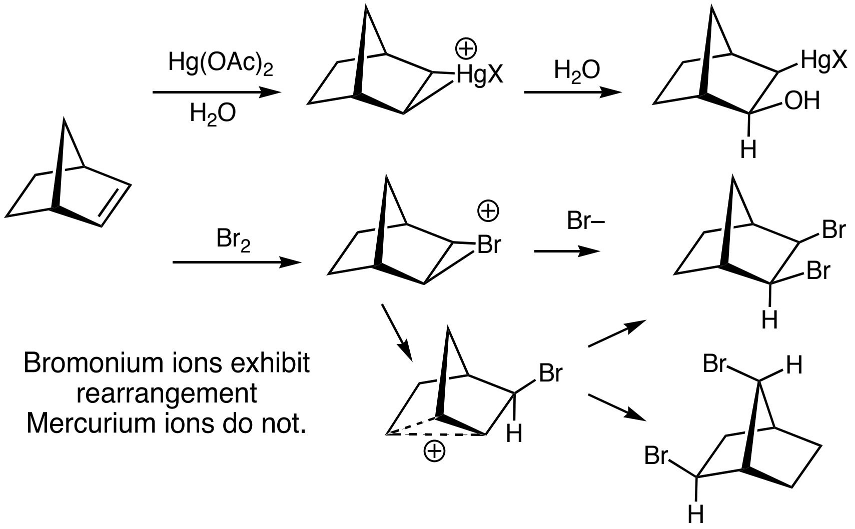
nonstereoselective radical chain process

Formate is an excellent source of hydride ion for late transition and heavy main-group metals

Bromonium and Mercurium Ions; Similarities vs Differences

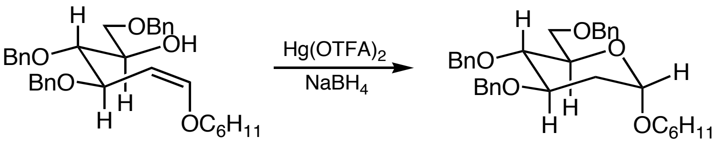


Norbornene Additions: An interesting comparision



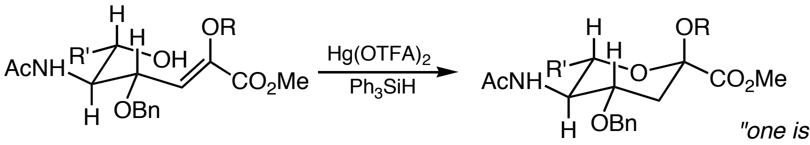
Bromonium ions exhibit rearrangement
Mercurium ions do not.

Diastereoselective ring closures via oxymercuration



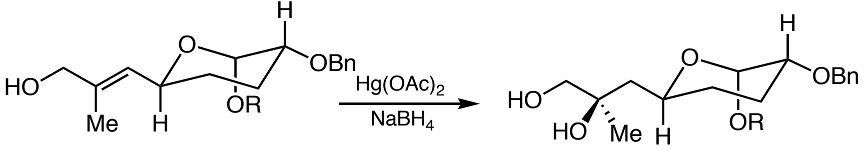
α:β = 96 : 4

Mukaiyama, *Chem. Lett.* **1981**, 683



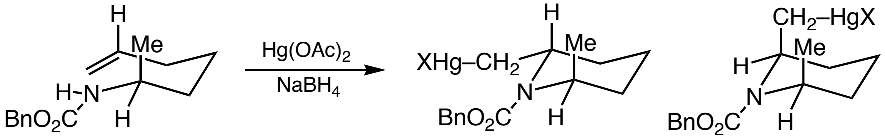
"one isomer"

Sinay, *Tet. Lett.* **1984**, *25*, 3071



Isobe, *Tet. Lett.* **1985**, *26*, 5199

■ Kinetic vs Thermodynamic control:



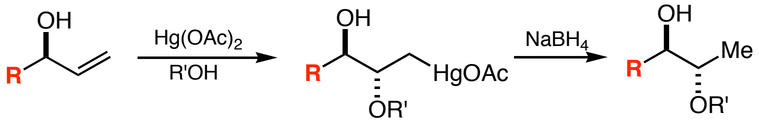
Harding, *JOC* **1984**, 49, 2838

$Hg(OAc)_2$: short rxn times : 40 : 60

$Hg(OTFA)_2$: longer rxn times : 2 : 98

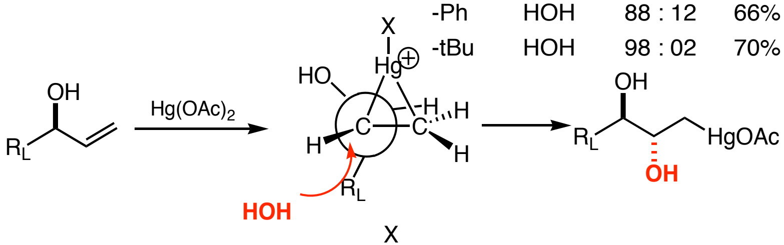
With more electrophilic Hg(II) salt, more polar solvents, and longer rxn times, the rxn may be rendered reversible.

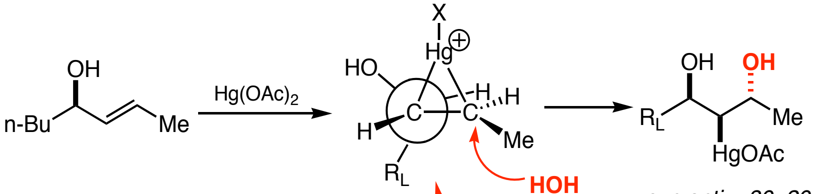
■ Acyclic allylic alcohols:



Giese, *Tet. Lett.* **1985**, *26*, 1197

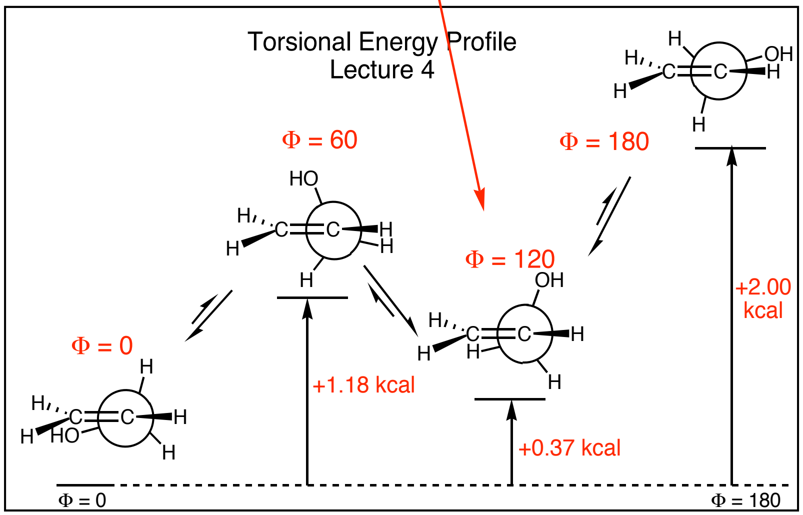
R	R'OH	Ratio	yield
-Et	HOH	76 : 24	65%
-Et	MeOH	93 : 07	72%
-Ph	HOH	88 : 12	66%
-tBu	HOH	98 : 02	70%





syn:anti = 80 :20

Chamberlin, *Tetrahedron* **1984**, *40*, 2297

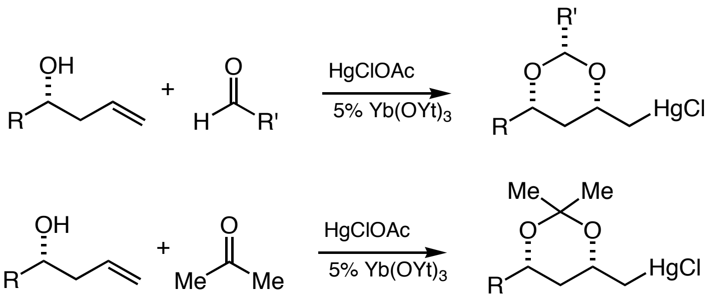


Oxymercuration Examples

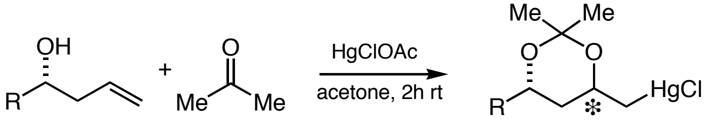
Oxymercuration via Hemiketals & Hemiacetals

J. L. Leighton et. al, *Org. Lett.* **2000**, *2*, 3197-3199

■ General Reaction: diastereoselection >10:1



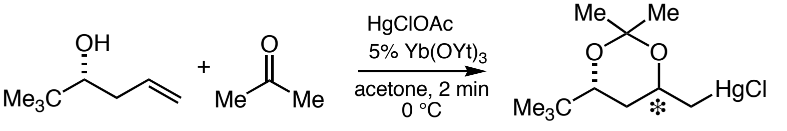
■ Mechanistic Observations:



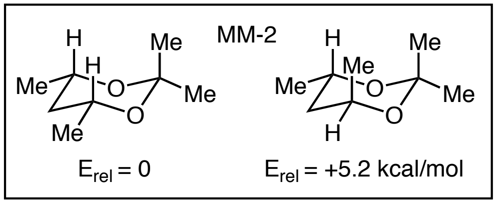
~1:1-mixture of diastereomers
Product formed in low yield.
much recovered starting material

Lewis acid addends were surveyed. the logic for this step was two-fold:

(A) Lewis acid would promote the formation of the putative hemiketal imtermediate.
(B) Lewis acid would promote reversability of the oxymercuration process

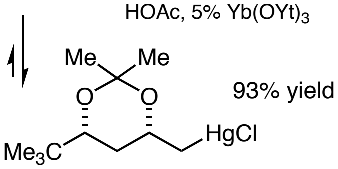


~1:1-mixture of diastereomers



$E_{rel} = 0$

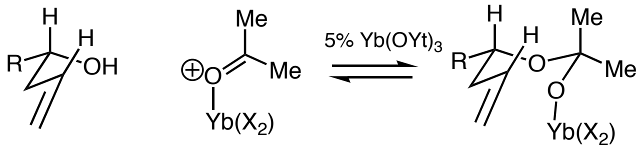
$E_{rel} = +5.2$ kcal/mol



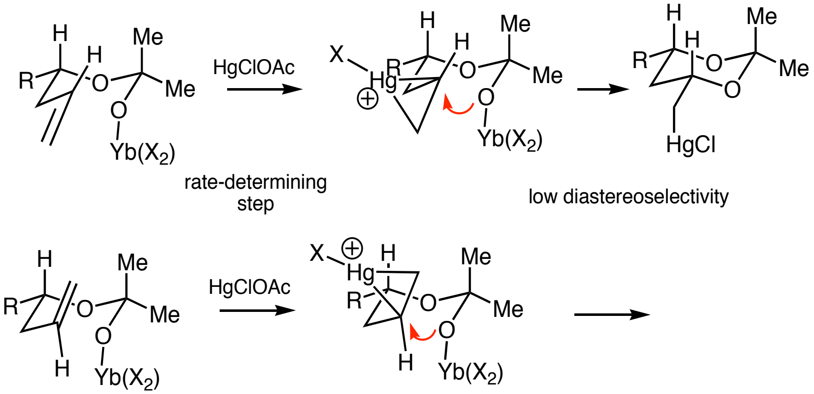
93% yield

Proposed Mechanism

■ Lewis acid catalyzes formation of hemiketal



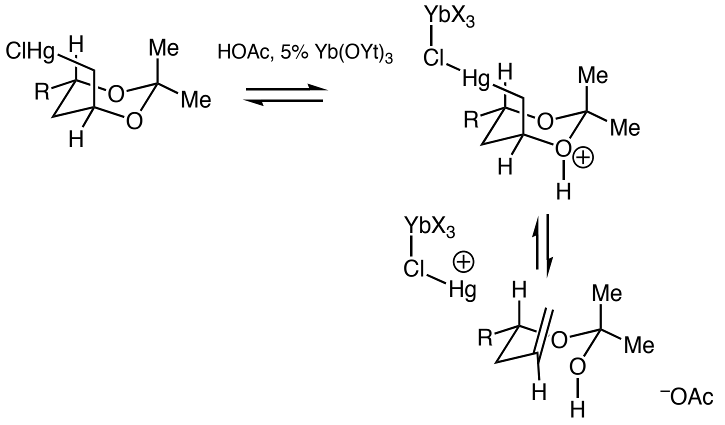
■ The Oxymercuration Step (Kinetic Phase)



rate-determining step

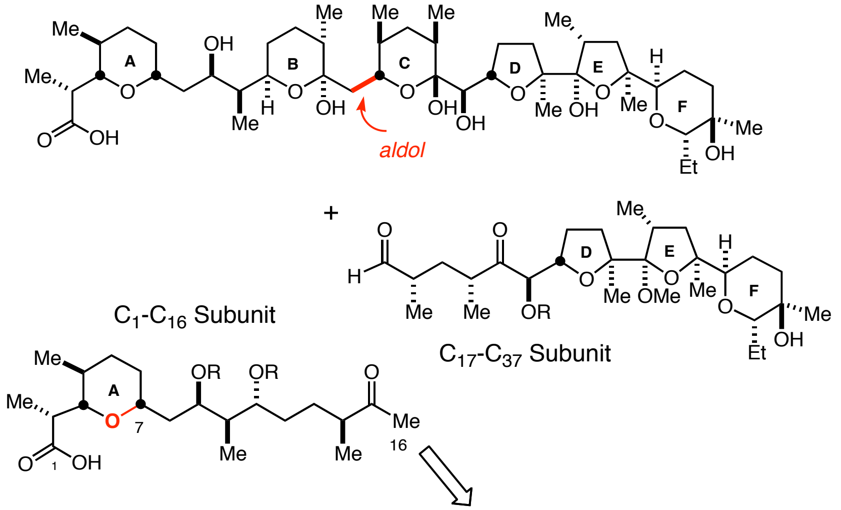
low diastereoselectivity

Leighton presumes that mercurium ion formation is rate-determining under kinetic conditions. At higher temperatures and longer reaction times the products are shown to interconvert.

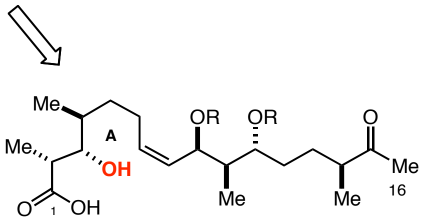


Oxymercuration Examples: X-206 & Ionomycin Syntheses

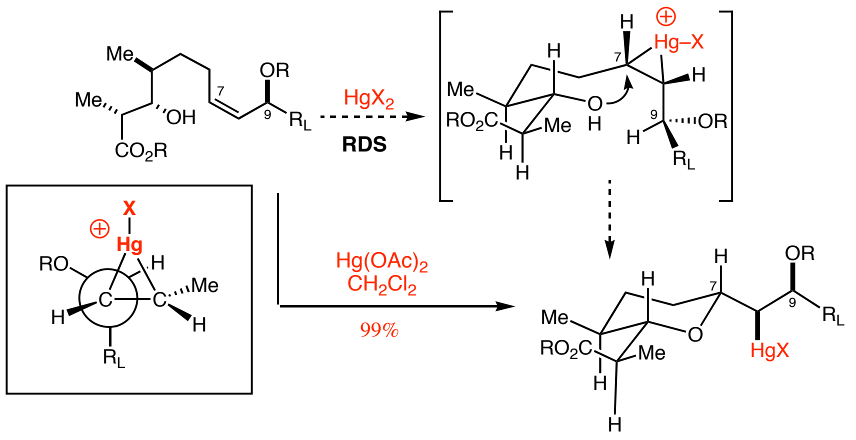
X-206 Synthesis (with S. Bender, *JACS* 1988, *110*, 2506)



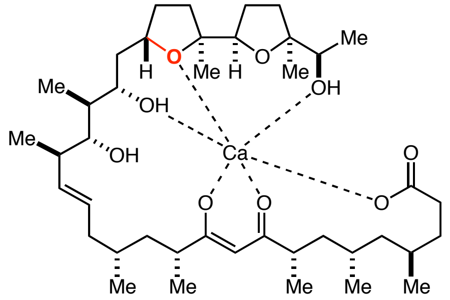
Assemblage strategy for Ring A:



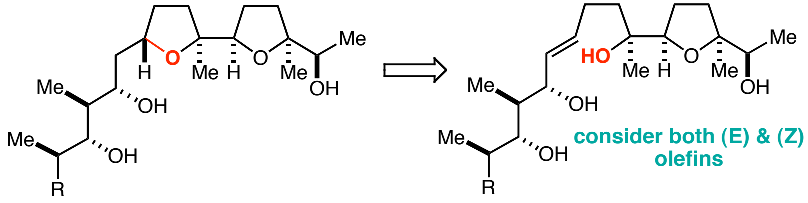
Predicted stereochemical outcome:



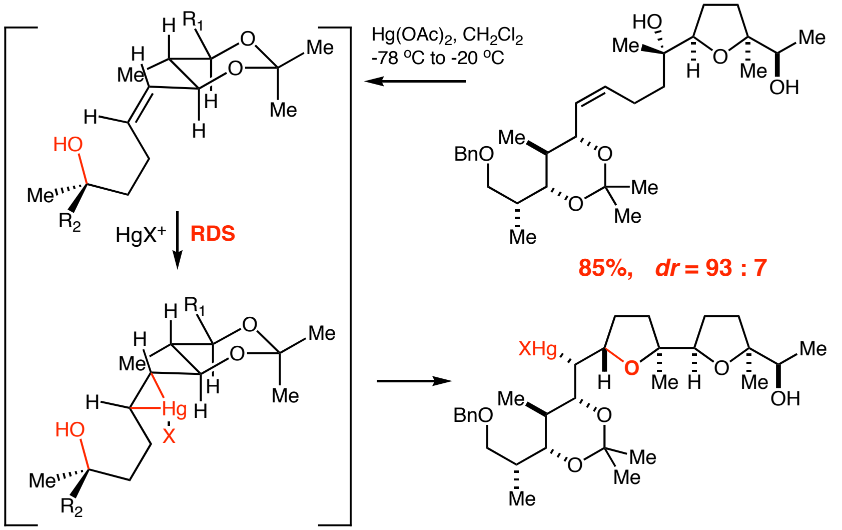
Ionomycin Synthesis (with Dow & Shih, *JACS* 1990, *112*, 5290)



Ionomycin Calcium Complex



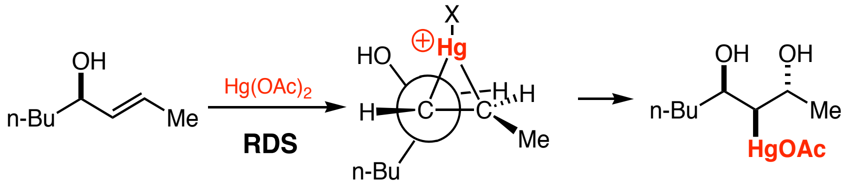
consider both (E) & (Z) olefins



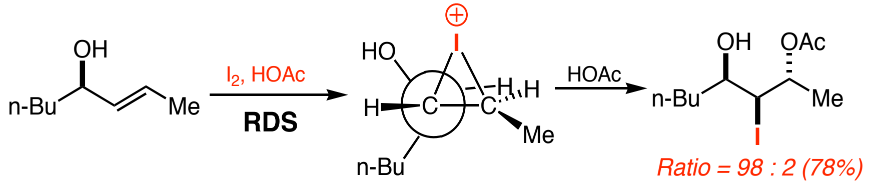
85%, *dr* = 93 : 7

Related Olefin Addition Rxns: Halogen Electrophiles

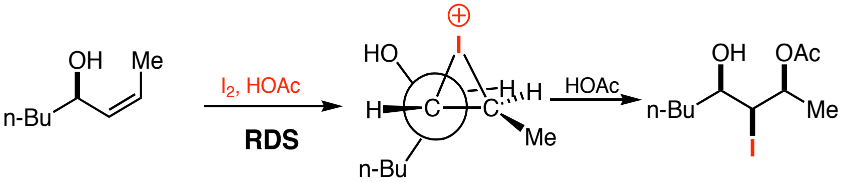
Other electrophilic olefin addition reactions afford the same stereochemical outcome



ratio = 80 :20



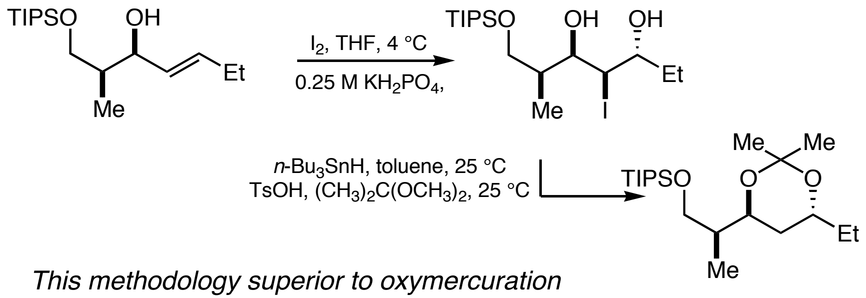
Ratio = 98 : 2 (78%)



Chamberlin, *Tetrahedron* **1984**, *40*, 2297

Ratio = 94 : 6 (85%)

Evans, Kaldor, Jones, *J. Am. Chem. Soc.* **1990**, *112*, 7001.



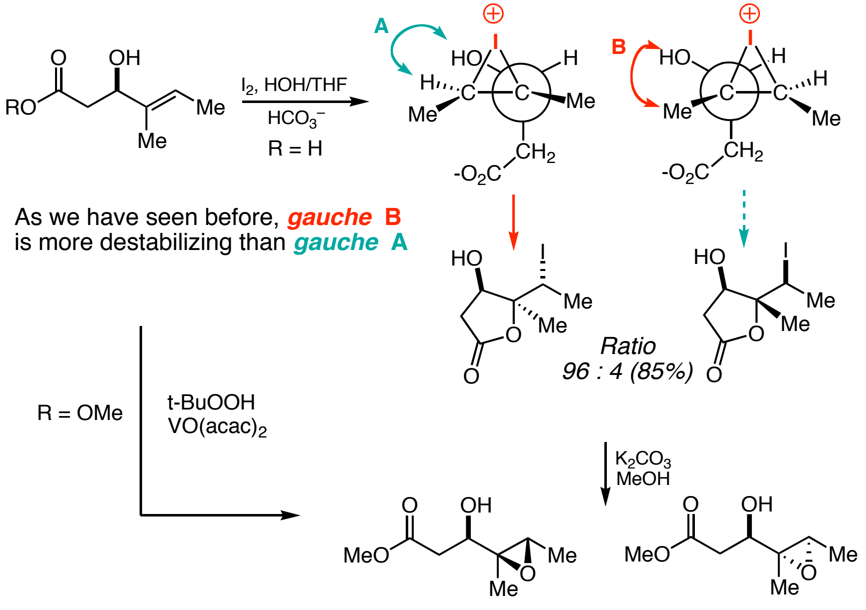
This methodology superior to oxymercuration alternative which was evaluated first

diastereoselection 96 : 4

67% overall

Iodine-induced lactonization is also highly stereoselective

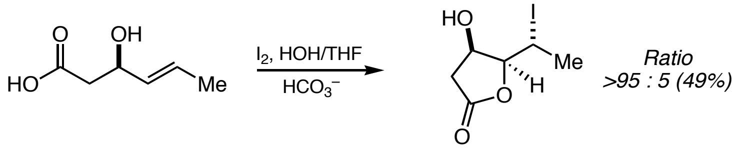
- Chamberlin (*JACS* **1983**, *105*, 5819)



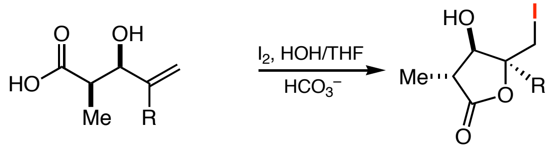
As we have seen before, ***gauche*** **B** is more destabilizing than ***gauche*** **A**

Lactonization Ratio = 96 : 4

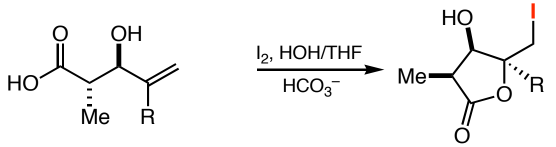
- Other cases:



Ratio
>95 : 5 (49%)



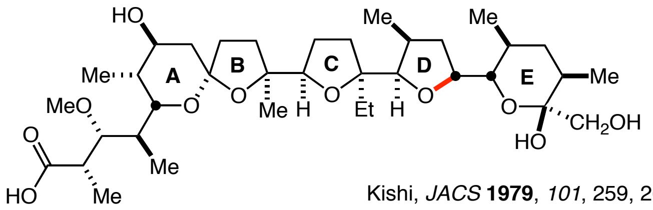
R = H: *77 : 23 (74%)*
R = Me: *42 : 58 (81%)*



R = H: *87 : 13 (41%)*
R = Me: *90 : 10 (94%)*

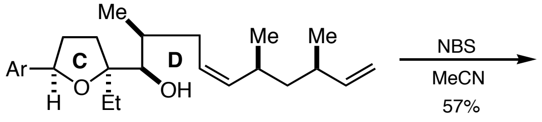
Related Olefin Addition Rxns

Halogen-induced heterocyclization in the synthesis of monensin



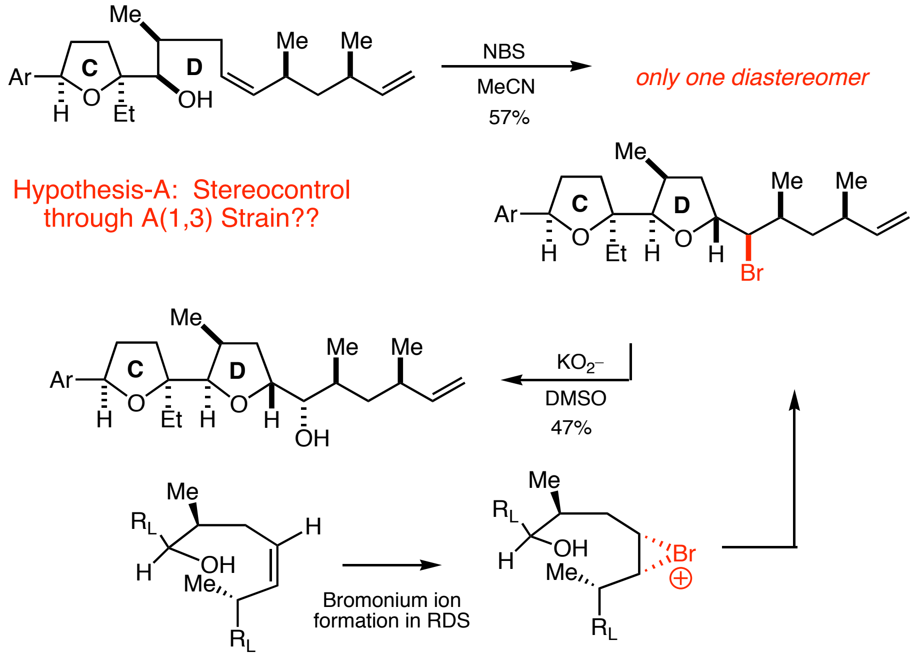
Kishi, *JACS* **1979**, *101*, 259, 260, 262
Still, *JACS* **1980**, *103*, 2117-2121

■ The Kishi Ring D Construction:



only one diastereomer

■ The Kishi Ring D Construction:

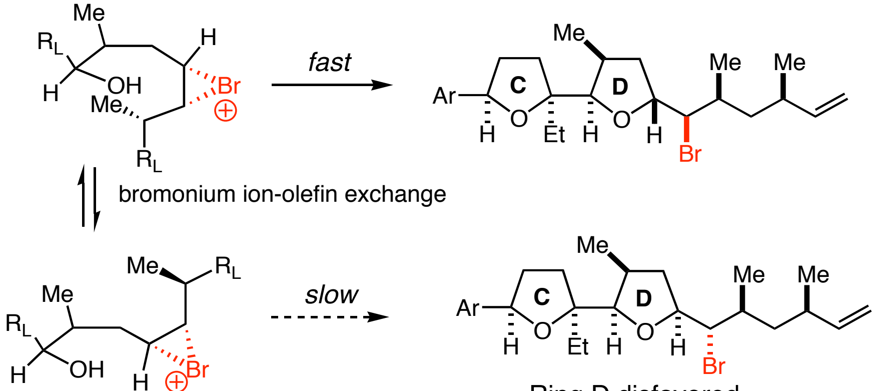


only one diastereomer

Hypothesis-A: Stereocontrol through A(1,3) Strain??

Bromonium ion formation in RDS

Hypothesis-B: Stereocontrol through Reversal of Bromonium Ion Intermediate



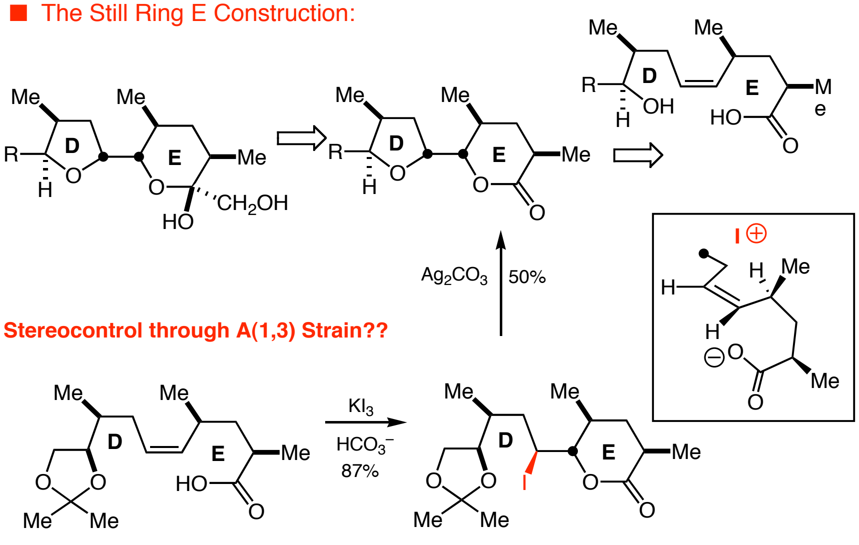
fast

bromonium ion-olefin exchange

slow

Ring D disfavored

■ The Still Ring E Construction:

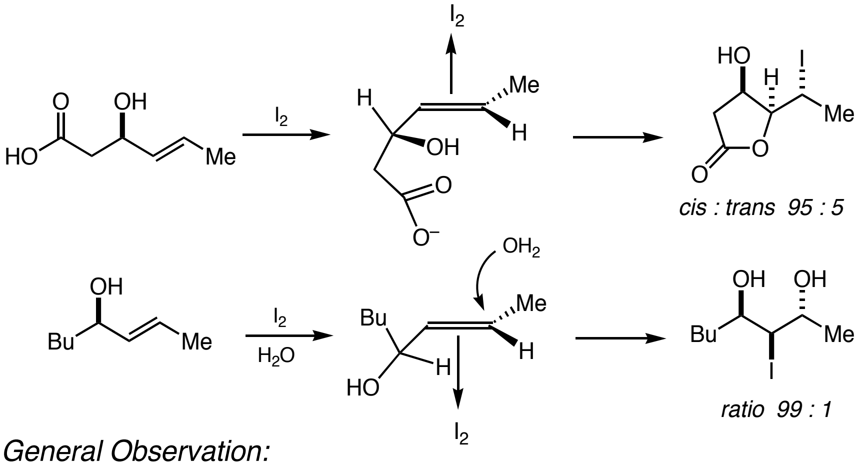


Stereocontrol through A(1,3) Strain??

EI(+)-induced heterocyclization ⇨ Cardillo, *Tetrahedron* **1990**, *46*, 3321-3408
Bartlett, *Asymmetric Synthesis* **1984**, *3*, Chap 6, 411-454

Applications in Synthesis

A complete turnover in olefin diastereofacial selectivity observed when adding *internal* and *external* nucleophiles



cis : trans 95 : 5

ratio 99 : 1

General Observation:

For electrophiles that react via onium intermediates (I_2, Br_2, $Hg(OAc)_2$, PhSeCl), the major diastereomer from electrophile-induced cyclization is **opposite** to that observed in the analogous intermolecular electrophilic addition.

For a review of elctrophilic induced olefin cyclization reactions see:
G. Cardillo & M. Orena, *Tetrahedron* **1990**, *46*, 3321.

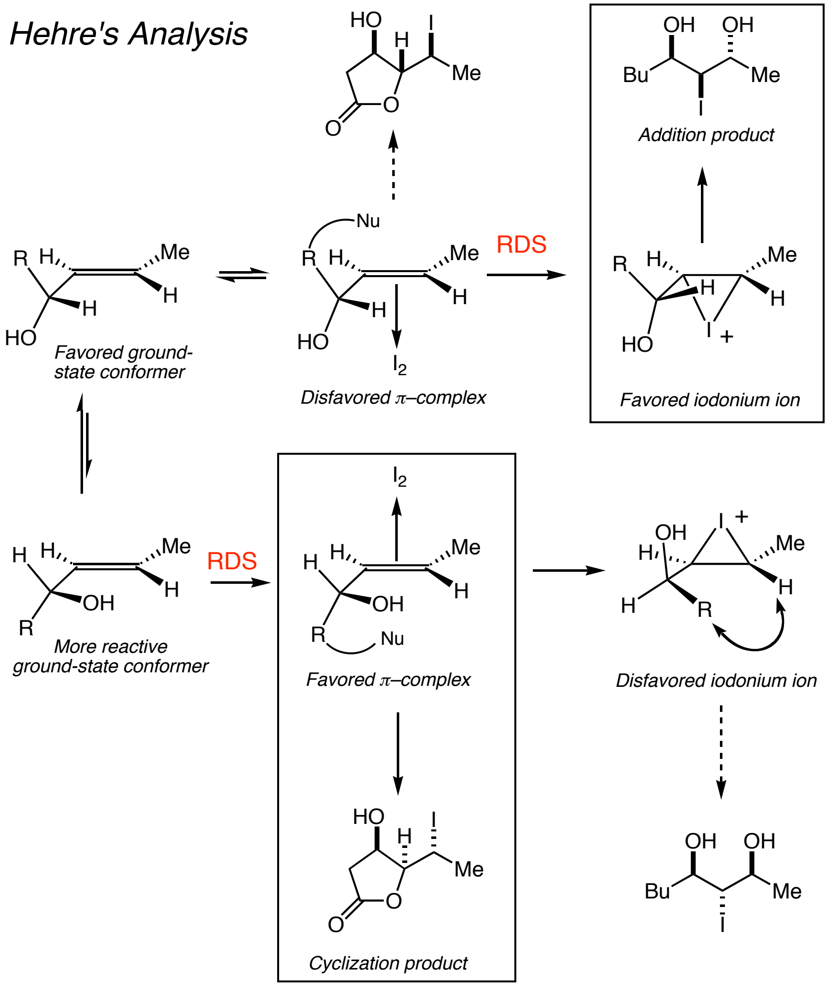
Chamberlin & Hehre's Rationalization

- "Facial preferences in electrophilic addition reactions are *not* invariant with respect to the location of the transition state along the reaction coordinate."
- *Change in diastereoselectivity is a consequence of a change in the* ***rate-limiting step***
  - Addition reactions: Formation of an **onium ion intermediate** (subsequently trapped by a Nu from the medium)
  - Cyclization reactions: Intramolecular attack on a π–**complex** (not an onium ion)
- Analysis of the stereoselectivity of electrophilic addition to chiral olefins:

  1. Relative abundances of conformational minima
  2. *Relative reactivities of the available forms*
  3. Stereoselectivies of the individual conformers

Chamberlin & Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 672-677.

Hehre's Analysis

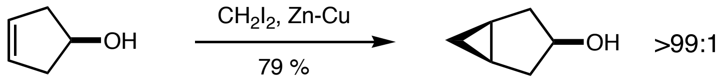


Houk: Argument for the "inside alkoxy effect" in π–complex formation

- π–complex cyclizes if R contains a Nu and its formation is rate determining
- Onium ion formation is rate determing in the addition reactions
- "The presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of transition state.

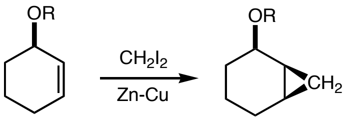
The Simmons-Smith Reaction

For a recent general review of the Simmons-Smith reaction see:
Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



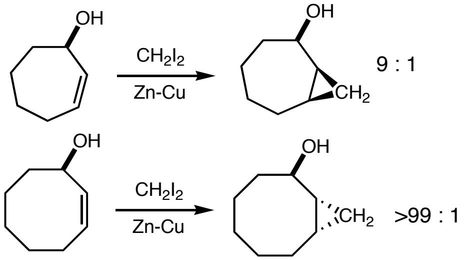
S. Winstein, *JACS* **1959**, *81*, 6523; **1961**, *83*, 3235; **1969**, *91*, 6892

A large rate acceleration relative to simple olefins was observed.

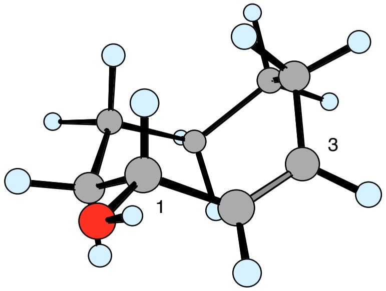


R = OMe: >99:1 Dauben, *JACS* **1963**, *85*, 468

R = OAc: 4:1 Sawada, *JOC* **1968**, *33*, 1767



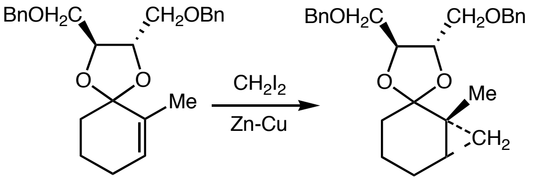
epoxidation also gives anti adduct



O–C_1–C_2–C_3 dihedral = 165 °

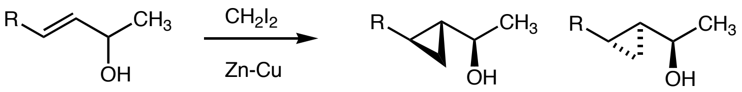
S. Winstein, *JACS*, **1969**, *91*, 6892

Absolute control of stereochemistry is possible through chiral ketal auxiliaries



diastereoselection 20:1

Yamamoto, *JACS*, **1985**, *107*, 8254
Mash, *JACS*, **1985**, *107*, 8256
Yamamoto, *Tetrahedron*, **1986**, *42*, 6458

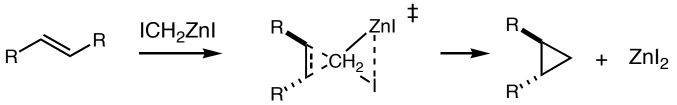


M. Pereyre and Co-workers
J. Chem. Res. (S) **1979**, 179

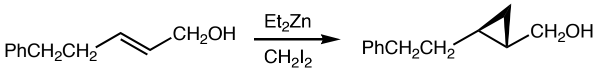
R	Ratio		
CH_3	57	:	43
Et	64	:	36
tBu	67	:	33

The classical mechanism

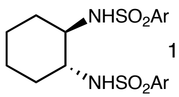
CH_2I_2 + Zn $\longrightarrow$ ICH_2ZnI



Enantioselective Simmons-Smith Variants: Kobayashi, *Tet. Let.* **1992**, *33*, 2575



80% ee (82% yield)

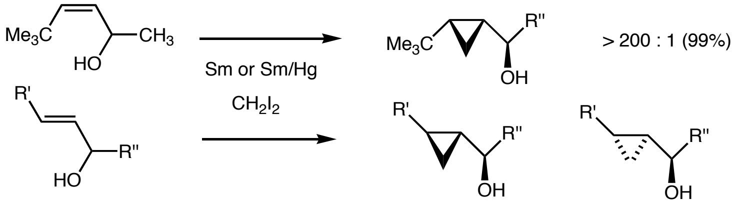


10 mol%

These results suggest that the transition state might be binuclear.

Construct a reasonable transition structure which accomdates the data

Low-valent Samarium Variants: Molander, *JOC* **1987**, *52*, 3942



> 200 : 1 (99%)

Isolated alkenes and homoallylic alcohols are inert to these reaction conditions.

G. A. Molander and J. B. Etter
J. Org. Chem. **1987**, *52*, 3942

R'	R''	Ratio		
Ph	nBu	1	:	1.4
Ph	iPr	> 200	:	1
Ph	tBu	> 200	:	1
tBu	CH_3	1	:	5.1
tBu	iPr	> 200	:	1

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 11

Pericyclic Reactions–1

- Introduction to Pericyclic Reactions
- Electrocyclic Reactions
- Sigmatropic Reactions
- Cycloaddition Reactions

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Wednesday,
October 11, 2006

Other Reading Material:

- Woodward-Hoffmann Theory
  R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.

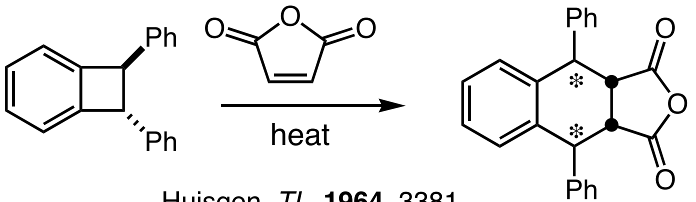
- Frontier Molecular Orbital Theory
  I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.

- Dewar-Zimmerman Theory
  T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, Harper & Row, New York, 1987.

- General Reference
  R. E. Lehr and A. P. Marchand, *Orbital Symmetry: A Problem Solving Approach*, Academic Press, New York, 1972.

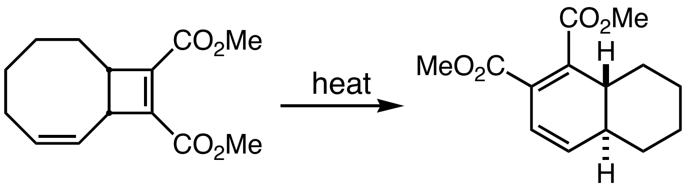
Problems of the Day:

Predict the stereochemical outcome of this reaction.



Huisgen, *TL*, **1964**, 3381.

Suggest a mechanism for the following reaction.



Bloomfield, *TL*, **1969**, 3719.

Pericyclic Reactions - Introduction/Definitions

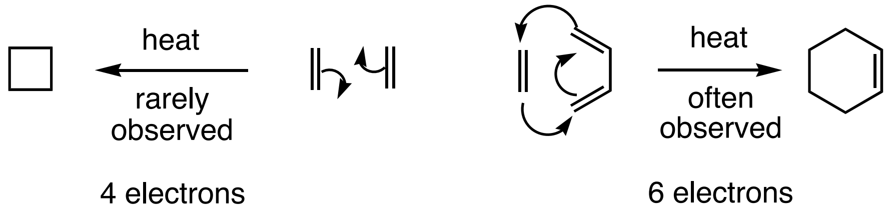
A pericyclic reaction is characterized as a change in bonding relationships that takes place as a ***continuous, concerted reorganization of electrons***.

The term "***concerted***" specifies that there is ***one single transition state*** and therefore ***no intermediates*** are involved in the process. To maintain ***continuous electron flow***, pericyclic reactions occur through ***cyclic transition states***.

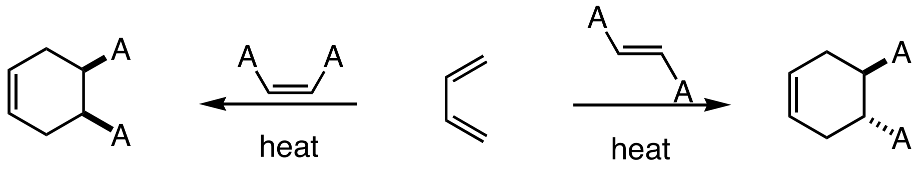
More precisely: The cyclic transition state must correspond to an arrangement of the ***participating orbitals*** which has to ***maintain a bonding interaction*** between the reaction components throughout the course of the reaction.

Some factors to consider in our analysis:

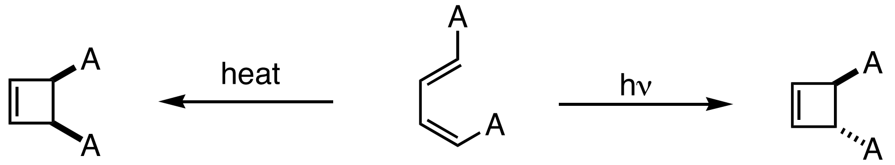
The number of electrons involved has a profound influence on reactivity:



Pericyclic reactions are stereospecific:



Reactions behave differently depending on the conditions used (i.e. thermal versus photochemical conditions):



The Theories:

Three theories are commonly used to explain and predict pericyclic reactions. We will only concern ourselves with two of these theories.

1) Fukui: Frontier Molecular Orbital Interactions

Much easier to use than the original orbital symmetry arguments

HOMO/LUMO interactions

2) Dewar-Zimmerman: Aromatic Transition States

The easiest to apply for all reaction types, but it is not as easy to understand why it it valid

Aromatic or antiaromatic transition states

3) Woodward-Hoffmann: Conservation of Orbital Symmetry

First theory to explain and predict the outcome of many reactions

Correlation diagrams

The Five Major Classes of Pericyclic Reactions

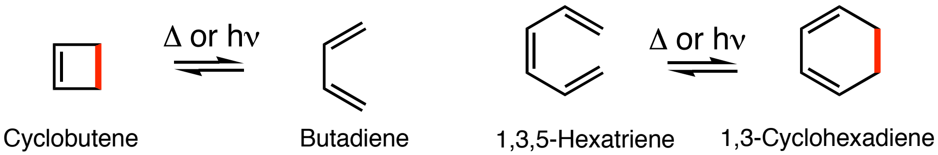
(1) ELECTROCYCLIC RING CLOSURE/RING OPENING:

An electrocyclic ring closure is the creation of a new sigma bond at the expense of the terminal p orbitals of a conjugated pi system. There is a corresponding reorganization of the conjugated pi system. We classify the reaction according to the number of electrons involved.

Examples:

A 4 e^- electrocyclic reaction

A 6 e^- electrocyclic reaction



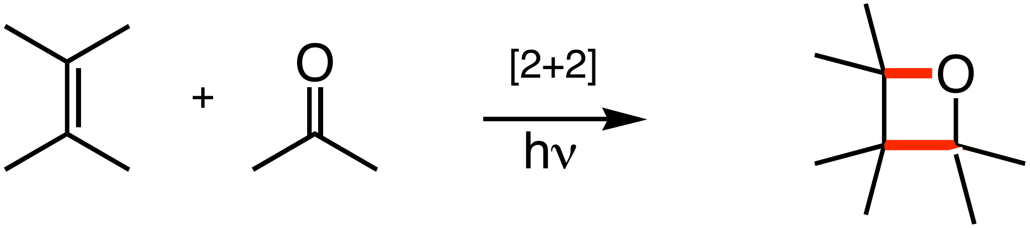
(2) CYCLOADDITION REACTIONS/CYCLOREVERSION REACTIONS:

A cycloaddition reaction is the union of two smaller, independent pi systems. Sigma bonds are created at the expense of pi bonds.

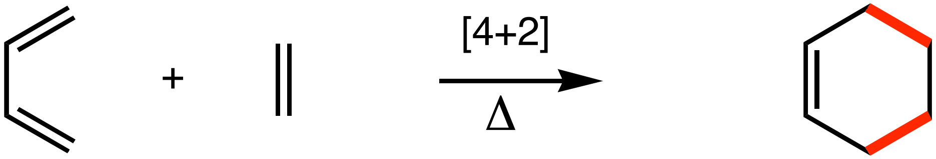
Cycloaddition reactions are referred to as [**m + n**] additions when a system of **m** conjugated *atoms* combines with a system of **n** conjugated *atoms*.

A cycloreversion is simply the reverse of a cycloaddition.

Examples:



A 2+2 cycloaddition.
The Paterno-Büchi
reaction.



A 4+2 cycloaddition.
The Diels-Alder reaction.

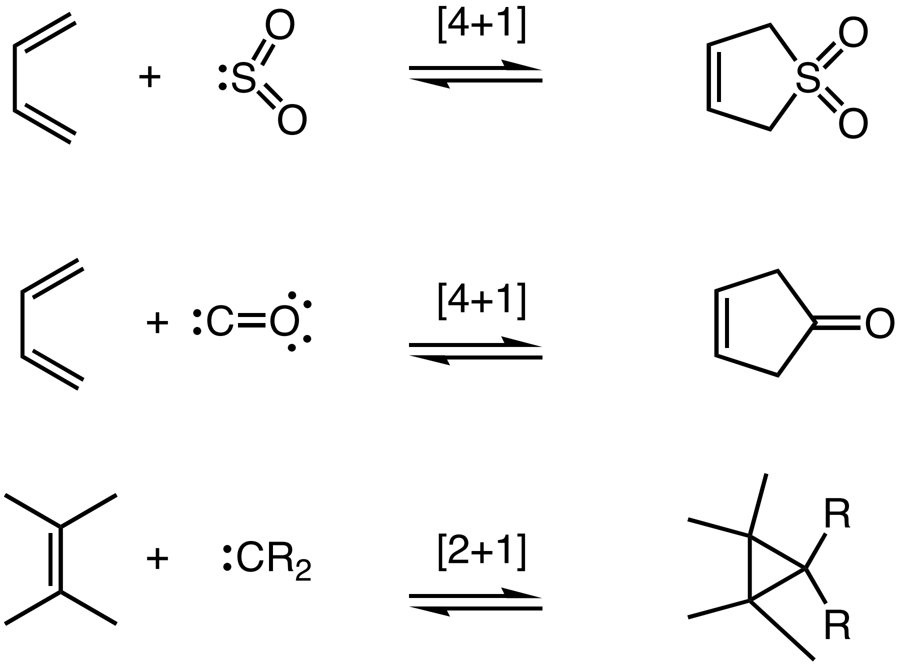
(3) CHELETROPIC REACTIONS:

Cheletropic reactions are a special group of cycloaddition/cycloreversion reactions.

Two bonds are formed or broken at a single atom.

The nomenclature for cheletropic reactions is the same as for cycloadditions.

Examples:



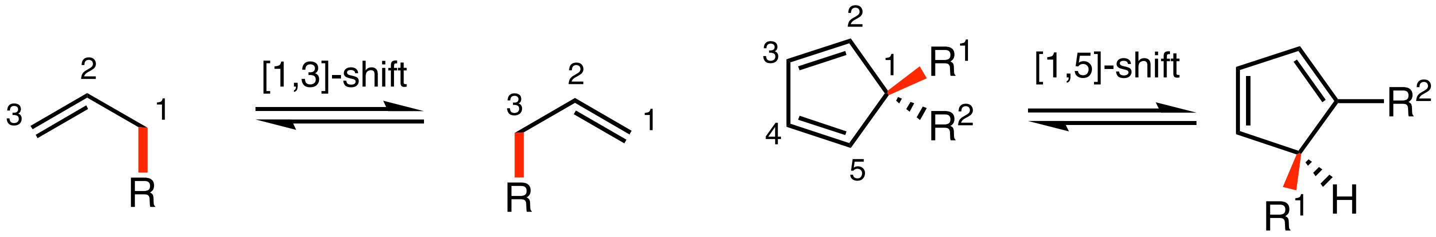
(4) SIGMATROPIC REARRANGEMENTS:

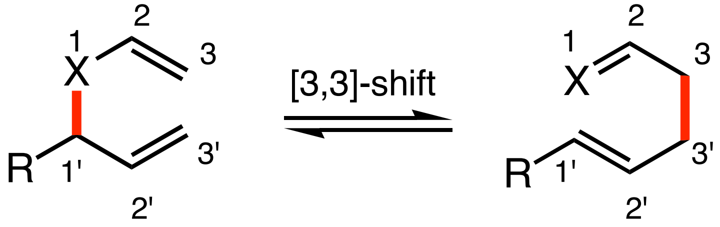
A sigmatropic rearrangement is the migration of a sigma bond from one position in a conjugated system to another position in the system, accompanied by reorganization of the connecting pi bonds.

The number of pi and sigma bonds remains constant.

The rearrangement is an [**m,n**] shift when the sigma bond migrates across **m** atoms of one system and **n** atoms of the second system.

Examples:





$X=CR_2$, Cope rearrangement

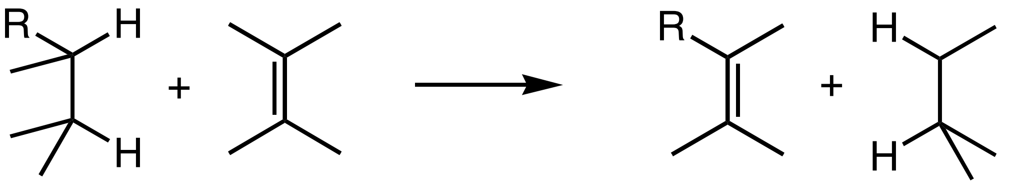
X=O, Claisen rearrangement

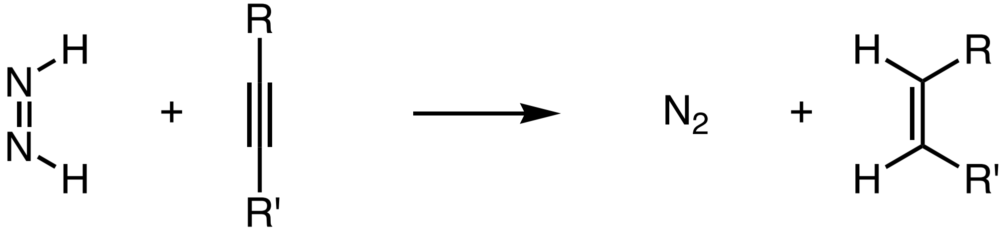
(5) GROUP TRANSFER REACTIONS:

In a group transfer reaction one or more groups get transferred to a second reaction partner.

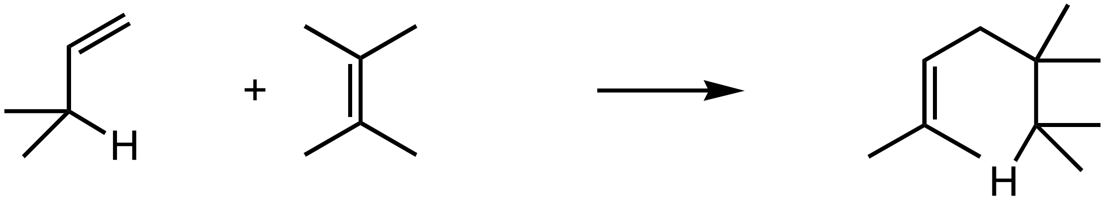
Examples:

Hydrogen Transfer:





Ene Reaction:



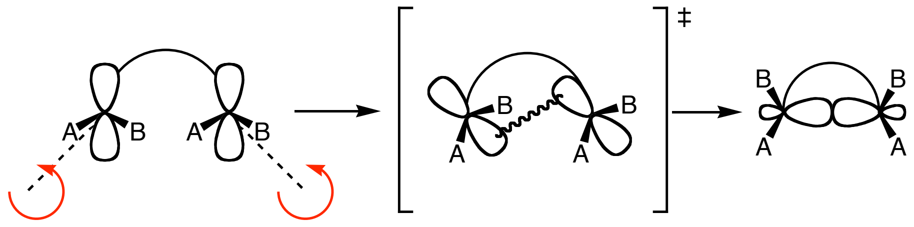
ELECTROCYCLIC RING CLOSURE/RING OPENING:

The Stereochemical issues:

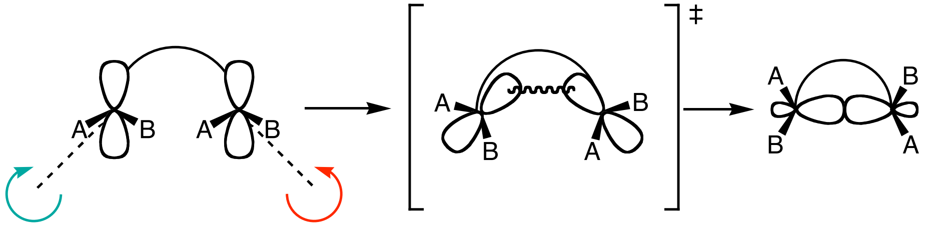
Ring closure can occur in two distinct ways. This has consequences with regard to:

- ■ The orbital lobes that interact
- ■ The disposition of substituents on the termini

Conrotatory Closure: The termini rotate in the **same direction**



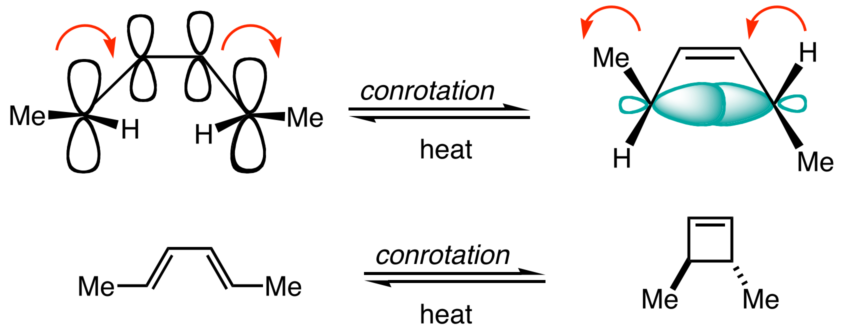
Disrotatory Closure: The termini rotate in **opposite directions**



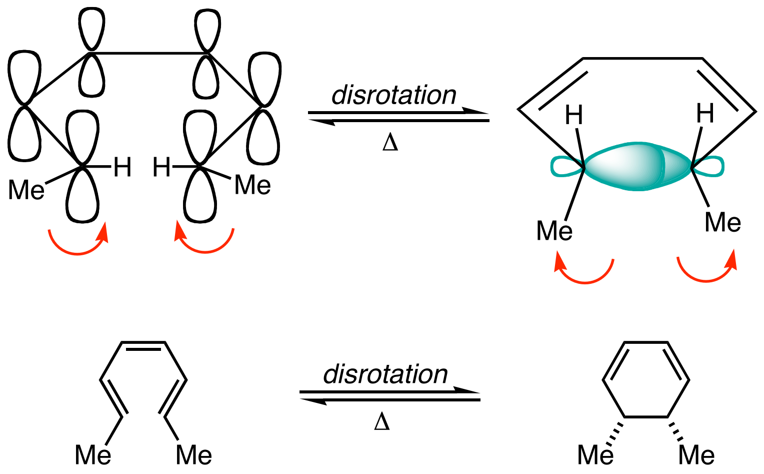
Empirical Observations:

It was noted that butadienes undergo conrotatory closure under thermal conditions, while hexatrienes undergo disrotatory closure under thermal conditions. The microscopic reverse reactions also occur with the same rotational sense (i.e. cyclobutenes open in a conrotatory sense when heated, and cyclohexadienes open in a disrotatory sense when heated.)

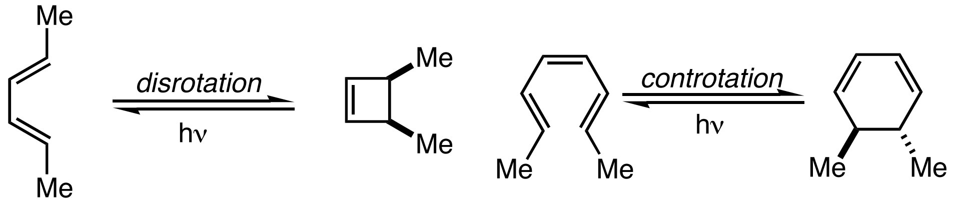
Butadiene to cyclobutene: A 4-electron (4q) system



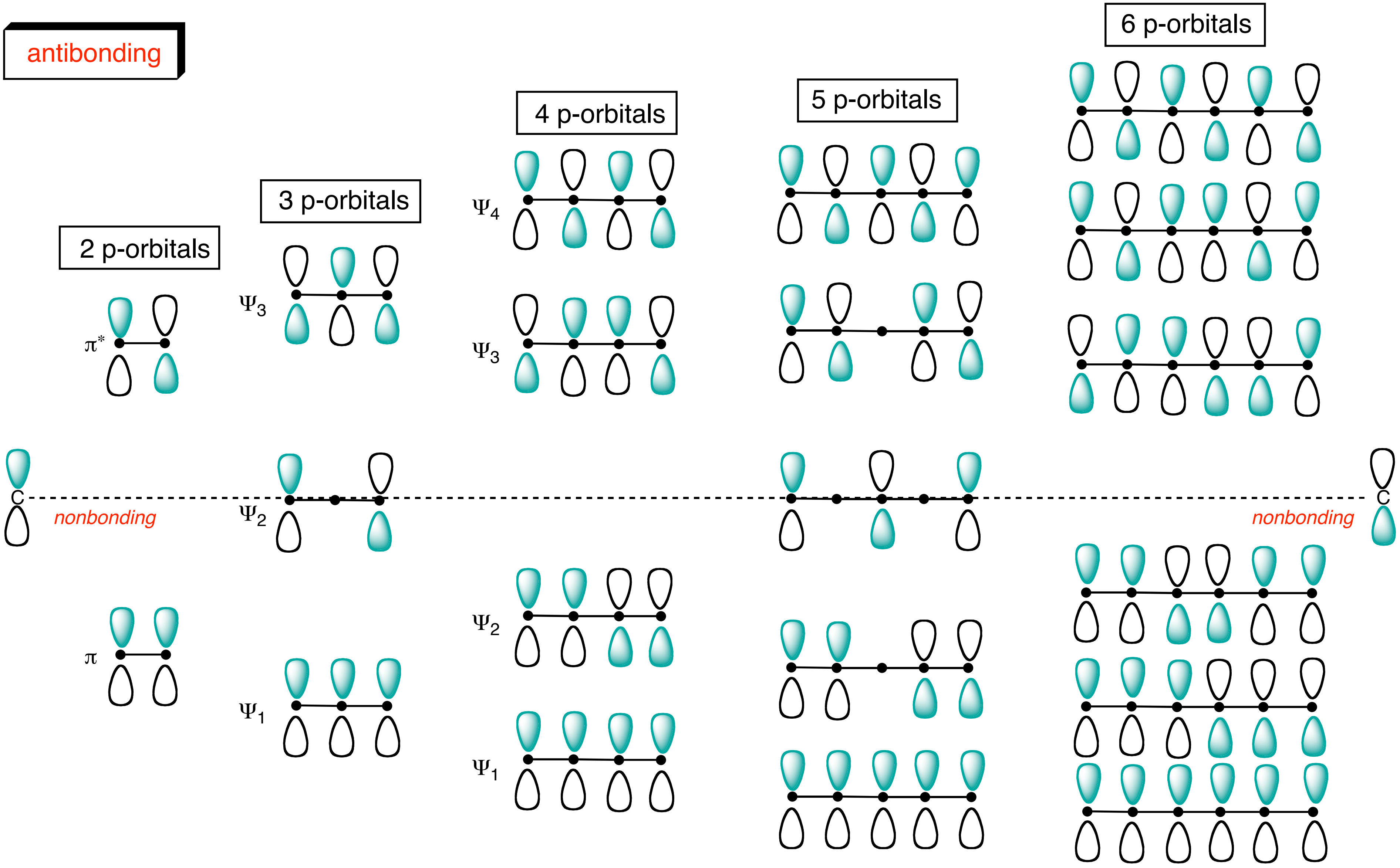
Hextriene to cyclohexadiene: A 6-electron (4q+2) system



It was also noted that changing the "reagent" from heat to light reversed this reactivity pattern. Under photochemical conditions 4 electron systems undergo disrotatory motion, while 6 electron systems undergo conrotatory motion.



Conjugated pi systems



bonding

There are no nodal planes in the most stable bonding MO. With each higher MO, one additional nodal plane is added. The more nodes, the higher the orbital energy.

FMO Treatment of Electrocyclic reactions.

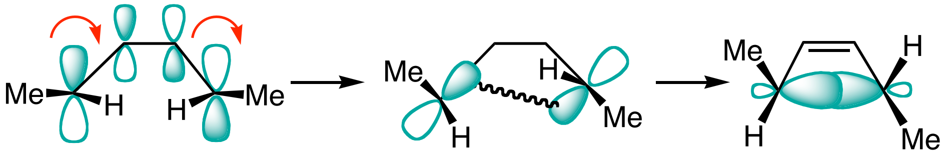
Examine the interactions that occur in the HOMO as the reaction proceeds.

If the overlap is constructive (i.e. same phase) then the reaction is "allowed."

If the overlap is destructive (different phases) then the reaction is "forbidden."

Thermal Activation:

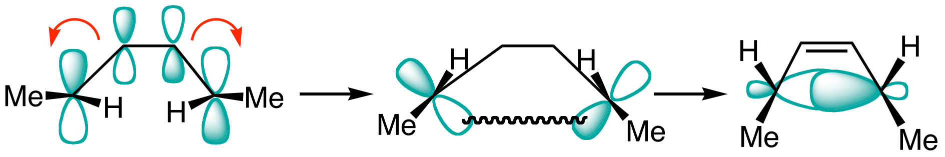
Conrotatory Closure: (Allowed and observed)



Ψ_2 (diene HOMO)

Constructive overlap

Disrotatory Closure: (Forbidden and not observed)



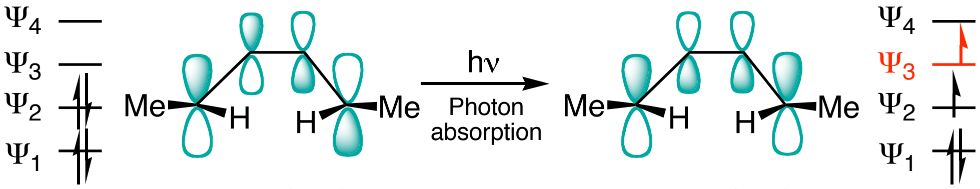
Ψ_2 (diene HOMO)

Destructive overlap

A similar analysis for the hexatriene system proves that under thermal conditions, disrotation is allowed and conrotation is forbidden.

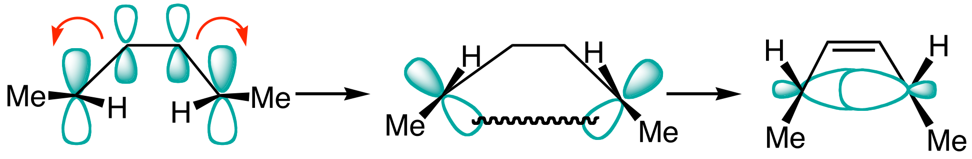
Photochemical Activation:

When light is used to initiate an electrocyclic rxn, an electron is excited from Ψ_2 to Ψ_3. Treating Ψ_3 as the HOMO now shows that disrotatory closure is allowed and conrotatory closure is forbidden.



Ψ_2 (HOMO) Ψ_3 (HOMO)

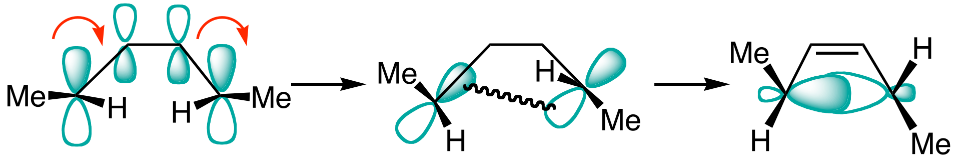
Disrotatory Closure: (Allowed and observed)



Ψ_3 (new HOMO)

Constructive overlap

Conrotatory Closure: (Forbidden and not observed)



Ψ_3 (new HOMO)

Destructive overlap

We have so far proven which *ring closures* are allowed and which are forbidden. Do we now have to go back and examine all the *ring openings*?

NO!

The principle of microscopic reversiblity says that if the reaction is allowed in one direction, it must be allowed in the other direction.

The Dewar-Zimmerman analysis is based on identifying transition states as aromatic or anti-aromatic. We will not go into the theory behind why this treatment works, but it will give the same predictions as **FMO** or **Orbital Symmetry** treatments, and is fundamentally equivalent to them.

Using the Dewar-Zimmerman Model:

Choose a basis set of 2p atomic orbitals for all atoms involved (1s for hydrogen atoms).

Assign phases to the orbitals. Any phases will suffice. It is **not** important to identify this basis set with any molecular orbital.

Connect the orbitals that interact in the starting compound, before the reaction begins.

Allow the reaction to proceed according to the geometry postulated. Connect those lobes that begin to interact that were not interacting in the starting materials.

Count the number of phase inversions that occur as the electrons flow around the circuit. Note that a phase inversion **within** an orbital **is not counted**.

Based on the phase inversions, identify topology of system.

Odd number of phase inversions: **Möbius topology**

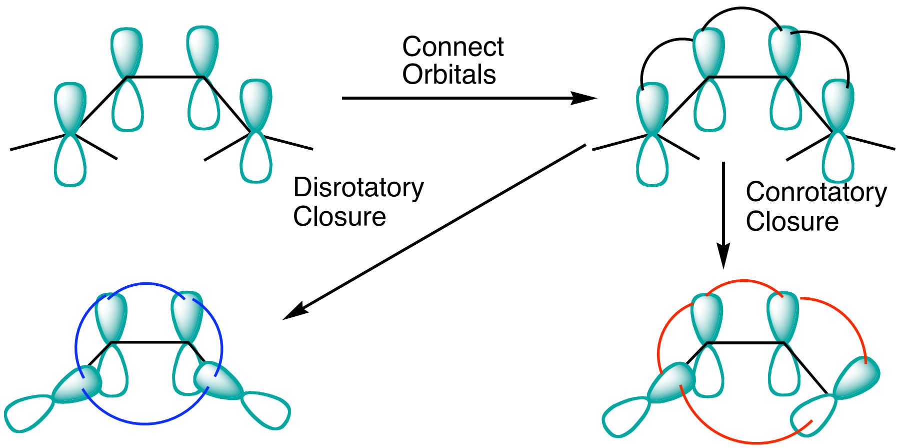
Even number of phase inversions: **Hückel topology**

Assign the TS as aromatic or antiaromatic, based on number of electrons present.

System	Aromatic	Antiaromatic
Hückel	4q + 2	4q
Möbius	4q	4q + 2

If **TS** is aromatic, then the rxn will be thermally allowed.

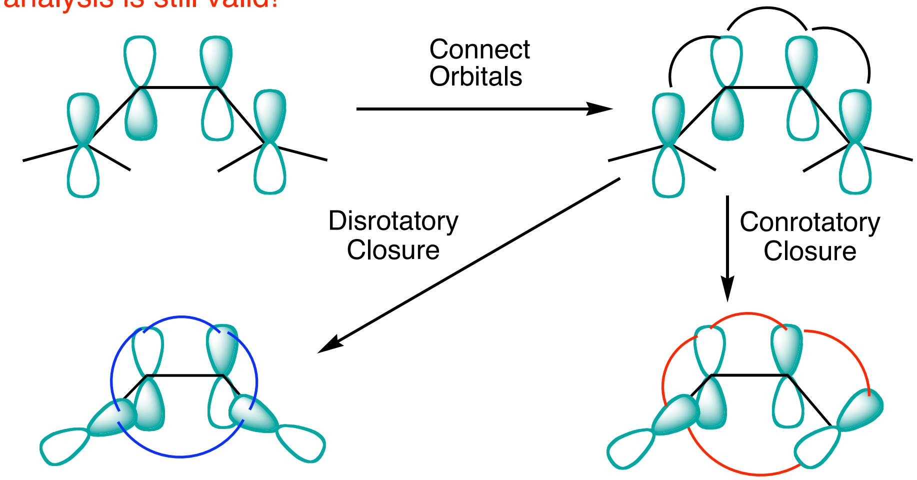
If **TS** is antiaromatic, then the rxn will be photochemically allowed.



Zero Phase Inversions
∴Hückel Topology
4 electrons in system
∴ Antiaromatic and
Forbidden

One Phase Inversion
∴Möbius Topology
4 electrons in system
∴ Aromatic and
Allowed

Note that I can change the phase of an abitrary orbital and the analysis is still valid!



Two Phase Inversions
∴Hückel Topology
4 electrons in system
∴ Antiaromatic and
Forbidden

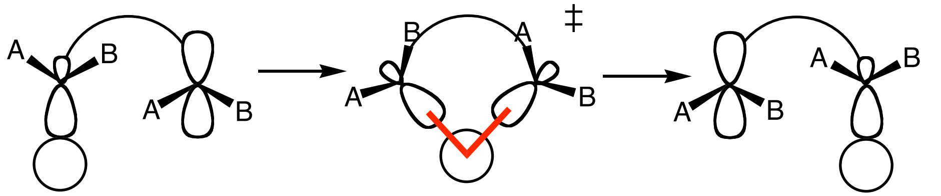
Three Phase Inversions
∴Möbius Topology
4 electrons in system
∴ Aromatic and
Allowed

[1,3]-Sigmatropic Rearrangements: FMO Analysis

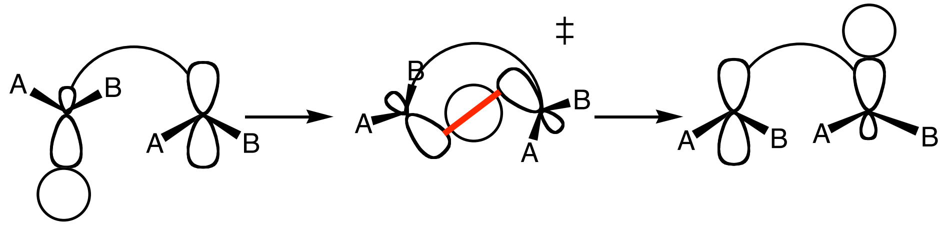
The Stereochemical issues:

The migrating group can move across the conjugated pi system in one of two ways. If the group migrates on the same side of the system, it is said to migrate **suprafacially** with respect to that system. If the group migrates from one side of the pi system to the other, it is said to migrate **antarafacially**.

Suprafacial migration: The group moves across the same face.



Antarafacial migration: The group moves from one face to the other.



Sigmatropic Rearrangements: FMO Analysis

Imagine the two pieces fragmenting into a cation/anion pair, (or radical pair) next examine the HOMO/LUMO interaction.

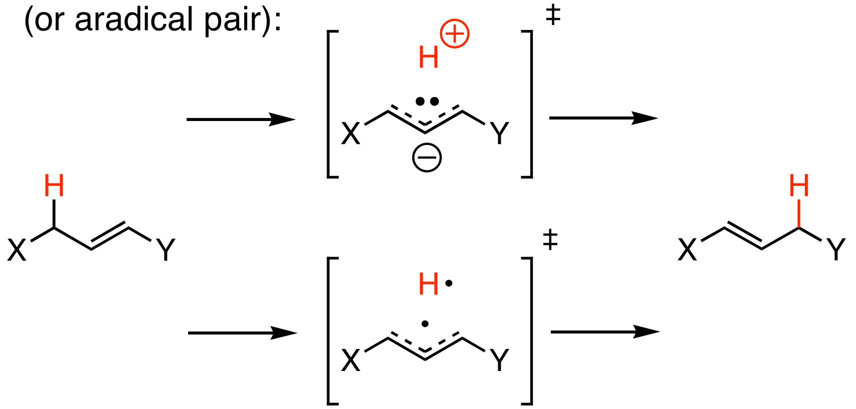
If the overlap is constructive at both termini then the reaction is allowed. If the overlap is destructive at either terminus then the reaction is forbidden.

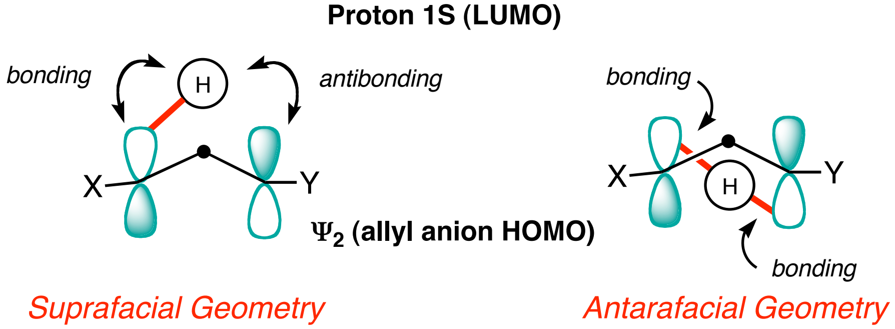
If the migrating atom is carbon, then we can also entertain the possiblity of the alkyl group migrating with inversion of configuration (antarafacial on the single atom).

If the migrating atom is hydrogen, then it cannot migrate with inversion.

[1,3] Sigmatropic Rearrangements (H migration)

Construct TS by considering an allyl anion and the proton (or aradical pair):





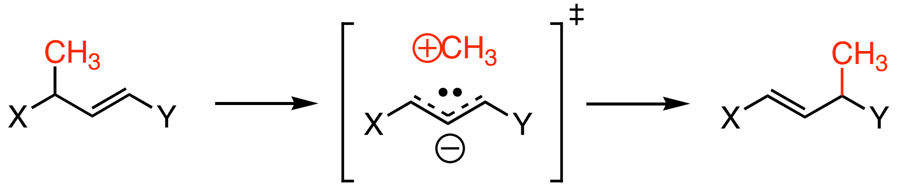
The analysis works if you consider the other ionic reaction, or consider a radical reaction. In each case it is the same pair of orbitals interacting.

Suprafacial migration is forbidden and the bridging distance too great for the antarafacial migration. Hence, [1,3] hydrogen migrations are not observed under thermal conditions.

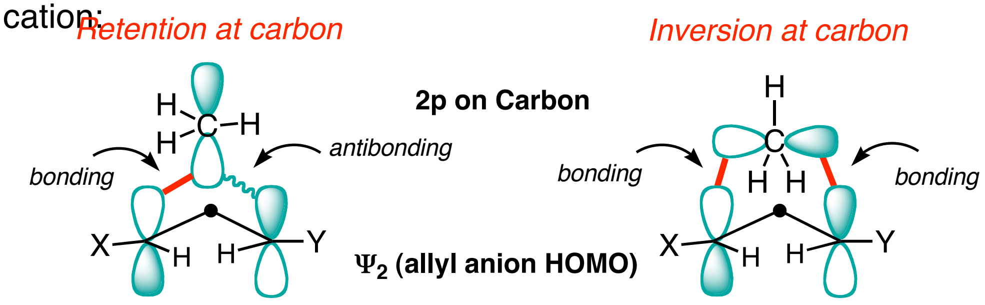
Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially. How would you predict this using FMO?

[1,3]-Sigmatropic Rearrangements

[1,3] Sigmatropic Rearrangements (C migration)



Construct TS by considering an allyl anion and the methyl cation;



Suprafacial on allyl fragment *Suprafacial on allyl fragment*

The analysis works if you consider the other ionic reaction, or consider a radical reaction. In each case it is the same pair of orbitals interacting.

Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially with retention of stereochemistry.

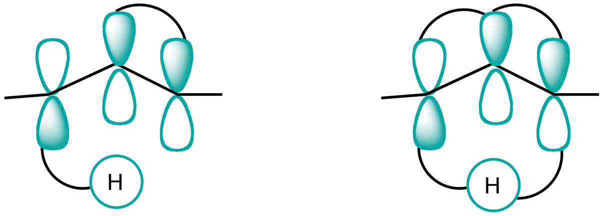
Stereochemical constraints on the migration of carbon with inversion of configuration is highly disfavored on the basis of strain. Such rearrangements are rare and usually only occur in highly strained systems.

Using a similar analysis, one can prove that [1,5] hydrogen and alkyl shifts should be allowed when suprafacial on the pi component and proceeding with retention. Refer to Fleming for more applications of FMO theory to [1,n] sigmatropic shifts.

Sigmatropic Rearrangements: Dewar-Zimmerman

D–Z also predicts [1,3] suprafacial migration to be forbidden.

The basis set of s and p orbitals with arbitrary phase:

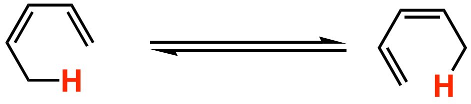


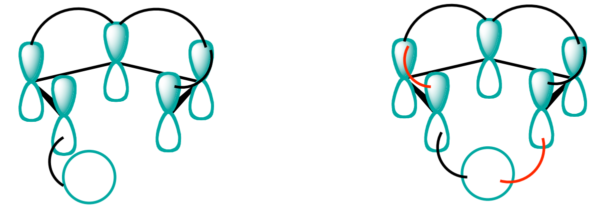
Orbital interactions in the parent system

Completing the circuit across the bottom face

Two Phase Inversions
Hückel Topology
Four Electrons
Forbidden thermally

The [1,5] shift of a hydrogen atom across a diene.





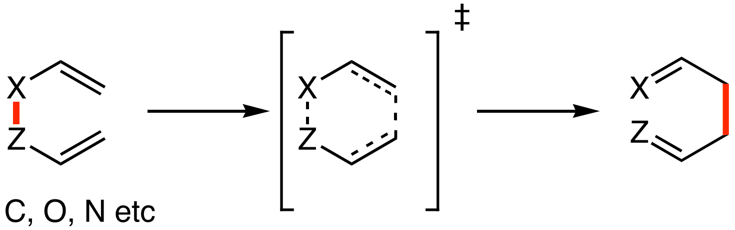
Orbital interactions in the parent system

Completing the circuit across the bottom face

Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

[3,3] Rearrangements:

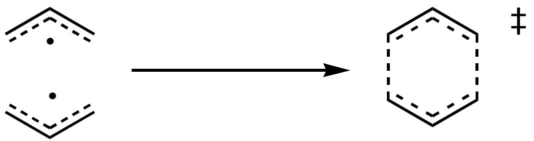
A thermally allowed reaction is possible in either of two geometries, the "chair" or the "boat" geometry. Depicted below is the "chair" geometry. You should be able to work out the details of the "boat" geometry yourself.

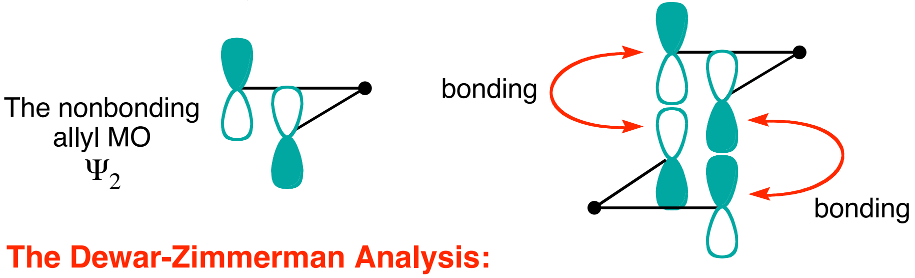


X & Z = C, O, N etc

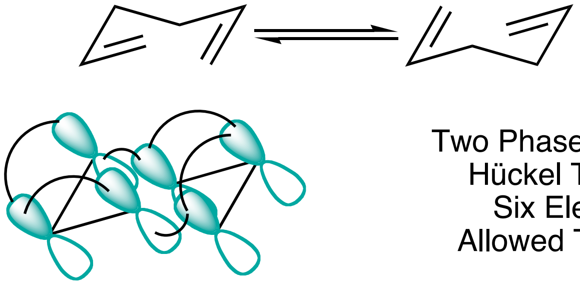
The FMO Analysis:

Bring two Allyl radicals together to access for a possible bonding interaction between termini.





The Dewar-Zimmerman Analysis:



Two Phase Inversions
Hückel Topology
Six Electrons
Allowed Thermally

■ The Toggle Algorithm:

The toggle algorithm is a simple way to take one reaction of each class that you remember is allowed (or forbidden) and derive if the reaction is allowed or forbidden under new conditions.

■ How does it work?

All of the various parameters of the pericyclic reaction are the input variables, the "switches."
The output is either "allowed" or "forbidden."
Write out all the relevant parameters of a reaction together with the known result.
Each time you change a parameter by one incremental value ("toggle a switch"), the output will switch.
This is the prediction of the reaction under the new parameters.

■ So it's nothing really new, is it?

No, its just a convenient way to rederive predictions without memorizing a table of selection rules.

An Example:

Take the [1,3] sigmatropic rearrangement of an alkyl group. We know this is forbidden under thermal conditions in a supra-supra manner, and so we make it the first entry in the table.

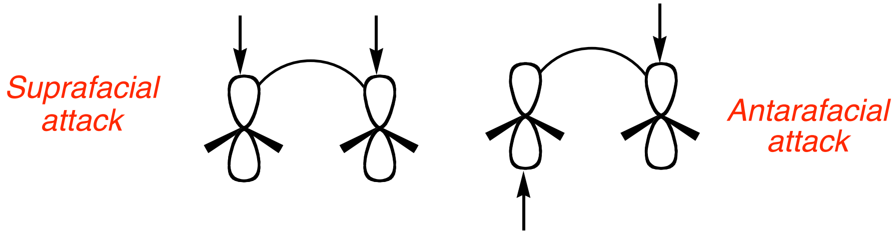
Rearrangement	Conditions	Component 1	Component 2	Output
[1,3]	Heat	Suprafacial	Suprafacial	Forbidden
[1,3]	Heat	Antarafacial	Suprafacial	Allowed
[1,3]	Light	Antarafacial	Suprafacial	Forbidden
[1,5]	Heat	Suprafacial	Suprafacial	?

Each incremental change in the "input" registers changes the "output" register by one. Multiple changes simply toggle the output back and forth. What is the prediction in the last line?

Cycloaddition Reactions

The Stereochemical issues:

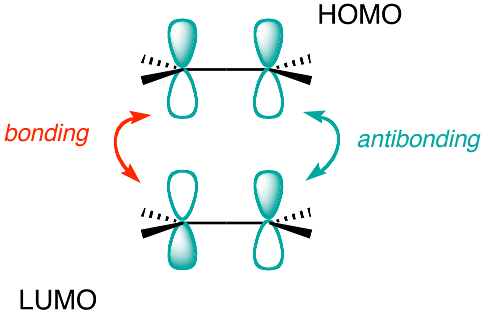
In a cycloaddition, a pi system may be attacked in one of two distinct ways. If the pi system is attacked from the same face, then the reaction is **suprafacial** on that component. If the system is attacked from opposite faces, then the reaction is **antarafacial** on that component.



The [2+2] Cycloaddition: FMO Analysis

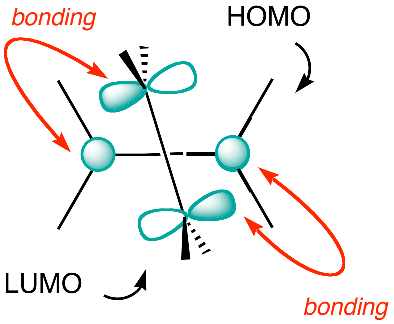
For the [2+2] cycloaddition two different geometries have to be considered.

Suprafacial/Suprafacial



Forbidden

Antarafacial/Suprafacial

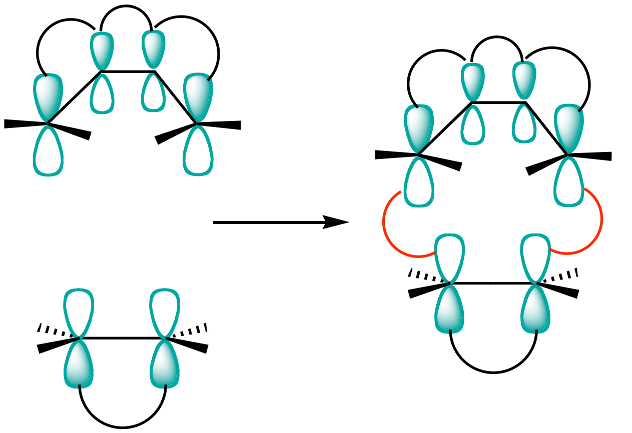


Allowed

The simplest approach (Supra/Supra) is forbidden under thermal activation. The less obvious approach (Antara/Supra) is allowed thermally but geometrically rather congested. It is believed to occur in some very specific cases (e.g. ketenes) where the steric congestion is reduced.

The [4+2] Cycloaddition: Dewar-Zimmerman

The most well known cycloaddition is the Diels-Alder reaction between a four pi component (the diene) and a two pi component (the dienophile). An exhaustive examination of this reaction is forthcoming, so we will limit ourselves to a simple examination.



Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

Summary:

- There are three fundamentally equivalent methods of analyzing pericyclic reactions: Two are much simpler than the third.
  - Fukui Frontier Molecular Orbital Theory
  - Dewar-Zimmerman Hückel-Möbius Aromatic Transition States
  - Woodward-Hoffmann Correlation Diagrams

- Some methods are easier to use than others, but all are equally correct and no one is superior to another. Conclusions drawn from the correct application of one theory will not be contradicted by another theory.

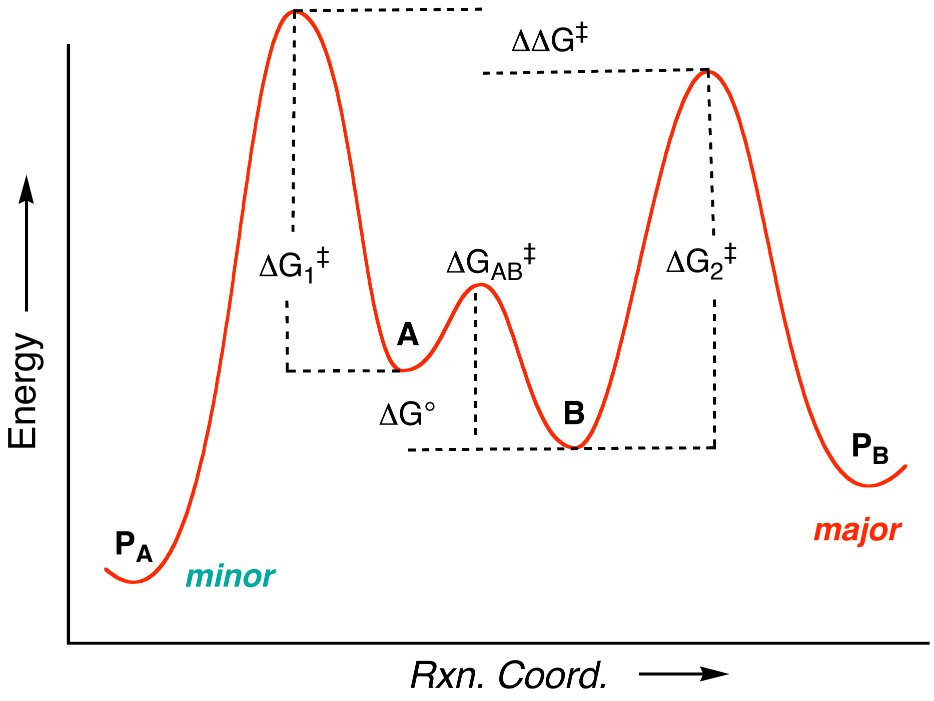
- The principle of microscopic reversibility allows us to look at a reaction from either the forward direction or the reverse direction.

- There is a general trend that reactions will behave fundamentally different under thermal conditions and photochemical conditions.

Question 3. (15 points). Assume that you have a rapidly equilibrating mixture of two conformers **A** and **B** from which two products, $\mathbf{P_A}$ and P_B are produced (eq 1). In the case at hand, $k_2 > k_1$.

$$\mathbf{P_A} \xleftarrow[\boxed{\text{slower}}]{k_1} \mathbf{A} \underset{\text{fast}}{\underset{k_B}{\overset{k_A}{\rightleftharpoons}}} \mathbf{B} \xrightarrow[\boxed{\text{slow}}]{k_2} \mathbf{P_B} \qquad (1)$$

Part A. (10 points). Draw an energy diagram that reflects the situation where the equilibrium population of conformers is the same as the product ratio.



Exam Average

73.5

Part B. (5 points). Provide a concise statement of this circumstance in terms of free energy relationships.

Under this constraint, $\Delta G_1^{\ddagger}$ must equal $\Delta G_2^{\ddagger}$. Accordingly, $\Delta\Delta G^{\ddagger}$ will equal $\Delta G°$.

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 12

Pericyclic Reactions–2

- Electrocyclic Reactions
- Cheletropic Reactions

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

"Electronic Control of Stereoselectivities of Electrocyclic Reactions of Cyclobutenes: A Triumph of Theory in the Prediction of Organic Reactions" Houk et al. *Accounts Chem. Res.* **1996**, *29*, 471-477 **(handout)**

"Some New Nazarov Chemstry," Tius, *Eur. J. Chem*. **2005,** 2193-2206 **(pdf)**

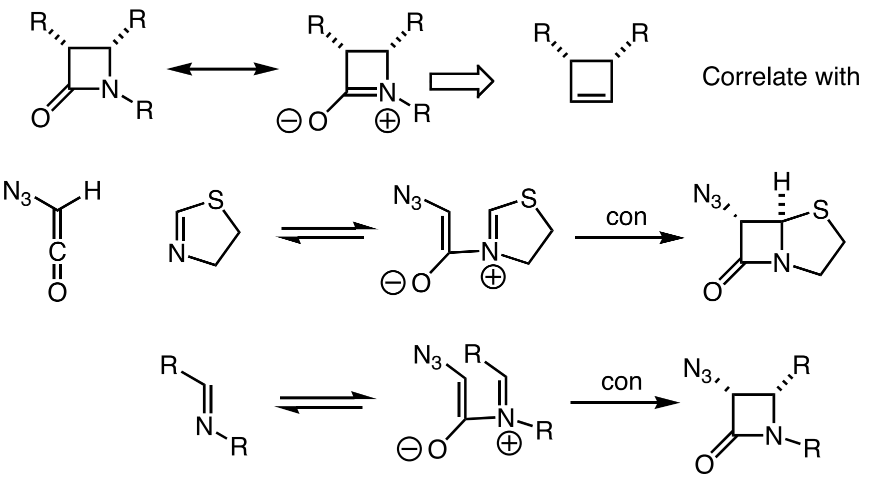
C. Palomo, "Asymmetric Synthesis of β-Lactams by Stauginger Ketene-Imine Cycloaddition Reaction, Eur. *J. Org. Chem.* **1999,** 3223-3235 **(pdf)**

D. A. Evans

Monday,
October 16, 2006

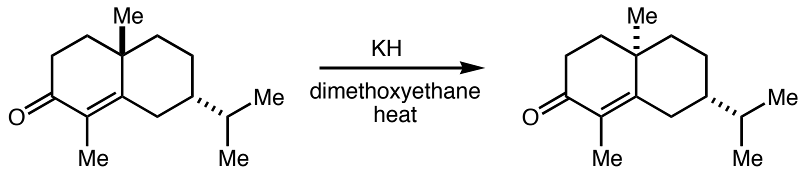
Other Reading Material:

C. Palomo, "Asymmetric Synthesis of β-Lactams by Stauginger Ketene-Imine Cycloaddition Reaction, Eur. *J. Org. Chem. 1999*, 3223-3235.

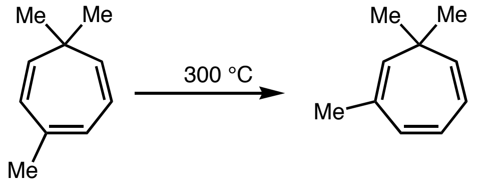


Problems of the Day:

Database Problem 159. The illustrated bicyclic ketone undergoes an isomerization in the presence of a strong base such as potassium hydride upon heating. After quenching the reaction, the new product has been found to have undergone a rather surprising isomerization at the quaternary center.



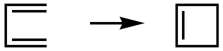
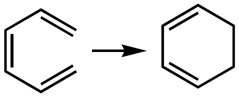
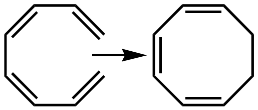
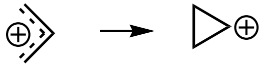
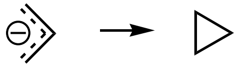
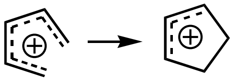
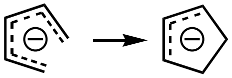
Database Problem 315. Berson and co-workers have studied the thermal isomerization illustrated below (*JACS* **1966,** *88*, 2494-2502). Provide a rationalization of these results. Three-dimensional drawings are recommended.

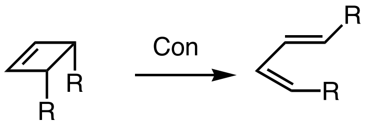


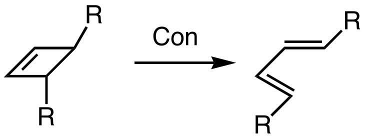
Electrocyclic Processes-1

Electrocyclic Reaction - Selection Rules

	Ground State (Thermal process)	Excited State (Photochemical Process)
4n π e^- (n = 1,2...)	conrotatory	disrotatory
4n+2 π e^- (n = 0,1,2...)	disrotatory	conrotatory

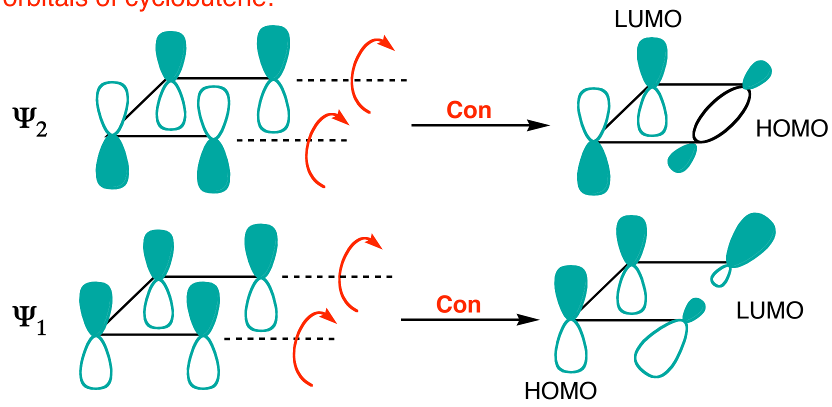
Examples	Ground State	Excited State
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory



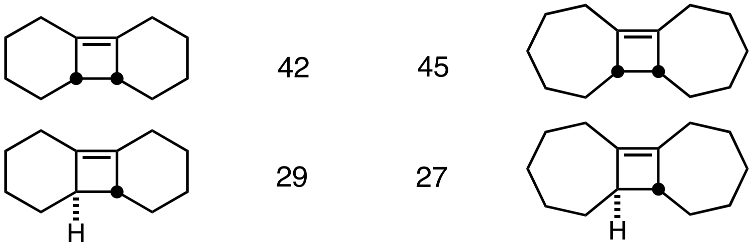


Sterically favored

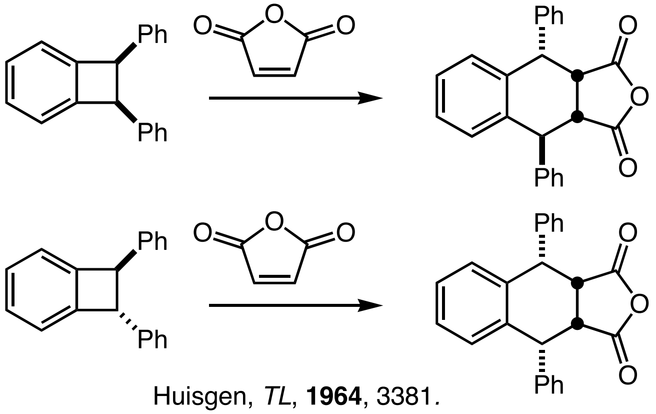
Controtation Ψ_1 and Ψ_2 on to the indicated bonding and anti-bonding orbitals of cyclobutene:



Activation Energy (kcal/mol)
for electrocyclic ring opening



Criegee, *Chem. Ber.* **1968**, *101*, 102.

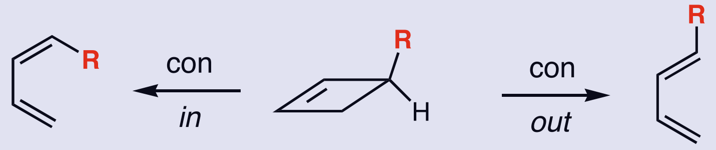


Huisgen, *TL*, **1964**, 3381.

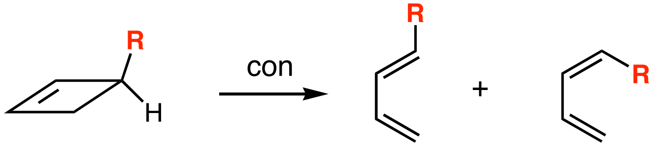
Electrocyclic Processes-2: Torquoselectivity

Torquoselectivilty is defined as the predisposition of a given R substituent for a given conrotatory motion

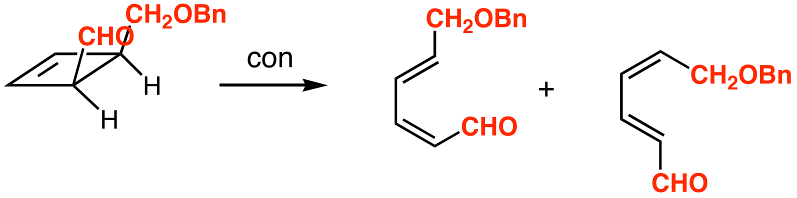
Houk et al. *Acc. Chem. Res* **1996**, 29, 471



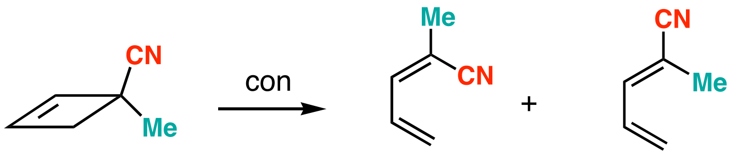
Examples: Donor substituents prefer con–out mode
Pi acceptor substituents prefer con–in mode



R = Me	**only**	none
R = CHO	none	**only**

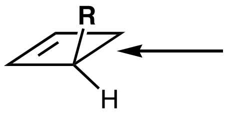


ratio: >20:1

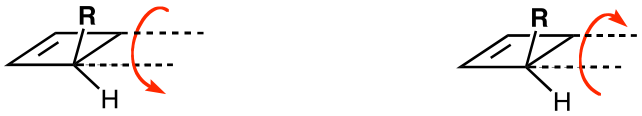


ratio: 4:1

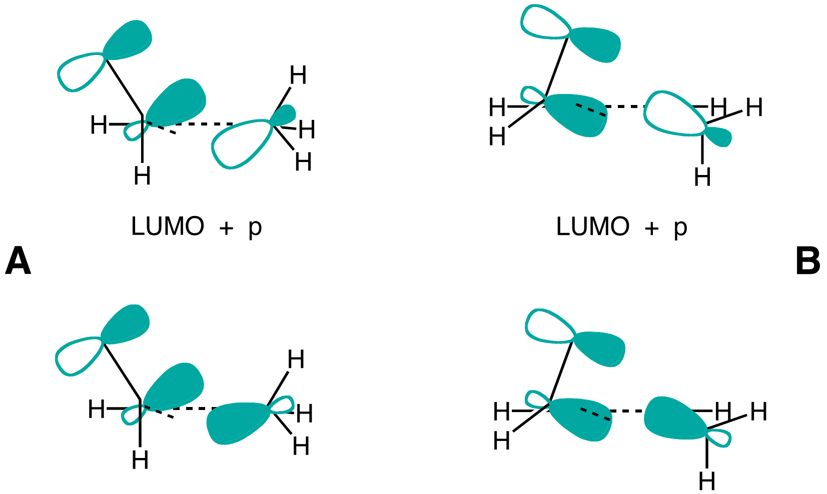
How do we explain? Donor substituents prefer con–out mode
Pi acceptor substituents prefer con–in mode



View the 2 conrotatory modes by looking at the breaking sigma bond from this perspective



Outward Motion *Inward Motion*



HOMO + p HOMO + p

As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B**, is better in **B**. (Houk)

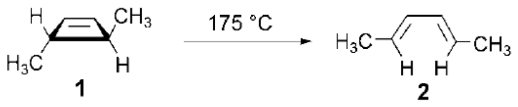
destabilizing 4 electron interation for donor substituents

stabilizing 2 electron interation for acceptor substituents

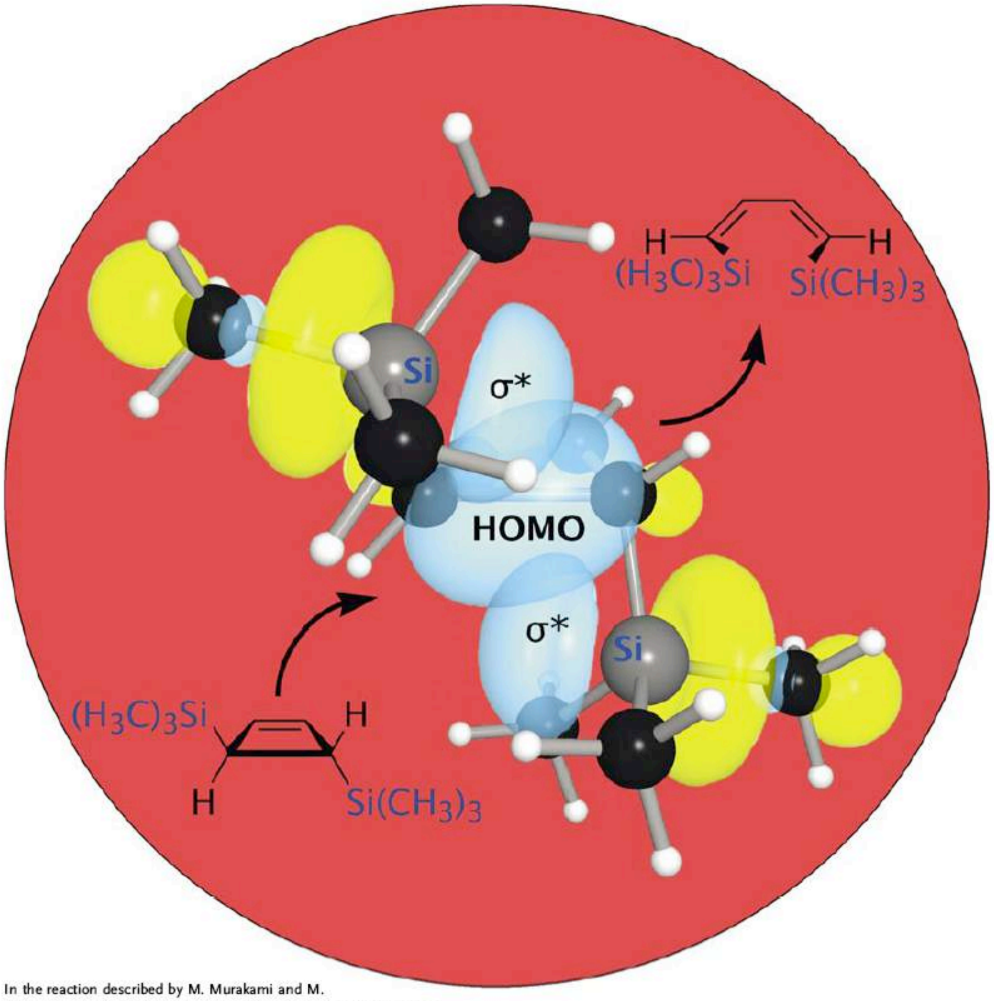
Electronic Effects

Synthesis and Thermal Ring Opening of *trans*-3,4-Disilylcyclobutene

Masahiro Murakami and Munehiro Hasegawa*



Scheme 1. Ring-opening reaction of *trans*-3,4-dimethylcyclobutene **1**.



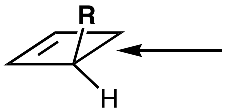
In the reaction described by M. Murakami and M.

Electrocyclic Processes-2: Torquoselectivity

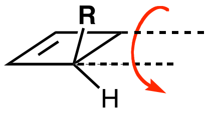
How do we explain?

Donor substituents prefer con–out mode

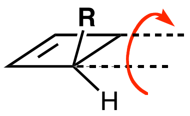
Pi acceptor substituents prefer con–in mode



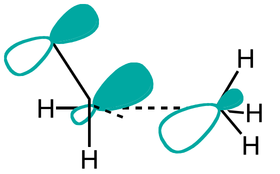
View the 2 conrotatory modes by looking at the breaking sigma bond from this perspective



Outward Motion

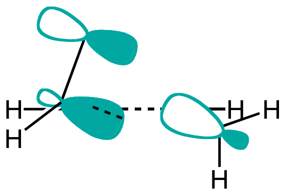


Inward Motion



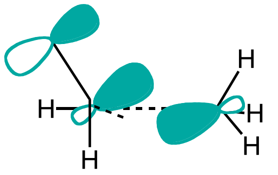
LUMO + p

A

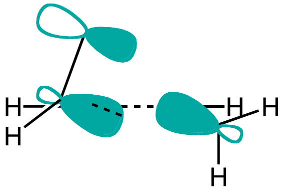


LUMO + p

B



HOMO + p

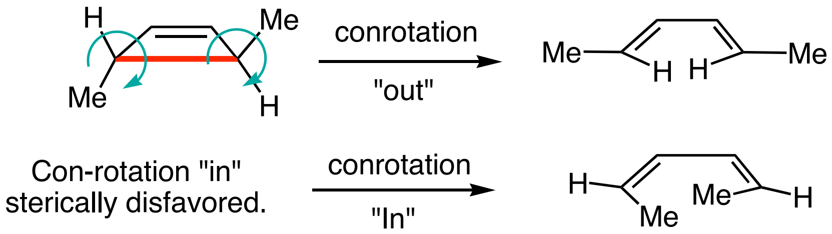


HOMO + p

As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B**, is better in **B**. (Houk)

destabilizing 4 electron interation for donor substituents

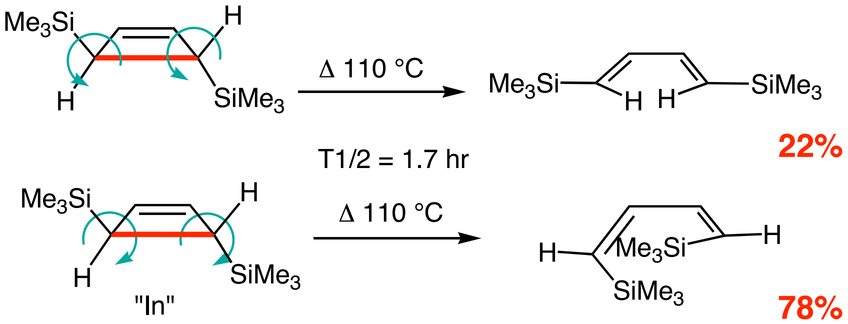
stabilizing 2 electron interation for acceptor substituents



Con-rotation "in" sterically disfavored.

Murakakami *Angew. Chem. Int. Ed.* **2004,** *43*, 4873

What abut Silyl Substituents?



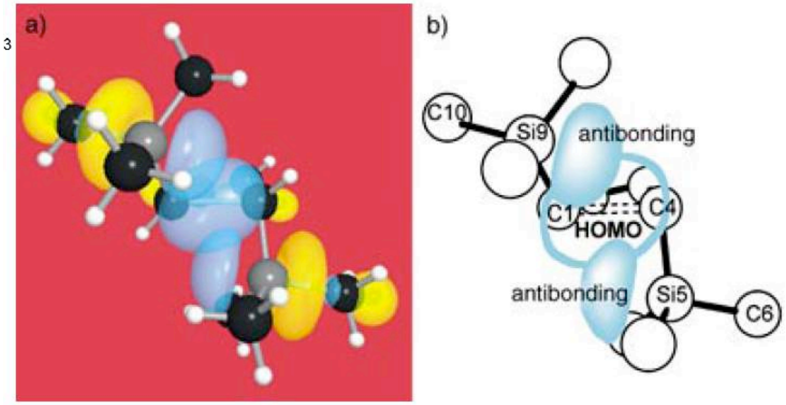
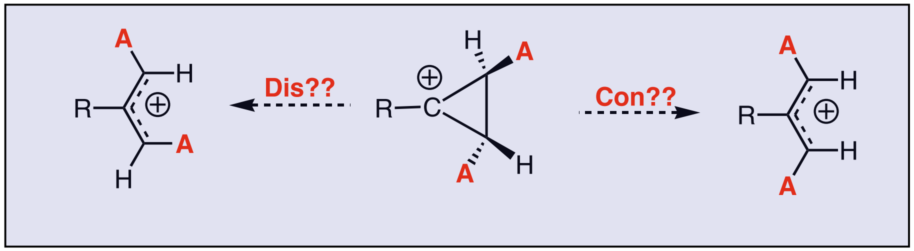
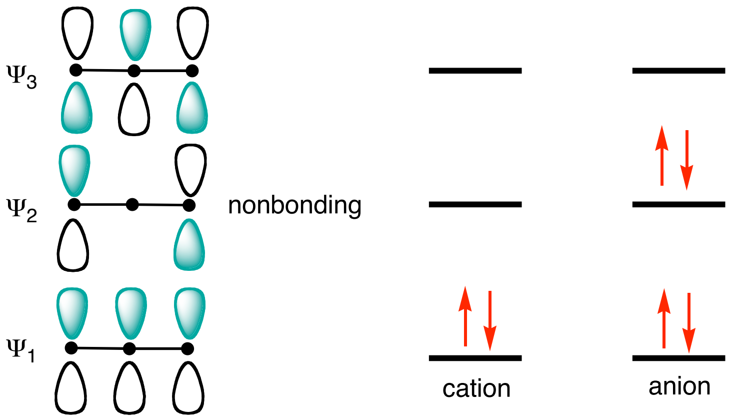


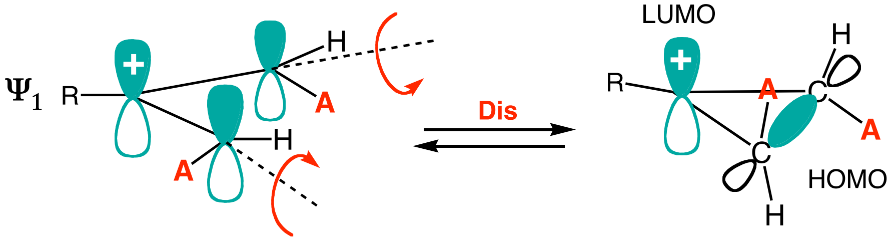
Figure 2. Overlap of the two antibonding orbitals on the silicon atoms with the HOMO in the inward transition state.

Electrocyclic Processes-3: 3-Atom Electrocyclizations

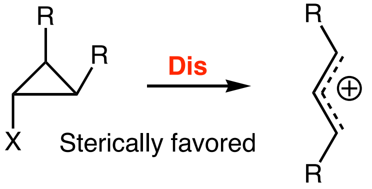
Three-Atom Electrocyclizations (2 electrons)



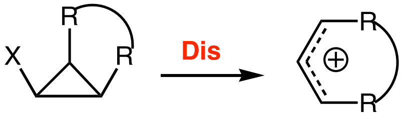




Note that there are two disrotatory modes



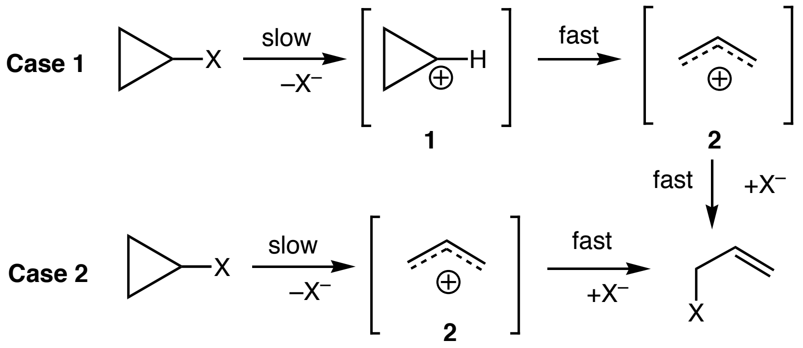
Sterically favored

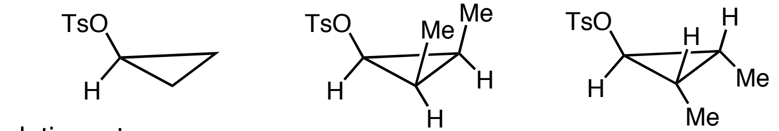


Favored for R = ring

Solvolysis of Cyclopropyl Derivatives

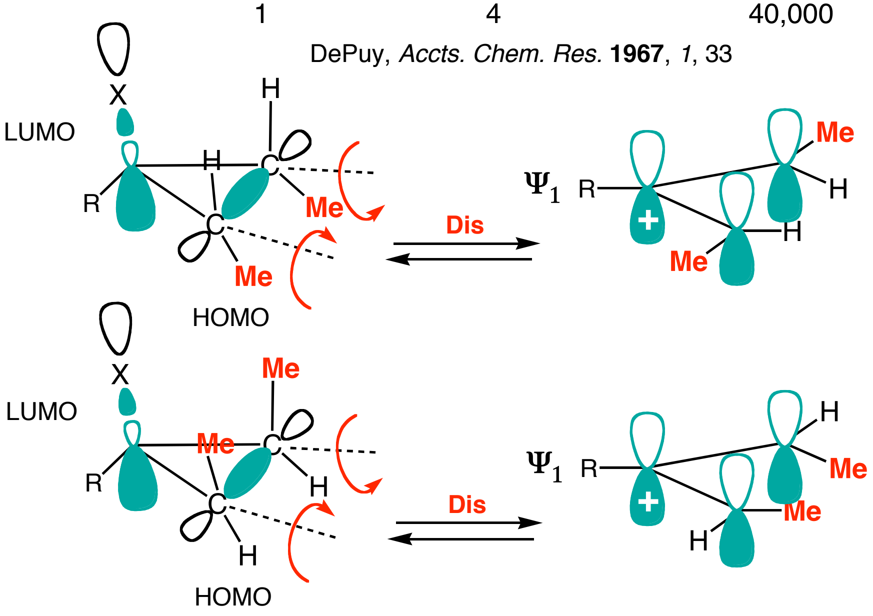
Does solvolysis proceed via cation **1** followed by rearrangement to **2** (Case 1), or does it proceed directly to **2** (Case 2)?





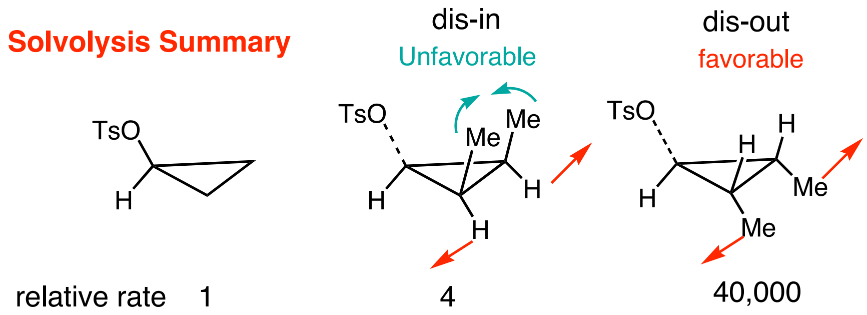
relative rate 1 4 40,000

DePuy, *Accts. Chem. Res.* **1967**, *1*, 33



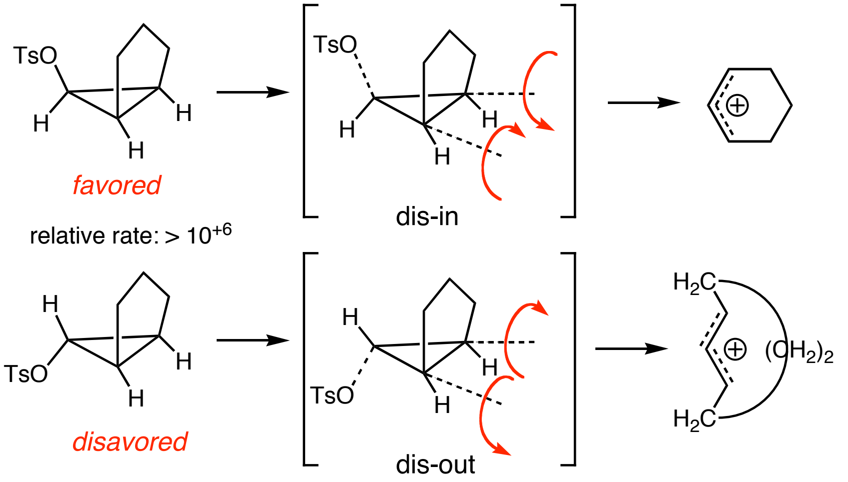
Electrocyclic Processes-3: 3-Atom Electrocyclizations

Solvolysis Summary

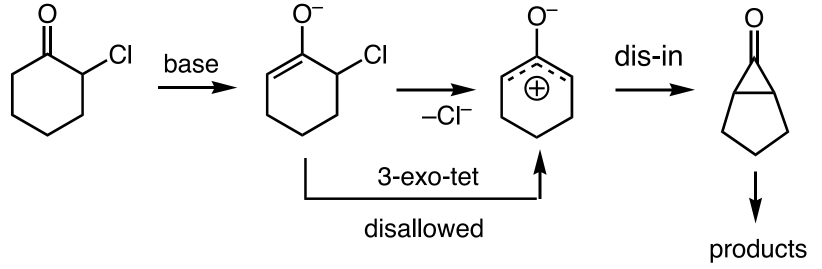


Ring-fused Cyclopropyl Systems

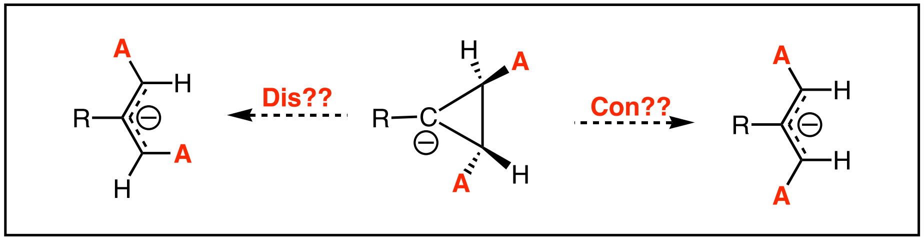
When the cis substiltutents on the cyclopropyl ring are tied together in a ring the following observsations have been made

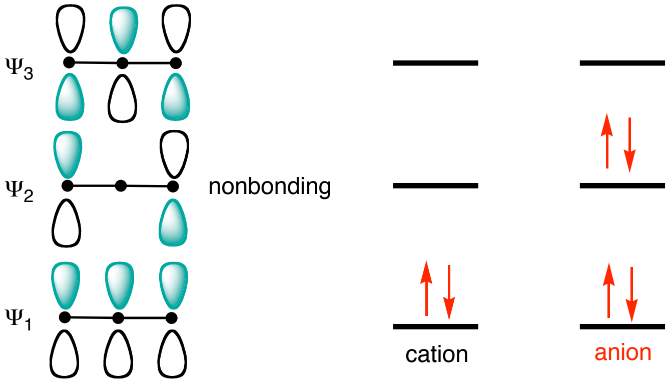


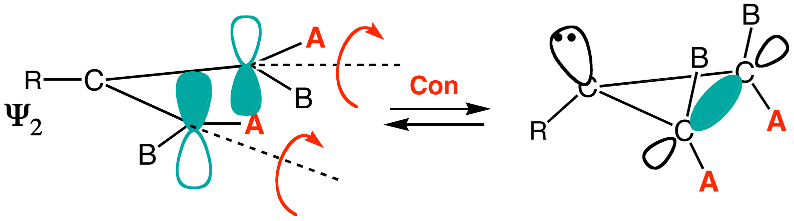
Revisiting the Favorski rearrangement: (Carey, Part A, pp 506-8)



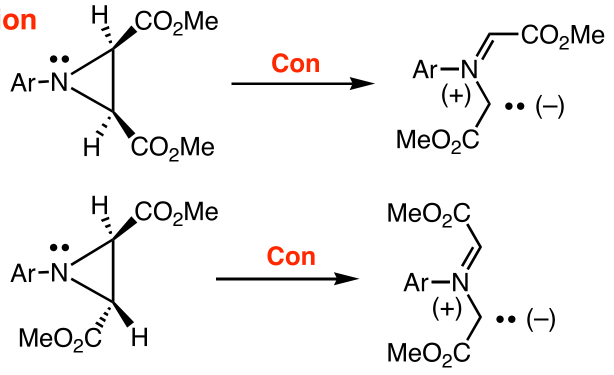
Three-Atom Electrocyclizations (4 electrons)





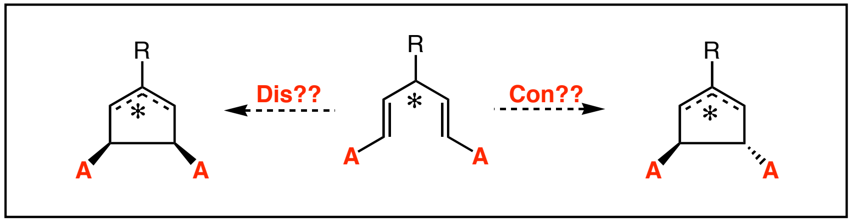


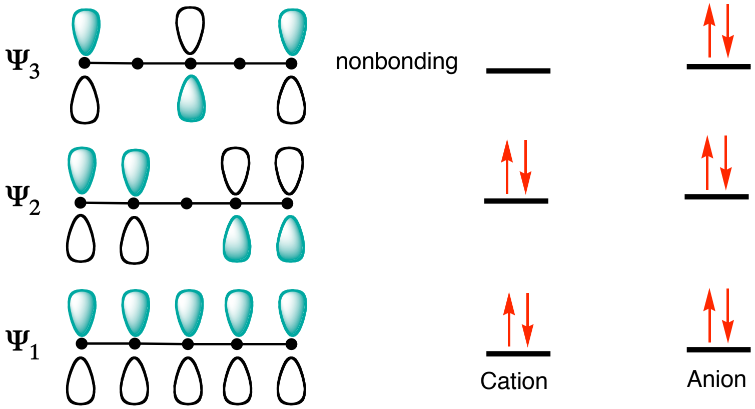
Observation



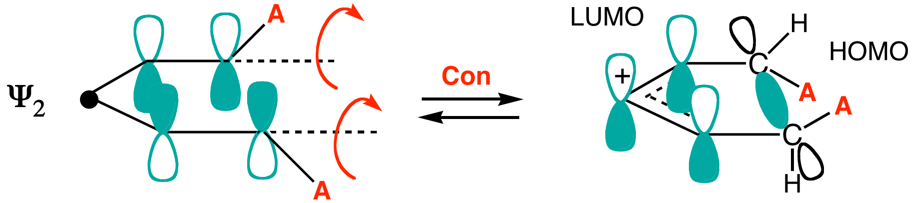
Electrocyclic Processes-3

Five-Atom Electrocyclizations (4 electrons)

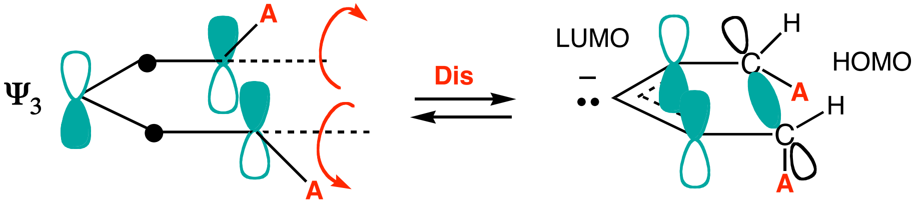




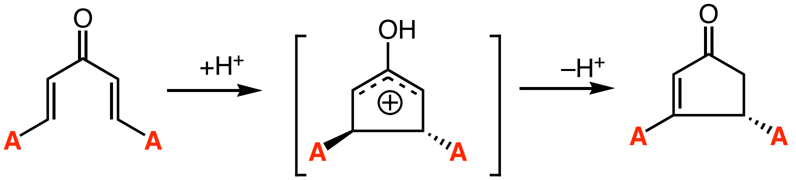
Pentadienyl Cation



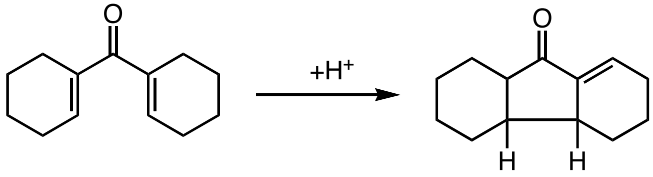
Pentadienyl Anion



The Nazarov Reaction

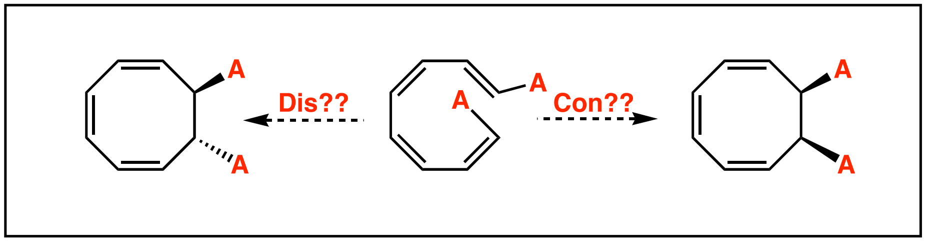


Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5; pp 751.

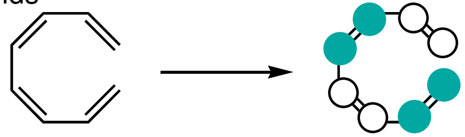


predict stereochemistry

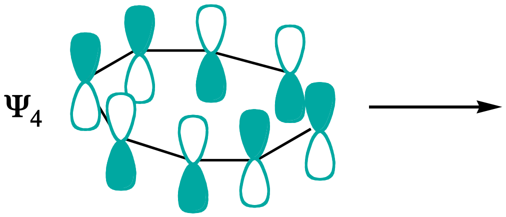
Eight-Atom Electrocyclizations (8 electrons)



Let's use the "Ready" shortcut to find the homo: Nodes will appear at single bonds

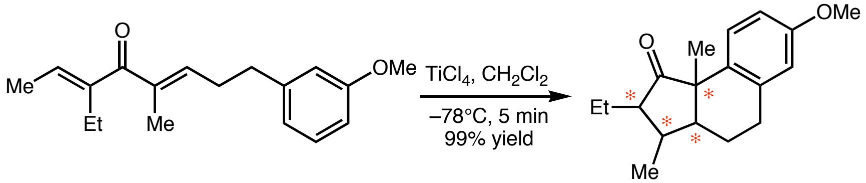


symmetry of homo



Closure should be conrotatory

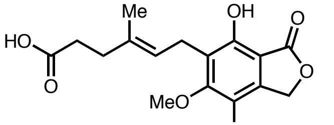
Problem 122. The interesting transformation illustrated below was recently reported by F. West and co-workers (*Org. Lett.* **2001**, *3*, 3033-3035). The pivotal reaction upon which this transformation was designed is a pericyclic process that affords a pivotal element of stereocontrol.



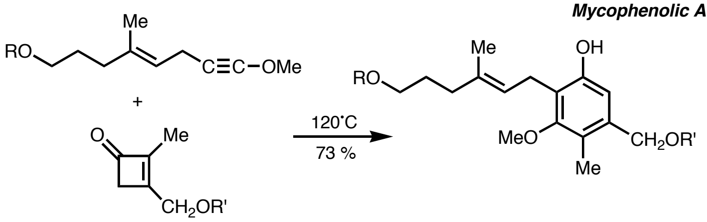
Part A. Identify the pericyclic process that intervenes in the illustrated transformation and illustrate the relative configuration(s) stereocenter(s) that are generated.

Part B. Provide a mechanism for the overall transformation. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

Problem 158. Danheiser and coworkers (JACS **1986**, *108*, 806) have described an innovative synthesis of the antifungal agent mycophenolic acid. The crucial reaction which resulted in the assemblage of the highly substituted phenolic ring is provided below.



Mycophenolic Acid

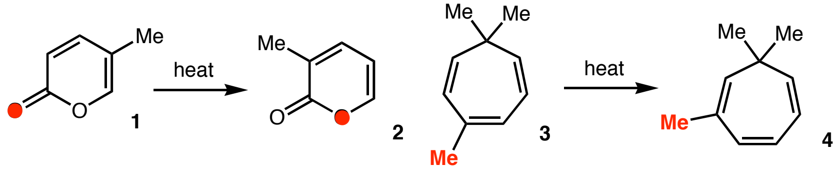


Provide a concise mechanism for this reaction in the space below.

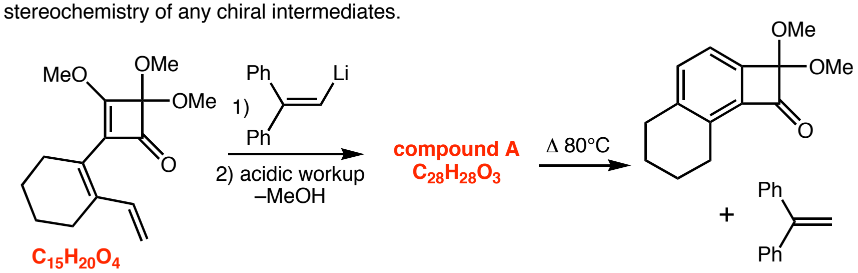
Problem 161. The following transformations entail an "apparent" methyl migration. Address the questions posed below.

Part A. Provide a mechanism for the transformation of **1** to **2**. I represents an ^{18}O label. Classify all pericyclic processes should they intervene.

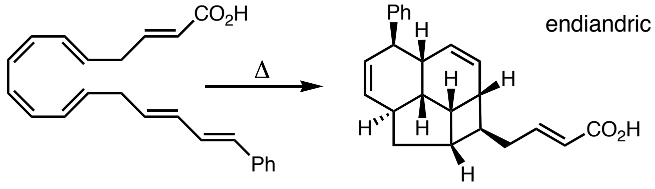
Part B. Provide a mechanism for the transformation of **3** to **4**. Classify all pericyclic processes should they intervene.



Problem 215. Provide a mechanism for the following set of transformations (*J. Org. Chem.* **1999**, *64*, 2170). It should be noted that compound **A** exhibits a strong carbonyl frequency in the infrared spectrum. Clearly indicate the structure of compound **A** and the relative stereochemistry of any chiral intermediates.

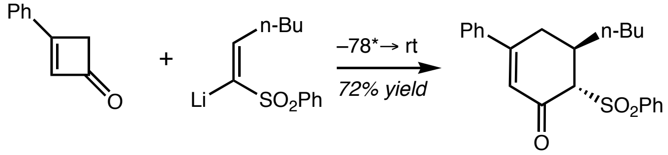


Problem 718. Black proposed that the biosynthesis of endiandric acid B involved a series of pericyclic reactions beginning with the given acyclic starting material. Propose a mechanism for this transformation. You may find it helpful to start with the product and work backwards. Hint: The last step of this mechanism is a Diels-Alder reaction.

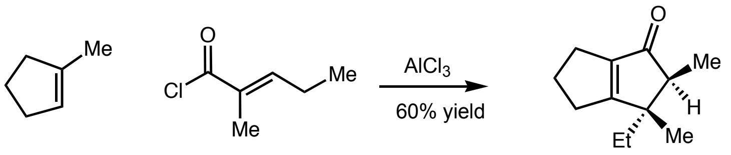


endiandric acid B

Problem 736. Please provide a mechanism for the following transformation recently reported by Magomedov and co-workers (*JACS* **2004**, 126, 16265) This is one of seven cases reported. *Be sure to classify any pericyclic processes that intervene.*



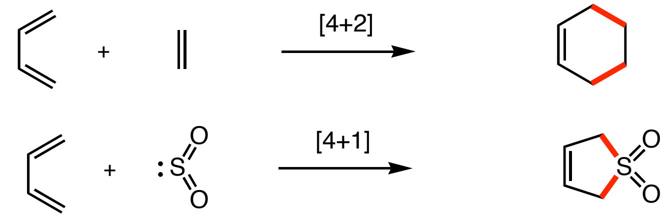
Problem 780. Santilli and co-workers reported this Lewis acid catalyzed reaction (Santilli etal. *JACS* **1991, 113,** 8062-8069). Please provide a reasonable mechanism for this transformation that includes the rationalization of the stereochemical outcome of the transformation.



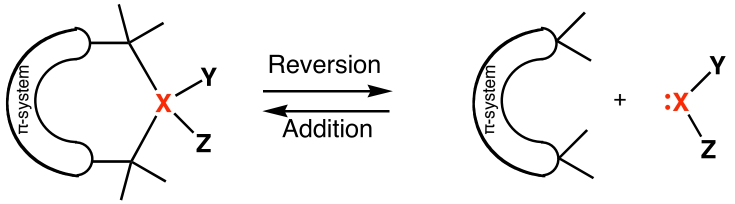
Cheletropic Processes-1

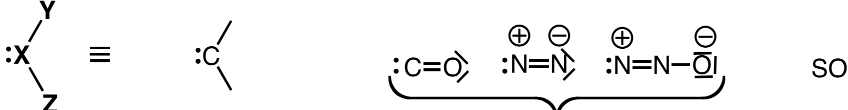
CHELETROPIC REACTIONS: [n+1] Cycloadditions (or Cycloreversions)

Concerted processes in which 2 σ-bonds are made (or broken) which terminate at a single atom.



General



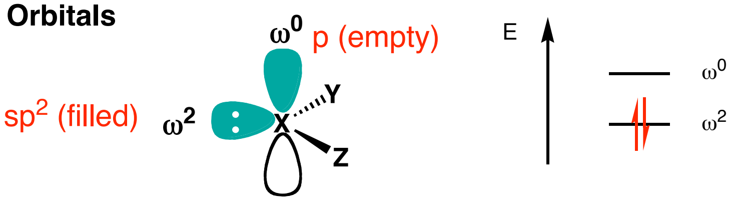


Singlet-Carbene Addition (and Reversion)

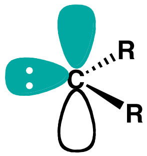
Cycloreversion only

Reversion and Addition

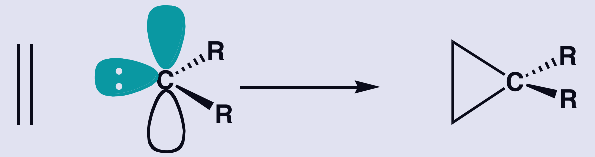
Frontier Orbitals



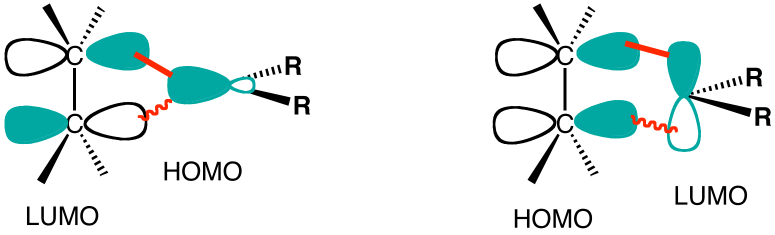
Question: what is orientation of carbene relative to attacking olefin??



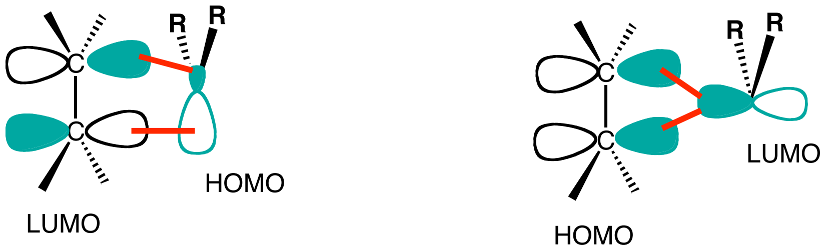
2 + 1 CheletropicReaction: Olefins + Singlet Carbene



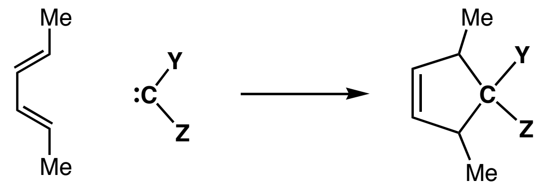
Linear Approach: 2 HOMO-LUMO Interactions



Nonlinear Approach: 2 HOMO-LUMO Interactions



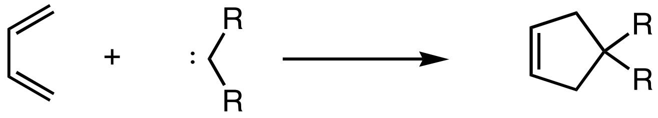
Carry out the analysis of the indicated hypothetical transformation



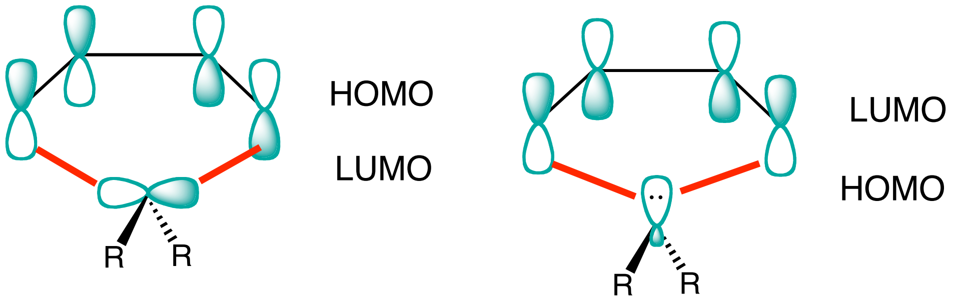
predict approach geometry of carbene

Problem 726. A [4+1] cycloaddition between a diene and a carbene has recently been reported by Spino and co-workers (*JACS*, **2004**, *126*, 9926).

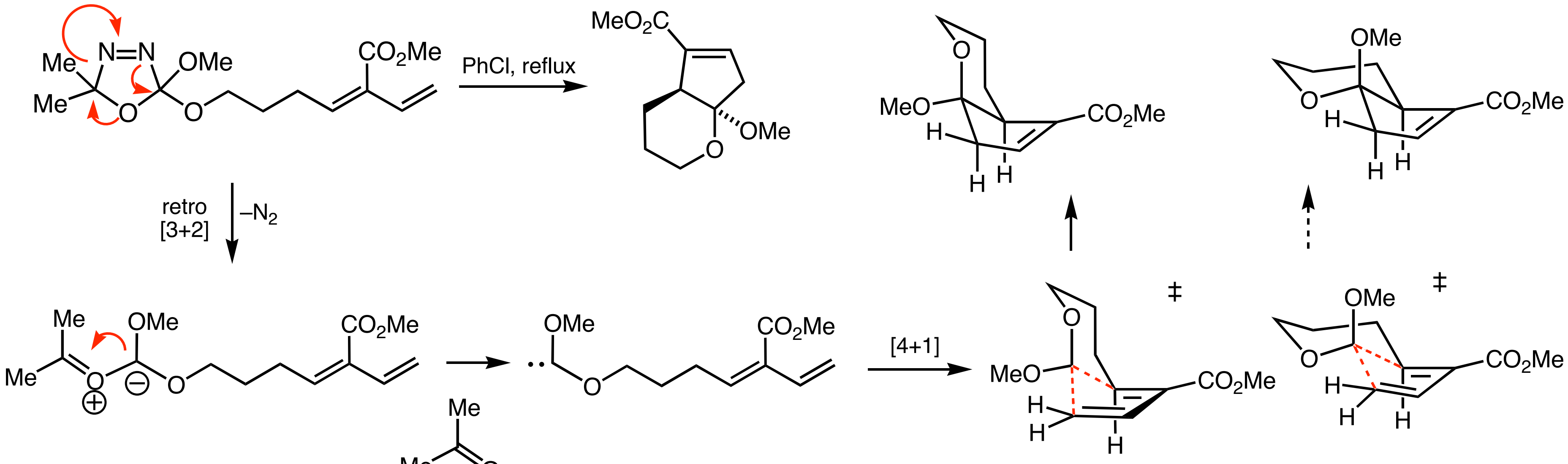
Part A. Using a Dewar-Zimmerman or an FMO analysis, determine if this reaction is thermally allowed. Be sure to consider both the approach and the geometry of the carbene carefully.



FMO Analysis



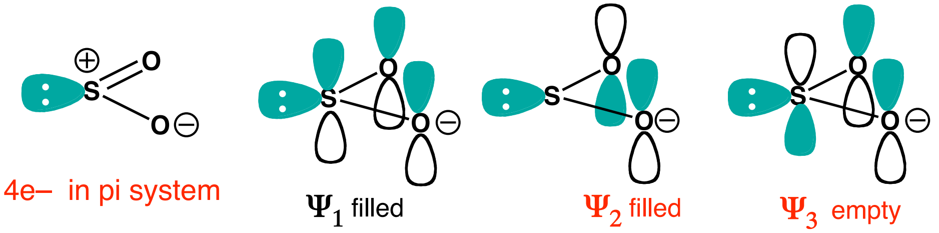
Part B. Provide a mechanism for the following reaction reported by Spino.

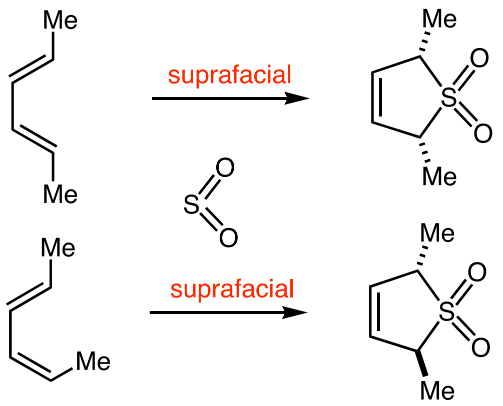


most stable TS has *cis* ring fusion

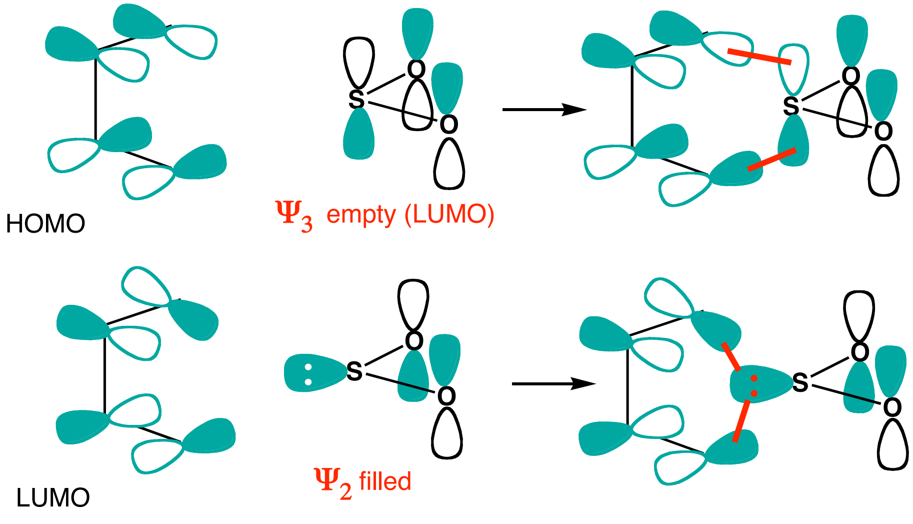
Cheletropic Processes-2

Let's now consider SO_2 as the one-atom component

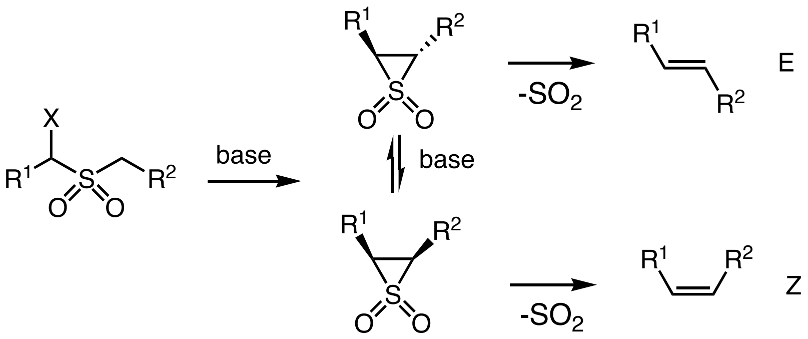




reactions are:
stereospecific & reversible

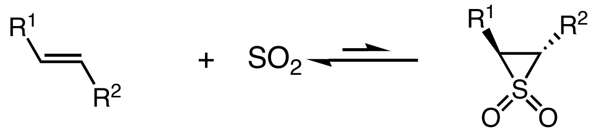


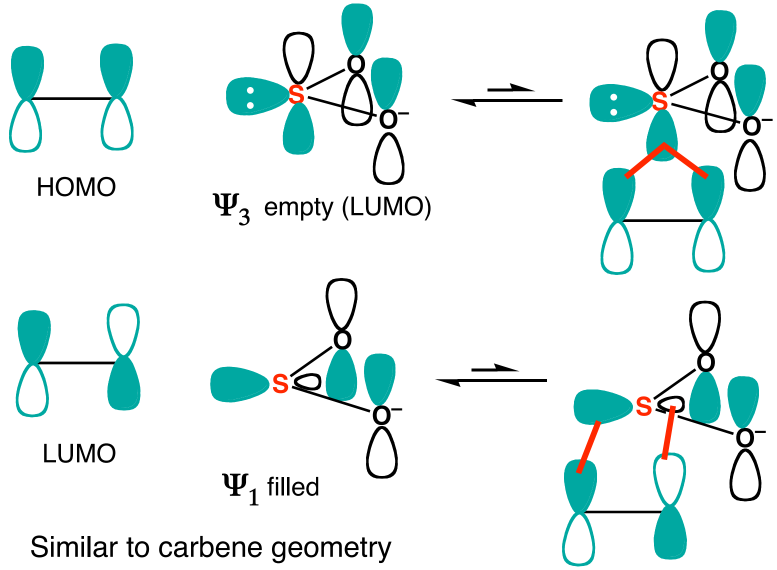
Key step in the *Ramberg Bäcklund* Rearrangement



Clough, J. M. *The Ramberg-Backlund Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861.
"The Ramberg-Backlund Rearrangement.", Paquette, L. A. *Org. React. (N.Y.)* 1977, *25*, 1.

Analysis of the Suprafacial SO_2 Extrusion (nonlinear)





Similar to carbene geometry

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 13

Pericyclic Reactions–3

- Introduction to Sigmatropic Rearrangements
- [2,3] Sigmatropic Rearrangements

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

"Pericyclic Reaction Transition States: Passions and Punctilios, 1935-1995 Houk, *Accts. Chem. Res.* **1995**, *28,* 81-90 **(handout)**

"Thermal Reactions of 7-d- and 8-d-Bicyclo[4.2.0]oct-2-enes" Baldwin, Leber, and Powers, *JACS* **2006,** *128,* 10020 **(handout)**

Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55 **(handout)**
(Sulfoxide Rearrangement)

Nakai, *Chem. Rev.* **1986**, *86*, 885-902 (Wittig Rearrangement) **(pdf)**

D. A. Evans

Wednesday
October 18, 2006

Other Reading Material:

[2,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapter 4.6:

Nakai, T.; Mikami, K. *Org. React. (N.Y.)* **1994**, *46*, 105-209.

Hoffmann, *Angew. Chem. Int. Ed.* **1979**, *18*, 563-572 (Stereochemistry of)

Nakai, *Chem. Rev.* **1986**, *86*, 885-902 (Wittig Rearrangement)

Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55 (Sulfoxide Rearrangement)

Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358-364 (Sulfur Ylilde Rearrangements)

[3,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)

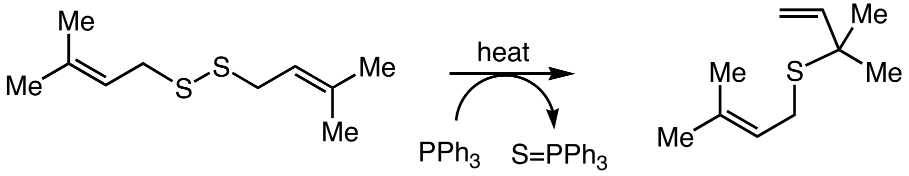
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)

Paquette, L. A. (1990). “Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement.” Angew. Chem., Int. Ed. Engl. 29: 609.

Problems of the Day:

Provide a mechanism for this transformation.



For study on this [2,3] rxn See Baldwin *JACS* **1971**, *93*, 6307

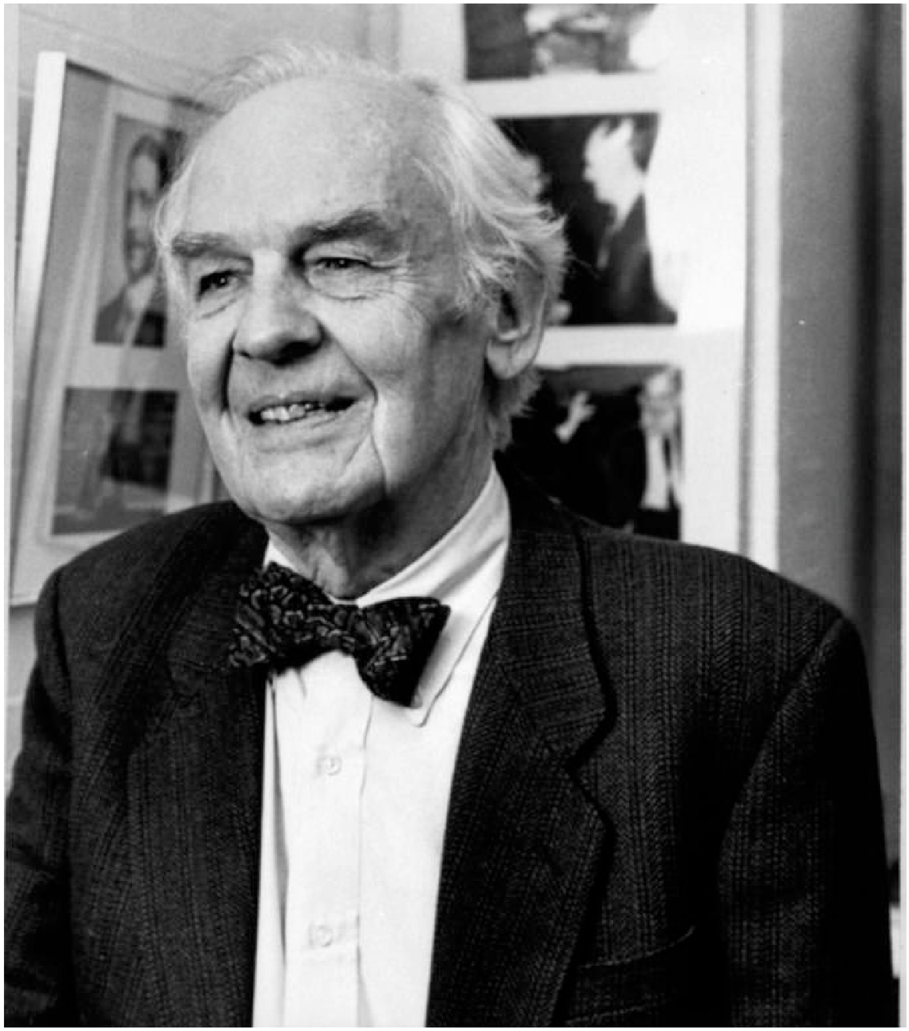
Professor William von Eggers Doering

born: 22 June, 1917, Fort Worth Texas

Professor Doering's parents were both musicians, and met while they were both studying music in Leipzig. When World War I broke out, they moved to the United States, and his father became a vital statistician. His father eventually got a job teaching at Harvard University's School of Public Health, and the family moved to Cambridge. Doering was influenced by his teachers during his early education to pursue science. After graduating from high school, Doering attended Harvard University, where he was inspired to major in chemistry. At Harvard, he took courses with Arthur Lamb, Louis Fieser, Elmer Kohler, and Paul Bartlett. Kohler encouraged Doering to continue on to graduate school, so he earned his Ph.D. in organic chemistry at Harvard in 1943. During his years as a graduate student, he did some research with Louis Fieser on new explosives, including TNT, as well as anti-mustard gas work with Eric Ball. After he completed his PHD, he joined Woodward's team at Harvard, who ultimatelysynthesized quinine. Less than a year later, Doering took an instructorship at Columbia University Doering and spent nine years at Columbia before moving on to Yale University in 1952.

Profesor Doering's major interests have been organic structures and reaction mechanisms. He established the aromatic nature of tropones, tropolones and the tropylium ion. Studies on thermal rearrangements showed that a chair-like transition state is preferred for the Cope rearrangement, and that degenerate Cope rearrangements in bi- and tricyclic systems lead to molecules with "fluxional" structures (i.e. bullvalene). Doering brought carbene chemistry to the attention of organic chemists; he studied carbene insertions, additions to multiple bonds, and intramolecular rearrangements. His interests have been wide-ranging, and he made contributions to the mechanism of solvolysis of tertiary systems, the Diels-Alder reaction, the Baeyer-Villiger rearrangement, the stereochemistry and internal rotations in non-concerted diradical processes, and cis-trans isomerism in higher polyenes.

Professor continues his research to this day and has an active research group in the Naito Laboratory.



Latest paper

"Effect on Kinetics by Deuterium in the 1,5-Hydrogen Shift of a Cisoid-Locked 1,3(Z)-Pentadiene,2-Methyl-10 methylene-bicyclo[4.4.0]dec-1-ene: Evidence for Tunneling?

William von E. Doering* and Xin Zhao

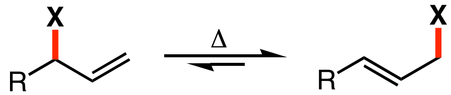
JACS **2006,** *128*, 9080-9085

Sigmatropic Rearrangements-1

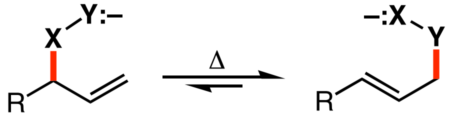
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

■ Examples:

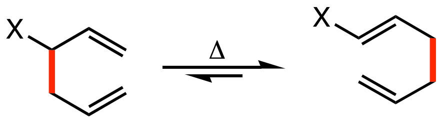
[1,3] Sigmatropic rearrangement



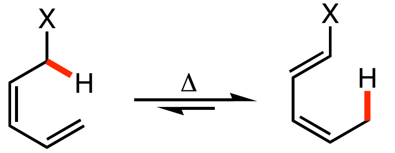
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

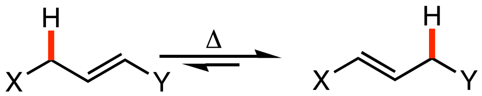


[1,5] Sigmatropic rearrangement

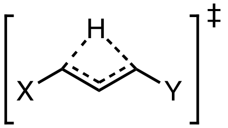


■ [1,3] Sigmatropic Rearrangements (H migration)

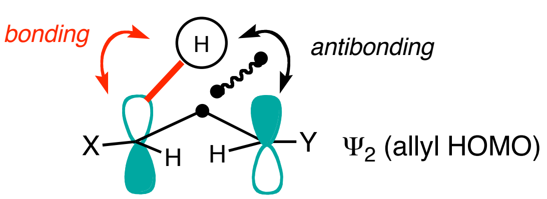
consider the 1,3-migration of H



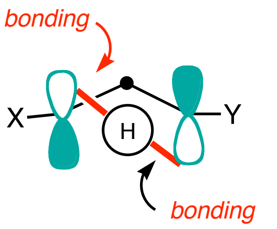
Consider the orbitals needed to contruct the transition state (TS).



■ Construct TS by uniting an allyl and H radical:



Suprafacial Geometry

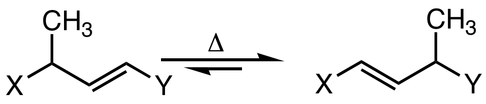


Antarafacial Geometry

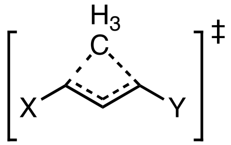
Bridging distance too great for antarafacial migration.

■ [1,3] Sigmatropic Rearrangements (C migration)

consider the 1,3-migration of Carbon

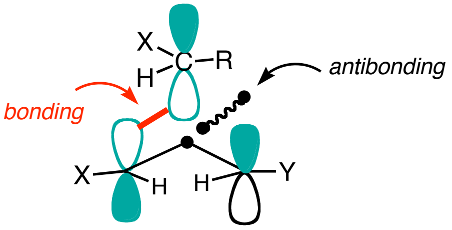


Consider the orbitals needed to contruct the transition state (TS).



Construct TS by uniting an allyl and Me radicals:

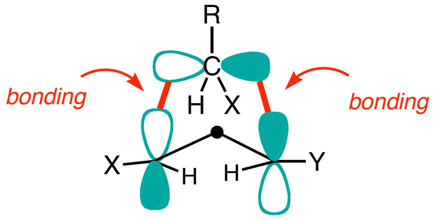
Retention at carbon



Suprafacial on allyl fragment

Sychronous bonding to both termini cannot be achieved from this geometry

Inversion at carbon



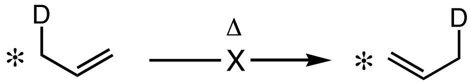
Suprafacial on allyl fragment

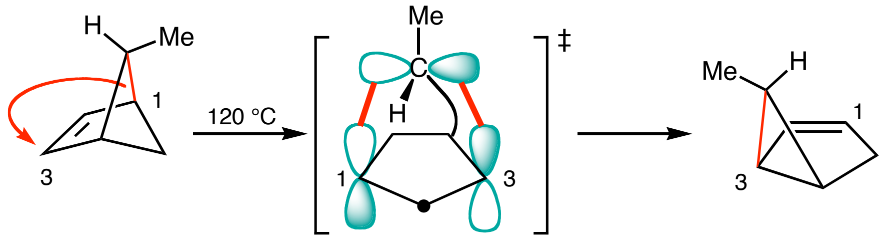
Sychronous bonding to both termini is possible from this geometry

❐ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

no observed scrambling of labels



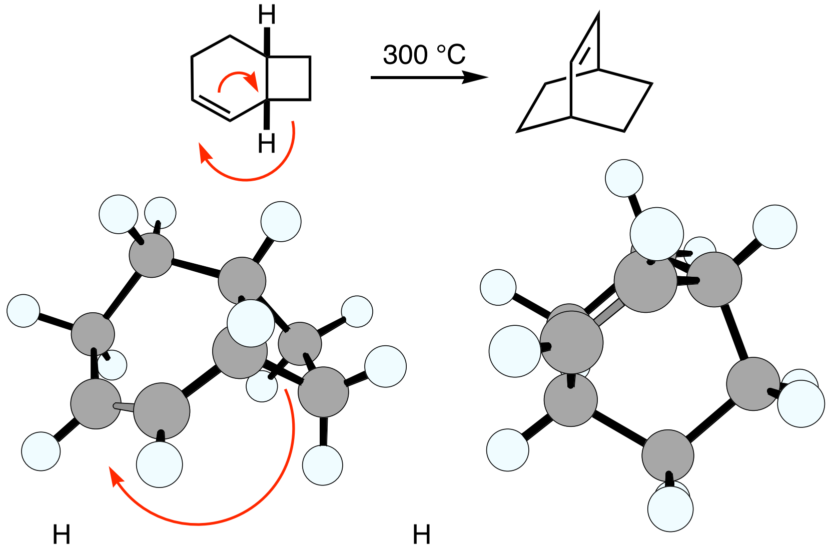


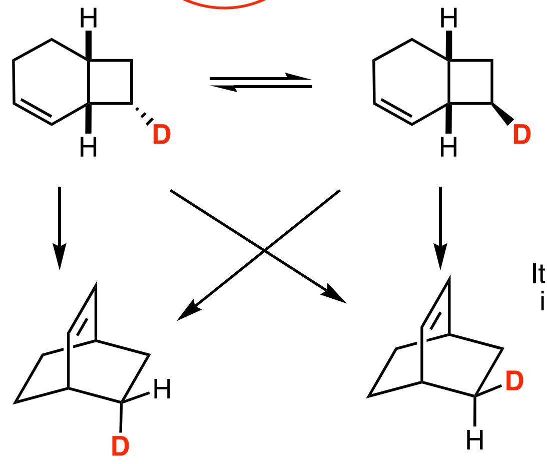
These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

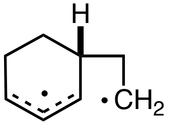
Sigmatropic Rearrangements-1a

■ [1,3] Sigmatropic Rearrangements (C migration)

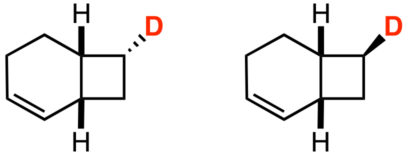
"Thermal Reactions of 7-d- and 8-d-Bicyclo[4.2.0]oct-2-enes," Baldwin, Leber, and Powers, *JACS* **2006,** *128,* 10020 **(handout)**





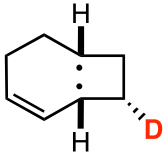


It is concluded that diradical intermediates are involved



No equilibration

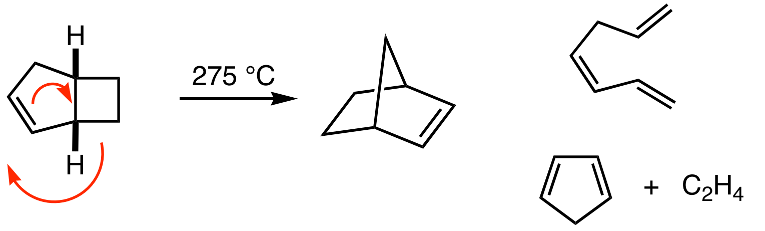
therefore

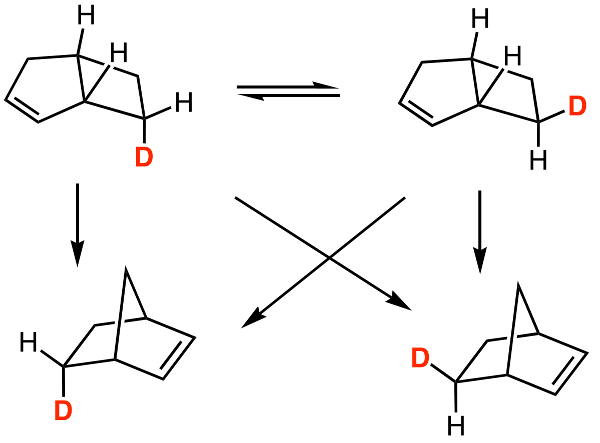


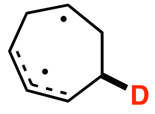
insignificant

■ [1,3] Sigmatropic Rearrangements (C migration)

"New Thermal Reactions of Deuterium-Labeled Bicyclo[3.2.0]hept-2-enes: Bicyclic Skeletal Inversion and Epimerization at C7," *JACS* **2001,** *123,* 8396 **(pdf)**

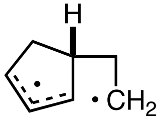






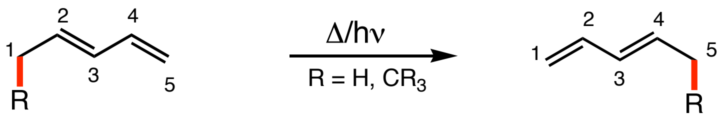
significant

It is concluded that diradical intermediates are involved

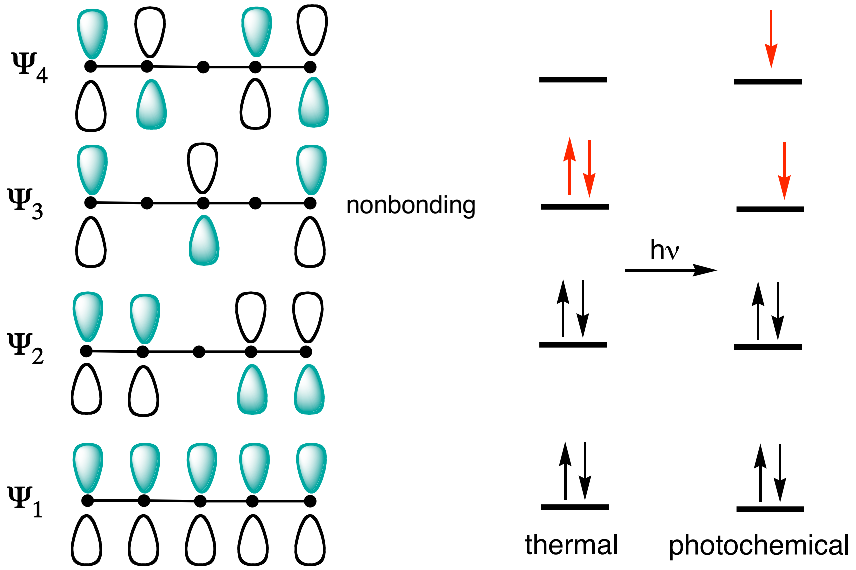


(2) (a) Cocks, A. T.; Frey, H. M. *J. Chem. Soc. A* **1971**, 2564–2566. (b) Baldwin, J. E.; Belfield, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 296–297. (c) Klärner, F.-G.; Drewes, R.; Hasselmann, D. *J. Am. Chem. Soc.* **1988**, *110*, 297–298. (d) Baldwin, J. E.; Belfield, K. D. *J. Phys. Org. Chem.* **1989**, *2*, 455–466. (e) Carpenter, B. K. *Acc. Chem. Res.* **1992**, *25*, 520–528. (f) Carpenter, B. K. *J. Am. Chem. Soc.* **1995**, *117*, 6336–6344. (g) Wilsey, S.; Houk, K. N.; Zewail, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 5772–5786. (h) Baldwin, J. E.; Leber, P. A. *J. Am. Chem. Soc.* **2001**, *123*, 8396–8397.

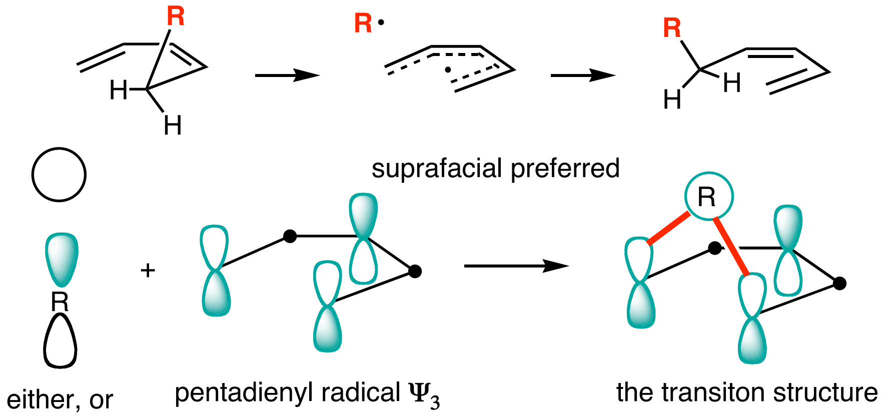
SIGMATROPIC REACTIONS - FMO-Analysis



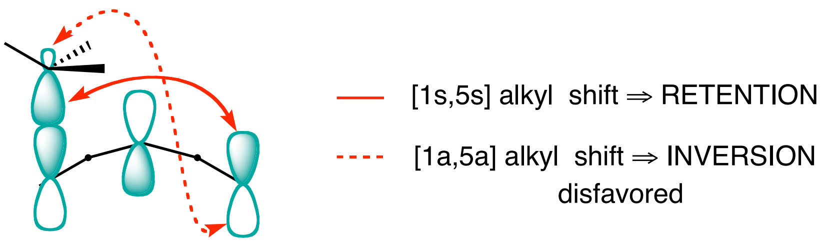
[1,5] Sigmatropic Rearrangements (H migration)



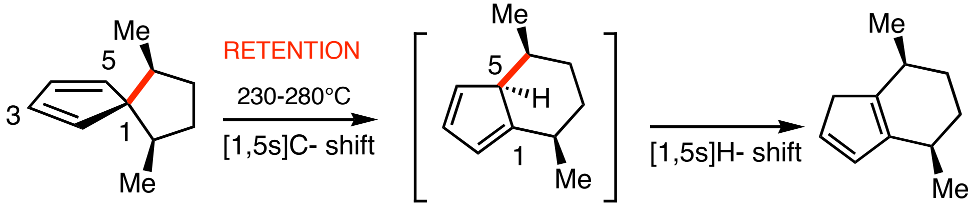
View as cycloadditon between following species:



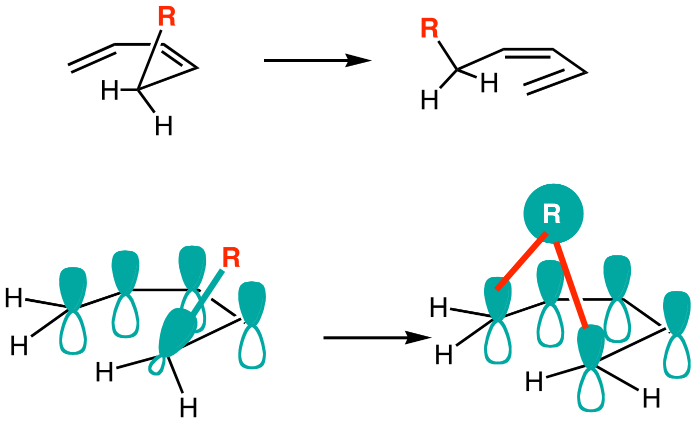
[1,5] Sigmatropic Rearrangements (C migration)


[1s,5s] alkyl shift ⇒ RETENTION
[1a,5a] alkyl shift ⇒ INVERSION
disfavored

[1,5] (C migration): Stereochemical Evaluation



Dewar–Zimmerman Analysis: Retention



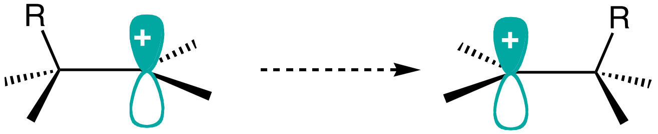
0 phase inversions ⇒ Huckel toplogy
6 electrons
therefore, allowed thermally

Sigmatropic Rearrangements: An Overview

[1,2] Sigmatropic Rearrangements: Carbon

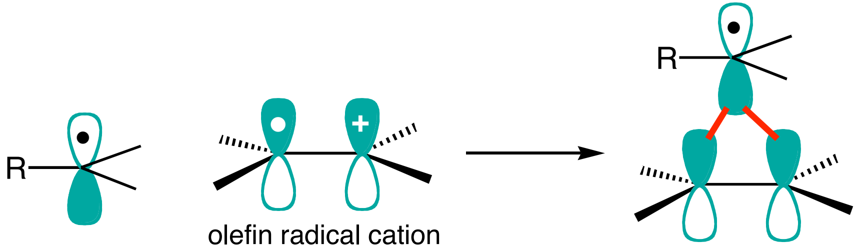
[1,2]-Sigmatropic rearrangements to cationic centers allowed.

Wagner-Meerwein Rearrangement



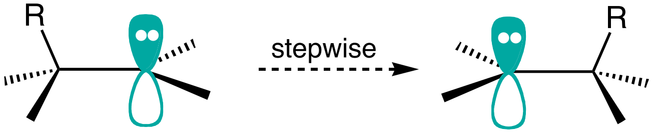
consider as cycloaddition

FMO analysis



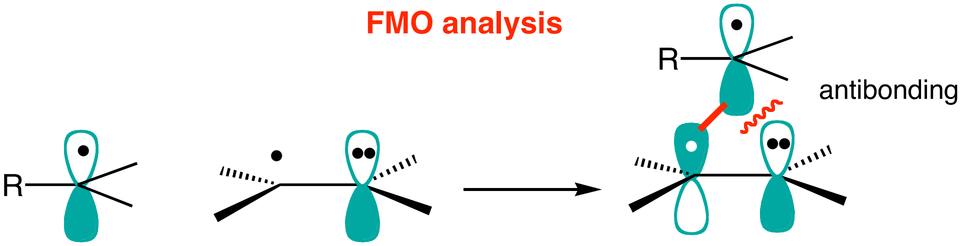
transition state

[1,2]-Sigmatropic rearr to carbanionic centers not observed



consider as cycloaddition

FMO analysis



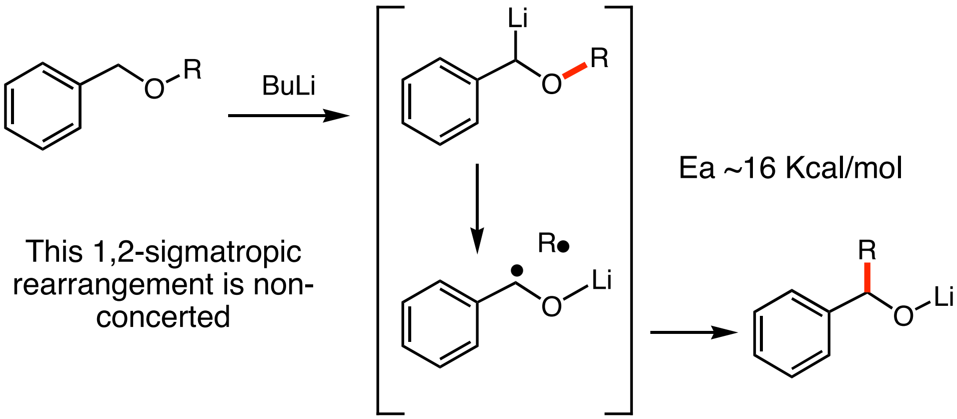
olefin radical anion

transition state

The Wittig Rearrangement [1,2]

"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

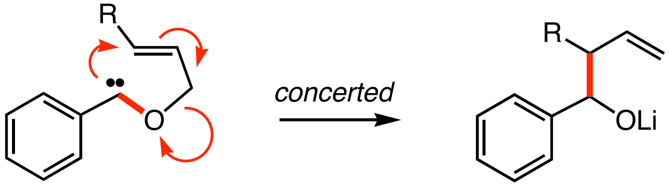
Marshall, J. A. *The Wittig Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.



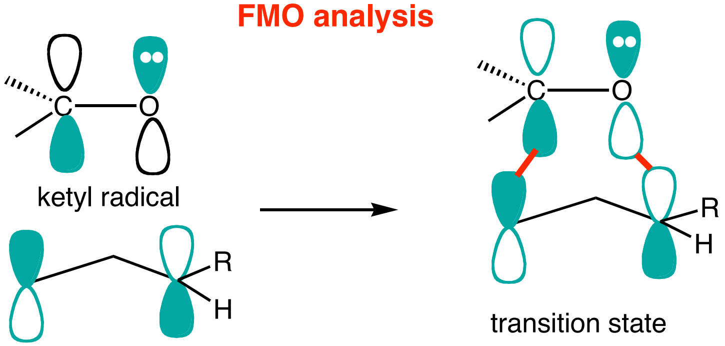
Ea ~16 Kcal/mol

This 1,2-sigmatropic rearrangement is non-concerted

The Wittig Rearrangement [2,3]



FMO analysis



Allyl radical

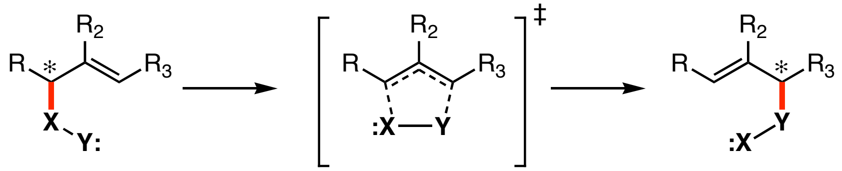
transition state

The $\Delta\Delta G^{\ddagger}$ between concerted and non-concerted pathways can be quite small

[2,3]-Sigmatropic Rearrangements: An Introduction

[2,3] Sigmatropic Rearrangements

■ The basic process:



X & Y = permutations of C, N, O, S, Se, P; however X is usually a heteroatom

Attributes: Stereoselective olefin construction & chirality transfer

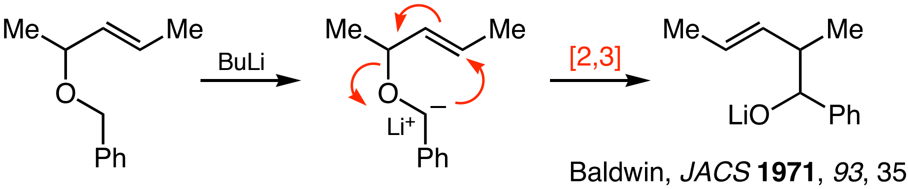
■ **Representative X-Y Pairs:**

N–O (amine oxides)
S–C (sulfur ylids)
O–C (Wittig rearrangement)
N–C (nitrogen ylids)
S–S (disulfides)

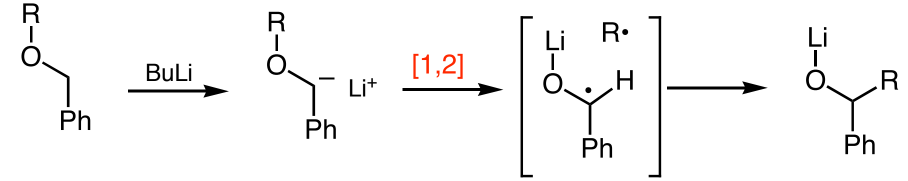
S–P, S–N, S–O (sulfoxides)
O–P (phosphites)
N–N, Cl$^+$–C (haloium ylids)
P–C, C–C (homoallylic anions).

An important early paper: Baldwin, *J. Chem. Soc., Chem. Comm.* **1970**, 576

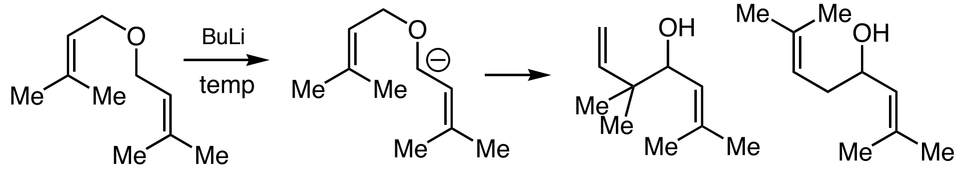
■ X - O, Y = C; Wittig Rearrangement:



Baldwin, *JACS* **1971**, *93*, 3556

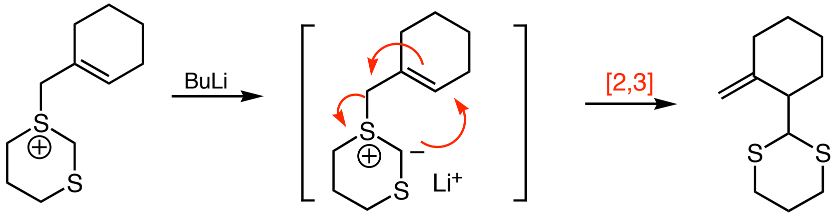


Garst, *JACS* **1976**, *98*, 1526



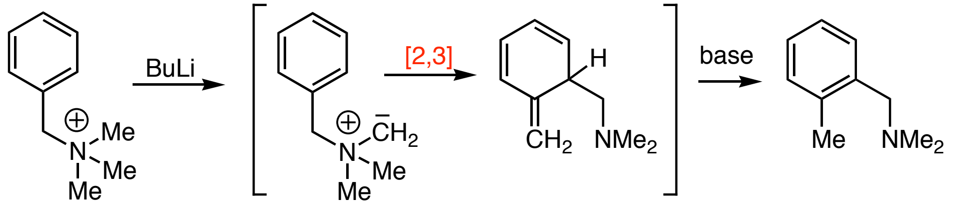
Rautenstrauch, *Chem Commun*. **1979**, 1970 –25 °C ~70% ~30%

■ X - S, Y = C; Sulfonium Ylide Rearrangement:



Lythgoe, *Chem Commum* **1972**, 757

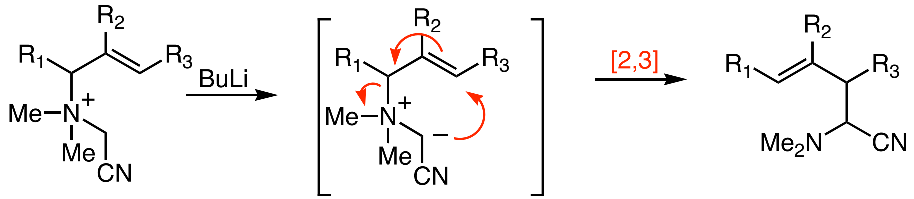
■ X - N, Y = C; Ammonium Ylide Rearrangement:



Review, Pines, *Org. Rxns* **1970**, *18*, 416

Sommelet-Hauser:

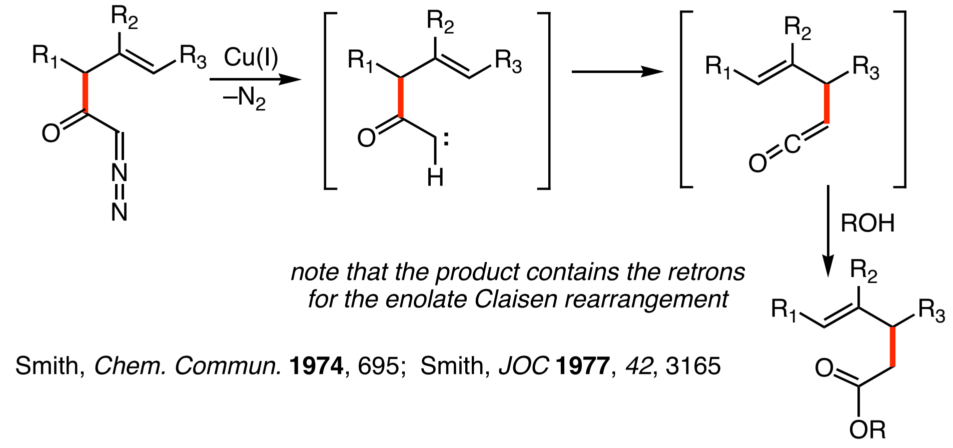
Modern versions of Stevens:



Buchi, *JACS* **1974**, *96*, 7573
Mander, *JOC* **1973**, *38*, 2915
important extension lacking CN FG; Sato, *JACS* **1990**, *112*, 1999

[2,3]-Sigmatropic Rearrangements: Introduction-2

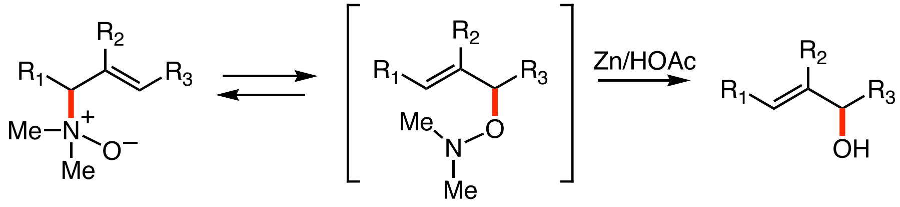
■ X - O, Y = C; An all-carbon Rearrangement



note that the product contains the retrons for the enolate Claisen rearrangement

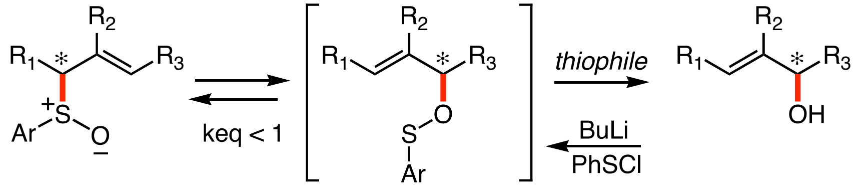
Smith, *Chem. Commun.* **1974**, 695; Smith, *JOC* **1977**, *42*, 3165

■ X - N, Y = O; Meisenheimer Rearrangement



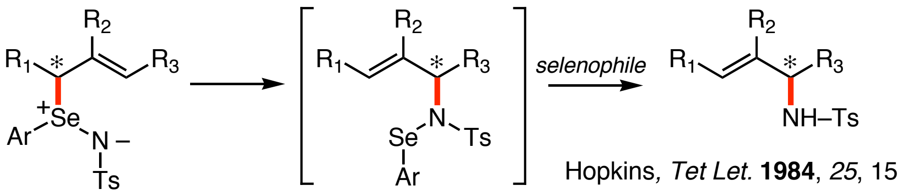
Tanabe, *Tet Let.* **1975**, 3005

■ X - S, Y = O; Sulfoxide Rearrangement



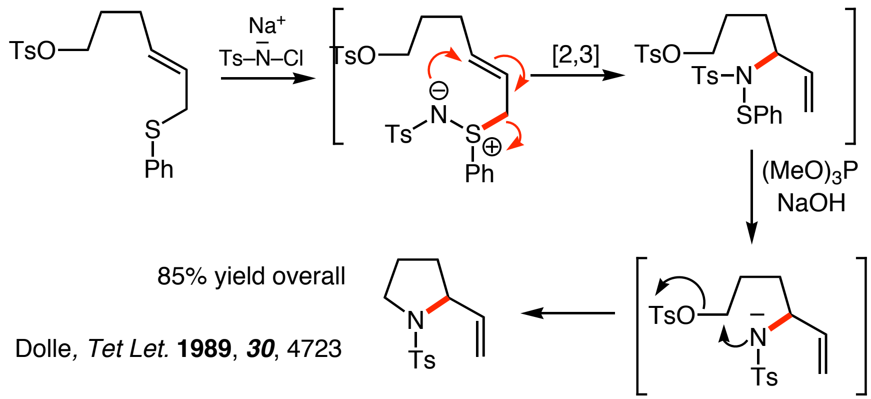
Evans, *Accts. Chem. Res.* **1974**, *7*, 147

■ X - Se, Y = N; Related Rearrangement



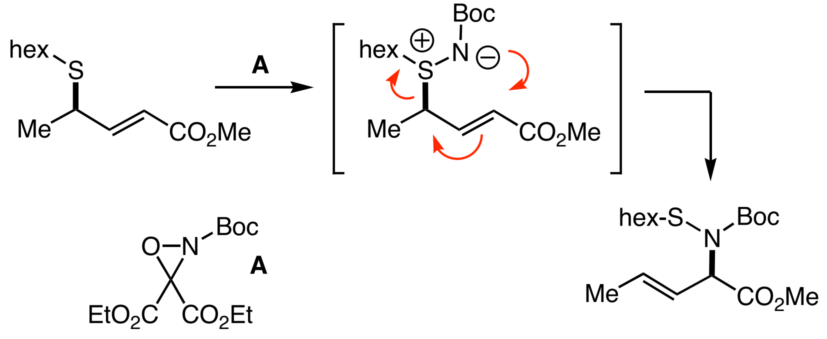
Hopkins, *Tet Let.* **1984**, *25*, 15
Hopkins, *JOC* **1984**, *49*, 3647
Hopkins, *JOC* **1985**, *50*, 417

■ X - S, Y = N; Related Rearrangement



85% yield overall

Dolle, *Tet Let.* **1989**, *30*, 4723

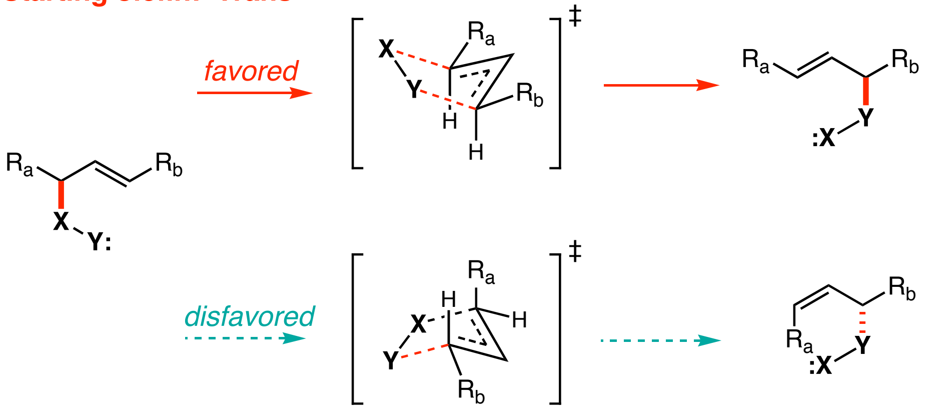


Armstrong et al. *J. Org. Chem.* **2006**, *71*, 4028

[2,3]-Sigmatropic Rearrangements: Olefin Geometry

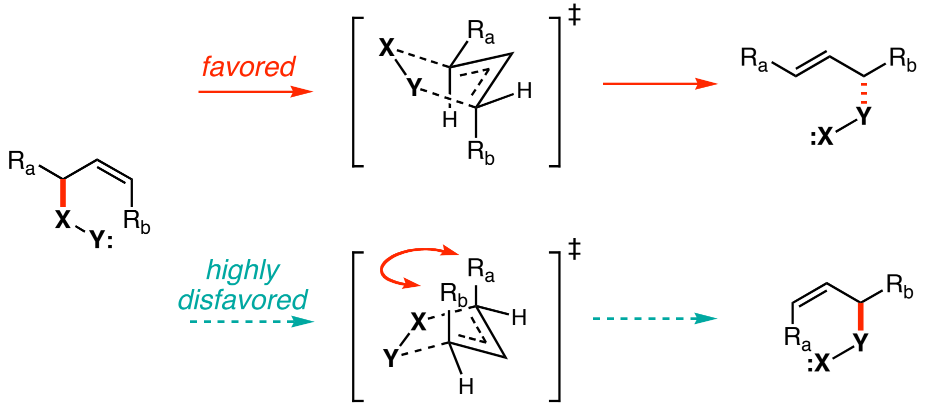
■ 1,2-Disubstitution: Good Trans Olefin Selectivity

Starting olefin: Trans



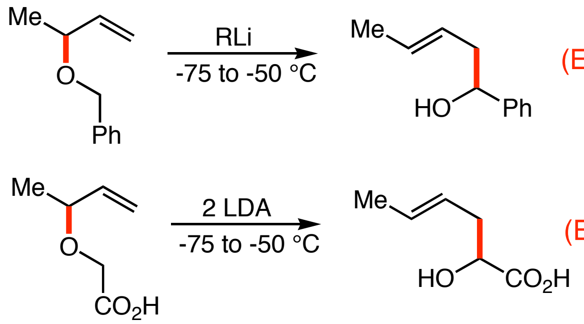
R_a & R_b prefer to orient in pseudo-equatorial positions during rearrangement; nevertheless, this is a delicately balanced situation

Starting olefin: Cis



Conclusions

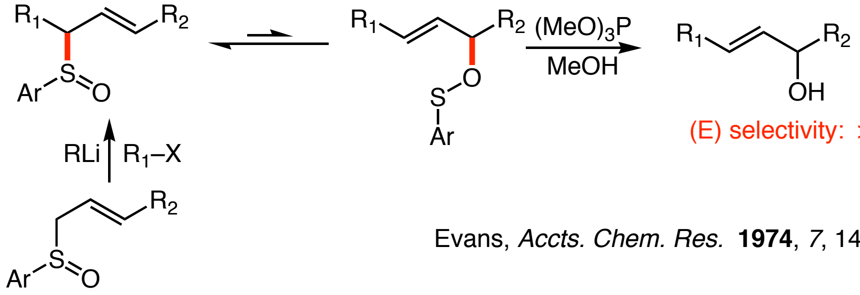
- ❏ Olefin geometry dictates sense of asymmetric induction in rearrangement
- ❏ (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction
- ❏ Product olefin geometry can be either (E) or (Z) from (E) starting material
- ❏ Product olefin geometry will be (E) from (Z) starting material



(E) selectivity: "only isomer"

(E) selectivity: 75%

Nakai, *Tet. Lett* **1981**, *22*, 69

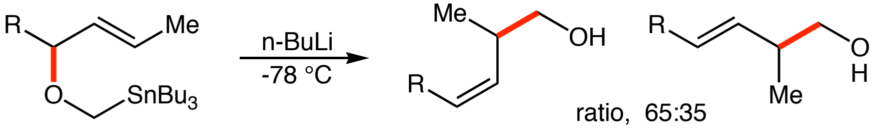


(E) selectivity: >95%

Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55

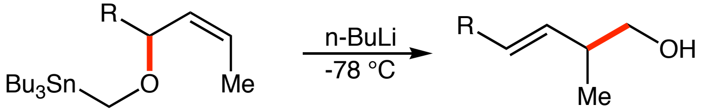
The preceeding transition state models do not explain some of the results:

❏ Cis selectivity has been observed: Still JACS **1978**, *100*, 1927.



ratio, 65:35

❏ However, Cis selectivity is dependent on starting olefin geometry



only (E) isomer (91%)

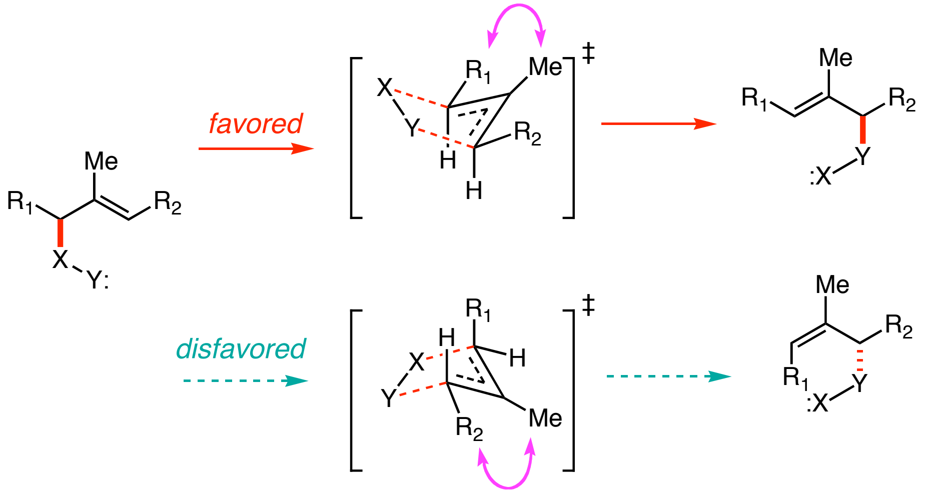
Several theoretical studies have been published: Good reading

Houk JOC **1991**, *56*, 5657 (Sulfur ylide transition states)

Houk JOC **1990**, *55*, 1421 (Wittig transition states)

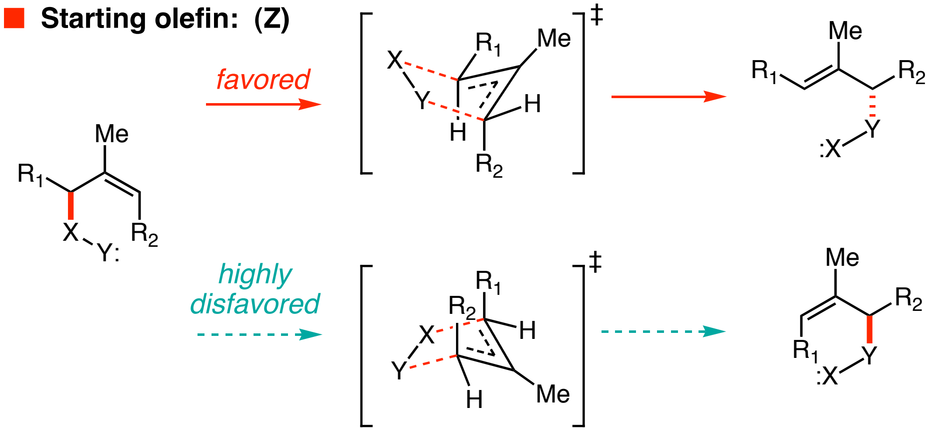
[2,3]-Sigmatropic Rearrangements: Olefin Geometry

■ Starting olefin: (E) Trisubstituted



R_1–Me interaction can destabilize the (E) transition state while (Z) TS might be destabilized by R_1 interactions with both X-Y and allyl moiety.

■ Starting olefin: (Z)



Conclusions

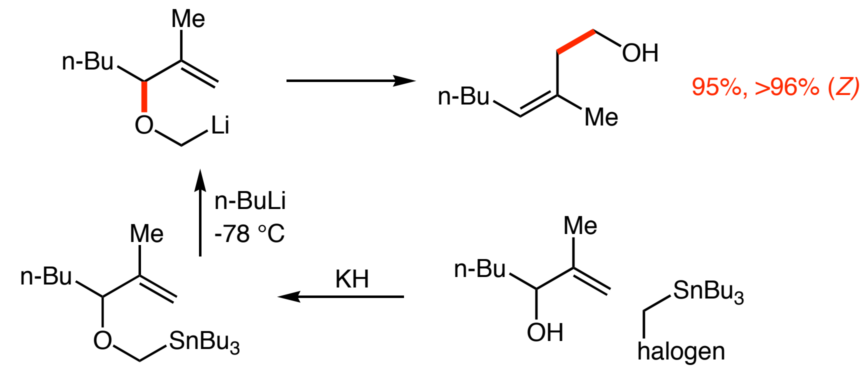
❑ Olefin geometry dictates sense of asymmetric induction in rearrangement

❑ (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction

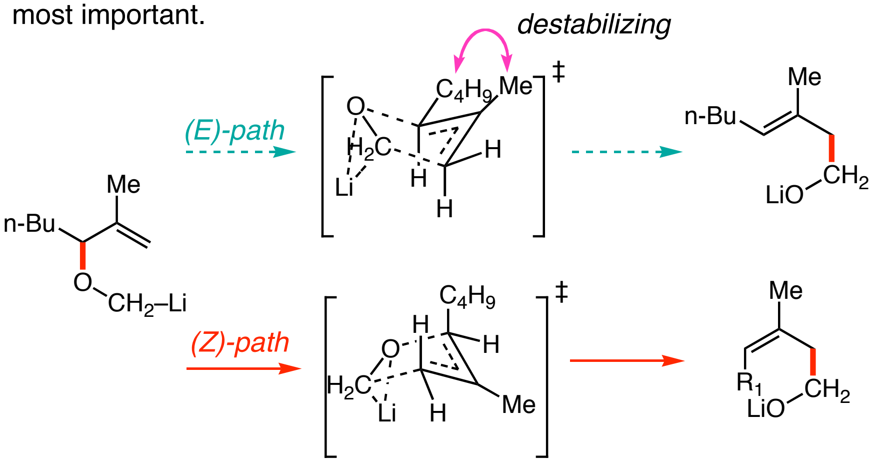
❑ Product olefin geometry can be either (E) or (Z) from (E) starting material

❑ Product olefin geometry will be (E) from (Z) starting material

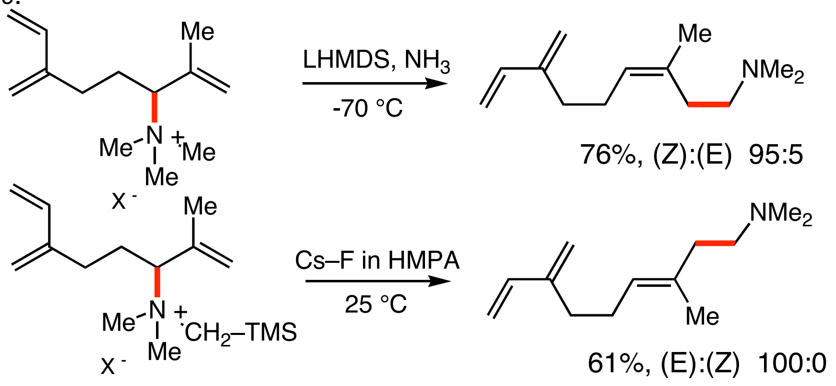
■ (Z) selectivity has been observed: Still JACS **1978**, *100*, 1927.



Still says that the TS is early, so that the 1,2 interactions in the TS are most important.

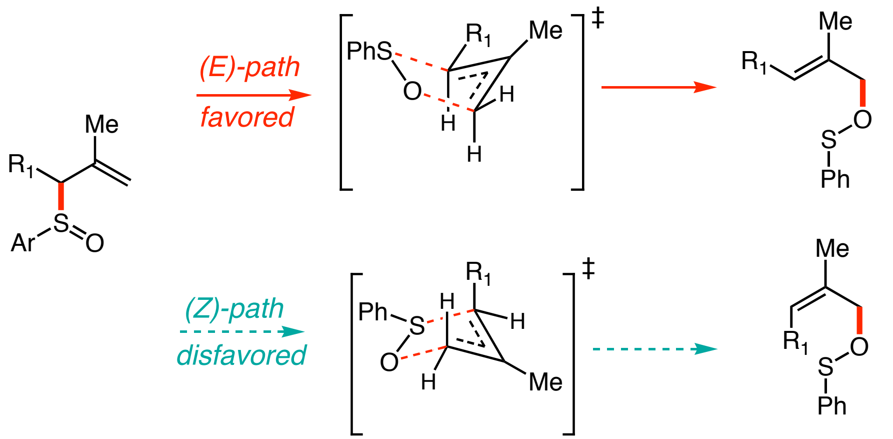


■ (Z) selectivity has also been observed by others: Sato JACS **1990**, *112*, 1999.

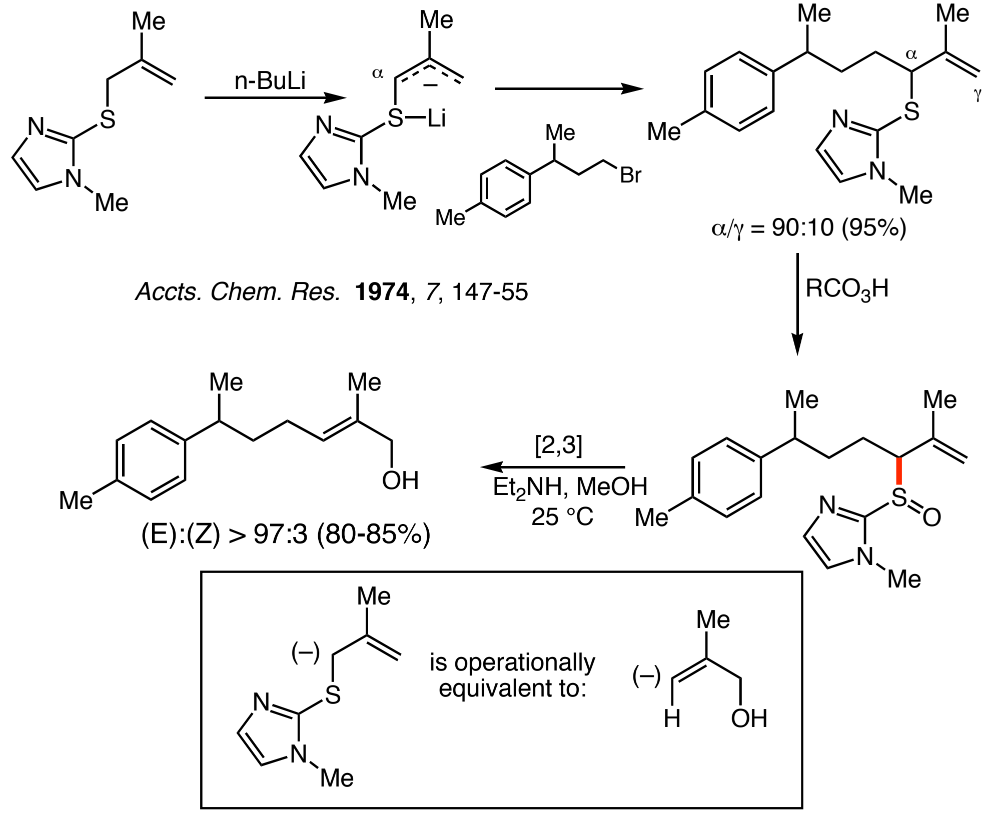


[2,3]-Sigmatropic Rearrangements: Olefin Geometry

Trisubstituted olefins via [2,3]-rearrangement of sulfoxides:

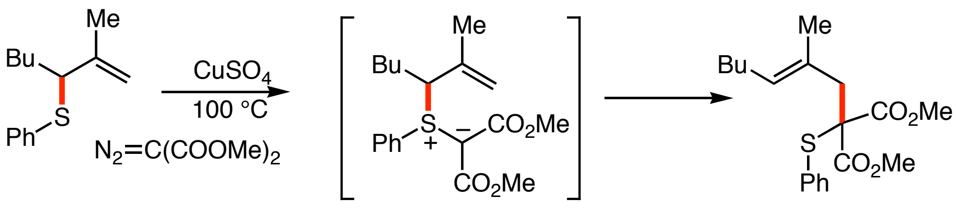


- In contrast to the previous cases exhibiting (Z) selectivity rearrangements (E)-selective rearrangments has been observed:



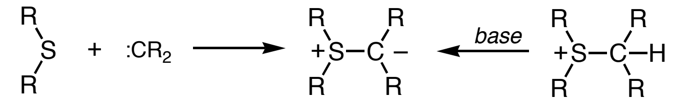
Accts. Chem. Res. **1974**, *7*, 147-55

Trisubstituted olefins via [2,3]-rearrangement of sulfonium ylides:



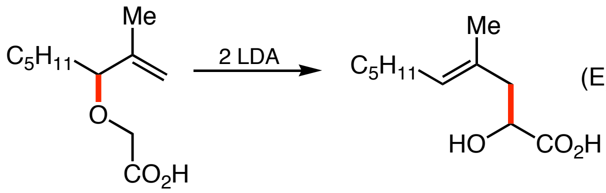
(E):(Z) > 90:10 (70%)

A general procedure for the direct synthesis of sulfur ylides:



pKa ~ 18 (DMSO

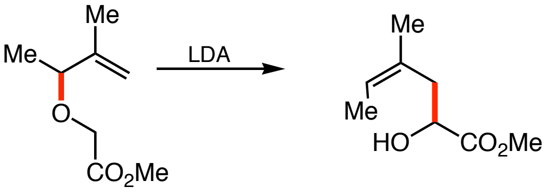
Trisubstituted olefins via Wittig [2,3]-rearrangement:



(E):(Z) > 95:5 (74%)

Nakai, *Tet Let* **1981**, *22*, 69

However, this reaction is not general:

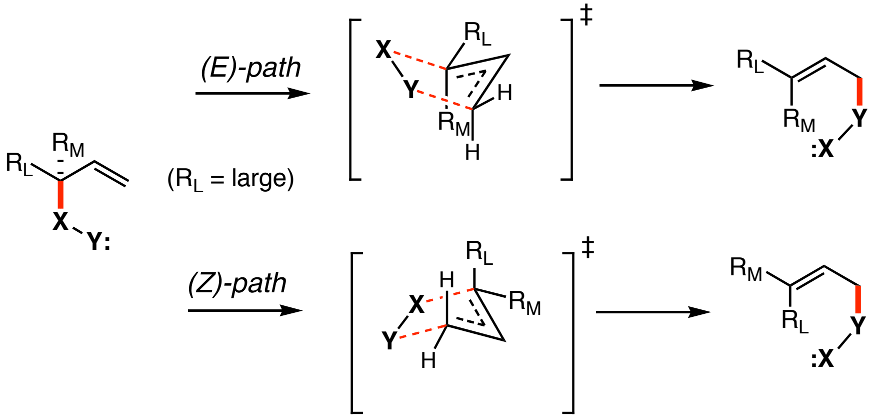


(E):(Z) 31:69

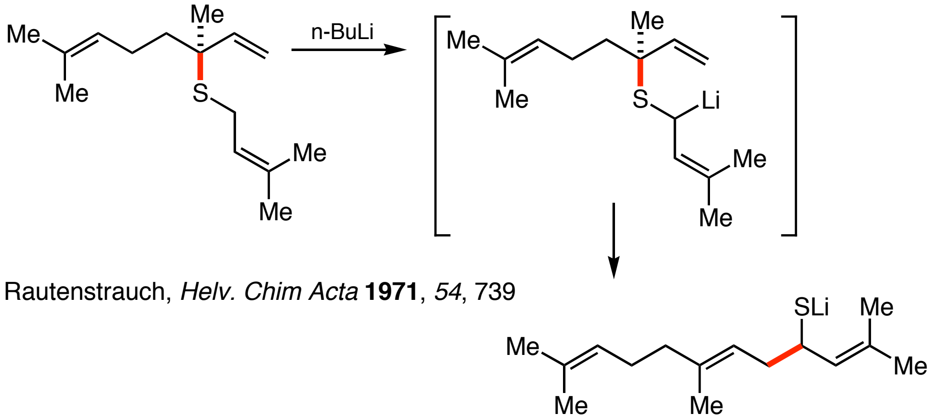
Nakai, *Tet Let* **1986**, *27*, 4511

[2,3]-Sigmatropic Rearrangements: Olefin Geometry

- Trisubstituted olefins via [2,3]-rearrangement:

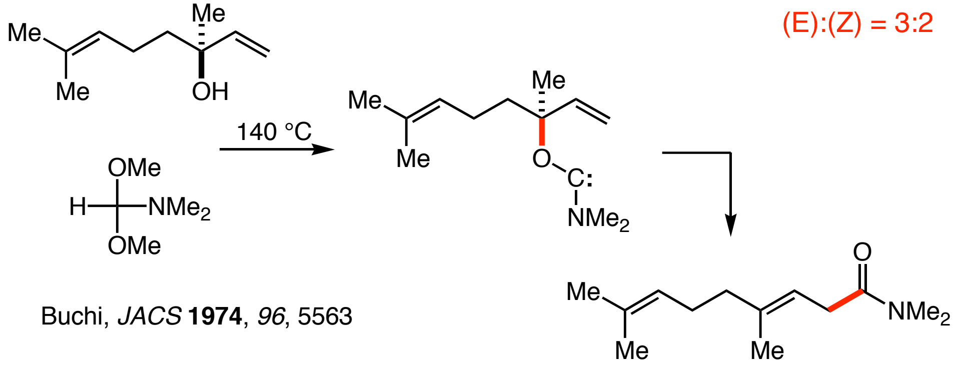


One might project that the (E) path will be moderately favored with selectivity depending on size difference between R_L & R_M



Rautenstrauch, *Helv. Chim Acta* **1971**, *54*, 739

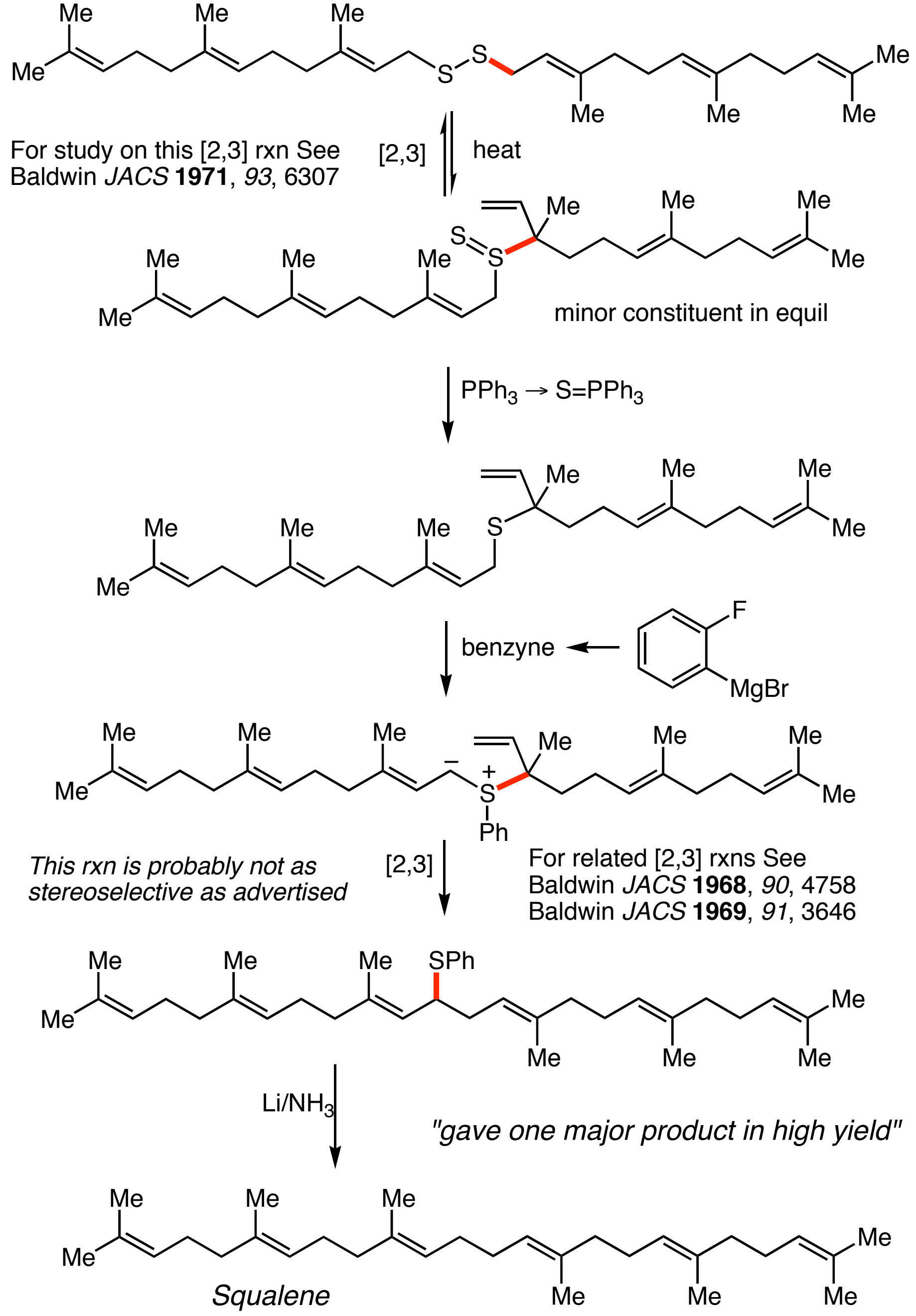
(E):(Z) = 3:2



Buchi, *JACS* **1974**, *96*, 5563

poorly selective

An elegant squalene synthesis **Ollis, *Chem. Commun* 1969, 99**



For study on this [2,3] rxn See Baldwin *JACS* **1971**, *93*, 6307

minor constituent in equil

This rxn is probably not as stereoselective as advertised

For related [2,3] rxns See
Baldwin *JACS* **1968**, *90*, 4758
Baldwin *JACS* **1969**, *91*, 3646

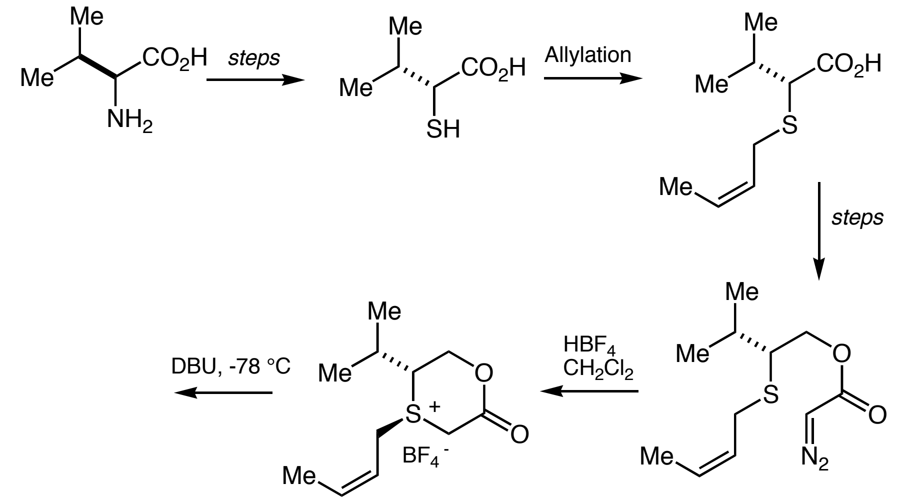
"gave one major product in high yield"

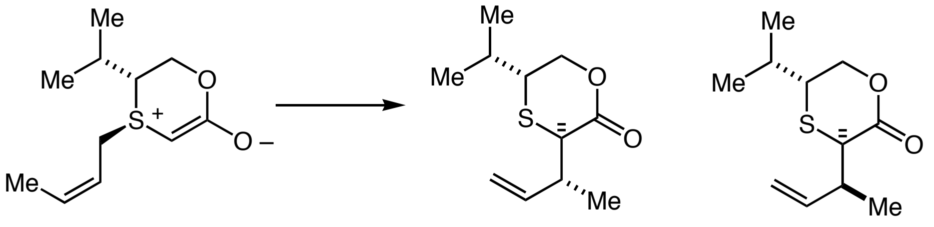
Squalene

[2,3]-Sigmatropic Rearrangements: Chirality Transfer

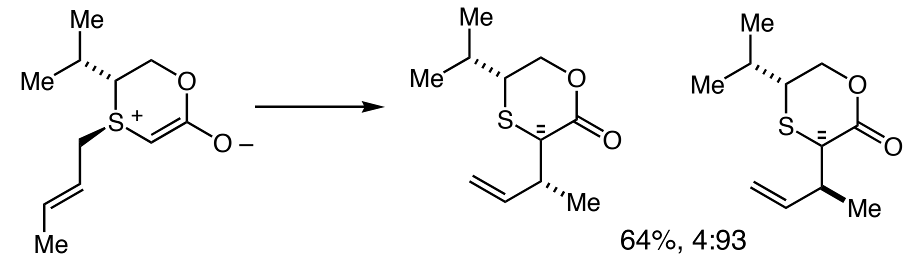
[2,3] Sulfur Ylide Rearrangement Using a Chiral Auxiliary

Kurth JOC **1990**, *55*, 2286 and TL **1991**, *32*, 335



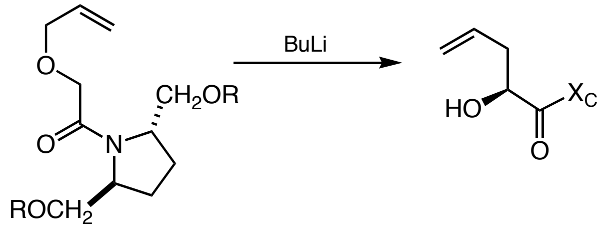


66%, 94:4

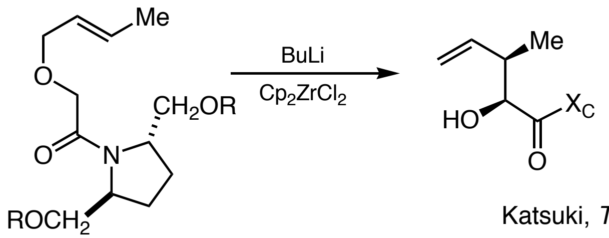


64%, 4:93

Chiral Auxiliaries can also be used in the Wittig Rearrangement



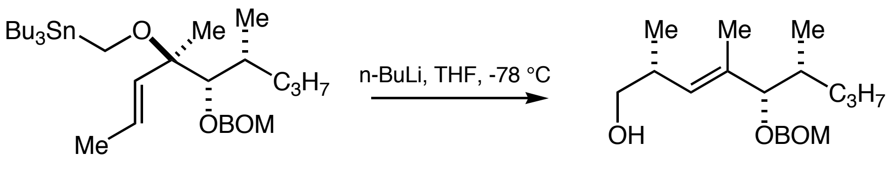
96% de (61%)



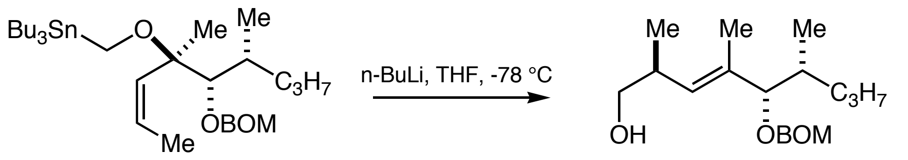
97% syn; 96% de (43%)

Katsuki, *Tet Lett* **1986**, *27*, 4577

Internal Relay of Stereochemistry in C–C Constructions



diastereoselection > 100:1 (57%)



Kallmerten TL **1988**, *29*, 6901.

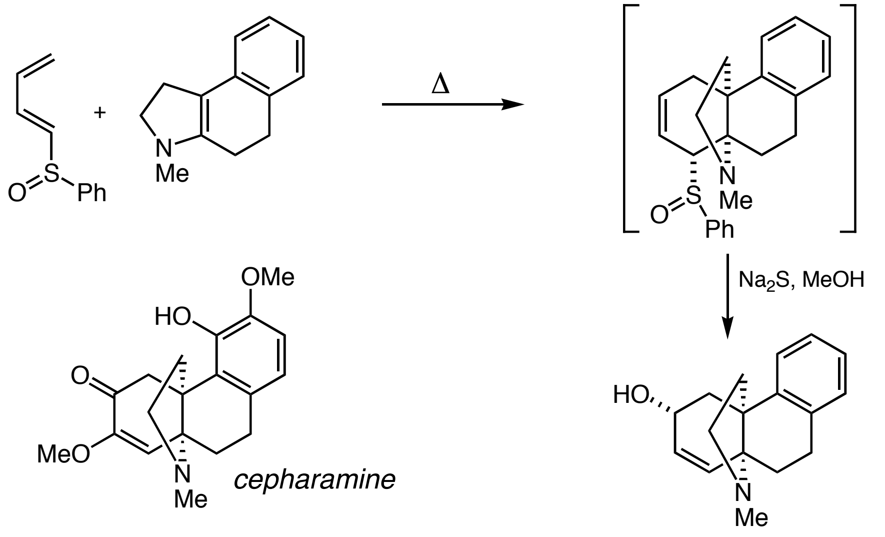
diastereoselection > 100:1 (64%)

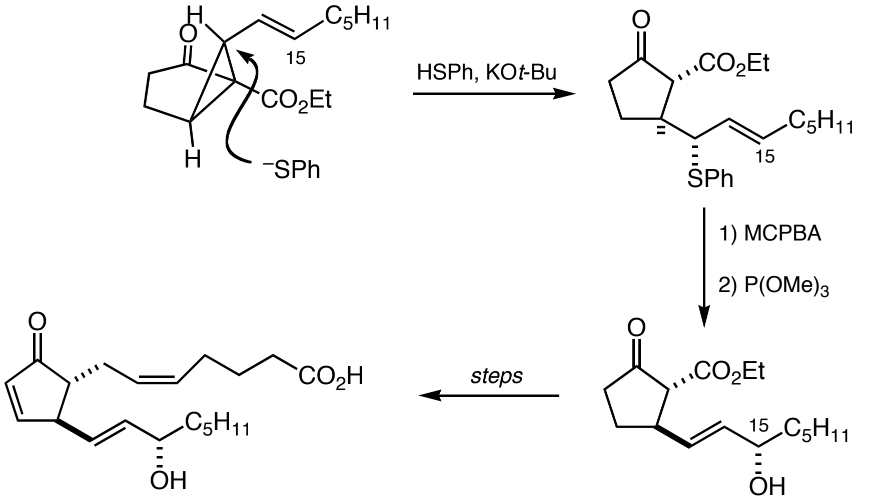
See these papers for other applications
- Kallmerten TL **1993**, *34*, 753.
- Kallmerten TL **1993**, *34*, 749.
- Kallmerten SynLet **1992**, 845.

[2,3]-Sigmatropic Rearrangements: Chirality Transfer

Internal Relay of Stereochemistry in C–O Constructions

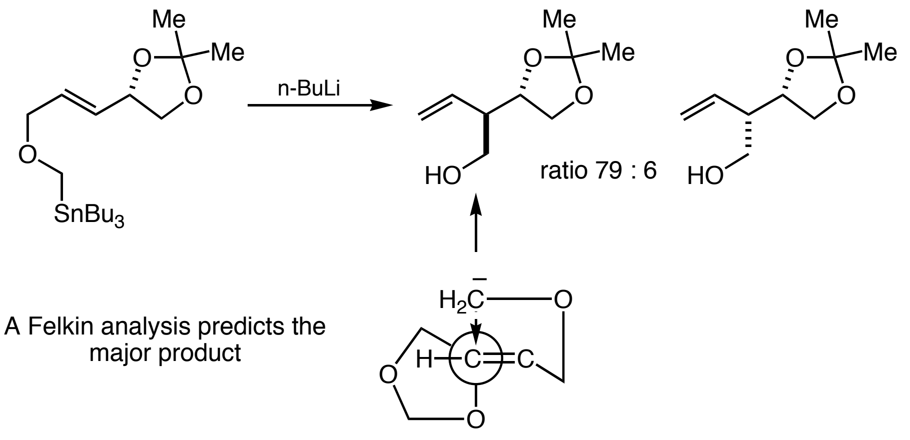
Tandem [4+2] & [2,3] Process: Evans, Bryan, Sims *J. Am. Chem. Soc.* **1972**, 2891.





Taber *J. Am. Chem. Soc.* **1977**, *99*, 3513.
Kondo *Tet. Lett.* **1978**, 3927.

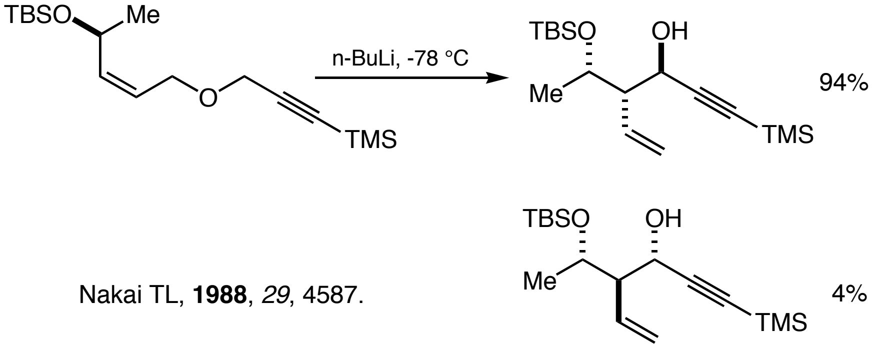
Cases where the chirality is exocyclic to the rearrangement



A Felkin analysis predicts the major product

Bruckner, *Angew. Chem. Int. Ed.* **1988**, *27*, 278

Allylic Ethers to Make Three Contiguous Stereocenters

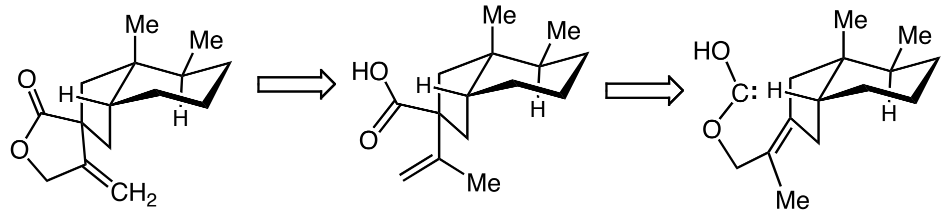


Nakai TL, **1988**, *29*, 4587.

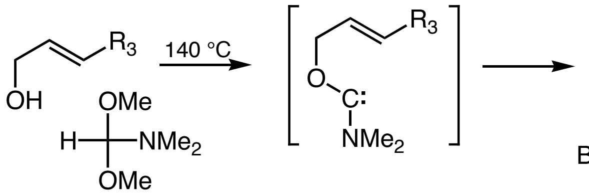
Can you rationalize the stereochemical outcome of this reaction?

[2,3]-Sigmatropic Rearrangements: Chirality Transfer

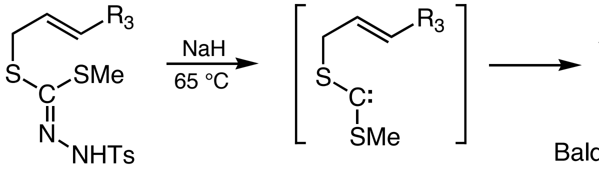
The Synthesis of Bakkenolide-A *(Evans JACS* **1977**, *99,* 5453)



- Candidate processes:

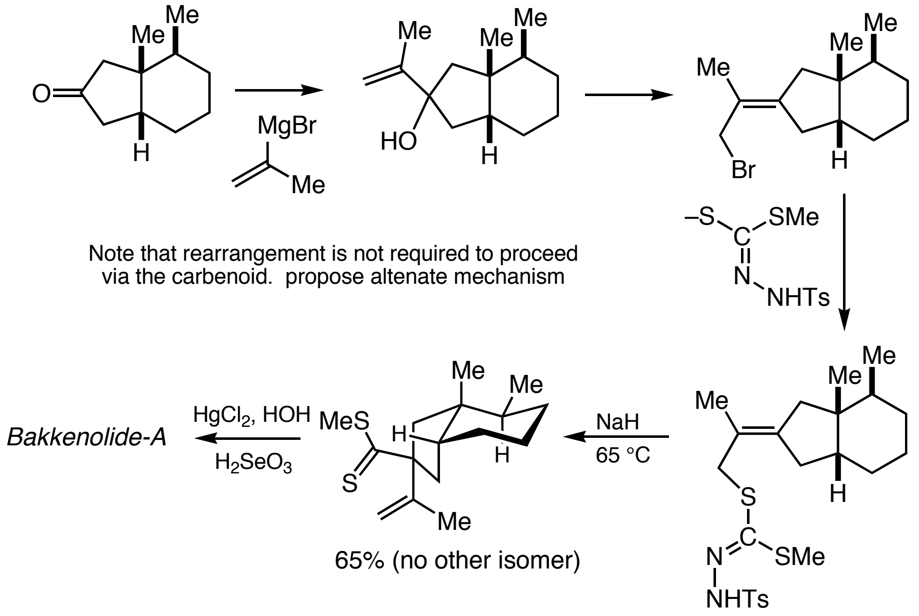


Buchi, *JACS* **1974**, *96*, 5563



Baldwin, *Chem Comm* **1972**, 354

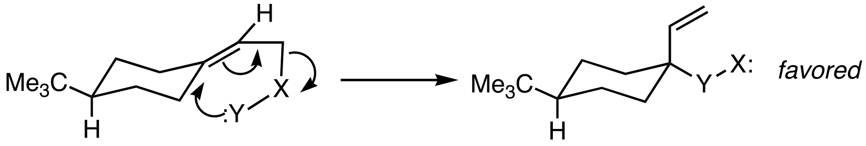
- The synthesis:

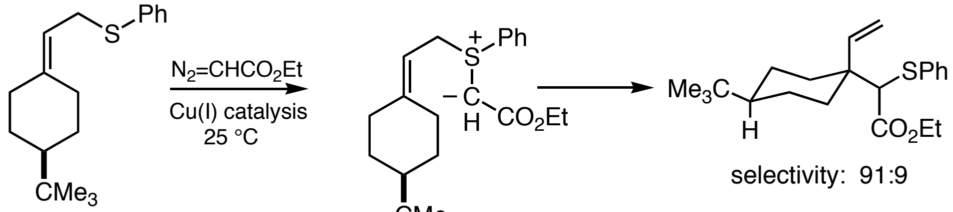


Note that rearrangement is not required to proceed via the carbenoid. propose altenate mechanism

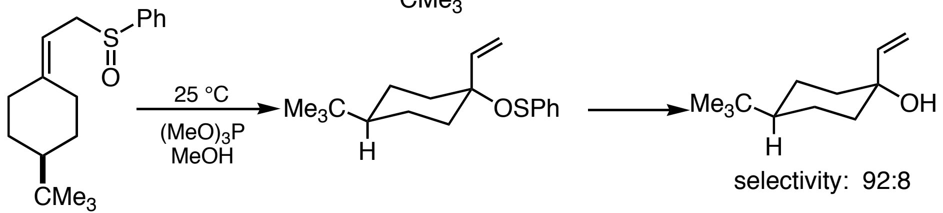
65% (no other isomer)

[2,3] Sigmatropic rearrangements respond to subtile steric effects



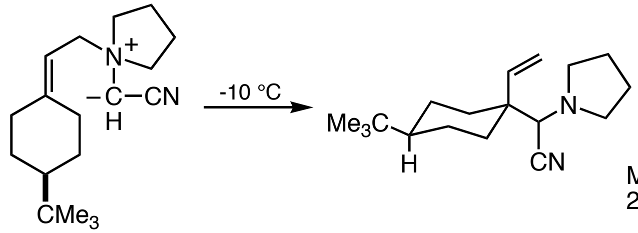


selectivity: 91:9



selectivity: 92:8

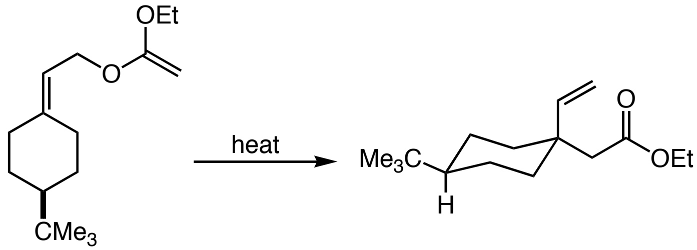
Evans, *JACS*, **1972**, *94*, 3672



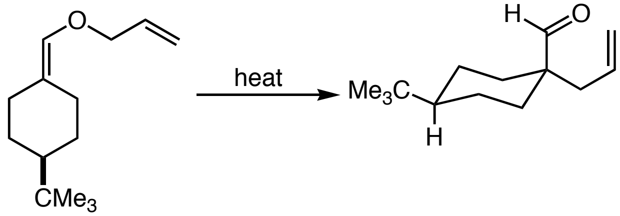
selectivity: 90:10

Mander, *JOC*, **1973**, *38*, 2915

- The comparison of analogous [2,3] & [3,3] rearrangements:



selectivity: 52:48



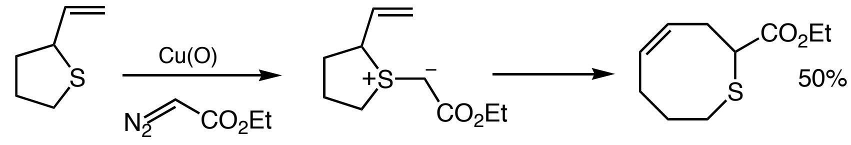
selectivity: 75:25

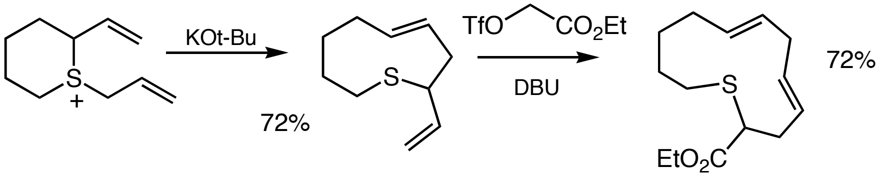
House, *JOC* **1975**, *40*, 86

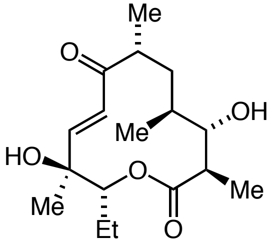
[2,3]-Sigmatropic Rearrangements: Ring Expansion & Contraction

Ring expansion reactions have been investigated

Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358



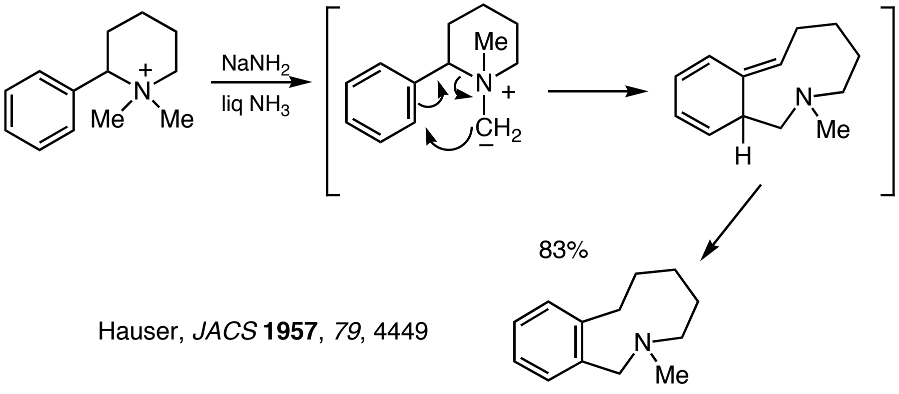




Methynolide has been synthesized by Vedejs using this ring-expansion methodology

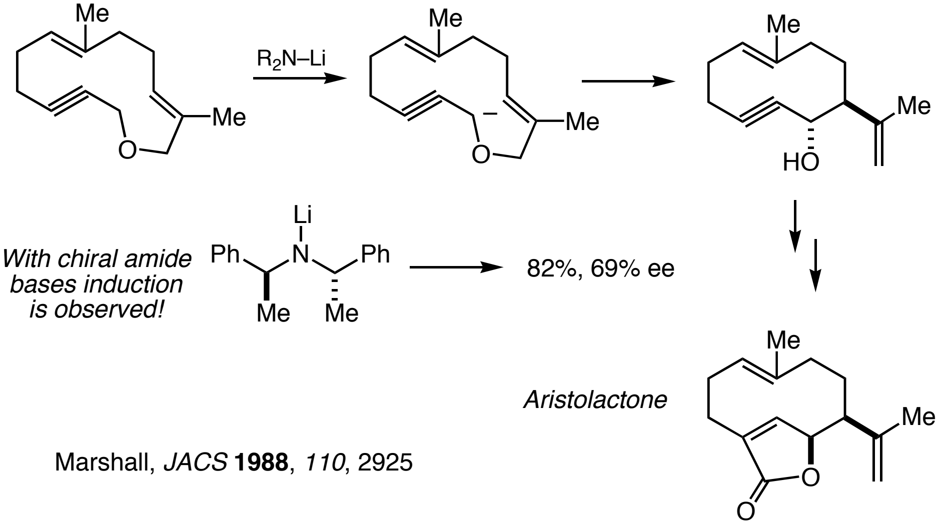
Vedejs, *JACS* **1989**, *111*, 8430

An early ring expansion using the Sommelet-Hauser Rearrangement



Hauser, *JACS* **1957**, *79*, 4449

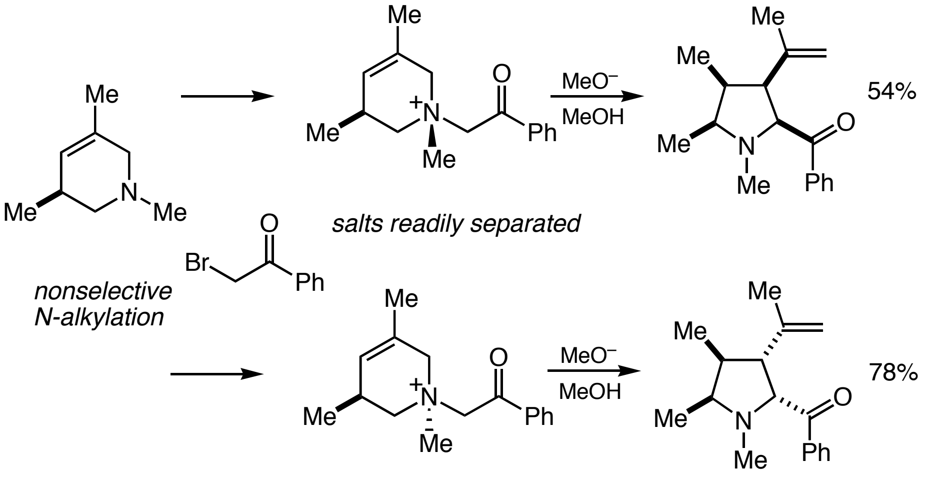
A ring contraction using the Wittig Rearrangement



With chiral amide bases induction is observed!

Marshall, *JACS* **1988**, *110*, 2925

A ring contraction using the Stevens Rearrangement



salts readily separated

nonselective N-alkylation

Both rearrangements afford a single isomer

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 14

Pericyclic Reactions–4

- [3,3] Sigmatropic Rearrangements: Introduction
- Cope Rearrangements & Variants
- Claisen Rearrangements & Variants

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

K. Houk, *Transition Structures of Hydrocarbon Pericyclic Rxns*
Angew Chem. Int. Ed. Engl. **1992**, *31*, 682-708

K. Houk, *Pericyclic Reaction Transition States: Passions & Punctilios, Accts. Chem. Res.* **1995**, *28,* 81-90
Angew Chem. Int. Ed. Engl. **1992**, *31*, 682-708

D. A. Evans

Friday,
October 20, 2006

Other Reading Material:

[3,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)

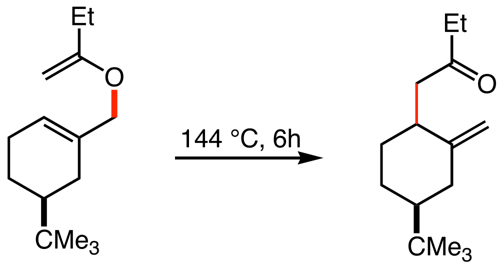
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)

Paquette, L. A. (1990). “Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement.” Angew. Chem., Int. Ed. Engl. 29: 609.

Problems of the Day:

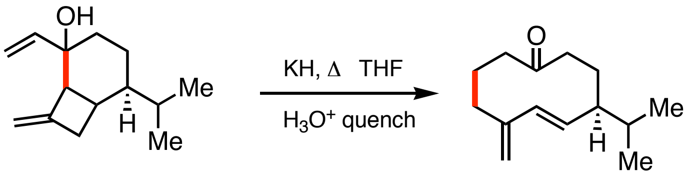
Predict the stereochemical outcome of this Claisen rearrangement



diastereoselection
>87:13

Ireland, *JOC* 1983, *48*, 1829

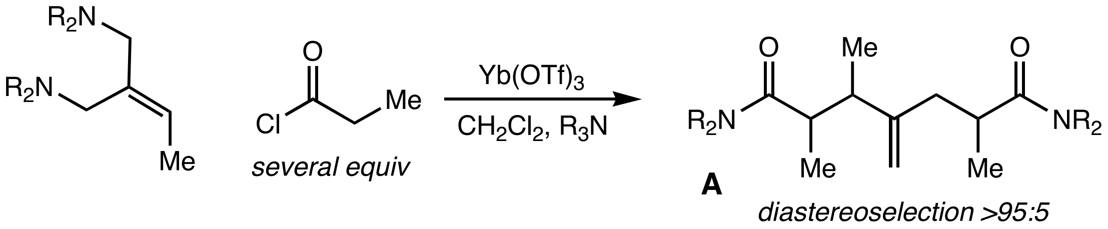
Provide a mechanism for the indicated transformation



Schreiber, *JACS* **1984***, 106,* 4038

Database Problem number 117: Key words: Rearrangement + Claisen

In a recent article, MacMillan and Yoon (*JACS* **2001**, *123*, 2448) reported the complex rearrangement illustrated below.

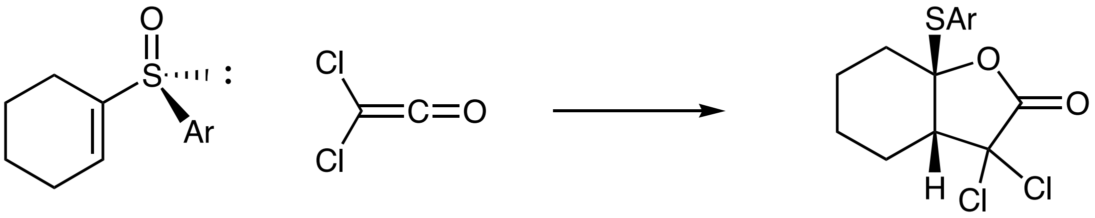


Part A. Provide a mechanism for this overall transformation. In answering this question, you should illustrate those transition states where stereocenters are generated and where stereochemcal information is relayed.

Part B. From your answer in Part A, illustrate the stereochemical relationships in the diamide product **A**.

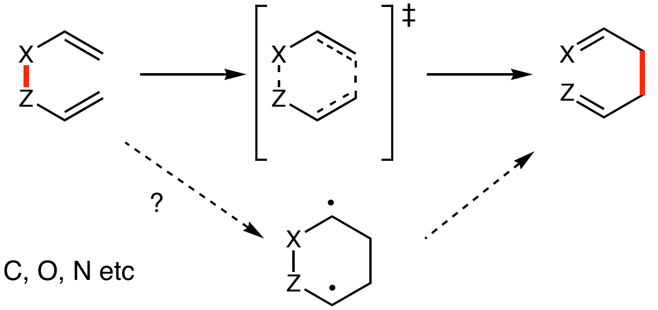
Database Problem number 195: Key words: Rearrangement + Claisen

Provide a mechanism for the indicated transformation that accounts for the observed stereochemical outcome (*JACS*, **1984**, 7643).

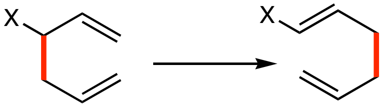


General Reviews:

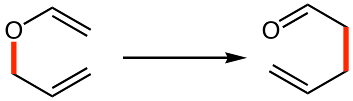
S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)
T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen



X & Z = C, O, N etc

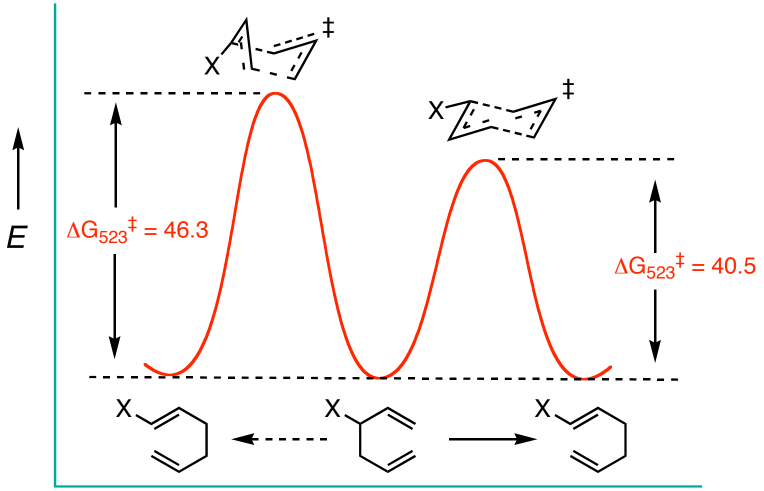


Cope Rearrangement, Ea = 33.5 kcal/mol

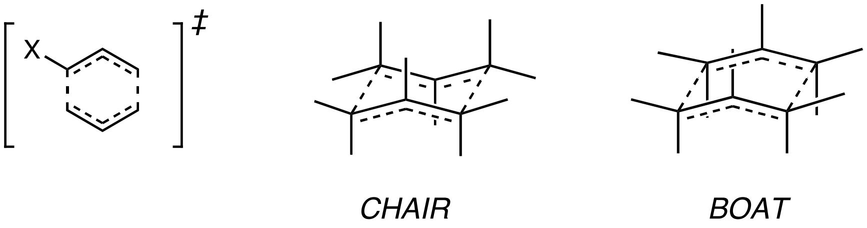


Claisen Rearrangement Ea = 30.6 kcal/mol

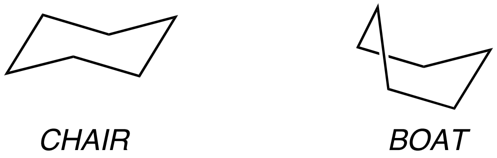
The Reaction Energetics Goldstein, *JACS* **1972**, *94*, 7147



The CopeTransition States



Relative Energy $\Delta\Delta G^{\ddagger}$: 0 + 5.8 kcal/mol

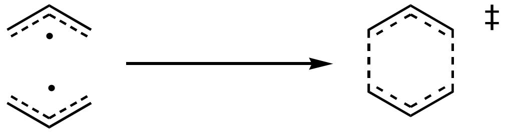


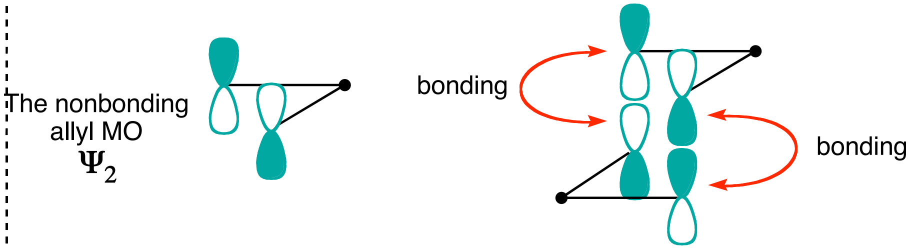
Relative Energy $\Delta G°$: 0 + 5.3 kcal/mol

The Boat and Chair geometries for these transition structures are well defined.

The FMO Analysis (Fleming page 101)

Bring two allyl radicals together to access for a possible bonding interaction between termini.

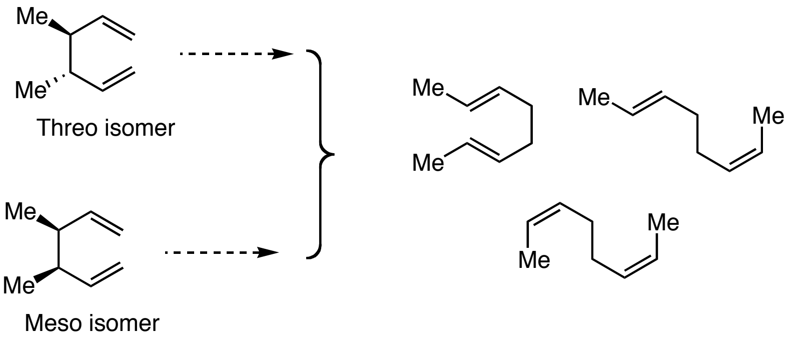




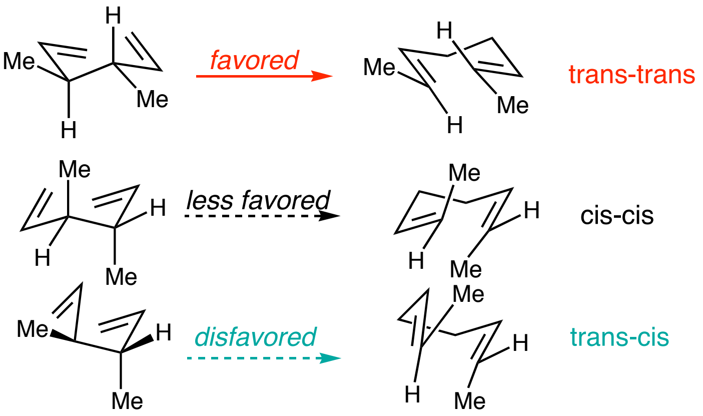
It is evident that synchronous bonding is possible in this rearrangement

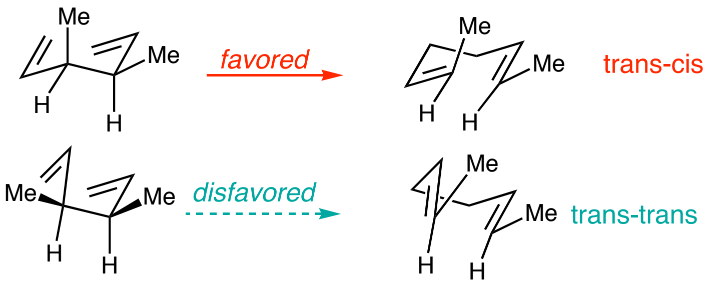
Doering/Roth Experiments: ***Tetrahedron* 18, 67, (1962):**

The Geometry of the transition state (boat vs chair) can be analyzed via the rearrangement of substituted 1,5-dienes:

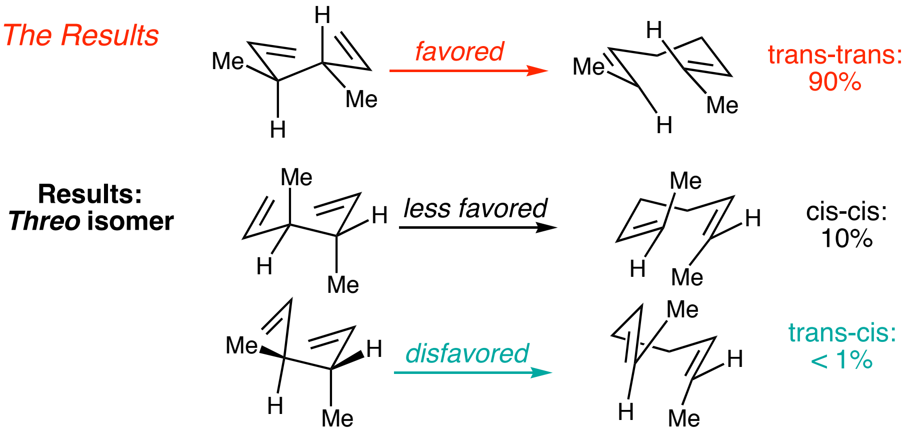


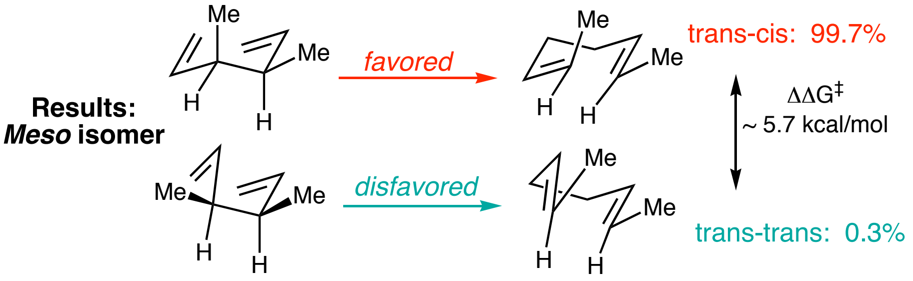
- Measure product composition from rearrangement of each diene isomer



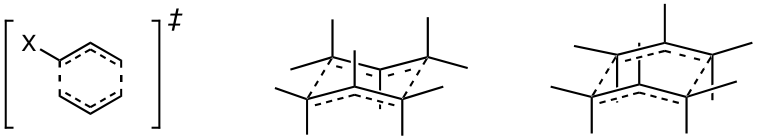


The Results

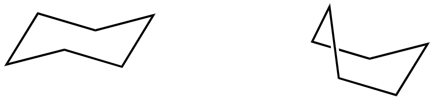




The CopeTransition States



	CHAIR	*BOAT*
Relative Energy $\Delta\Delta G^{\ddagger}$:	0	+ 5.8 kcal/mol

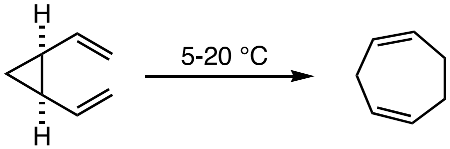


	CHAIR	*BOAT*
Relative Energy $\Delta G°$:	0	+ 5.3 kcal/mol

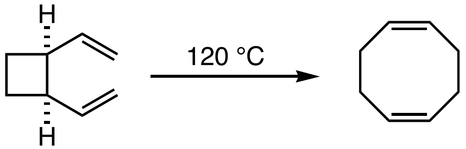
The Boat and Chair geometries for these transition structures are well defined.

Strain–Accelerated Cope Rearrangements

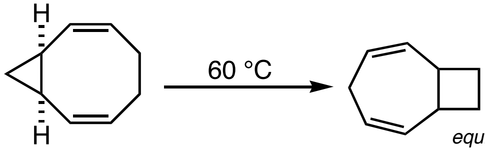
Ring Strain can be employed to drive the Cope process:



Brown *Chem. Commun.* **1973**, 319



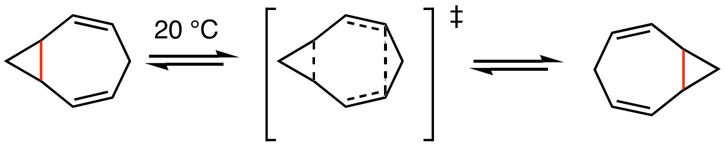
Vogel *Annalen* **1958**, *615*, 1



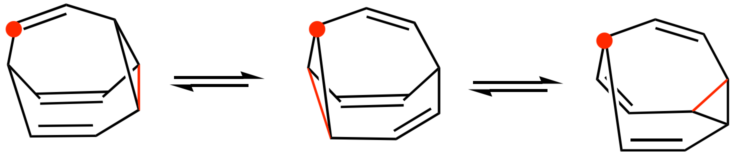
Reese *Chem. Commun.* **1970**, 1519

equilibrium stongly favors this isomer

Ring Strain can be employed to drive the Cope process:



W. von E. Doering's Bullvalene

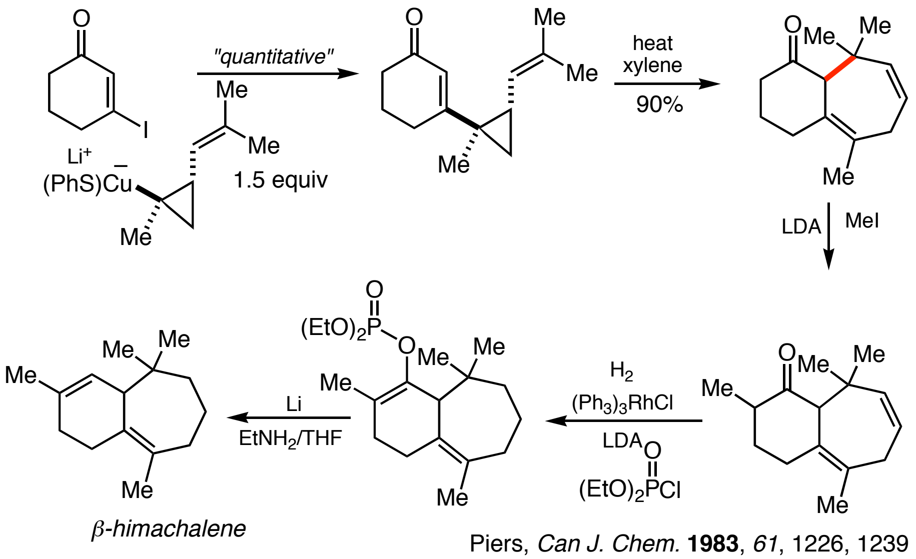


Bullvalene: Ea = 13.9 kcal/mol

At 100 °C one carbon is observed in nmr spectrum

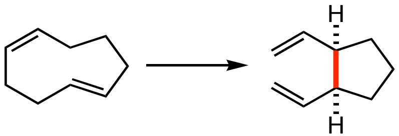
Carey, Vol 1, page 630–631

■ Ring extension via divinylcyclopropane rearrangement

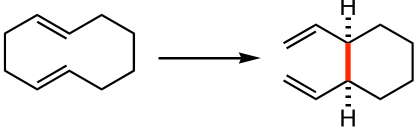


Piers, *Can J. Chem.* **1983**, *61*, 1226, 1239

■ Position of Equilibrium dictated by ring strain issues:

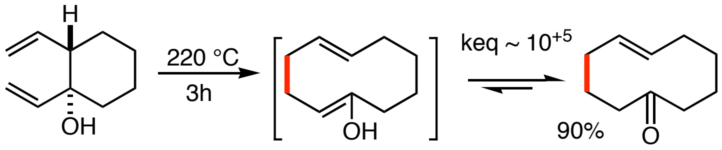


Vogel *Angew. Chem. Int. Ed.* **1963**, *2*, 739



Wharton *J. Org. Chem.* **1973**, *38*, 4117

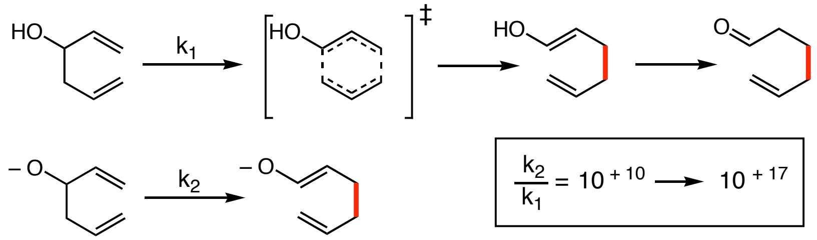
■ However, tautomerism can shift the equilibrium:



Marvell, *Tet. Lett.* **1970**, 509

Energetically, how much does tautomerization give you?

Accelerated Cope Rearrangements

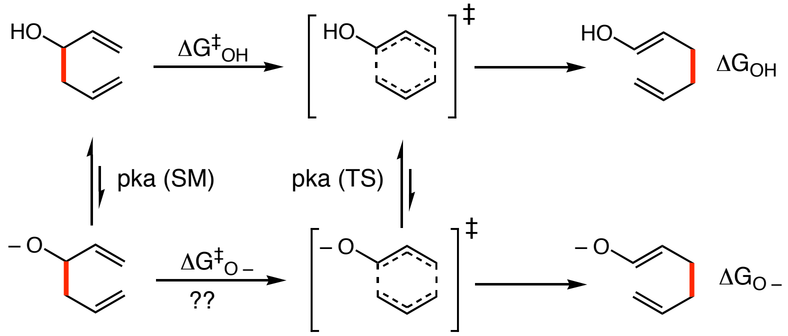


$$\frac{k_2}{k_1} = 10^{+10} \longrightarrow 10^{+17}$$

Evans, Golob, *JACS* **1975**, *97*, 4765.

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
"Recent applications of anionic oxy-Cope rearrangements."
Paquette, L. A. *Tetrahedron* 1997, *53*, 13971-14020

A priori Estimate of the Acceleration (DAE)



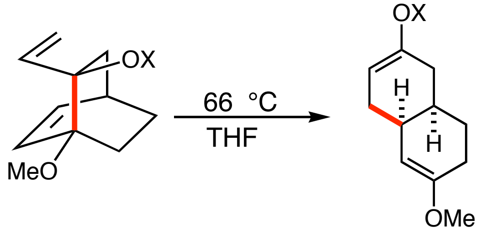
$$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} + 2.3RT\,[\,pka_{TS} - pka_{SM}]$$

$$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} + 2.3RT\,[18 - 29] \quad \text{(in DMSO)}$$

$$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} + 1.4\,[-11]$$

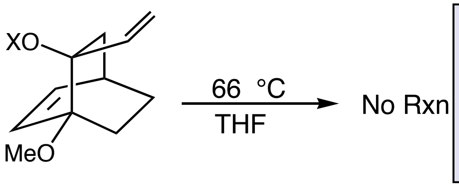
$$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} - 15 \text{ kcal/mol at 298 K (in DMSO)}$$

Documentation of Alkoxy Substituent Effect



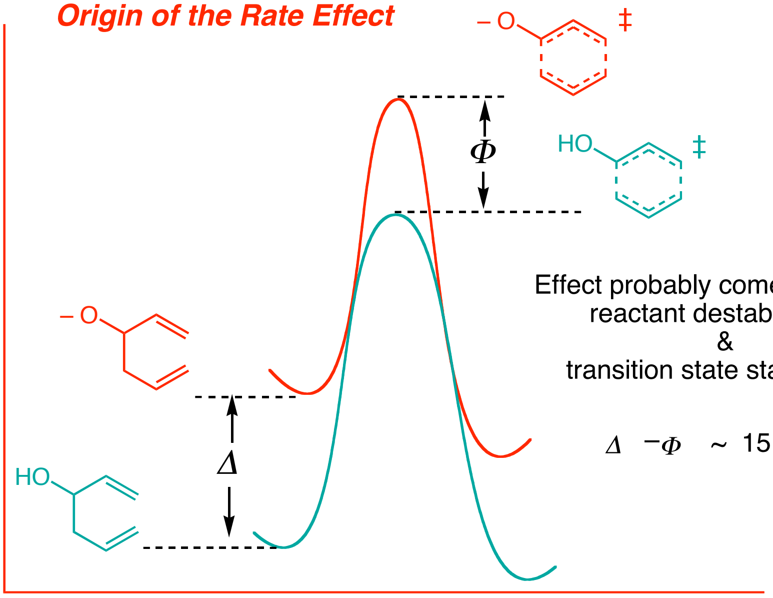
–OX	Half-life	
–OH	(66 yrs)	66 °C
–OLi	no rxn	
–ONa	1.2 hrs	
–OK	1.4 min	
–OK	11 hrs	10 °C
(HMPT) $-O^{-}\,{}^{+}K$	4.4 min	

10^{+12} rate acceleration



$$\Delta\Delta G^{\ddagger}_{estimate} = 15 \text{ kca mol}^{-1}$$
$$\Delta\Delta G^{\ddagger}_{experiment} = 13 \text{ kca mol}^{-1}$$

Origin of the Rate Effect



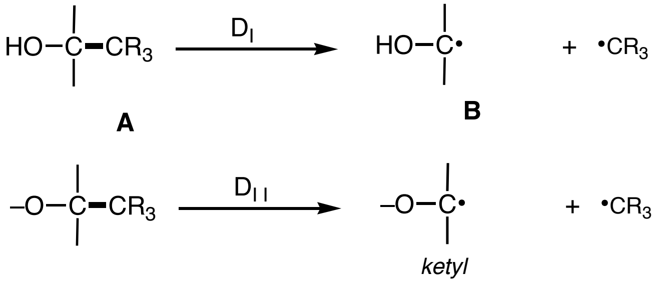
Effect probably comes from both
reactant destabilization
&
transition state stabilization

$\Delta - \Phi \sim 15$ kcal/mol

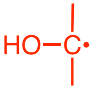
Maximal rates are observed under conditions where reactant is maximally destabilized

Anionic Substituent Effects: Bond Homolysis

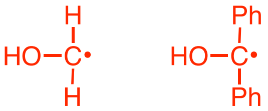
Substituent Effects in Bond Homolysis



$$D_I - D_{II} = 2.3\ RT\ [pka\ (\mathbf{A}) - pka\ (\mathbf{B})]$$



Acidities of these radicals are known in H_2O, Hayon, *Accts. Chem. Res.* **1974**, *7*, 114

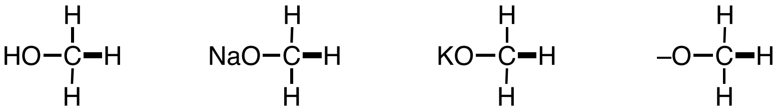


(H_2O) pKa = 10.7 pKa = 9.2

In DMSO, $\Delta D = 2.3\ RT\ [29 - 18] \sim 15$ kcal/mol

■ Substituent Effect based on ab initio calculations

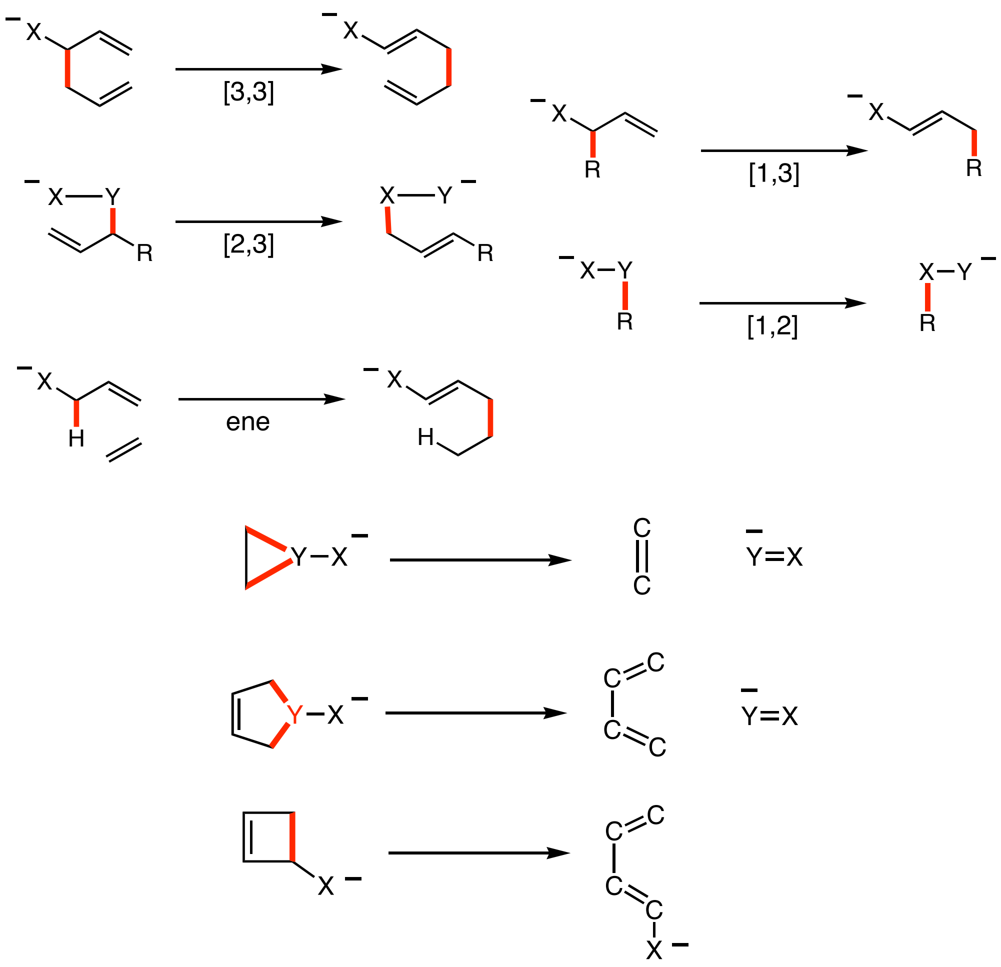
(Evans, Goddard, *JACS* **1979**, *101*, 1994)

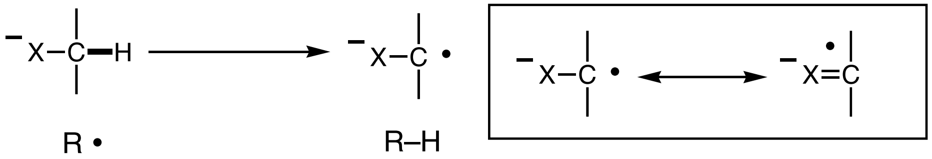


BDE = 90.7 (BDE = 91.8 expt) BDE = 80.6 BDE = 79.0 BDE = 74.2

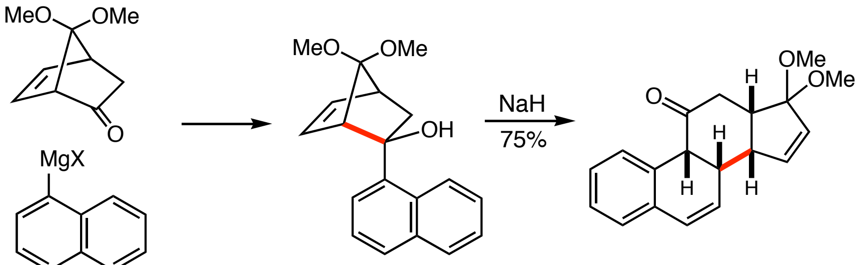
ΔD
+16.5 kcal/mol

Substituent Effects in Molecular Rearrangements

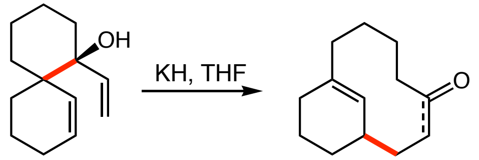




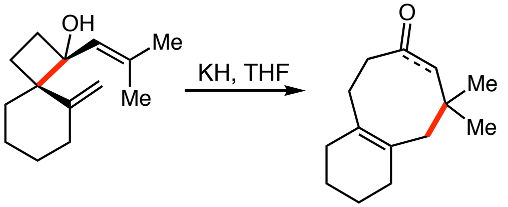
Anionic Oxy-Cope Rearrangement: Applications



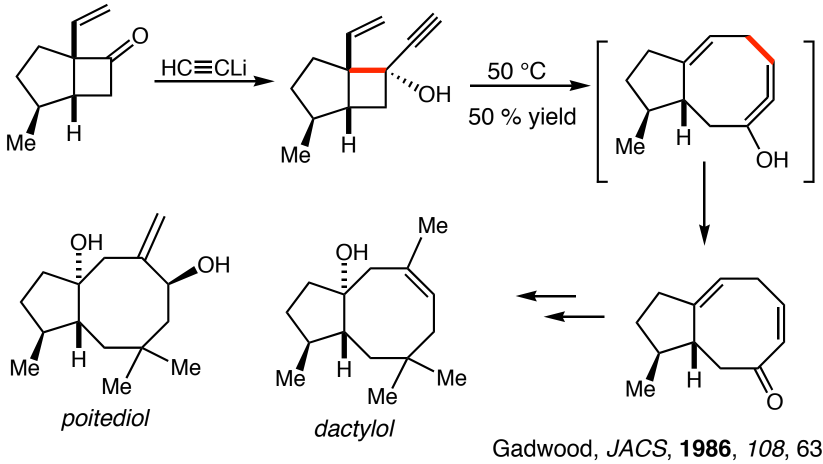
Jung, JACS **1978**, *100*, 4309
Jung, JACS **1980**, *102*, 2463



Levine, JOC **1981**, *46*, 2199

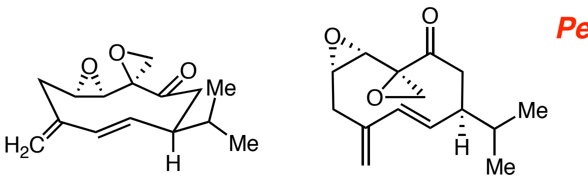


Gadwood, *JOC*, **1982**, *47*, 2268

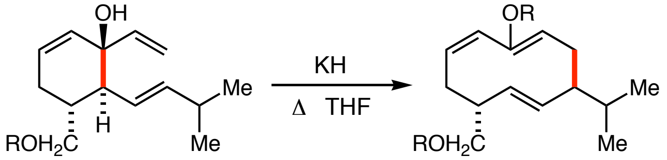


Gadwood, *JACS*, **1986**, *108*, 6343

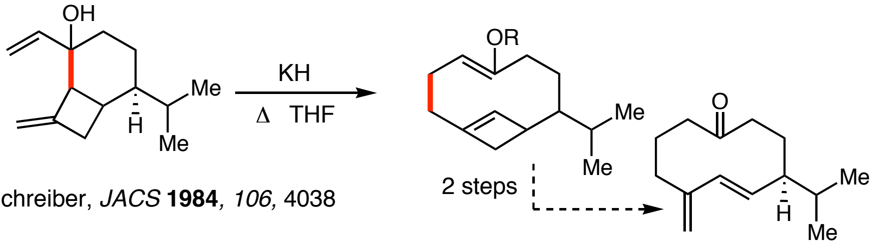
Periplanone-B Synthesis



200 µg from 75,000 virgin female cockroaches

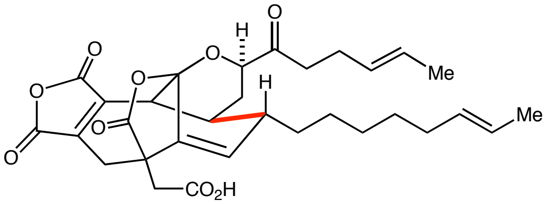


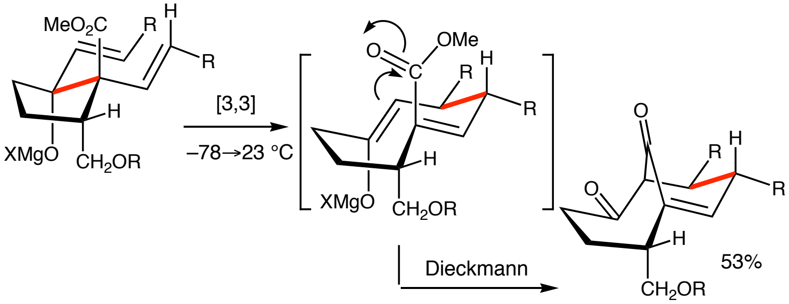
Still, *JACS* **1979**, *101*, 2493



Schreiber, *JACS* **1984**, *106*, 4038

Synthesis of (+)-CP-263,114: Shair, *JACS* **2000**, *122*, 7424-7425.

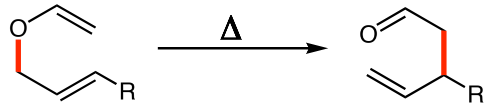




General Reviews:

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Ch 7.2
Ziegler, *Accts. Chem. Res.* **1977**, *10*, 227 (Claisen)
Bennett, *Synthesis* **1977**, 589 (Claisen)
Blechert, *Synthesis* **1989**, 71 (HeteroCope)
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)
Ziegler, *Chem Rev.* **1989**, *89*, 1423 (Claisen)

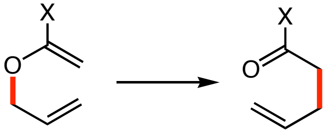
The Reaction:



$\Delta H \sim -20$ kcal mol^{-1}

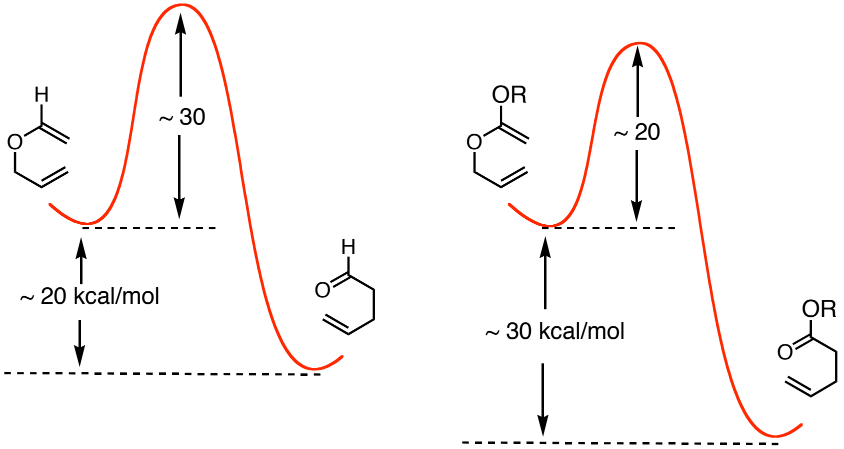
There is good thermodynamic driving force for this reaction.
Bonds Broken: C-C$_\pi$ (65 kcal mol^{-1}) & C-O$_\sigma$ (85 kcal mol^{-1})
Bonds Made: C-O$_\pi$ (85 kcal mol^{-1}) and C-C$_\sigma$ (85 kcal mol-^{1})

Thermodynamics of Claisen Variants:



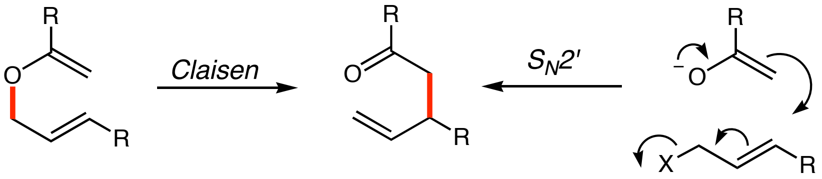
Substituent	ΔH (kcal mol^{-1})
X = H	–16
X = OH	–31
X = NH_2	–30

(Benson estimates)

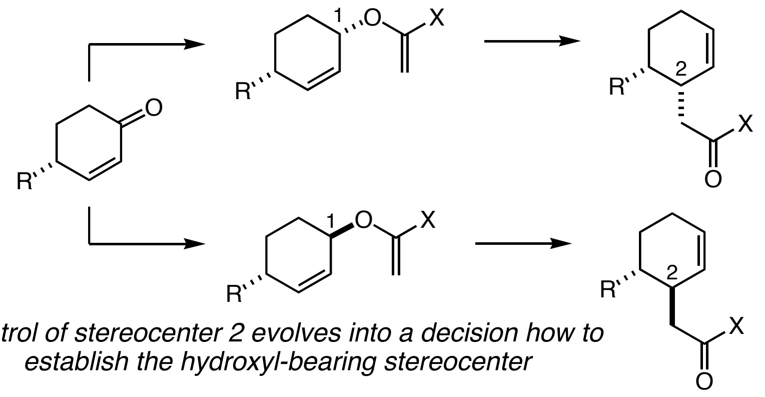


Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

Recognition Pattern for Organic Synthesis: An Enforced SN2'

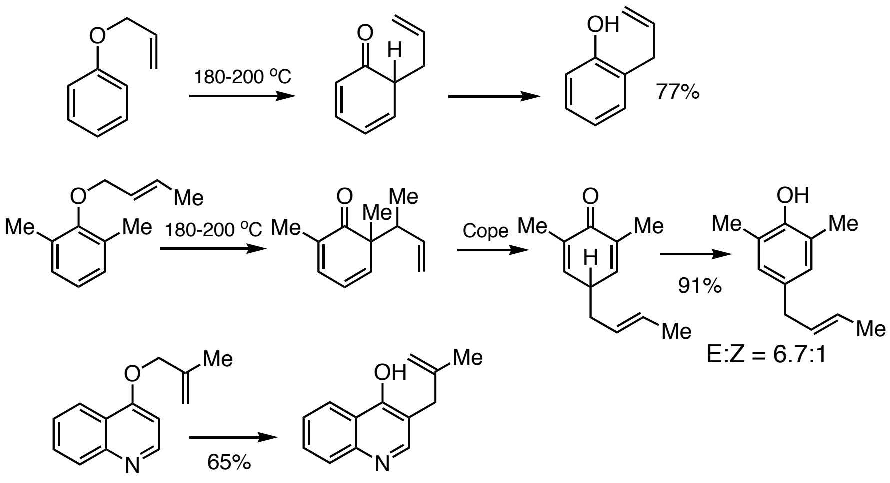


Stereochemical outcome is syn and controlled by hydroxyl stereocenter

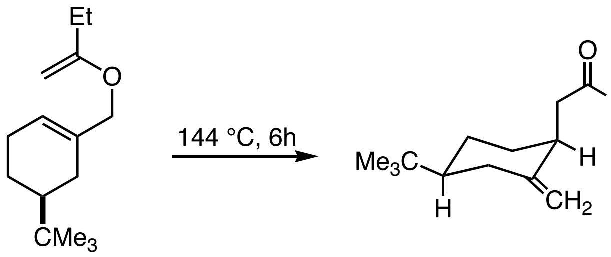


Control of stereocenter 2 evolves into a decision how to establish the hydroxyl-bearing stereocenter

Rearrangements of Aryl Allyl Ethers: Traditional Applications

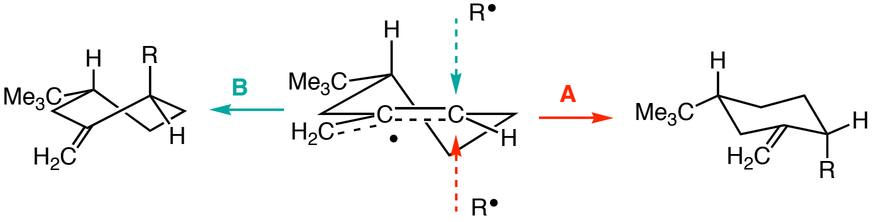


■ Endocyclic Olefins: Ireland, *JOC* 1983, *48*, 1829

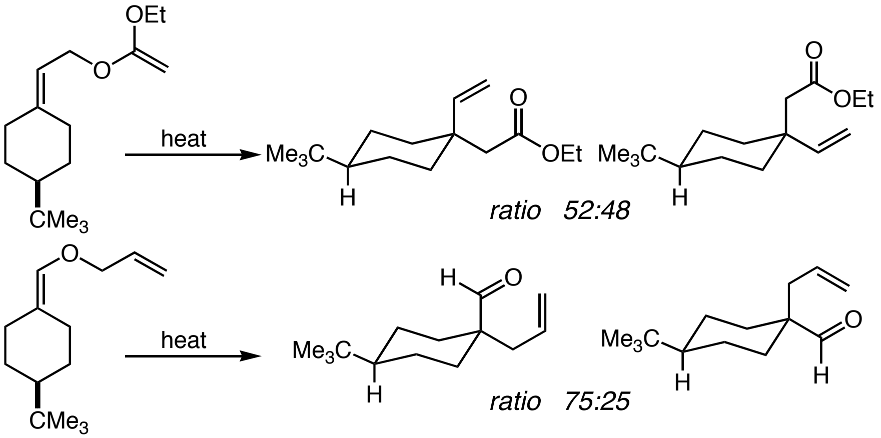


diastereoselection >87:13

For endocyclic olefins, overlap between developing sigma and pi bonds required. Best overlap for forming chair geometry. As shown below, bring a radical up to either face of the allylic radical. As the bond is formed, overlap must be maintained. **Path A** evolves into a **chair** conformation while **Path B** evolved into a **boat** conformation.



■ Exocyclic Olefins: House, *JOC* 1975, *40*, 86

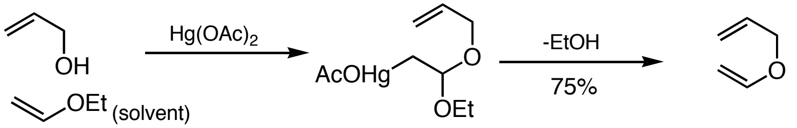


ratio *52:48*

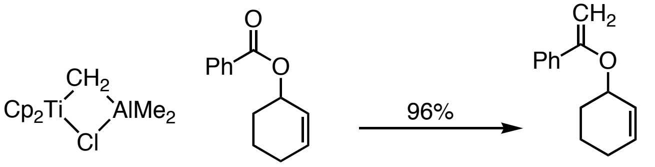
ratio *75:25*

for exoocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack." A related case is provided below.

Synthesis of Allyl Vinyl Ethers

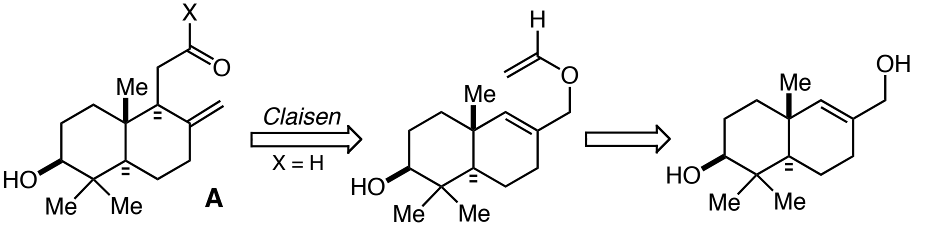


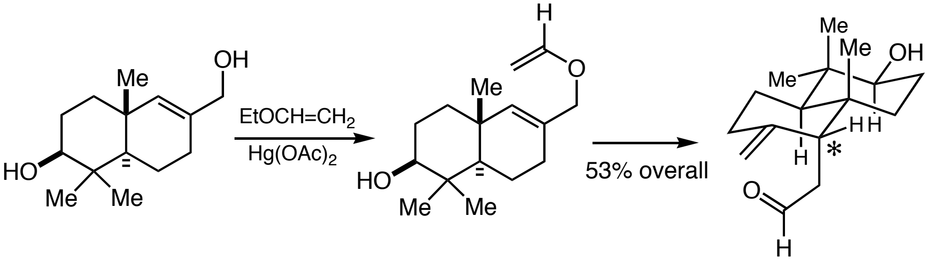
Watanabe, Conlon, *JACS* **1957**, *79*, 2828
Bronsted acids can also serve as catalysts



Use of Tebbe's Reagent: Evans, Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3272.
(review) S. H. Pines, *Organic Reactions* **1993**, *43*, 1

The Ireland approach to the bicyclic acid A: *JOC* **1962**, *27*, 1118



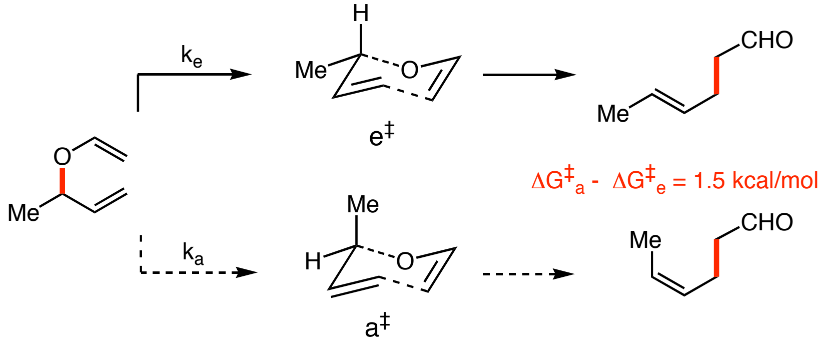


The new stereocenter (*) introduced via the rearrangement had the wrong configuration!

The Claisen Rearrangement: Stereoselective Olefin Synthesis

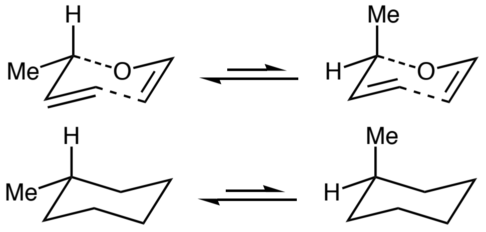
Claisen Rearrangement as vehicle for stereoselective olefin synthesis

Consider the following rearrangement:



$\Delta G^‡_a$ - $\Delta G^‡_e$ = 1.5 kcal/mol

Faulkner & Perrin (Tet. Lett. 2783 (**1969**) have made the correlation between $\Delta\Delta G^‡$ for rearrangement & ΔG° for the corrresponding cyclohexane# equilibria:

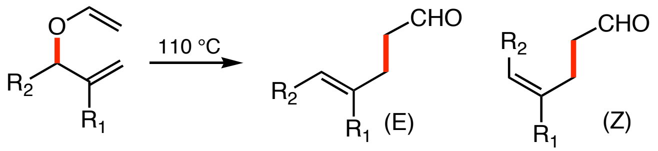


$\Delta\Delta G^‡$ = +1.5 kcal/mol

ΔG° = +1.75 kcal/mol

#Note: The A-value of 2-methyl-tetrahydropyran is +2.86 kcal/mol (Lecture No. 6)

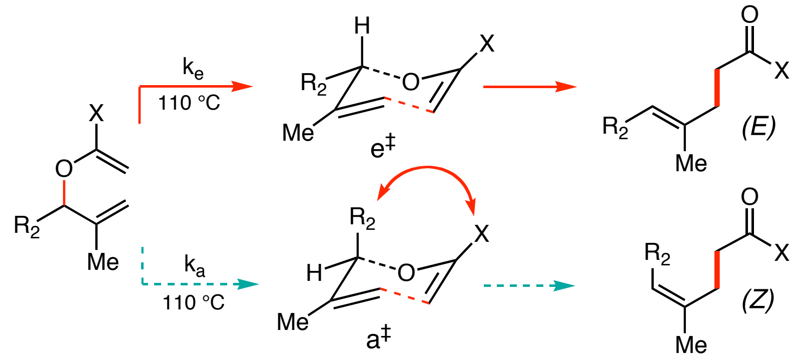
They then suggest that there is a good correlation between cyclohexane "A-values" & $\Delta\Delta G^‡$ for the rearrangement process. Their case is fortified by the following expamples:



R_1	R_2	(E):(Z) found	(E):(Z) predicted
Me–	Et–	90:10	91:9
Me–	iPr–	93:07	94:6
Et–	Et–	90:10	91:9

Faulkner, *JACS* **1973**, *95*, 553

Faulkner suggests that the installation of other substituents on Claisen transition states will lead to enhanced reaction diastereoselection:

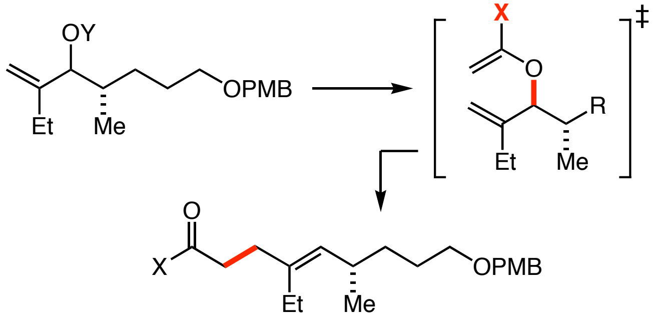


The R_2↔X interaction should destabilize $a^‡$ as X gets progressively larger.

	X	(E):(Z) found
	H–	90:10
For R_2 = Et	Me–	>99:1
	MeO–	>99:1
	Me_2N–	>98:2

Faulkner, *Tet Let* **1969**, 3243
Faulkner, *JACS* **1973**, *95*, 553
Johnson, *JACS* **1970**, *92*, 741

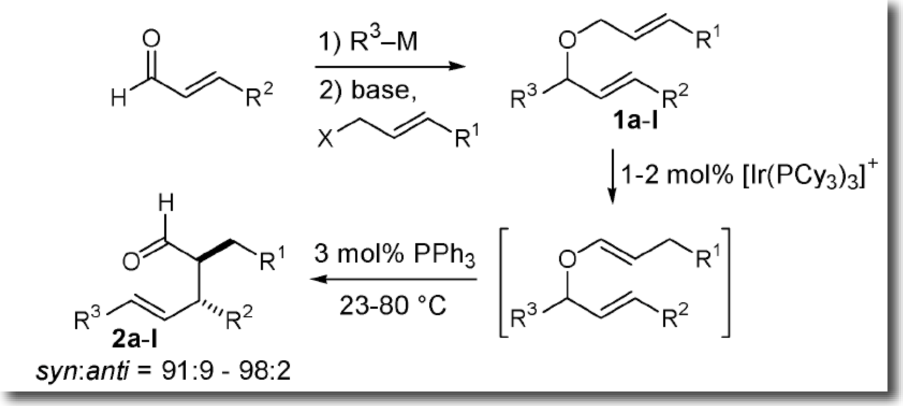
■ Another comparison: (DAE) M. DiMare, Ph. D. Harvard University, 1988



procedure	conditions	X	T, °C	(E):(Z) ratio
Y = Ac, Ireland	LDA, TMSCl	TMSO–	-78→+55	97:3
Y = H, Johnson	$HC(OMe)_3$, H^+	MeO–	130	94:6
Y = H, Eschenmoser	$MeC(OMe)_2NMe_2$	Me_2N–	80	97.5:2.5

Catalyzed Olefin Isomerization Leading to Highly Stereoselective Claisen Rearrangements of Aliphatic Allyl Vinyl Ethers

Scott G. Nelson,* Christopher J. Bungard, and Kan Wang

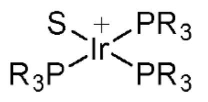


1a-l

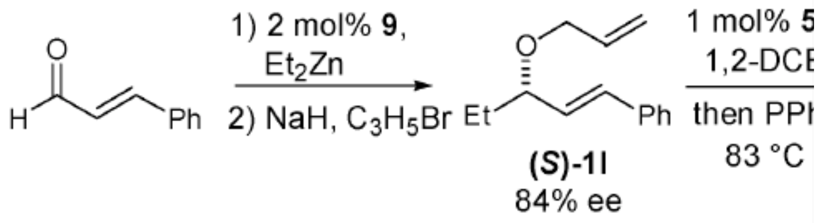
2a-l

syn:*anti* = 91:9 - 98:2

13000 ■ J. AM. CHEM. SOC. 2003, *125*, 13000−13001



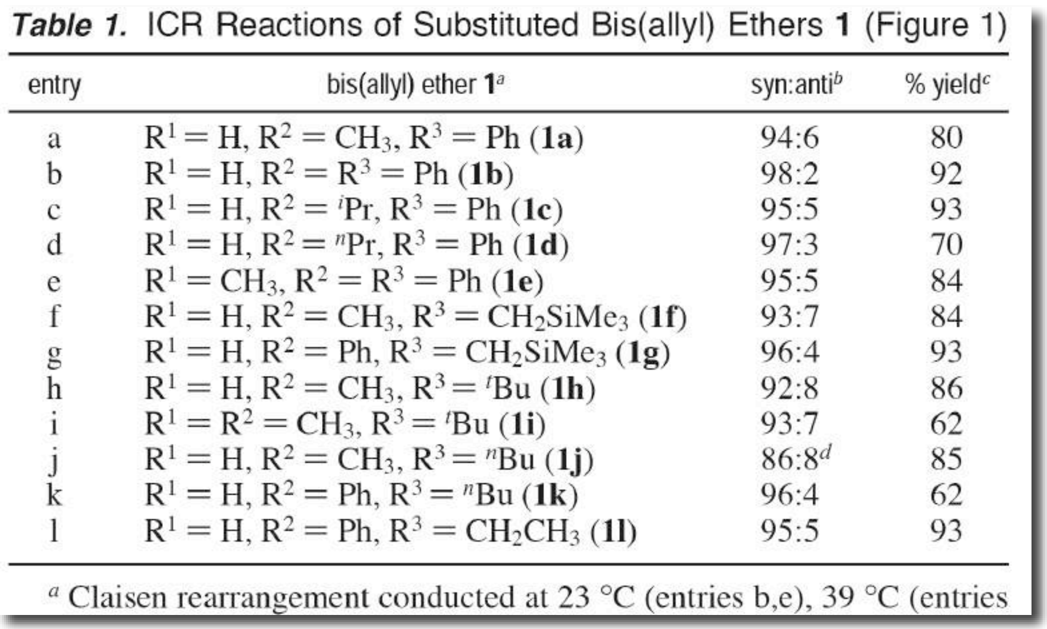
5a-c



(*S*)-**1l**
84% ee

9=(*S*)-*N*-methyl-α,α-diphenylprolinol

Table 1. ICR Reactions of Substituted Bis(allyl) Ethers **1** (Figure 1)



entry	bis(allyl) ether **1**[a]	syn:anti[b]	% yield[c]
a	$R^1 = H, R^2 = CH_3, R^3 = Ph$ (**1a**)	94:6	80
b	$R^1 = H, R^2 = R^3 = Ph$ (**1b**)	98:2	92
c	$R^1 = H, R^2 = {}^iPr, R^3 = Ph$ (**1c**)	95:5	93
d	$R^1 = H, R^2 = {}^nPr, R^3 = Ph$ (**1d**)	97:3	70
e	$R^1 = CH_3, R^2 = R^3 = Ph$ (**1e**)	95:5	84
f	$R^1 = H, R^2 = CH_3, R^3 = CH_2SiMe_3$ (**1f**)	93:7	84
g	$R^1 = H, R^2 = Ph, R^3 = CH_2SiMe_3$ (**1g**)	96:4	93
h	$R^1 = H, R^2 = CH_3, R^3 = {}^tBu$ (**1h**)	92:8	86
i	$R^1 = R^2 = CH_3, R^3 = {}^tBu$ (**1i**)	93:7	62
j	$R^1 = H, R^2 = CH_3, R^3 = {}^nBu$ (**1j**)	86:8[d]	85
k	$R^1 = H, R^2 = Ph, R^3 = {}^nBu$ (**1k**)	96:4	62
l	$R^1 = H, R^2 = Ph, R^3 = CH_2CH_3$ (**1l**)	95:5	93

[a] Claisen rearrangement conducted at 23 °C (entries b,e), 39 °C (entries

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 15

Pericyclic Reactions–5

- Claisen Rearrangements & Variants

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Wipf, P. *Claisen Rearrangements.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 827. **(handout)**

D. A. Evans

Monday
October 23, 2006

Other Reading Material:

Enders, D.; Knopp, M.; Schiffers, R. "Asymmetric [3.3]-sigmatropic rearrangements in organic synthesis." *Tetrahedron: Asymmetry* **1996**, *7*, 1847-1882

Ziegler, F. E. "The Thermal Aliphatic Claisen Rearrangement." *Chem. Rev.* **1988**, *88*, 1423.

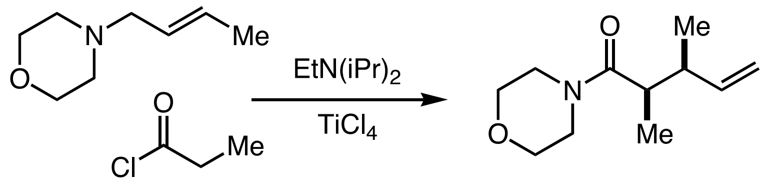
Gajewski, J. J. "The Claisen rearrangement. Response to solvents and substituents: The case for both hydrophobic and hydrogen bond acceleration in water and for a variable transition state." *Acc. Chem. Res.* **1997**, *30*, 219-225.

Tietze, L. F. "Domino reactions in organic synthesis." *Chem. Rev.* **1996**, *96*, 115-136.

Parsons, P. J.; Penkett, C. S.; Shell, A. J. "Tandem reactions in organic synthesis: Novel strategies for natural product elaboration and the development of new synthetic methodology." *Chem. Rev.* **1996**, *96*, 195-206.

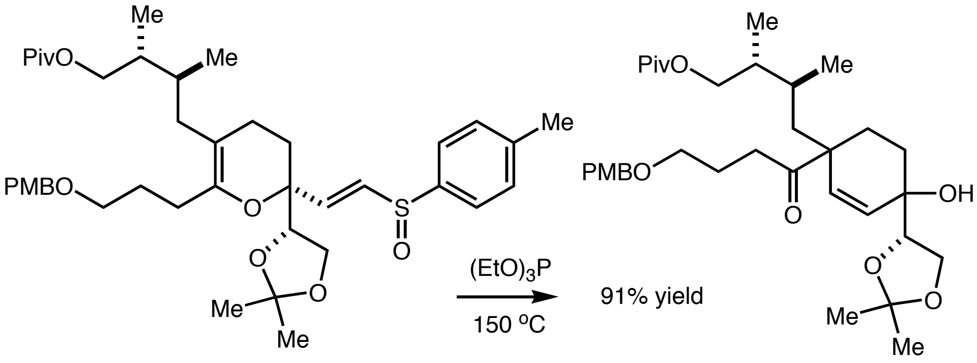
Problems of the Day:

Propose a mechanism for this transformation



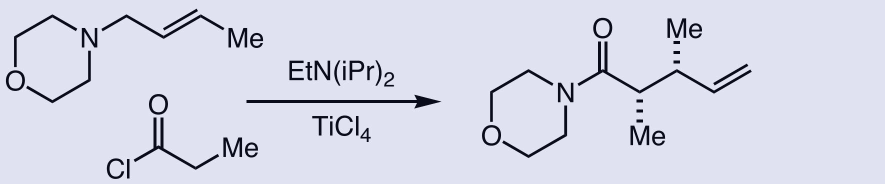
MacMillan, *JACS* **1999**, *121*, 9726

Problem 816. As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*OL*, **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the stereochemical outcome.

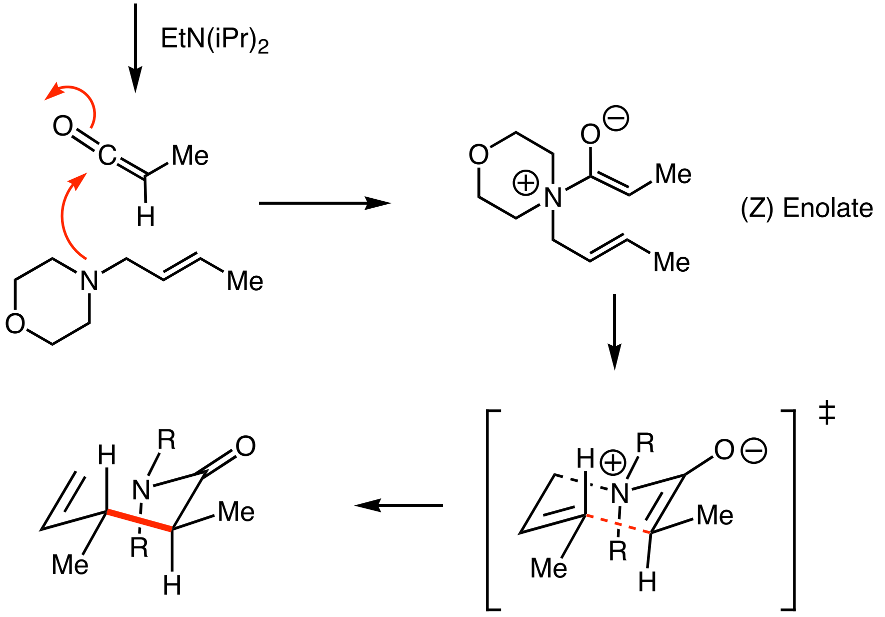


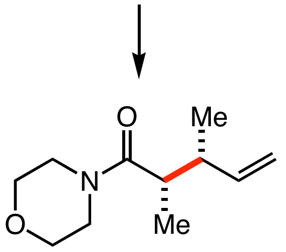
Pericyclic Reactions: Part–5

Propose a mechanism for this transformation

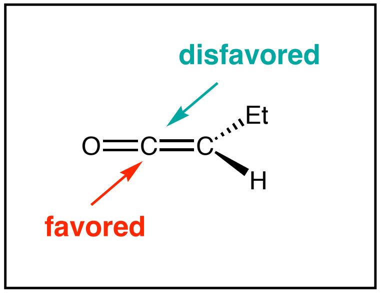


MacMillan, *JACS* **1999**, *121*, 9726

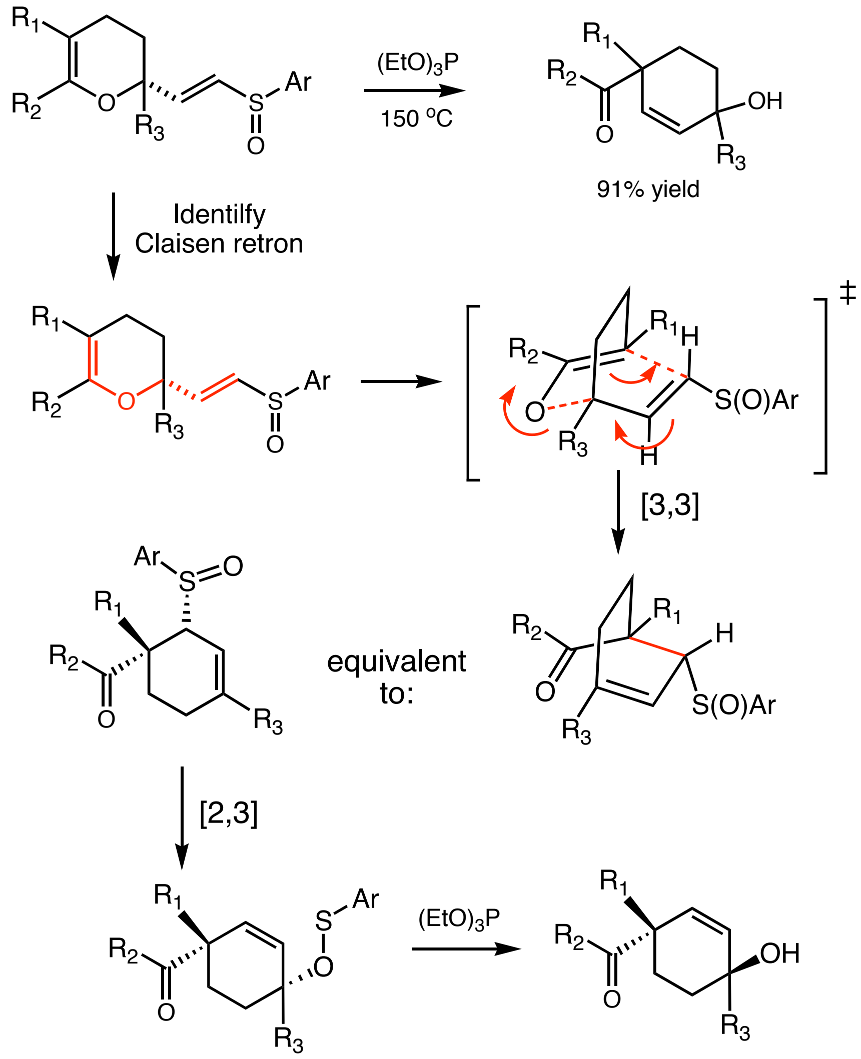




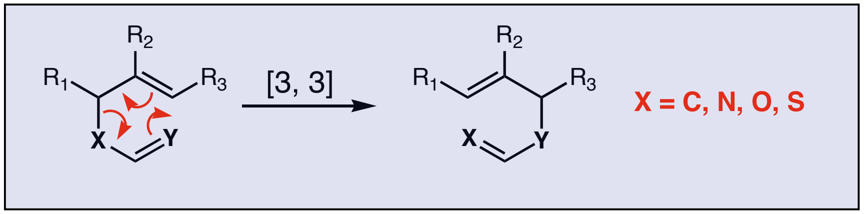
Key to Problem solution:



Problem 816. As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*OL*, **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the stereochemical outcome.

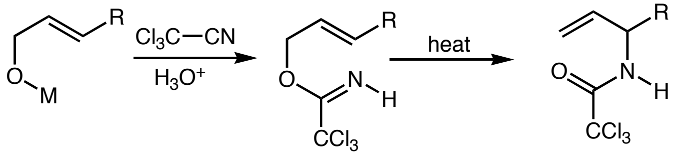


Allylic Rearrangements via [3,3] Processes

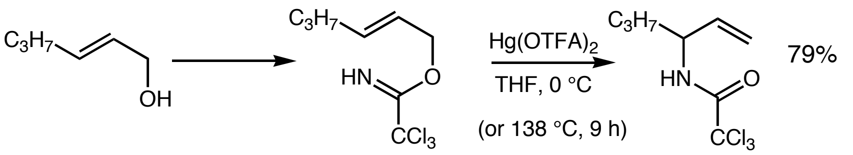


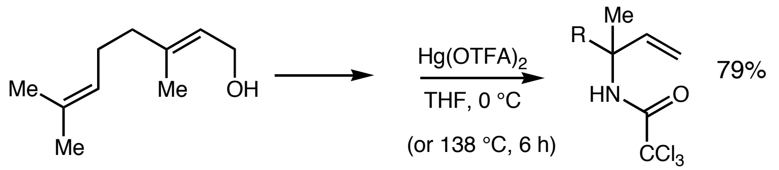
X = O; Y = N:

The Trichloroacetimidate Rearrangement, Overman, *JACS* **1974**, *96*, 597

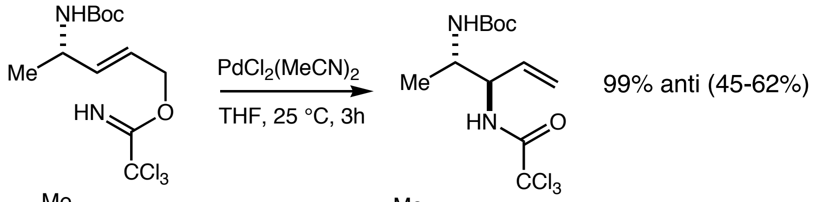


This reaction is also catalyzed by Hg(II) ion

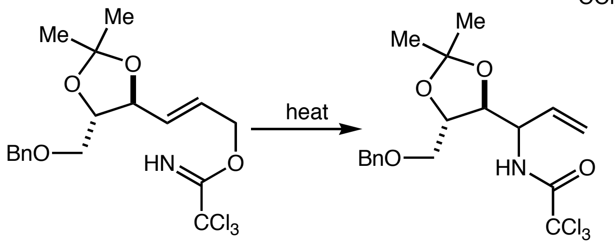




For an excellent review see: Overman, *Angew. Chem. Int. Ed.* **1984**, *23*, 579

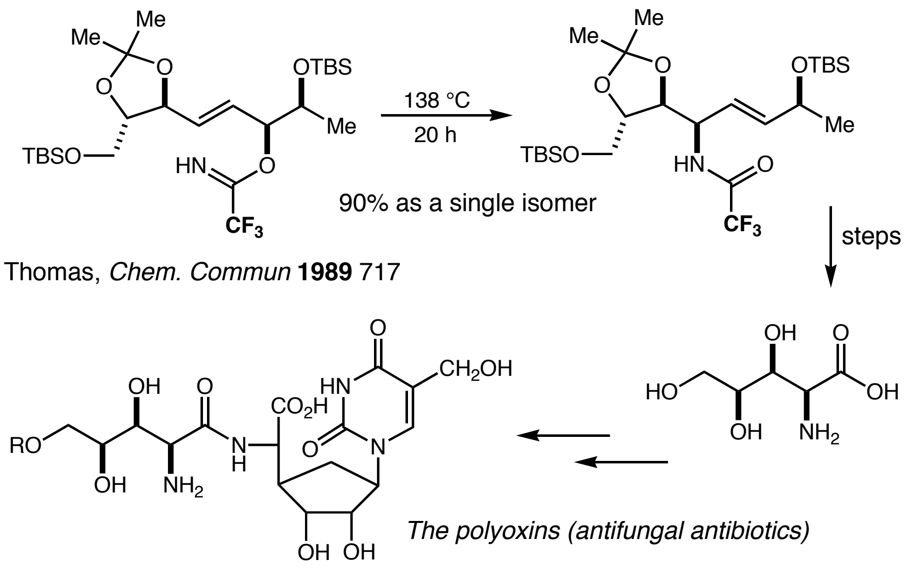


Gonda, *Synthesis* **1993** 729



a 1:1 mixture was obtained

Saksena, *JOC* **1986** *51*, 5024

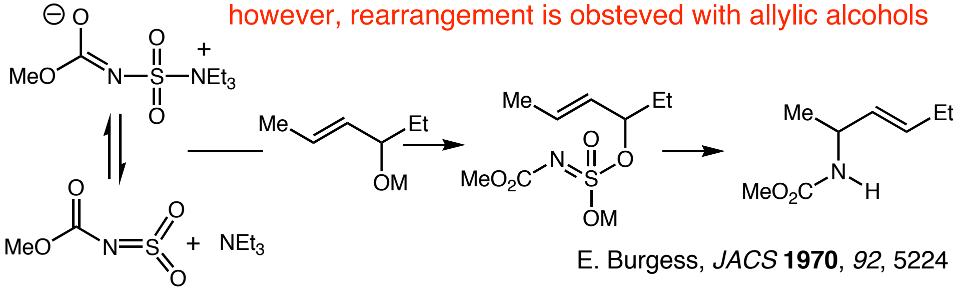


Thomas, *Chem. Commun* **1989** 717

The polyoxins (antifungal antibiotics)

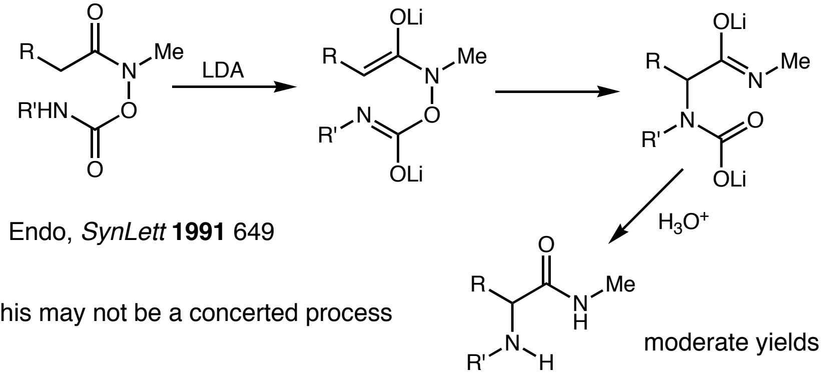
The "Burgess Reagent" is normally used for alcohol dehydration

however, rearrangement is obsteved with allylic alcohols



E. Burgess, *JACS* **1970**, *92*, 5224

A new approach to the synthesis of α-amino acids

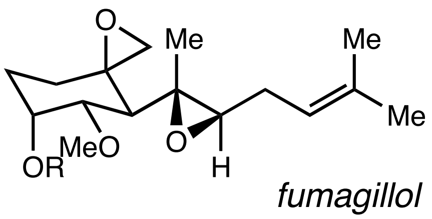


Endo, *SynLett* **1991** 649

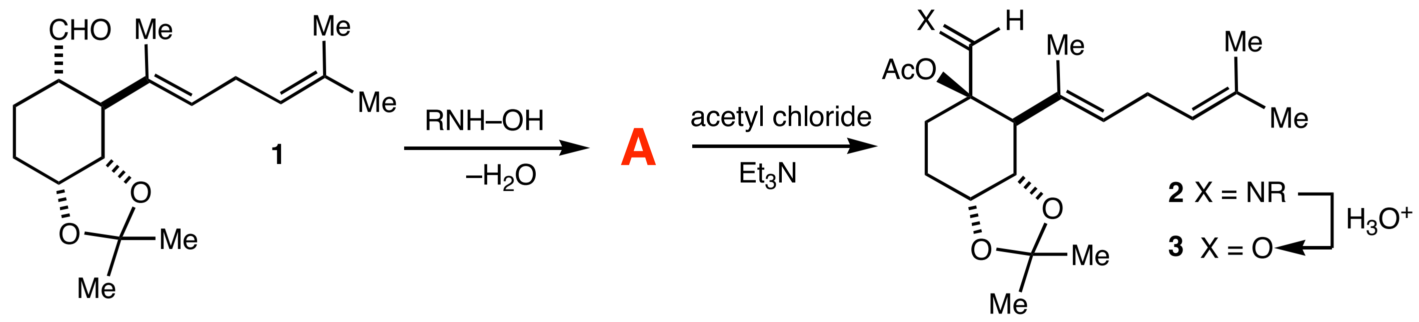
This may not be a concerted process

moderate yields

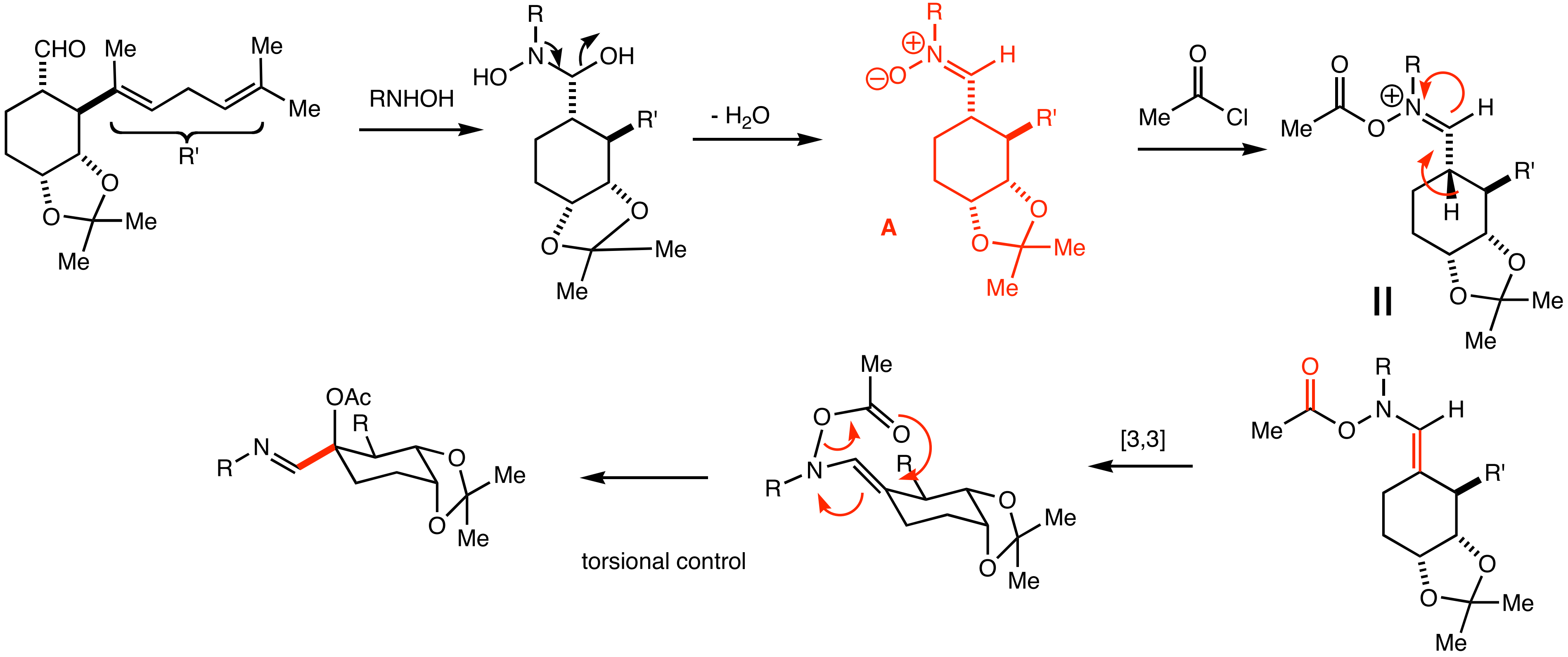
Problem 108. The fumagillin natural products possess several interesting biological properties including antibiotic activity against *Staphylococcus auereus*. In Sorensen's recent synthesis of fumagillol (*Angew. Chem, Int. Ed*. **1999**, *38*, 971), intermediate **1** was transformed into its a-oxygenated counterpart **3** through the indicated reaction sequence.



fumagillol

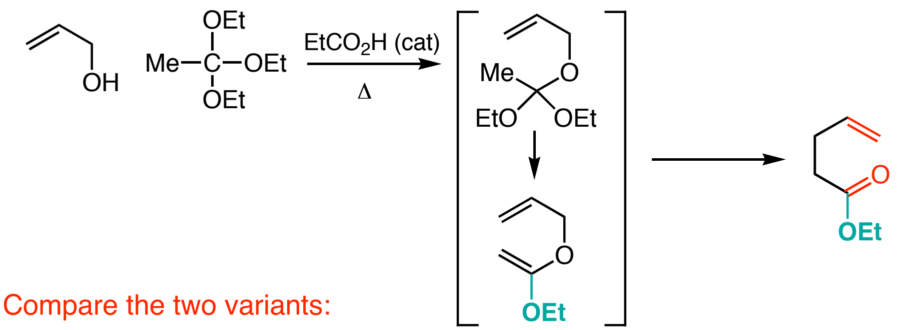


In the space below, identify the structure of intermediate **A** and provide a mechanism for the transformation of **1** into **2**.

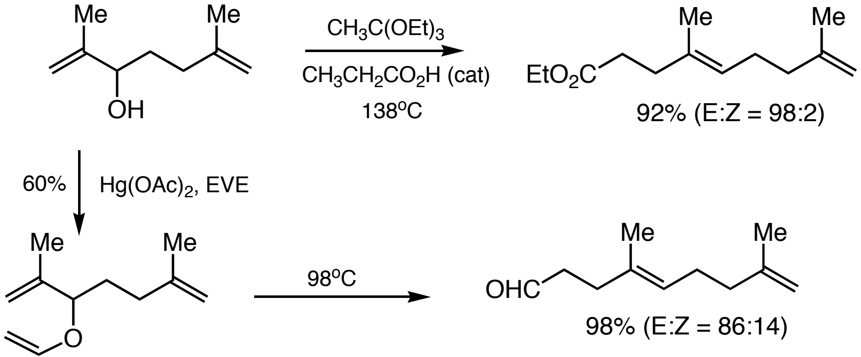


Johnson Orthoester Claisen

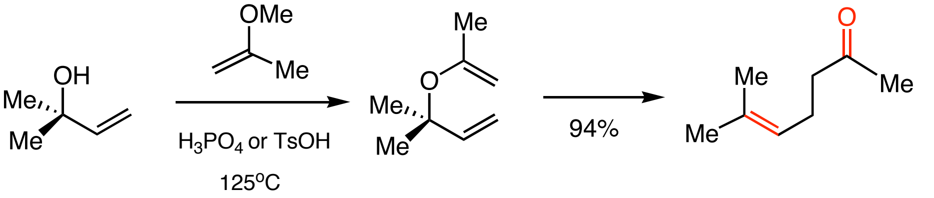
- Lead paper: Johnson, Faulkner, Peterson, *JACS* **1970**, *92*, 741

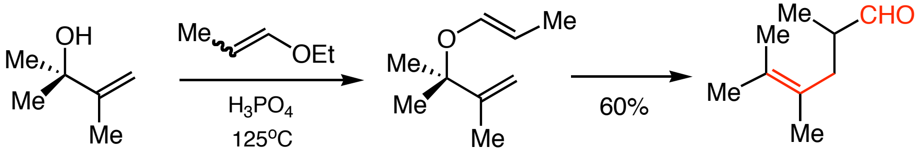


- Compare the two variants:



The Saucy Marbet Alternative

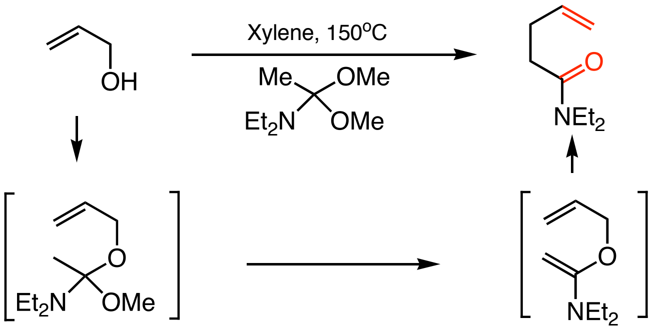


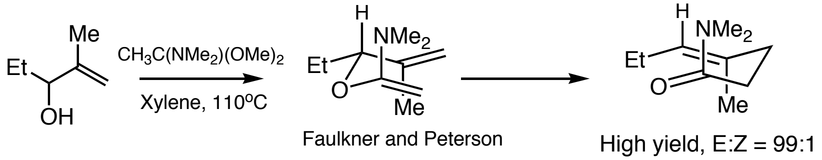


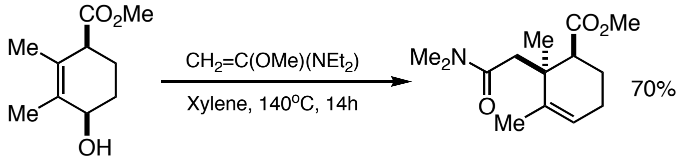
Saucy, Marbet, *Helv. Chim. Acta* **1967**, *50*, 2091,2095

Eschenmoser-Claisen

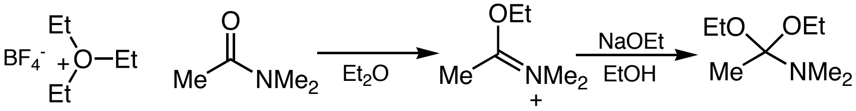
Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425; *Helv. Chim.Acta* **1969**, *52*, 1030.



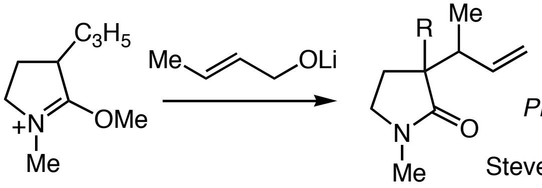




- Synthesis of Amide Acetals

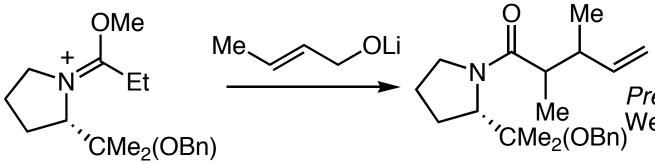


- Reactions to ponder:



diastereoselection 6:1
Predict the major diastereomer

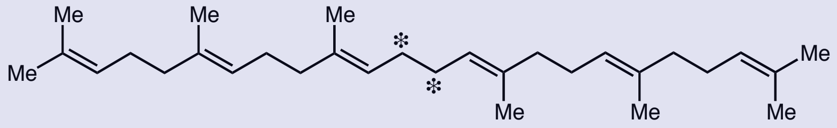
Stevenson, *Tet. Let.* **1991**, *32*, 4199



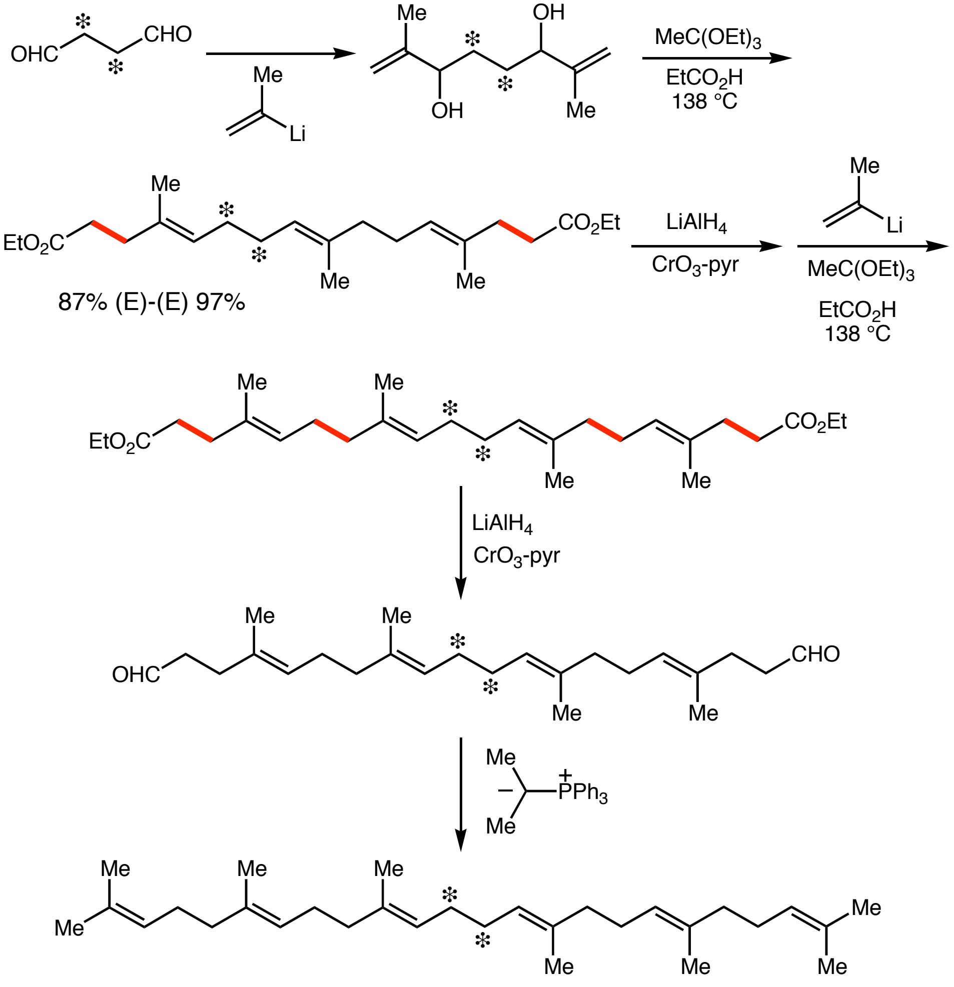
Predict the major diastereomer
Welch, *JACS* **1987**, *109*, 6716

Applications of the Claisen Rearrangement

The Johnson Squalene Synthesis: JACS 1970, 92, 741

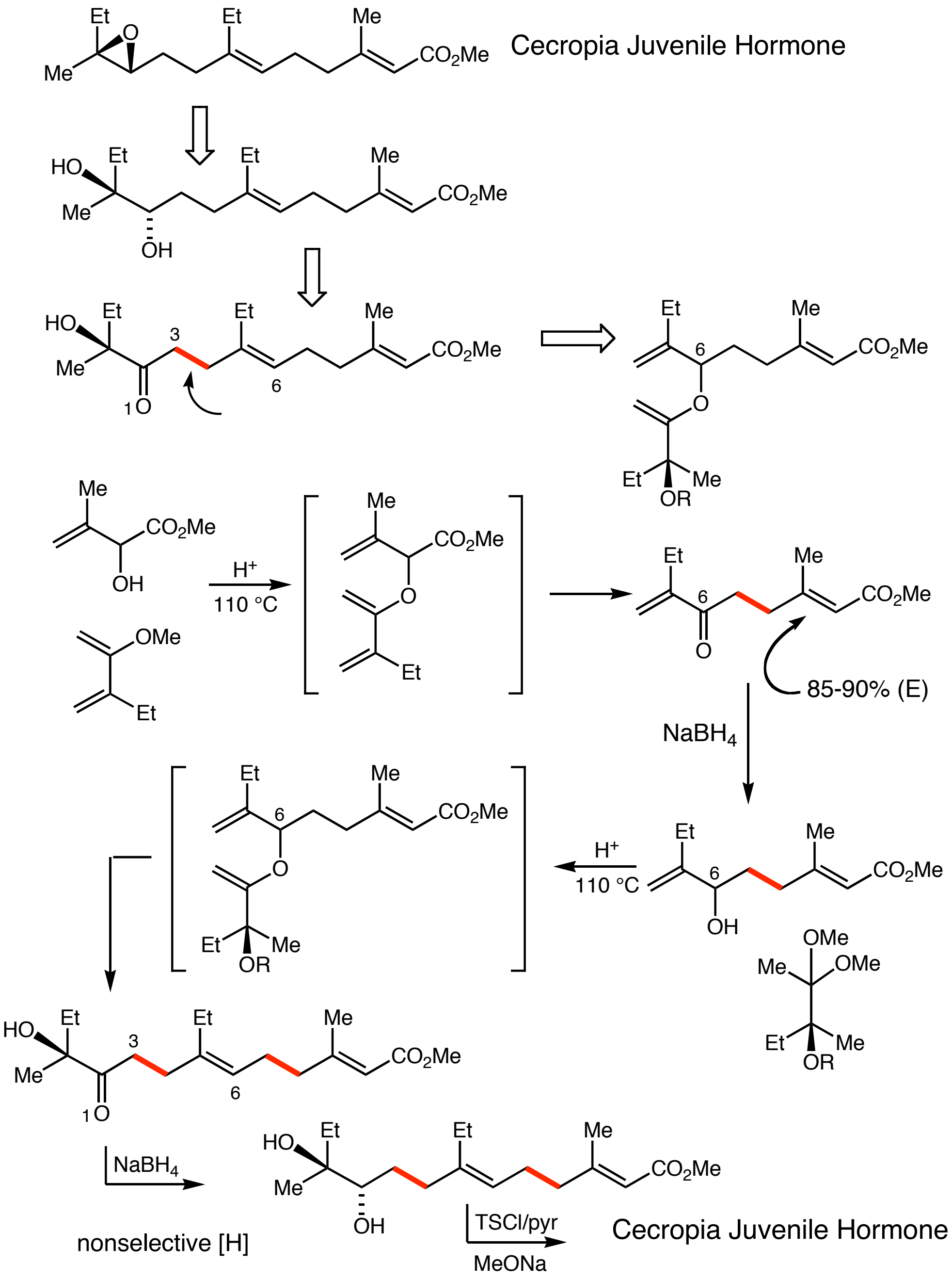


Observations: Molecule contains an obvious symmetry plane
The trisubstituted C=C's are the issue



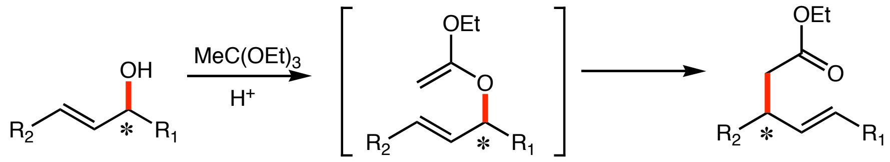
Isomeric purity is Ca 95%

*The Faulkner Juvenile Hormone Synthesis: JACS **1973**, 95, 553*

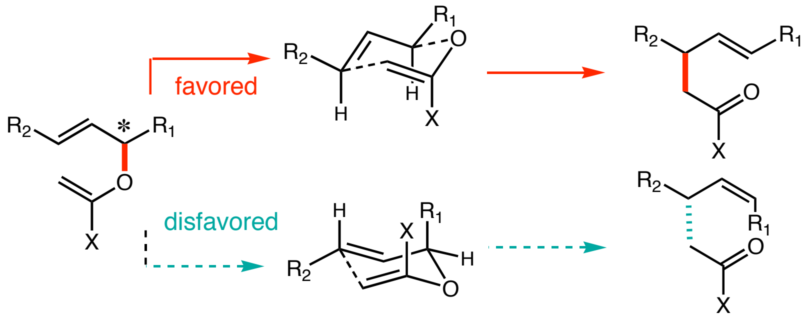


Chirality transfer via the Claisen rxn is an integral aspect of the general utility of process

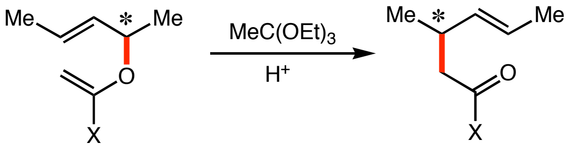
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)



Such chirality permutation processes are only as stereoselective as the energy difference between diastereomeric chair transiltion states:

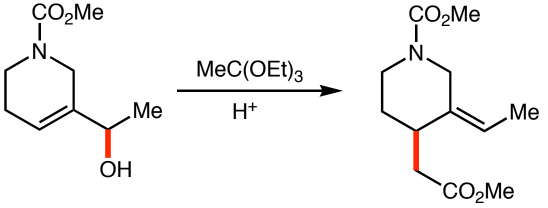


Note that chirality transfer is coupled to olefin geometry in product. Prior arguments (Faulkner) imply that the X substituent will play significant role in promoting selectivity.



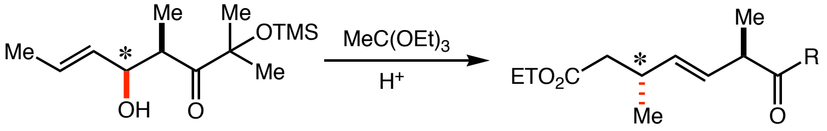
ee > 90%
(E)-selection > 90%

R. K. Hill
JOC **1972**, *37*, 3737



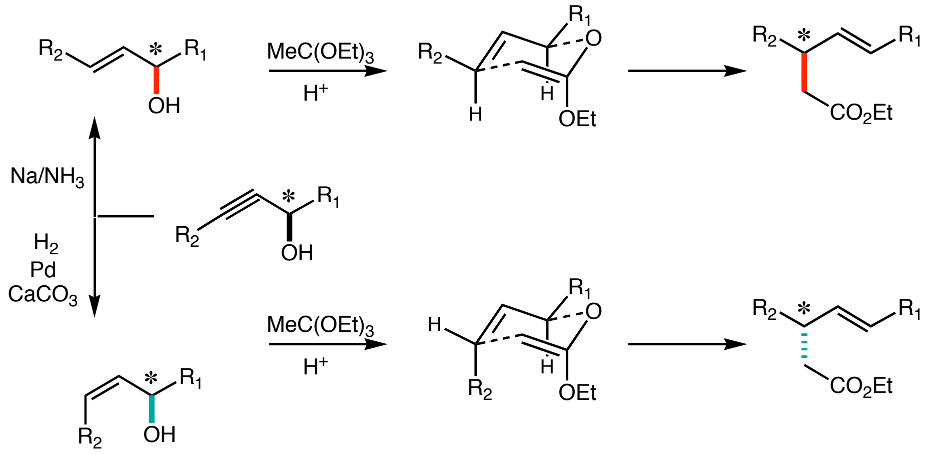
68% enantiomerically pure

Uskokovic,
JACS **1979**, *101*, 6742

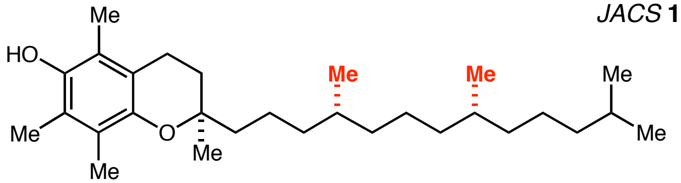


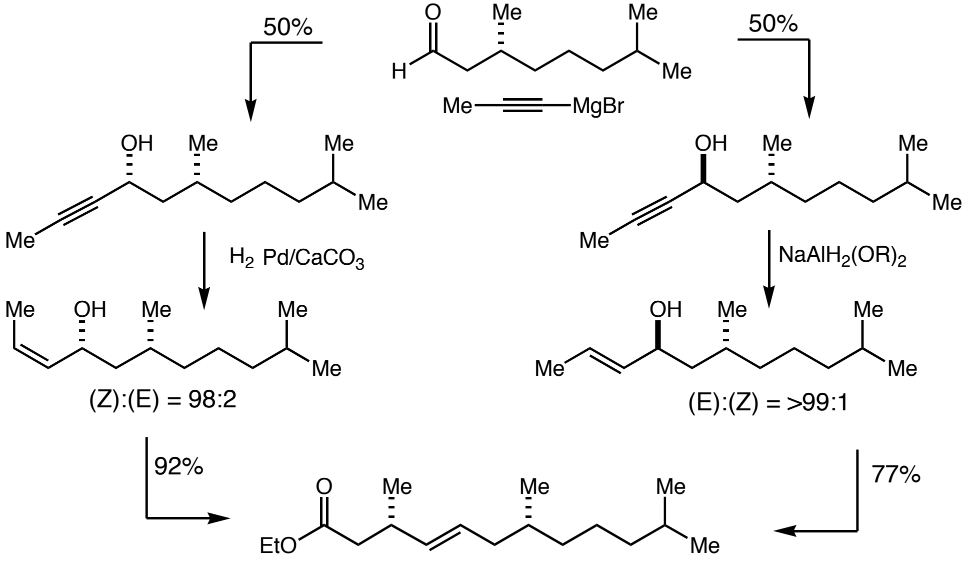
Heathcock
JOC **1988**, *53*, 1922

Sense of Asymmetric induction may be controlled by olefin geometry



Since stereoselection in reduction of acetylenes is >98%, either product accessible
tocopherol (Vitamin E) Cohen *JOC* **1976**, *41*, 3497
JACS **1979**, *101*, 6710



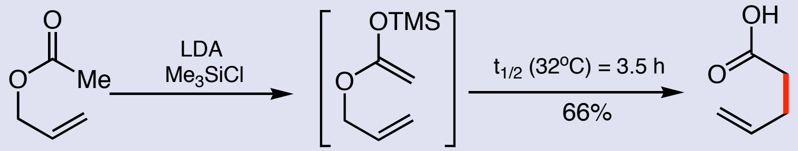


diastereoselection ~ 99% from both routes

Ireland-Enolate Claisen

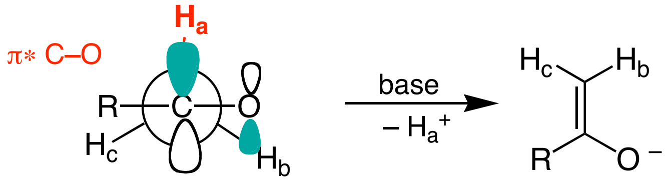
Recent Review: *Tetrahedron* **2002**, *58*, 2905-2928

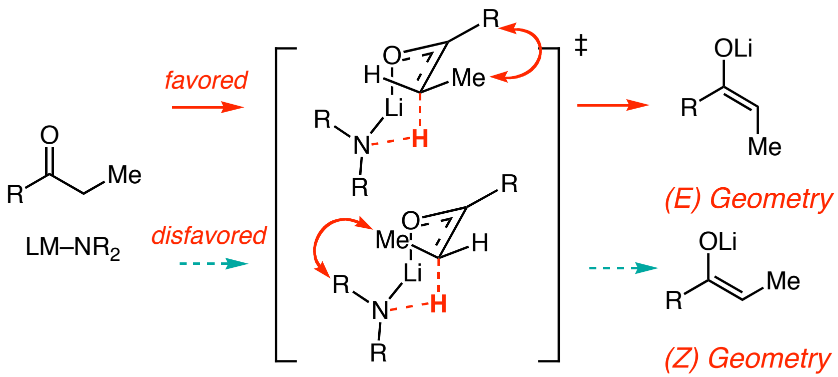
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868



■ Enolization: Amide Bases

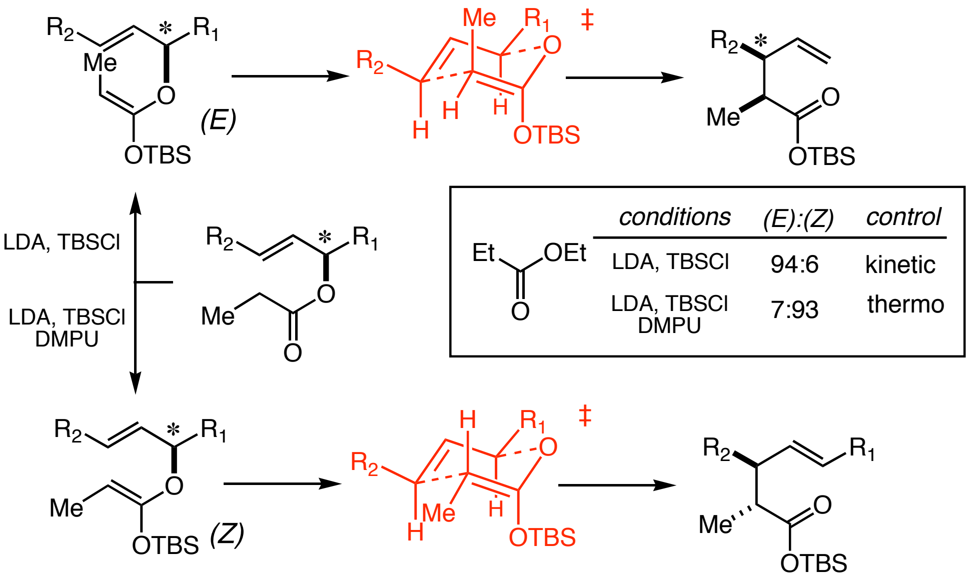
Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π∗ C–O





The Ireland Model (*JACS* **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650

Substituted enolates afford an additional stereocenter

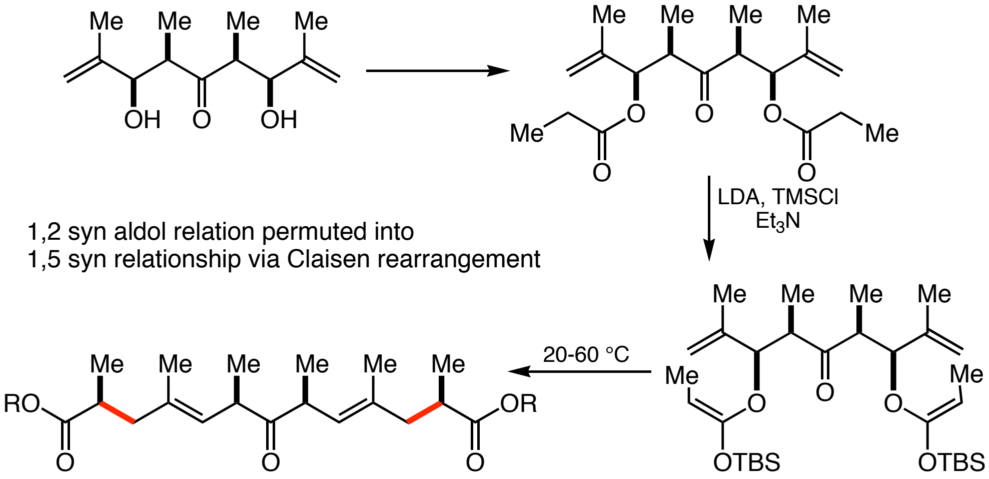


conditions	(E):(Z)	control
LDA, TBSCl	94:6	kinetic
LDA, TBSCl DMPU	7:93	thermo

key study: Ireland, *JOC* **1991**, *56*, 650 and earlier cited papers

Double Claisen Rearrangements are also possible

Paterson, *Tet Lett* **1991**, *32*, 7601

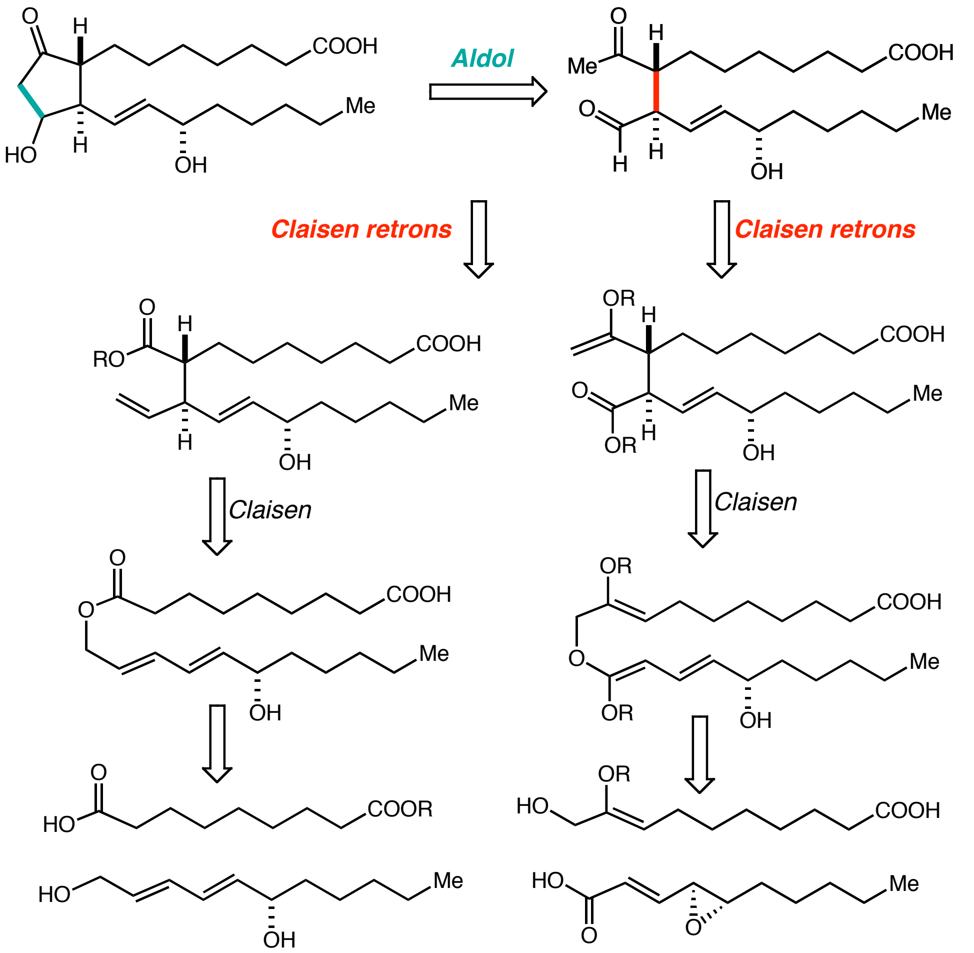


1,2 syn aldol relation permuted into
1,5 syn relationship via Claisen rearrangement

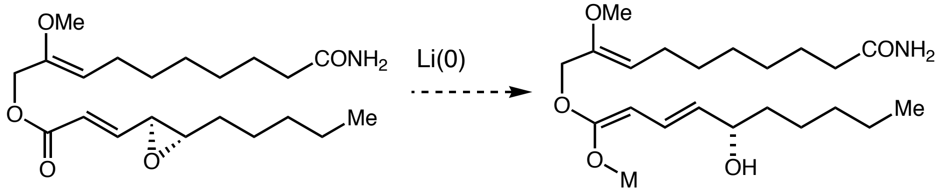
63% yield (diastereoselection 86%)

Ireland Claisen Rearrangements: Prostaglandin Synthesis

Consider the prostaglandin nucleus

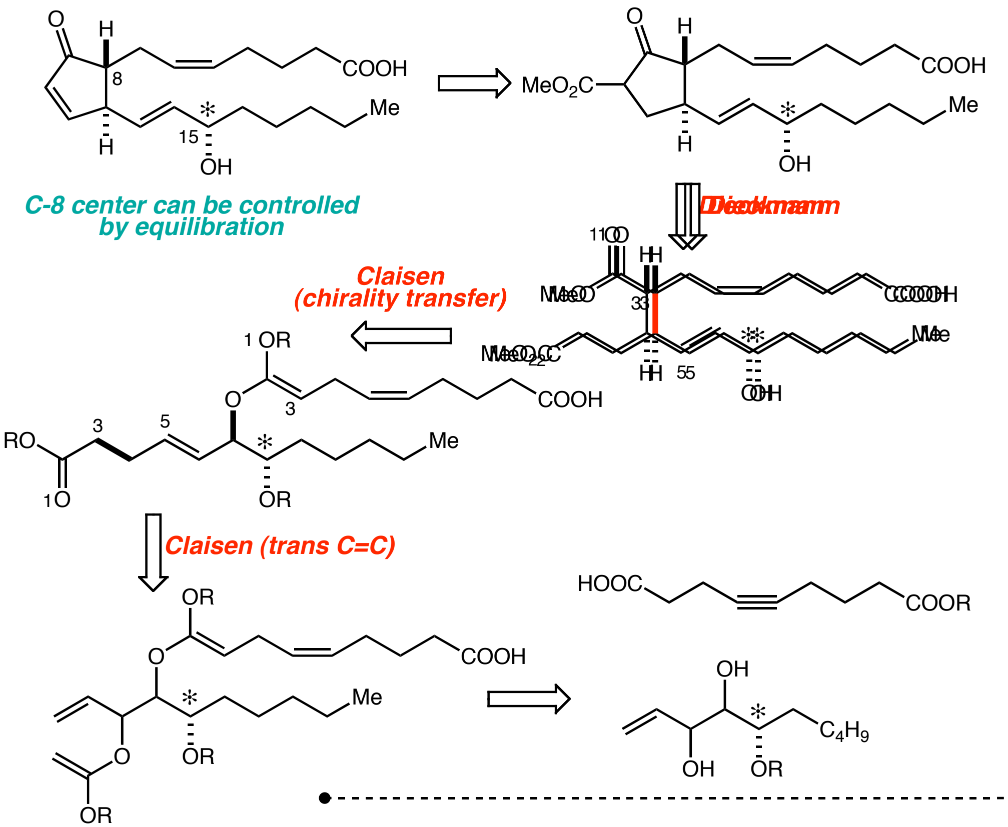


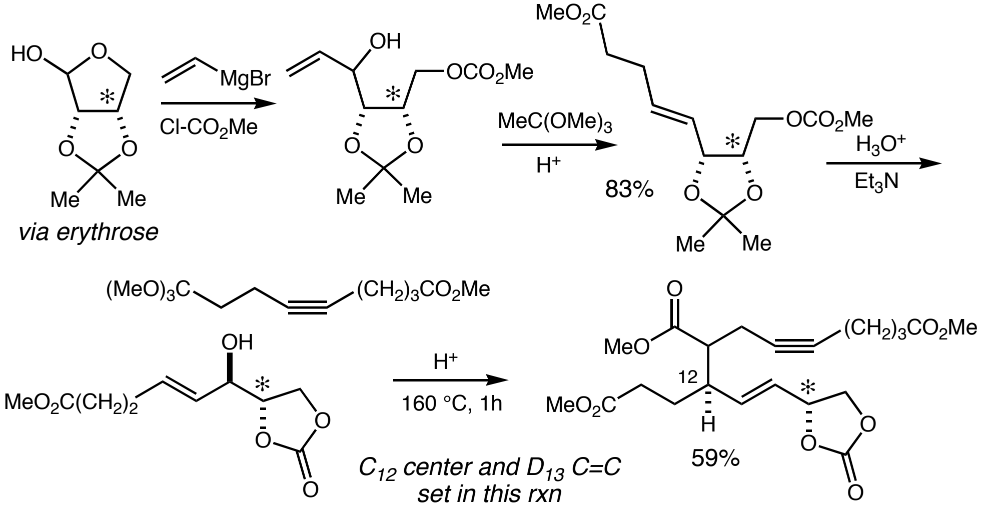
Unrealized plan to generate the required enolate



An Application PGA$_1$: Ireland *JOC* **1976**, *41*, 986; *Aldrichimica Acta* **1988**, *21*, 59

PP-A2 Synthesis, G. Stork, JACS **1976**, *98,* 1583



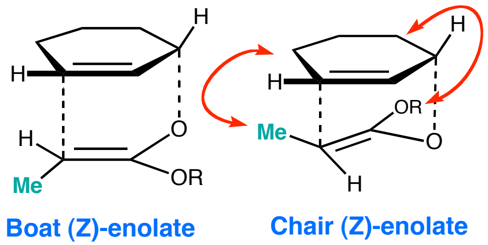


Boat transition states more accessible in Claisen than in Cope rearrangements

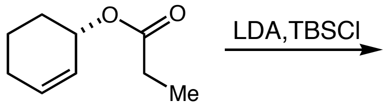
A case where the chair-boat preference depends on enol geometry

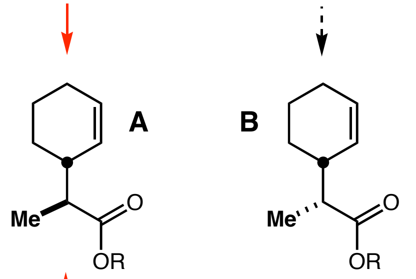
Factors controlling diastereoselection
Enolate geometry
Chair vs Boat transition states

Bartlett, *JOC* **1981**, *46*, 3896
Ireland, *JACS* **1991**, *56*, 3572

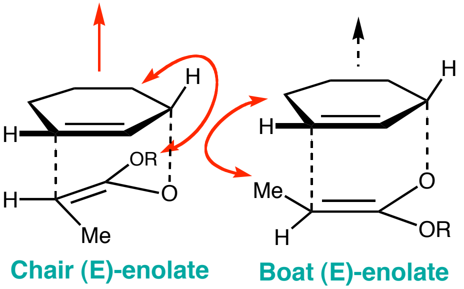


Ireland study supports Bartlett's conclusions



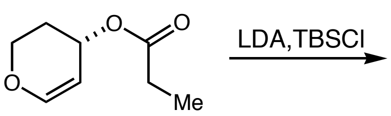


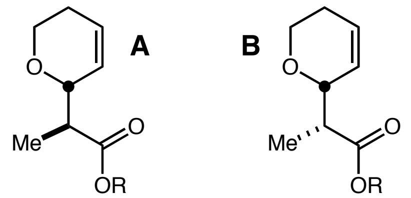
conditions	(E):(Z)	A:B	TS
LDA,THF	83:17	84:16	(E)-chair
LDA,THF DMPU	04:96	72:28	(Z)-boat



Boat geometies can be favored in these and related systems

In this case the boat geometry is preferred from either enol geometry

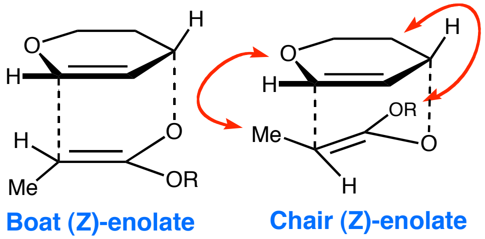


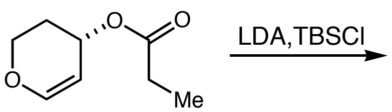


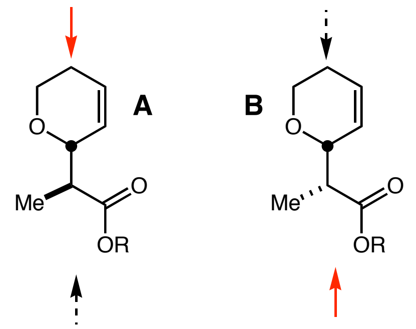
conditions	A:B	TS
LDA,THF	29:71	(E)-boat
LDA,THF DMPU	86:14	(Z)-boat

The analysis:

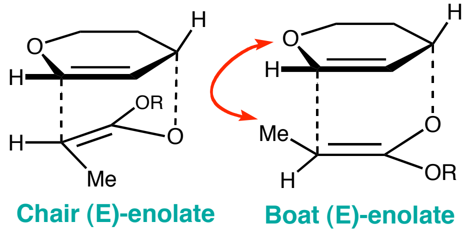
Ireland, *JACS* **1991**, *56*, 3572



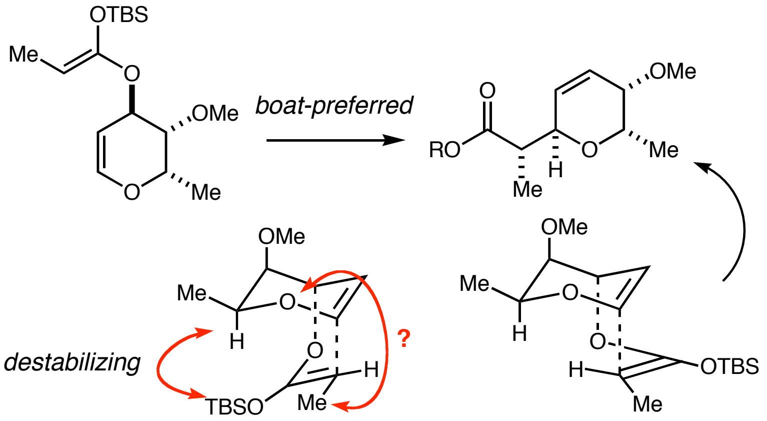




conditions	A:B	TS
LDA,THF	29:71	(E)-boat
LDA,THF DMPU	86:14	(Z)-boat



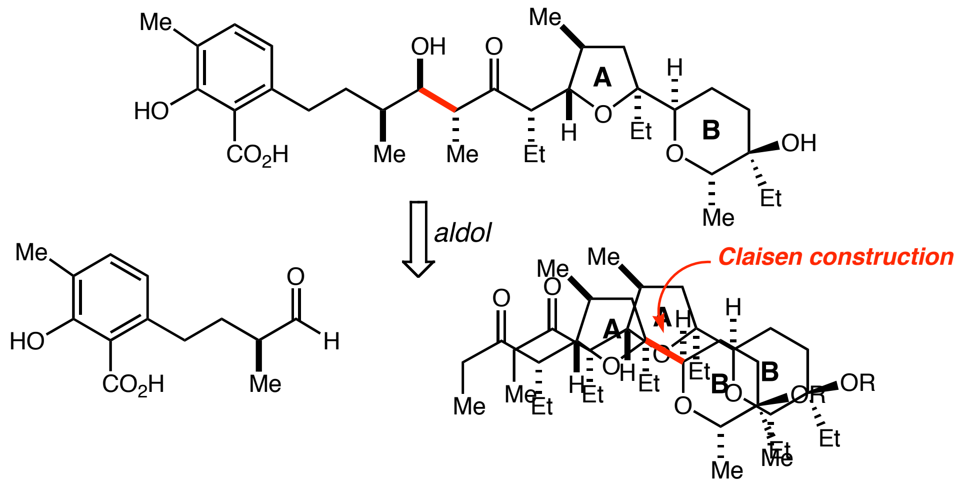
A further example:



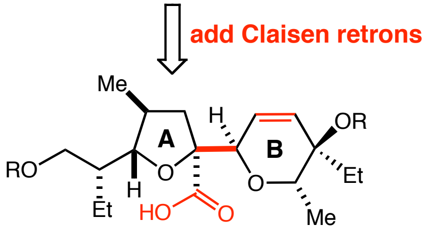
It appears that both of the indicated interactions contribute to the destabilization of chair geometry

Ireland Claisen Rearrangements: Ionophore Synthesis

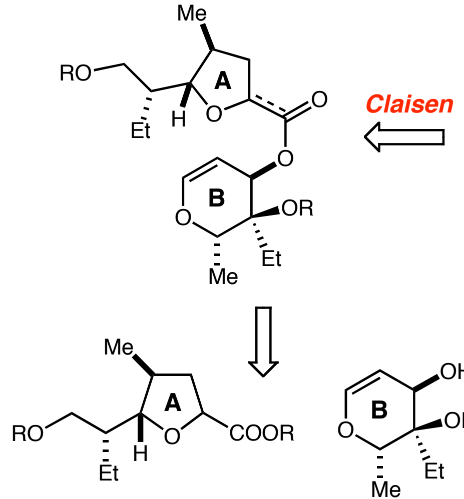
Ireland lasalocid synthesis: JACS **1983**, *105,* 1988



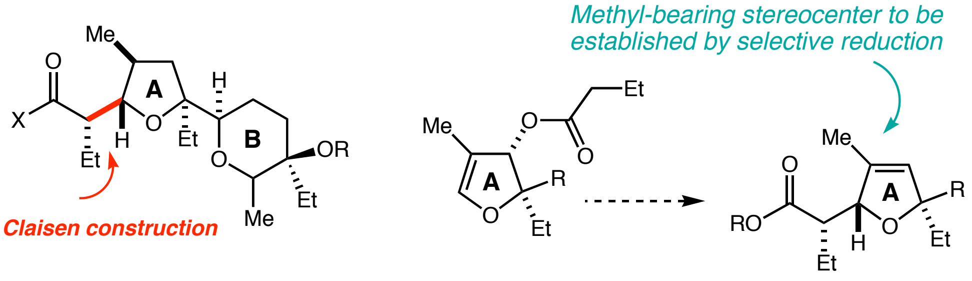
Note that neither retron for Claisen exists in this intermediate



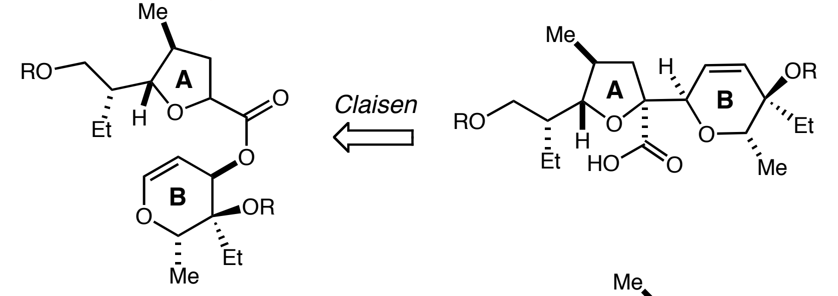
enolate face selectivity is anticipated problem. This results in CO_2H epimers

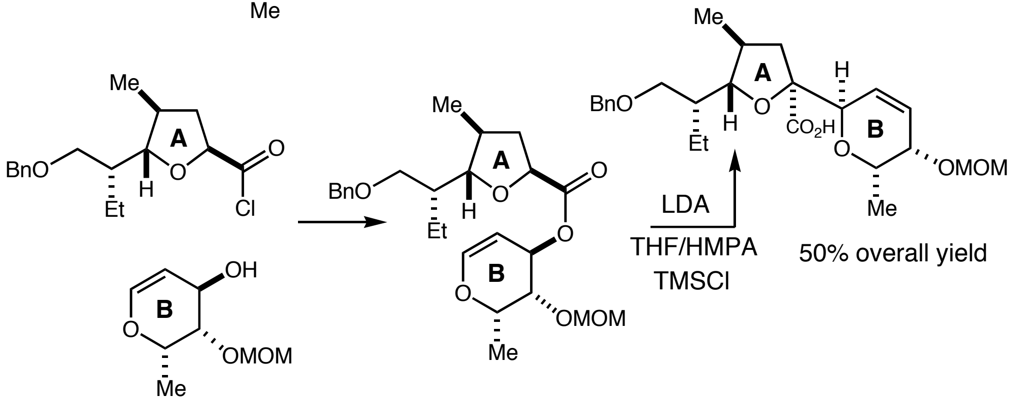


Here is another potential Claisen construction

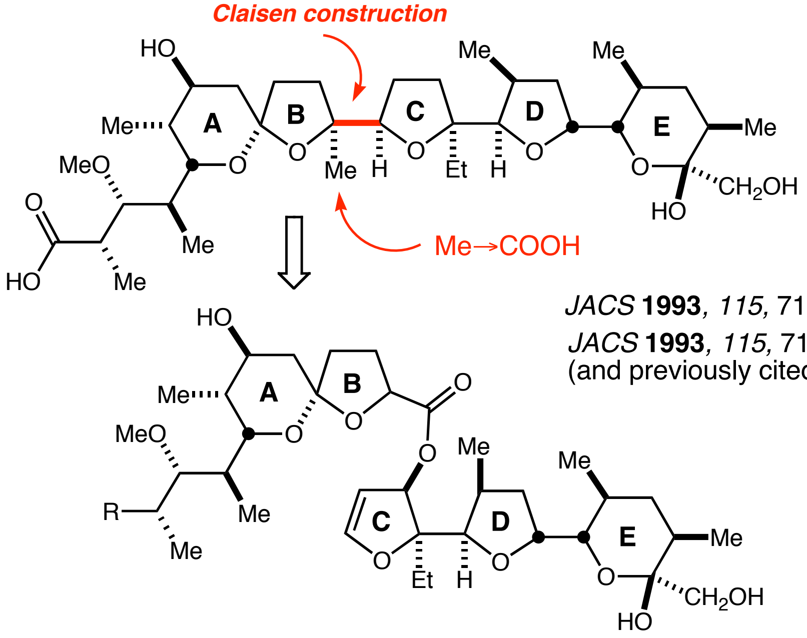

Methyl-bearing stereocenter to be established by selective reduction
Me
O
A
H
X
Et
H
Et
B
O
OR
Et
Me
Claisen construction
Me
O
Et
O
A
O
R
Et
O
Me
A
R
RO
O
Et
H
Et

The relevant rearrangements:





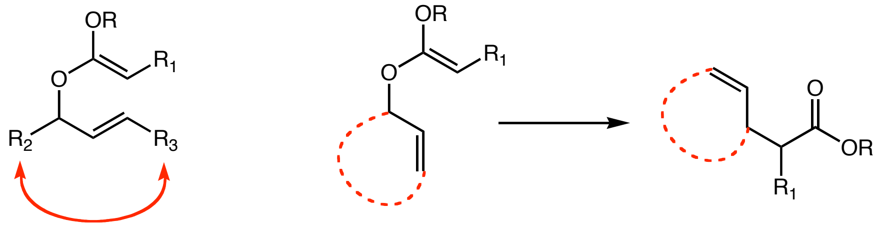
The Ireland monensin synthesis:



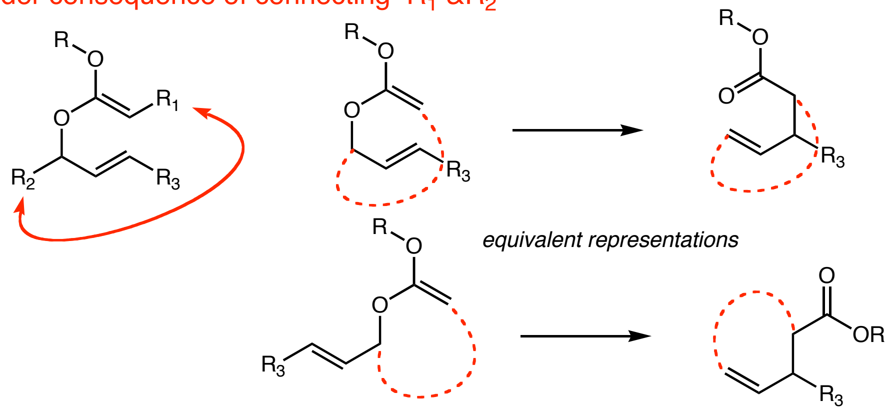
JACS **1993**, *115,* 7152-65
JACS **1993**, *115,* 7166-72
(and previously cited papers)

Ireland Claisen Rearrangements: Cyclic Enolates

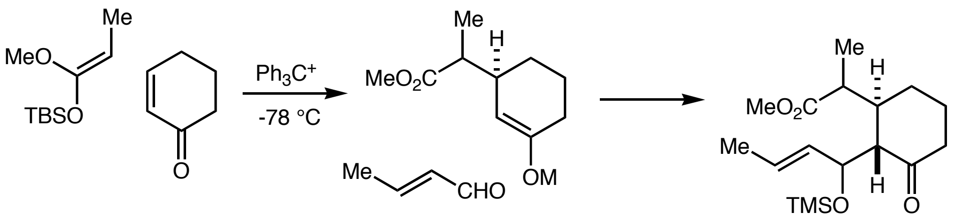
The previous cases were derived from a connection between R$_2$ &R$_3$



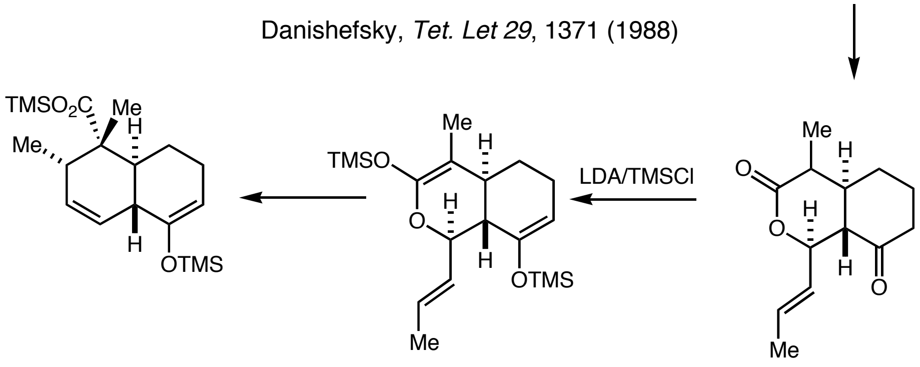
Consider consequence of connecting R$_1$ &R$_2$



Examples:



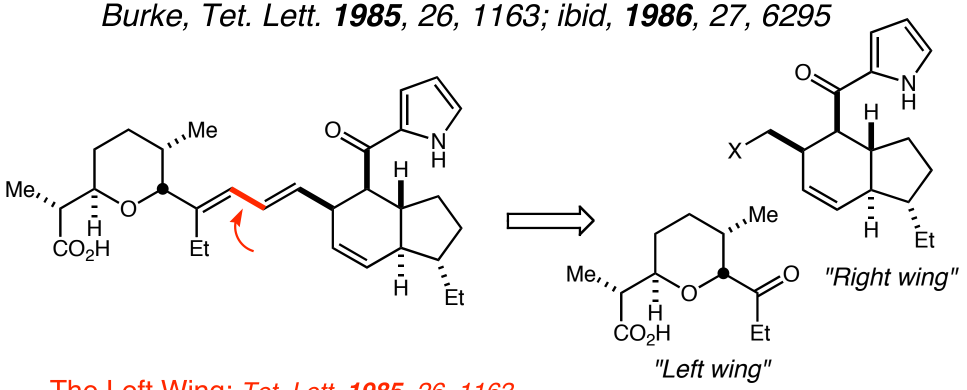
Danishefsky, *Tet. Let 29*, 1371 (1988)



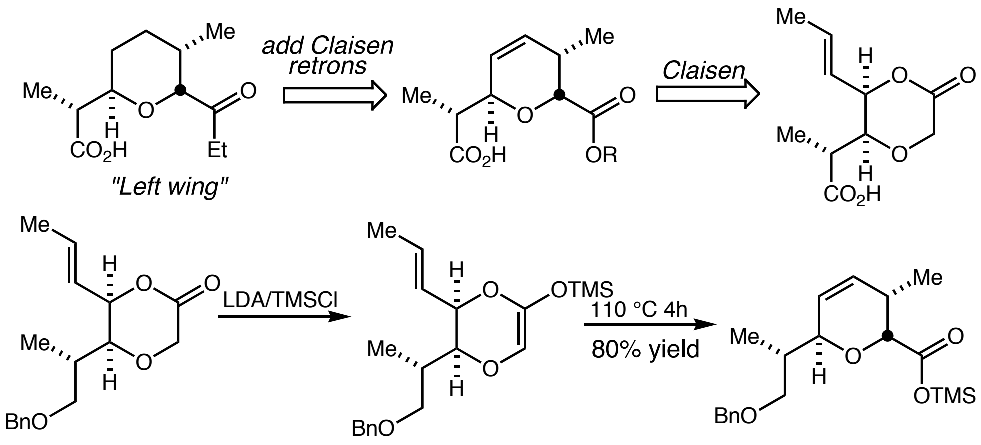
see also Danishefsky, *JACS* **1980**, *102*, 6889, 6891

The Indanomycin Synthesis,

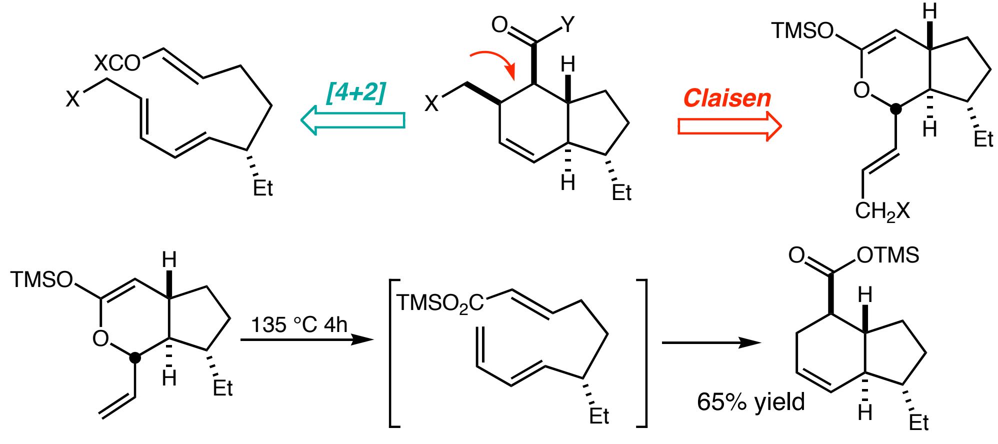
Burke, Tet. Lett. ***1985****, 26, 1163; ibid,* ***1986****, 27, 6295*



The Left Wing: *Tet. Lett.* ***1985****, 26, 1163*



The Right Wing: *Tet. Lett.* ***1986****, 27, 6295*

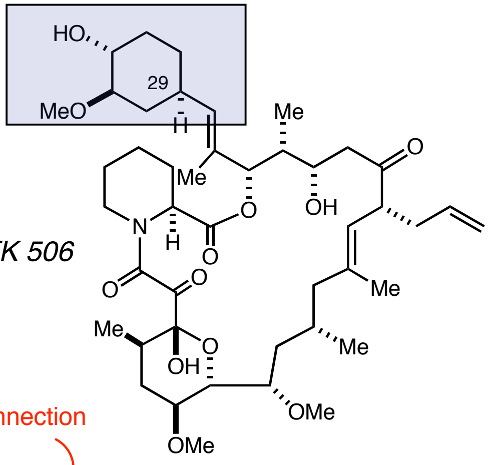


The "apparent" Claisen process is more complicated than anticipated.

Ireland Claisen Rearrangements: Cyclic Enolates

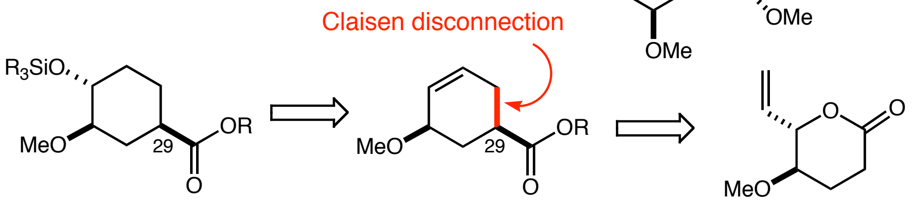
The FK 506 application

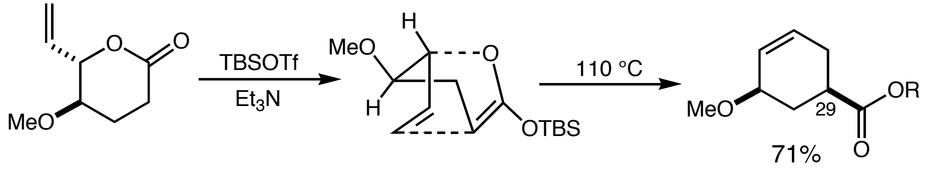
Schreiber Synthesis *JACS* **1990**, *112*, 5583



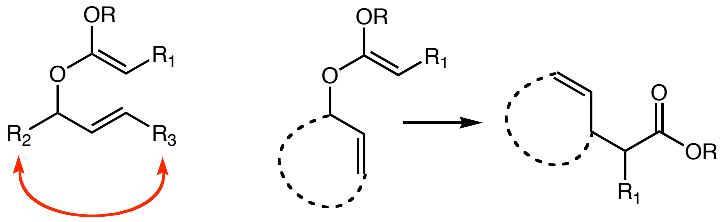
FK 506

The Schreiber Route:

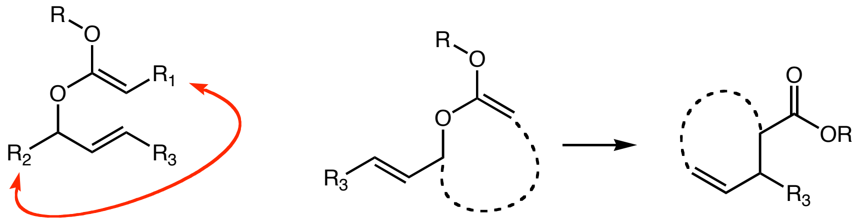




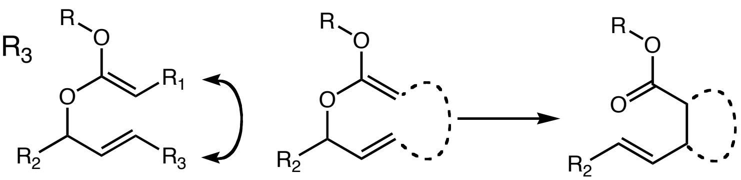
The previous cases were derived from a connection between R_2 &R_3



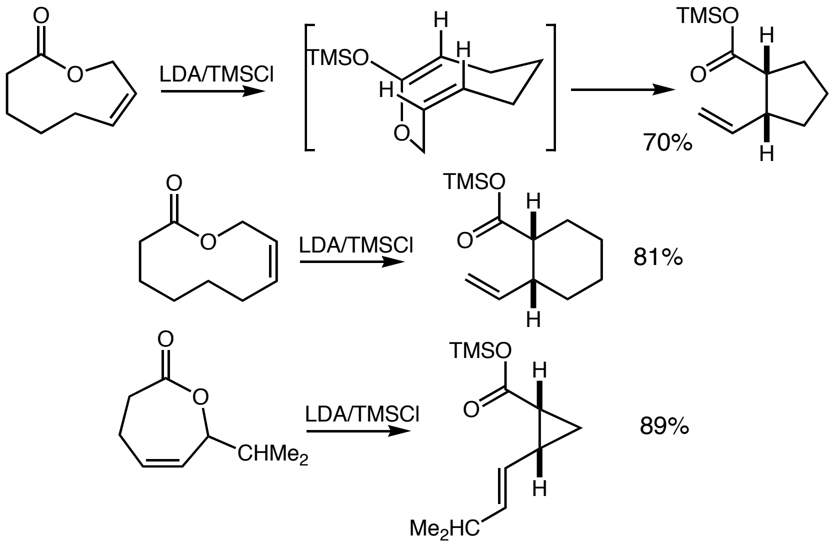
and R_1 &R_2



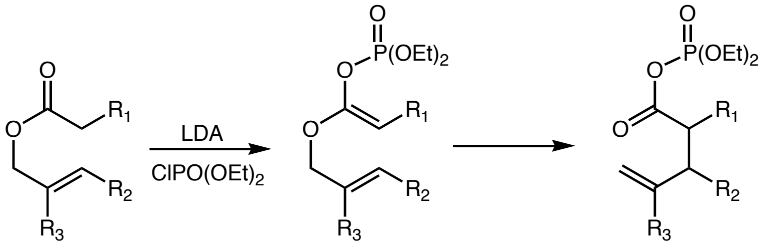
Now connect R_1 &R_3



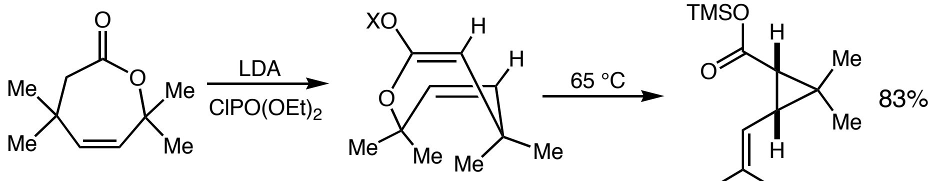
Examples: Funk, *JACS* **1982**, *104*, 4030



Recent improvments: Funk, *JACS* **1993**, *115*, 8847



chrysanthemic acid application

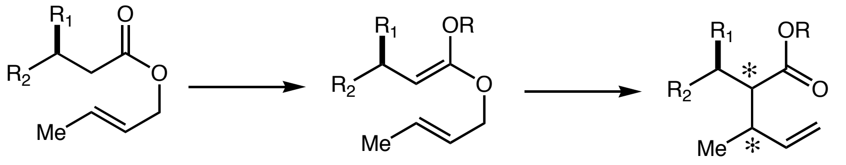


X = TMS; $T_{1/2}$ = 58 min

X = $PO(OEt)_2$; $T_{1/2}$ = 10 min

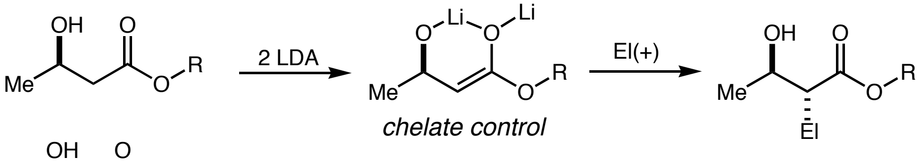
Claisen Rearrangements: Acyclic Cases with Stereoinduction

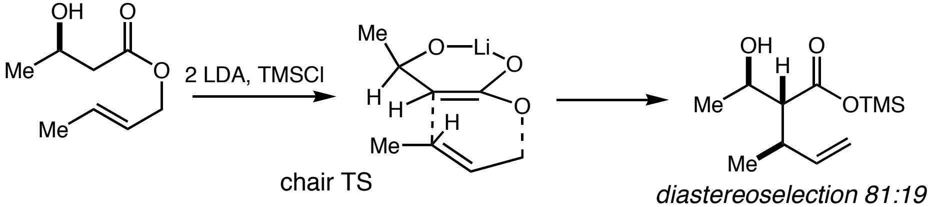
Exocyclic Stereochemical Issues



These rearrangements present many of the same issues which were encountered during our discussion of carbonyl addition with regrad to assymmetric induction.

Chelate Control: β-Hydroxy ester enolates: Kurth, *JOC* **1985**, *50*, 1840

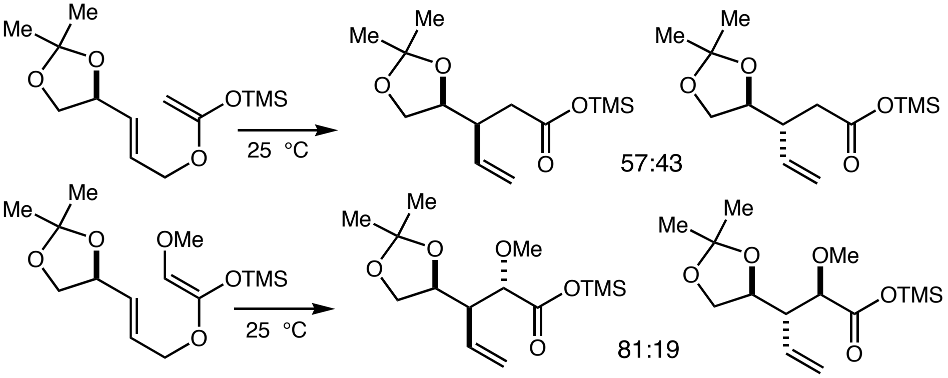


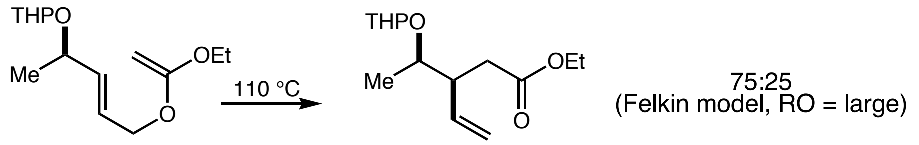


diastereoselection 81:19

We again see the consequence of chelate-organized asymmetric induction

Felkin Control ?: Cha, *Tet. Lett.* **1984**, *25*, 5263

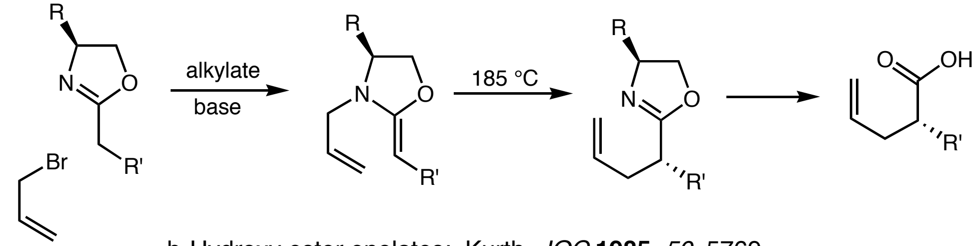




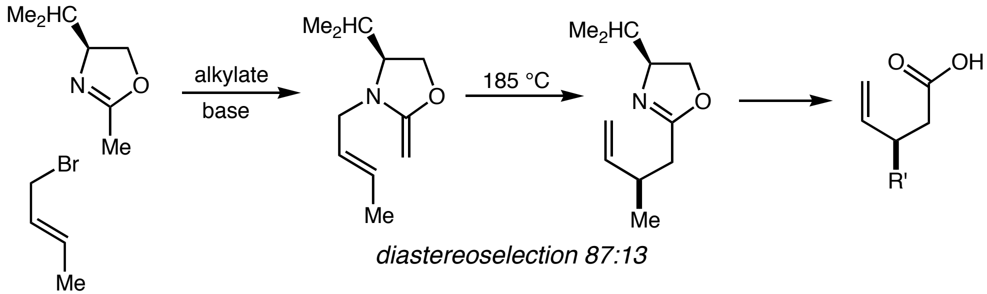
75:25
(Felkin model, RO = large)

Takano, *Tet. Lett.* **1985**, *26*, 865

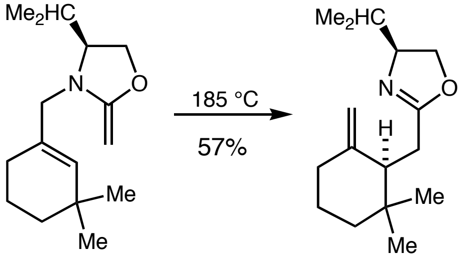
N-Allylketene-N-O-Acetals: Kurth, *JACS* **1985**, *107*, 443



b-Hydroxy ester enolates: Kurth, *JOC* **1985**, *50*, 5769

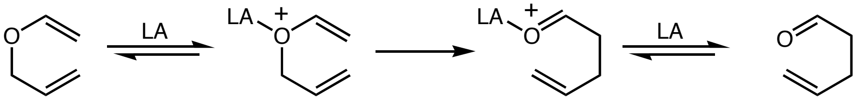


diastereoselection 87:13



diastereoselection 94:6

The Claisen Rearrangement is subject to acid catalysis



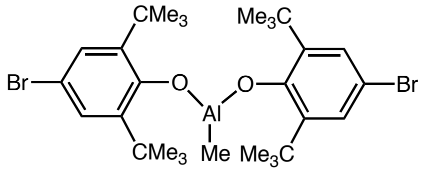
BF_3-HOAc: Bryusova, *J. Gen. Chem. (USSR)* **1941**, *11*, 722
BCl_3: Gerrard, *Proc. Chem. Soc.* **1957**, 19;
Schmid, Helv. Chem. Acta 1973. 56, 14
Et_2AlCl: Sonnenberg, *J. Org. Chem.* **1970**, *35*, 3166
$TiCl_4$: Mukaiyama, *Chem. Lett.* **1975**, *35*, 1041
$(RO)_2AlMe$: Yamamoto, *JACS.* **1988**, *110*, 7922
$(RO)_2AlMe$: Yamamoto, *Tet. Lett.* **1989**, *30*, 1265
$(RO)_2AlMe$: Yamamoto, *JACS.* **1990**, *112*, 316
$LiClO_4$: Reetz, *Tetrahedron.* **1993**, *49*, 6025

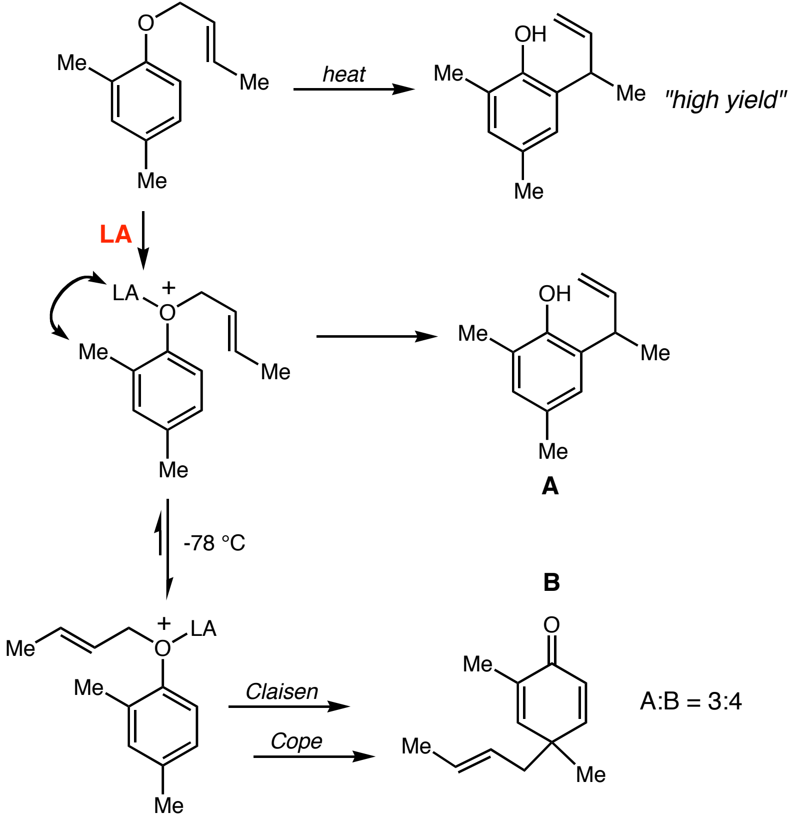
Lewis Acid Catalyzed Claisen Rearrangements

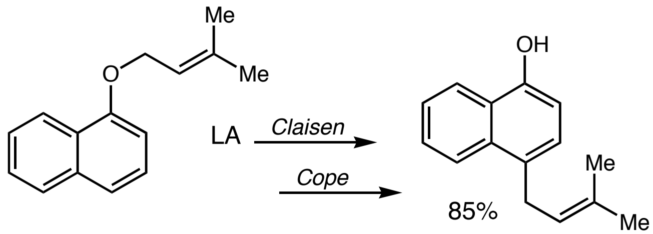
Catalyzed Claisen Rearrangement of Allyl-phenyl Ethers

$(RO)_2AlMe$: Yamamoto, *Tet. Lett.* **1990**, *31*, 377

The Lewis Acid (LA)





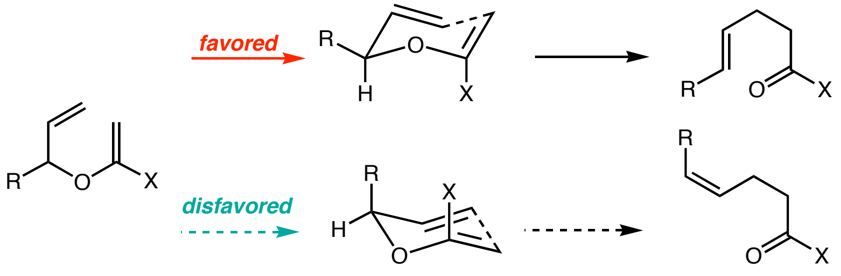


The hindered Lewis acid will alter the partitioning of the Claisen process to the two ortho positions

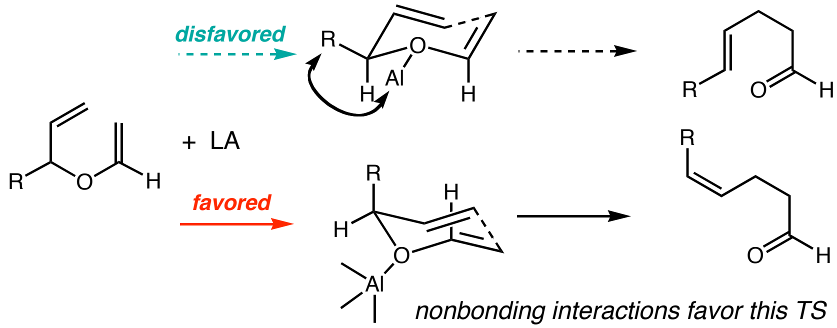
Catalyzed Claisen Rearrangement of Allyl-vinyl Ethers

$(RO)_2AlMe$: Yamamoto, *JACS.* **1990**, *112*, 316

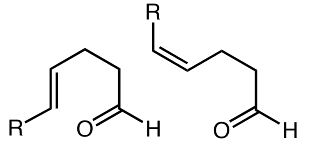
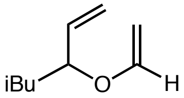
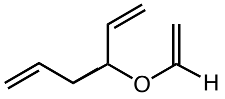
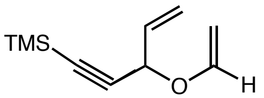
The thermal process



The catalyzed process



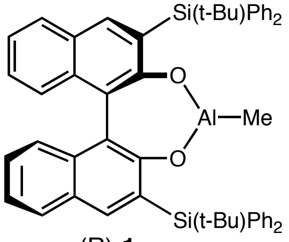
nonbonding interactions favor this TS

		
	43%	19:81
	40%	07:93
	94%	03:97

Lewis Acid Catalyzed Claisen Rearrangements

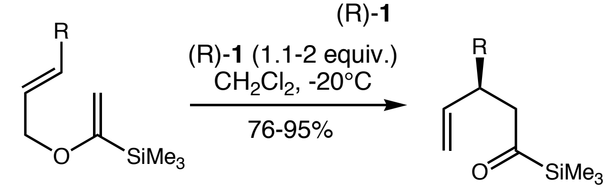
Chiral Lewis Acid Promoted Claisen Rearrangements

Yamamoto, *JACS.* **1990**, *112*, 7791
Yamamoto, *Tet. Asymmetry* **1991**, *2*, 647-662

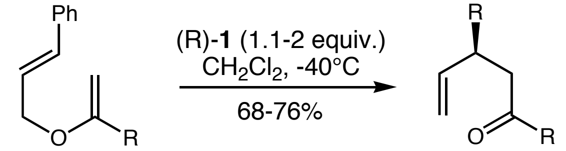


(R)-**1**

Note that these reactions are not catalytic



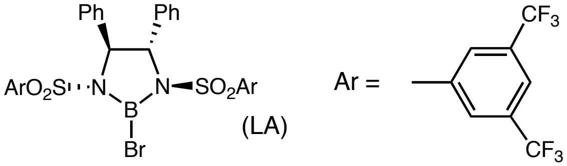
R	% ee
Ph	88%
C_6H_{11}	71%

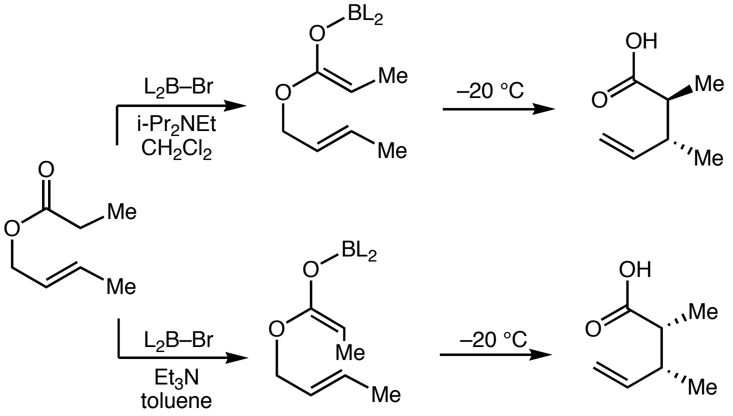


R	% ee
$SiMe_2Ph$	90%
$GeMe_3$	93%

Enantioselective Claisen Rearrangements: Metal-Centered Chirality

Corey, *JACS.* **1991**, *113*, 4026



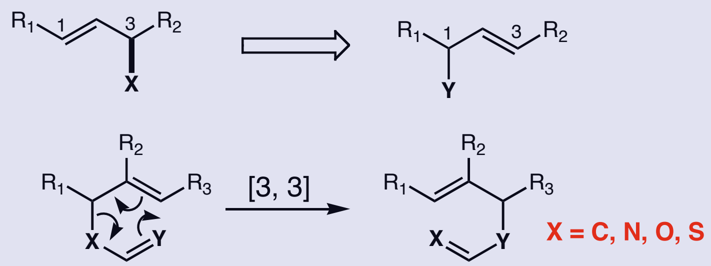


Threo: erythro 99:1
>97% ee (75%)

Threo: erythro 10:90
96% ee (65%)

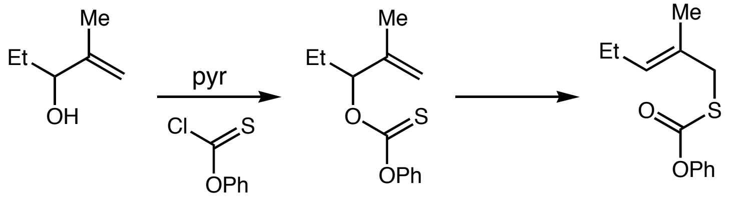
8 cases reported

Allylic rearrangements may be included as a subset of other sigmatropic processes:



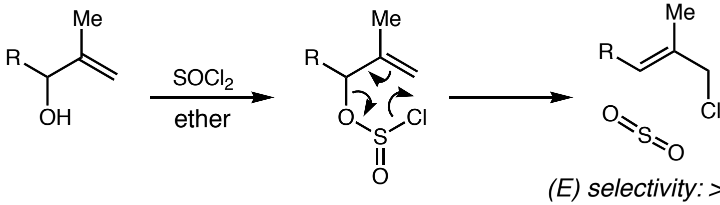
X = C, N, O, S

X = O; Y = S Faulkner, *Synthesis* **1971** 175 (see pg 183)



(E) selectivity: 96.5%

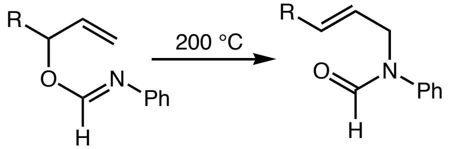
A stereochemically related case Johnson, *JACS* **1970** *92*, 735



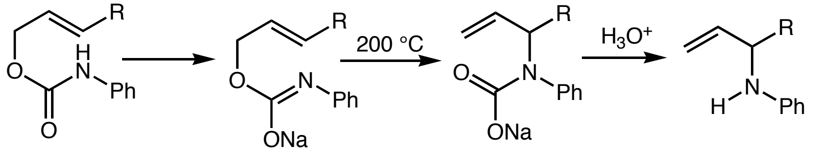
(E) selectivity: >98%

X = O; Y = N

Roberts, *JACS* **1960** *82*, 1950



Hill, *JOC* **1968** *33*, 1111



http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 16

Cycloaddition Reactions-1

- **Cycloadditions: Introduction**
- **Ketene Cycloadditions**
- **The Diels-Alder Reaction**

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Pavel Nagorny

Wednesday,
October 25, 2006

The Diels-Alder Cycloaddition Reactions

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(electronic handout)**

The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, *41*, 1668-1698 **(electronic handout)**

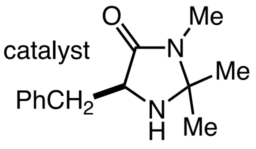
Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, *41*, 1650-1667 **(electronic handout)**

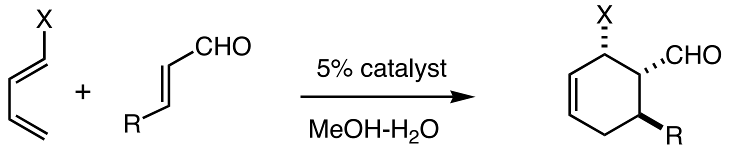
Chemistry and Biology of Biosynthetic Diels–Alder Reactions Emily M. Stocking and Robert M. Williams, *Angew Chem. Int. Ed.* **2003**, *42*, 3078-3115 **(electronic handout)**

Problem of the Day:

Rationalize the sense of asymmetric induction for this Diels-Alder Reaction reported by MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**

catalyst

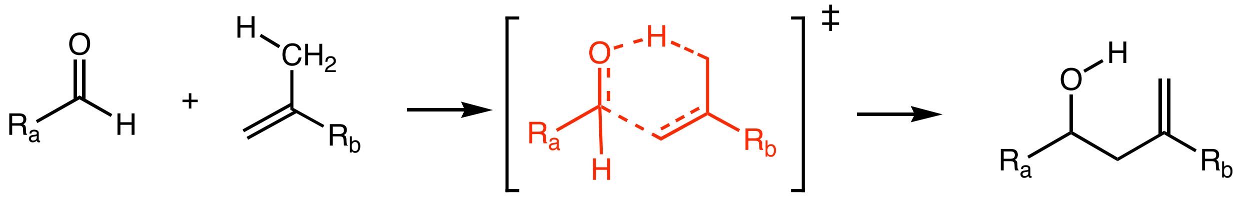




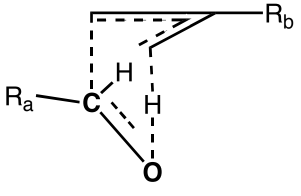
The Carbonyl Ene Reaction

The carbonyl ene reaction is a very powerful transformation that I want to introduce to you. Accordingly, I have prepared a series of problems taken from the Problems Database to familiarize you with this reaction. **Problem 210** is provided as an introduction to the FMO analysis for the process. Subsequent problems have the ene reaction imbedded in reaction cascades.

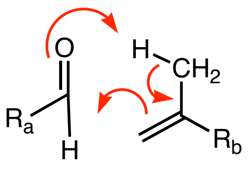
Problem 210. Question and Answer. The carbonyl ene reaction is illustrated below. Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.

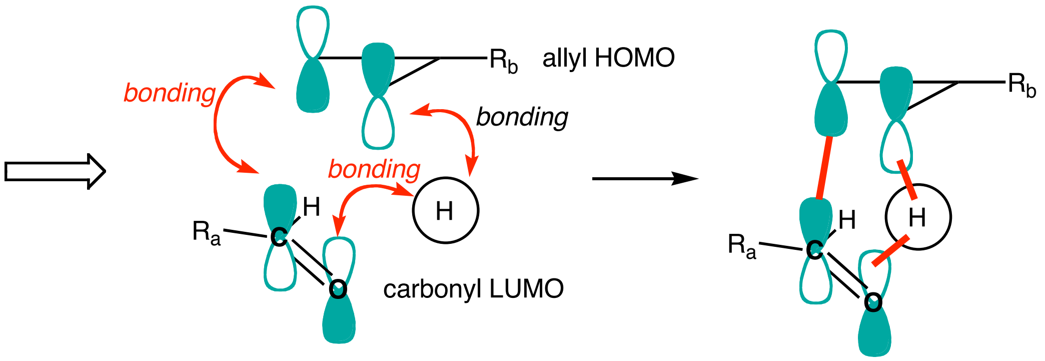


Answer



The ene transition state





View the ene TS as a 3-component cycloaddition

One possible analysis:
allyl anion: 4 e^-
Proton
carbonyl: 2 e^-

[$2\pi s + 2\pi s + 2\sigma s$]

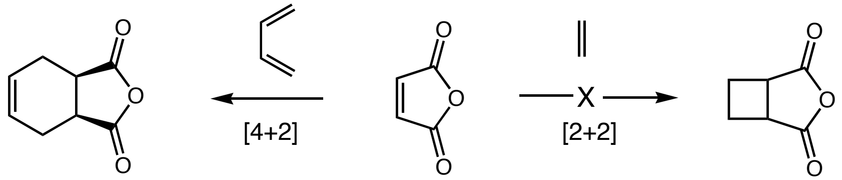
$6\pi e^-$ "cycloaddition"

suprafacial

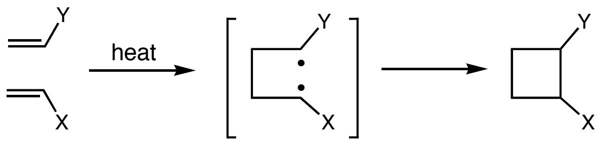
thermally allowed

Cycloaddition Reactions-1

Why does maleic anhydride react easily with 1,3-butadiene, but not with ethylene? So what are the "rules"?



■ The related reaction of 2 ethylenes is nonconcerted: [2 + 2] cycloaddition

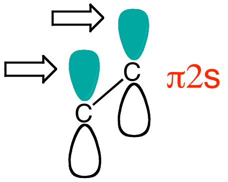


■ We also know that the photochemical variant is concerted

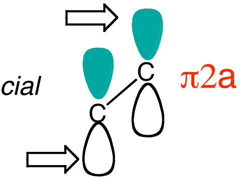
The frontier orbitals of the reacting species must have the proper symmetries

■ Nomenclature

suprafacial

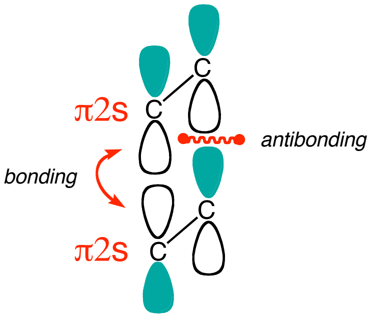


antarafacial

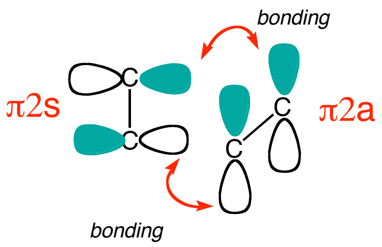


Using this nomenclature, the Diels-Alder reaction is a $\pi 4s + \pi 2s$ cycloaddition

■ Consider [2 + 2] cycloaddition: Thermal activation $[\pi 2s + \pi 2s]$

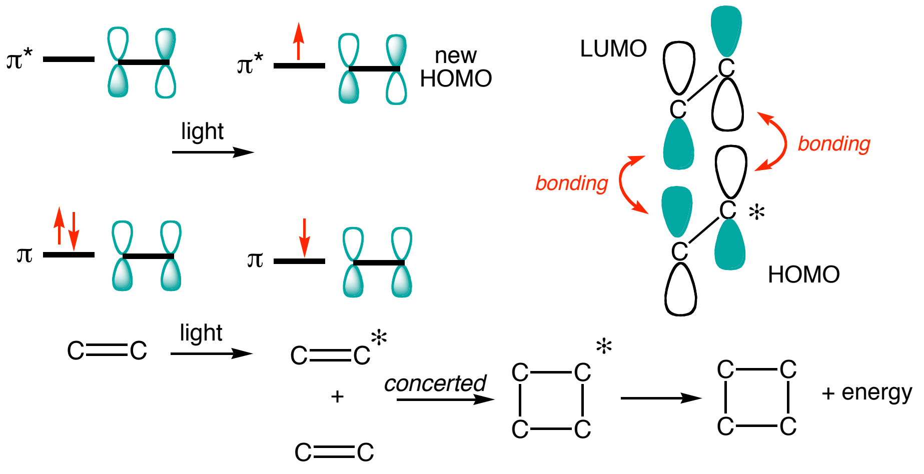


$[\pi 2s + \pi 2s]$ "forbidden"

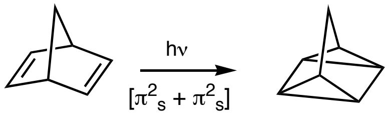


$[\pi 2s + \pi 2a]$ "allowed"

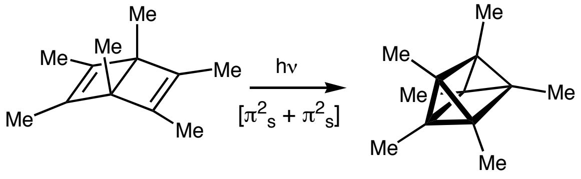
■ Consider [2 + 2] cycloaddition: Photochemical activation $[\pi 2s + \pi 2s]$



[2+2] Cycloaddition - Examples



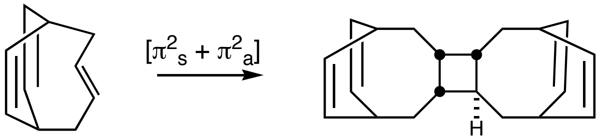
Quadricyclane Dauben, *Tet.* **1961**, *15*, 197.



Dewar benzene-Derivative

Prismane-Der.

Schäfer, *AC* **1967**, *79*, 54.

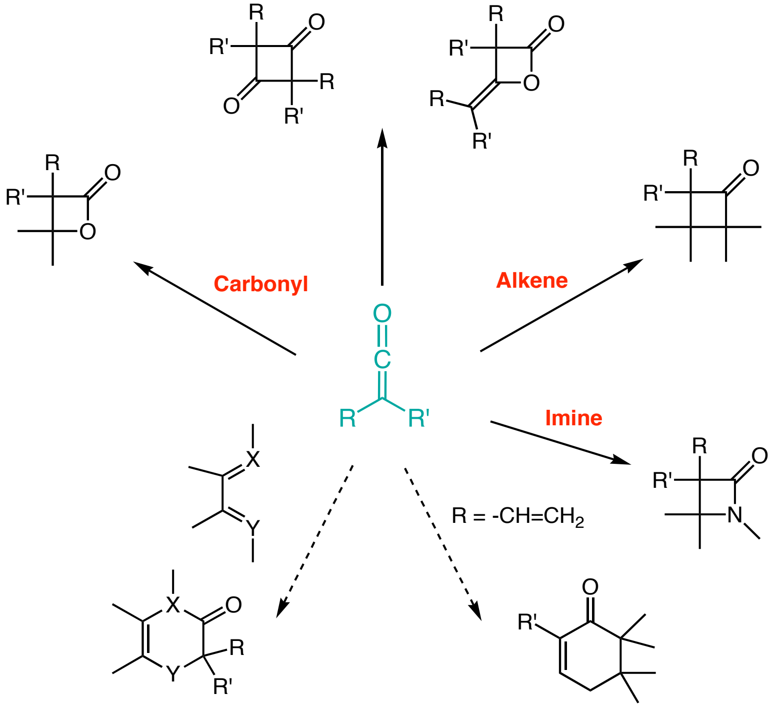


must be antarafical for indicated stereochem

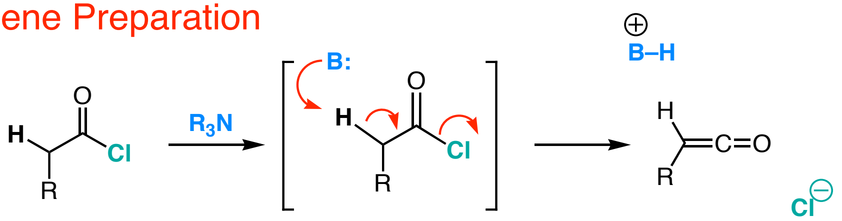
TL **1967**, 4357, 4723.

Cycloaddition Reactions-2

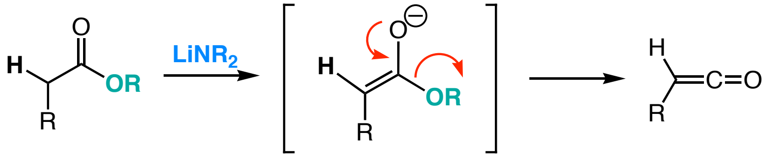
Summary of Ketene Cycloadditions



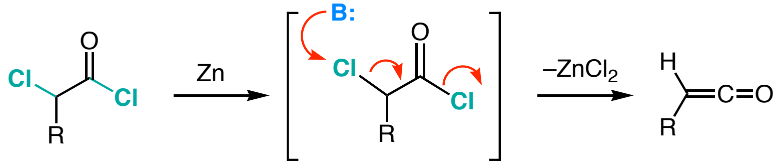
Ketene Preparation



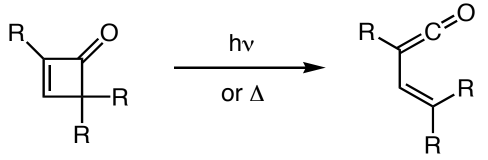
E2 Elimination

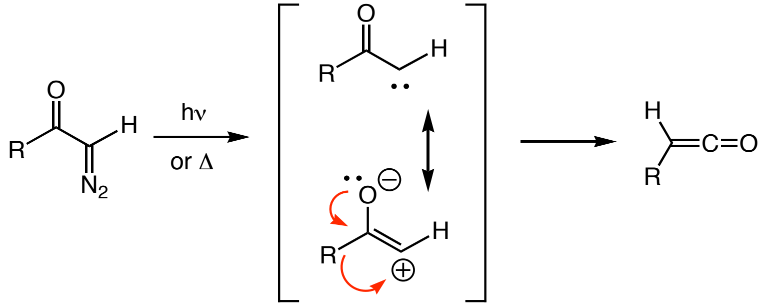


E1cb Elimination

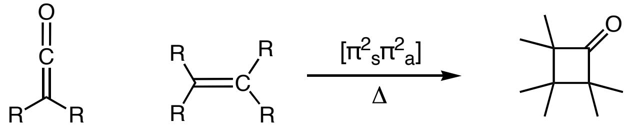


Electrocyclic Ring Opening

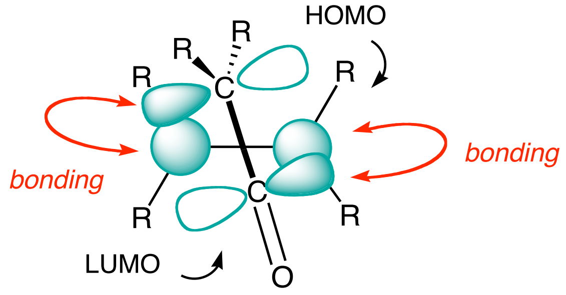




Cycloaddition: FMO Analysis

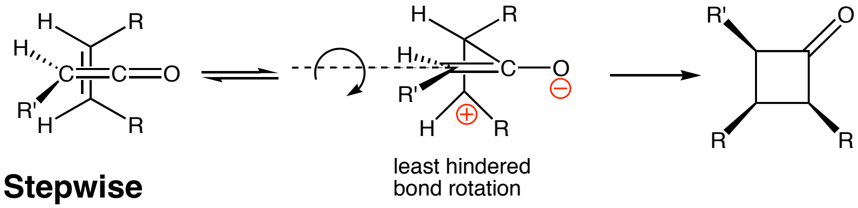


Antarafacial **Suprafacial**



Cycloaddition Reactions-3

[2+2]: Stepwise Versus Concerted



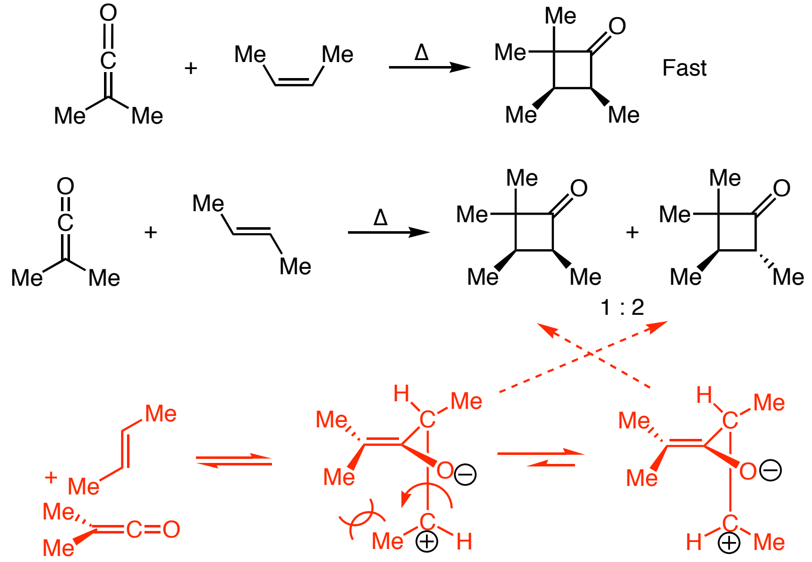
Stepwise

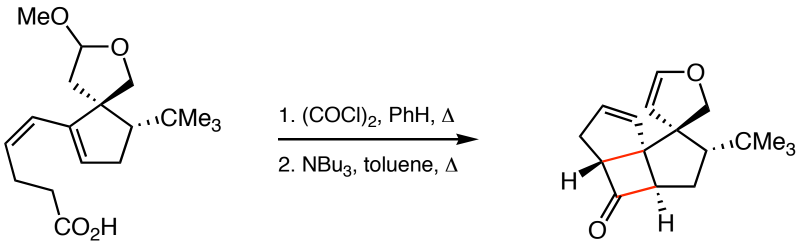
- Very large polar effects
- E olefins yield a mixture of *cis* and *trans* products
- Solvent effects observed, but it could merely be a ground state effect
- KIE seen for many reactions support stepwise mechanism
- Calculations show a highly asynchronus transition state.
- Stereochemical consequence can be rationalized by stepwise mechanism

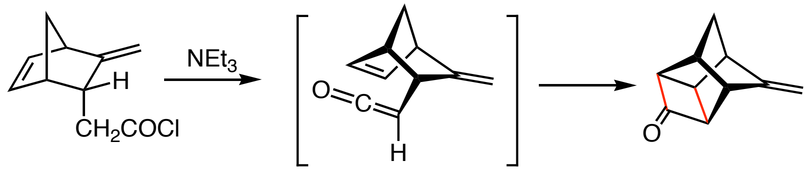
Concerted

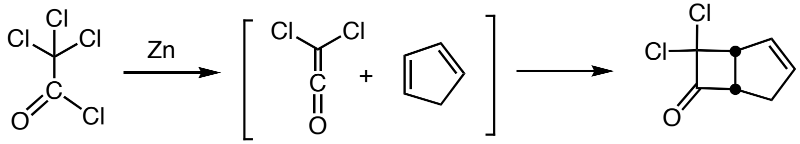
- Ketenes add stereoselectively to Z alkenes.
- Z olefins are much more reactive than E olefins

Ketene-Alkene [2+2]

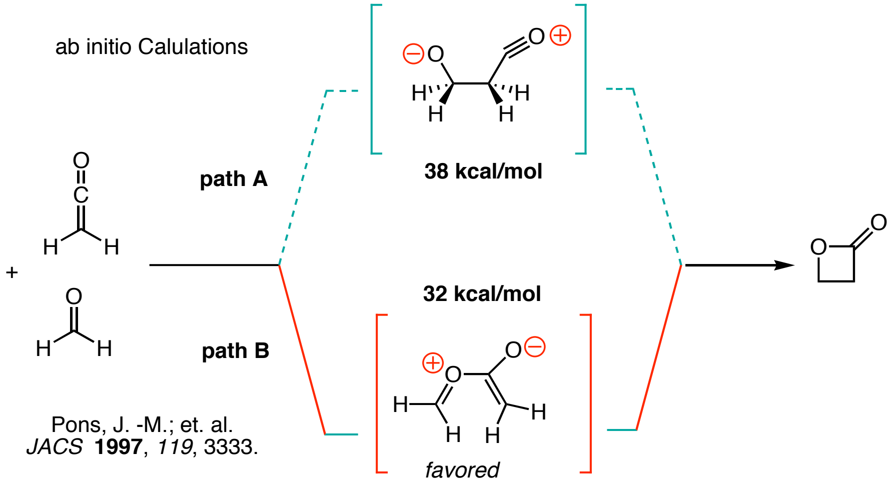






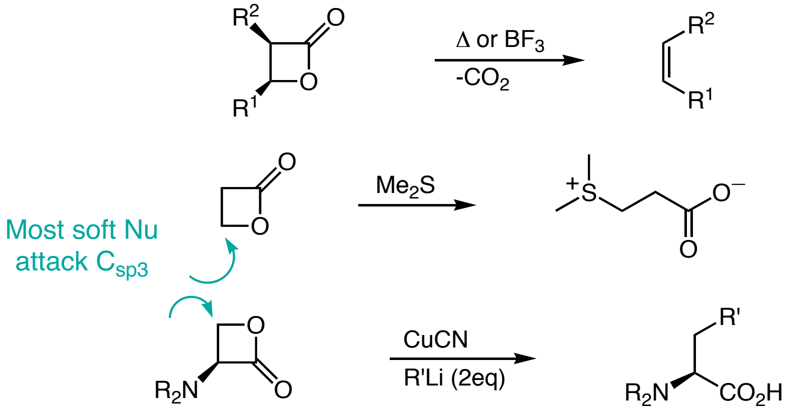


Ketenes + Aldehydes Afford β-Lactones



Pons, J. -M.; et. al.
JACS **1997**, *119*, 3333.

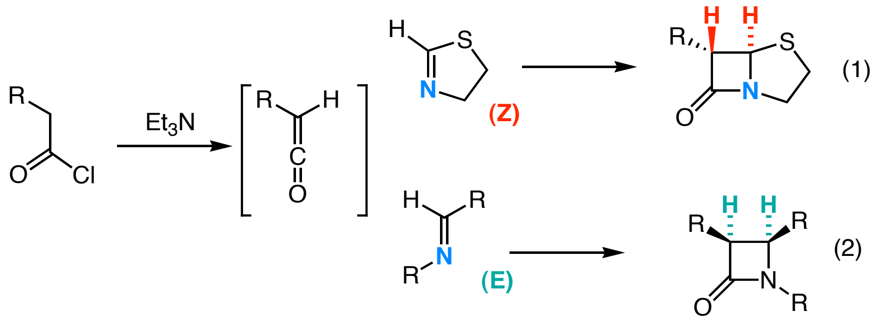
Transformations of β-Lactones



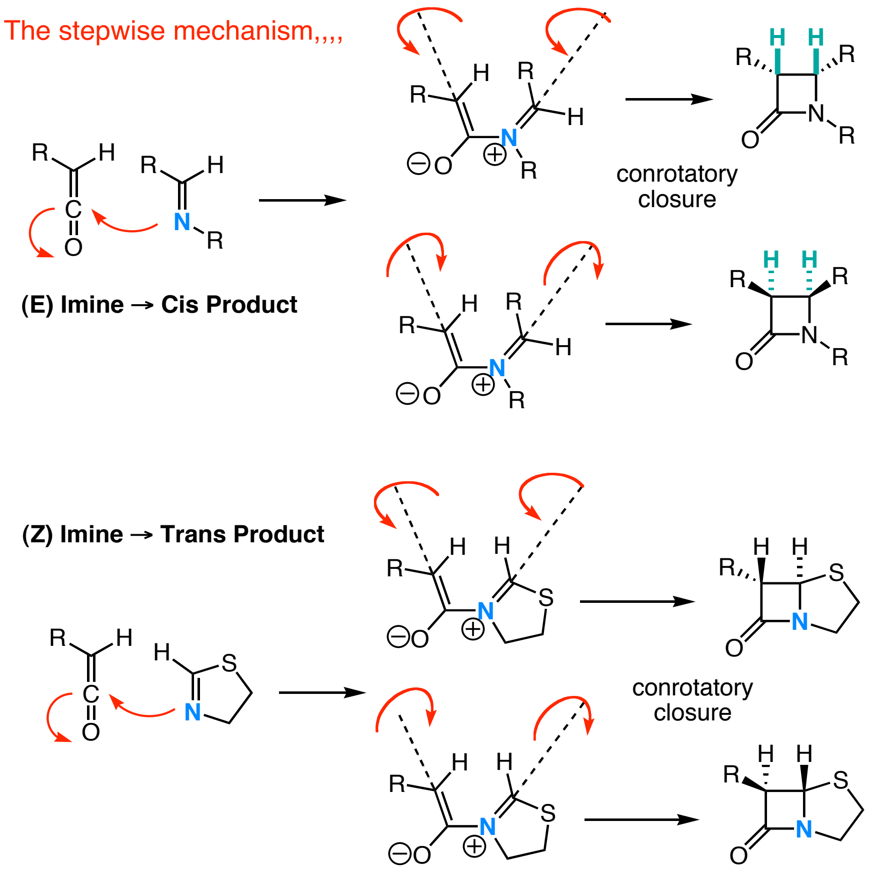
Vederas et al *JACS* **1987**, *107*, 4649.

The Staudinger Reaction

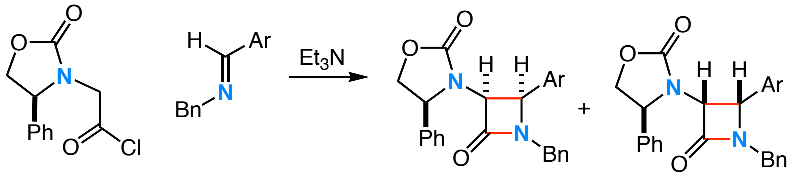
In this process, the illustrated ketene, generated *in situ* from an acid chloride, undergoes reaction with the indicated substrates to form β-lactams in a stereoselective process. When the azo-methine (RN=CHR) geometry in the reactant is (Z) the product stereochemistry is trans (eq 1). In a complementary fashion, the (E) imine affords the cis-substituted product (eq 2). While this transformatlion could be viewed as a [2s+2a] cycloaddition, it is felt that this reaction is stepwise.



The stepwise mechanism,,,,



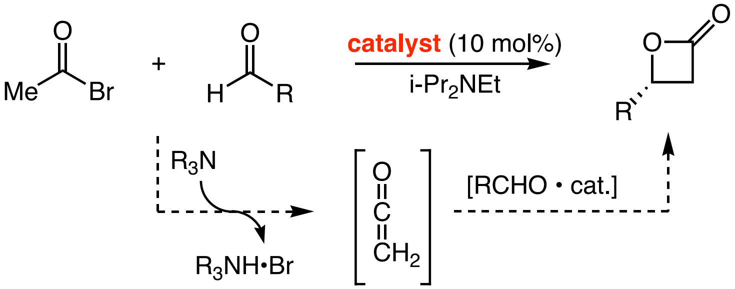
There are two contortaory modes. If you control the conrotatory mode, you control the absolute stereochemistry of the reaction:

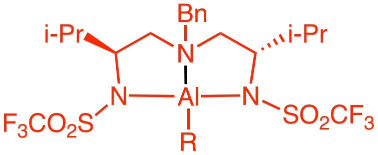


Evans, Sjogren *Tet. Lett.* **1985**, *26*, 3783, 3787.
See also Evans, Williams, *Tet. Lett.* **1988**, *29*, 5065.

diastereoselection > 95:5
80-90% yields

Enantioselective Ketene-Aldehyde Cycloadditons

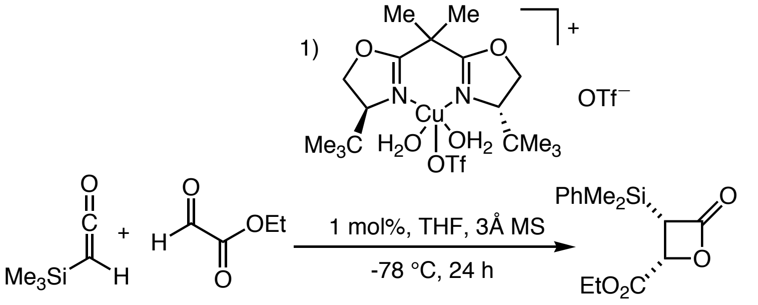




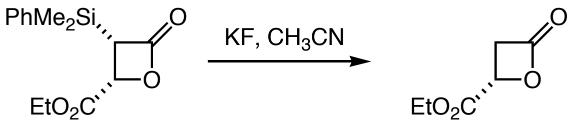
cat. = **5a**: R = Me
5b: R = Cl

entry	Aldehyde **2** (R)	catalyst [time (h), temp (°C)]	% yield	% ee **3** (configuration)
a	BnOCH$_2$–	**5b** (8, -40)	91	92 (*R*)
b	PhCH$_2$CH$_2$—	**5a** (16, -50)	93	92 (*S*)
	PhCH$_2$CH$_2$—	**5a** (72, -78)	89	95 (*S*)
c	CH$_2$CH(CH$_2$)$_8$—	**5b** (16, -50)	91	91 (*S*)
d	Me$_2$CHCH$_2$—	**5a** (24, -50)	80	93 (*S*)
e	BnOCH$_2$CH$_2$–	**5b** (16, -40)	90	91 (*S*)
f	TBDPSOCH$_2$–	**5b** (16, -40)	74	89 (*R*)
g	BnOCH$_2$—≡—	**5a** (16, -50)	86	93 (*R*)
h	Me$_3$C—≡—	**5a** (16, -50)	91	85 (*R*)
i	C$_6$H$_{11}$–	**5b** (24, -40)	56	54 (*R*)

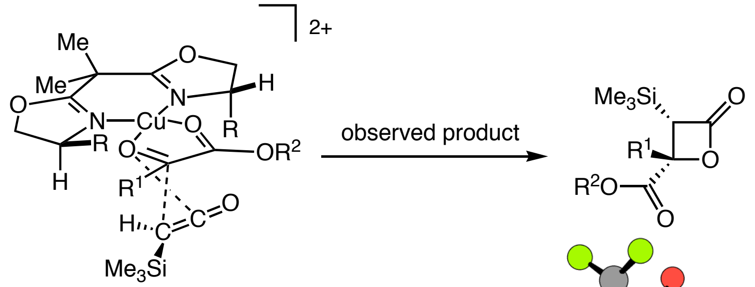
Nelson, S. G.; Peelen, T. J.; Wan, Z. *JACS*, **1999**, 121, 9742-9743

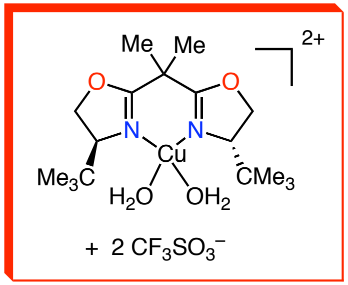


77% yield, 93% ee

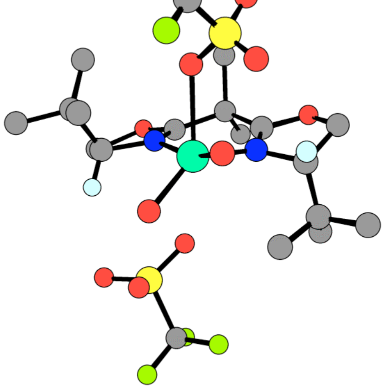


3: >99% yield, 92% ee





+ 2 CF$_3$SO$_3^-$



with J. Janey, *Org. Lett.* **2001**, *3*, 2125-2128

Articles and monographs of Significance

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(pdf)**

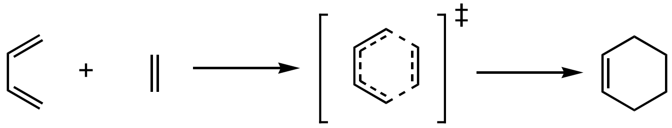
The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, *41*, 1668-1698 **(pdf)**

Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, *41*, 1650-1667 **(pdf)**

Chemistry and Biology of Biosynthetic Diels–Alder Reactions
Emily M. Stocking and Robert M. Williams, *Angew Chem. Int. Ed.* **2003**, *42*, 3078-3115 **(pdf)**

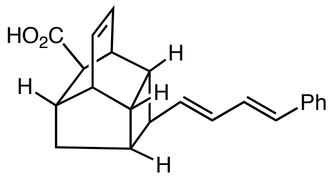
Recent Advances in Natural Product Synthesis by Using Intramolecular Diels-Alder Reactions, Tadano et al. *Chem Rev.* **2005,** *105,* ASAP **(pdf)**

■ The Reaction:

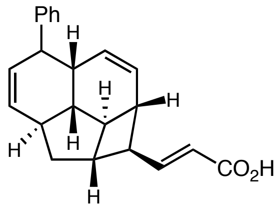


■ Representative natural products displaying the Diels-Alder retron:

These natural products could well have incorporated the DA rxn into the biosynthesis

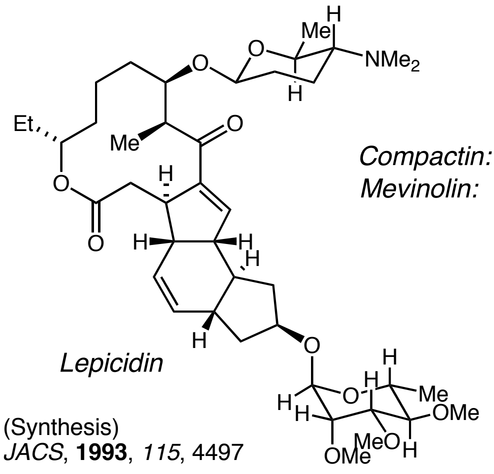


Endiandric Acid C



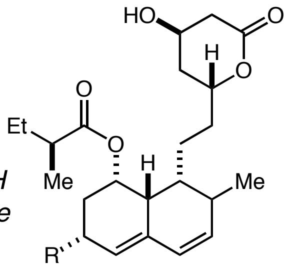
Endiandric Acid B

(Syntheses)
Nicolaou, *JACS* **1982**, *104*, 5555-5562



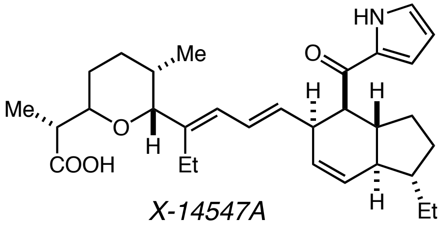
Lepicidin

(Synthesis)
JACS, **1993**, *115*, 4497



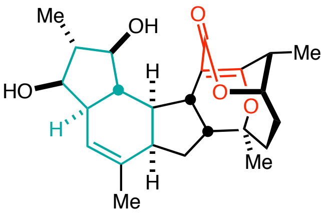
Compactin: R = H
Mevinolin: R = Me

(Biosynthesis) *JACS* **1985**, *107*, 3694
Clive, *JACS* **1988**, *110*, 6914
Kozikowski, *JOC* **1987**, *52*, 3541
Keck, *JOC* **1986**, *51*, 2487
Grieco, *JACS* **1986**, *108*, 5908
Heathcock, *JACS* **1985**, *107*, 3731
Girotra, *Tet. Let.* **1983**, *24*, 3687
Hirama, *JACS* **1982**, *104*, 4251

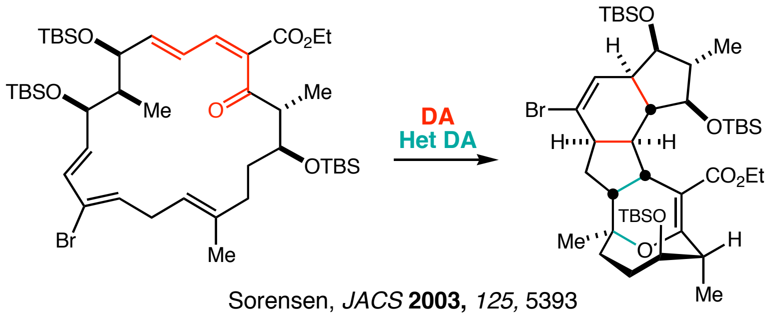


X-14547A

Roush *JOC* **1984**, *49*, 3429
Nicolaou *JOC* **1985**, *50*, 1440
Ley *Chem. Commun.* **1983**, 630



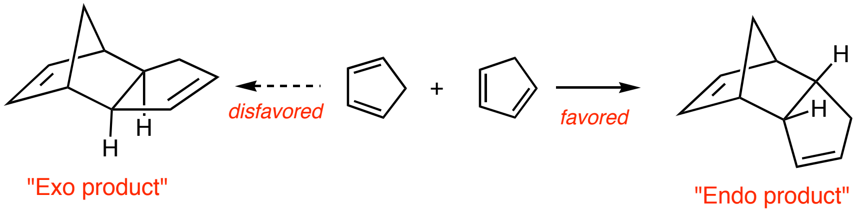
ent-FR182877 (WS9885B)
J. Antibiotics **2000**, *53*, 204



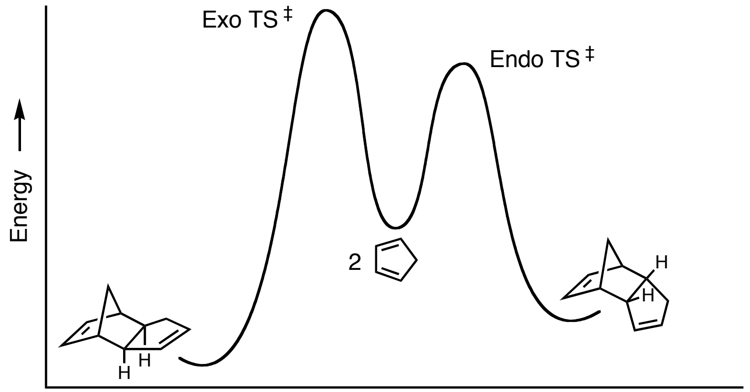
Sorensen, *JACS* **2003,** *125,* 5393
Evans, *JACS* **2003,** *125,* 13531

The Alder Endo Rule

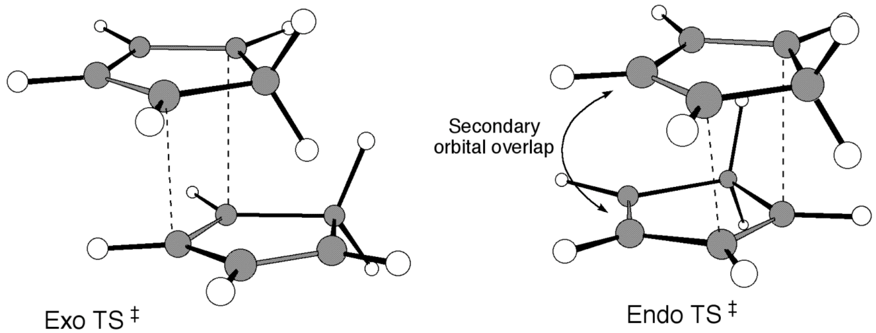
The following observation illustrates an example of the Alder Rule which will be defined below.



Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.

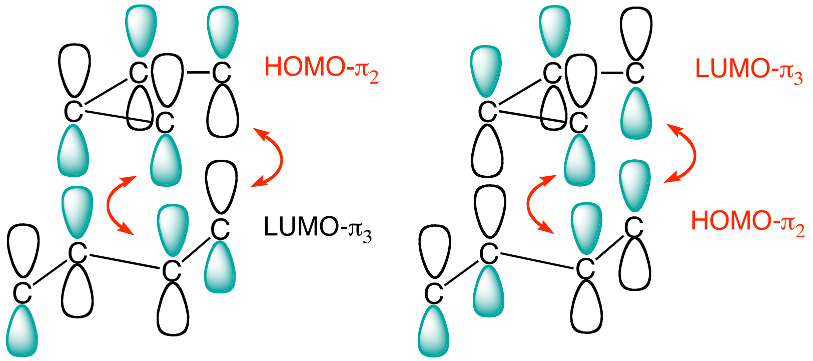


- Of the two possible transition states, the one having the "greatest accumulation of interacting double bonds will be preferred" (the Alder Endo Rule). Secondary orbital overlap is noted below.



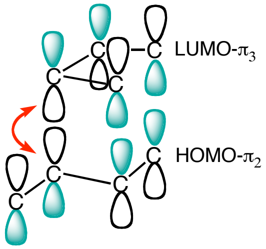
Orbital Symmetry Considerations for Diels Alder Reaction

If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



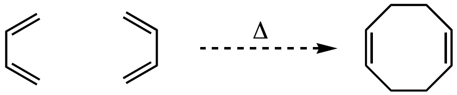
Frontier MO Explanation for the Endo Rule

- Secondary (transient) orbital overlap can also occcur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

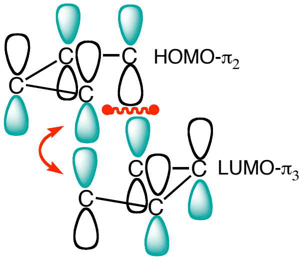


The Other Dimerization Possibility for Butadiene

Does the possibility for the following concerted dimerization exist?

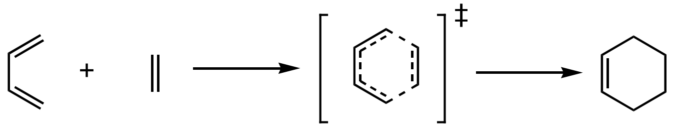


- Note that the termini only match at one end for the HOMO-LUMO pairing. Hence we say that the symmetry requirements for the reaction in question are not met. This does not mean that the reaction will not occur, only that the reaction will not be concerted. Such reactions are called "symmetry-forbidden".



Diels-Alder Reaction: The Transition Structure

Transition State Modelling is Coming of Age

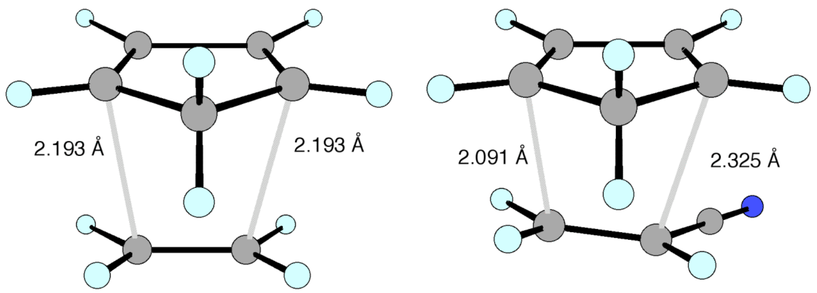


- The lengths of the forming C–C bonds are Ca. 1.5 times the normal bond distance. This factor comes out of the *ab initio* work of Jorgensen & Houk

leading references:
Jorgensen, *JACS* **1993**, *115*, 2936-2942
Houk, Jorgensen, *JACS* **1989**, *111*, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
Houk *Angew. chem. Int. Ed.* **1992**, *31*, 682-708

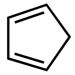
- Bond formation is not synchronus with substituted dienophiles (Jorgensen)

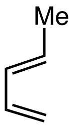


exptl $\Delta H^{\ddagger}$ = 22.5 kcal/mol
$\Delta S^{\ddagger}$ = -32.1 eu
rel rate = 1

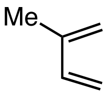
$\Delta H^{\ddagger}$ = 14.0 kcal/mol
$\Delta S^{\ddagger}$ = -38.3 eu
rel rate = 10^{+5}

- Diene Reactivity as measured against Maleic anhydride

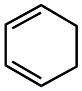

log k = 4.96

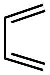


log k = 2.36



log k = 2.19

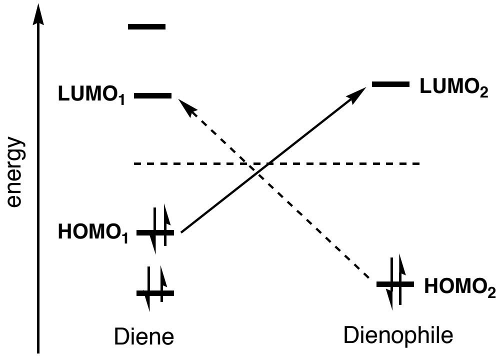

log k = 2.12


log k = 1.83

Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

- Lewis Acid Catalysis of the reaction is possible:

Yates & Eaton, *JACS* **1960**, *82*, 4436

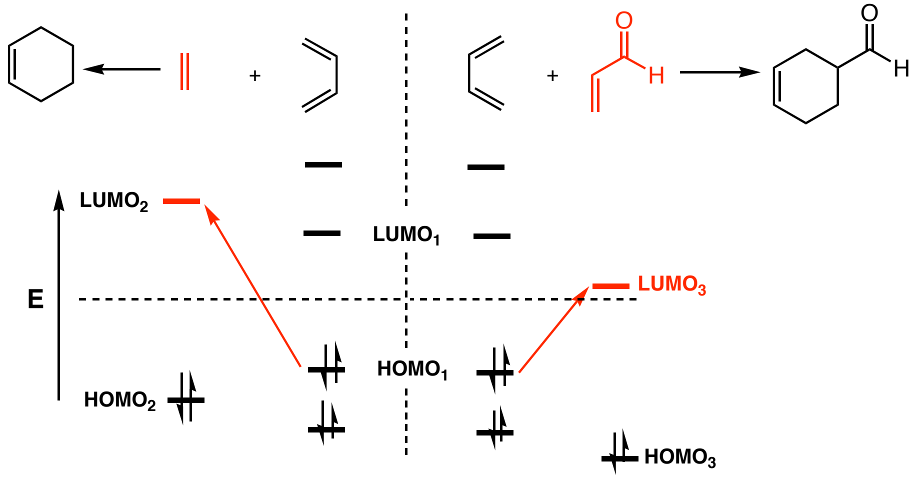


The Critical Energy Difference:

E(LUMO$_1$) - **E**(HOMO$_2$)
or
E(LUMO$_2$) - **E**(HOMO$_1$)

- The closer the two orbitals are in energy, the better they interact
- As ΔE decreases for the relevant ground state FMOs, rxn rates increase

Ethylene & Butadiene Vs Butadiene & Acrolein

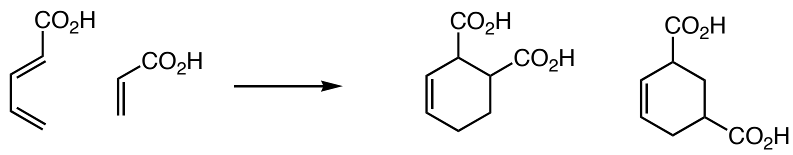


ΔE (LUMO$_3$-HOMO$_1$) < ΔE (LUMO$_2$-HOMO$_1$) ⟹ *Rate Acceleration*

Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

Diels-Alder Reaction: Regiochemistry

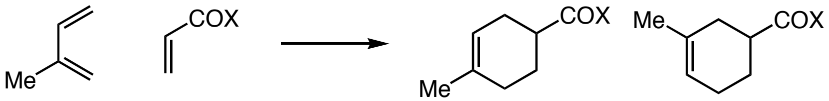
Orientation of Reacting Partners



favored *disfavored*

4.5 : 01 @ 100 °C

Lewis acid catalysis improves orientation



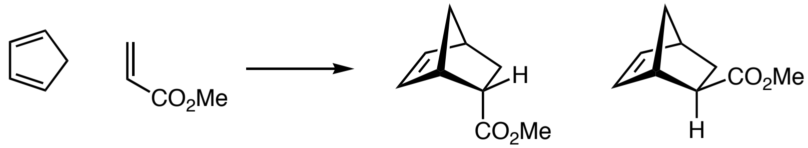
favored *disfavored*

toluene, 120 °C 59 : 41

C_6H_6, $SnCl_4$, 25 °C 96 : 04

*In general, 1-substituted dienes are more regioselective than their 2-substituted counterparts: Sauer, Angew. Chem. Int. Ed., **1967**, 6, 16-33*

Lewis acid catalysis improves endo diastereoselection



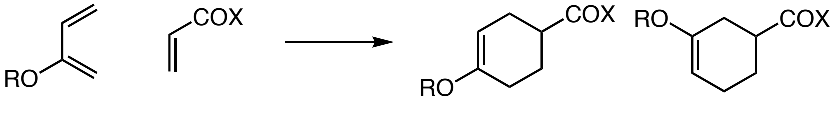
favored *disfavored*

CH_2Cl_2, 0 °C 80 : 20

C_6H_6, $SnCl_4$, 25 °C 95 : 05

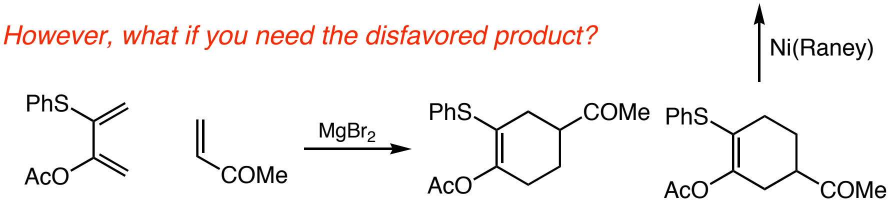
DA Reactions Part II: The Reaction Mechanism, Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

Here is an interesting problem in reaction design



favored *disfavored*

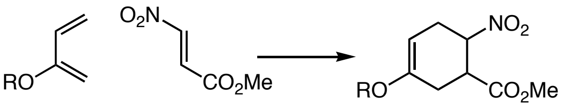
However, what if you need the disfavored product?



Trost, *JACS* **1980**, *102*, 3554

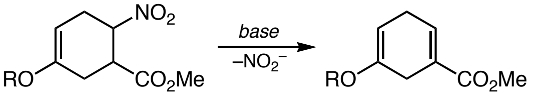
disfavored *favored*

By employing a removable substituent, it is possible to access the normally disfavored product diastereomer

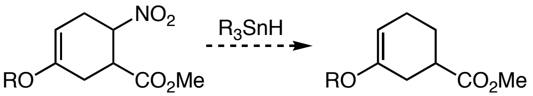


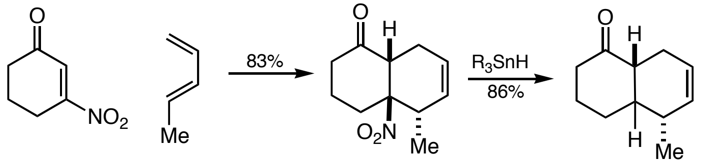
Danishefsky, *JACS* **1978**, *100*, 2918: The NO_2 FG completely dominates directivity

It then can be removed by elimination



or by reduction
Ono, *Tet.* **1985**, 4013



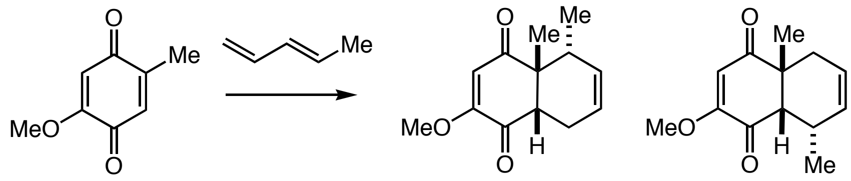


mixture of ring-fusion isomers

Ono, *Chem. Commun.* **1982**, 33-34

Diels-Alder Reaction: Regiochemistry

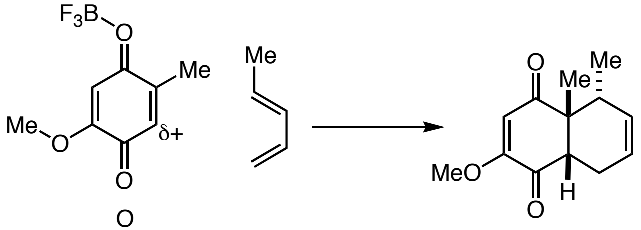
Instructive Issues of Regiocontrol with Quinone Dienophiles



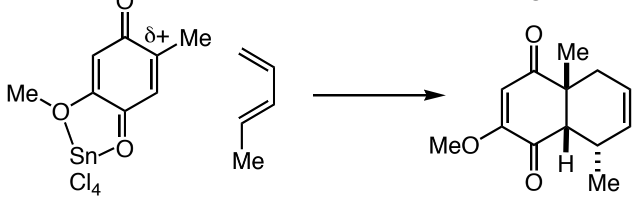
Orientation of Reacting Partners controlled by Lewis acid structure

Reusch *JOC* **1980**, *45*, 5013

Conditions	Ratio
thermal (100 °)	50 : 50
BF_3•OEt_2 (-20 °)	80 : 20
$SnCl_4$ (-20 °)	<5 : 95



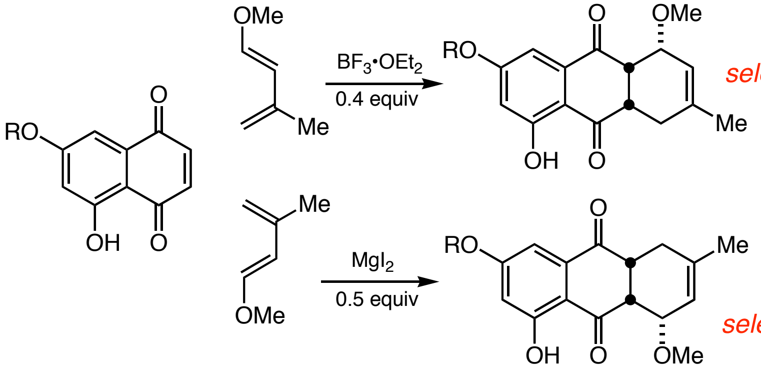
selection 80 : 20



selection >95 :5

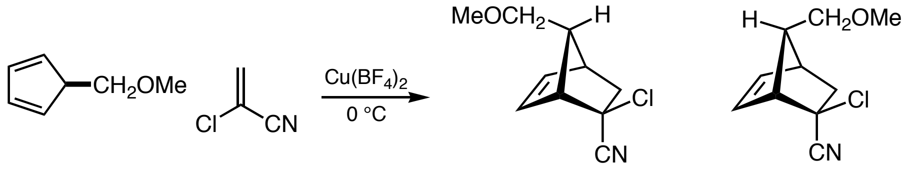
Similar results provided by Stoodley *Chem. Comm.* **1982**, 929

Kelly *Tet. Let.* **1978**, 4311



selection >95 :5

selection >95 :5

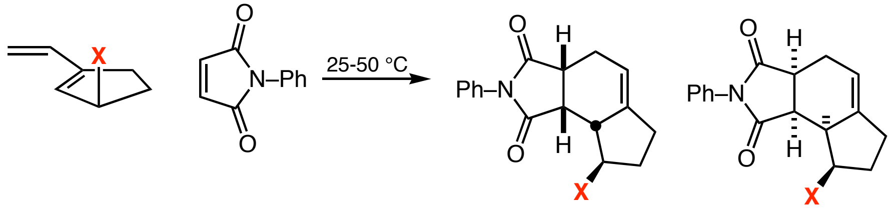


Corey, *JACS* **1969**, *91*, 5675

Ratio: 90 : 10

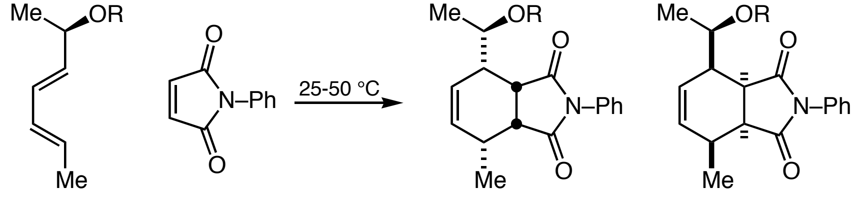
Diels-Alder Reactions with Chiral Dienes

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**
4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347



X =	Ratio
–OH	36 : 64
–Me	83 : 17
–OMe	>97 : 3

Overman, *JACS* **1988**, *110*, 4625

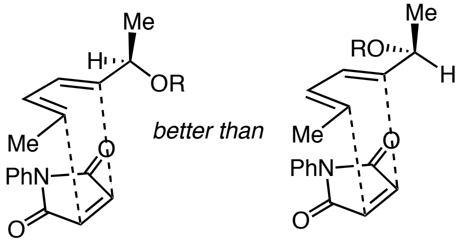


Franck, *Tet. Lett.* **1985**, *26*, 3187
Franck, *JACS* **1988**, *110*, 3257

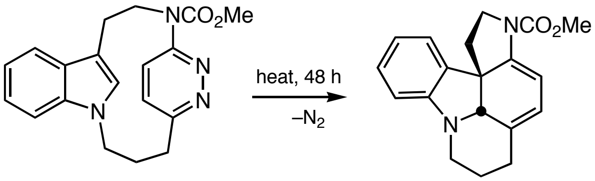
R = Me: Ratio; 83 : 17
R = Me_3Si: Ratio; 88 : 12

Comments on the Transition State

- Avoid Eclipsing allylic substituents
- better donor (Me) anti to forming bond
- avoid gauche OR interaction

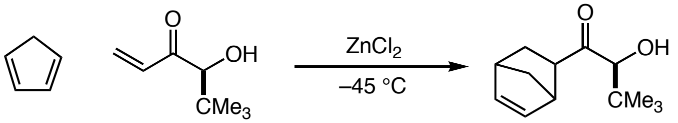


Problem 76, Bodwell has disclosed an interesting thermally initiated reaction cascade that was designed to cuminate in a formal synthesis of strychnine(*Angew. Chem. Int. Ed* **2002**, *41*, 3261). One of his reported transformations is illustrated below.



Provide a detailed mechanism for this reaction cascade. Your answer should include three-dimensional structures that accurately depict ground and transition state representations.

Problem 86. In 1983 Masamune introduced a new family of chiral controllers for the Diels-Alder reaction (*J. Org. Chem.* **1983**, *48*, 4441).

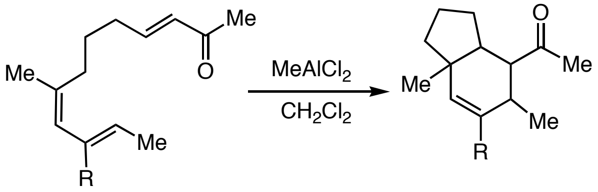


(1)

exo:endo = 94:6
endo diastereoselection >99:1

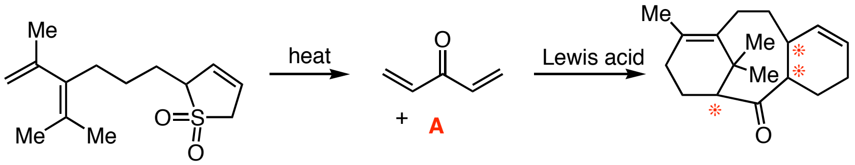
Please provide a mechanism for the reaction shown in equation 1. Be sure to include clear transition state drawings in your answer, and predict the stereochemistry of the major product diastereomer.

Problem 112. In a recent article, Roush reported the highly endo-selective, Lewis acid catalyzed Diels-alder reaction illustrated below (*Org. Lett* **2001**, *3*, 957). Using your knowledge of Diels-Alder transition states, draw the transition state of this reaction, and from this drawing, predict the relative stereochemical relationships that are to be anticipated in the product.

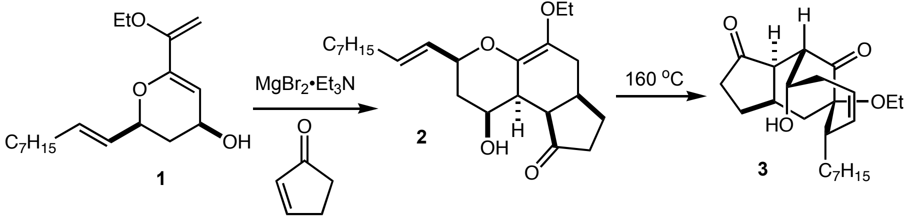


diastereoselection >99:1

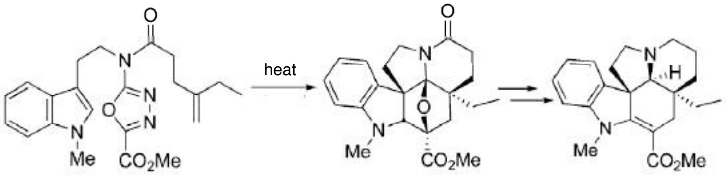
Problem 157. A short reaction sequence that results in the rapid assemblage of the taxane skeleton has been reported by Winkler (*Tetrahedron Lett.* **1995**, *36*, 687). This transformation is illustrated below wherein intermediate **A** is subsequently induced to react with divinyl ketone.
Provide a concise mechanism for this reaction. For full credit, the relative stereochemical relationships at the indicated stereocenters must be provided.



Problem 739. The rapid assembly of the bicyclo[5.3.1]undecane core of penostatin F was recently reported by Barriault and coworkers (*Org. Lett.* **2004**, *6*, 1317). In this remarkable transformation dihydropyran **1** is converted to the highly complex tricycle **3** in only two operations. Please provide a detailed mechanism for this reaction sequence. Be sure to indicate all pericyclic reactions.

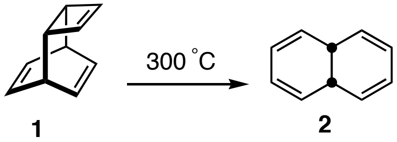


Problem 778. Boger and co-workers recently reported the synthesis of the indole alkaloid minovine (**1**). This pivotal transformations leads to the construction of the minovine skeleton. Provide plausible mechanisms for this transformation.



Minovine (1)

Problem 794. Doering and Rosenthal reported the interesting conversion of Nenitzescu's hydrocarbon (**1**) to dihydro-naphthalene (**2**). Provide a mechanistic rationalization for this transformation. (Reference: Doering, W.v.E.; Rosenthal, J.W., *JACS* **1966**, *88*, 2078)



http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 17

Cycloaddition Reactions-2

The Diels-Alder Reaction: Absolute Stereocontrol

■ Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(pdf)**

D. A. Evans

Friday,
October 27, 2006

Diels-Alder Must-Read List

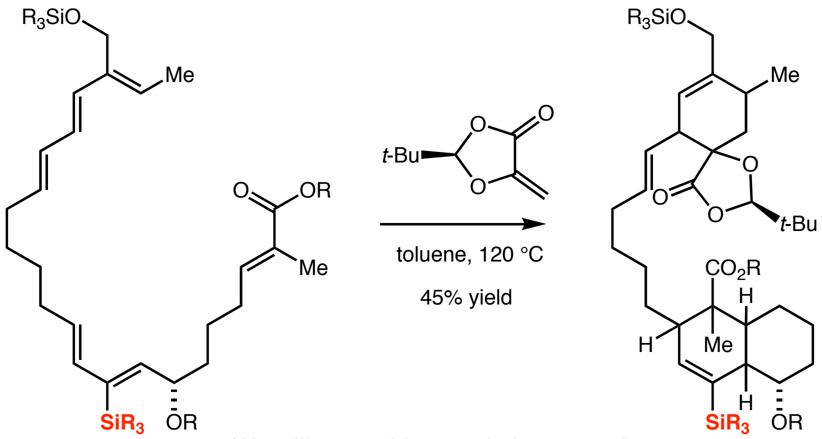
The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, *41*, 1668-1698 **(pdf)**

Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, *41*, 1650-1667 **(pdf)**

Chemistry and Biology of Biosynthetic Diels–Alder Reactions
Emily M. Stocking and Robert M. Williams, *Angew Chem. Int. Ed.* **2003**, *42*, 3078-3115 **(pdf)**

Recent Advances in Natural Product Synthesis by Using Intramolecular Diels-Alder Reactions, Tadano et al. *Chem Rev*. **2005,** *105,* 4779-4807 **(pdf)**

Problem 894. Roush and Sciotti have reported the illustrated complex Diels-Alder reaction in conjunction with their synthesis of chlorothricolide (*JACS* **1998**, *120*, 7411). In prior studies, they had documented that the dienophile was highly exo-selective. The absolute stereochemical relationships in the reactants are as indicated. Predict the sense of asymmetric induction for both cycloadditions and assign all stereochemical relationships in the product. Comment on the significance of the vinyl-silicon substituent.



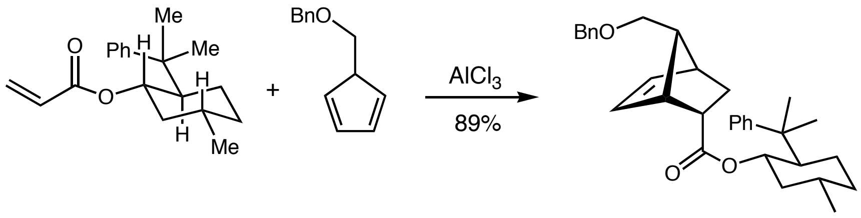
We will cover this case in lecture today.

Chiral Auxiliary Controlled Diels-Alder Reactions

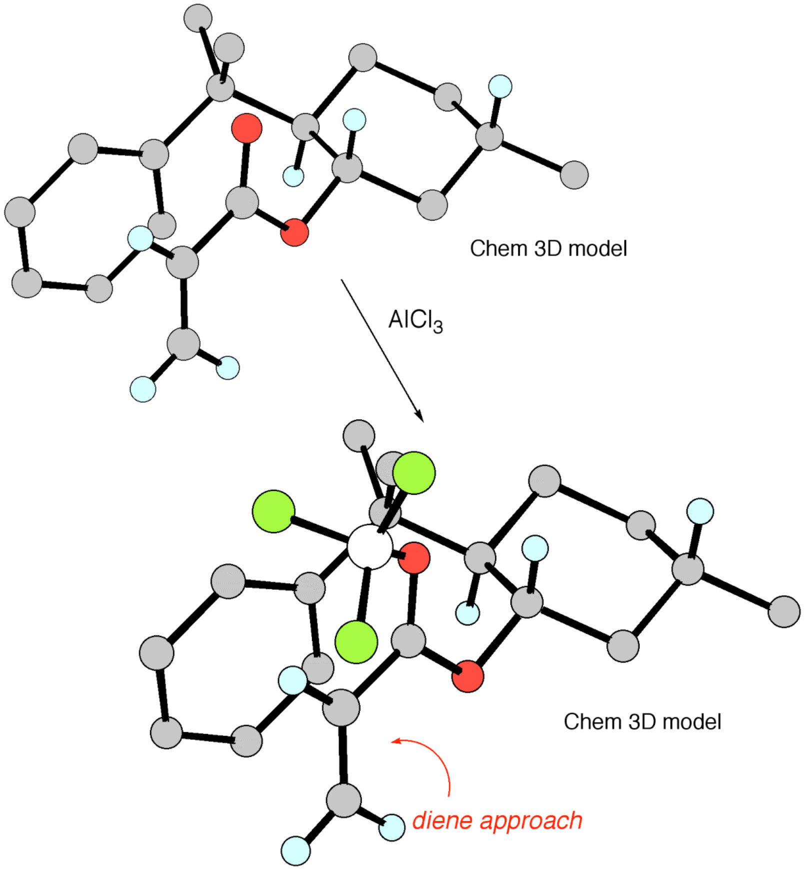
Review:
Oppolzer in *Comprehensive Organic Synthesis* 1992, *Vol. 4*, 315-399.

■ Ester-Type Chiral Auxiliaries

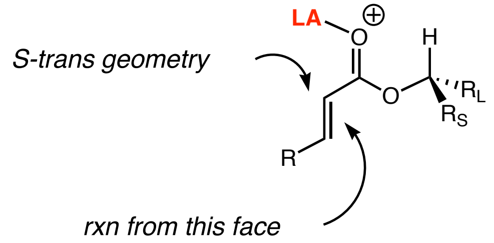
Corey *JACS* **1975**, *97*, 6908.



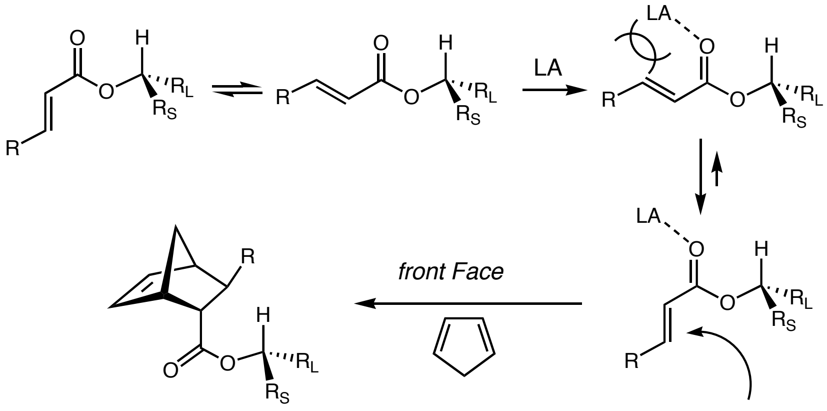
Diastereomer Ratio Not Given



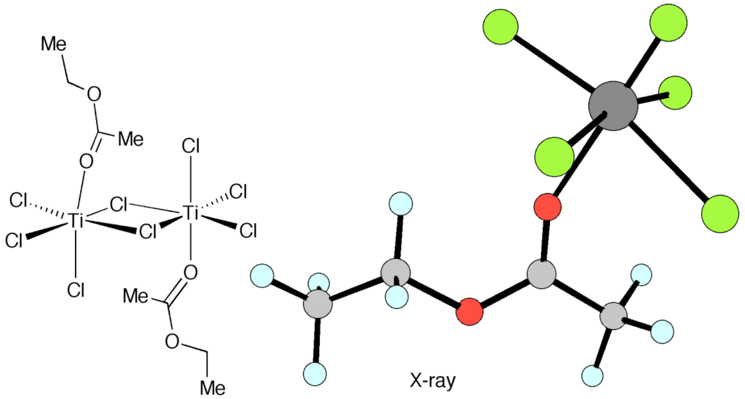
Non-Chelate Ester-Type Chiral Auxiliaries



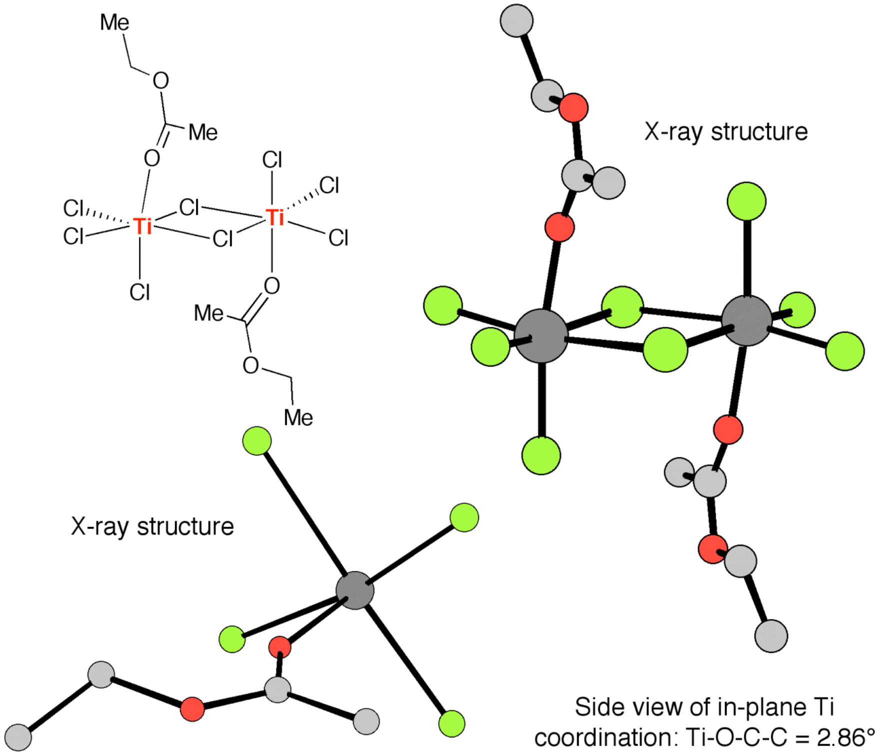
Lewis Acid-Ester Complex Conformation Dictates Diastereoselection



See Oppolzer *ACIEE* **1984**, *23*, 876.



Representative η_1–titanium complexes with organic compounds

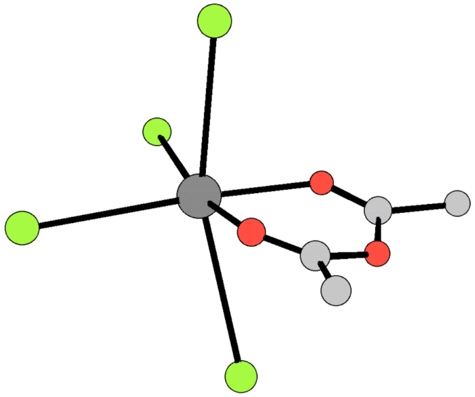


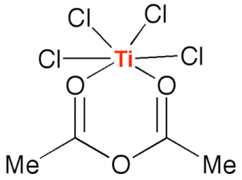
X-ray structure

X-ray structure

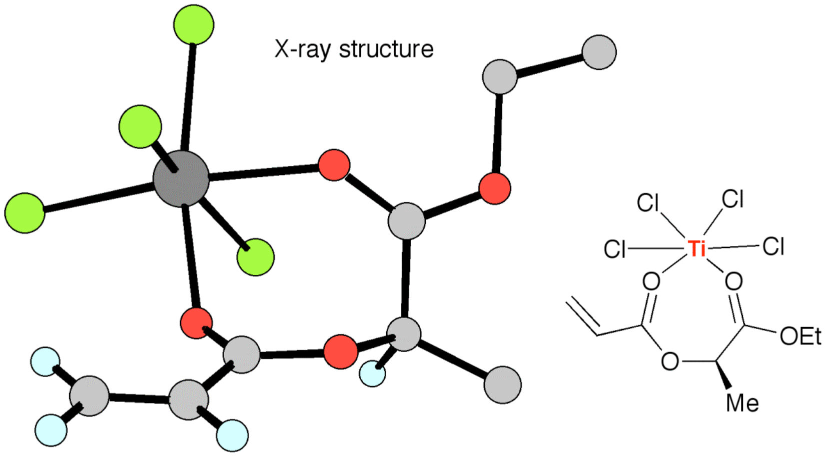
Side view of in-plane Ti coordination: Ti-O-C-C = 2.86°

Ti–O–C angle = 152 °

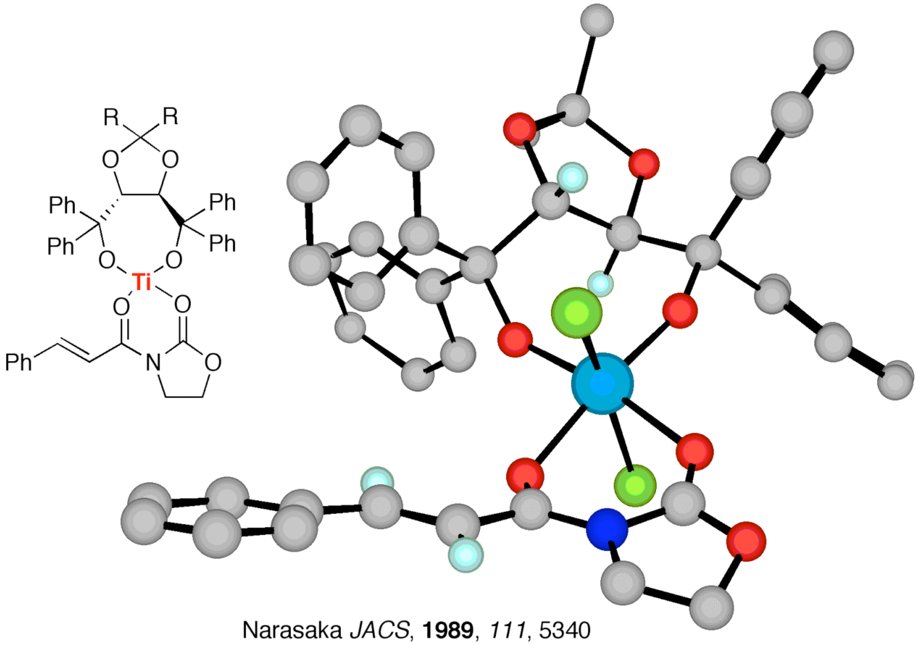




Representative η_1–titanium complexes with organic compounds



X-ray structure



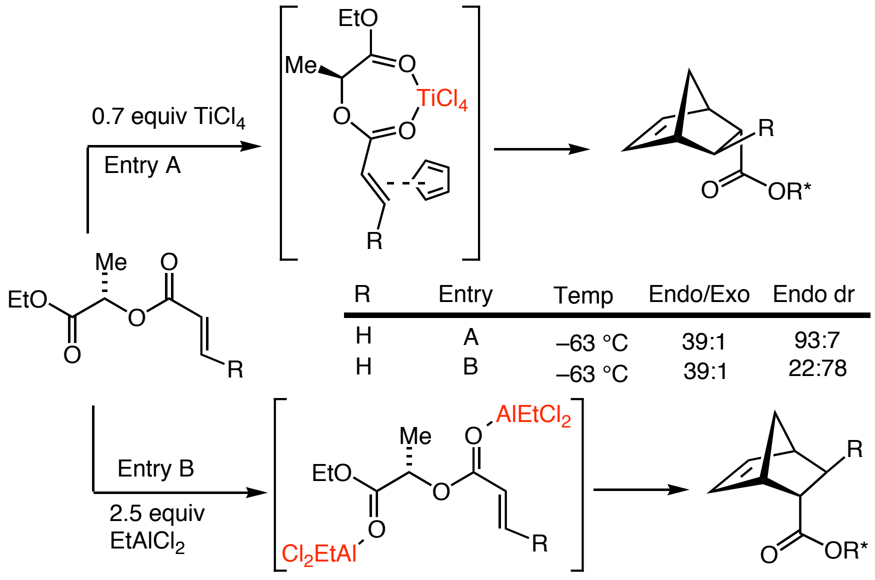
Narasaka *JACS*, **1989**, *111*, 5340

A. Jorgensen, *JACS*, **1995**, *117*, 4435

X-ray structure

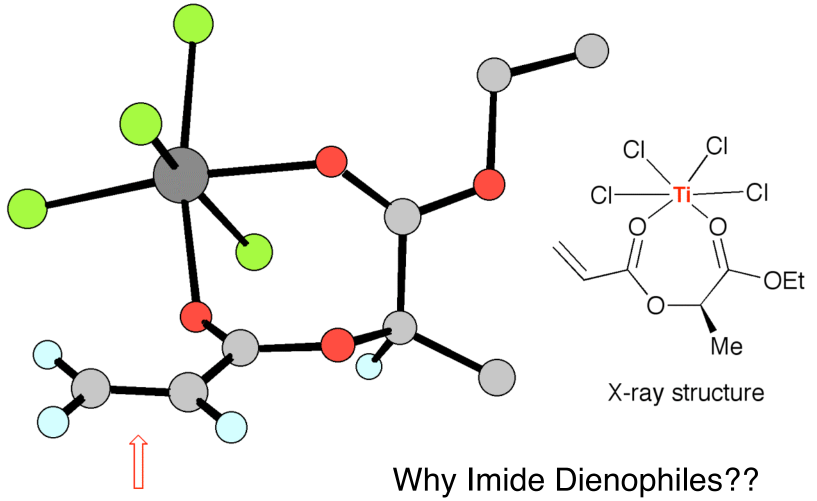
Chiral Auxiliary Controlled Diels-Alder Reactions-2

Ester-Type Chiral Auxiliaries: Chelating Dienophiles



R	Entry	Temp	Endo/Exo	Endo dr
H	A	–63 °C	39:1	93:7
H	B	–63 °C	39:1	22:78

Helmchen *Tetrahedron Lett.* **1984**, *25*, 2191.
ACIEE **1985**, *24*, 112. *Tetrahedron Lett.* **1985**, *26*, 3095.

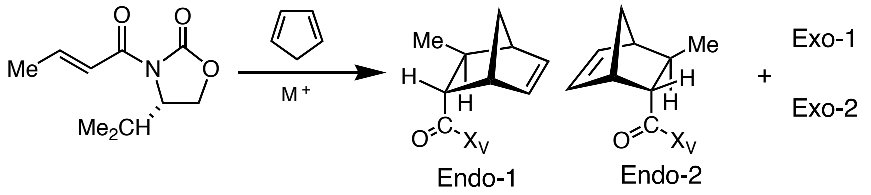


X-ray structure

Why Imide Dienophiles??
They are ~ 100-1000X more reactive

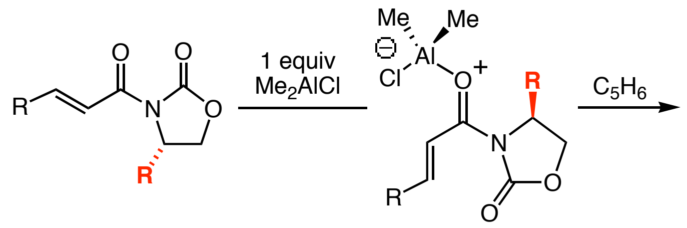
Chelating Imide-type Chiral Auxiliaries
Metal ion Dependent Diastereoselection

Evans *JACS*, **1984**, *106*, 4261.
Evans *JACS*, **1988**, *110*, 1238.



Lewis Acid (1.2 equiv)	Temp.	Endo-1 / Endo-2	Σ Endo / Exo
SnCl$_4$	25	2.7	92 : 8
SnCl$_4$	–78	3.1	93 : 7
TiCl$_4$	–78	2.6	91 : 9
AlCl$_3$	–78	1.5	80 : 20
(2.0 equiv) **Et$_2$AlCl**	–78	**15.7**	**>99 : 1**
(0.7 equiv) **Et$_2$AlCl**	–78	**4.4**	**92 : 8**

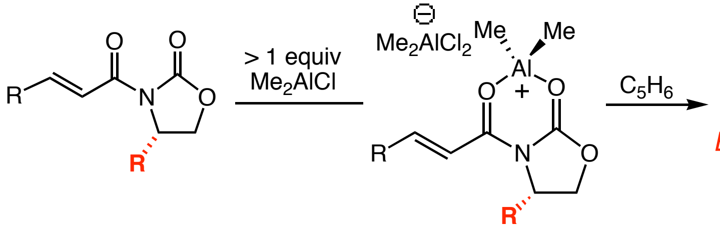
Binding Mode Dictates Diastereoselectivity



1 Point Binding

⇩

Endo/Exo = 4 :1
Rel. Rate = 1



2 Point Binding

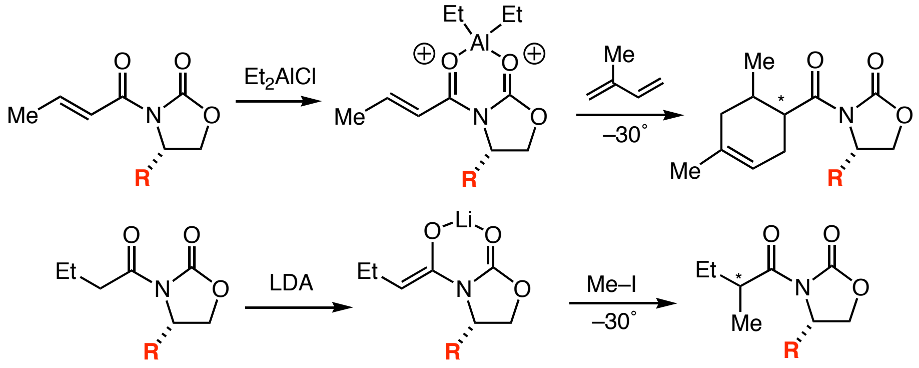
⇩

Endo/Exo = >20:1
Rel. Rate = 100

Chiral Auxiliary Controlled Diels-Alder Reactions-3

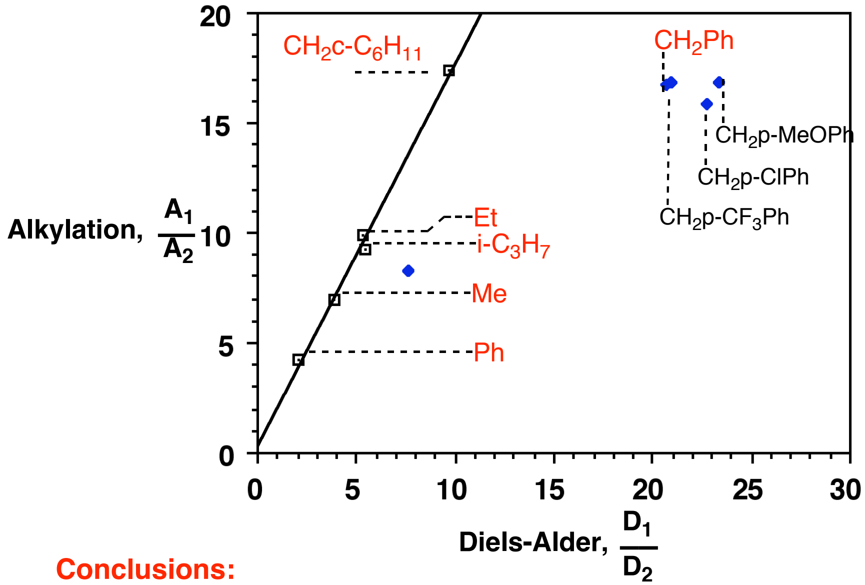
A Case for Π-Stacking: *Angew Chem, Int Ed.* **1987**, *26*, 1184

Compare the alkylation rxn which is dominated by steric effects with the DA rxn which may be controlled by both steric and electronic effects



$$\Delta\Delta G^{\ddagger} = 2.3\ RT\ \text{Log}\ P_1/P_2$$

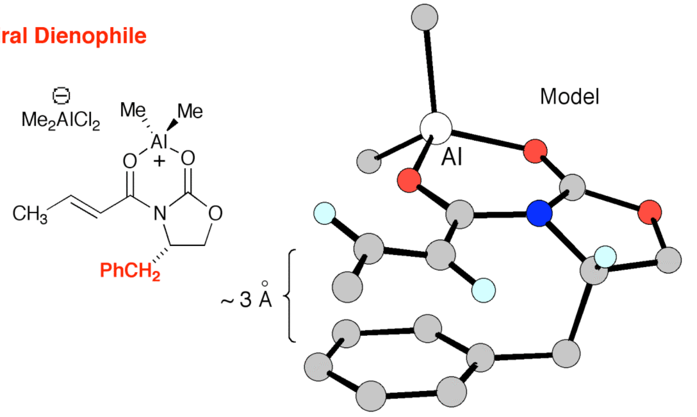
PLOT ΔΔG‡ FOR EACH RXN AS A FUNCTION OF THE SUBST., R.



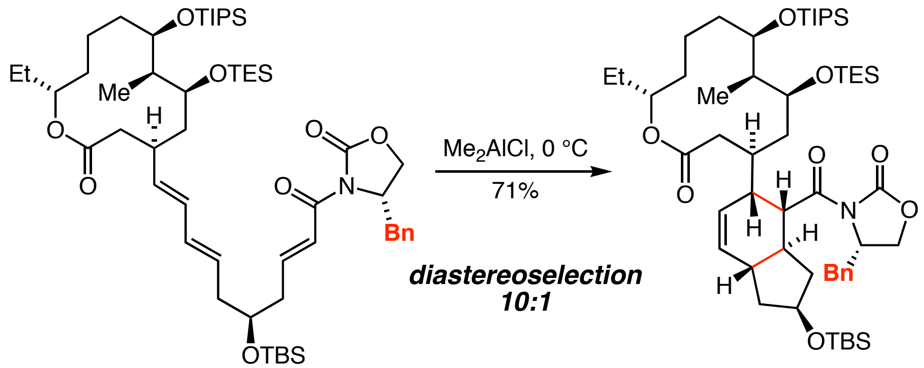
Conclusions:

Steric effects correlate well for the two reactions
Added electronic effects from Bn group enhance facial bias

The Chiral Dienophile

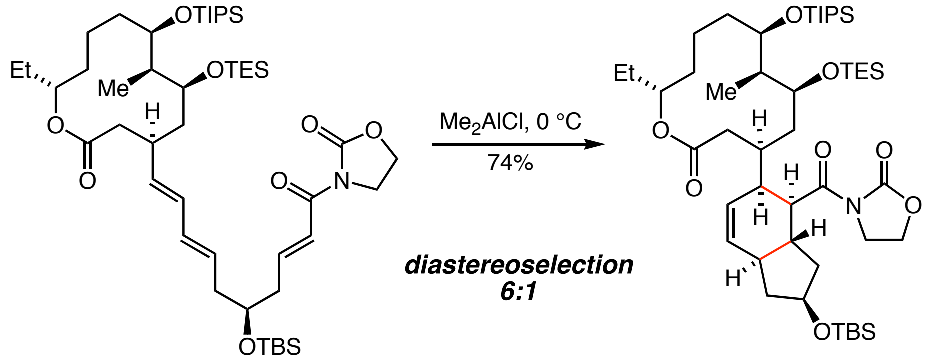


A Complex Application



diastereoselection 10:1

The control experiment with no chiral auxiliary:

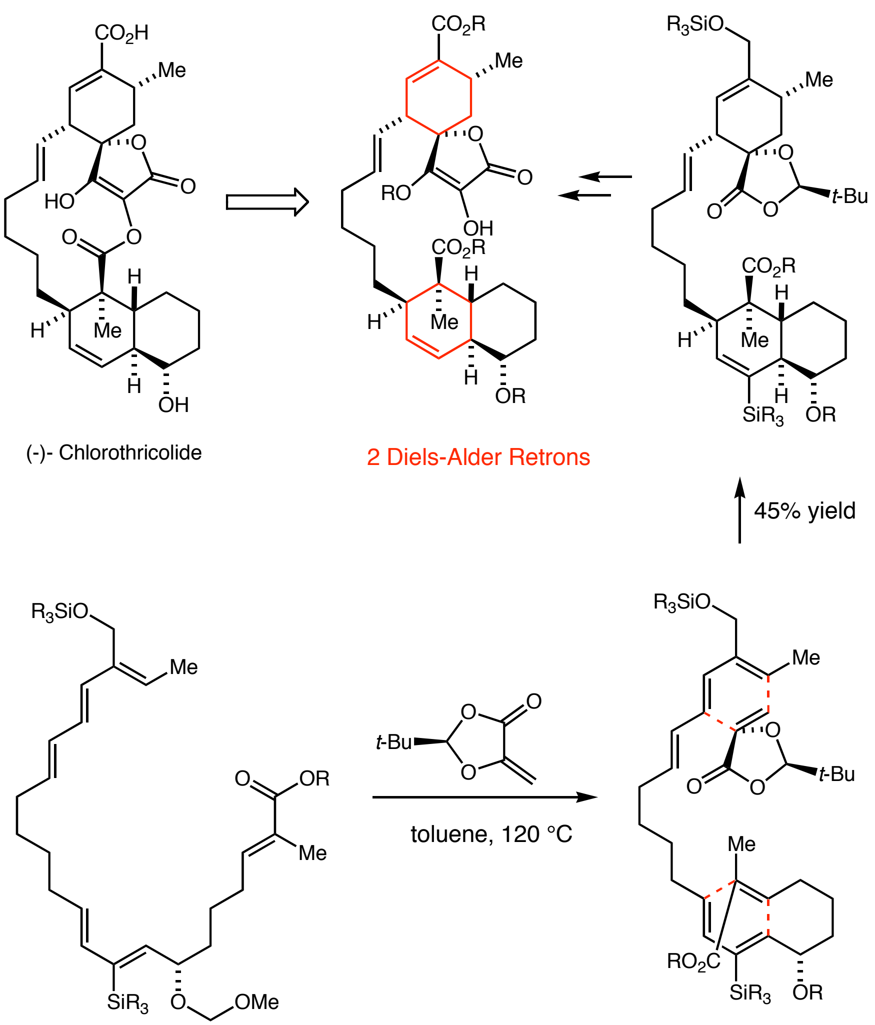


diastereoselection 6:1

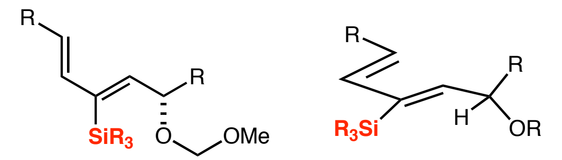
Evans, BlackLepicidin Synthesis, *JACS*, **1993**, *115*, 4497

A Complex DA Application: The Synthesis of Chlorothricolide

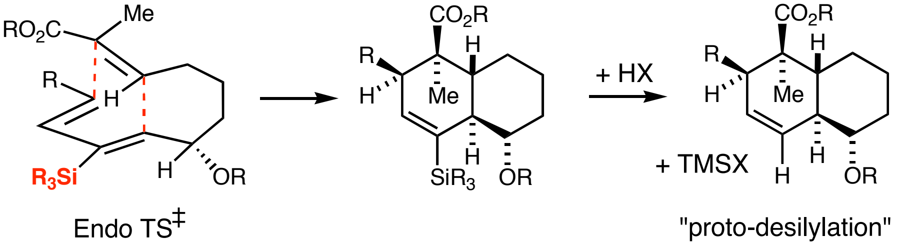
Roush, Sciotti *J. Am. Chem. Soc.* **1998**, *120*, 7411-7419.



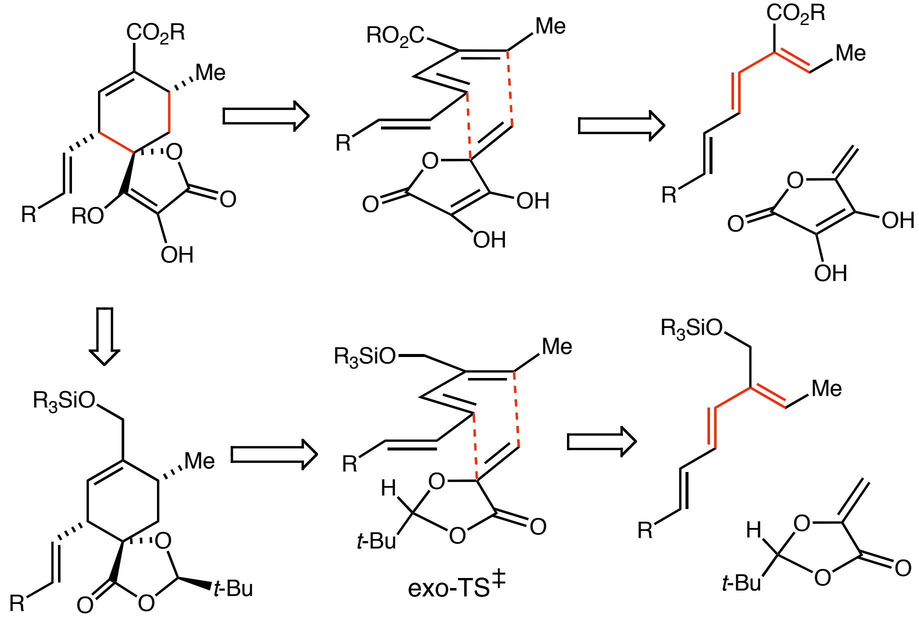
The Intramolecular Diels-Alder Reaction



SiR$_3$ substituent installed to exploit A(1,3) bias orienting the dienophile on the proper face of the diene/

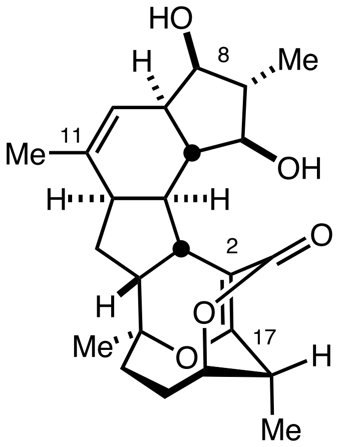


The Bimolecular Diels-Alder Reaction



Roush had earlier shown that this dienophile is quite exo-selective

Structures of FR182877 & Hexacyclinic acid



(—)-FR182877

isolated from *Streptomyces sp.#9885*

cytotoxic (IC_{50} <73 ng/ml): MCF-7, A549, HT-29, Jurkat, P388, B16.
Sato, B. *J. Antibiot.* **2000**, 123, 204, 615.
Corrected Structure: *J. Antibiot.* **2002**, C-1.

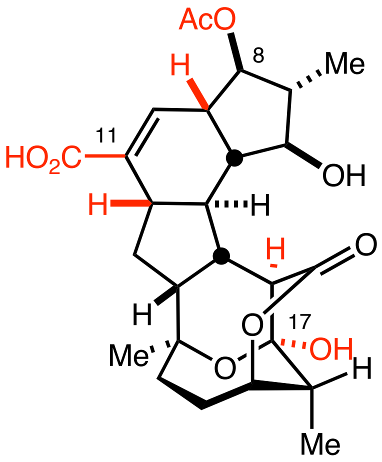
Structural Differences:

Acylation at C_8 hydroxyl

Oxidation at C_{11}

endo vs. *exo* Diels-Alder retron

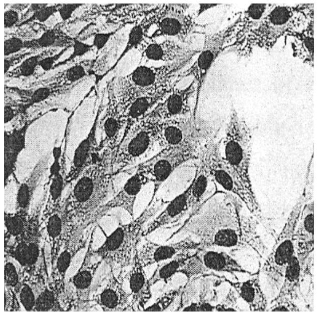
Hydration across
C_2-C_{17} double bond



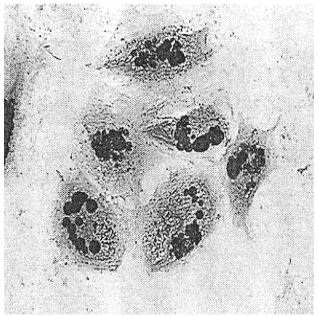
Hexacyclinic Acid

isolated from *Streptomyces cellulosae* (strain S1013)

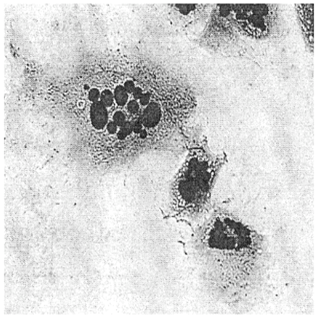
14 μmol/L cytotoxicity (HMO2, HEPG2, and MCF7)
Hofs, R., et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 3258.



BHK cells: Control

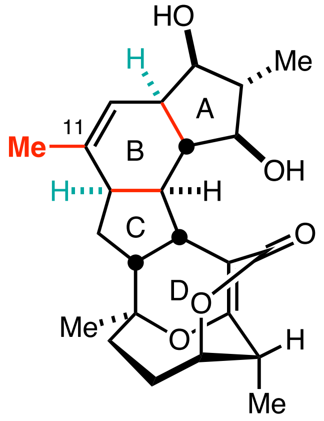


FR182877

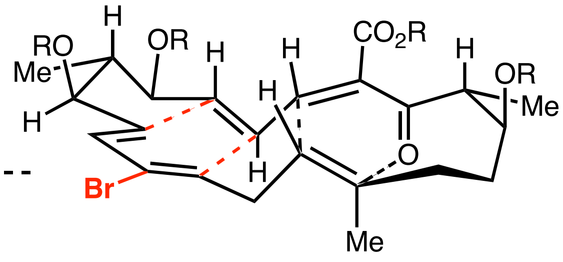


Taxol

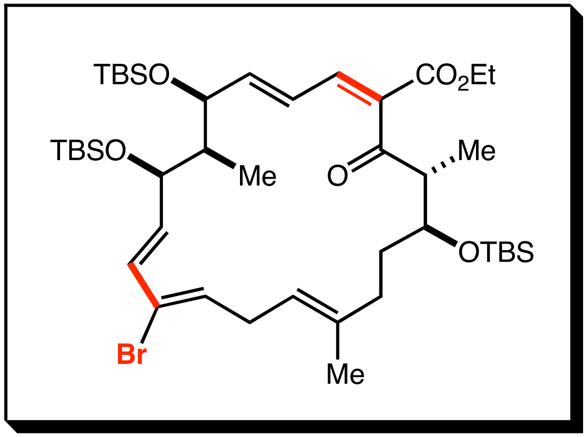
Hypothesis: A Transannular Diels-Alder Cycloaddition Cascade

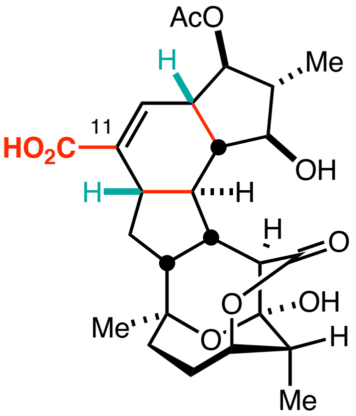


FR182877

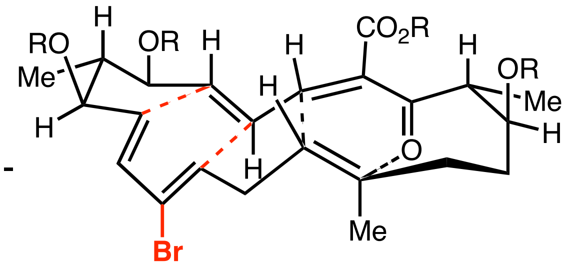


endo-TS‡

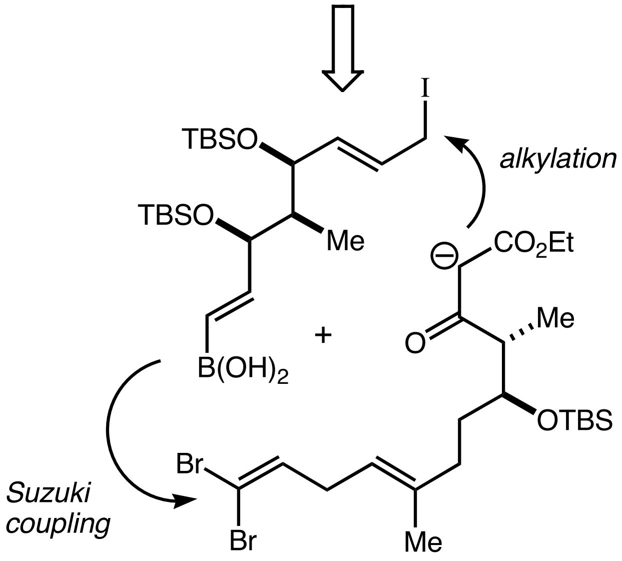




Hexacyclinic acid



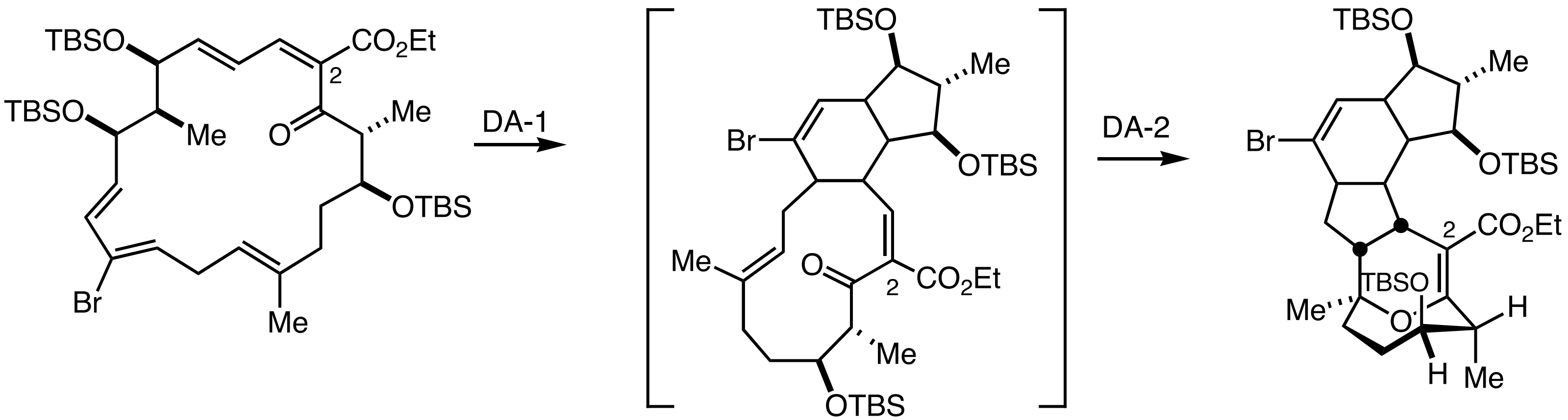
exo-TS‡

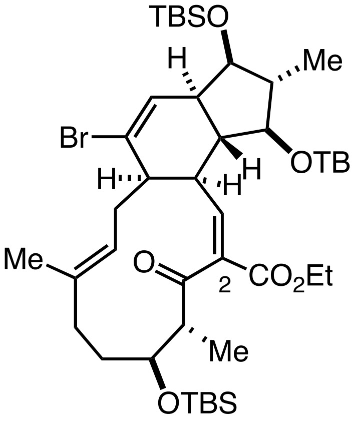


Evans & Starr, JACS **2003,** *125, 13531*

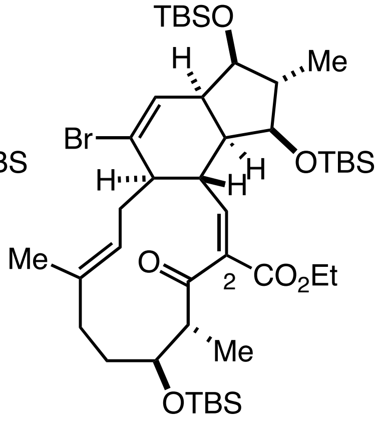
Sorensen, JACS **2003,** *125, 5393*

Diels-Alder Cycloaddition Cascade Stereochemical Options

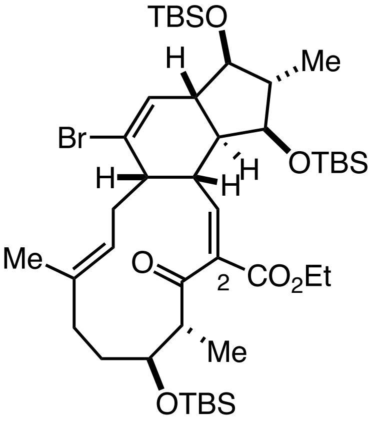




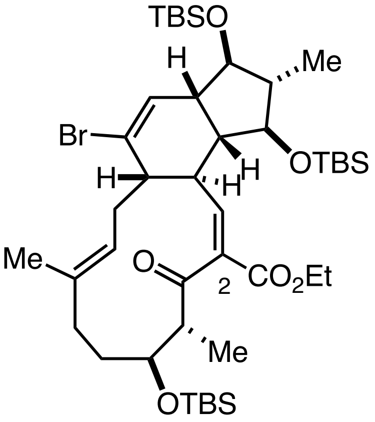
Endo-1



Exo-1



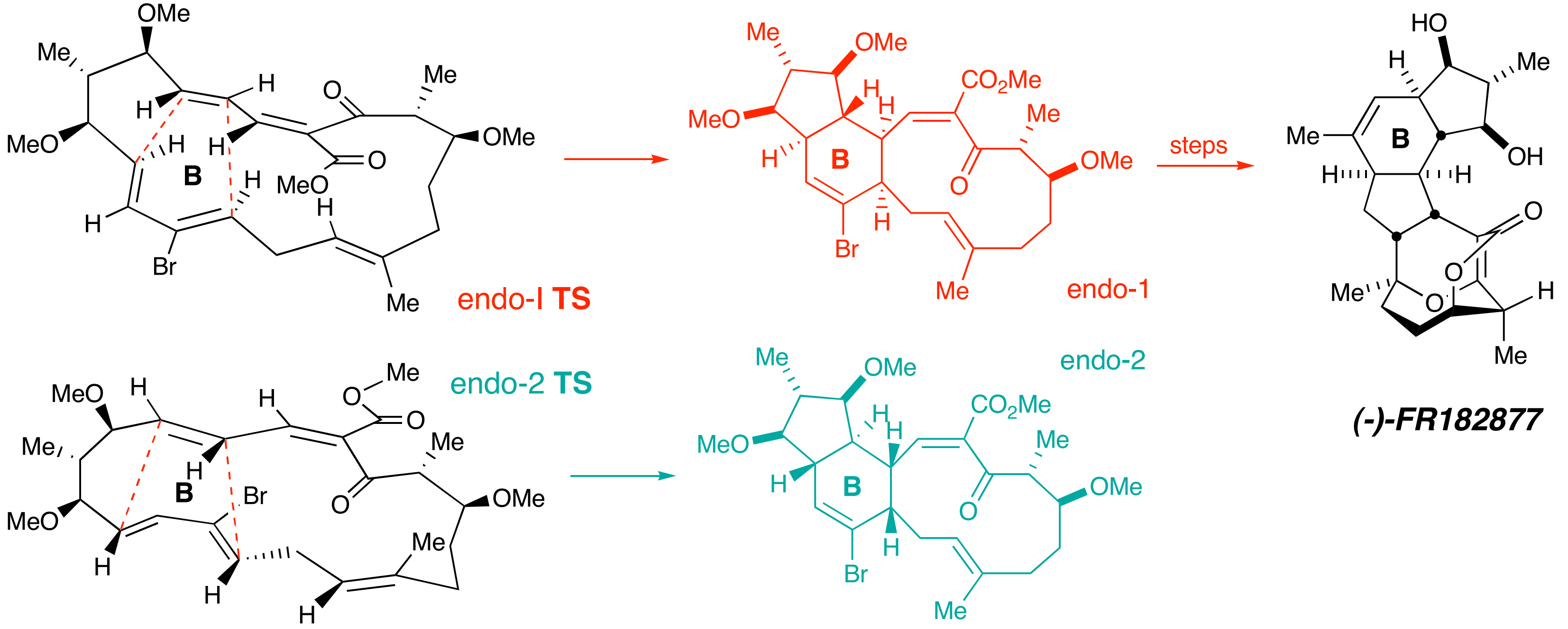
Endo-2



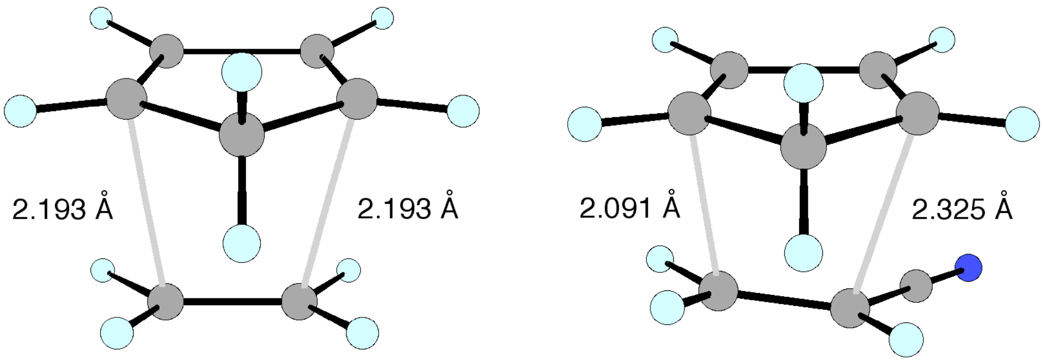
Exo-2

The first cycloaddition must be diastereoselective!!

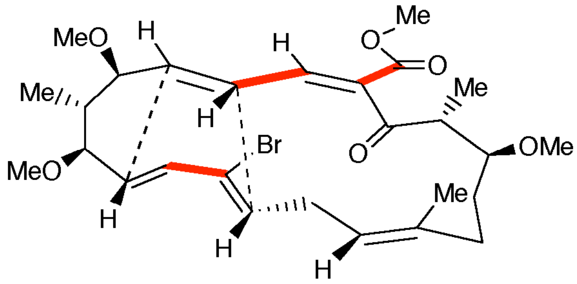
Analysis of Face Selectivities of the Cycloaddition Steps



Analysis Procedure: Carry out semi-empirical calculations on transition structures where the forming bonds are varied from 2.9 → 2.1Å. For this analysis, a symmetrical transition state is presumed.

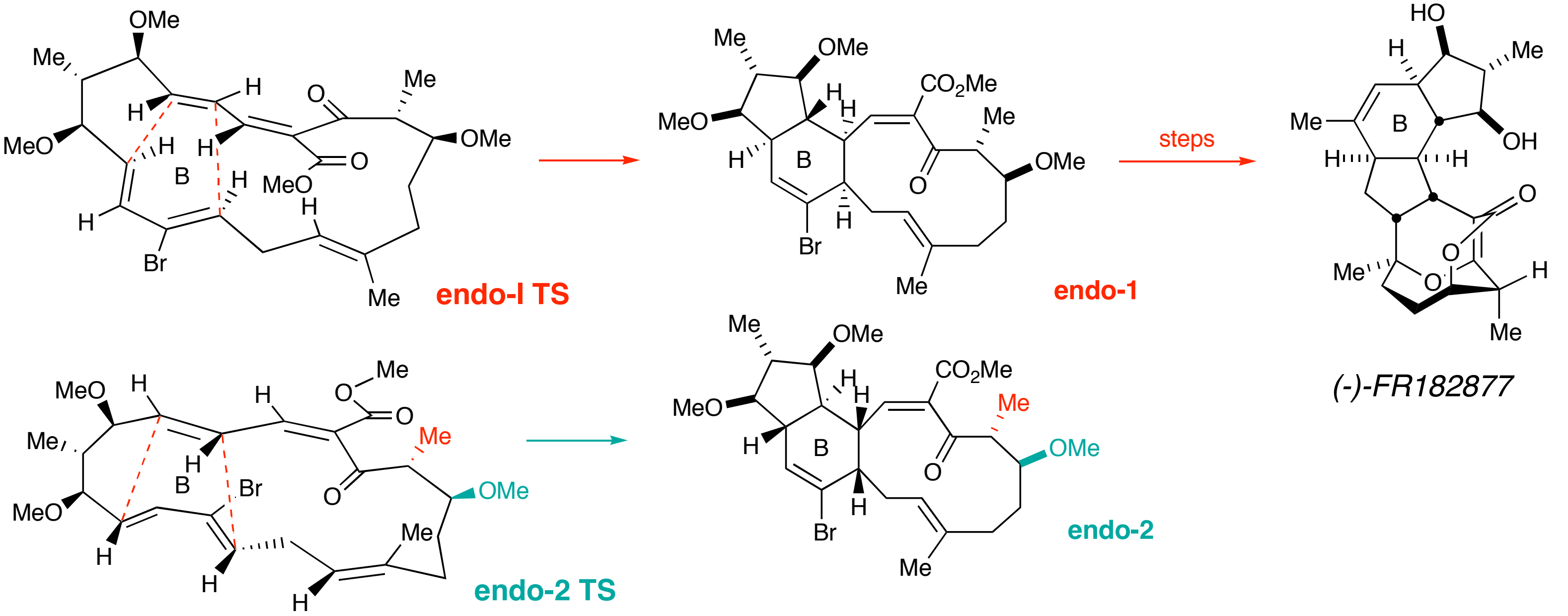


Houk *Angew. chem. Int. Ed.* **1992**, *31*, 682-708

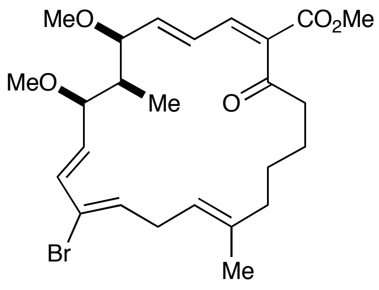


dihedral angle restrictions employed in calculations

Analysis of Face Selectivities of the Cycloaddition Steps

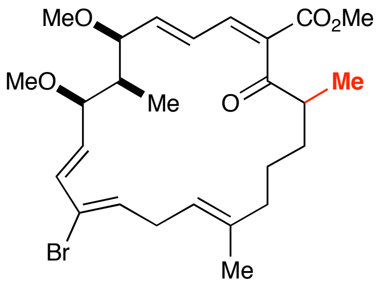


Semi-empirical calculations (PM3) carried out on all of the indicated macrocycles

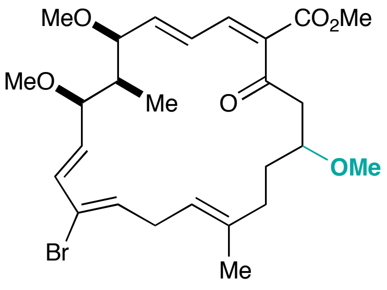


control

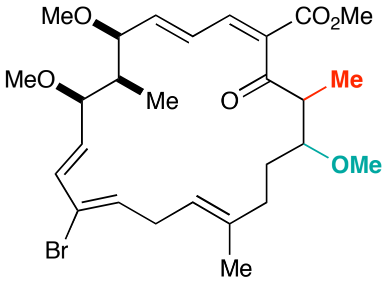
endo-I TS ~ **endo-2 TS**



(19R), (19S)



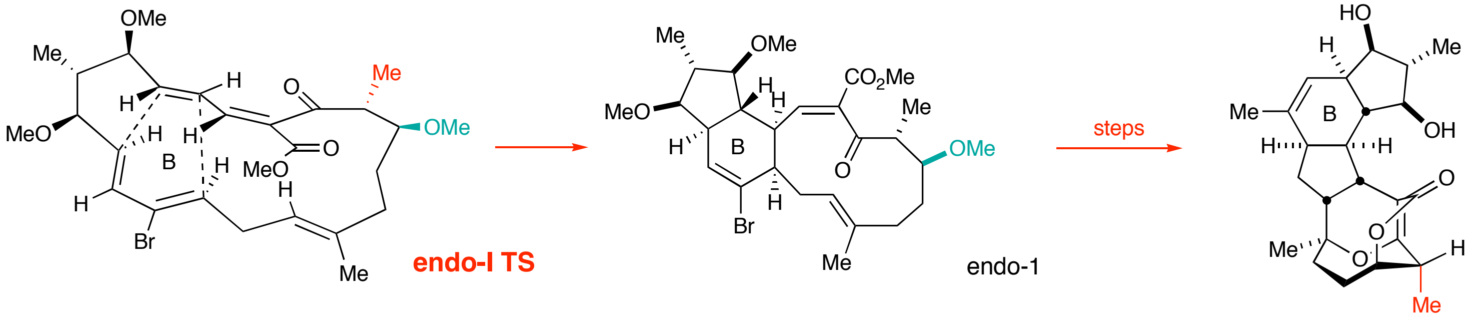
(18R), (18S)



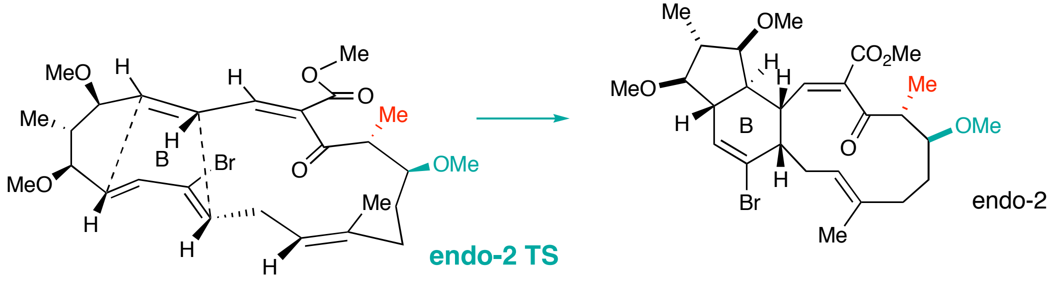
all 4 diastereoisomers

Evans & Starr, JACS **2003,** *125, 13531*

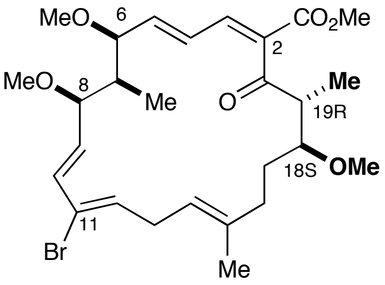
DA face selectivity controlled by by C_{18}–C_{19} stereocenters



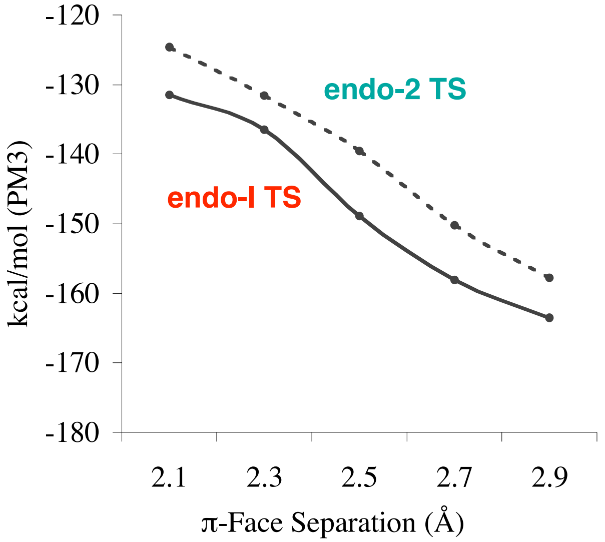
(-)-FR182877

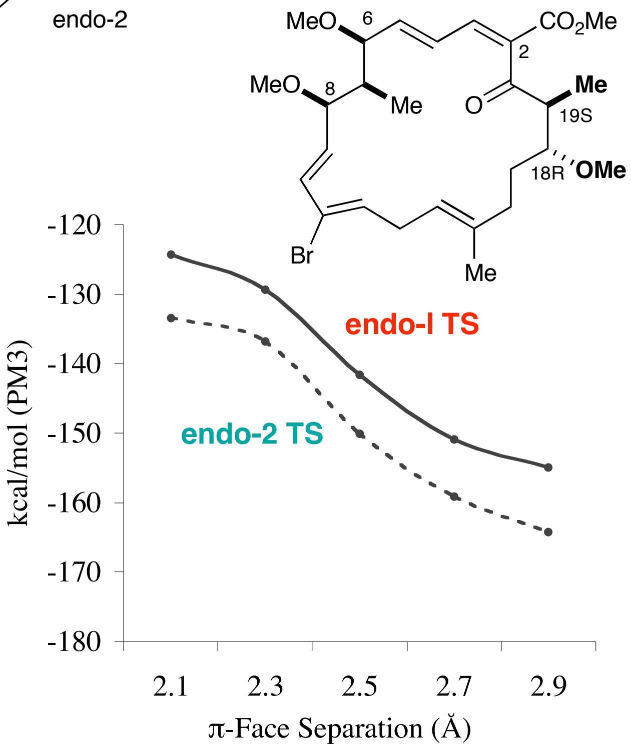


$\Delta\Delta E^{\ddagger}$ = 5–9 kcal/mol @ 2.1 Å

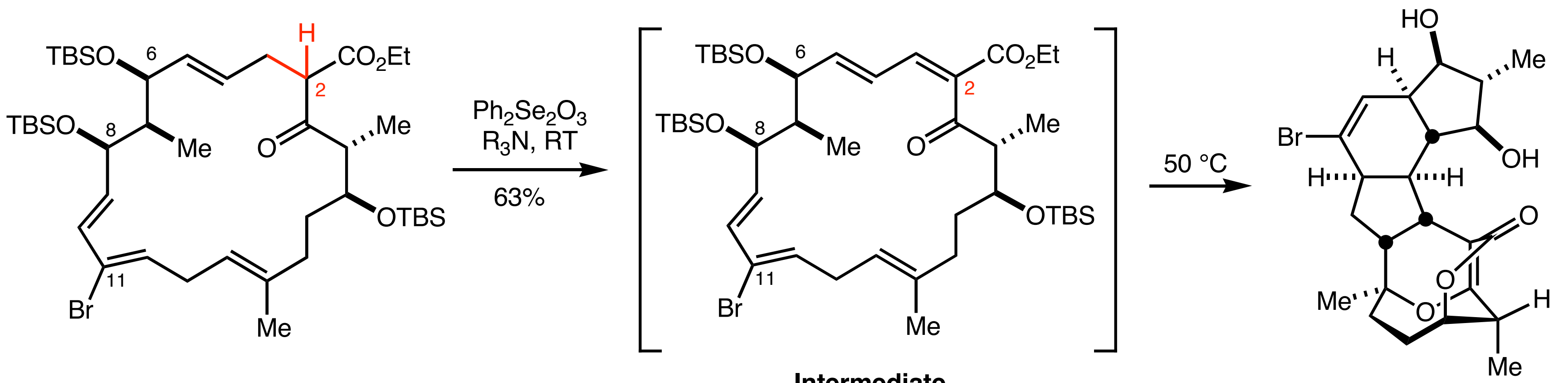


(natural configuration)



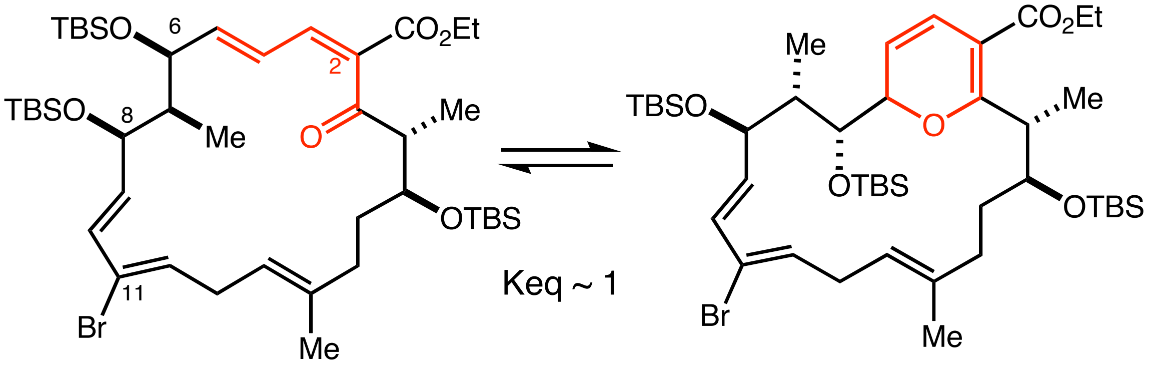


The Transannular Diels-Alder Step



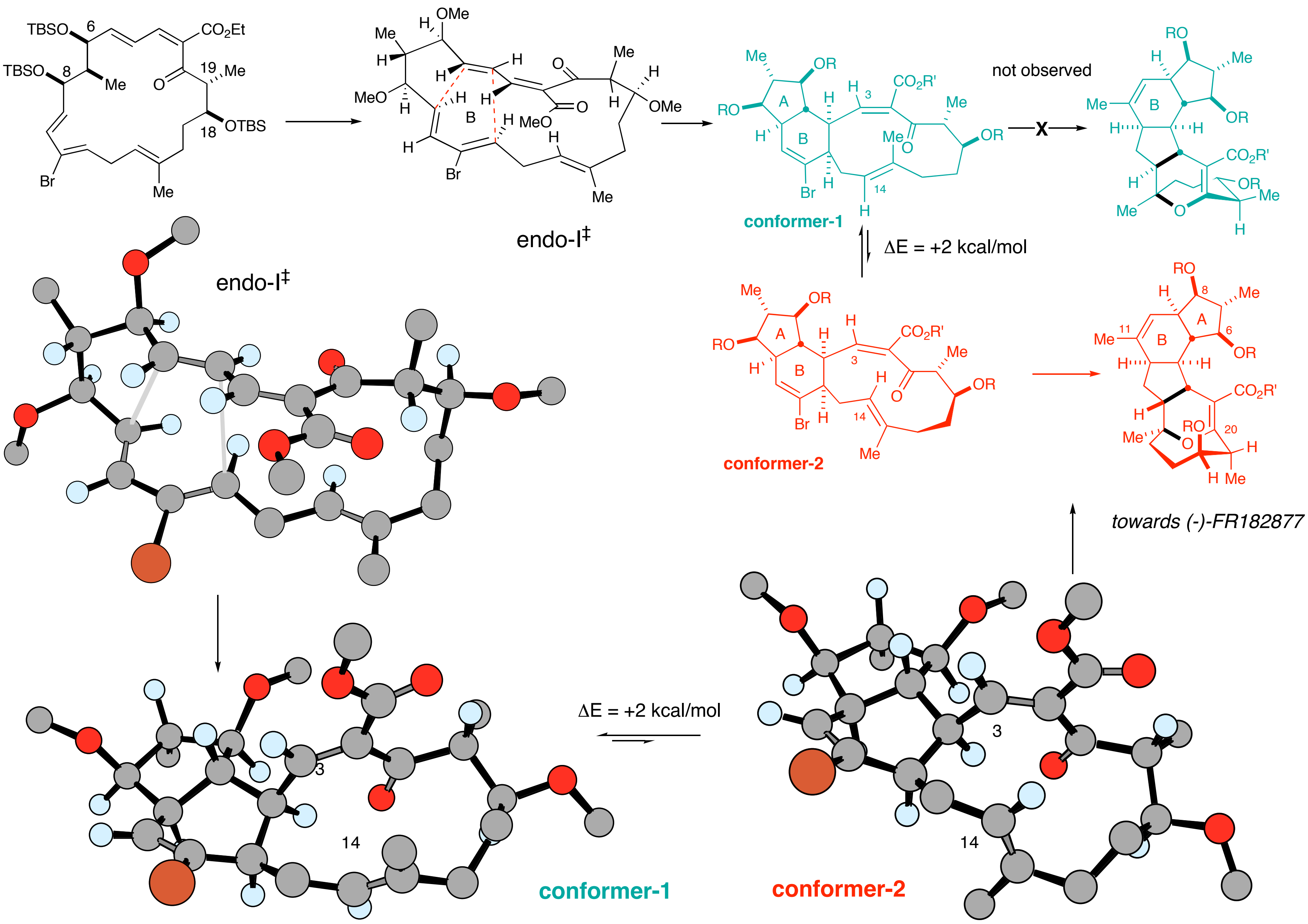
Intermediate

Selenium byproducts removed by hexane precipitation.
Intermediate heated at 50 °C

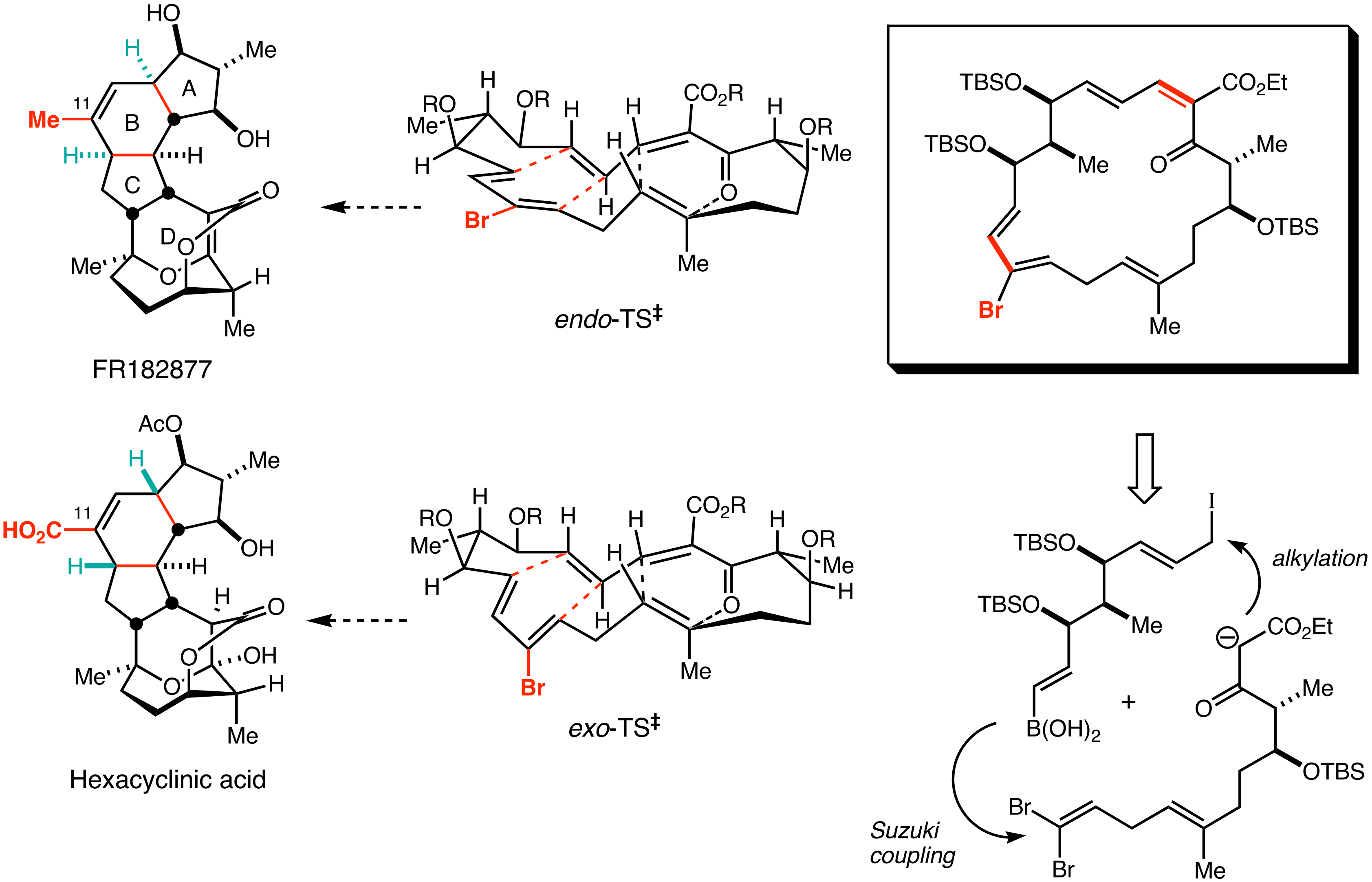


Both intermediates are observed

Summary of Cycloaddition Cascade



Hypothesis: A Transannular Diels-Alder Cycloaddition Cascade


FR182877

endo-TS‡

Hexacyclinic acid

exo-TS‡

Evans & Starr, JACS **2003,** *125, 13531*

Sorensen, JACS **2003,** *125, 5393*

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 18

Cycloaddition Reactions-3

- **The Diels-Alder Reaction**
  Enantioselective Processes

- Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

"*Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions*". Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335. **(handout)**

The formyl C–H…O hydrogen bond as a critical factor in enantioselective Lewis-acid catalyzed reactions of aldehydes, Corey, Lee, *Chem Commun.* **2001,** 1321 **(handout)**

New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction, MacMillan, D. *JACS* **2000**, *122*, 4243 **(handout)**

D. A. Evans

Monday
October 30, 2006

The Diels-Alder Cycloaddition Reactions

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(pdf)**

The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, *41*, 1668-1698 **(pdf)**

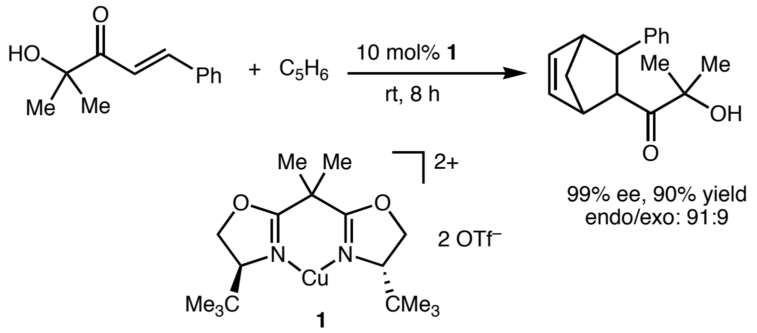
Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, *41*, 1650-1667 **(pdf)**

Chemistry and Biology of Biosynthetic Diels–Alder Reactions
Emily M. Stocking and Robert M. Williams, *Angew Chem. Int. Ed.* **2003**, *42*, 3078-3115 **(pdf)**

Chiral Lewis Acids in Catalytic Asymmetric Reactions, Narasaka, *Synthesis*, **1991**, 1-11 **(pdf)**

Carbonyl-Lewis Acid Complexes Schreiber, *Angew. Chem. Int. Ed.*, **1990**, *29*, 256-272 **(pdf)**

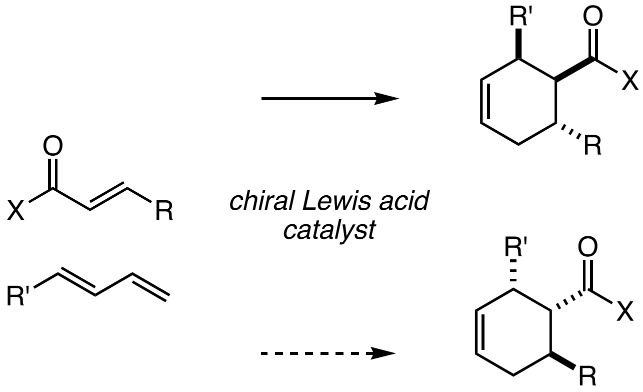
Problem 363. The C_2-symmetric cationic Cu(II) complex **1** is a chiral Lewis acid catalyst that exhibits good chelating potential. Palomo has reported the utilization of **1** in the catalyzed Diels-Alder reaction is illustrated below (*JACS*, **2003**, *125*, 3943). Provide the absolute stereochemistry of the product of this reaction. Provide a 3-dimensional drawing of the transition state for this reaction.



99% ee, 90% yield
endo/exo: 91:9

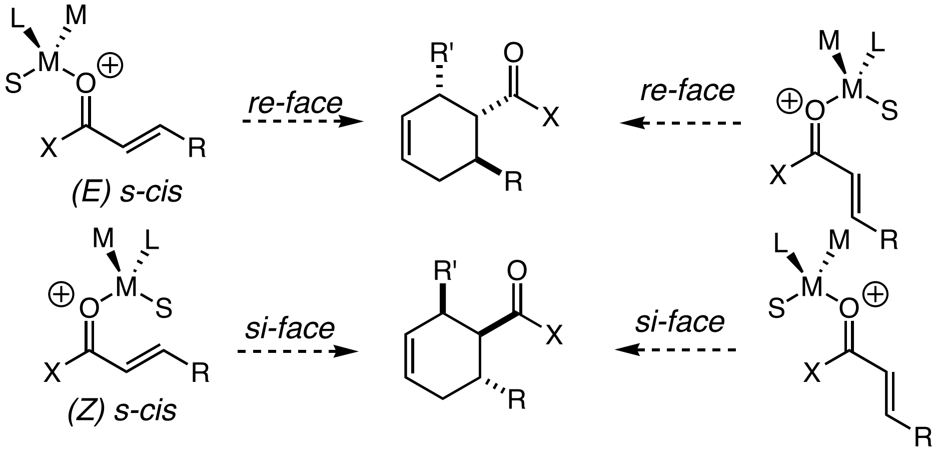
The Diels-Alder Reaction: Enantioselective Catalysis

The Design of Enantioselective Diels-Alder Catalysts



Problem A: Reacting conformation of the dienophile

The S-cis versus S-trans dienophile conformation is coupled to the geometry of the Lewis acid-dienophile complex & both issues determine face selection

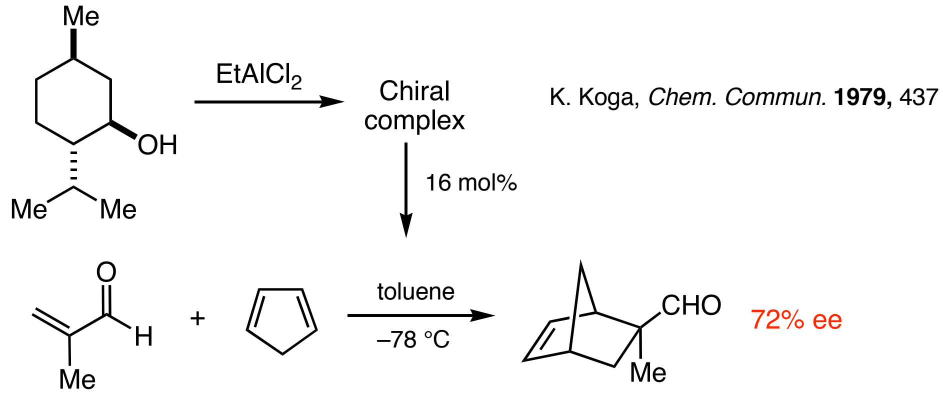


Theoretical Studies on Conformations of Acrolein & Methyl Acrylate & their Lewis Acid Complexes
Houk, *JACS*, **1987**, *109*, 14-23

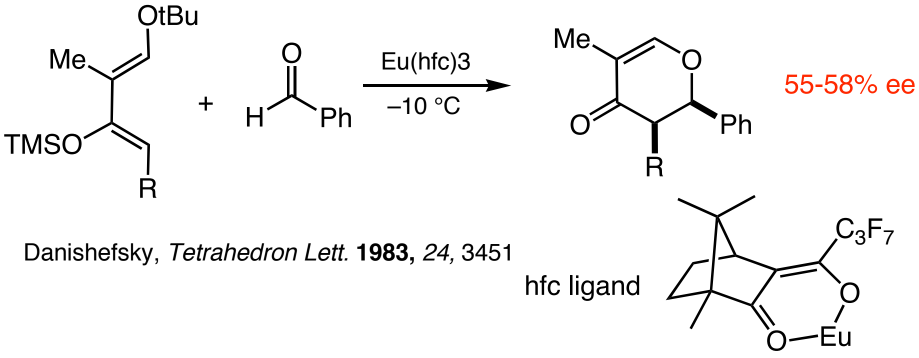
Problem B: Design of a well-defined Dienophile-LA Complex

Early Empirical Studies

Chiral Lewis Acids in Catalytic Asymmetric Reactions
Narasaka, *Synthesis*, **1991**, 1-11 **(pdf)**



K. Koga, *Chem. Commun.* **1979,** 437

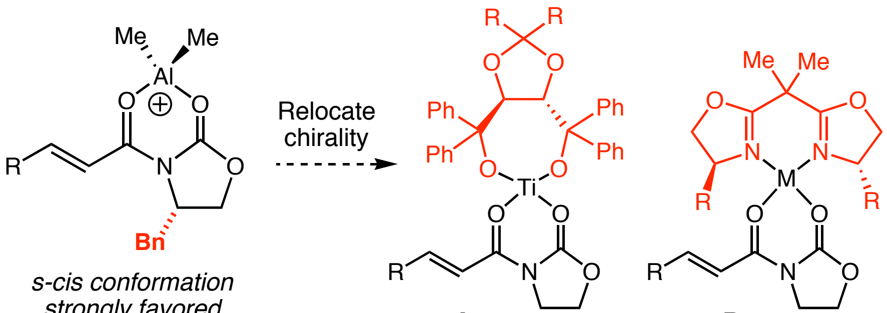


Danishefsky, *Tetrahedron Lett.* **1983,** *24,* 3451

The Diels-Alder Reaction: Enantioselective Catalysis

Transition from Chiral Auxiliary Control to Asymmetric Catalysis

with Chapman, Bisaha, *JACS*, **1984**, *106*, 4261, *JACS*, **1988**, *110*, 1238

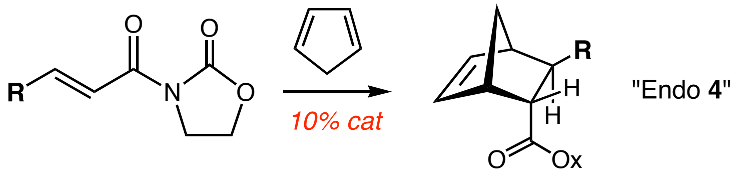


s-cis conformation strongly favored

Relocate chirality

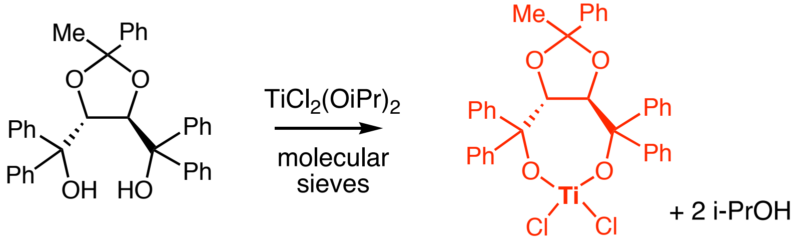
A **B**

Narasaka *JACS*, **1989**, *111*, 5340



10% cat

"Endo **4**"



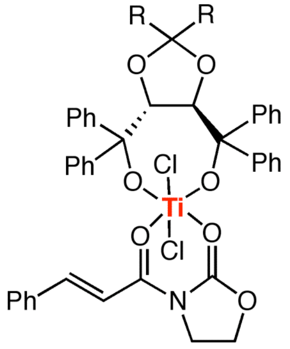
$TiCl_2(OiPr)_2$

molecular sieves

+ 2 i-PrOH

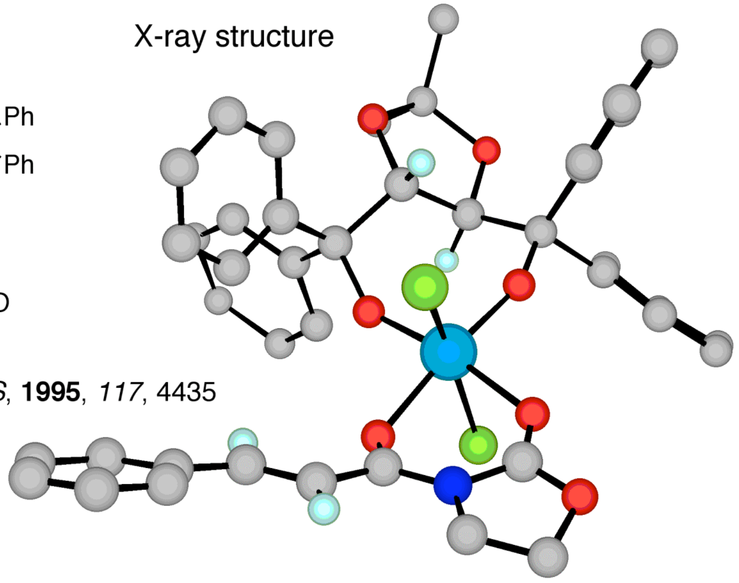
Table III. Asymmetric Diels–Alder Reaction Using a Catalytic Amount of Titanium Reagent

R	reaction temp/°C	endo/exo[a] **4**:**5**	% yield	optical purity of **4**/% ee[b]
Me	0	92:8	87	91
Ph	room temp	88:12	72	64
n-Pr	0	91:9	79	72
H	−40	96:4	93	64

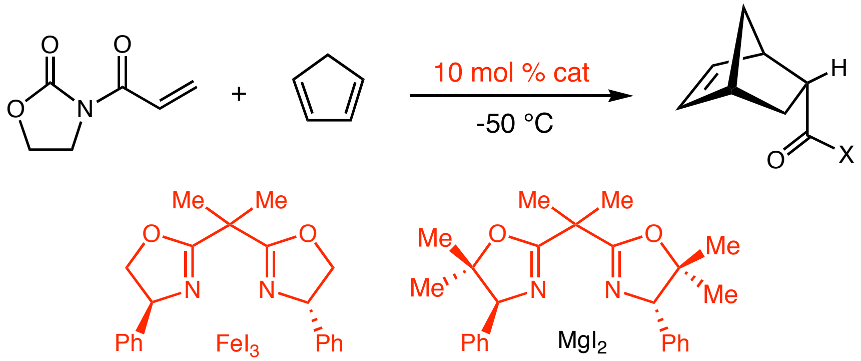


A. Jorgensen, *JACS*, **1995**, *117*, 4435

X-ray structure



The hunt for the "best" catalytic metal center has begun!



10 mol % cat

-50 °C

76% ee

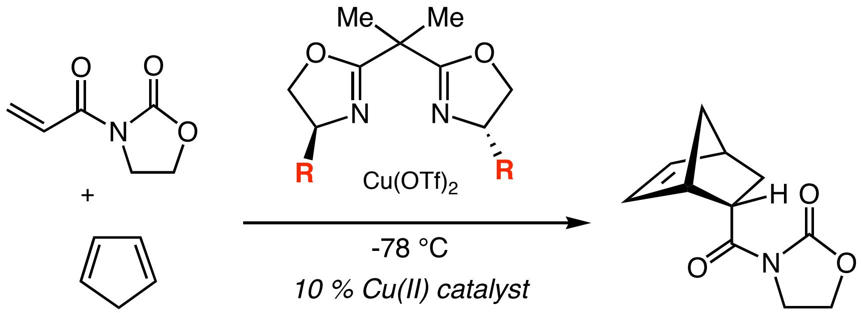
86% ee

Fe(3+) Corey *JACS*, **1991**, *113*, 728; Mg(2+) Corey *Tet. Lett.* **1992**, *45*, 6807

These catalysts are superior for unsubstituted dienophiles

The Diels-Alder Reaction: Enantioselective Catalysis

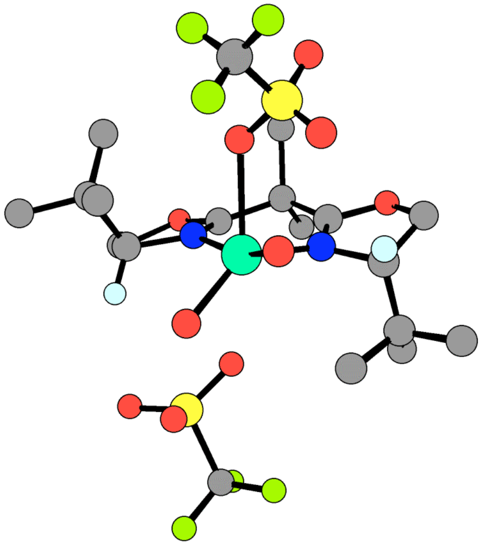
Cu(II) Lewis Acids: Evans, Miller, Lectka, *JACS* **1993**, *115*, 6460.

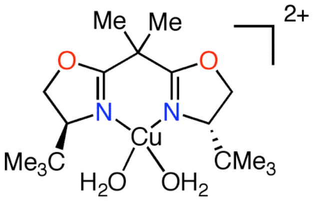


Catalyst (R)	Endo ee
R = Ph	30%
R = CHMe$_2$	58%
R = CMe$_3$	>98%

Temp	Endo ee
–50 °C	98%
0 °C	92%
25 °C	86%

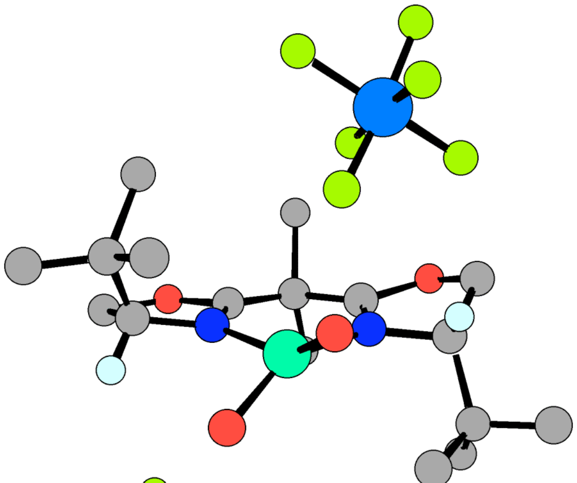
Bis(oxazoline)Cu(OTf)$_2$•2H$_2$O X-ray Structure

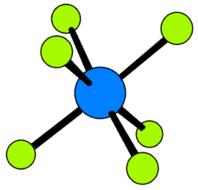


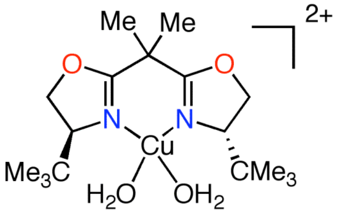


+ 2 $CF_3SO_3^-$

Bis(oxazoline)Cu(SbF$_6$)$_2$•2H$_2$O X-ray Structure

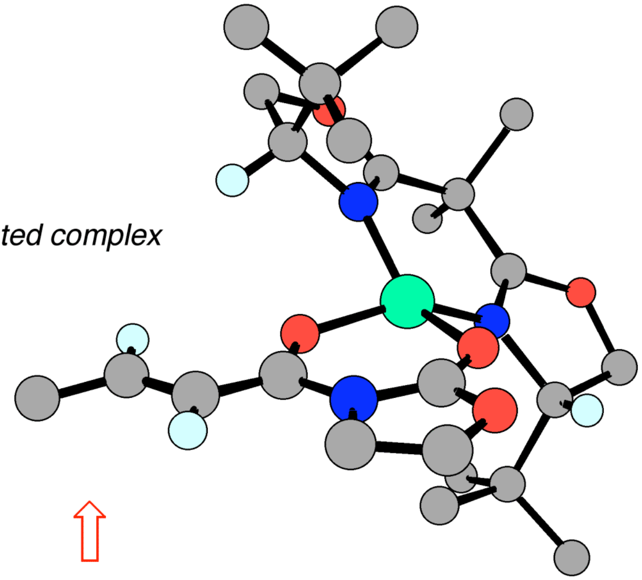






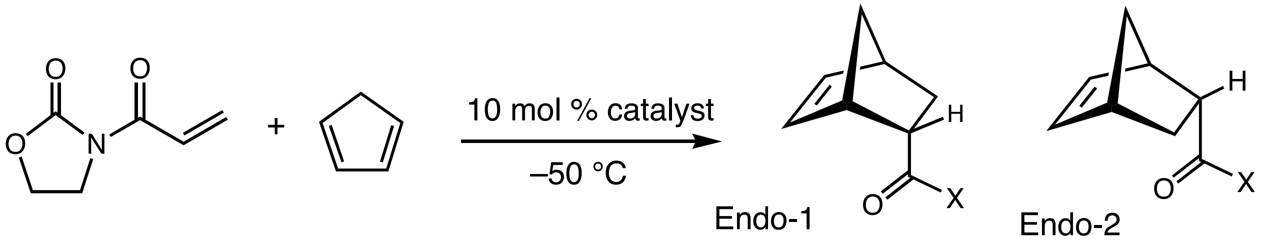
+ 2 SbF_6^-

Computer generated complex
PM3

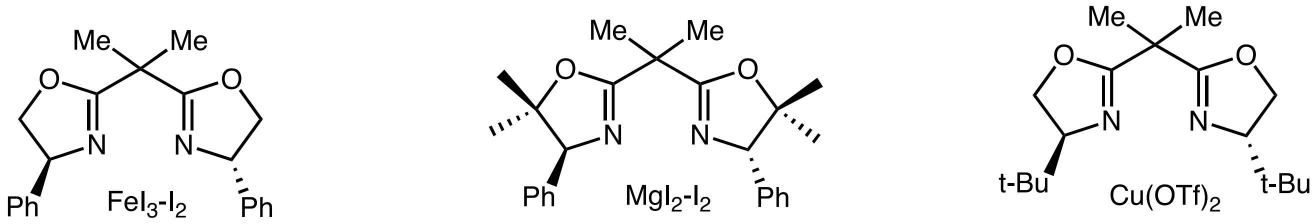


All reactions occur from this face

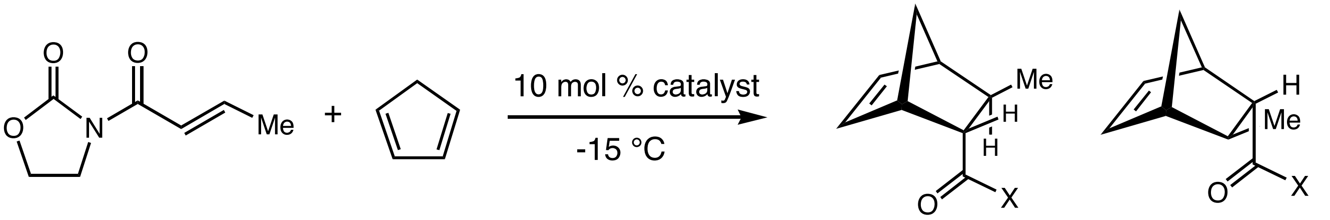
Metal-Box Complexes: A Comparison



Endo/Exo = 94:6	Endo/Exo = 95:5	Endo/Exo = 97:3
Endo ratio = 88:12 (Endo-2)	Endo ratio = 93:7 (Endo-2)	Endo ratio = 99:1 (Endo-1)



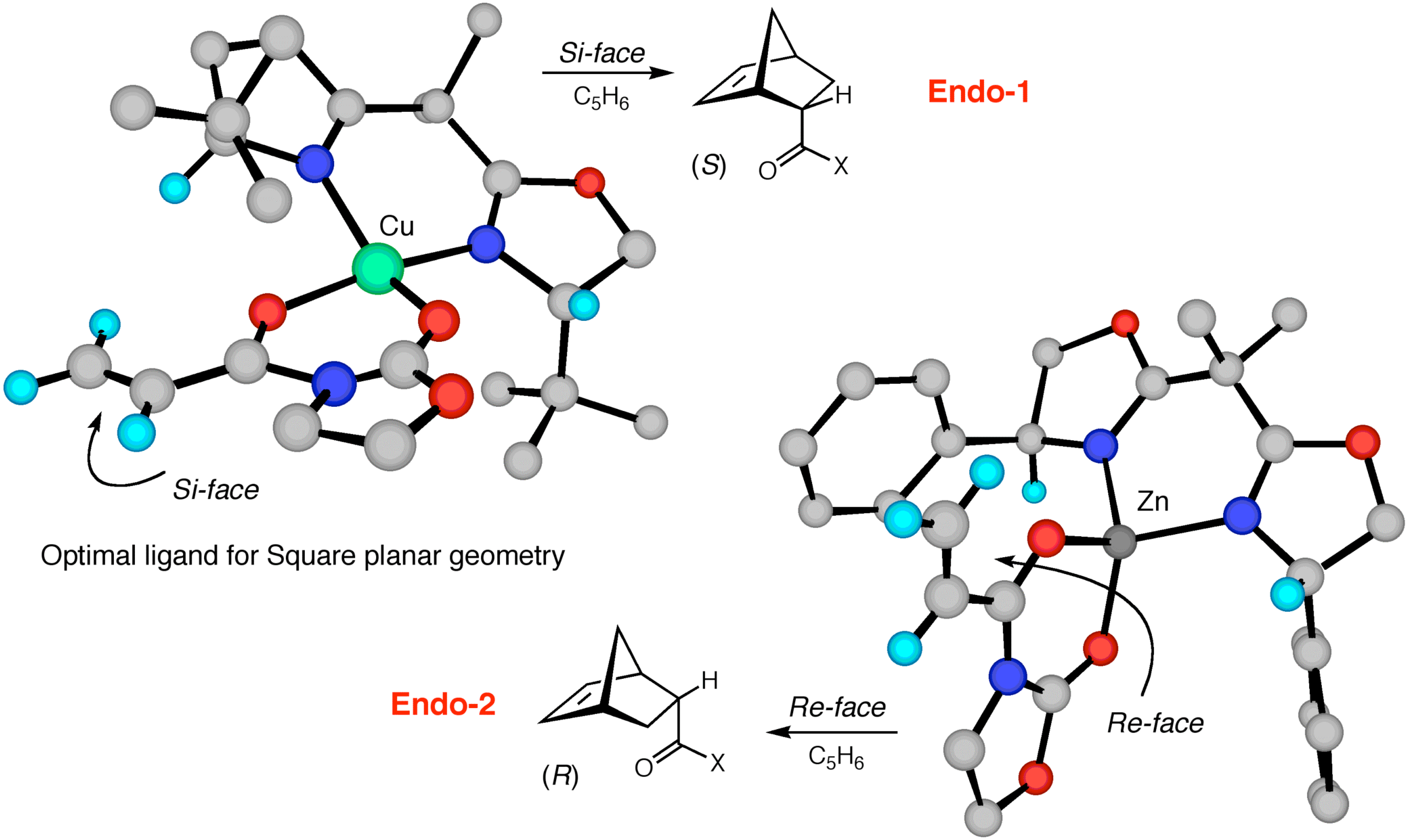
Endo/Exo = 76:24	Endo/Exo = 80:20	Endo/Exo = 96:4
Endo ratio = 66:34	Endo ratio = 50:50	Endo ratio = 98:2



with S. Miller, JACS **1999,** *121,* 7559-7573

Comparison between Square planar and tetrahedral Catalysts

Computer generated structures of the Cu(t-bu-box)(2+) & Zn(Ph-box)(2+)-dienophile complexes

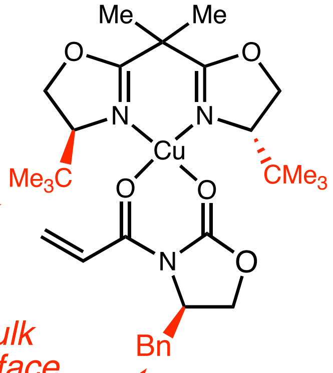


Optimal ligand for Square planar geometry

Optimal ligand for tetrahedral geometry

Torsional Rigidity of Catalyst-Substrate Complex

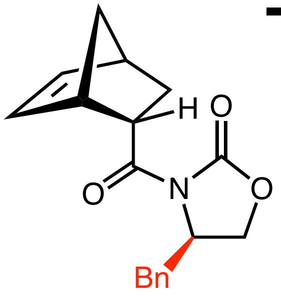
Expected Outcome



steric bulk on same face

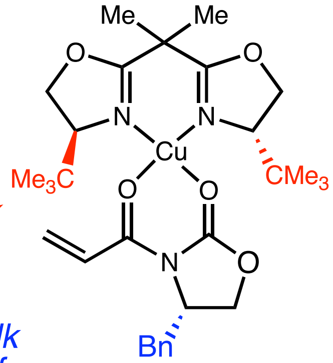
C_5H_6, -78 °C

Matched case if Cu center square-planar



highly diastereoselective

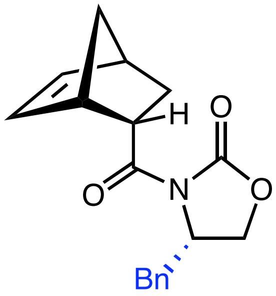
catalyst control



steric bulk on opposite faces

C_5H_6, -78 °C

Mismatched case if Cu center square-planar



poorly diastereoselective

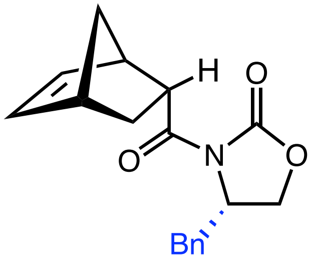
slow reaction

torsional pressure

Tetrahedral Complex

C_5H_6, -78 °C

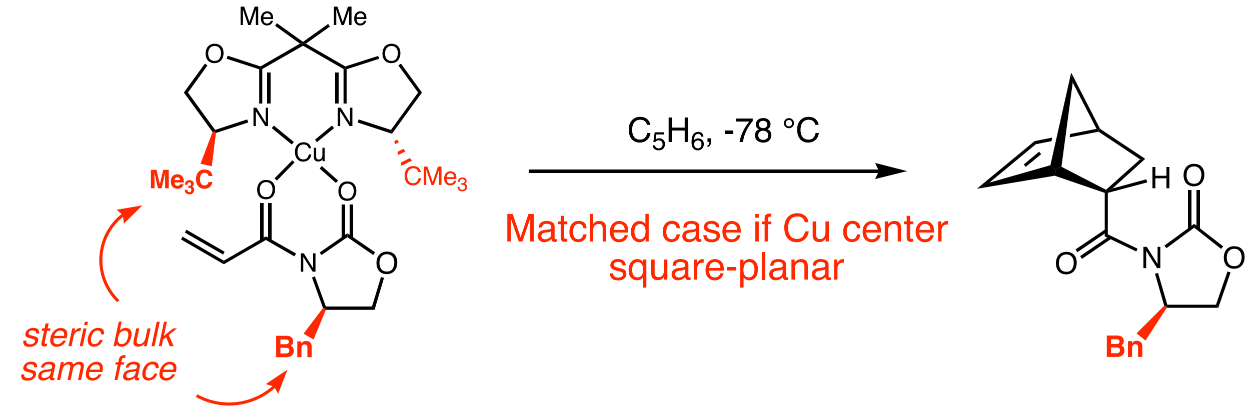
Matched case if Cu center Tetrahedral



substrate control

This test for torsional rigidity may be applied to any catalyst-substrate complex

Torsional Rigidity of Catalyst-Substrate Complex



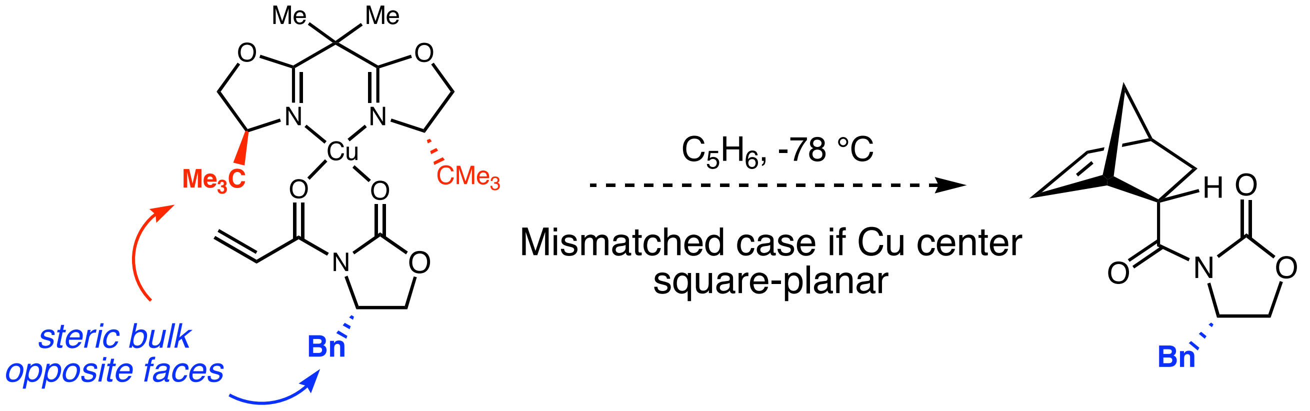
steric bulk
same face

Matched case if Cu center
square-planar

Outcome

Endo(1): *Endo*(2) ≥ 99:1

100% conversion



steric bulk
opposite faces

Mismatched case if Cu center
square-planar

Endo(1): *Endo*(2) = 68:32

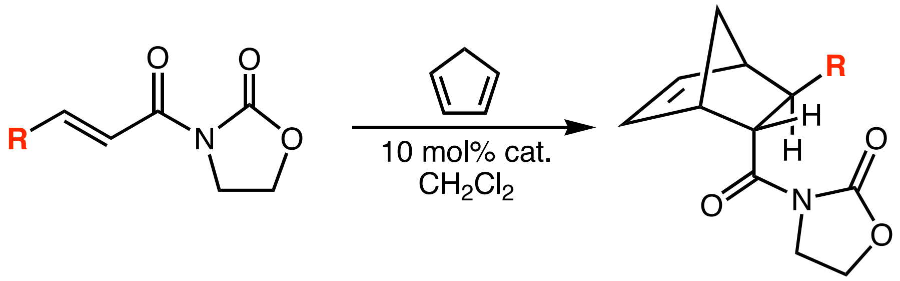
20% conversion

Catalyst control

Cu(II) strongly resists distortion from square planar to tetrahedral. Other metals such Mg(II), Fe(III), and Zn(II) succumb to internal stereochemical "pressure."

JACS **1999,** *121,* 7559-7573; *JACS* **1999,** *121,* 7582-7594

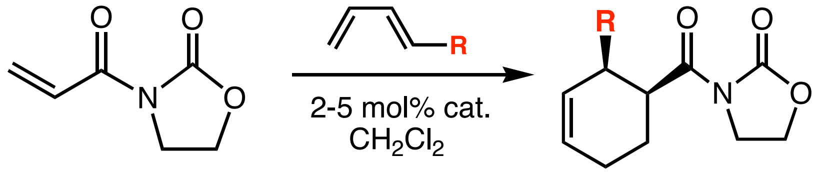
Diels-Alder Reaction Scope: (Box)Cu$(SbF_6)_2$•$2H_2O$ Catalyst



	counterion	time	endo ee	yield
R = Me +25 °C	X = TfO^-	8 h	94% ee	95%
	X = SbF_6^-	8 h	96% ee	98%

	counterion	time	endo ee	yield
R = Ph +25 °C	X = TfO^-	24 h	90% ee	85%
	X = SbF_6^-	24 h	96% ee	95%

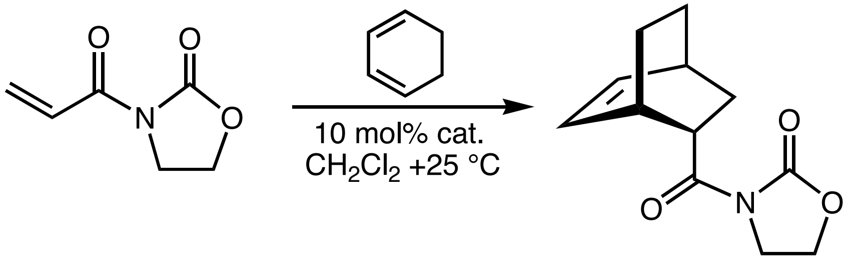
	counterion	time	endo ee	yield
R = Cl +25 °C	X = TfO^-	24 h	53% ee	----
	X = SbF_6^-	18 h	94% ee	95%



	counterion	time	endo ee	yield
R = Me +25 °C	X = TfO^-	12 h	86% ee	72%
	X = SbF_6^-	12 h	94% ee	89%

	counterion	time	endo ee	yield
R = Ph -20 °C	X = TfO^-	12 h	86% ee	72%
	X = SbF_6^-	24 h	97 % ee	95%

	counterion	time	endo ee	yield
R = OAc 0 °C	X = SbF_6^-	24 h	97 % ee	100%

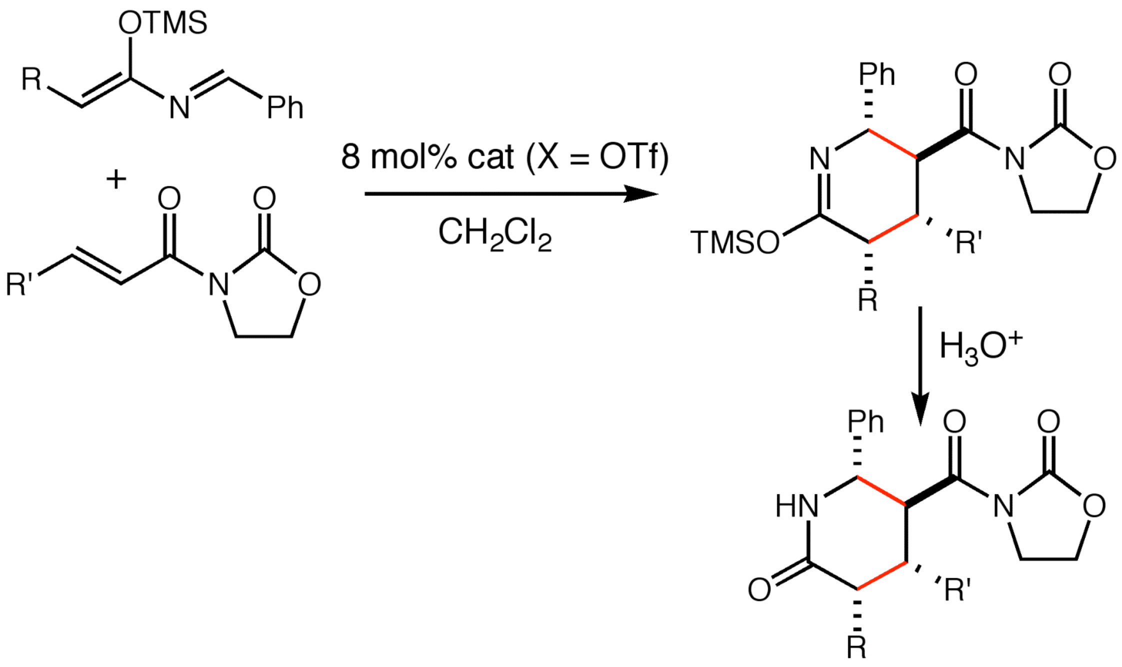


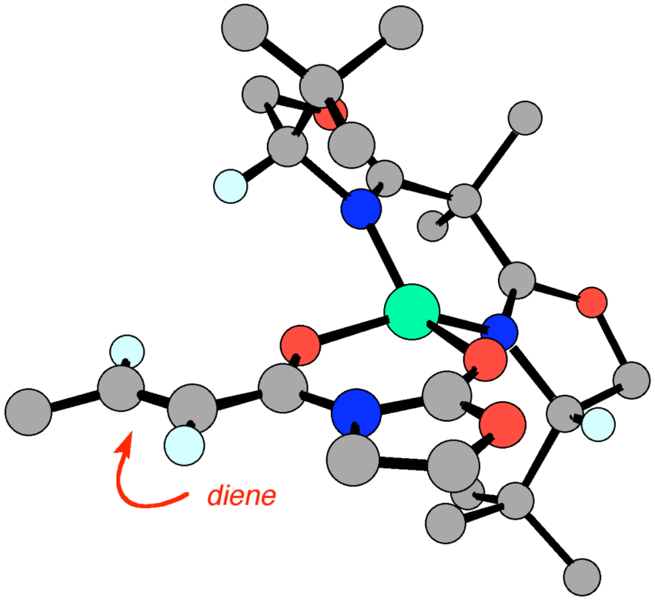
counterion	time	endo ee	yield
X = TfO^-	48 h	82% ee	90%
X = SbF_6^-	5 h	93% ee	90%

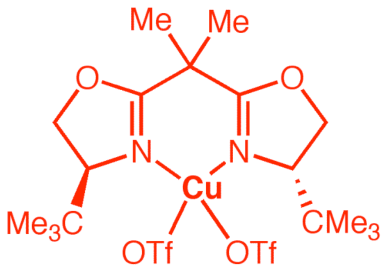
JACS **1999**, 121, 7559-7573; *JACS* **1999**, 121, 7582-7594

Extensions may be made to Heterodienes

Jnoff & Ghosez, *JACS* **1999**, *121*, 2617





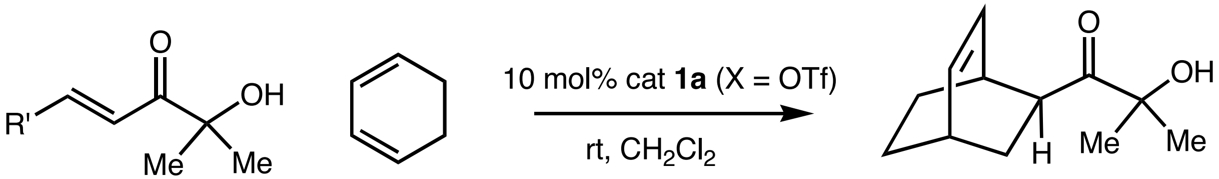


The Catalyst (2-5 mol %)

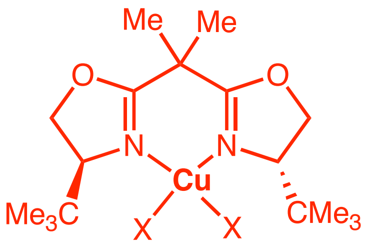
R	R'	T °C	*endo/exo*	yield (%)	% ee
Me	Me	-45	>99:1	80	**95**
Me	Me	rt	>99:1	96	**94**
H	H	-45	6:1	83	**98**
Me	H	-45	>99:1	96	**98**
H	Me	rt	>99:1	80	**93**

Extensions may be made to other Dienophiles

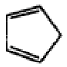
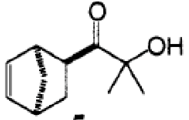
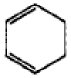
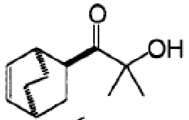
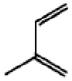
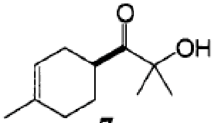
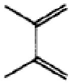
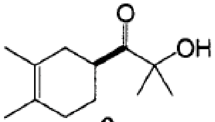
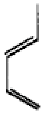
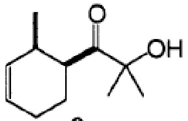
C. Palomo et al., *JACS* **2003**, *125*, 13942-13943



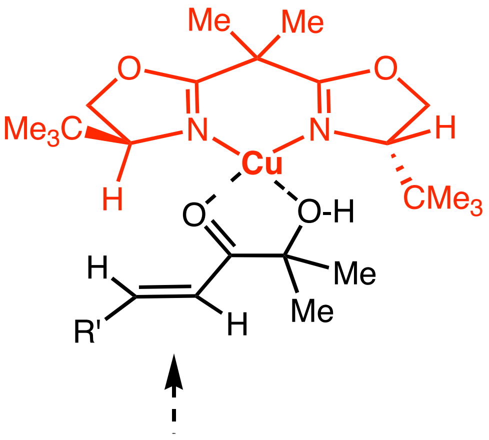
endo: exo >99:1
>98% ee, 93% yield



catalyst **1a**: X = OTf
catalyst **1d**: X = SbF_6

diene	cat.	T, °C	t, h	isom. ratio^{b}	*endo:exo*^{c}	product	yield, %	ee %^{d}
	**1a**	−78	2.5	--	>99:1	 **5**	99	>99
	**1a**	25	2	--	>99:1	 **6**	93	≥98
	**1a**	25	1.5	99:1	--	 **7**	88	81
	1a	−20	30	>99:1	--		87	88
	1d	−20	14	>99:1	--		85	94
	1d	−20	20	>99:1	--		85	90^{e}
	**1a**	−20	20	--	--	 **8**	75	89
	1d	−20	13	--	--		80	94
	1d	−20	20	--	--		90	90^{e}
	**1a**	25	8	50:50	--	 **9**	--	nd
	1d	25	2	76:24	--		--	nd
	1d	−10	15	88:12	--		95	>99

Stereochemical Model

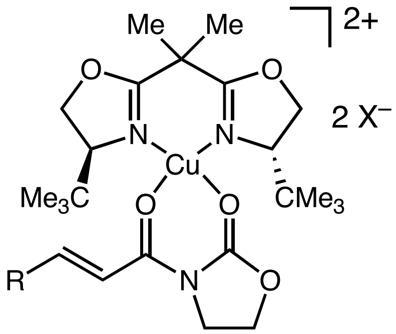


Diene Approach

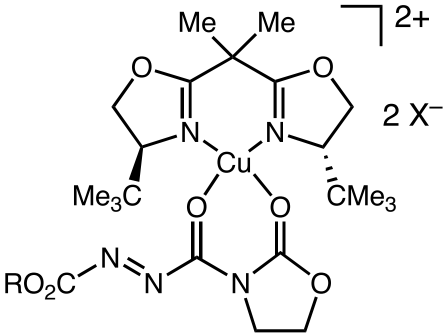
Chiral Cu(2+) Complexes as Chiral Lewis Acids

Cu(box) and Cu(pybox) catalyst-substrate complexes implicated in enantioselective reactions.

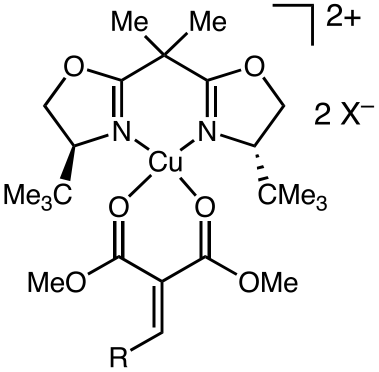
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335. **(pdf)**



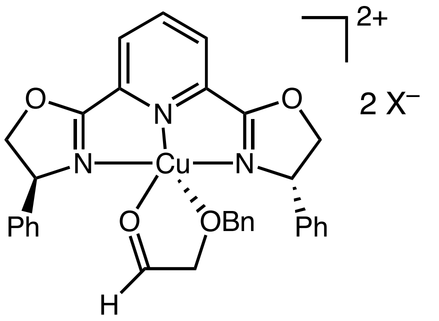
Cycloaddition Reactions
Michael Reactions



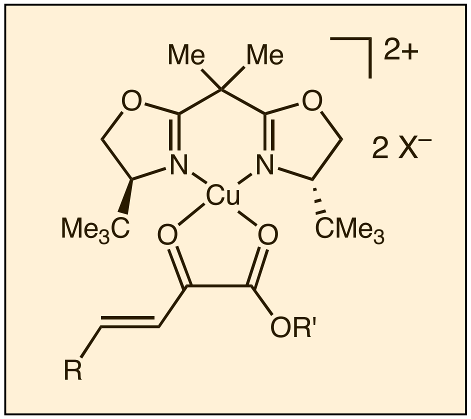
Enol Amination Reactons

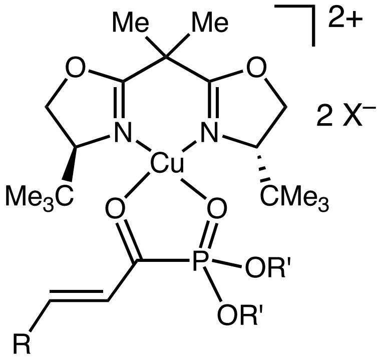


Michael Reactions

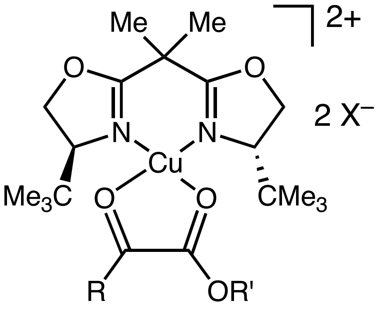


Aldol Reactions



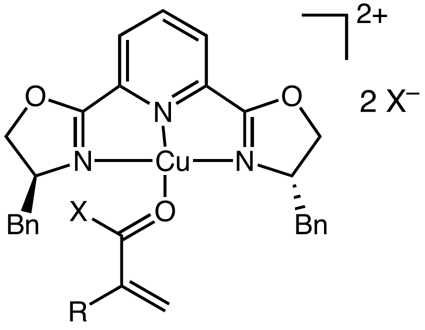


Hetero Diels-Alder Reactions



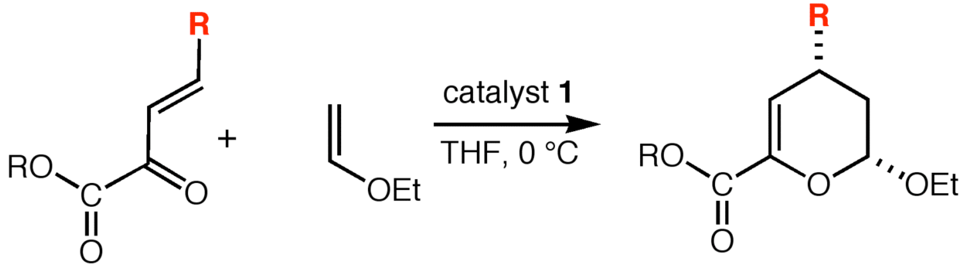
R = H, Cycloaddition Reactions
Ene Reactions

R = Alkyl, Cycloaddition Reactions
Aldol Reactions



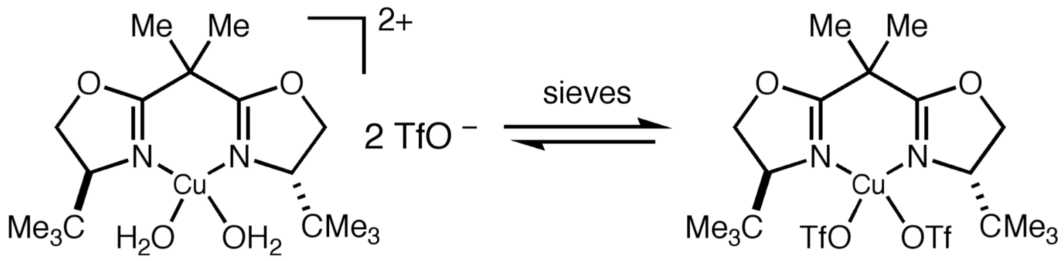
Diels-Alder Reactions

Unsaturated α-Keto Esters in Hetero-Diels-Alder Reactions



R = Me, Ph, $CHMe_2$, OR, SR,

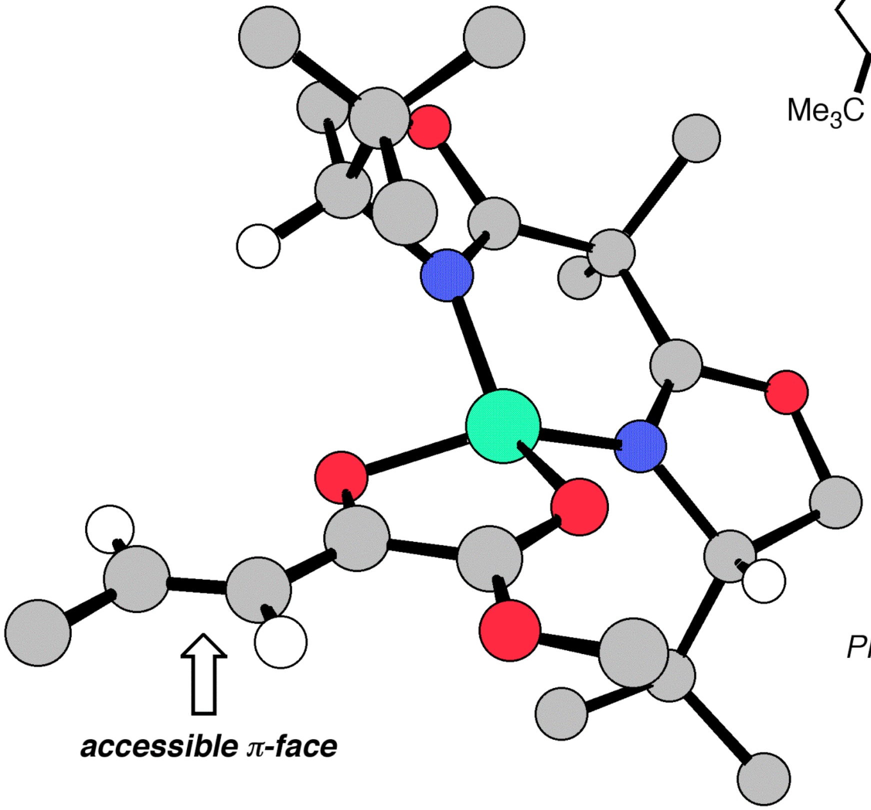
>95% ee
endo diastereoselection >20:1



1 (aquo)

1

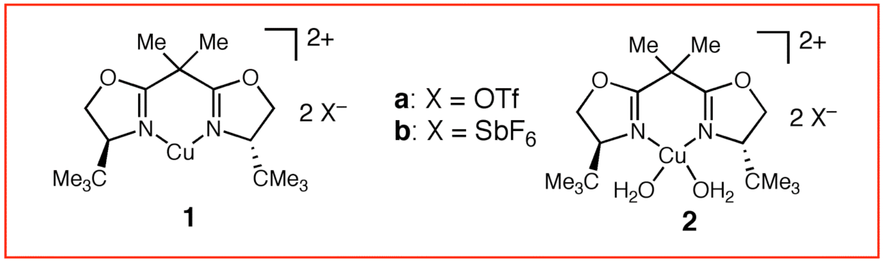
The bench-stable aquo complex may be used in the presence of sieves at 2 mol %.



PM3 Structure

with Jeff Johnson & Ed Olhava, *JACS*, **2000**, *122*, 1635

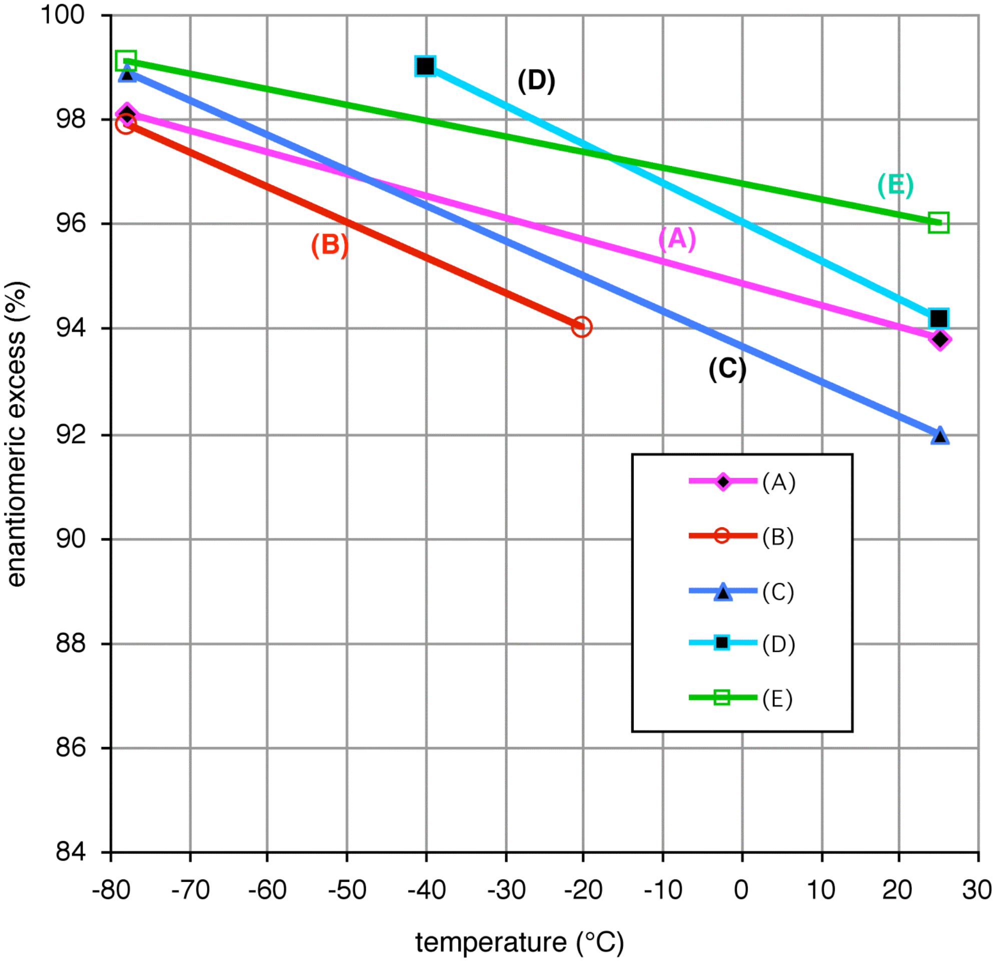
Temperature–Enantioselection Profile for [Cu((S,S)-t-Bu-box)]$(X)_2$ Catalysts



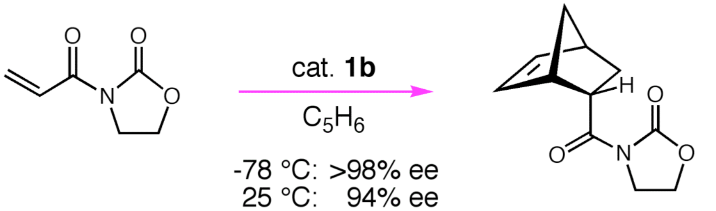
1

a: X = OTf
b: X = SbF_6

2

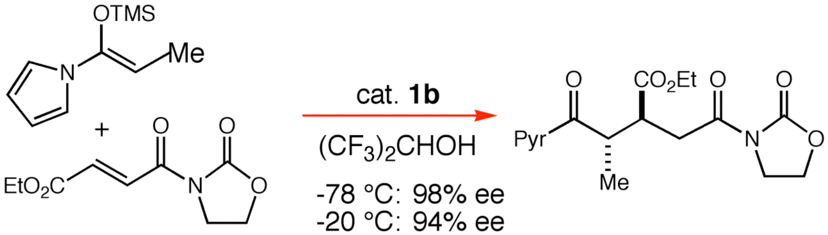


(A)



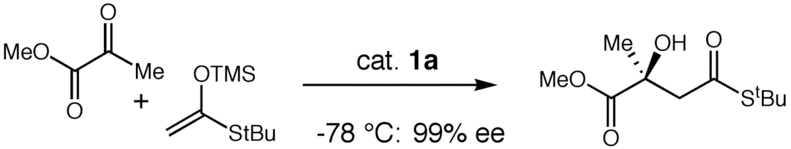
cat. **1b**
C_5H_6
-78 °C: >98% ee
25 °C: 94% ee

(B)



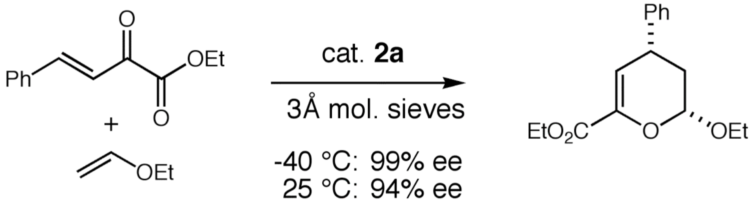
cat. **1b**
$(CF_3)_2CHOH$
-78 °C: 98% ee
-20 °C: 94% ee

(C)



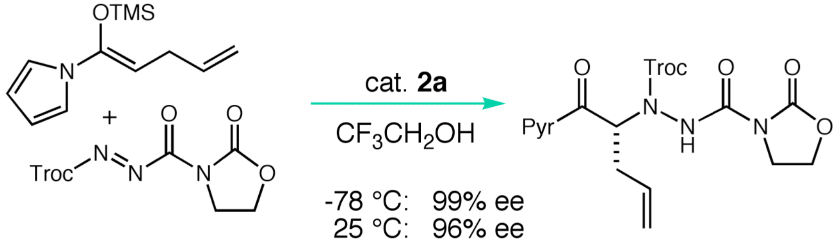
cat. **1a**
-78 °C: 99% ee
25 °C: 92% ee

(D)



cat. **2a**
3Å mol. sieves
-40 °C: 99% ee
25 °C: 94% ee

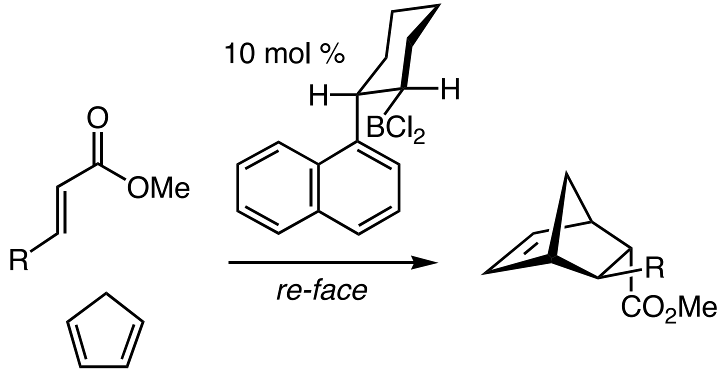
(E)



cat. **2a**
CF_3CH_2OH
-78 °C: 99% ee
25 °C: 96% ee

"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335. **(pdf)**

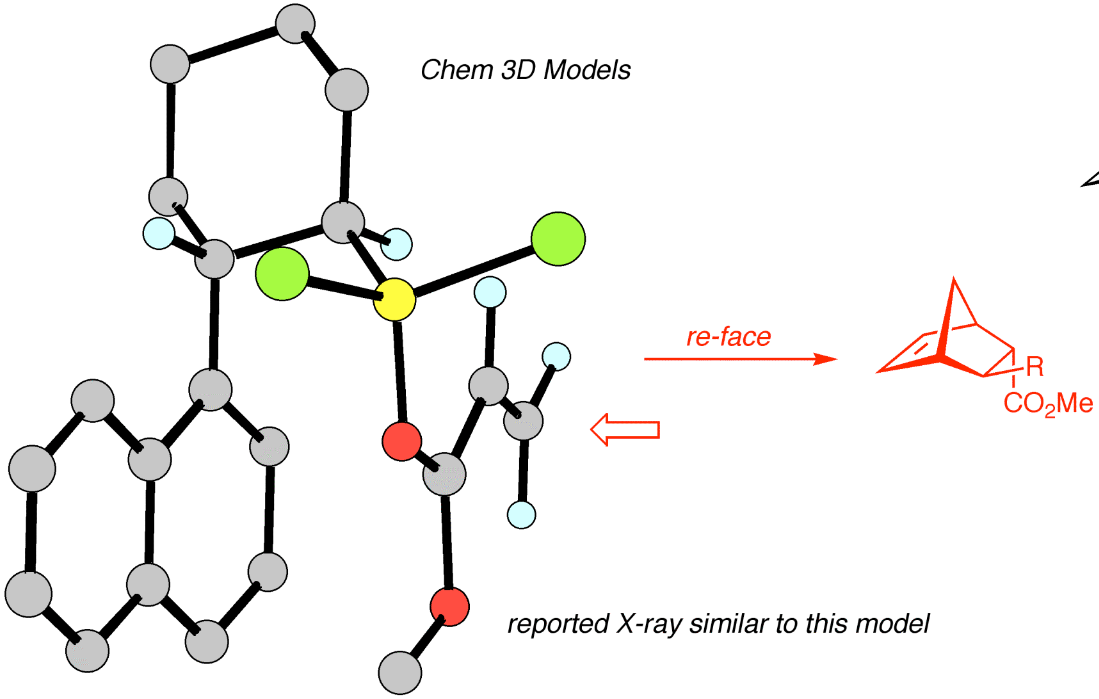
Boron-Based Catalyst: Hawkins *JACS* 1991, *113*, 7794



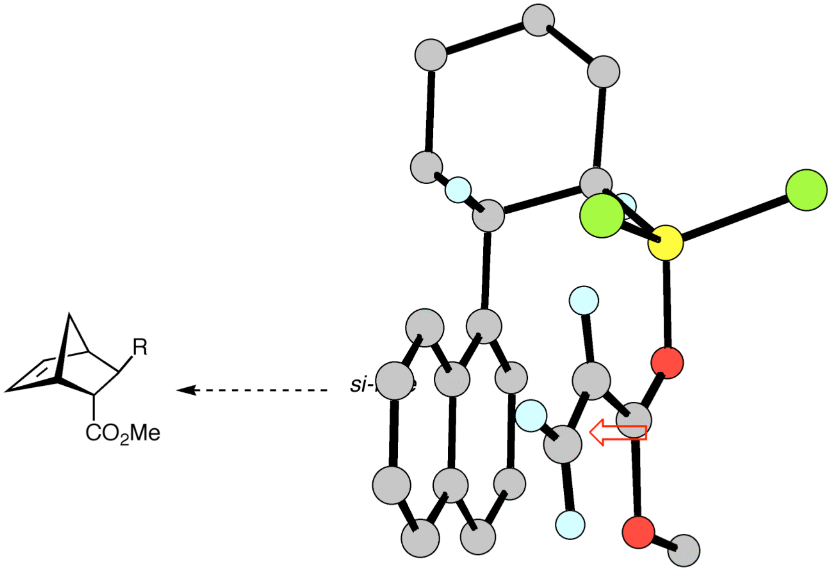
R	Temp (°C)	Endo ee
H	-78	97 %
Me	-20	91 %
CO$_2$Me	-78	92 %

Endo/Exo Ratios not provic

Chem 3D Models

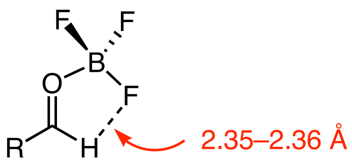


reported X-ray similar to this model

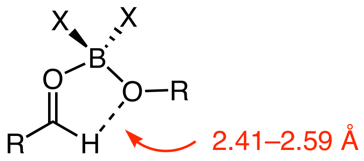


The pragmatic Issue: The cost of producing the chiral catalyst

A New Hydrogen Bonding Motif



sum of the van der Waals radii:
2.67 Å (H = 1.20 Å and F = 1.47 Å).

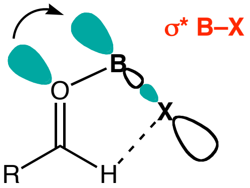


sum of the van der Waals radii:
2.72 Å (H = 1.20 Å and O = 1.52 Å).

The formyl C–H…O hydrogen bond as a critical factor in enantioselective Lewis-acid catalyzed reactions of aldehydes,
Corey, Lee, *Chem Commun.* **2001,** 1321 **(pdf)**

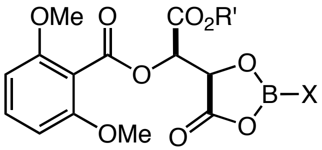
"There may also be a contribution from an anomeric effect in which electrons from the noncomplexed lone pair on aldehyde oxygen delocalize into the σ*orbital of the eclipsed B–F or B–O bond. The authors of one study[1] attributed a value of 6 kJ mol to the anomeric effect and 9 kJ mol21 to the formyl hydrogen bond.[4]

(1) M. D. Mackey and J. M. Goodman, *Chem. Commun.*, **1997,** 2383

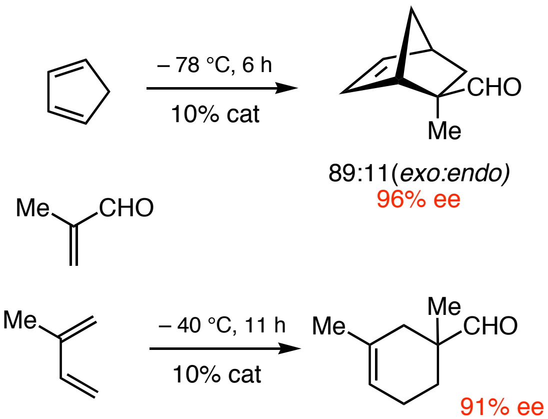


A possiible anomeric effect

Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *JACS* **1988,** *110,* 6254.

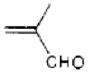
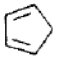
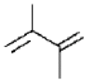
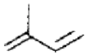
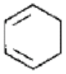
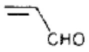
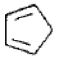
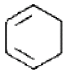
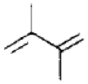
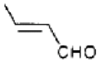
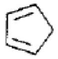
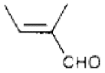
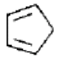


R' = H or Alkyl
X = H or Acyloxy

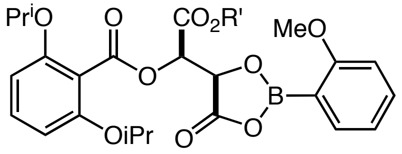


89:11(*exo:endo*)
96% ee

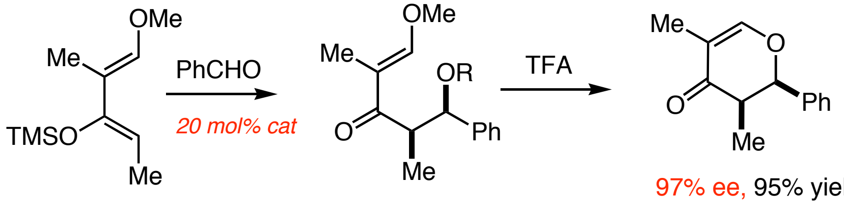
91% ee

dienophile	diene	isomers,^{c} endo/exo	ee,^{d} %
		11/89	96^e
		10/90	96^g
			97
		97/3^h	93
		98/2^h	91
		93/7	82
		88/12	84^e
		>99/1	80^i
			84^j
		90/10	2^k
		3/97	90

Yamamoto et al. *J. Org. Chem.* **1992,** *57,* 1951-1952

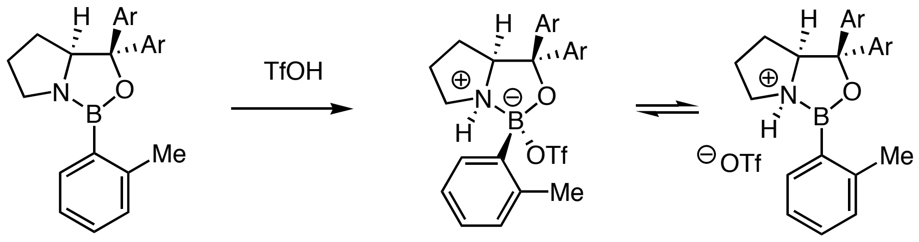


Note modifications to catalyst



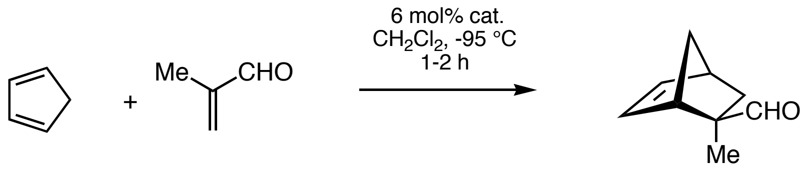
97% ee, 95% yield

Oxazaborolidine Catalysts: **Corey *JACS* 2002, *124*, 3808.**



Ar = Ph or 3,5- Me_2-Ph

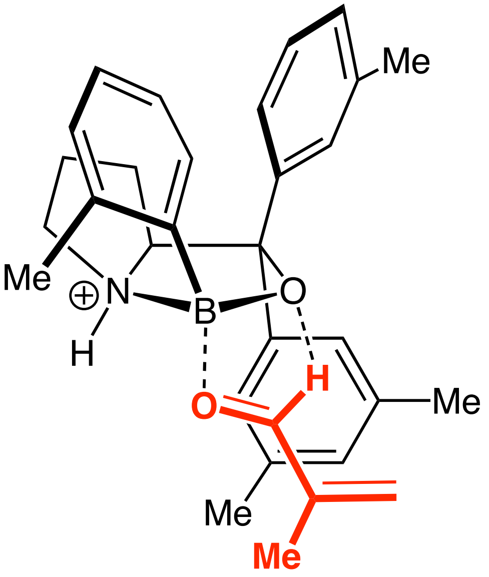
active catalyst

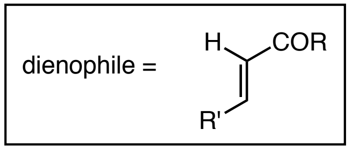


99% yield 89:11(*exo:endo*) 96% ee

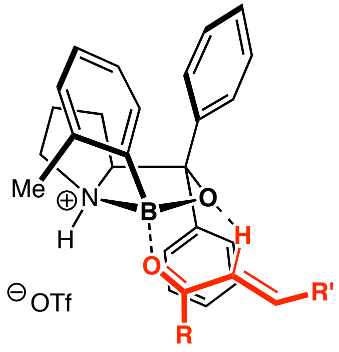
Organized formyl CH–O hydrogen bonded complex
Aryl groups screen back face of dienophile
Π– stacking may also be involved
exo or *endo* selectivity varies with the diene

Stereochemical Model:





R= H, alkyl OH, OR



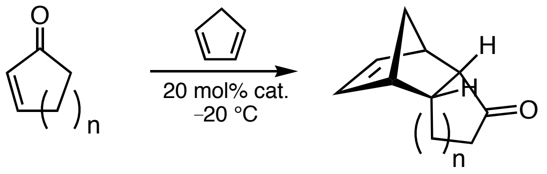
Alkene CH - O interaction may organize complex

Aryl groups screen back face of dienophile

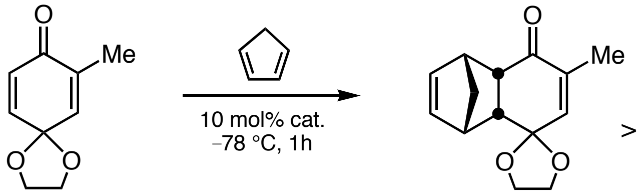
Π– stacking may also be involved

endo product is observed* Note the opposite facial selectivity

Examples: Corey *JACS* **2002** *124*, 9992.



n	time	endo ee	yield
n = 1	14 h	96% ee	92%
n = 2	15 h	96% ee	95%
n = 3	22 h	94% ee	93%



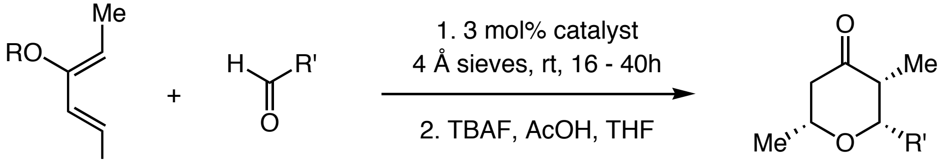
80% yield
> 98:2 *endo:exo*
92% ee

Switching the counterion from triflate OTt(–) to triflamide $(Tf)_2N(–)$ expands dienophile scope: Corey *JACS* **2003**, *125*, 6388.

Hetero-Diels-Alder Reactions – Enantioselective Catalysis

Chromium (III) Schiff-Base Catalysts:

Jacobsen *Angew. Chem. Int. Ed.* 1999, *38*, 2398.



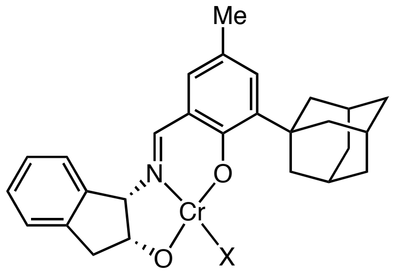
1. 3 mol% catalyst
4 Å sieves, rt, 16 - 40h

2. TBAF, AcOH, THF

R = TMS, TES, TBS

R' = aryl, alkyl, heteroaromatic

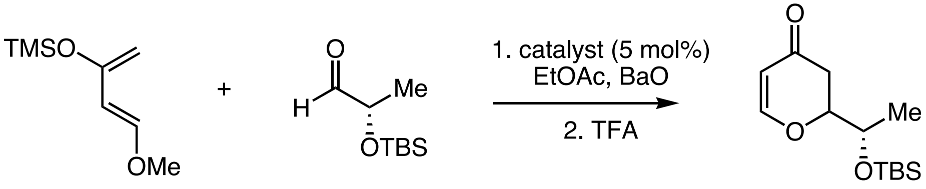
> 95% de
(all cis)
90-99% ee
72-97% yield



X = Cl, SbF_6

- The catalyst is a water-bridged dimer
- Sieves may be needed to open up a binding site for the aldehyde
- Single-point binding to the aldehyde
- A variety of mono- and di-oxygenated dienes are good substrates

Catalyst-Controlled Diastereoselective HDA:



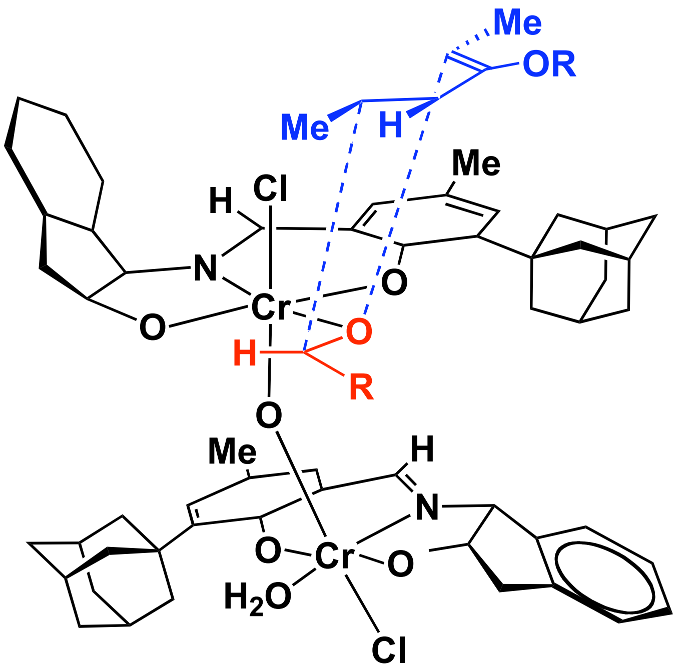
1. catalyst (5 mol%)
EtOAc, BaO

2. TFA

catalyst	yield	dr	ee
achiral catalyst	81%	1:2.0	nd
(1*R*,2*S*)-Cl	96%	1:12	>99%
(1*S*,2*R*)-Cl	97%	15:1	>99%

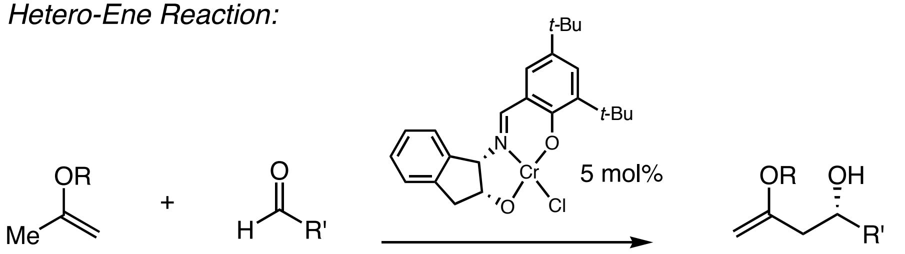
Org. Lett. **2002**, *4*, 1795.

Stereochemical Model:



HDA

Hetero-Ene Reaction:



BaO or4 Å sieves
base, acetone, 4˚C

R = TMS, Me

R' = Ar, alkyl

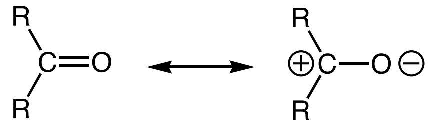
70 - 96% ee
77 - 97% yield

JACS, **2002**,*124*, 2882.; *Angew. Chem. Int. Ed.* **2003**, *42*, 4771.

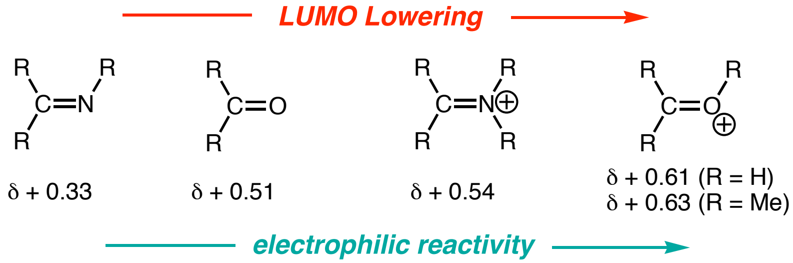
MacMillan introduces a new catalyst:

MacMillan, D. *JACS* **2000**, *122*, 4243.

■ C=X Polarization



Partial Charge: As the familiar polar resonance structure above indicates, the carbonyl carbon supports a partial positive charge due to the polarization of the sigma and pi system by the more electronegative heteroatom. The partial charges for this family of functional groups derived from molecular orbital calclulations (ab initio, 3-21(G)*, HF) are illustrated below:



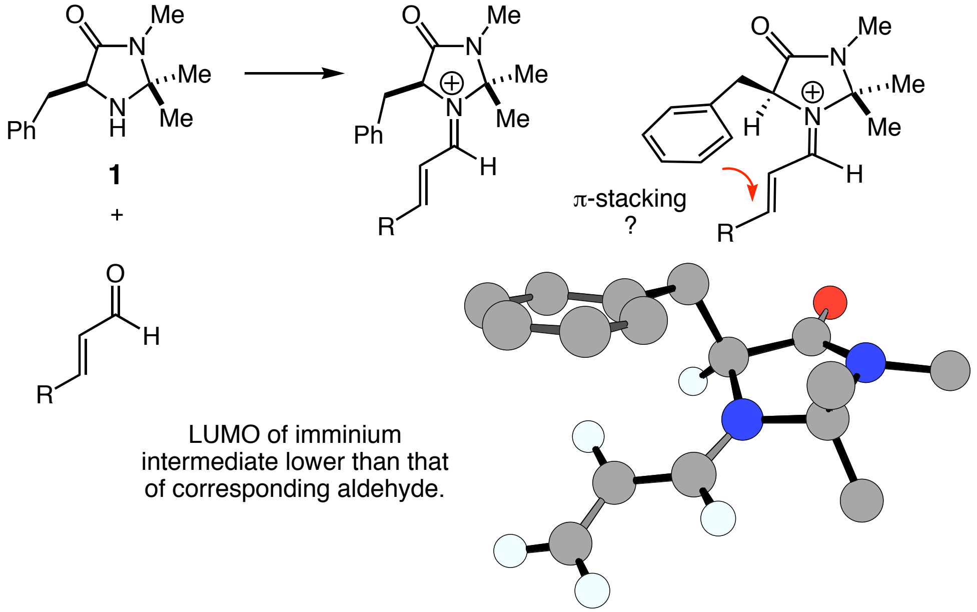
δ + 0.33

δ + 0.51

δ + 0.54

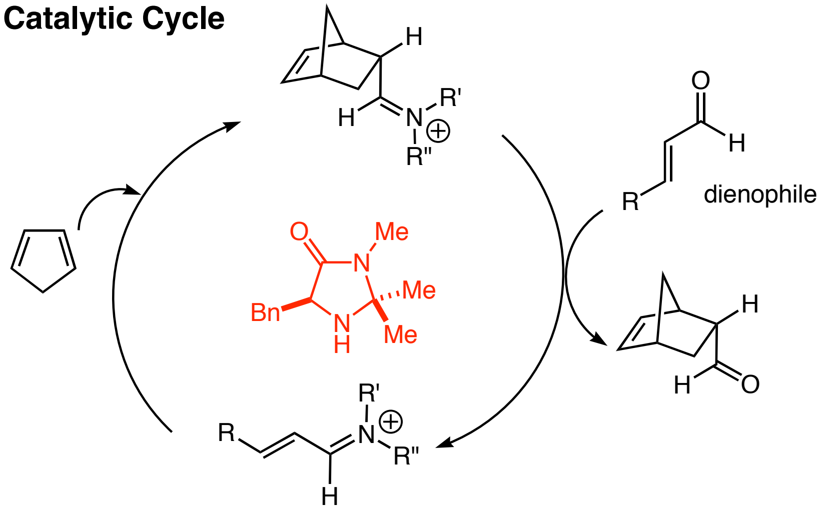
δ + 0.61 (R = H)
δ + 0.63 (R = Me)

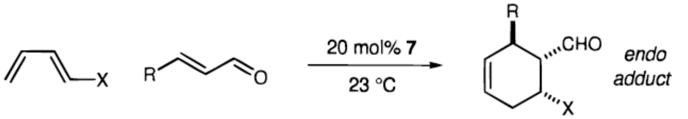
Diels-Alder Catalysis via chiral Iminium Ions

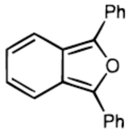
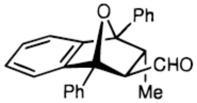
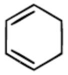
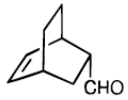
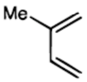
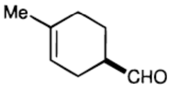
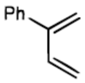
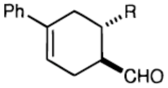
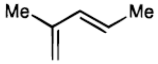
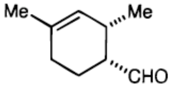
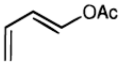
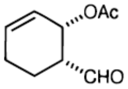


LUMO of imminium intermediate lower than that of corresponding aldehyde.

The Catalytic Cycle





entry	diene	R	product	yield	*exo*:*endo*	% ee[a]
1		Me		75	35:1	96[c]
2		H		82	1:14	94[d]
3		H		84	--	89
4		H		90	--	83
5		Me		75	--	90
6		H		75	1:5	90
7		H		72	1:11	85

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 19

Dipolar cycloaddition Reactions

Merged Cycloaddition–Cycloreverion Processes, G. Borg, Evans Group Seminar **(Handout)**

"The Concerted Nature of 1,3-Dipolar Cycloadditions and the Question of Diradical Intermediates," R; Huisgen, *J. Org. Chem.* **1976,** *41,* 403 **(Handout)**
"Asymmetric 1,3-Dipolar Cycloaddition Reactions", Jorgensen, *Chem Rev*. **1998,** *98,* 863-909 **(pdf)**

"Total Synthesis of (-)-Colchicine via a Rh-Triggered Cycloaddition Cascade'" Schmalz, *Org. Lett*. **2005,** *7*, 4317 **(pdf)**

D. A. Evans

Wednesday
November 1, 2006

Dipolar Cycloaddition Reactions

General References
Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.

Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley, **1984,** Volumes 1 & 2,

Padwa, A. Generation and utilization of carbonyl ylides via the tandem cyclization-cycloaddition method." *Acc. Chem. Res.* **1991**, *24*, 22. **(pdf)**

Confalone, P. N.; Huie, E. M. *The [3+2] Nitrone-Olefin Cycloaddition Reaction Org. React. (N.Y.)* **1988**, *36*, 1.

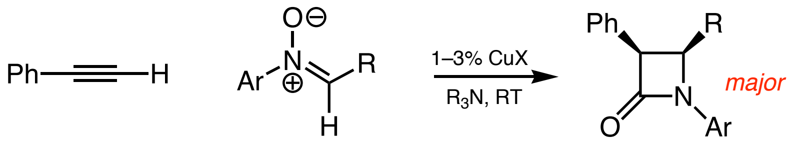
S. Kanemasa, *Metal Assisted 1,3-Dipolar Cycloaddition Reactions,* SynLett **2002**, 1371-1387 **(pdf)**

"Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides", Coldham, *Chem Rev*. **2005,** *105,* 2765-2809 **(pdf)**

"The Firestone Papers, *J. Org. Chem.* **1972,** *37,* 2181; *J. Org. Chem.* **1976,** *41,* 2212. **(Handout)**

Problem of the Day (Database Problem 4

Provide a plausible mechanism for this transformation in the space below. *In attacking this question, it is important that you are aware of the transformation that transpires when terminal acetylenes are treated with Cu(I) or Ag(I) in the presence of an amine base.*



In 1995 Miura and co-workers reported the remarkable reaction illlustrated below (*J. Org. Chem.* **1995**, *60*, 4999). Recently, Fu has reported an enantioselective variant of this transformation (*J. Am. Chem. Soc.* **2002**, *124*, 4572). In most instances, the cis adduct is formed in large excess (>90%). There is really no thoughtful mechanism in the literature for this transformation. You will be graded on "reasonability"

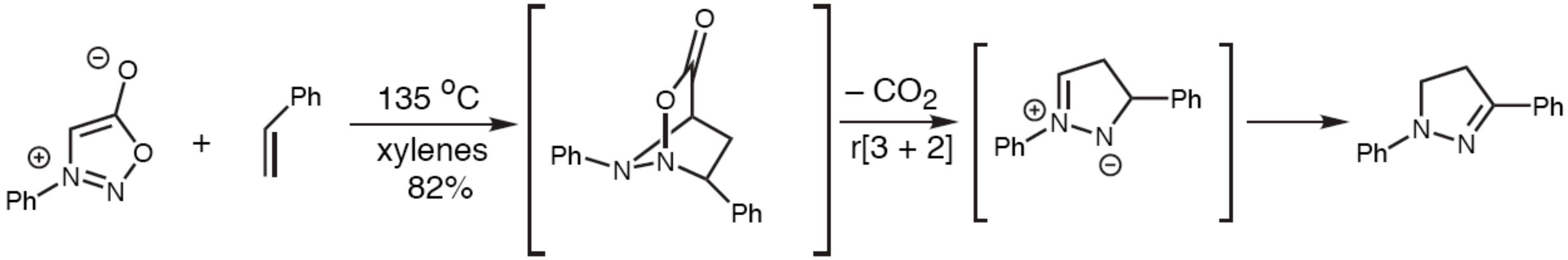
Handout 18A

Merged Cycloaddition–Cycloreversion Processes

Evans Group Seminar
May 3, 2002
Mr. George Borg

[3 + 2]–r[3 + 2] Reactions of Sydnones

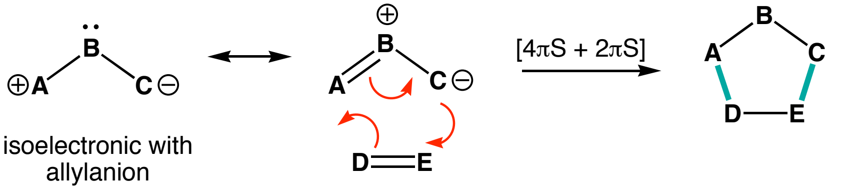
- Reactions of sydnones with alkenes produce 2-pyrazolines:



Huisgen, *Chem. Ber.* **1968**, *101*, 552-563.

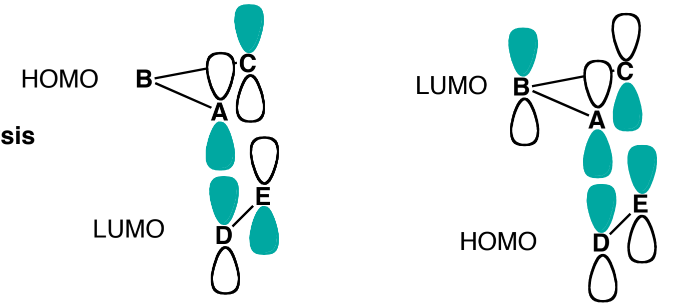
Dipolar Cycloaddition Reactions: An Introduction

The General Reaction Family



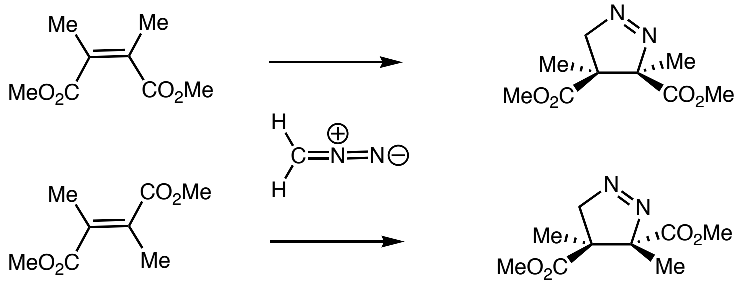
isoelectronic with allylanion

FMO Analysis

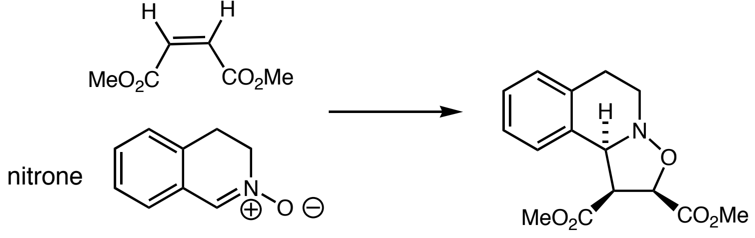


The specific set of reaction partners, will define the dominant frontier orbitals

Reaction Stereospecificity: The Dipolariphile (Padwa, Vol 1, pp 61-90)



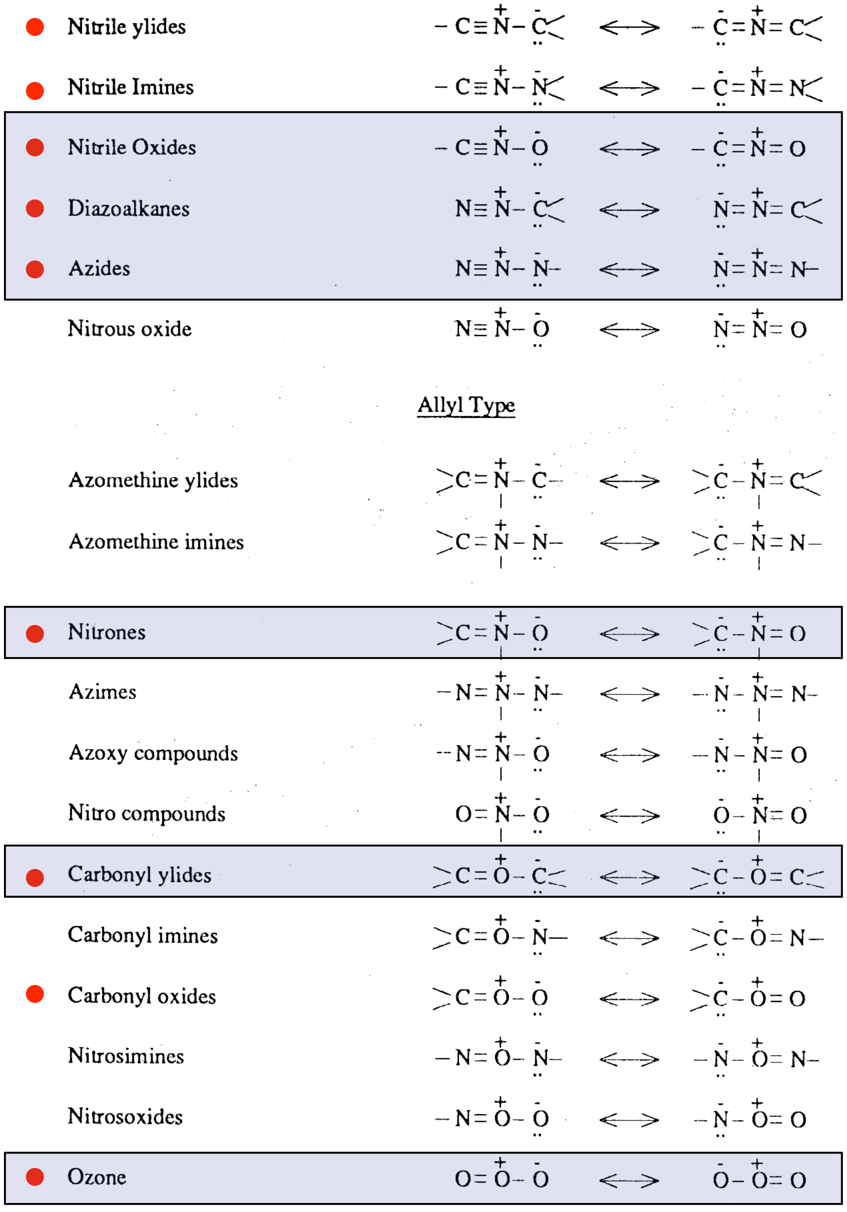
Rinehart, *JACS* **1962**, *84*, 3736



Fumarate gives trans cycloadduct

Huisgen, *Chem. Ber.* **1969**, *102*, 736

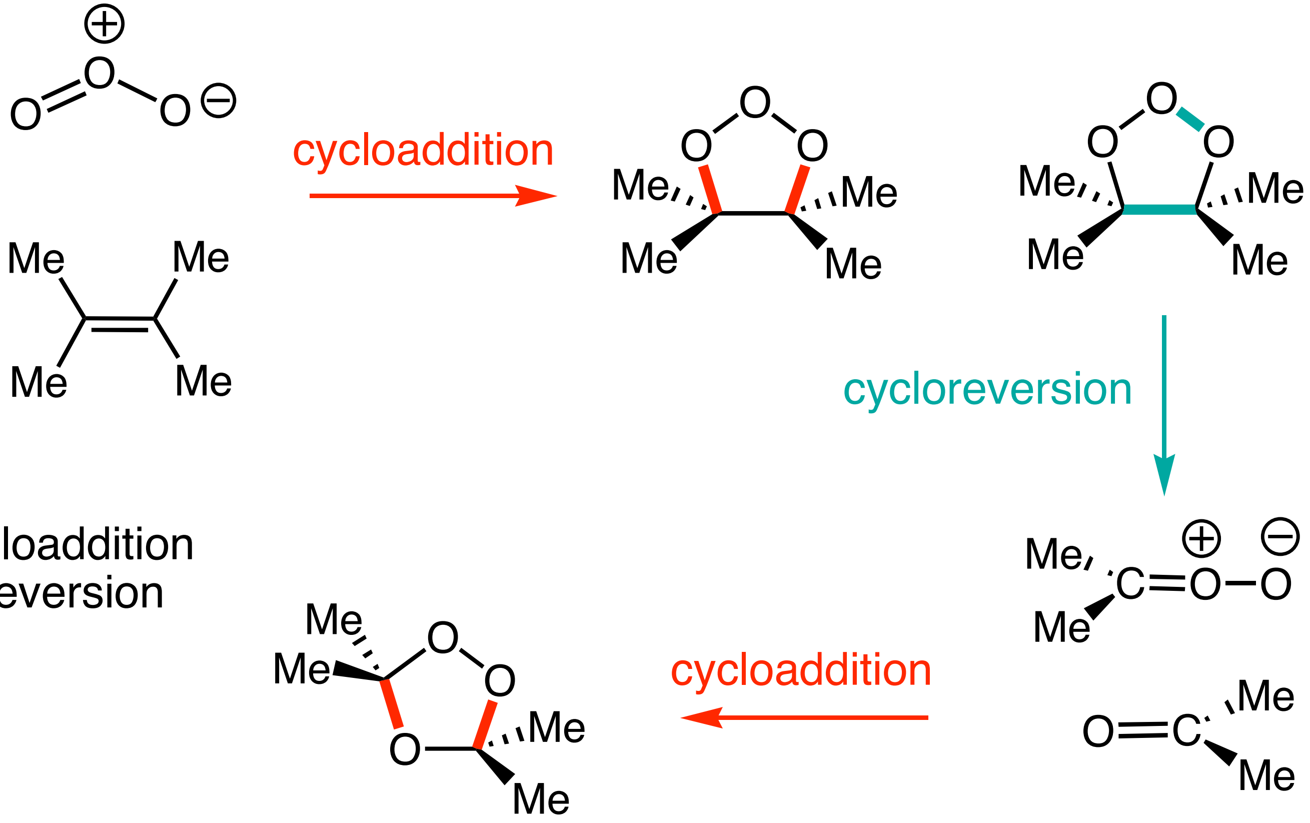
Classification of 1,3-Dipoles Containing C, N, & O Atoms



●	Nitrile ylides	$-C\equiv\overset{+}{N}-\overset{-}{C}<$	⟷	$-\overset{-}{C}=\overset{+}{N}=C<$
●	Nitrile Imines	$-C\equiv\overset{+}{N}-\overset{-}{N}<$	⟷	$-\overset{-}{C}=\overset{+}{N}=N<$
●	Nitrile Oxides	$-C\equiv\overset{+}{N}-\overset{-}{O}$	⟷	$-\overset{-}{C}=\overset{+}{N}=O$
●	Diazoalkanes	$N\equiv\overset{+}{N}-\overset{-}{C}<$	⟷	$\overset{-}{N}=\overset{+}{N}=C<$
●	Azides	$N\equiv\overset{+}{N}-\overset{-}{N}-$	⟷	$\overset{-}{N}=\overset{+}{N}=N-$
	Nitrous oxide	$N\equiv\overset{+}{N}-\overset{-}{O}$	⟷	$\overset{-}{N}=\overset{+}{N}=O$
	Allyl Type			
	Azomethine ylides	$>C=\overset{+}{N}-\overset{-}{C}-$	⟷	$>\overset{-}{C}-\overset{+}{N}=C<$
	Azomethine imines	$>C=\overset{+}{N}-\overset{-}{N}-$	⟷	$>\overset{-}{C}-\overset{+}{N}=N-$
●	Nitrones	$>C=\overset{+}{N}-\overset{-}{O}$	⟷	$>\overset{-}{C}-\overset{+}{N}=O$
	Azimes	$-N=\overset{+}{N}-\overset{-}{N}-$	⟷	$-\overset{-}{N}-\overset{+}{N}=N-$
	Azoxy compounds	$-N=\overset{+}{N}-\overset{-}{O}$	⟷	$-\overset{-}{N}-\overset{+}{N}=O$
	Nitro compounds	$O=\overset{+}{N}-\overset{-}{O}$	⟷	$\overset{-}{O}-\overset{+}{N}=O$
●	Carbonyl ylides	$>C=\overset{+}{O}-\overset{-}{C}<$	⟷	$>\overset{-}{C}-\overset{+}{O}=C<$
	Carbonyl imines	$>C=\overset{+}{O}-\overset{-}{N}-$	⟷	$>\overset{-}{C}-\overset{+}{O}=N-$
●	Carbonyl oxides	$>C=\overset{+}{O}-\overset{-}{O}$	⟷	$>\overset{-}{C}-\overset{+}{O}=O$
	Nitrosimines	$-N=\overset{+}{O}-\overset{-}{N}-$	⟷	$-\overset{-}{N}-\overset{+}{O}=N-$
	Nitrosoxides	$-N=\overset{+}{O}-\overset{-}{O}$	⟷	$-\overset{-}{N}-\overset{+}{O}=O$
●	Ozone	$O=\overset{+}{O}-\overset{-}{O}$	⟷	$\overset{-}{O}-\overset{+}{O}=O$

(After R.Huisgen, J.Org.Chem., 1976, 41, 403.)

Ozonolysis: The Prototypical Case

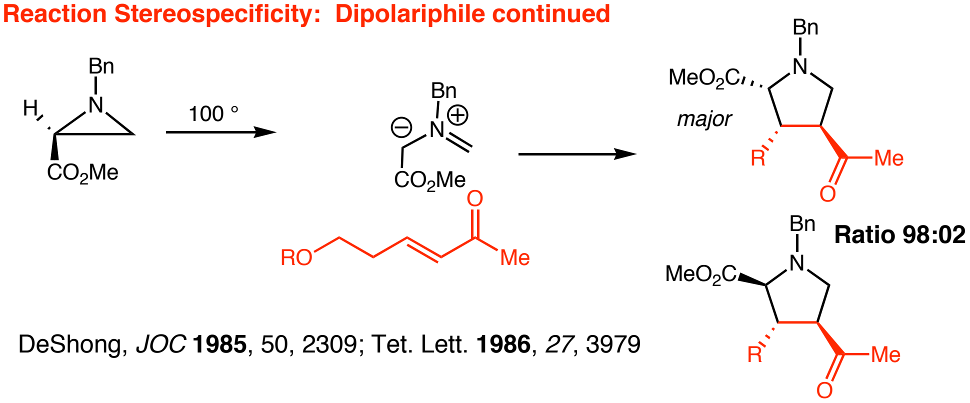


Rapid cycloaddition
& cycloreversion

Criegee, R. "Mechanism of Ozonolysis." *Angew. Chem., Int. Ed*. **1975** *14,* 745.

Dipolar Cycloaddition Reactions: An Introduction

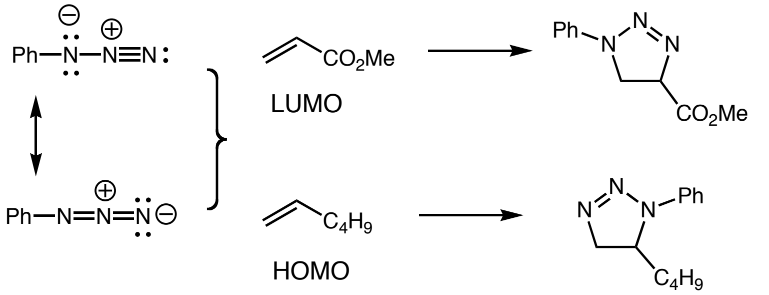
Reaction Stereospecificity: Dipolariphile continued



DeShong, *JOC* **1985**, 50, 2309; Tet. Lett. **1986**, *27*, 3979

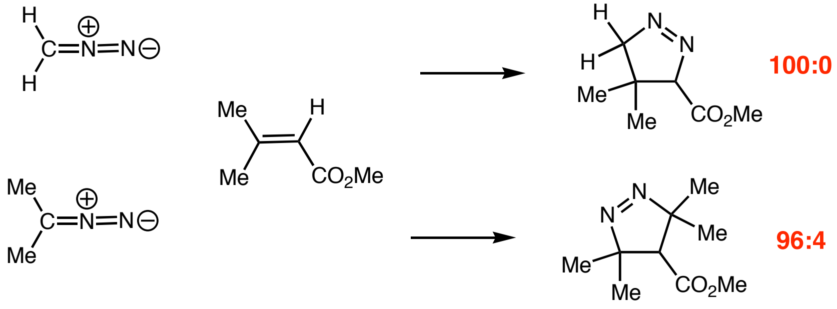
We will return to the other stereochemical element of this reaction shortly

Reaction Regiochemistry (Padwa, Vol 1, pp 135)



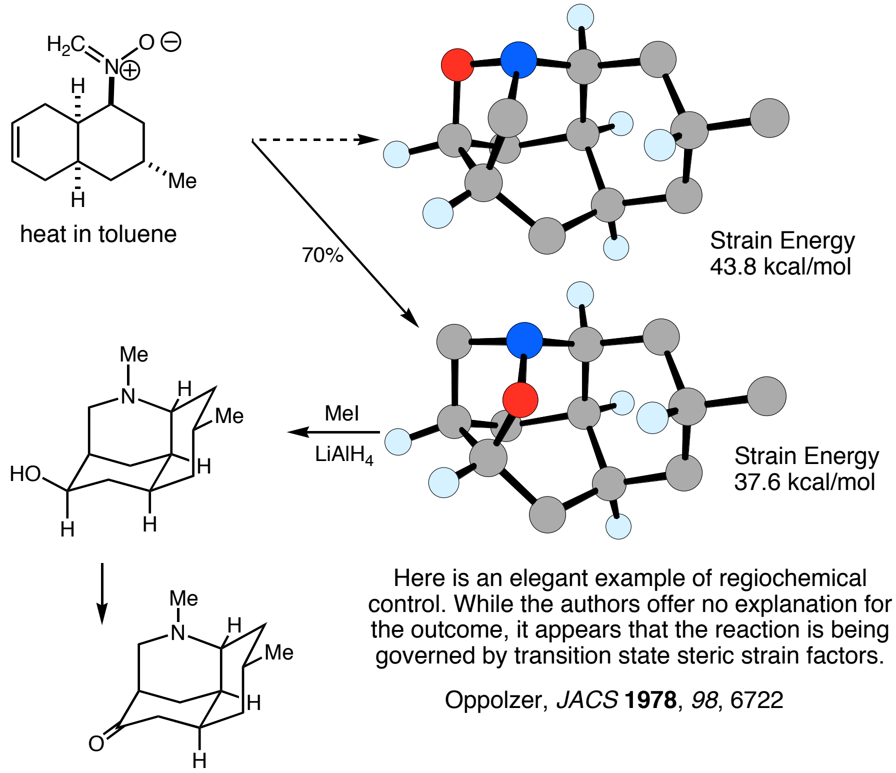
The specific set of reaction partners, will define the dominant frontier orbitals

Steric effects will frequently alter regioselectivity (Padwa, Vol 1, pp 144)



Steric effects are also important considerations in reaction regiochemistry

Ring strain factors may control regioselectivity

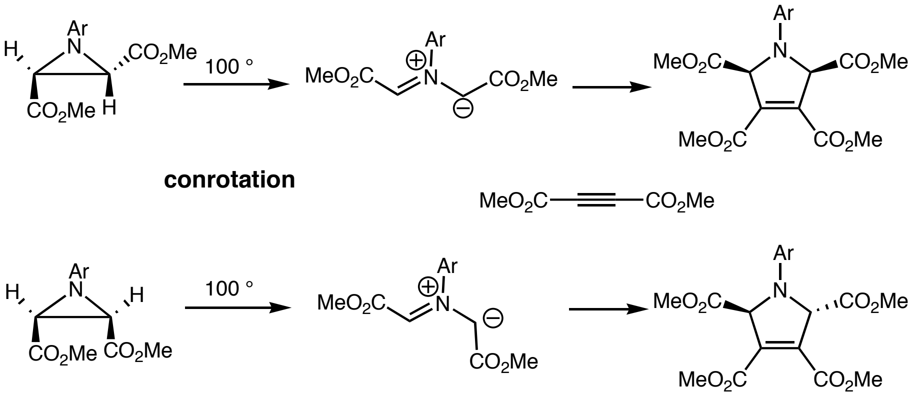


Here is an elegant example of regiochemical control. While the authors offer no explanation for the outcome, it appears that the reaction is being governed by transition state steric strain factors.

Oppolzer, *JACS* **1978**, *98*, 6722

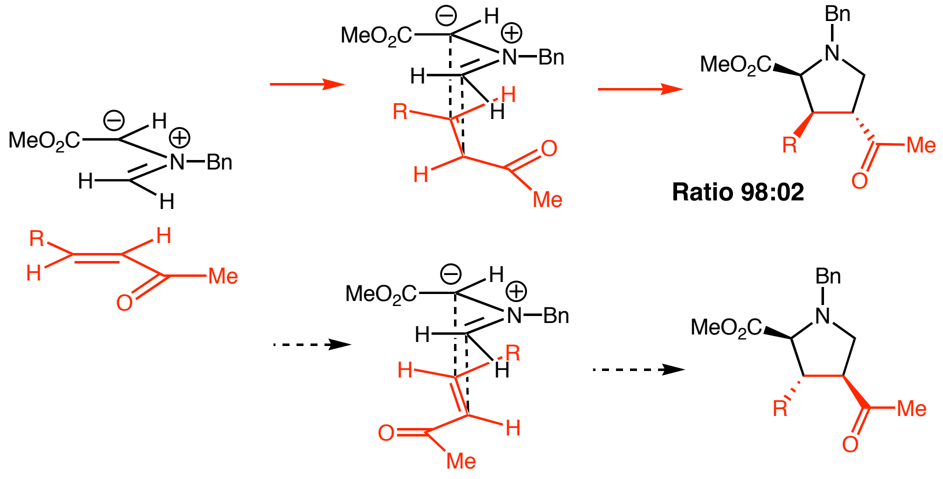
Reaction Diastereoselectivity

Huisgen et al, *Angew.Chem. Int. Ed.* **1969**, *8*, 604



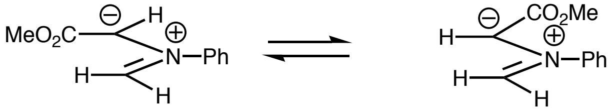
Relative Orientation of Reaction Partners

DeShong, *JOC* **1985**, 50, 2309; Tet. Lett. **1986**, *27*, 3979



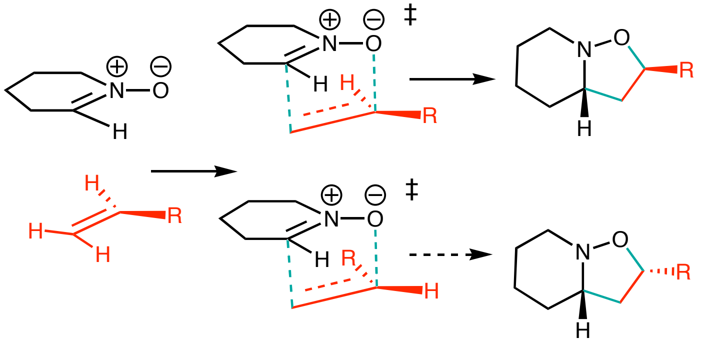
Ratio 98:02

The above analysis is clouded by the fact that the geometry of the 1, 3-dipole is not fixed.



Monosubstituted Olefins.

In the following study, 1,3-dipole isomerism is not an issue

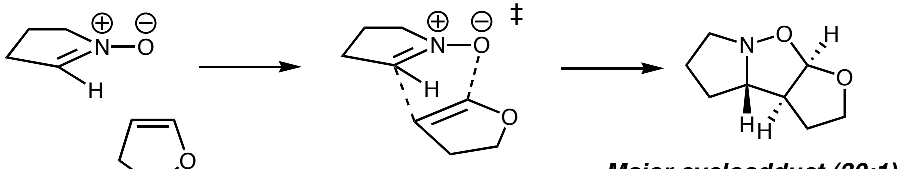


Ph	Me	CO_2Me
78%	100%	82%
22%	0%	18%

Diastereoselection appears to be dictated by steric effects

Tufariello, *Accounts. Chem. Res.* **1979**, *12*, 396-1403

Cis Disubstituted Olefins.



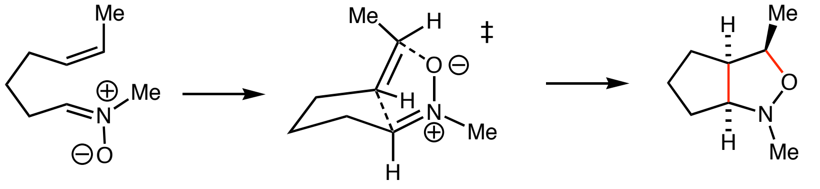
Major cycloadduct (30:1)

The preceding trend appears to be reinforced by cis disubstitution

I. Washita et al, *Chem lett* **1979**, 1337

Intramolecular Reaction Variants

N. LeBel et al, *JACS* **1964**, *86*, 3759

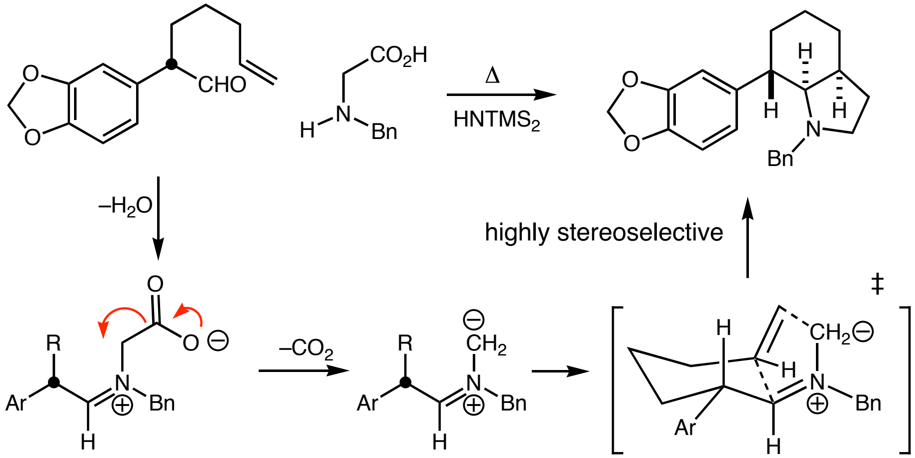


Orientation probably driven by ring strain as in Oppolzer case (previous page)

"highly diastereoselective"

Intramolecular Reaction Variants

P. Confalone et al, Tet. Lett. **1984**, *25*, 4613



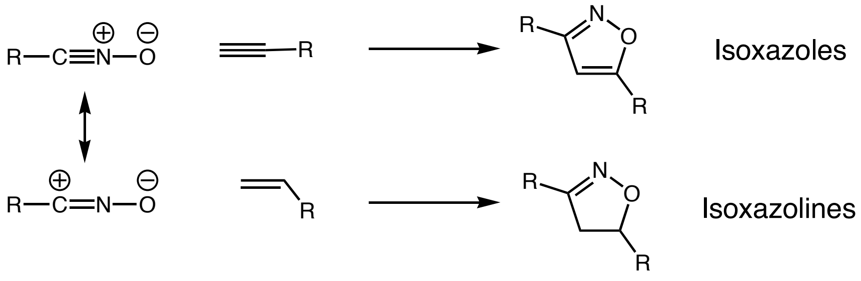
Conclusions on Reaction Diastereoselection

In general reaction diastereoselection appears to be dictated by steric and torsional rather than electronic factors

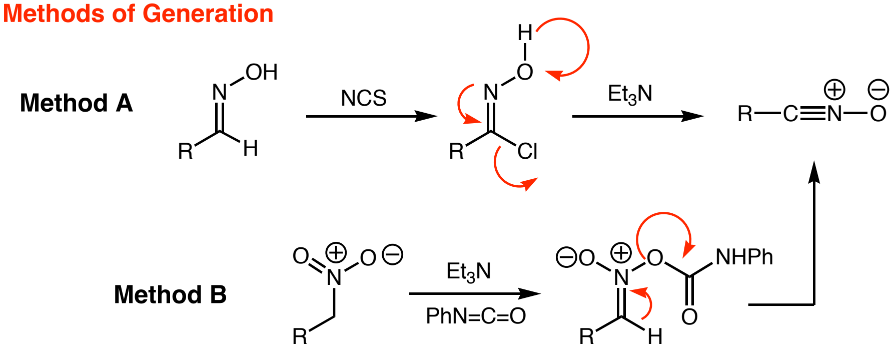
Dipolar Cycloaddition Reactions: Nitrile Oxide Cycloadditions

The Basic Reactions

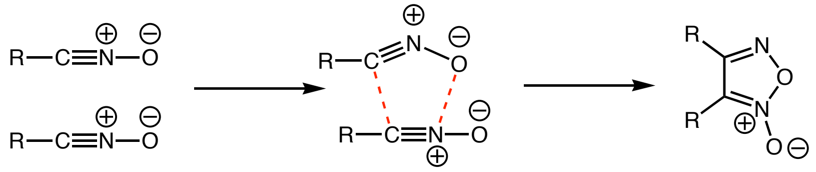
Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley, **1984,** Vol 1, Chapter 3



Methods of Generation



Stability Nitrile oxides are usually prepared in the presence of the olefin or acetylene acceptor. These intermediates are generally unstable and will dimerize if not given an alternative reaction course

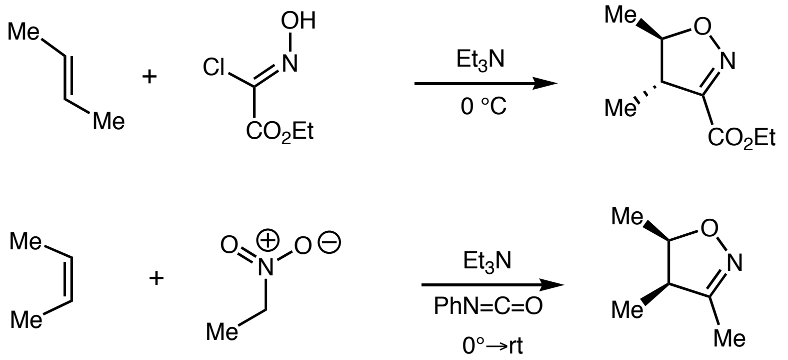


Regioselectivity Nitrile oxide cycloadditions with olefins and acetylenes are usually quite regioselective and in the direction as illustrated above.

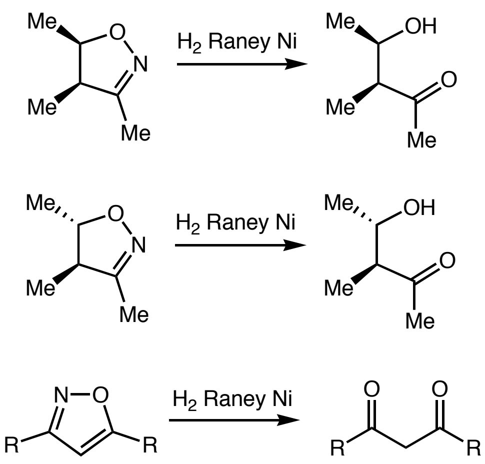
DeShong, *JOC* **1985**, 50, 2309; Tet. Lett. **1986**, *27*, 3979

Reactions with olefins are stereospecific

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.Chapter 6, pp 269–298



Oxazoline Cleavage



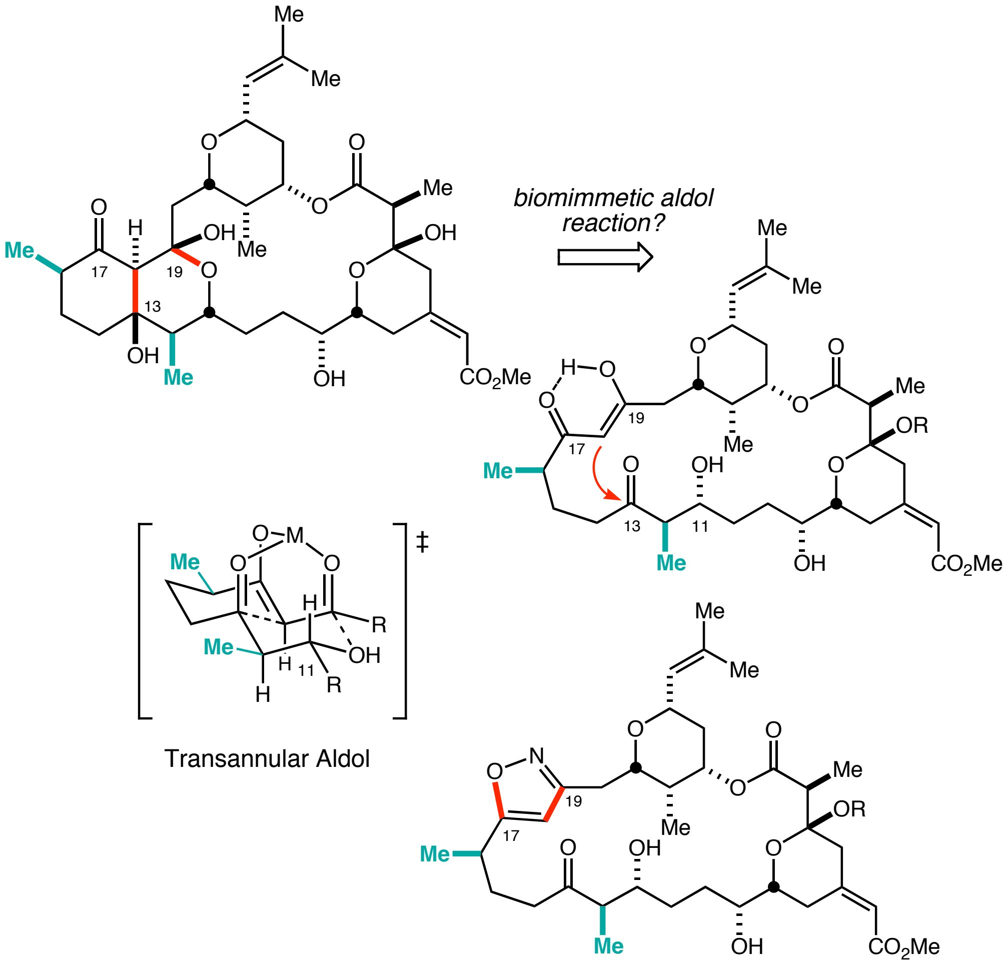
Non-aldol approach to aldol adducts

Non-aldol approach to 1,3-dicarbonyls

Preferred method for reducing oxazoles and oxazolines:
Nittta et al, *Chem. Comm.* **1982**, 877-878: $Mo(CO)_6$ MeCN

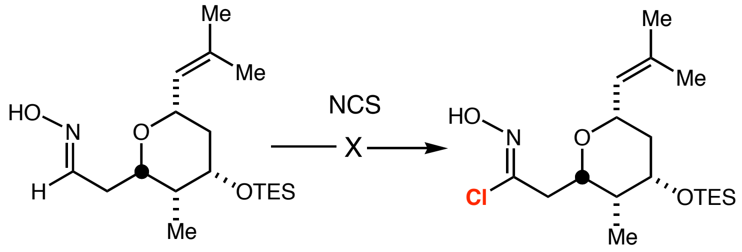
Nitrile Oxide Cycloadditions: Applications in Synthesis

Miyakolide Synthesis: with David Ripin & David Halstead, *JACS* **1999**, *121*, 6816-6826

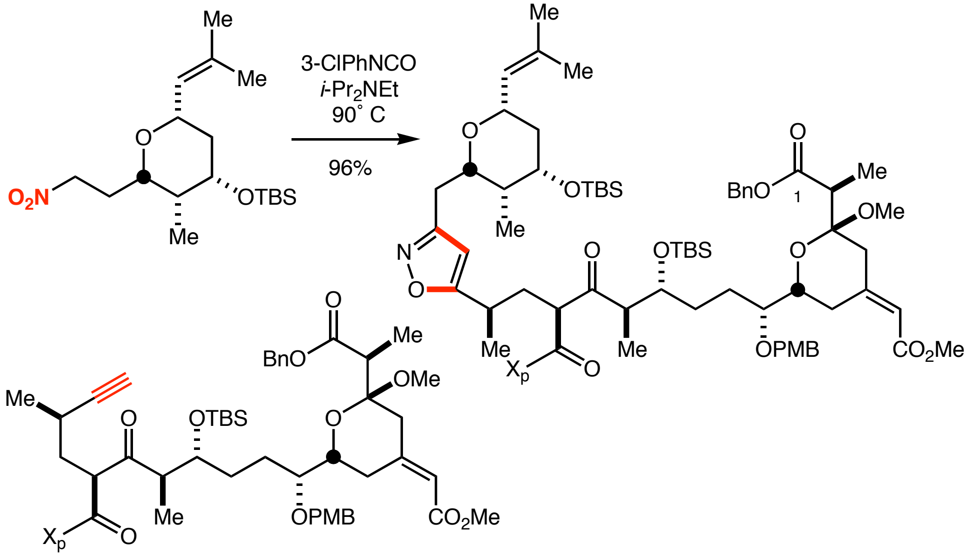


Transannular Aldol

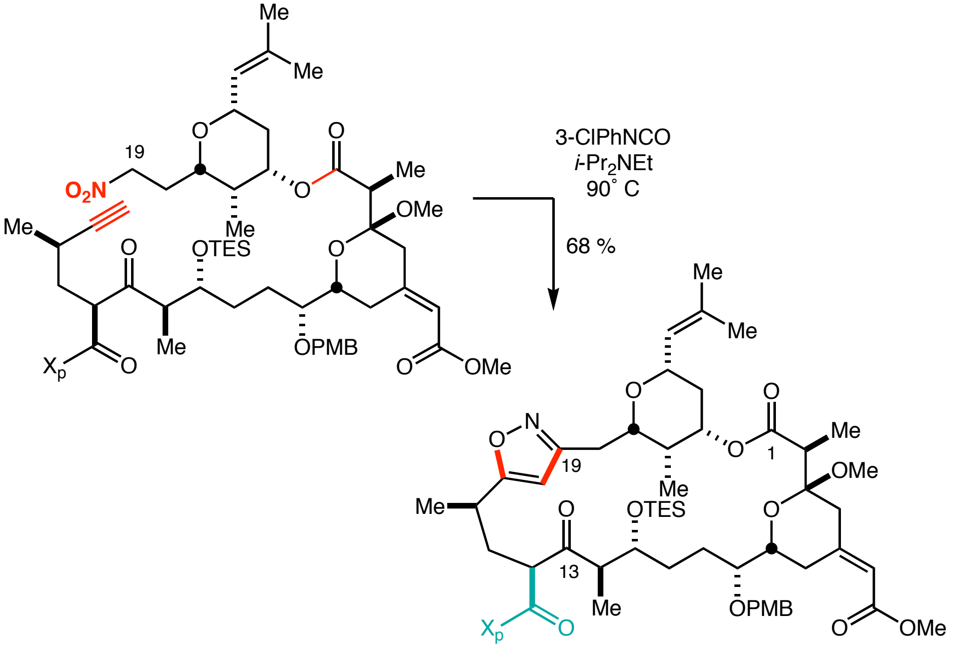
Competing olefin chlorination eliminated this approach to the nitrile oxide precursor



The Intermolecular Case



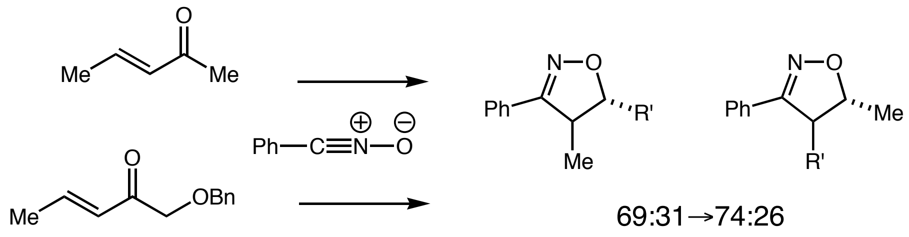
The Intramolecular Case



Nitrile Oxide Cycloadditions: Applications in Synthesis

Development of Directed Cycloadditions

Kanemasa at al, *JACS* **1994**, *116*, 2324-2339 **(electronic handout)**
Kanemasa at al, Metal-Assisted Stereocontrol of 1,3-Dipolar Cycloaddition Reactions
SynLett 2002, 1371-1387 **(electronic handout)**

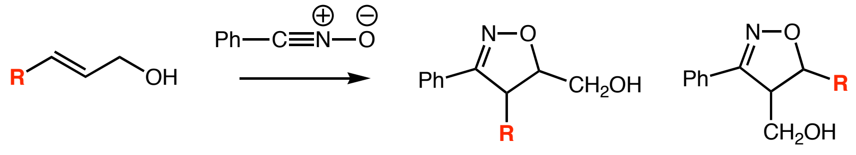


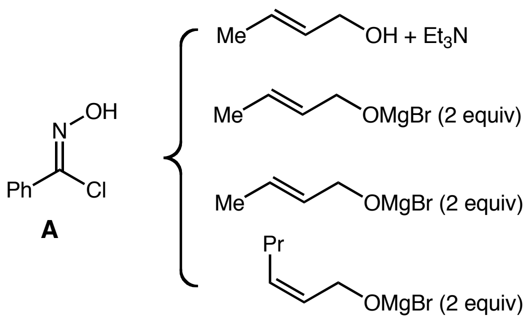
69:31→74:26

conditions; no cat, ZnI_2, $Ti(OiPr)_4$

While lewis acid activation is known, no change in regiochemistry was noted under above connditions

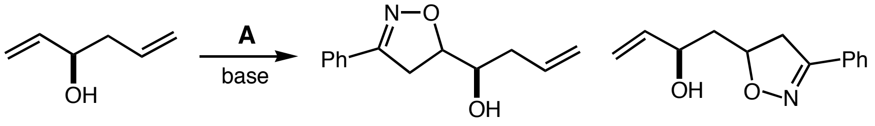
Magnesium alkoxides found to effect regiochemical control





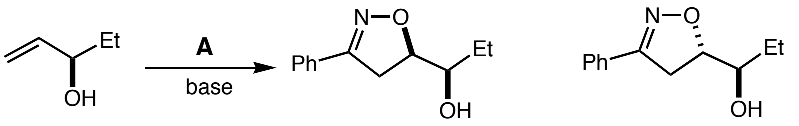
A

OH + Et_3N	46:54	82%
OMgBr (2 equiv)	>99:1	66%
OMgBr (2 equiv)	>99:1	68%
OMgBr (2 equiv)	98:2	73%

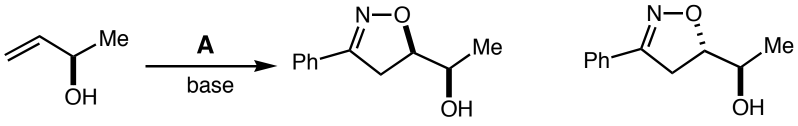


Et_3N	**67:33**
EtMgBr	**100:0**

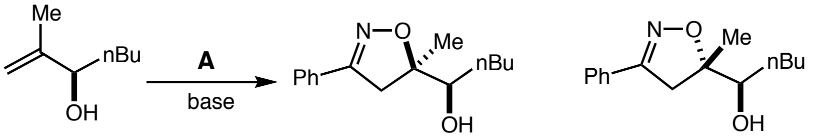
Reaction Diastereoselectivities



Et_3N	**67:33**	**60%**
EtMgBr	**95:5**	**75%**

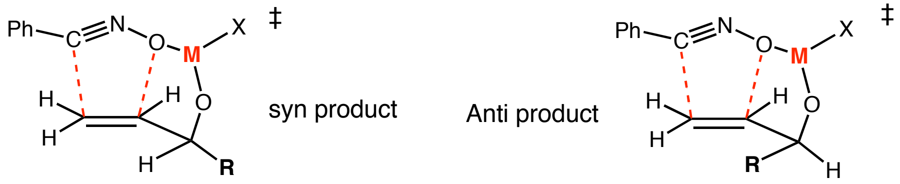


Et_3N	**61:39**	**60%**
EtMgBr	**96:4**	**75%**

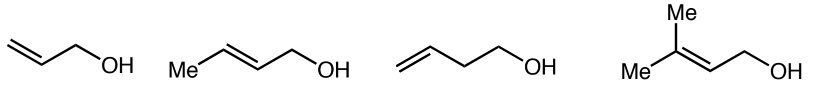


Et_3N	**60:40**	—
EtMgBr	**96:4**	**85%**

Stereochemical Rationale



Rate acceleratons

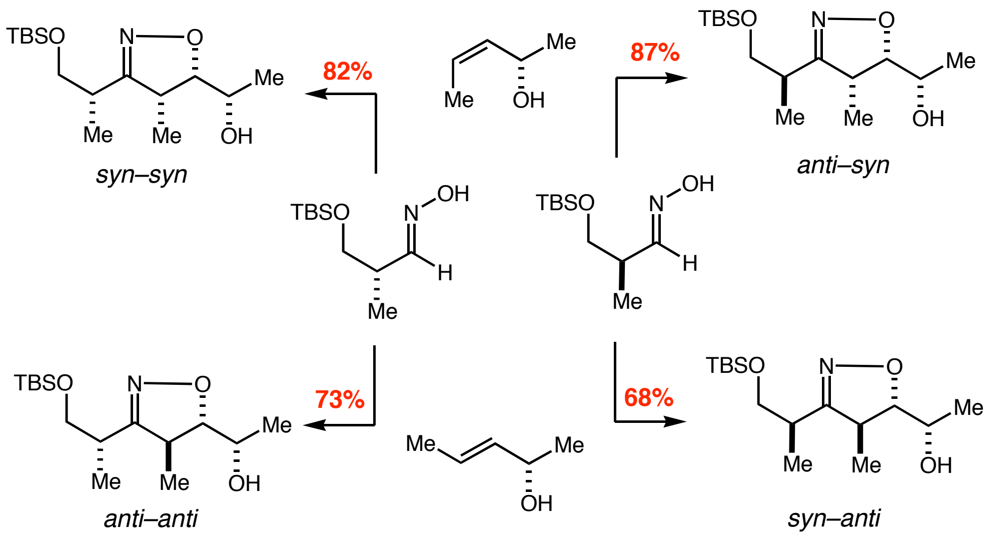


2030 6900 490 16,000

Nitrile Oxide Cycloadditions: Applications in Synthesis

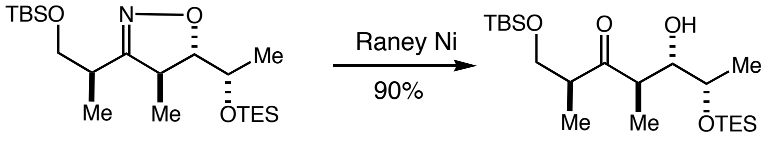
Applications in Polypropionate Synthesis

Carreira at al, *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085



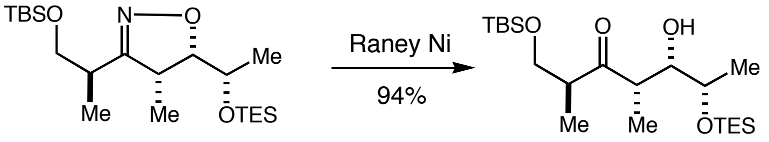
a, Oxime Chlorination: t-BuOCl; b, 3 Equiv EtMgBr, room temp, 12 h

Oxazoline Reduction



syn–anti

Lit Conditions: Curran, *JACS* **1983**, *105*, 5826; *JOC* **1984**, *49*, 3474



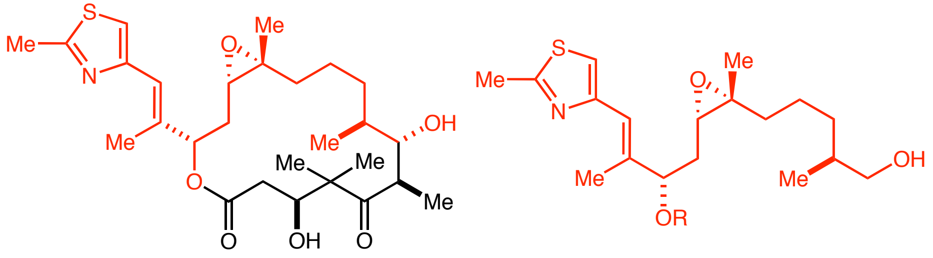
anti–syn

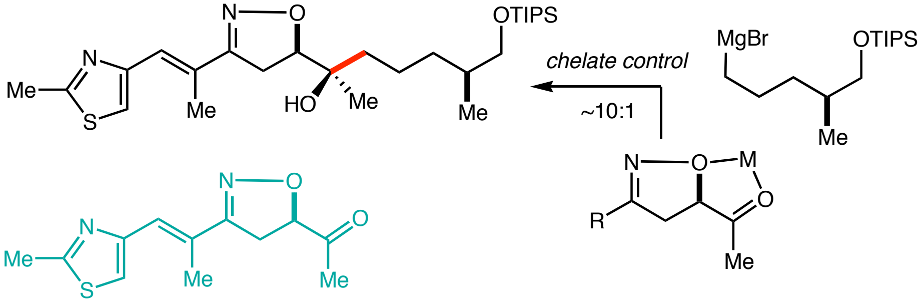
See also, Carreira et al. *Org. Lett.* **2004**, *6,* 2485-2488

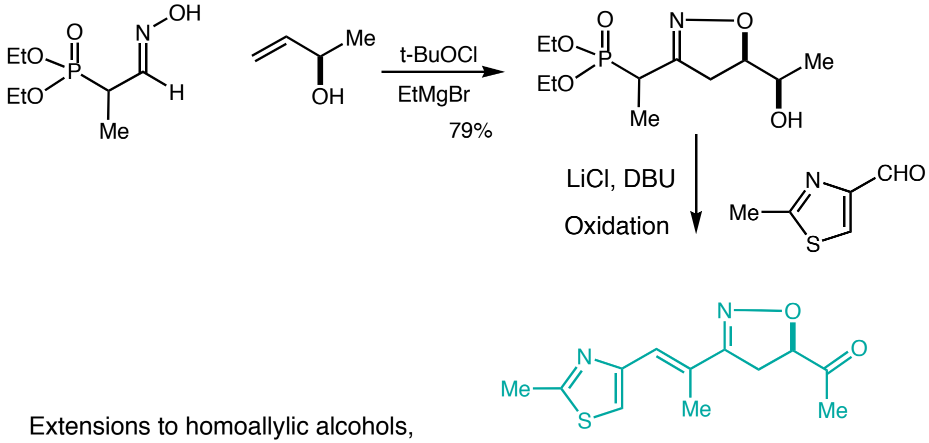
Applications to the Synthesis of Epothilones A, B

Carreira & Bode *JACS* **2001**, *123*, 2082–2085

Epothilone A: R = H
Epothilone B: R = Me







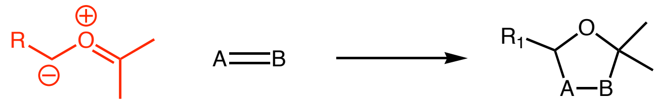
Extensions to homoallylic alcohols,
Carreira et al. *Org. Lett.* **2005**, *7,* 2011-2014

Carbonyl Ylides: Introduction

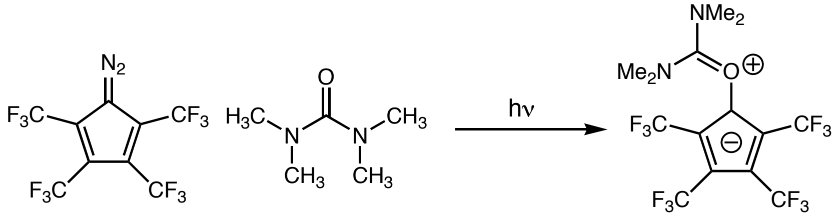
The Basic Reactions

Reviews - Ylides

Padwa, A.; Hornbuckle, S. F. *Chem. Rev*. **1991**, *91*, 263-309.
Padwa, A.; Krumpe, K. E. *Tetrahedron*. **1992**, *48*, 5385-5483.
Padwa, A. *Acc. Chem. Res*. **1991**, *24*, 22-28.

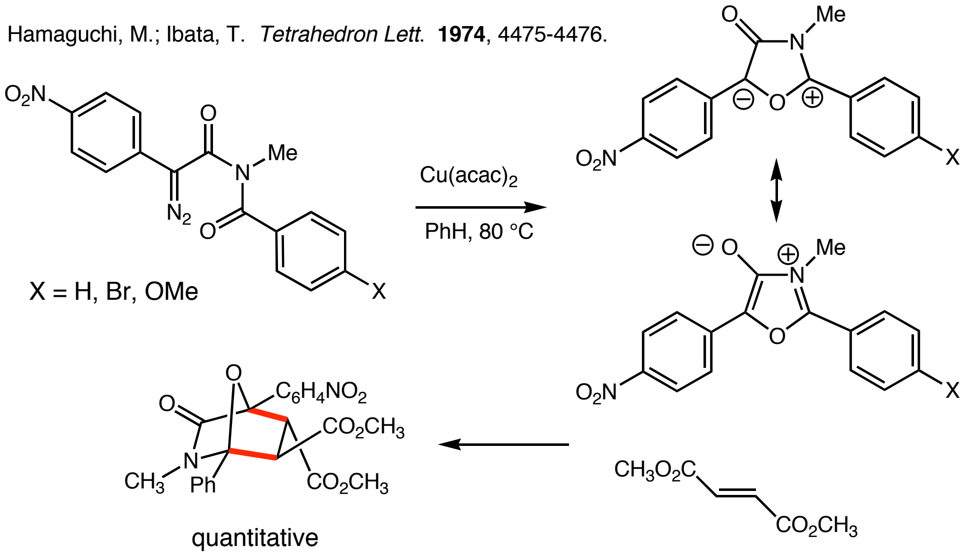


Stabilized (Isolable) Carbonyl Ylides



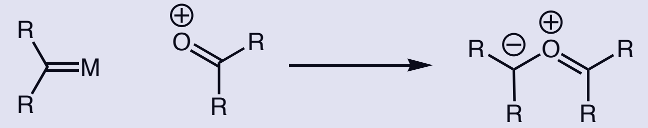
Arduengo, A. J., III; Janulis, E. P., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 5929-5930

Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475-4476.

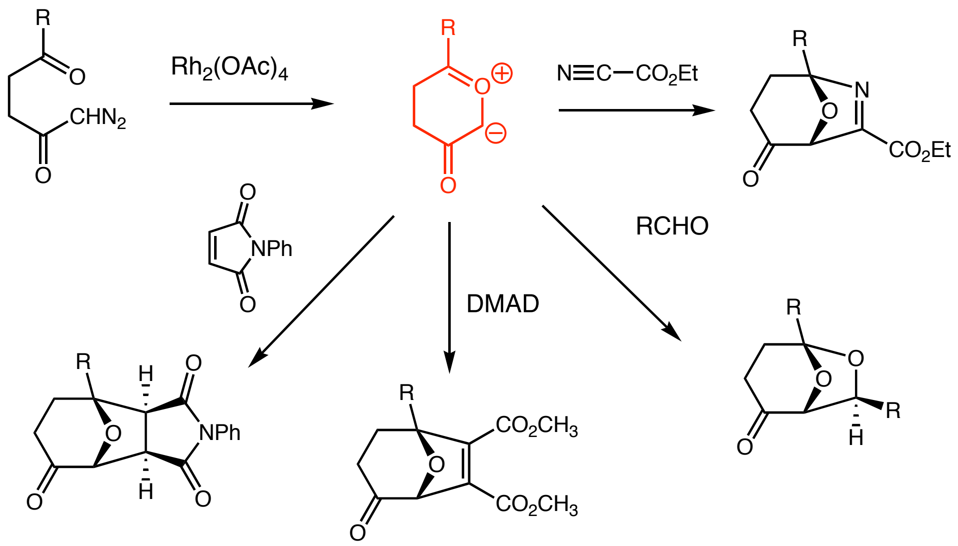


Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 499-502.

Carbenes Plus Carbonyl Groups

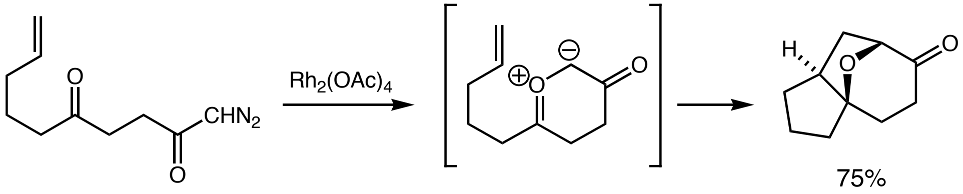


Tandem Intramolecular Cyclization–Intermolecular Cycloaddition



Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817-824.

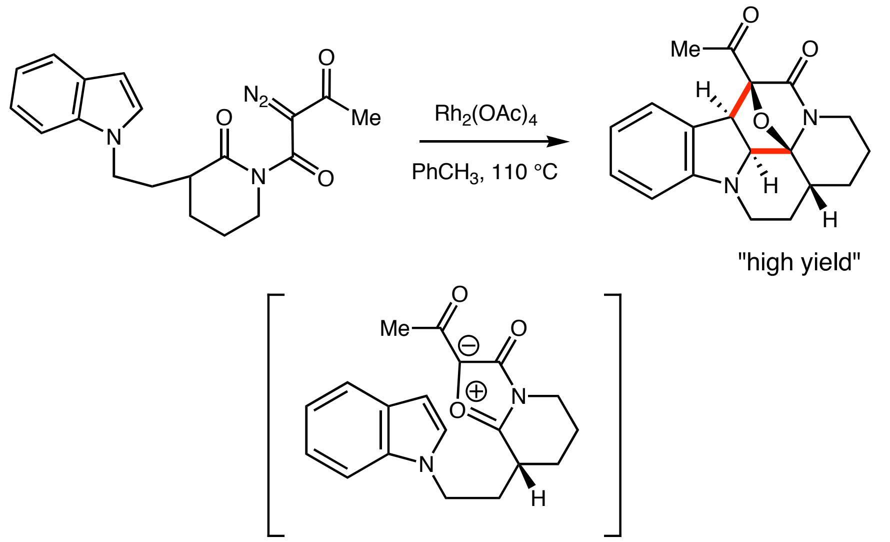
Intramolecular Variants



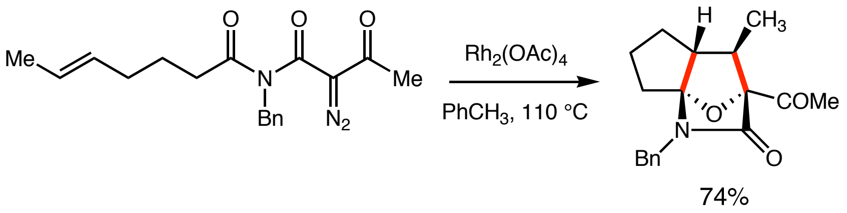
Can make 5-7 membered rings

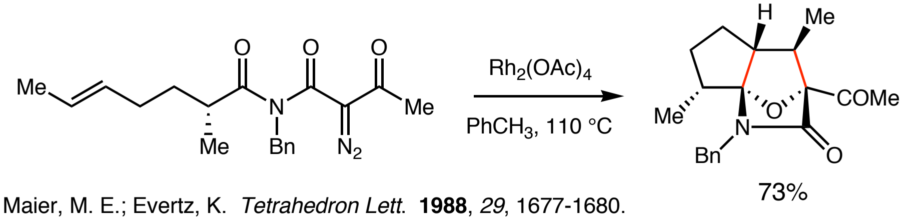
Carbonyl Ylides: Introduction

Carbonyl Ylide Cycloadditions of Diazoimides



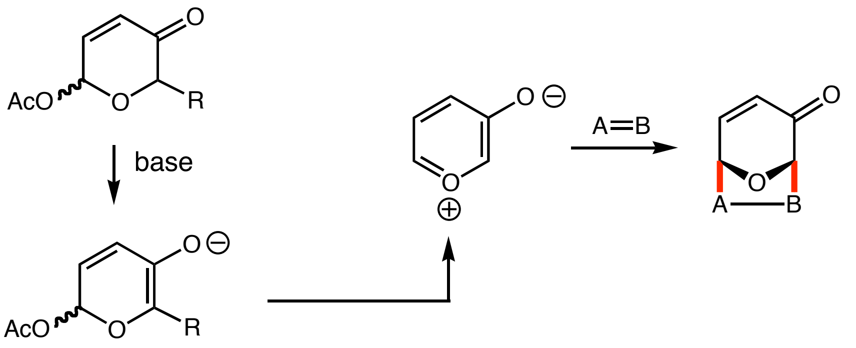
Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731-4734.

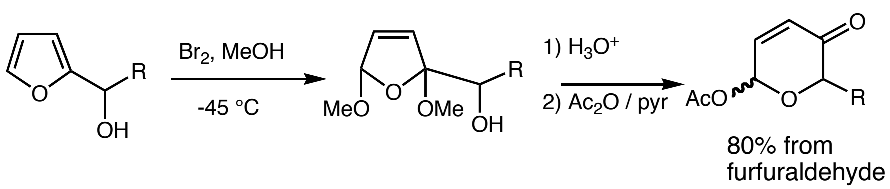


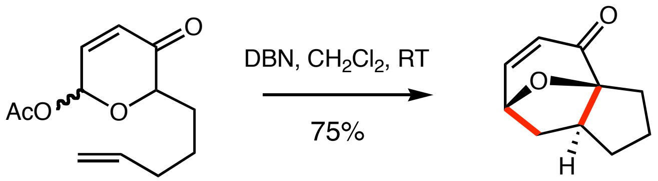


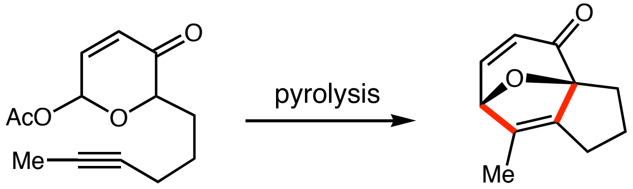
Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677-1680.

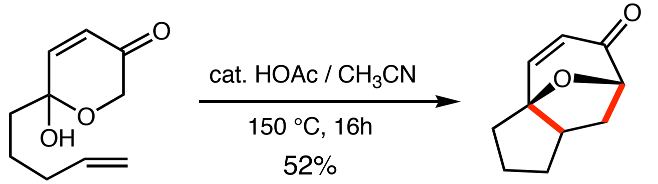
Cycloadditions with Oxidopyrylium Ylides











Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1056-1057

Total Synthesis of (–)-Colchicine via a Rh-Triggered Cycloaddition Cascade

Timm Graening, Virginie Bette, Jörg Neudörfl, Johann Lex, and Hans-Günther Schmalz*

Universität zu Köln, Greinstrasse 4, D-50939 Köln, Germany

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Received June 6, 2005

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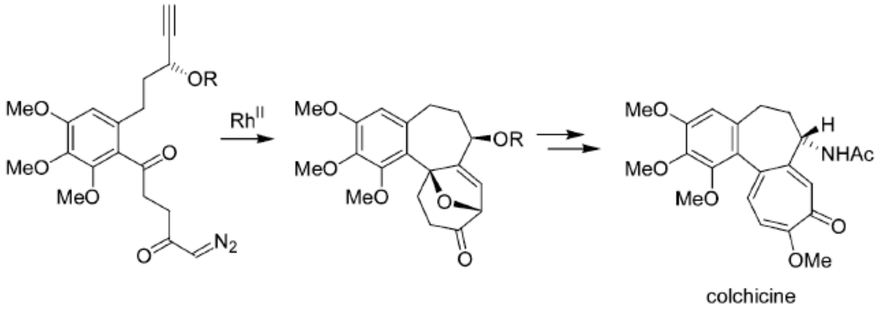
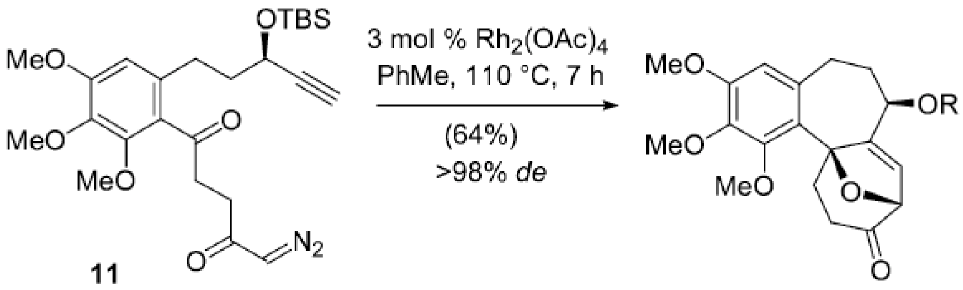
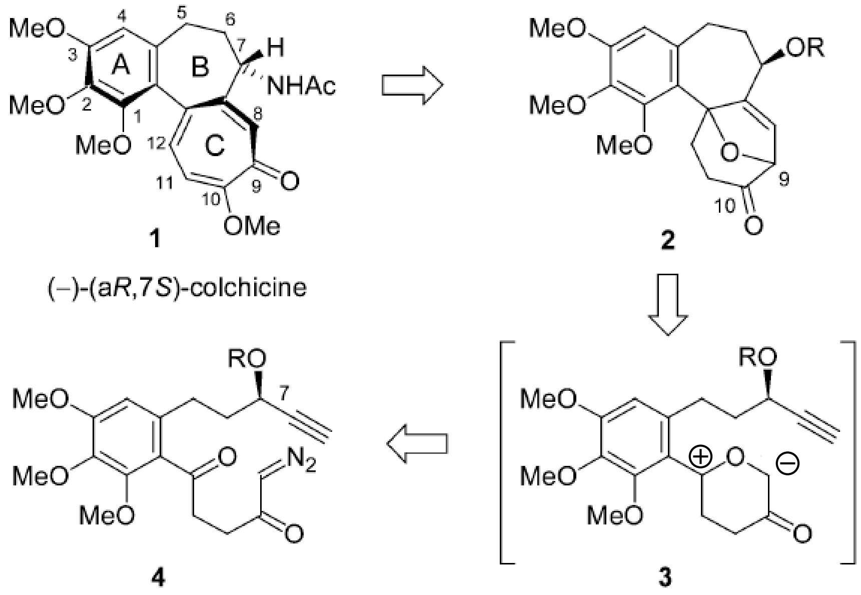
2005
Vol. 7, No. 20
4317–4320

Abstract

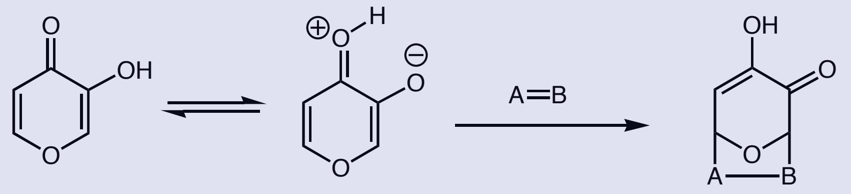


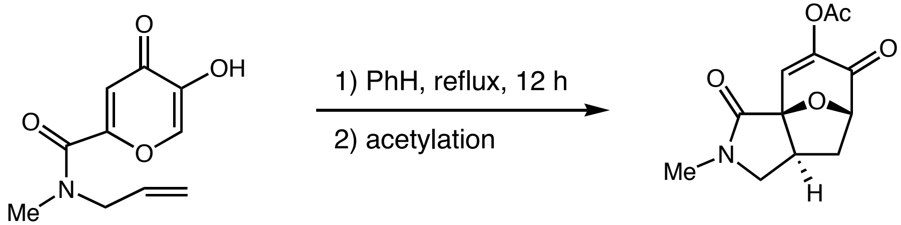


Scheme 1. Retrosynthetic Analysis



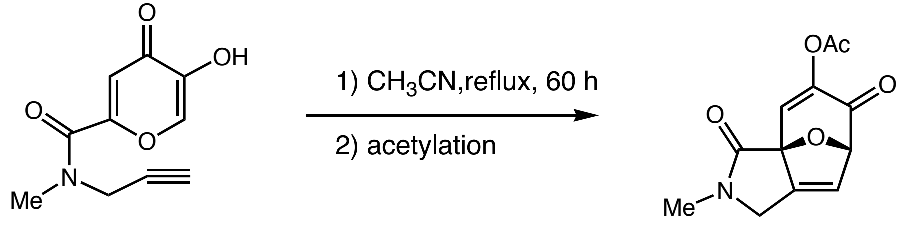
Cyclizations with 5-Hydroxy-4-Pyrones




1) PhH, reflux, 12 h

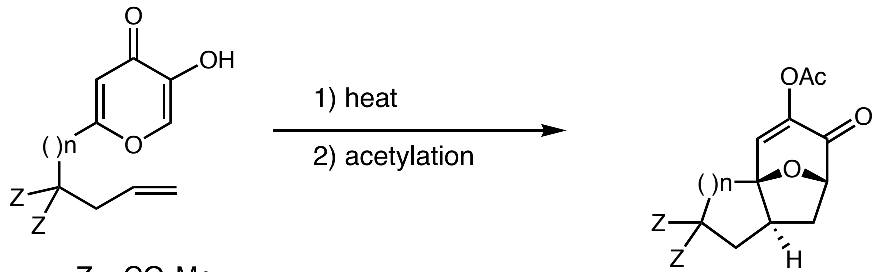
2) acetylation

55%


1) CH_3CN,reflux, 60 h

2) acetylation

42%


1) heat

2) acetylation

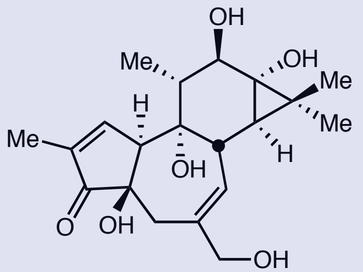
Z = CO_2Me

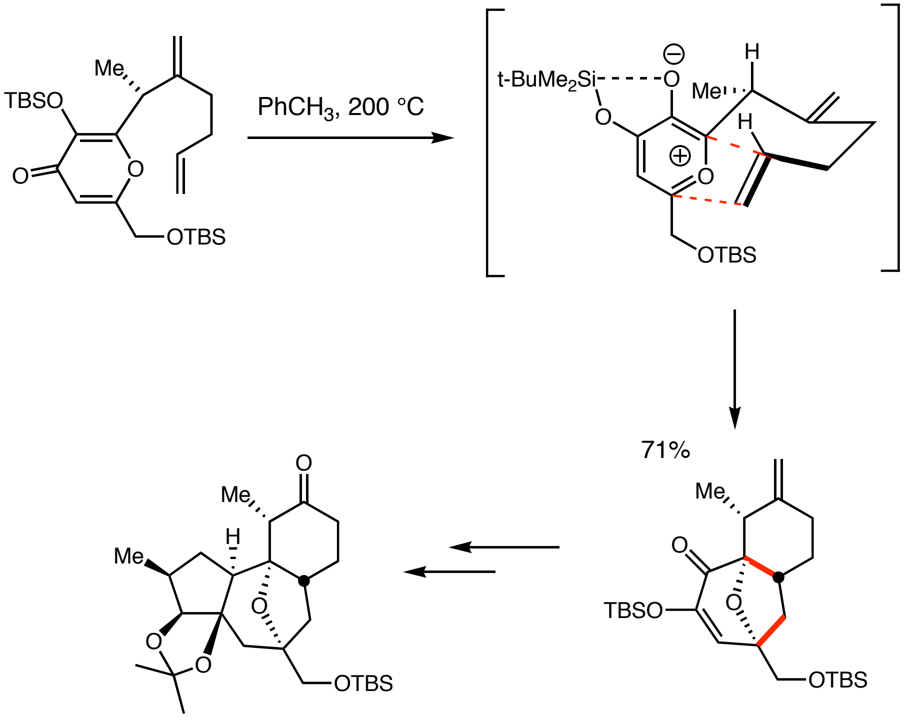
n = 1 : 70%

n = 2 : 65%

Garst, M. E.; McBride, B. J.; Douglass, J. G. III. *Tetrahedron Lett.* **1983**, *24,* 1675-1678.

Phorbol: The Hydroxypyrone Approach


Phorbol


$PhCH_3$, 200 °C

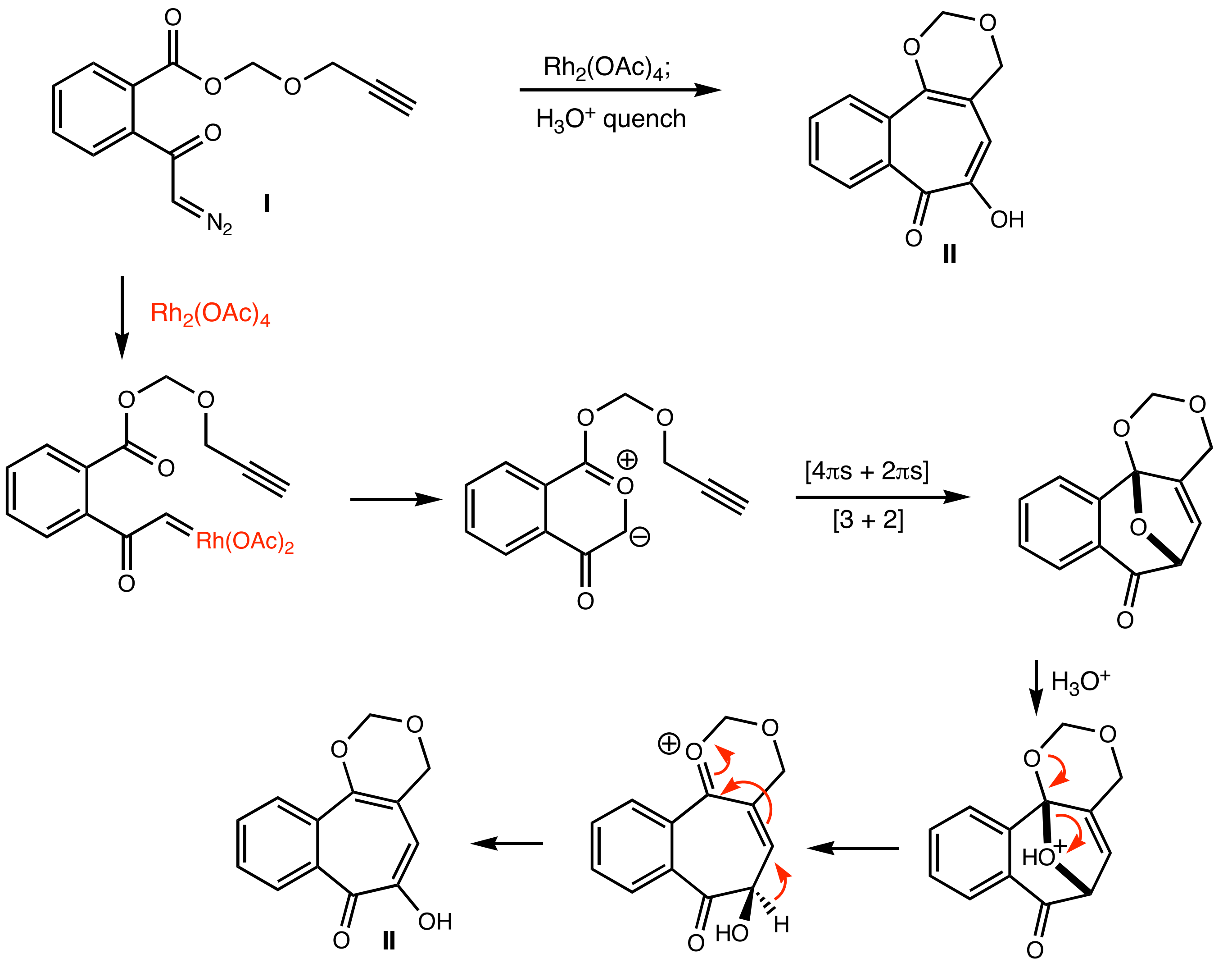
71%

Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956-4958

Database Problem 189

This question is taken from recent work reported by Jack Baldwin (*Org. Lett.*, **1999**, 1933 and 1937).

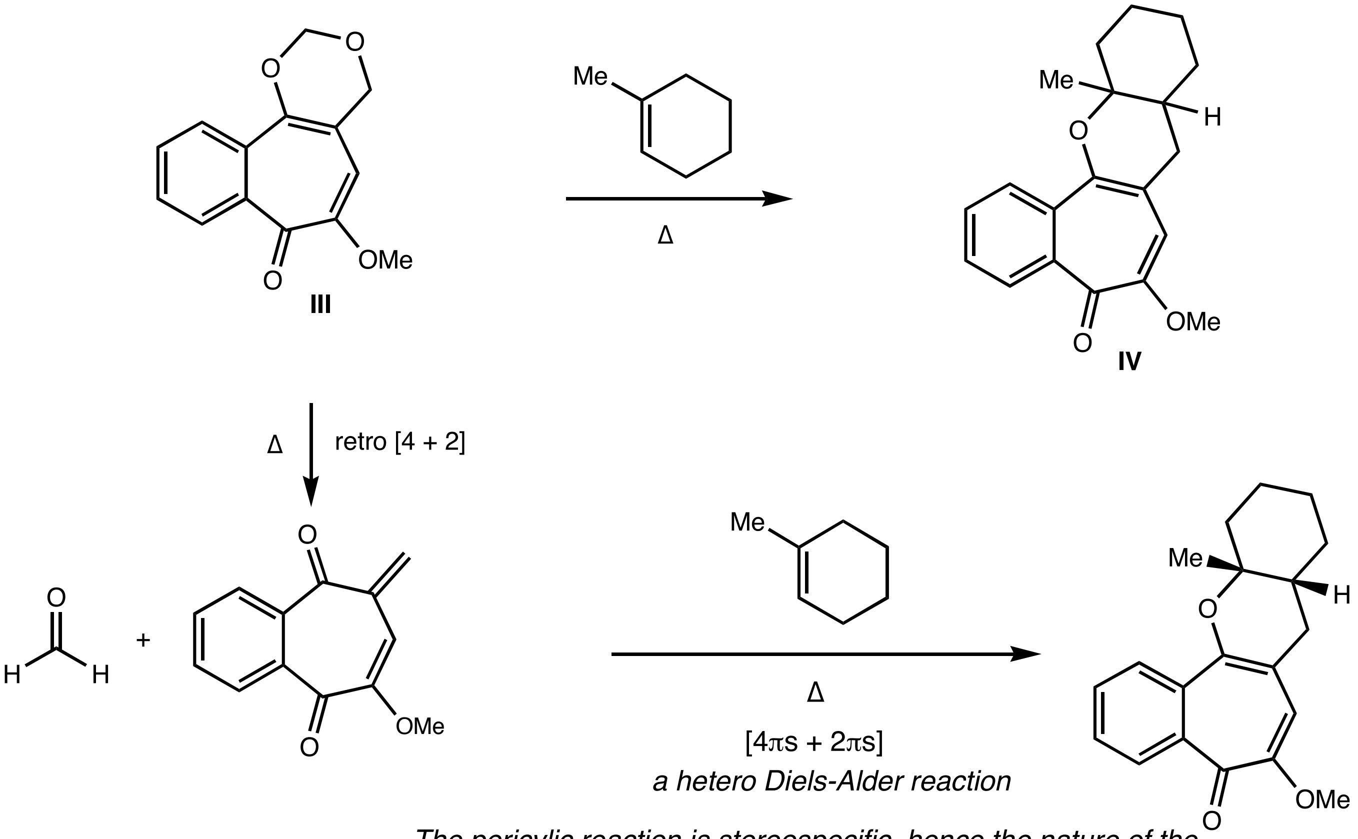
Part A. Provide a mechanism for the conversion of **I** to **II**.



Database Problem 189

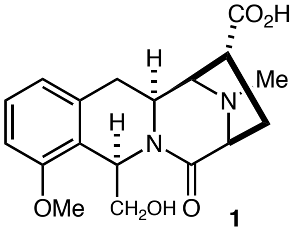
This question is taken from recent work reported by Jack Baldwin (*Org. Lett.*, **1999**, 1933 and 1937).

Part B. Compound **II** is protected as its methyl ether **III** and then transformed to **IV**. Provide a mechanism for the conversion of **III** to **IV**. Predict the relative stereochemistry at the starred (*) carbon atoms.

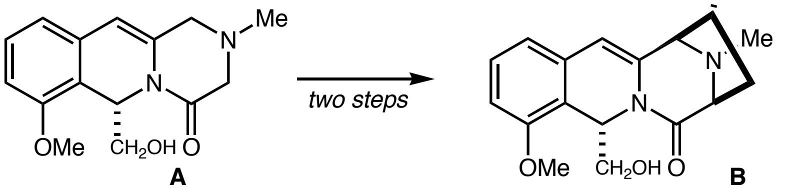


The pericylic reaction is stereospecific, hence the nature of the starting olefin defines the geometry observed in the product.

Problem 53. Williams recently reported an approach to the synthesis of quinocarcinamide (**1**) (*J. Org. Chem.* **1995**, *60*, 6791). The pivotal process that establishes the tetracyclic nucleus is the two-step transformation shown below (eq 1).



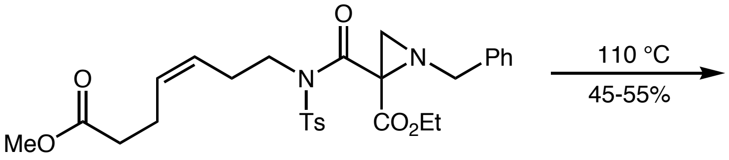
1



(1)

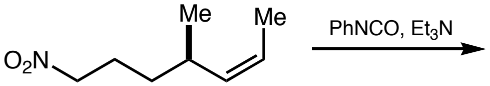
Devise a strategy for transforming A into B and clearly illustrate your answer in the space below. Full credit will be awarded to concise answers.

Problem 55. The following transformation was recently reported by Heathcock during studies directed toward the synthesis of sarain A
(*Tetrahedron Lett.* **1995**, *6*, 2381). From your knowledge of the functionality present in the starting material, deduce the structure (including stereochemistry) of the reaction product which has the same molecular weight as the starting material. Hint. the 1H NMR spectrum of the product reveals that the olefinic resonances have disappeared.



product structure

Problem 65. The following stereoselective nitrile oxide cycloaddition has been reported by Kozikowski (*Tetrahedron Lett.* **1982**, *23*, 2081;
J. Org. Chem. **1984**, 49, 2762). Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.

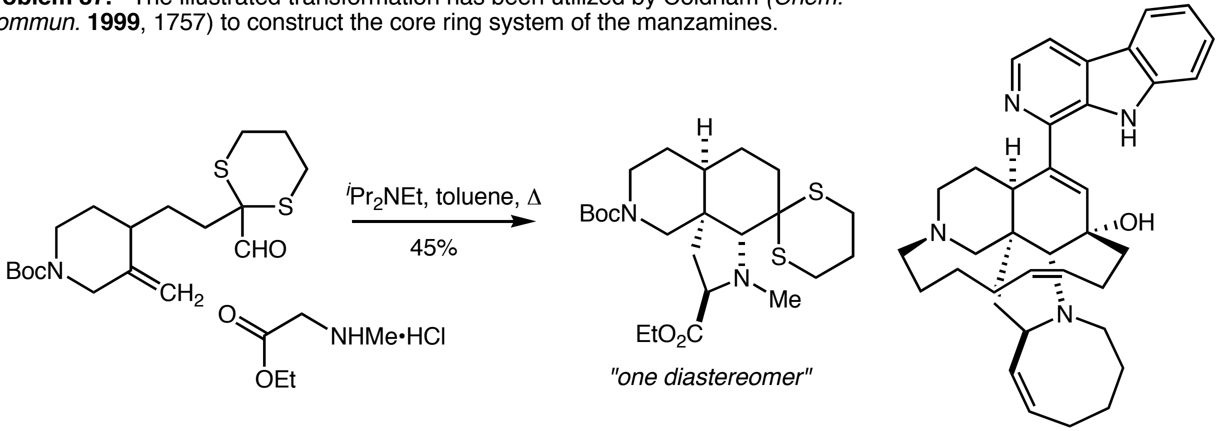


The product ?
Stereoselection: 16/1

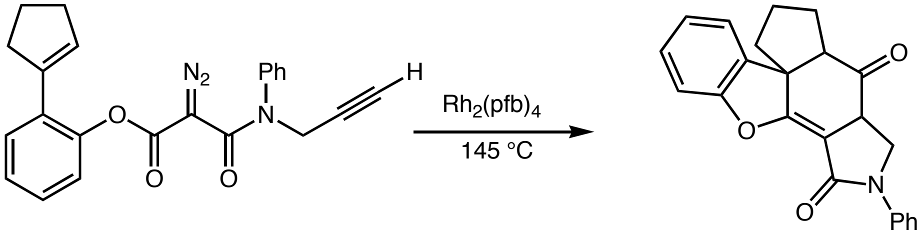
product structure

Carbonyl Ylides: Problems

Problem 87. The illustrated transformation has been utilized by Coldham *(Chem. Commun.* **1999**, 1757) to construct the core ring system of the manzamines.

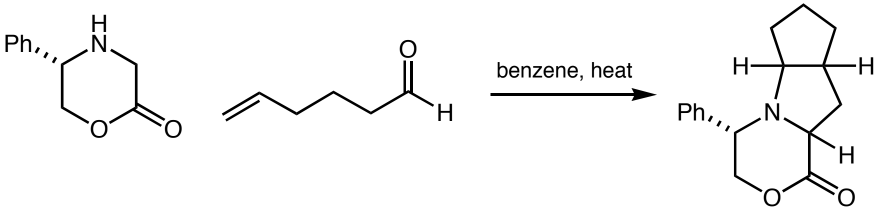


Problem 90. Padwa and co-workers recently disclosed the illustrated multistep polycyclisation as a possible route to the strychnine core (*Org. Lett.* **2001**, ASAP)



In the space below, provide a mechanism for the indicated transformation. *Hint: The management suggests that a carefull bidirectional analysis might help you to arrive at a sollution of this question.*

Problem 136. A recent paper by Harwood and Park highlights the rapidity which whch one may assemble complex architecture in a single chemical operation (*Tetrahedron Lett.* **1999**, *40*, 2907 and earlier cited references). The transformation in question is illustrated below. You are asked to address two aspects of this transformation.

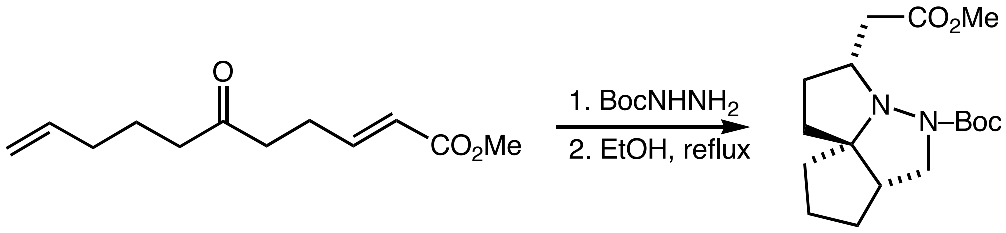


Part A. Provide a concise mechanism for the indicated transformation. For now, ignore the stereochemical aspects of the reaction.

Part B. Predict the stereochemical outcome of the reaction at the three new stereocenters, and provide a three-dimensional drawing of the transition state wherein these centers are produced.

Carbonyl Ylides: Problems

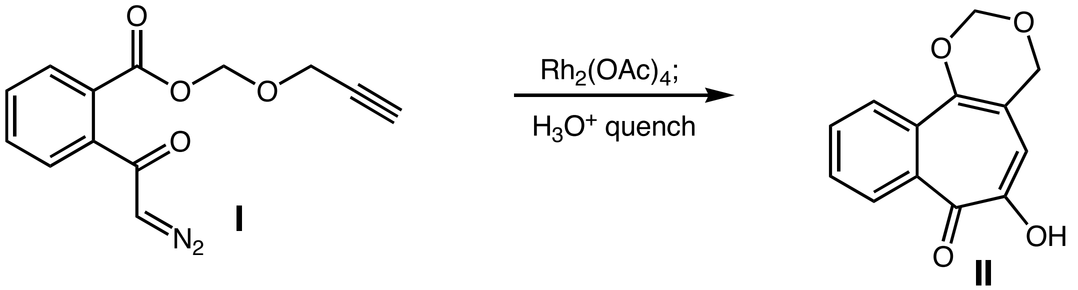
Problem 171. A recent paper by Dolle (*Tetrahedron Lett.* **1999**, *40*, 2907) highlights the rapidity which whch one may assemmble complex architecture in a single chemical operation. The transformation in question is illustrated below.



75% yield, one diastereomer

Provide a concise mechanism for the indicated transformation. In that step where the complex stereochemical relationships are established, a carefully rendered three dimensional illustration is requested.

Problem 189. This question is taken from recent work reported by Jack Baldwin (*Org. Lett.*, **1999**, 1933 and 1937). Provide a mechanism for the conversion of **I** to **II**.



http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 20

Acid-Base Properties of Organic Molecules

- Bronsted Acidity Concepts in the Activation of Organic Structures
- Medium Effects on Bronsted Acidity
- Substituent & Hybridization Effects on Bronsted Acidity
- Kinetic & Thermodynamic Acidity of Ketones
- Kinetic Acidity: Carbon vs. Oxygen Acids
- Tabulation of Acid Dissociation Constants in DMSO

Reading Assignment for this Lecture:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

"Equilibrium acidities in DMSO Solution", F. G. Bordwell.
Acc. Chem. Res. **1988**, *21*, 456-463. (**handout**)

D. A. Evans

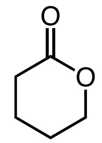
Friday
November 3, 2006

Here is a website containing Bordwell pKa data

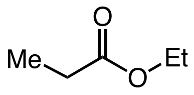
http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

Problems of the Day:

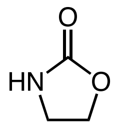
Explain why **1** and **3** are ~4 pKa units more acidic than their acyclic counterparts **2** and **4**. (*J. Org. Chem.* **1994**, *59*, 6456)



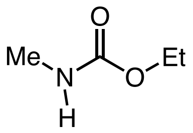
1



2



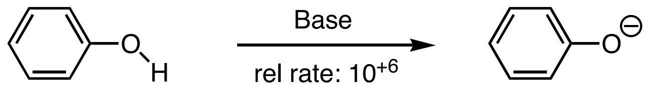
3



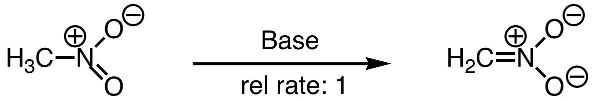
4

The thermodynamic acidities of phenol and nitromethane are both ~10; however, using a common base, phenol is deprotonated 10^{+6} times as fast. Rationalize

pKa(H_2O)
~10

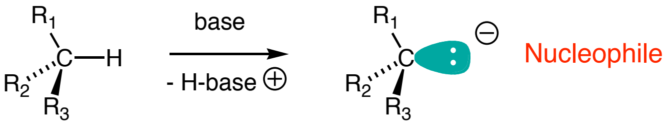


pKa(H_2O)
~10



Activation of Organic Molecules

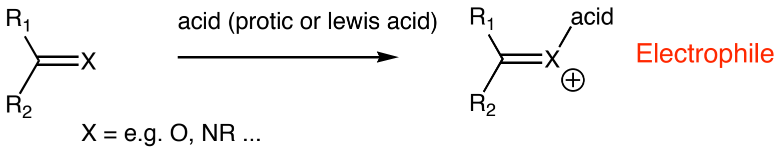
Base Activation



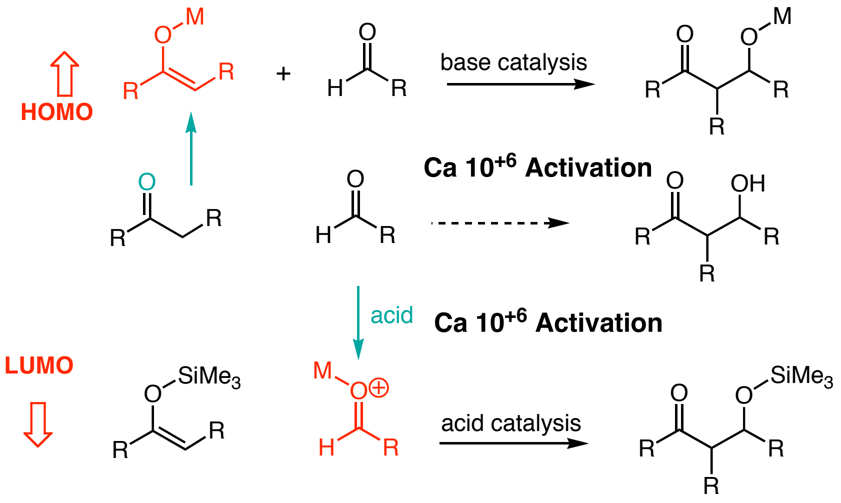
pK$_a$, describes quantitatively a molecule's propensity to act as an acid, i.e. to release a proton.

- Medium effects
- Structural effects (influence of substituents R_1)

Acid Activation



The Aldol Example



Definition of Ka

Let H–X be any Bronsted acid. In water ionization takes place:

$$\text{H–X} + \text{HOH} \rightleftharpoons \text{H}_3\text{O}^+ + \text{X–}$$

where $K_{eq} = \dfrac{[\text{H}_3\text{O}^+]\,[\text{X}^-]}{[\text{H–X}]\,[\text{HOH}]}$ **where [HOH] = 55.5 mol L^{-1}** (A)

Since [HOH] is, for all practical purposes, a constant value, the acid dissociation constant K$_a$ is defined without regard to this entity. e.g.

$$\text{H–X} \rightleftharpoons \text{H}^+ + \text{X–} \qquad \text{where } \text{H}^+ = \text{H}_3\text{O}^+$$

Hence $$\mathbf{K_a = \frac{[H^+]\,[X^-]}{[H–X]}} \qquad \textbf{(B)}$$

> From the above definitions, K$_a$ is related to K$_{eq}$ by the relation:
>
> $$\mathbf{K_a(H–X) = 55.5\ K_{eq}(H–X)} \qquad \textbf{(C)}$$

Autoionization of water

$$\text{HOH} + \text{HOH} \rightleftharpoons \text{H}_3\text{O}^+ + \text{HO}^-$$

$K_{eq} = 3.3 \times 10^{-18}$

From Eq C: $K_a = 55.5\ K_{eq} = 55.5(3.3 \times 10^{-18})$

Hence $K_a = 1.8 \times 10^{-16}$

Since pK$_a$ is defined in the following equation:

$\mathbf{pK_a = -\log_{10}[K_a]}$ The pK$_a$ of HOH is + 15.7

Keep in mind that the strongest base that can exist in water is HO$^-$.

Lets now calculate the acid dissociation constant for hydronium ion.

$$\text{H}_3\text{O}^+ + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{H}_2\text{O}$$

obviously: $K_{eq} = 1$

$K_a = [\text{HOH}] \times K_{eq}$ hence $K_a = 55.5$

$pK_a = -\log_{10} K_a = -1.7$

The strongest acid that can exist in water is H$_3$O$^+$.

Acidity Trends for Carbonyl & Related Compounds

The Gibbs Relationship

$$\Delta G^\circ = -RT \ln K$$

or

$$\Delta G^\circ = -2.3\,RT \log_{10} K$$

2.3 RT = 1.4

at T = 298 K

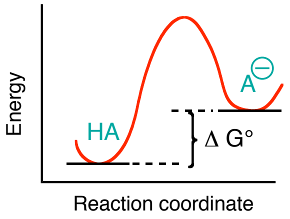
in kcal · mol^{-1}

$$\Delta G^\circ_{298} = -1.4 \log_{10} K_{eq}$$

$$\boxed{\Delta G^\circ_{298} = 1.4\, pK_{eq} \approx 1.4\, pK_a \qquad \text{with } pK = -\log_{10} K}$$

Hence, pK_a is proportional to the free energy change

K_{eq}	pK_{eq}	ΔG°
1	0	0
10	–1	–1.4
100	– 2	–2.8 kcal/mol

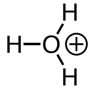
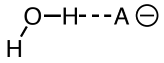
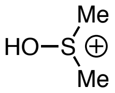


Medium Effects

Consider the ionization process:

$$H{-}A \;+\; \text{solvent} \;\rightleftharpoons\; A:^{-} \;+\; \text{solvent}(H^{+})$$

In the ionization of an acid in solution, the acid donates a proton to the medium. The more basic the medium, the larger the dissociation equilibrium. The ability of the medium to stabilize the conjugate base also plays an important role in the promotion of ionization. Let us consider two solvents, HOH and DMSO and the performance of these solvents in the ionization process.

	The Protonated Solvent	Conjug. Base Stabiliz.
Water		
DMSO		No H-bonding Capacity

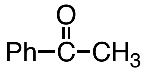
As shown above, although HOH can stabilize anions via H-bonding, DMSO cannot. Hence, a given acid will show a greater propensity to dissociate in HOH. As illustrated below the acidity constants of water in HOH, DMSO and in a vacuum dramatically reflect this trend.

Medium Effects on the pKa of HOH

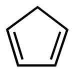
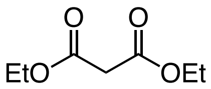
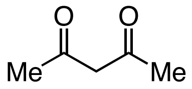
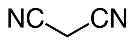
** The gas phase ionization of HOH is endothermic by 391 kcal/mol !!!

HOH pKa	Medium
15.7	HOH
31	DMSO
279 (est)**	Vacuum

Representative pKa Data

Substrate	DMSO	HOH	Δ pKa
HOH	31.2	15.7	15.5
HSH	14.7	7.0	7.7
MeOH	29.0	15.3	13.7
C_6H_5OH	18.0	9.9	8.1
$O_2N{-}CH_3$	17.2	10.0	7.2
 $Ph{-}C(=O){-}CH_3$	24.6	17	7.6

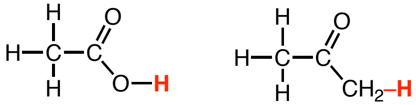
The change in pKa in going from water to DMSO is increasingly diminished as the conjugate base becomes resonance stabilized (Internal solvation!).

Substrate	DMSO	HOH	Δ pKa
	18.1	16.0	2.1
	16.4	13.3	3.1
	13.3	8.9	4.5
	11.1	11.2	0

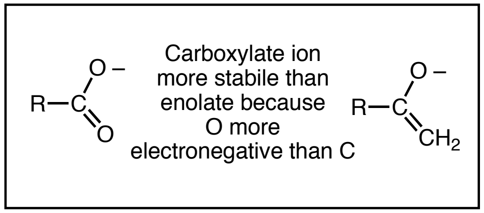
Acidity Trends for Carbonyl & Related Compounds

Substituent Effects

Electronegativity e.g. Compare Carboxylic Acids vs. Ketones



(H_2O)	$pK_A = 4.8$	$pK_A \approx 19$
(DMSO)	$pK_A = 12.3$	$pK_A \approx 26.5$



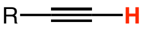
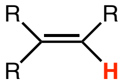
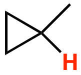
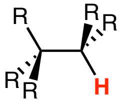
Carboxylate ion more stabile than enolate because O more electronegative than C

Hybridization - S-character of carbon hybridization

Remember:

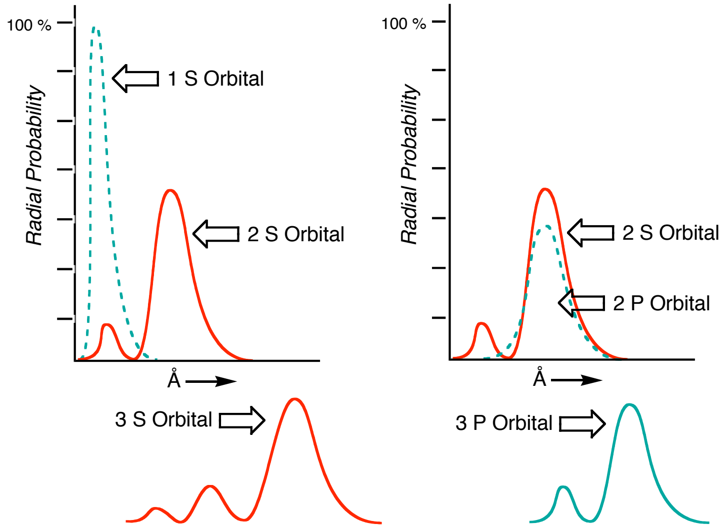
sp^3-orbitals	25% s-character
sp^2-orbitals	33% s-character
sp-orbitals	50% s-character

Carbon Acids

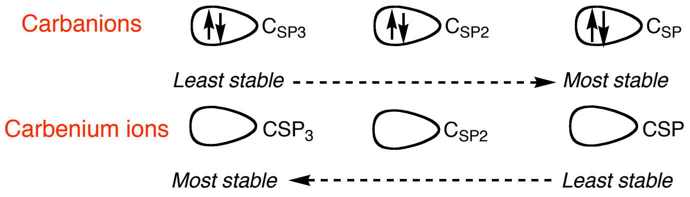
				
Hybridzation	sp	sp^2	$\approx sp^2$	sp^3
Bond Angle	180°	120°	≈ 120	109°
pK_a(DMSO)	23	≈ 44	≈ 39	≈ 60

Electrons in 2S states "see" a greater effective nuclear charge than electrons in 2P states.

This becomes apparent when the radial probability functions for S and P-states are examined: The radial probability functions for the hydrogen atom S & P states are shown below.



S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in s states see a higher nuclear charge. The above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital.

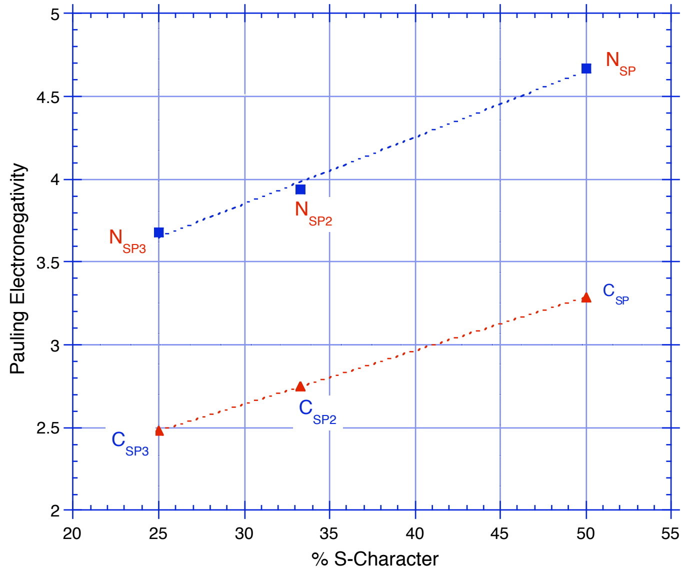


The above trends indicate that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

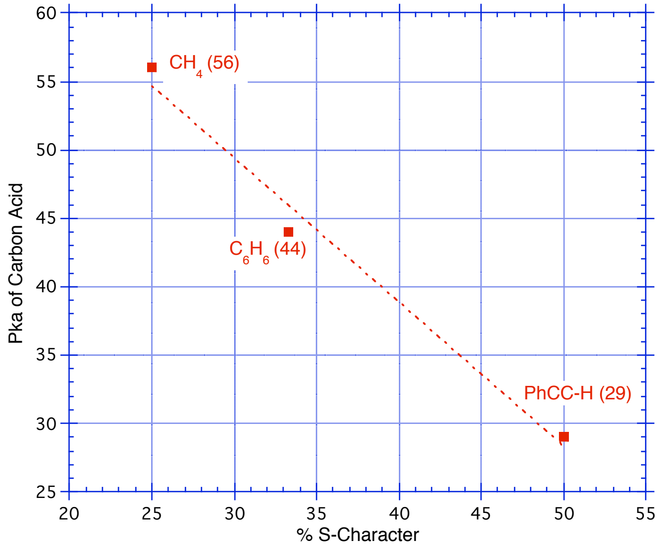
Acidity Trends for Carbonyl & Related Compounds

Hybridization vs Electronegativity

There is a linear relationship between %S character & Pauling electronegativity



There is a direct relationship between %S character & hydrocarbon acidity

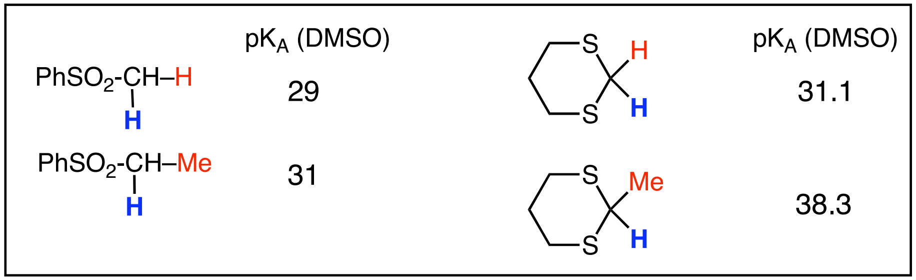


Substituent Effects

Alkyl Substituents on Localized Carbanions are Destabilizilng:

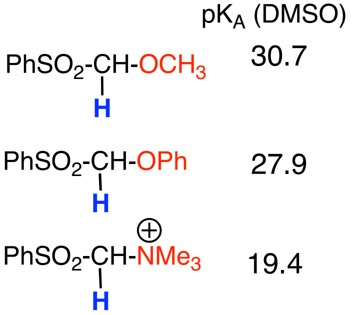
Steric hinderance of anion solvation

Compare: (*JACS* **1975**, *97*, 190)



	pK_A (DMSO)		pK_A (DMSO)
$PhSO_2\text{-}CH(H)\text{–}H$	29	1,3-dithiane (H, H)	31.1
$PhSO_2\text{-}CH(H)\text{–}Me$	31	2-Me-1,3-dithiane (Me, H)	38.3

Heteroatom-Substituents: - 1st row elements of periodic table



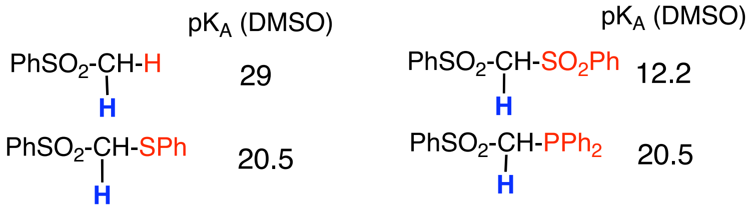
	pK_A (DMSO)
$PhSO_2\text{-}CH(H)\text{-}OCH_3$	30.7
$PhSO_2\text{-}CH(H)\text{-}OPh$	27.9
$PhSO_2\text{-}CH(H)\text{-}\overset{\oplus}{N}Me_3$	19.4

Inductive Stabilization versus Lone Pair Repulsion (-I vs +M -Effect) — for OCH₃ and OPh

Inductive Stabilization — for NMe₃

Heteroatom-Substituents: - 2nd row elements of periodic table

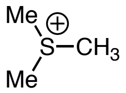
Strong carbanion stabilizing effect

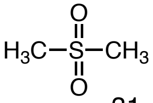


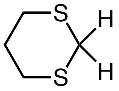
	pK_A (DMSO)		pK_A (DMSO)
$PhSO_2\text{-}CH(H)\text{-}H$	29	$PhSO_2\text{-}CH(H)\text{-}SO_2Ph$	12.2
$PhSO_2\text{-}CH(H)\text{-}SPh$	20.5	$PhSO_2\text{-}CH(H)\text{-}PPh_2$	20.5

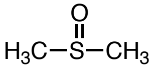
Acidity Trends for Carbonyl & Related Compounds

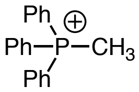
■ Carbanion Stabilization by 2rd–Row Atoms: SR, SO_2R, PR_3 etc


18.2 (DMSO)


31

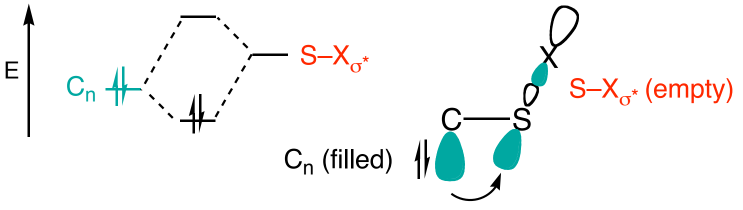

31


35


22.5

(*JACS* **1976**, *98*, 7498; *JACS* **1977**, *99*, 5633; *JACS* **1978**, *100*, 200).

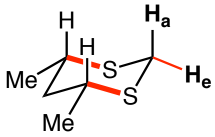
The accepted explanation for carbanion stabilization in 3rd row elements is delocalization into vicinal antibonding orbitals



This argument suggests a specific orientation requirement. This has been noted:

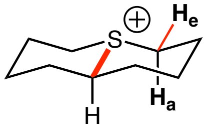
Anti (or syn) periplanar orientation of Carbanion-orbital and σ* orbital mandatory for efficient orbital overlap.

Rates for deprotonation with *n*-BuLi



$H_e : H_a = 8.6$

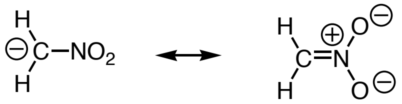
(*JACS* **1974**, *96*, 1811)

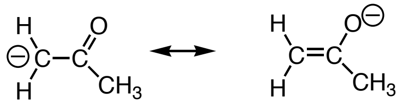


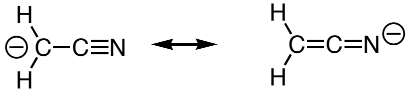
$H_e : H_a = 30$

(*JACS* **1978**, *100*, 200)

■ Conjugative Stabilization of Conjugate Base


17.2 pK_A (DMSO)

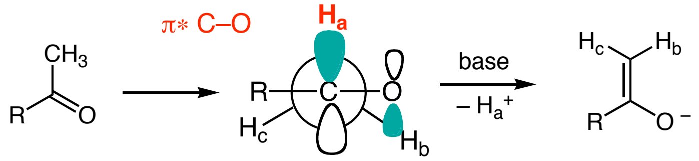

26.5


31.5

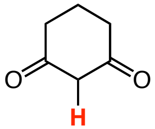
For efficient conjugative stabilization, rehybridization of carbanion orbital from n_{sp3} to n_p is required for efficient overlap with low-lying π*-orbital of stabilizing group. However, the cost of rehybridization must be considered.

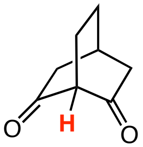
■ Stereoelectronic Requirement for Carbanion Overlap: Enolization of Carbonyl Compounds

Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π* C–O



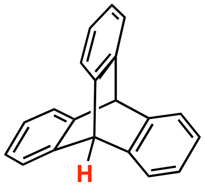
pK_A


5.2


C-H acidity not detectable

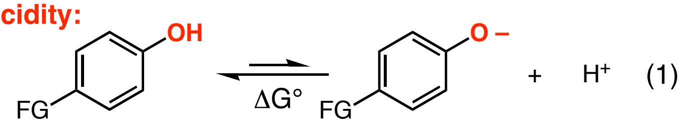
pK_A (DMSO)

Ph_3C–**H** 31.5


47.7

Phenol Acidity: An Analysis of Resonance & Inductive Effects

■ Phenol Acidity:

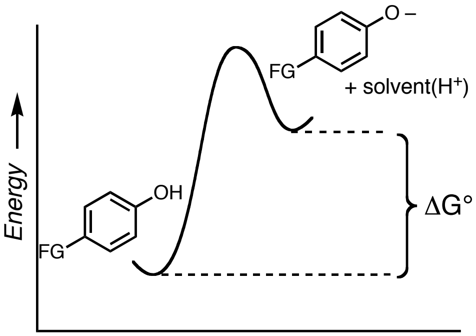


This topic has a number of take-home lessons. Most importantly, is is a useful construct on which to discuss the role of FG's in influencing the acidity of this oxygen acid.

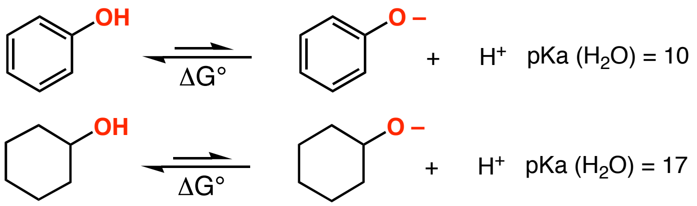
■ How does one analyze the impact of structure on pKa of a weak acid (pKa > 0) ?

■ The Approach:

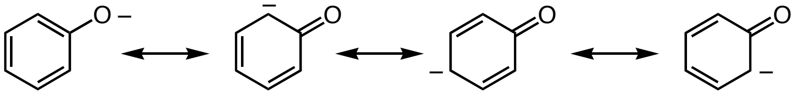
For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.



Why is phenol so much more acidic than cyclohexanol?



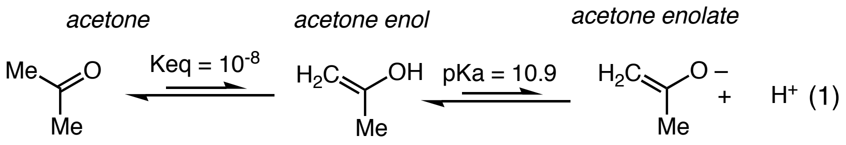
Loudon (pg 730): "The enhanced acidity of phenol is due largely to stabilization of its conjugate base by resonance."



Really!!

Is the benzene ring somehow special. i.e "larger resonance space."

Acetone enol:



The surprising facts is that the acetone enol has nearly the same pKa as phenol. Hence, the answer to the above question is no!

How important are inductive effects in the stabilization of $C_6H_5O^-$?

Consider the following general oxygen acid X–OH where X can only stabilize the conjugate base through induction:

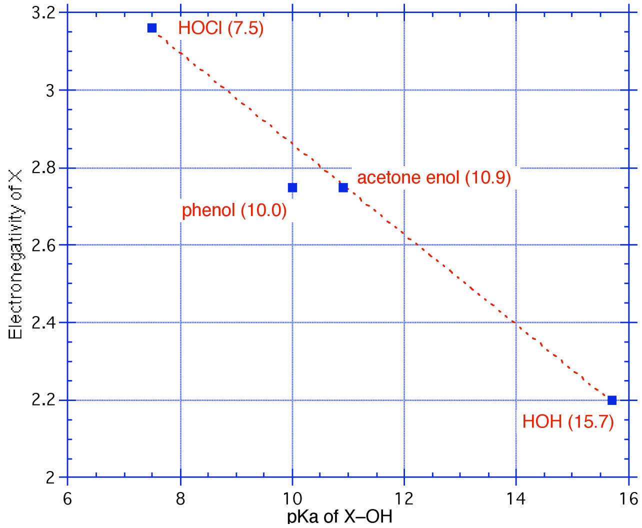
$$X{-}OH \rightleftharpoons X{-}O^- + H^+$$

As the electronegativity of X increases the acidity of X–OH increases.

X–OH	pKa(H_2O)
CH_3–OH	15.5
CF_3CH_2–OH	12.4
Cl–OH	7.5

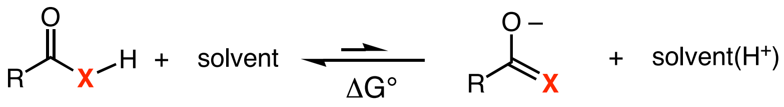
If you take the calculated electronegativity of an SP_2 carbon (2.75) you can see that there is a linear correlation between the electronegativity of X and the pKa of X–OH.

This argument suggests that the acidity of acetone enol is largely due to inductive stabilization, not resonance.



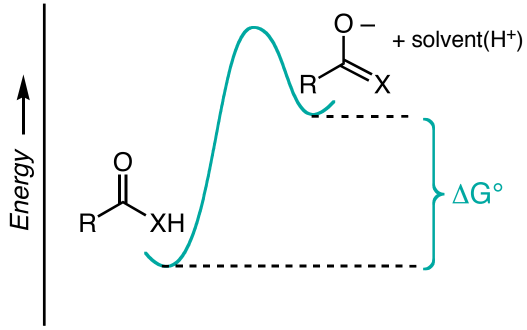
Weak Acids: Impact of Structure on Acidity

Ionization of a weak acid (pKa > 0)



Variables:
X = O (carboxylic acid)
X = NH (amide)
X = CH_2 (Ketone/ester)

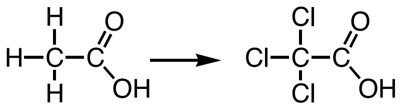
R = CR_3
R = OR
R = NR_2



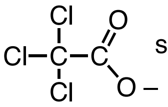
- The Question: How does one analyze the impact of structure on pKa ?
- The Approach:

For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.

Case I: Carboxylic Acids: Inductive Effects

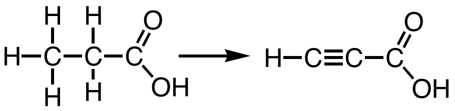


pKa = 4.8   pKa = 0.6

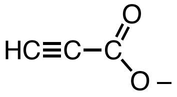


Carboxylate ion stabilized by increased electron-withdrawing CCl_3 group.

Case II: Carboxylic Acids: Inductive Effects & Carbon Hybridization

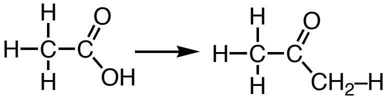


pKa = 4.9   pKa = 1.9

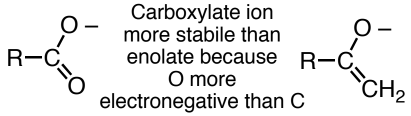


Carboxylate ion stabilized by increased electron-withdrawing SP-hybridized carbon

Case III: Carboxylic Acids vs Ketones:

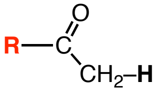


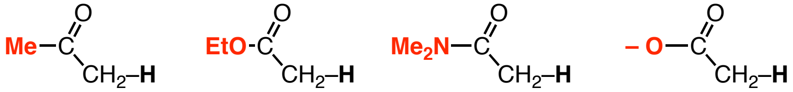
pKa = 4.8   pKa ~ 19



Carboxylate ion more stabile than enolate because O more electronegative than C

Case IV: Carboxylic Acids, Esters, Amides & Ketones:



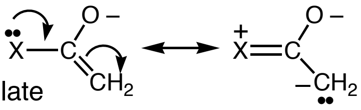


pKa ~ 26   pKa ~ 30   pKa ~ 34   pKa > 34 < 40

The Analysis:

In this series of compounds, there are two variables to consider:

- Inductive Effect: OEt > Me_2N > H_3C but (O–?)
- Resonance Effect:

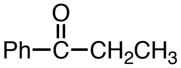


The degree to which substituent X: "contributes" electron density into enolate represents a destabilizing interaction:

Trend: O– > Me_2N > OEt

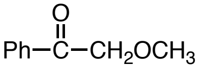
- Resonance donation dominates inductive electron withdrawal as indicated by the data.

Substituents on the α-carbon: Stabilization by either resonance, induction, or both is observed:



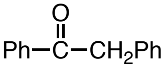
$$Ph-\overset{O}{\overset{\|}{C}}-CH_2CH_3$$

pKa = 24.4



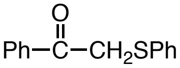
$$Ph-\overset{O}{\overset{\|}{C}}-CH_2OCH_3$$

pKa = 22.9



$$Ph-\overset{O}{\overset{\|}{C}}-CH_2Ph$$

pKa = 17.7



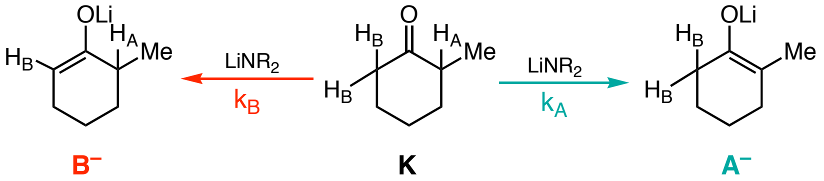
$$Ph-\overset{O}{\overset{\|}{C}}-CH_2SPh$$

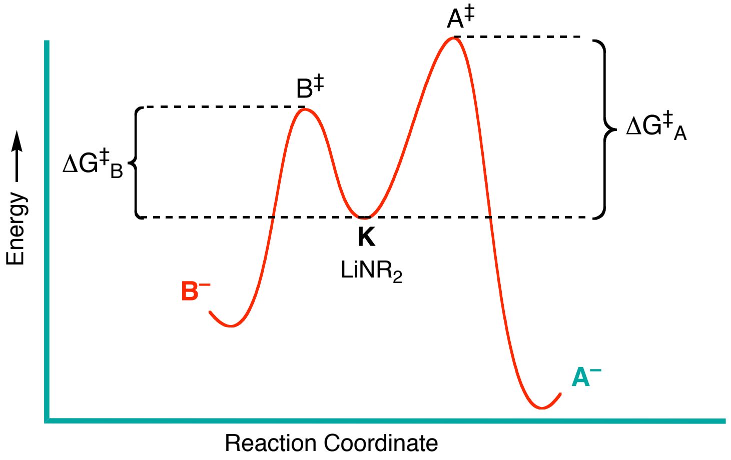
pKa = 17.1

Kinetic & Thermodynamic Acidity of Ketones

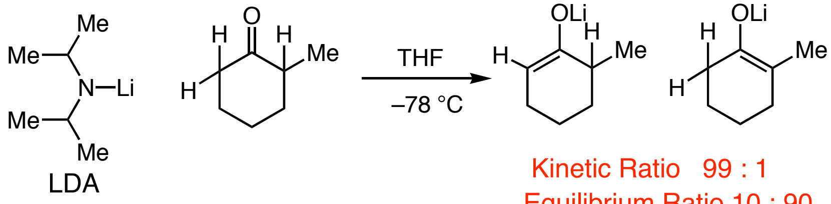
Kinetic Acidity: Rates of proton removal

Consider enolization of the illustrated ketone under non-equilibrating conditions:





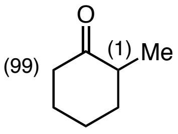
Kinetic acidity refers to the rate of proton removal. e.g. kA vs kB. For example, in reading the above energy diagram you would say that HA has a lower kinetic acidity than HB. As such, the structure of the base (hindered vs unhindered) employed plays a role in determining the magnitude of kA and kB. For the case shown above, $\Delta G^{\ddagger}$**A** will increase more than $\Delta G^{\ddagger}$**B** as the base becomes more hindered since the proton HA resides in a more sterically hindered environment. The example below shows the high level of selectivity which may be achieved with the sterically hindered base lithium diisopropylamide (LDA).



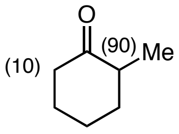
Kinetic Ratio 99 : 1

Equilibrium Ratio 10 : 90

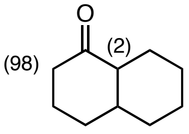
Kinetic & Equilibrium Ratios of Enolates Resulting from Enolization with LDA & Subsequent Equilibration



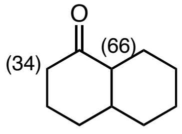
Kinetic Ratios



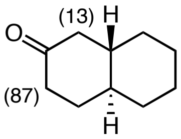
Equilibrium Ratios



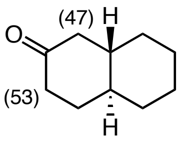
Kinetic Ratios



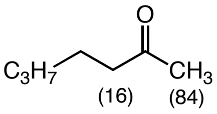
Equilibrium Ratios



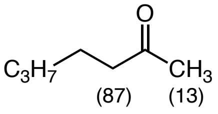
Kinetic Ratios



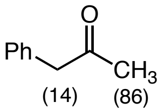
Equilibrium Ratios



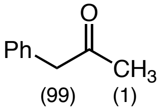
Kinetic Ratios



Equilibrium Ratios



Kinetic Ratios



Equilibrium Ratios

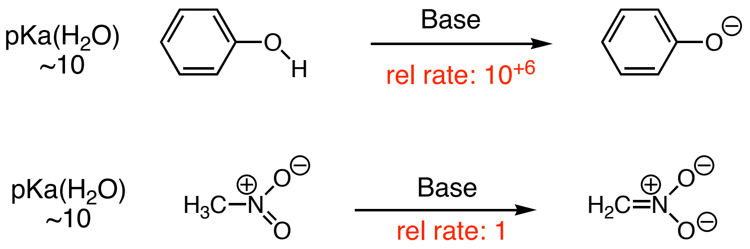
Note that alkyl substitution stabilizes the enolate (Why??). This effect shows up in the equilibrium ratios shown above.

Hence, enolization under "kinetic control with LDA allows you to produce the less-substituted enolate while subsequent equilibration by simply heating the enolate mixture allows equilibration to the more substituted enolate.

Kinetic Acidity: Carbon versus Oxygen Acids

Kinetic Acidity

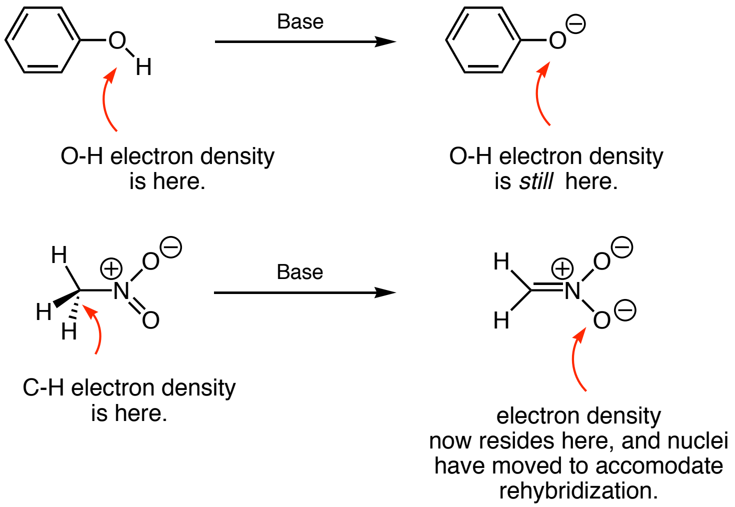
Observation: The thermodynamic acidities of phenol and nitromethane are both approximately 10; however, using a common base, phenol is deprotonated 10^{+6} times as fast.



Proton transfers from C-H Bonds are slow.

Why???

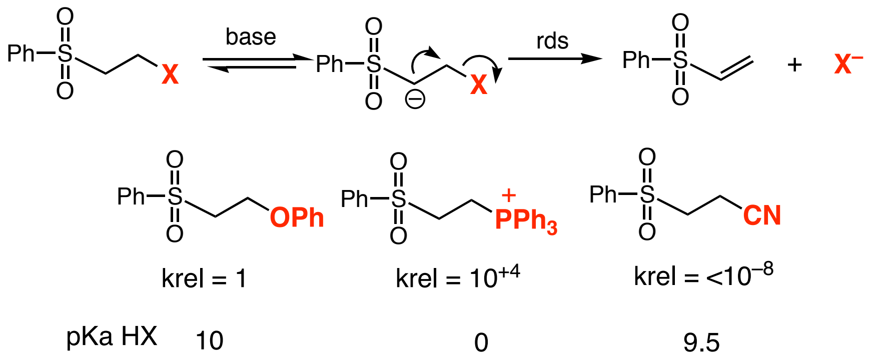
Carbon acids are stabilized by resonance. Hence, significant structural reorganization must accompany deprotonation.


Base
O-H electron density is here.
O-H electron density is *still* here.
Base
C-H electron density is here.
electron density now resides here, and nuclei have moved to accomodate rehybridization.

The greater the structural reorganization during deprotonation, the lower the kinetic acidity

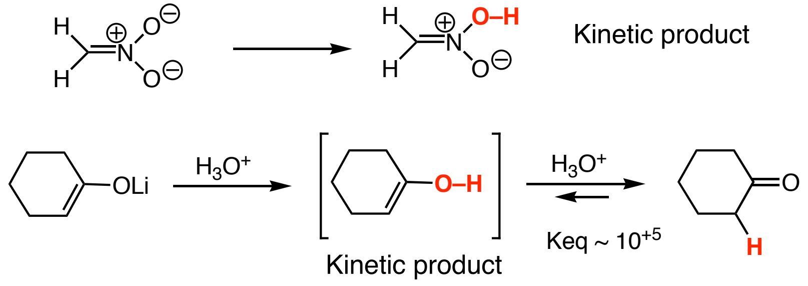
Kinetic Acidity vs. Leaving Group Ability: E1cb Elimination

Stirling, *Chem. Commun.* **1975**, 940



The greater the structural reorganization of leaving group during elimination, the slower the rate of elimination.

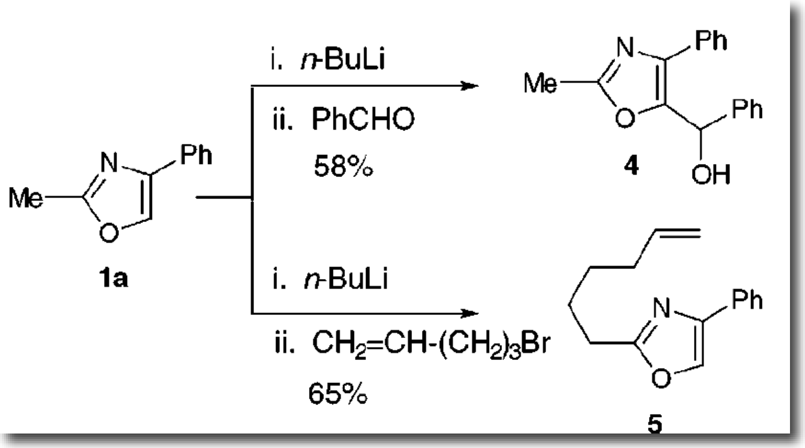
Protonation of Conjugate bases



Jack Hine: Least Motion Principle (*Adv. Phys. Org. Chem.* **1977**, *15*, 1) Lowry & Richardson, 3rd Edition, pp 205-206

Those elementary reactions that involve the least change in atomic posiitons will be favored

Please explain



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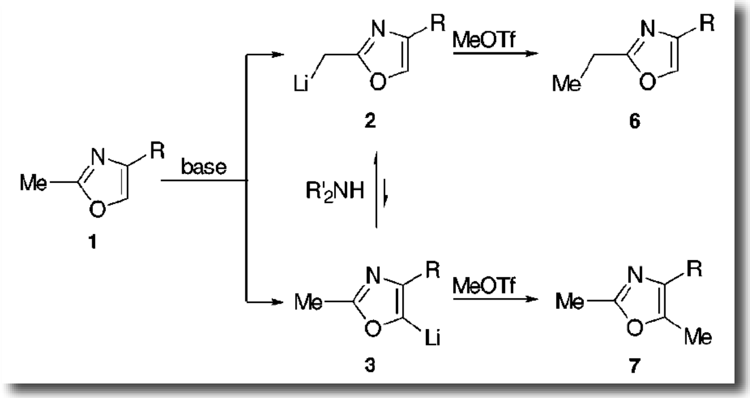


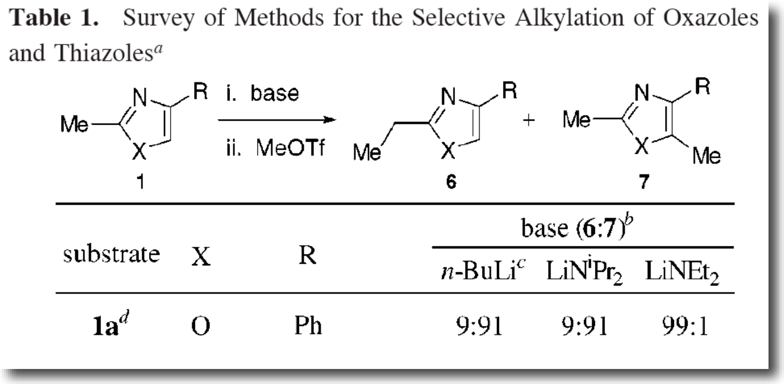


Table 1. Survey of Methods for the Selective Alkylation of Oxazoles and Thiazoles[a]

Me
N
X
R
1
i. base
ii. MeOTf
Me
N
X
R
6
+
Me
N
X
R
Me
7

substrate	X	R	base (**6**:**7**)[b]		
			n-BuLi[c]	LiN^{i}Pr$_2$	LiNEt$_2$
1a[d]	O	Ph	9:91	9:91	99:1

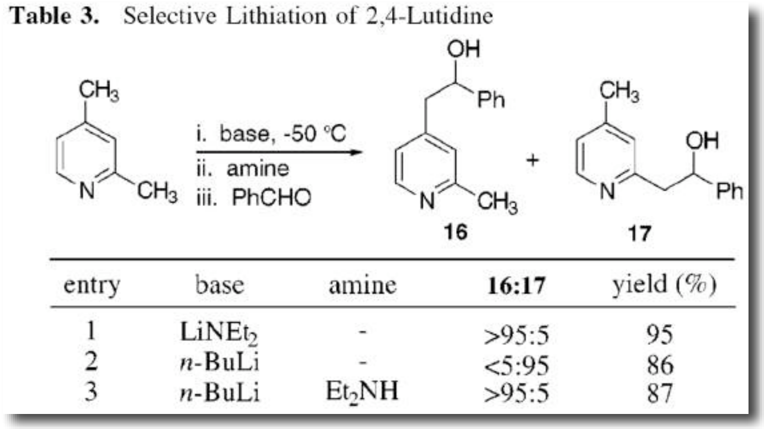


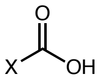
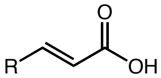
Table 3. Selective Lithiation of 2,4-Lutidine

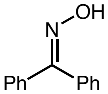
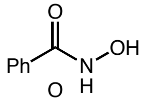
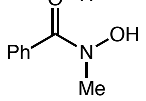
CH$_3$
N
CH$_3$
i. base, -50 °C
ii. amine
iii. PhCHO
OH
Ph
N
CH$_3$
16
+
CH$_3$
N
OH
Ph
17

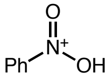
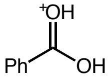
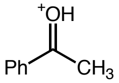
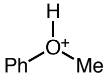
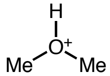
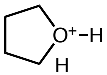
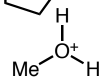
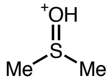
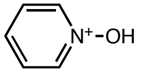
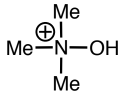
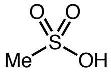
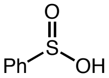
entry	base	amine	**16**:**17**	yield (%)
1	LiNEt$_2$	-	>95:5	95
2	*n*-BuLi	-	<5:95	86
3	*n*-BuLi	Et$_2$NH	>95:5	87

pKa's of Inorganic and Oxo-Acids

Substrate	pKa H_2O	(DMSO)
INORGANIC ACIDS		
H_2O	15.7	(32)
H_3O^+	-1.7	
H_2S	7.00	
HBr	-9.00	(0.9)
HCl	-8.0	(1.8)
HF	3.17	(15)
HOCl	7.5	
$HClO_4$	-10	
HCN	9.4	(12.9)
HN_3	4.72	(7.9)
HSCN	4.00	
H_2SO_3	1.9, 7.21	
H_2SO_4	-3.0, 1.99	
H_3PO_4	2.12, 7.21, 12.32	
HNO_3	-1.3	
HNO_2	3.29	
H_2CrO_4	-0.98, 6.50	
CH_3SO_3H	-2.6	(1.6)
CF_3SO_3H	-14	(0.3)
NH_4Cl	9.24	
$B(OH)_3$	9.23	
HOOH	11.6	

Substrate	pKa H_2O	(DMSO)
CARBOXYLIC ACIDS		
		
X= CH_3	4.76	(12.3)
CH_2NO_2	1.68	
CH_2F	2.66	
CH_2Cl	2.86	
CH_2Br	2.86	
CH_2I	3.12	
$CHCl_2$	1.29	
CCl_3	0.65	
CF_3	-0.25	
H	3.77	
HO	3.6, 10.3	
C_6H_5	4.2	(11.1)
o-$O_2NC_6H_4$	2.17	
m-$O_2NC_6H_4$	2.45	
p-$O_2NC_6H_4$	3.44	
o-ClC_6H_4	2.94	
m-ClC_6H_4	3.83	
p-ClC_6H_4	3.99	
o-$(CH_3)_3N^+C_6H_4$	1.37	
p-$(CH_3)_3N^+C_6H_4$	3.43	
p-$OMeC_6H_4$	4.47	
		
R= H	4.25	
trans-CO_2H	3.02, 4.38	
cis-CO_2H	1.92, 6.23	

Substrate	pKa H_2O	(DMSO)
ALCOHOLS		
HOH	15.7	(31.2)
MeOH	15.5	(27.9)
i-PrOH	16.5	(29.3)
t-BuOH	17.0	(29.4)
c-hex_3COH	24.0	
CF_3CH_2OH	12.5	(23.5)
$(CF_3)_2CHOH$	9.3	(18.2)
C_6H_5OH	9.95	(18.0)
m-$O_2NC_6H_4OH$	8.4	
p-$O_2NC_6H_4OH$	7.1	(10.8)
p-$OMeC_6H_4OH$	10.2	(19.1)
2-napthol		(17.1)
OXIMES & HYDROXAMIC ACIDS		
	11.3	(20.1)
	8.88 (NH)	(13.7)
		(18.5)
PEROXIDES		
MeOOH	11.5	
CH_3CO_3H	8.2	

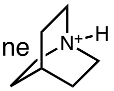
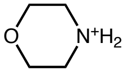
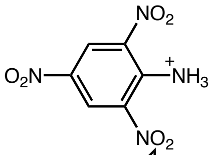
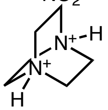
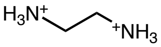
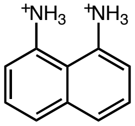
Substrate	pKa H_2O	(DMSO)
PROTONATED SPECIES		
	-12.4	
	-7.8	
	-6.2	
	-6.5	
	-3.8	
	-2.05	
	-2.2	
	-1.8	
	0.79	(+1.63)
		(+5.55)
SULFINIC & SULFONIC ACIDS		
	-2.6	
	2.1	

*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

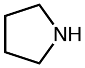
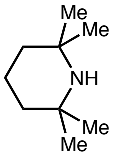
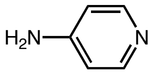
For a comprehensive compilation of Bordwell pKa data see: **http://www.chem.wisc.edu/areas/reich/pkatable/index.htm**

pKa's of Nitrogen Acids

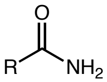
PROTONATED NITROGEN

Substrate	pKa H_2O	(DMSO)
N^+H_4	9.2	(10.5)
EtN^+H_3	10.6	
i-$Pr_2N^+H_2$	11.05	
Et_3N^+H	10.75	(9.00)
PhN^+H_3	4.6	(3.6)
$PhN^+(Me)_2H$	5.20	(2.50)
$Ph_2N^+H_2$	0.78	
2-napthal-N^+H_3	4.16	
$H_2NN^+H_3$	8.12	
HON^+H_3	5.96	
Quinuclidine 	11.0	(9.80)
Morpholine 	8.36	
N-Me morpholine	7.38	
	-9.3	
DABCO 	2.97, 8.82 (2.97, 8.93)	
	6.90, 9.95	
Proton Sponge 	-9.0, 12.0 (--, 7.50)	
$PhCN^+H$	-10	

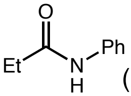
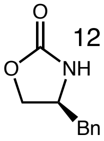
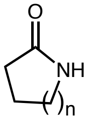
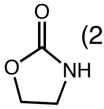
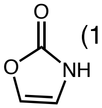
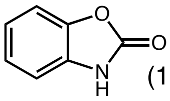
AMINES

Substrate	pKa H_2O	(DMSO)
HN_3	4.7	(7.9)
NH_3	38	(41)
i-Pr_2NH	(36 THF))	
TMS_2NH	26(THF)	(30)
$PhNH_2$		(30.6)
Ph_2NH		(25.0)
$NCNH_2$		(16.9)
		(44)
		(37)
		(26.5)

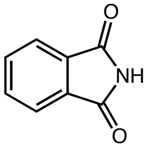
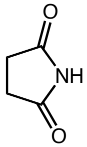
AMIDES & CARBAMATES



R=	pKa H_2O	(DMSO)
H		(23.5)
CH_3	15.1	(25.5)
Ph		(23.3)
CF_3		(17.2)
(urea) NH_2		(26.9)
OEt		(24.8)

Substrate	pKa H_2O	(DMSO)
		(21.6)
	12	(20.5)
		n= 1 (24.1) n= 2 (26.4)
		(20.8)
		(15)
		(12.1)

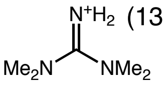
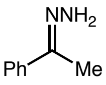
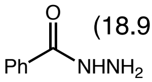
IMIDES

Substrate	pKa H_2O	(DMSO)
	8.30	
		(14.7)
Ac_2NH		(17.9)

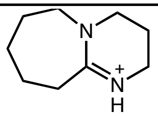
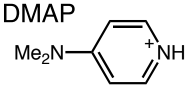
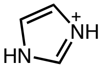
SULFONAMIDE

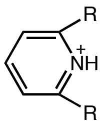
Substrate		pKa H_2O	(DMSO)
RSO_2NH_2	R = Me		(17.5)
	Ph		(16.1)
	CF_3	6.3	(9.7)
$MeSO_2NHPh$			(12.9)

GUANIDINIUM, HYRDAZONES,- IDES, & -INES

Substrate	pKa H_2O	(DMSO)
		(13.6)
		(21.6)
		(18.9)
$PhSO_2NHNH_2$		(17.2)
PhNHNHPh		(26.1)

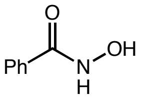
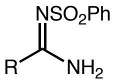
PROTONATED HETEROCYCLES

Substrate	pKa H_2O	(DMSO)
DBU 		(12) (estimate)
DMAP 	9.2	
	6.95	

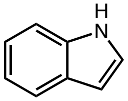
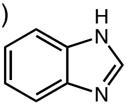
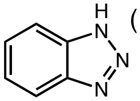
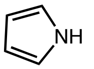
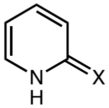
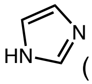
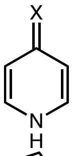
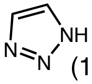
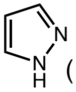
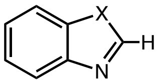
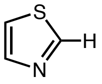
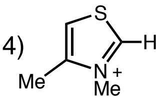
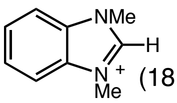
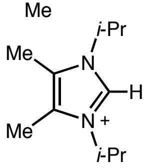


R=	pKa H_2O	(DMSO)
H (PPTS)	5.21	(3.4)
t-Bu	4.95	(0.90)
Me	6.75	(4.46)
Cl, H	0.72	

HYDROXAMIC ACID & AMIDINES

Substrate		pKa H_2O	(DMSO)
		8.88 (NH)	(13.7)
	R= Me		(17.3)
	Ph		(15.0)

HETEROCYCLES

Substrate		(DMSO)
		(20.95)
		(16.4)
		(11.9)
		(23.0)
	X= O	(24)
	X= S	(13.3)
		(18.6)
	X= O	(14.8)
	X= S	(11.8)
		(13.9)
		(19.8)
	X= O	(24.4)
	X= S	(27.0)
		(29.4)
		(16.5)
		(18.4)
		(24)

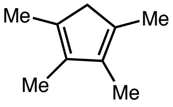
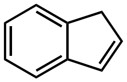
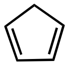
*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

For a comprehensive compilation of Bordwell pKa data see: **http://www.chem.wisc.edu/areas/reich/pkatable/index.htm**

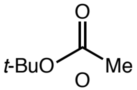
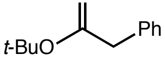
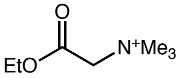
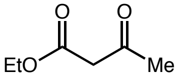
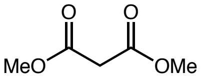
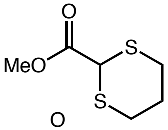
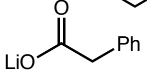
D.H. Ripin, D.A. Evans

pKa's of CH bonds in Hydrocarbons and Carbonyl Compounds

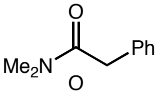
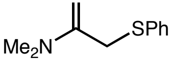
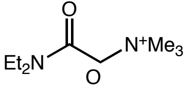
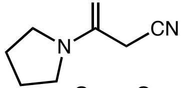
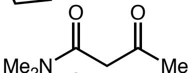
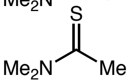
HYDROCARBONS

Substrate	pKa H_2O	(DMSO)
$(Me)_3CH$	53	
$(Me)_2CH_2$	51	
$CH_2{=}CH_2$	50	
CH_4	48	(56)
	46	
$CH_2{=}CHCH_3$	43	(44)
PhH	43	
$PhCH_3$	41	(43)
Ph_2CH_2	33.5	(32.2)
Ph_3CH	31.5	(30.6)
HCCH	24	
PhCCH	23	(28.8)
$XC_6H_4CH_3$		
X= *p*-CN		(30.8)
p-NO_2		(20.4)
p-COPh		(26.9)
		(26.1)
	20	(20.1)
	15	(18.0)
H_2	~36	

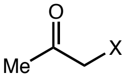
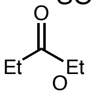
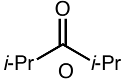
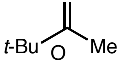
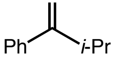
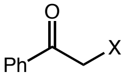
ESTERS

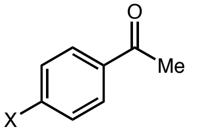
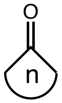
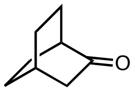
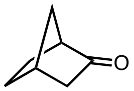
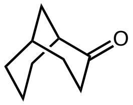
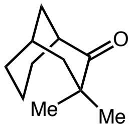
Substrate	pKa H_2O	(DMSO)
	24.5	(30.3)
		(23.6)
		(20.0)
	11	(14.2)
	13	(15.7)
		(20.9)
		[30.2 (THF)]

AMIDES

Substrate	pKa H_2O	(DMSO)
		(26.6)
		(25.9)
		(24.9)
		(17.2)
		(18.2)
		(25.7)

KETONES

Substrate	pKa H_2O	(DMSO)
		
X= H		(26.5)
Ph		(19.8)
SPh		(18.7)
$COCH_3$	9	(13.3)
SO_2Ph		(12.5)
	19-20	(27.1)
		(28.3)
		(27.7)
		(26.3)
		
X= H		(24.7)
CH_3		(24.4)
Ph		(17.7)
$COCH_3$		(14.2)
COPh		(13.3)
CN		(10.2)
F		(21.6)
OMe		(22.85)
OPh		(21.1)
SPh		(16.9)
SePh		(18.6)
NPh_2		(20.3)
N^+Me_3		(14.6)
NO_2		(7.7)
SO_2Ph		(11.4)

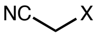
Substrate	pKa H_2O	(DMSO)
		
X= H		(24.7)
OMe		(25.7)
NMe_2		(27.5)
Br		(23.8)
CN		(22.0)
		
n= 4		(25.1)
5		(25.8)
6		(26.4)
7		(27.7)
8		(27.4)
		(28.1)
		(29.0)
		(25.5)
		(32.4)

*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

For a comprehensive compilation of Bordwell pKa data see: **http://www.chem.wisc.edu/areas/reich/pkatable/index.htm**

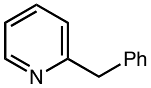
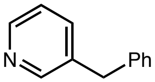
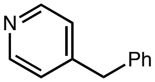
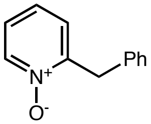
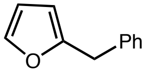
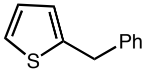
pKa's of CH bonds at Nitrile, Heteroaromatic, and Sulfur Substituted Carbon

NITRILES

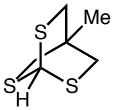
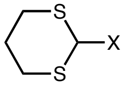


Substrate	pKa H_2O	(DMSO)
X= H		(31.3)
CH_3		(32.5)
Ph		(21.9)
COPh		(10.2)
$CONR_2$		(17.1)
CO_2Et		(13.1)
CN	11	(11.1)
OPh		(28.1)
N^+Me_3		(20.6)
SPh		(20.8)
SO_2Ph		(12.0)

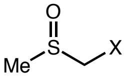
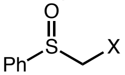
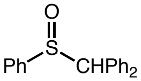
HETERO-AROMATICS

Substrate	pKa H_2O	(DMSO)
		(28.2)
		(30.1)
		(26.7)
		(25.2)
		(30.2)
		(30.0)

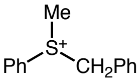
SULFIDES

Substrate	pKa H_2O	(DMSO)
$PhSCH_2X$		
X= Ph		(30.8)
CN		(20.8)
$COCH_3$		(18.7)
COPh		(16.9)
NO_2		(11.8)
SPh		(30.8)
SO_2Ph		(20.5)
SO_2CF_3		(11.0)
$POPh_2$		(24.9)
$MeSCH_2SO_2Ph$		(23.4)
$PhSCHPh_2$		(26.7)
$(PhS)_3CH$		(22.8)
$(PrS)_3CH$		(31.3)
		(30.5)
$(PhS)_2CHPh$		(23.0)
		
X= Ph		(30.7)
CO_2Me		(20.8)
CN		(19.1)
$RSCH_2CN$		
R= Me		(24.3)
Et		(24.0)
i-Pr		(23.6)
t-Bu		(22.9)
$PhSCH{=}CHCH_2SPh$		(26.3)
BuSH	10-11	(17.0)
PhSH	≈7	(10.3)

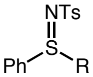
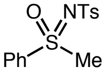
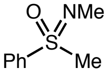
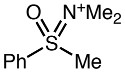
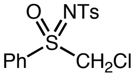
SULFOXIDES

Substrate	pKa H_2O	(DMSO)
		
X= H		(35.1)
Ph		(29.0)
SPh		(29.0)
		
X= H		(33)
Ph		(27.2)
SOPh		(18.2)
		(24.5)

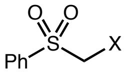
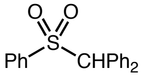
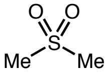
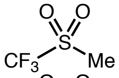
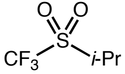
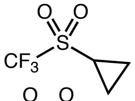
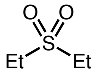
SULFONIUM

Substrate	pKa H_2O	(DMSO)
$Me_3S^+{=}O$		(18.2)
		(16.3)

SULFIMIDES & SULFOXIMINES

Substrate	pKa H_2O	(DMSO)
		
R= Me		(27.6)
i-Pr		(30.7)
		(24.5)
		(33)
		(14.4)
		(20.7)

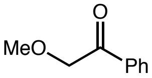
SULFONES

Substrate	pKa H_2O	(DMSO)
		
X= H		(29.0)
CH_3		(31.0)
t-Bu		(31.2)
Ph		(23.4)
$CH{=}CH_2$		(22.5)
CH=CHPh		(20.2)
CCH		(22.1)
CCPh		(17.8)
COPh		(11.4)
COMe		(12.5)
OPh		(27.9)
N^+Me_3		(19.4)
CN		(12.0)
NO_2		(7.1)
SMe		(23.5)
SPh		(20.5)
SO_2Ph		(12.2)
PPh_2		(20.2)
		(22.3)
		(31.1)
		(18.8)
		(21.8)
		(26.6)
		(32.8)
$(PhSO_2)_2CH_2Me$		(14.3)

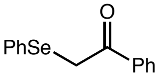
*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

pKa's of CH bonds at Heteroatom Substituted Carbon & References

ETHERS

Substrate	pKa H_2O	(DMSO)
CH_3OPh		(49)
$MeOCH_2SO_2Ph$		(30.7)
$PhOCH_2SO_2Ph$		(27.9)
$PhOCH_2CN$		(28.1)
		(22.85)

SELENIDES

Substrate	pKa H_2O	(DMSO)
		(18.6)
$PhSeCHPh_2$		(27.5)
$(PhSe)_2CH_2$		(31.3)
$PhSeCH_2Ph$		(31.0)
$PhSeCH{=}CHCH_2SePh$		(27.2)

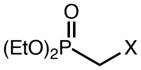
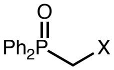
AMMONIUM

Substrate	pKa H_2O	(DMSO)
$Me_3N^+CH_2X$		
X= CN		(20.6)
SO_2Ph		(19.4)
COPh		(14.6)
CO_2Et		(20.0)
$CONEt_2$		(24.9)

PHOSPHONIUM

Substrate	pKa H_2O	(DMSO)
P^+H_4	-14	
MeP^+H_3	2.7	
Et_3P^+H	9.1	
$Ph_3P^+CH_3$		(22.4)
Ph_3P^+*i*-Pr		(21.2)
$Ph_3P^+CH_2COPh$		(6.2)
$Ph_3P^+CH_2CN$		(7.0)

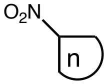
PHOSPONATES & PHOSPHINE OXIDES

Substrate	pKa H_2O	(DMSO)
		
X= Ph		(27.6)
CN		(16.4)
CO_2Et		(18.6)
Cl		(26.2)
$SiMe_3$		(28.8)
		
X= SPh		(24.9)
CN		(16.9)

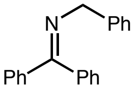
PHOSPHINES

Substrate	pKa H_2O	(DMSO)
$Ph_2PCH_2PPh_2$		(29.9)
$Ph_2PCH_2SO_2Ph$		(20.2)

NITRO

Substrate	pKa H_2O	(DMSO)
RNO_2		
R= CH_3	≈10	(17.2)
CH_2Me		(16.7)
$CHMe_2$		(16.9)
CH_2Ph		(12.2)
CH_2Bn		(16.2)
CH_2SPh		(11.8)
CH_2SO_2Ph		(7.1)
CH_2COPh		(7.7)
		
n= 3		(26.9)
4		(17.8)
5		(16.0)
6		(17.9)
7		(15.8)

IMINES

Substrate	pKa H_2O	(DMSO)
		(24.3)

Oxime ethers are ~ 10 pka units less acidic than their ketone counterparts Streitwieser, JOC 1991, 56, 1989

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JOC 41, 1883 (1976)
JOC 41, 1885 (1976)
JOC 41, 2786 (1976)
JOC 41, 2508 (1976)
JOC 42, 1817 (1977)
JOC 42, 321 (1977)
JOC 42, 326 (1977)
JOC 43, 3113 (1978)
JOC 43, 3095 (1978)
JOC 43, 1764 (1978)
JOC 45, 3325 (1980)
JOC 45, 3305 (1980)
JOC 45, 3884 (1980)
JOC 46, 4327 (1981)
JOC 46, 632 (1981)
JOC 47, 3224 (1982)
JOC 47, 2504 (1982)
Acc. Chem. Res. 21, 456 (1988)
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J. March (1985)
Unpublished results of W. P. Jencks

THF:
JACS 110, 5705 (1988)

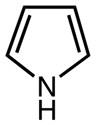
See cited website below for additional data

*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

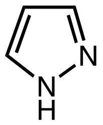
For a comprehensive compilation of Brodwell pKa data see: **http://www.chem.wisc.edu/areas/reich/pkatable/index.htm**

DMSO Acidities of Common Heterocycles

Bordwell, ACR, **1988**, *21*, 456
Bordwell http://www.chem.wisc.edu/areas/reich/pkatable/index.htm



23.0



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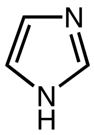

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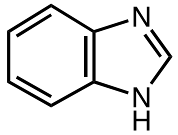
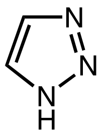
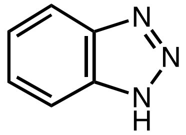


16.4



13.9



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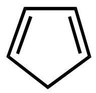
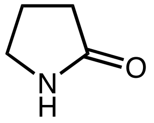


18.0



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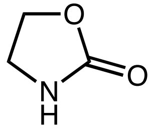

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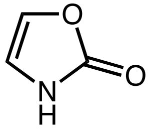

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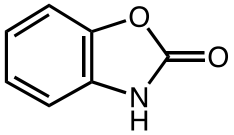

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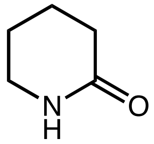

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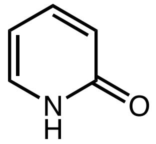

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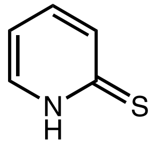

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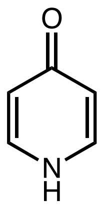

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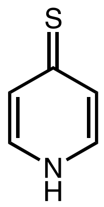

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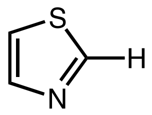

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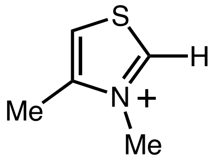
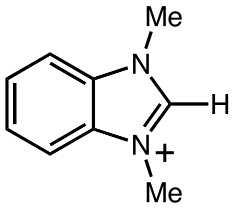
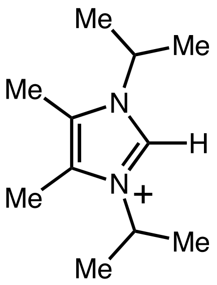


16.5



18.4



24

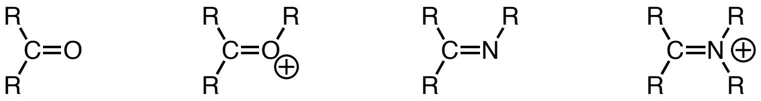
http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 21

Carbonyl and Azomethine Electrophiles-1



- Reactivity Trends
- C=X Stereoelectronic Effects
- Carbonyl Addition: Theoretical Models
- The Felkin-Anh-Eisenstein Model for C=O Addition
- Diastereoselective Ketone Reduction

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

D. A. Evans

Monday
November 6, 2006

Additional Reading Material Provided

Additions to 5- & 6-Membered Oxocarbenium Ions:

Woerpel et al. *JACS* **1999**, *121*, 12208
Woerpel et al. *JACS* **2000**, *122*, 168
Woerpel et al. *JACS* **2003**, *125*, 15521
Woerpel et al. *JACS* **2003**, *125*, 14149
Woerpel et al. *JACS* **2005**, *127*, 10879

"From Crystal Statics to Chemical Dynamics", H. B. Buergi, J. D. Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153-161. **(Handout)**

"On the Surprising Kinetic Stability of Carbonic Acid", K. R. Liedl et al., *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 892-894. **(Handout)**

"Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chim.* **1977**, *1*, 61-70.

"Around and Beyond Cram's Rule" A. Mengel & O. Reiser, Chem. Rev. 1999, 99, 1191-1223 **(Electronic Handout)**

Relevant Dunitz Articles

"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

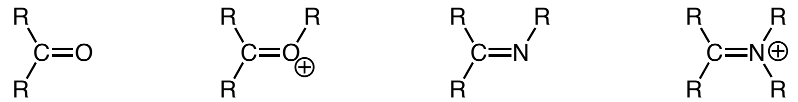
"Stereochemistry of Reaction Paths at Carbonyl Centers", *Tetrahedron* **1974**, *30*, 1563

"From Crystal Statics to Chemical Dynamics", *Acc. Chem. Res.* **1983**, *16*, 153. **(Handout)**

"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.", Burgi, H.-B. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 460.

C=X Electrophiles: Carbonyls, Imines & Their Conjugate Acids

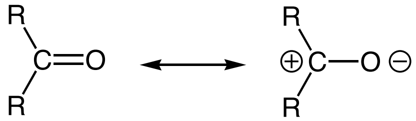
■ The Set of Functional Groups:



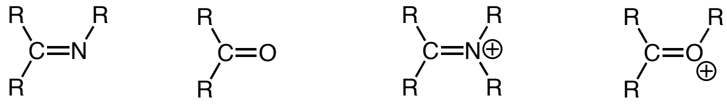
Aldehyde Ketone | Oxocarbenium ion | Aldimine Ketimine (Imine) | Iminium ion

These functional groups are among the most versatile sources of electrophilic carbon in both synthesis and biosynthesis. The ensuing discussion is aimed at providing a more advanced discussion of this topic.

■ C=X Polarization



Partial Charge: As the familiar polar resonance structure above indicates, the carbonyl carbon supports a partial positive charge due to the polarization of the sigma and pi system by the more electronegative heteroatom. The partial charges for this family of functional groups derived from molecular orbital calclulations (ab initio, 3-21(G)*, HF) are illustrated below:



δ + 0.33

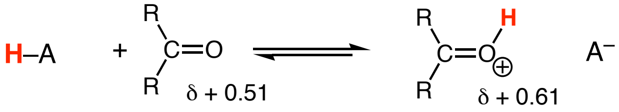
δ + 0.51

δ + 0.54

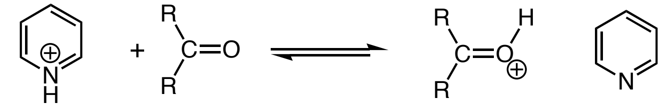
δ + 0.61 (R = H)
δ + 0.63 (R = Me)

——— *electrophilic reactivity* ———→

■ Proton Activation of C=X Functional groups



The electrophilic potential of the C=O FG may be greatly increased by either Lewis acid coordination of by protonation. The magnitude of this increase in reactivity is ~ 10^{+6}. Among the weakest Bronsted acids that may be used for C=O activation (ketalization) is pyridinium ion (pKa = 5). Hence, the Keq below, while quite low, is still functional.



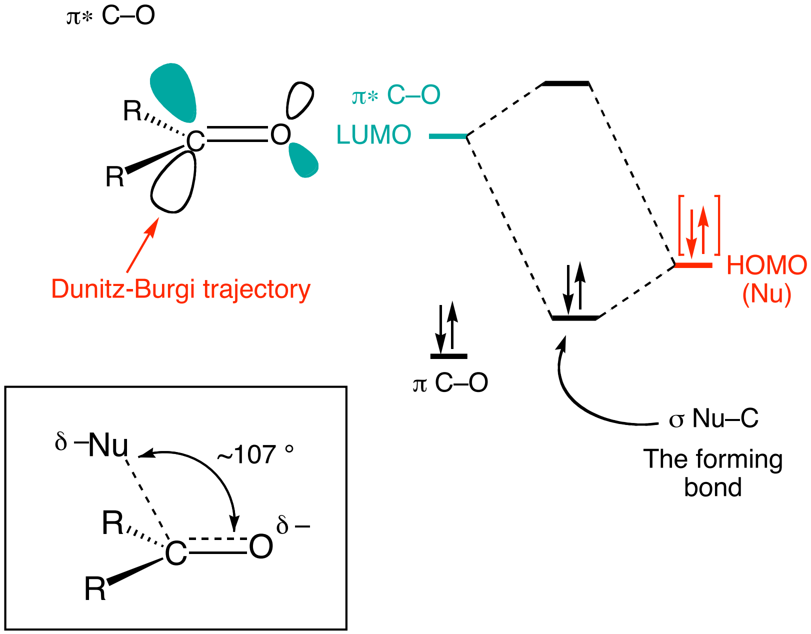
pka = +5

pka = –6

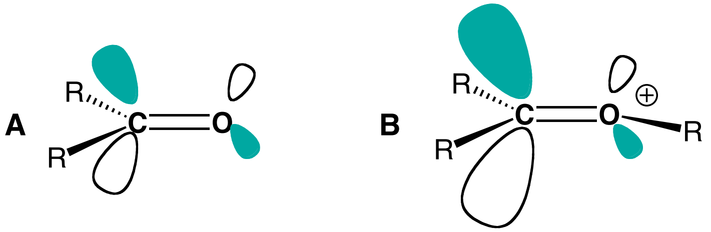
Keq ~ 10^{-11}

Stereoelectronic Considerations for C=O Addition

LUMO is π* C–O; **HOMO** Provided by Nu:



■ What about C=O vs C=O-R(+)?



The LUMO coefficient on carbon for **B** will be considerably larger than for **A.** Does this mean that there is a lower constraint on the approach angle for the attacking nucleophile? There is no experimental proof for this question; however, it is worthy of consideration

■ What was the basis for the Dunitz-Burgi analysis?

The Dunitz-Burgi Trajectory for C=O Addition

■ Relevant Dunitz Articles

"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

"Stereochemistry of Reaction Paths at Carbonyl Centers", *Tetrahedron* **1974**, *30*, 1563

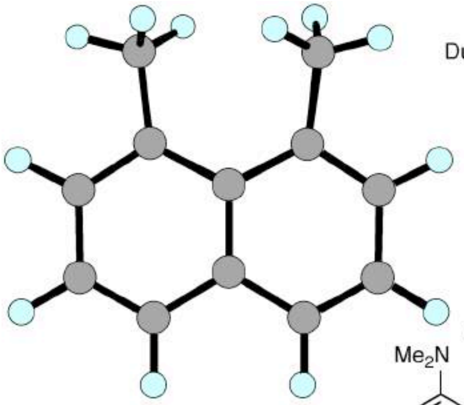
"From Crystal Statics to Chemical Dynamics", *Acc. Chem. Res.* **1983**, *16*, 153.

"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.", Buergi, H.-B. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 460.

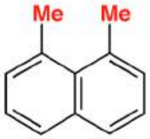
■ Dunitz Method of Analysis

A series of organic structures containing both C=O and Nu FG's disposed in a geometry for mutual interaction were designed. These structures positioned the interacting FGs at increasingly closer distances. The X-ray structures of these structures were determined to ascertain the direction of C=O distortion. The two families of structures that were evaluated are shown below.

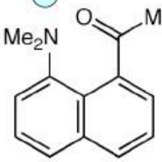
1,8-Disubstituted Naphthalenes. Substituents located at these positions are strongly interacting as illustrated by the MM2 minimized di-methyl-naphthalene structure shown below.



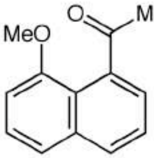
Dunitz, *Helv. Chem. Acta* **1978**, *61*, 2783



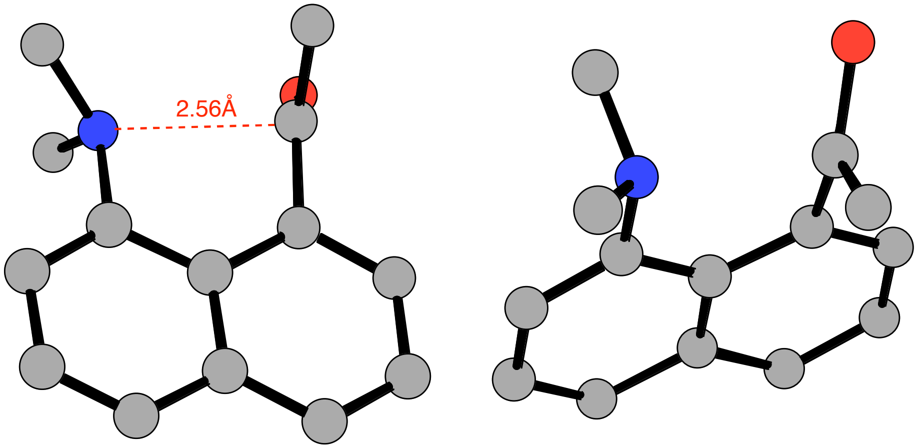
~ 7.6 kcal/moll
Lecture 4



A (shown)

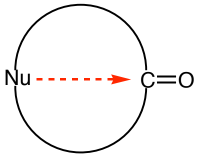


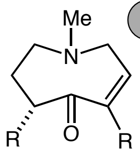
B



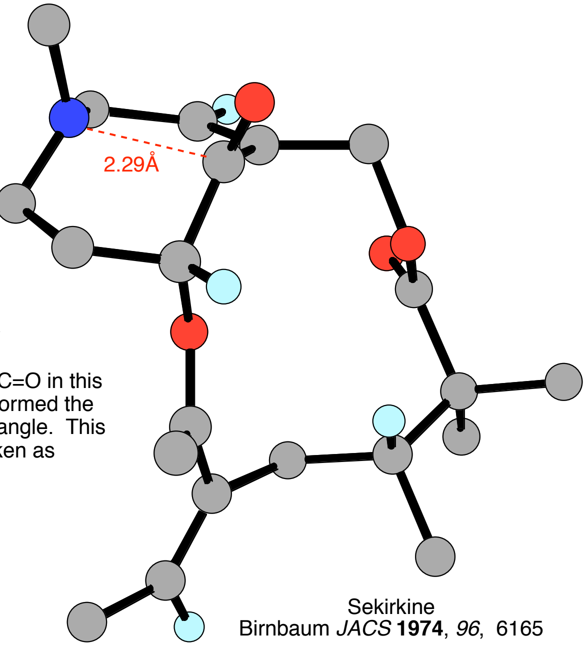
In this structure (**A**), at 2.56Å the C=O is starting to pyramidalize

Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine an C=O FGs. One example is shown below.





Analysis of distortion of C=O in this and related structures formed the basis of the 107° attack angle. This value should be taken as approximate.

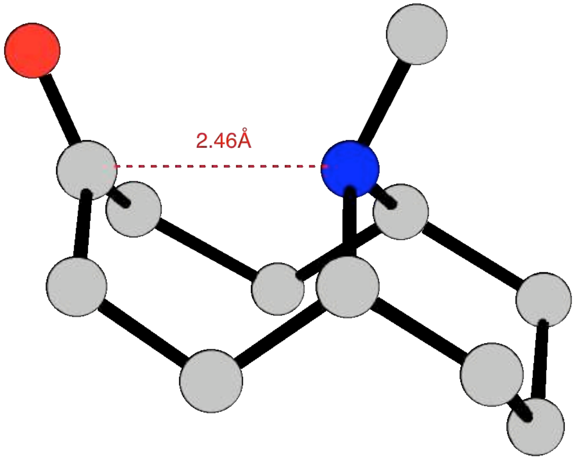


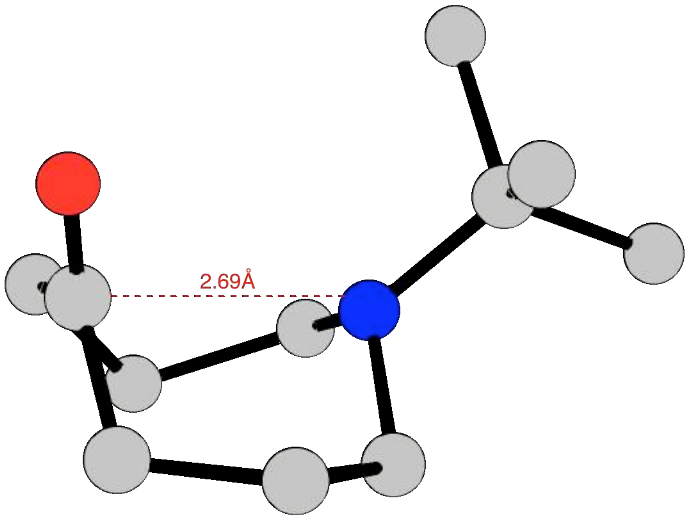
Sekirkine
Birnbaum *JACS* **1974**, *96*, 6165

The Dunitz-Burgi Trajectory for C=O Addition

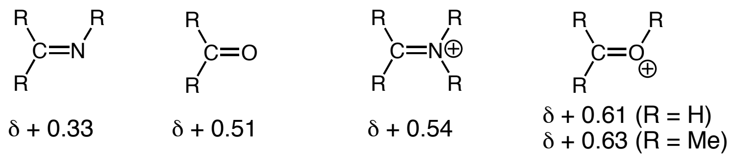
Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine an C=O FGs. Two examples are shown below.

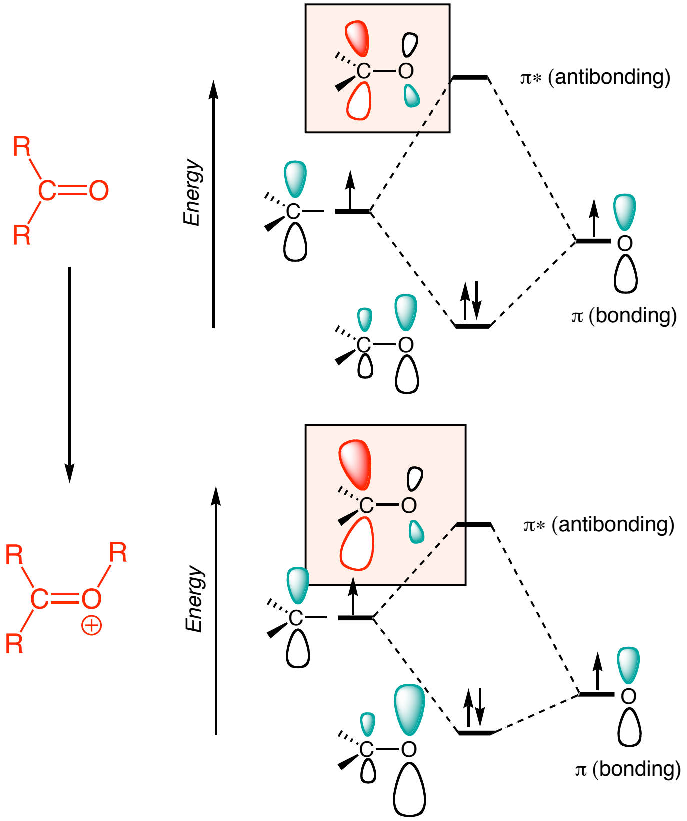
Sekirkine
Birnbaum *JACS* **1974**, *96,* 6165

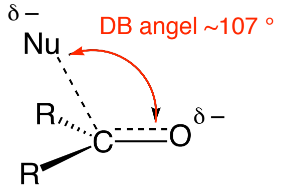


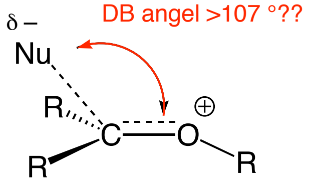


Should these crystallographic data be relevant to the addition to complexed C=O & Iminium Ions?









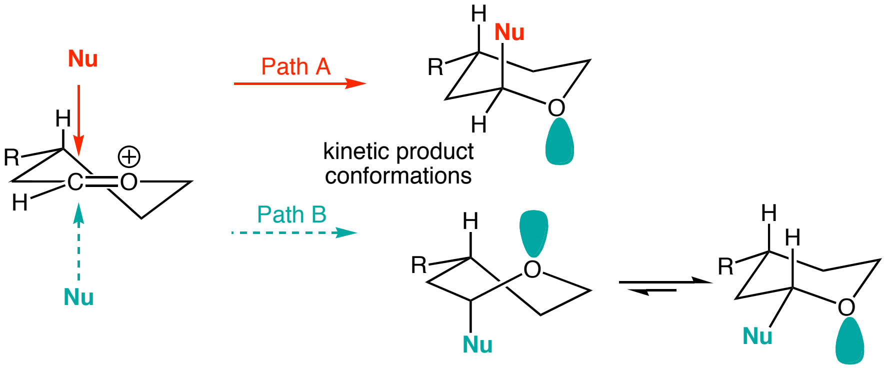
Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

Pivotal Articles

R. V. Stevens in
"Strategies and Tactics in Organic Synthesis", Vol. 1.
On the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts: a Powerful Heuristic Principle for the Stereorational Design of Alkaloid Synthesis.;
Lindberg, T., Ed.; Academic Press, 1984;

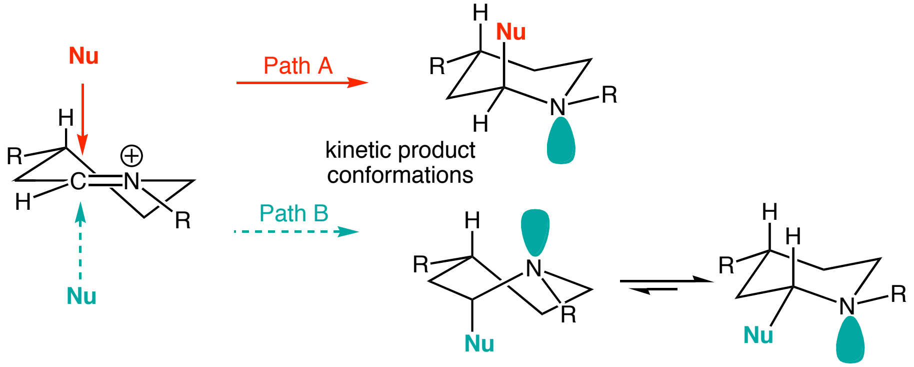
Eliel et al. , *JACS* **1969**, *91*, 536
Kishi et al. , *JACS* **1982**, *104*, 4976-8

The Proposal for Oxo-carbenium Ions (Eliel, Kishi)



kinetic product conformations

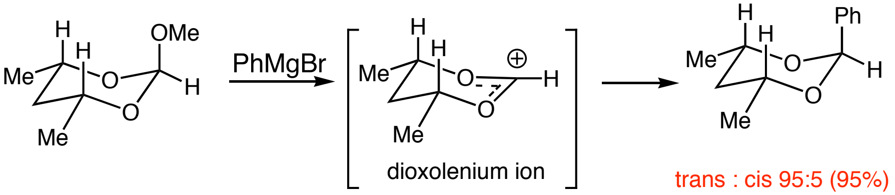
The Proposal for Iminium Ions (Stevens)



kinetic product conformations

It was proposed that chair-axial addition would be preferred as a consequence of the intervention of a transition state anomeric effect (Path A). Attack through Path B would necessitate the generation of the twist-boat kinetic product conformation thus destabilizing attack from the equatorial diastereoface. While Stevens espoused this concept for iminium ions in the late 70's, his untimely death at the age of 42 significantly delayed his cited publication.

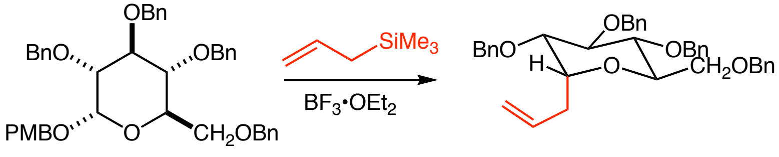
An early example from Eliel; *JACS* 1969, *91*, 536



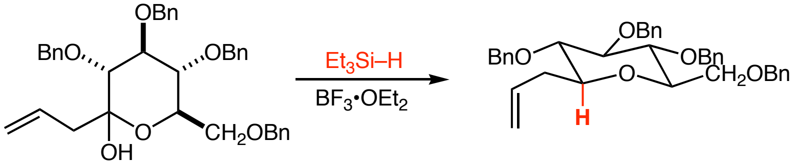
trans : cis 95:5 (95%)

Eliel was the first to attribute stereoelectronic factors to the addition of nucleophiles to cyclic oxo-carbenium ions.

Kishi Examples; *JACS* 1982, *104*, 4976-8



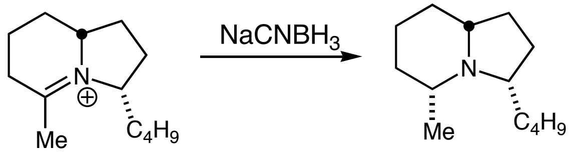
stereoselection 10:1 (55%)



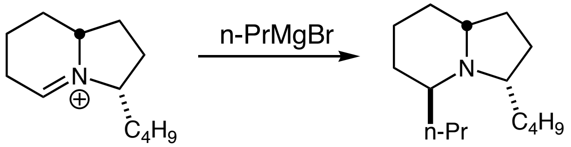
stereoselection 10:1 (55%)

Chair-axial attack on oxo-carbenium ion occurs for both carbon and hydride nucleophiles

Iminium Ions (Stevens) *cited reference*

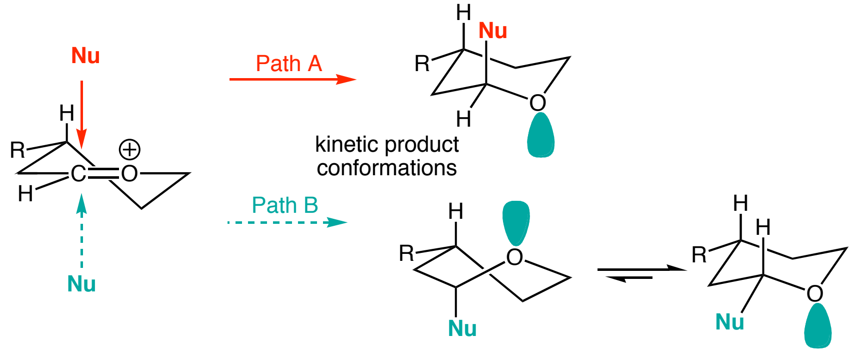


only one stereoisomer



Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

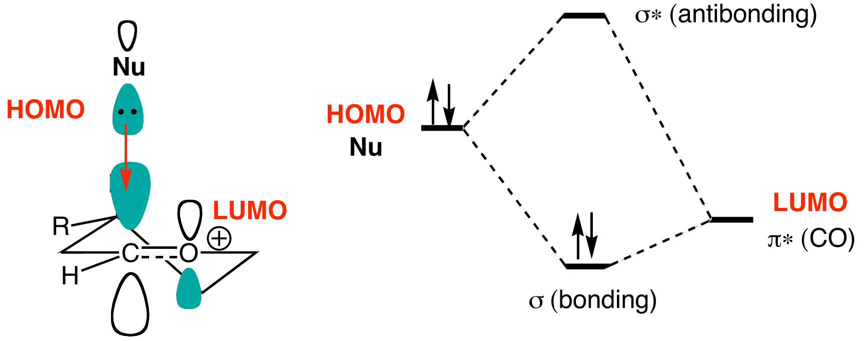
The Proposal for Oxo-carbenium Ions (Eliel, Kishi)



Stereoelectronic factors are important:
The forming C-Nu bond and the developing Oxygen lone pair are oriented antiperiplanar

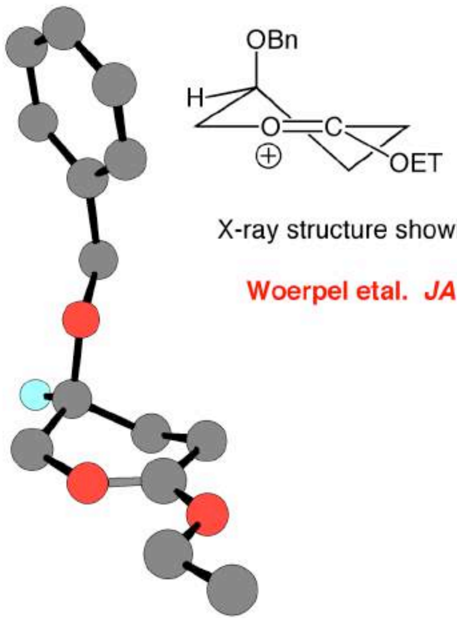
True for Path A and Path B!
Path A is preferred as it leads to a chair conformer (chair-axial addition)

MO-Description



Polar Substituents (Woerpel et al.)

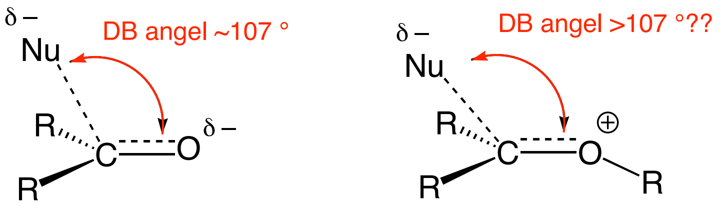
The most stable half-chair conformer is preferentially attacked.
Polar substituents exert a major influence.



X-ray structure showing axial OBn substituent.

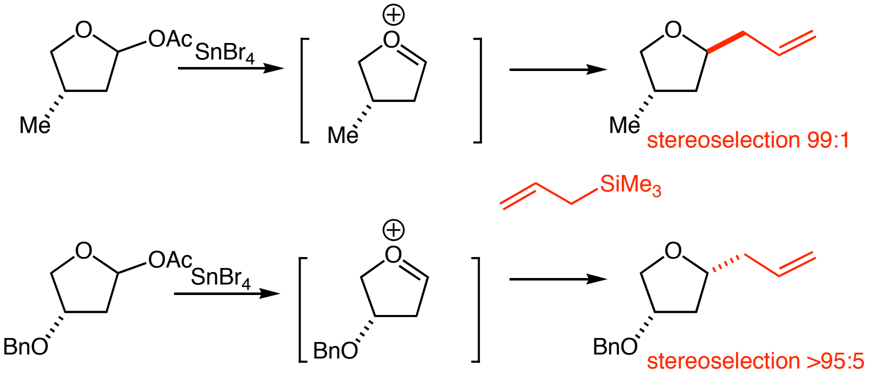
Woerpel etal. *JACS* 2005, *127,* 5322.

Dunitz, Buergi:



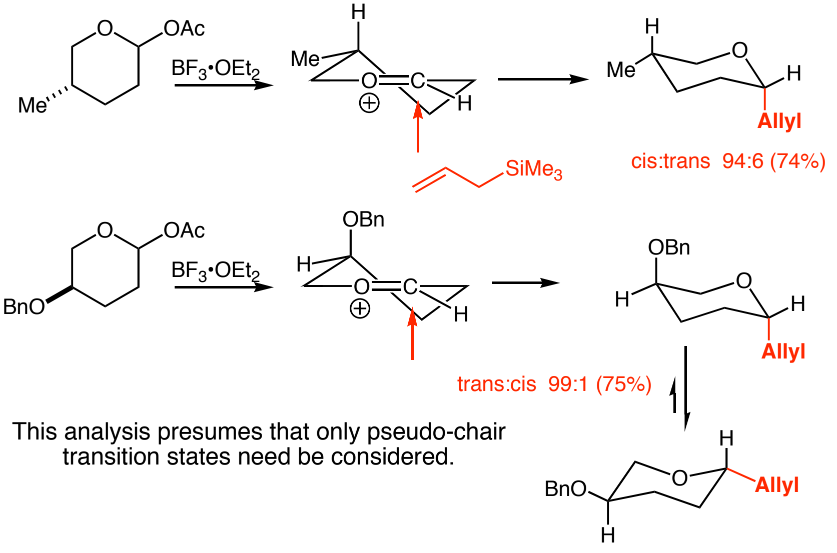
Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

5-Membered Oxocarbenium Ions: **Woerpel et al., *JACS* 1999, *121,* 12208; *JACS* 2003, *125,* 14149; *JACS* 2005, *127,* 10879.**



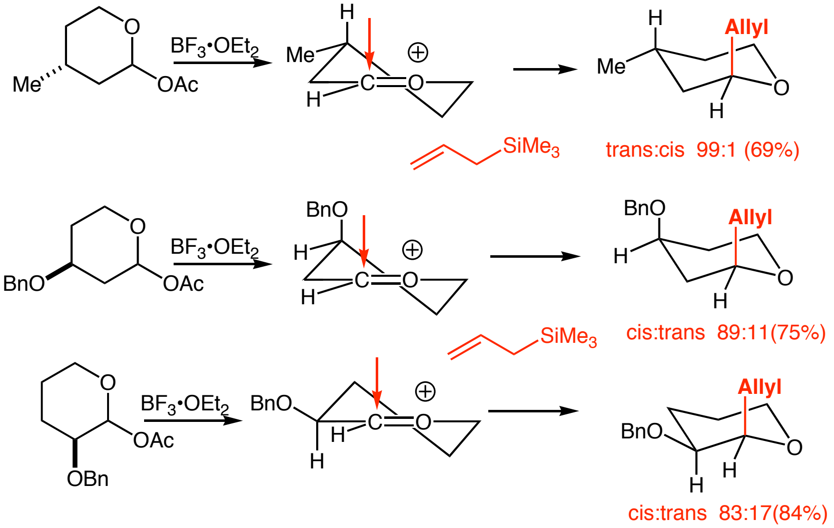
These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selectivity.

6-Membered Oxocarbenium Ions: **Woerpel et al., *JACS* 2000, *122,* 168; *JACS* 2003, *125,* 15521**



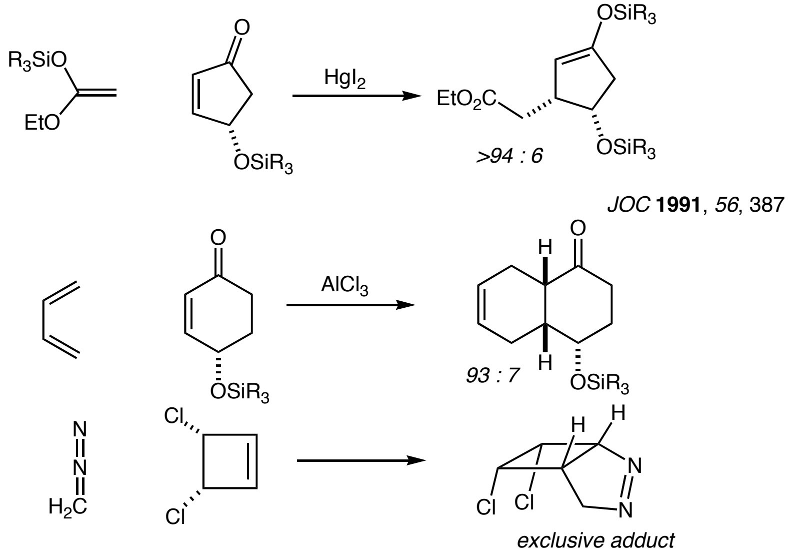
This analysis presumes that only pseudo-chair transition states need be considered.

Woerpel's model states that axial attack from the most stable chair conformer predicts the major product.



These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selectivity.

Are the preceding addition reactions somehow related to the apparently contrasteric reactions shown below??



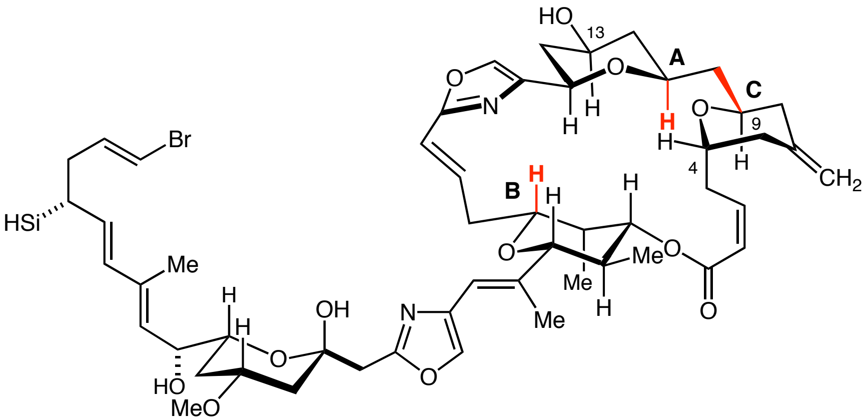
JOC **1991**, *56*, 387

Tet. Lett. **1988**, *29*, 6593

Selective Oxocarbenium Ion Additions in the Phorboxazole Synthesis

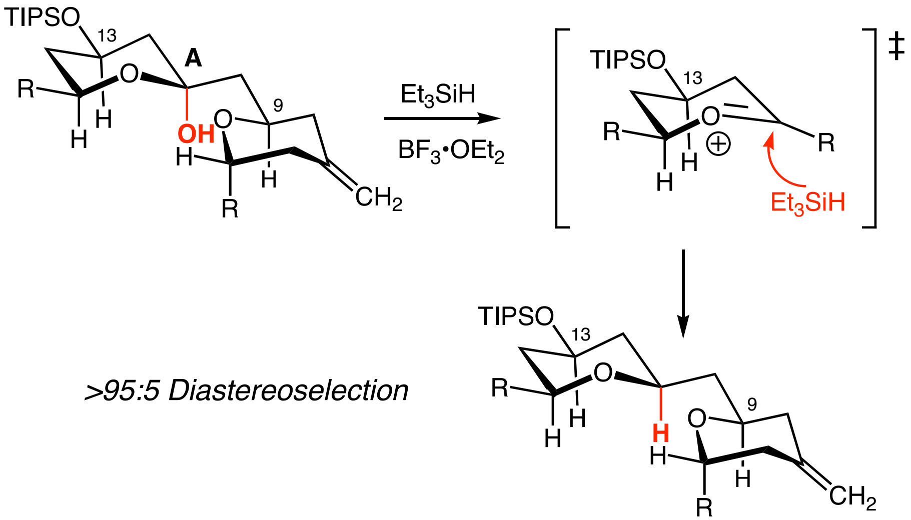
Phorboxazole B

Evans, Fitch, Smith, Cee, *JACS* ***2000***, *122, 10033*



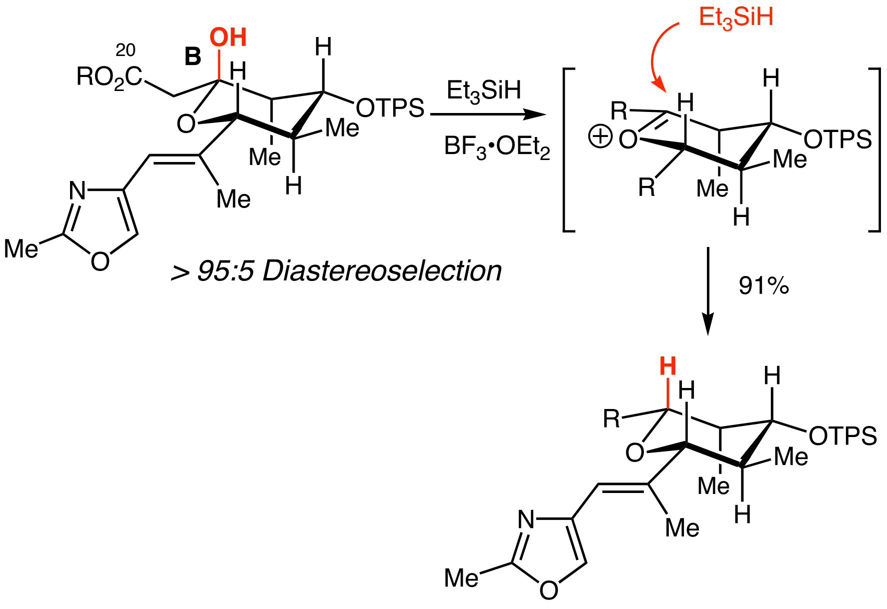
Stereochemical analogies:
Kishi et al., *JACS* **1982**, *104*, 4976-8

A: The C-11 Reduction



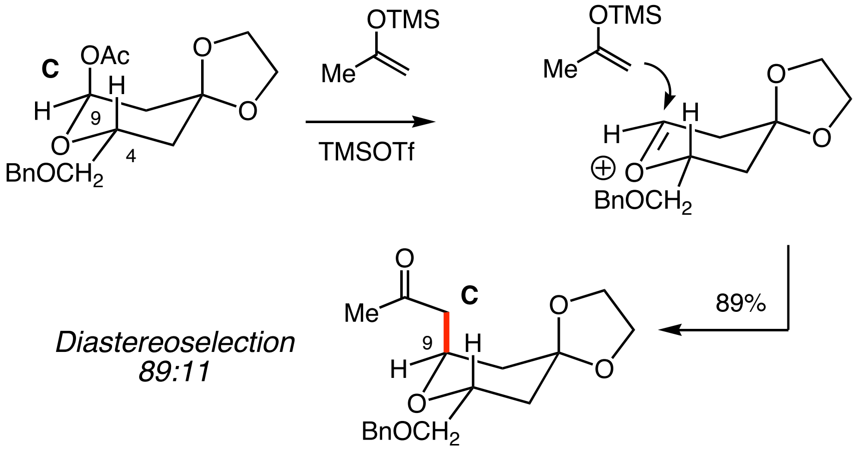
>95:5 Diastereoselection

B: The C-22 Reduction



> 95:5 Diastereoselection

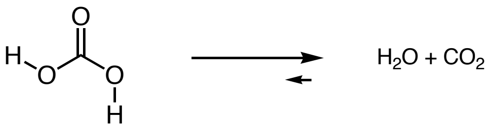
C: The C-9 C–C Bond Construction



Diastereoselection
89:11

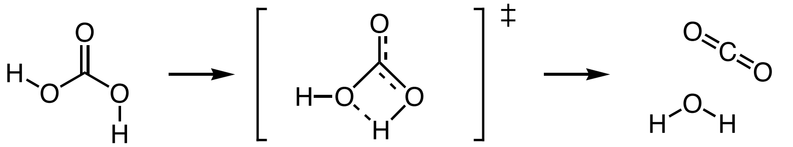
Carbonyl Addition Reactions: Transition State Geometry

Carbonic acid (Liedl et al., *Angew. Chem. Int. Ed.* 2000, *39*, 892)

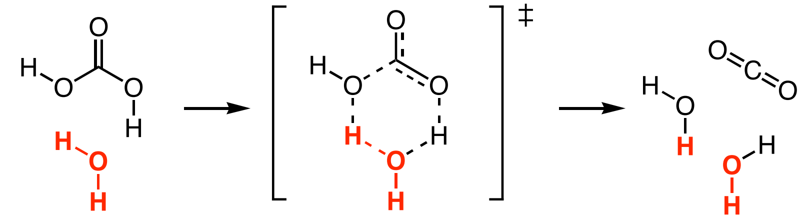


equilibrium in water: 1:99

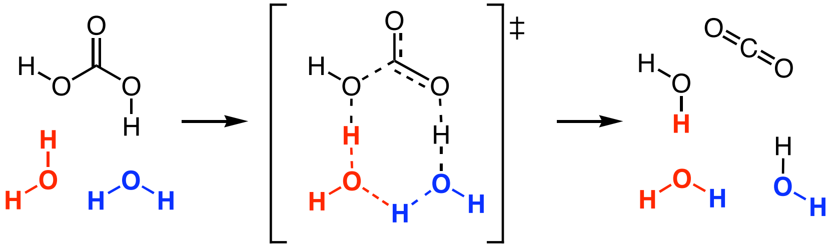
imagine how sparkling water would taste like if that equilibrium would be different...



calculated activation barrier: 44 kcal/mol



calculated activation barrier: 27 kcal/mol

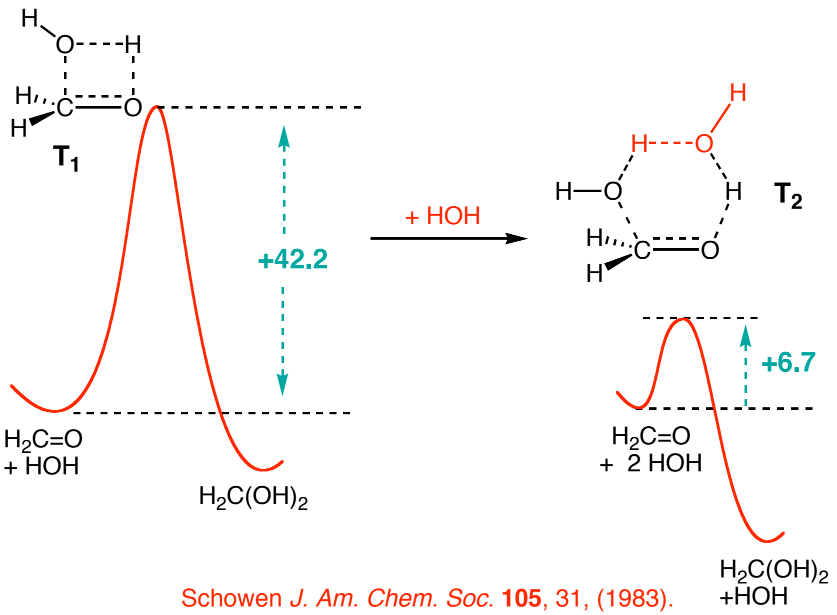


calculated activation barrier: 24 kcal/mol

4- vs 6-Membered Transition Structures for C=O Addition

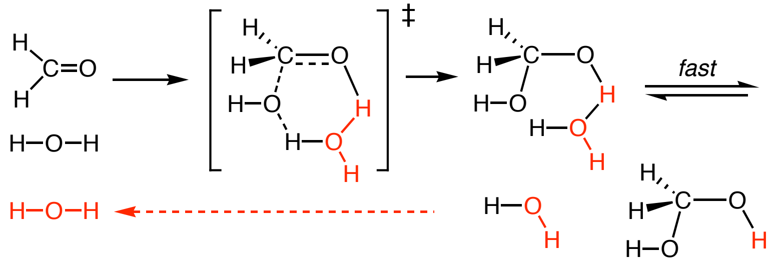
Consider carbonyl hydration:

$$H_2C{=}O \quad + \quad n\ HOH \longrightarrow H_2C(OH)_2 \quad + \quad (n-1)\ HOH$$



Schowen *J. Am. Chem. Soc.* **105**, 31, (1983).

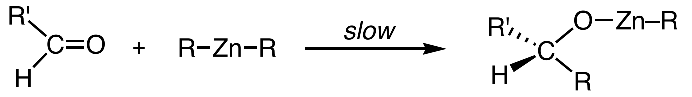
Overall Process: The value of the proton shuttle



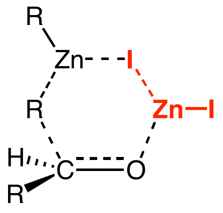
Transiton structure T_2 ~40 kcal/mol more stable than transition structure T_1.

Carbonyl Addition Reactions: Transition State Geometry

■ Do these results relate to "real" reactions? Yes!



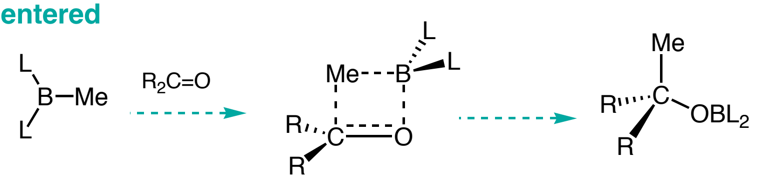
Observation: catalytic amounts of **ZnI_2** dramatically catalyze addition process.



bimetallic transition state

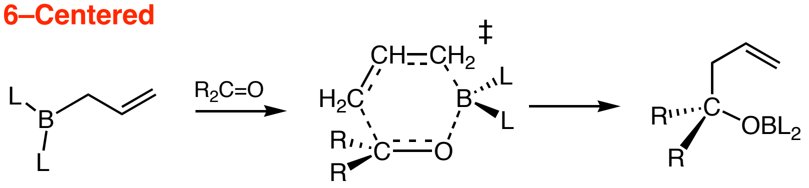
■ 4– Versus 6–Centered Transition States for Boron

4-Centered



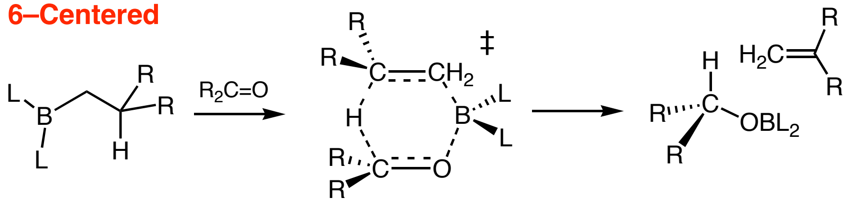
disfavored: rxn does not proceed!

6–Centered



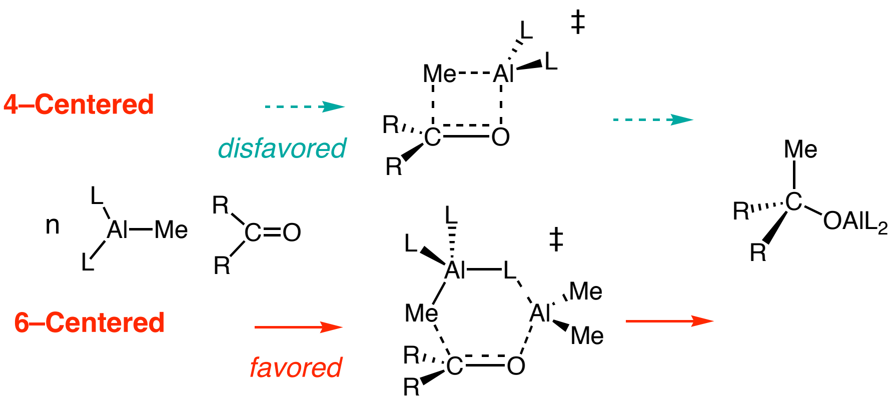
favored

6–Centered

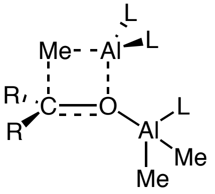


favored

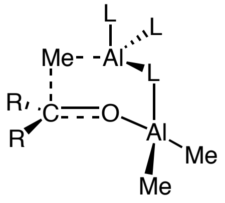
Carbonyl Addition: 4– Versus 6–Centered Transition States for Aluminum



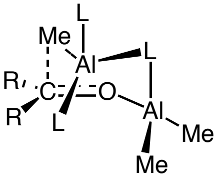
The Bimetallic Transition States are preferred



4-Centered

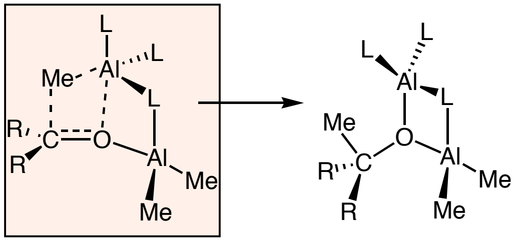


6-Centered Boat



6-Centered Chair

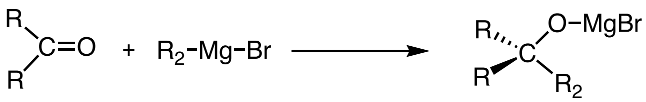
Bicyclic TS



Swain *JACS* **1951**, *73*, 870
Ashby *JACS* **1974**, *89*, 1967

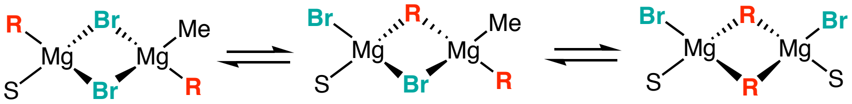
Carbonyl Addition Reactions: Transition State Geometry

Grignard Reagents:



The molecularity and transition structure for this reaction have not been carefully elucidated. The fact that the Grignard reagent is not a single species in solution greatly complicates the kinetic analysis.

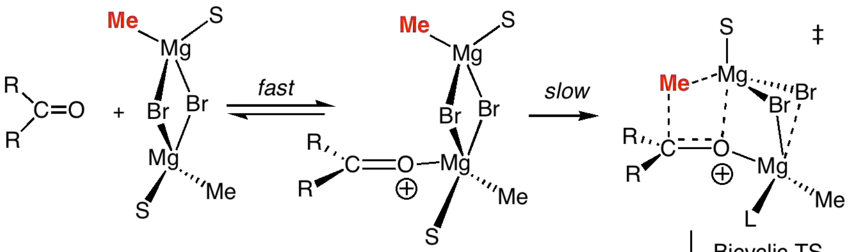
The Schlenk Equilibrium

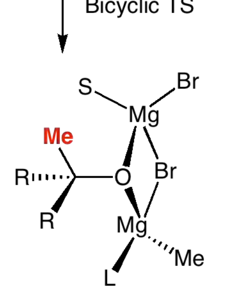


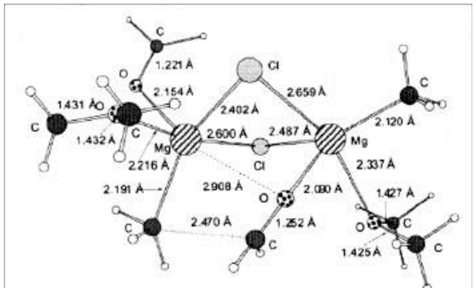
Solution structure of R–MgBr is in dynamic equilibrium through Schlenck equilibration

The Bimetallic (Binuclear) Mechanism for C=O Addition

Recent theoretical study: Yamazaki & Yambe, *J. Org. Chem.* **2002**, *67*, 9346



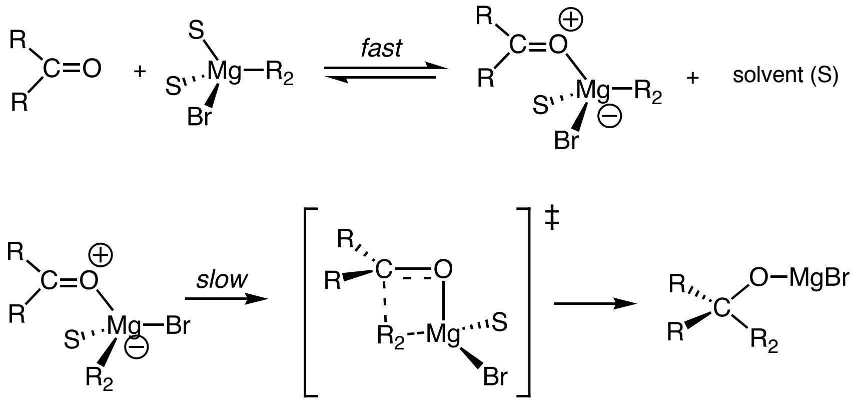




Yamazaki TS

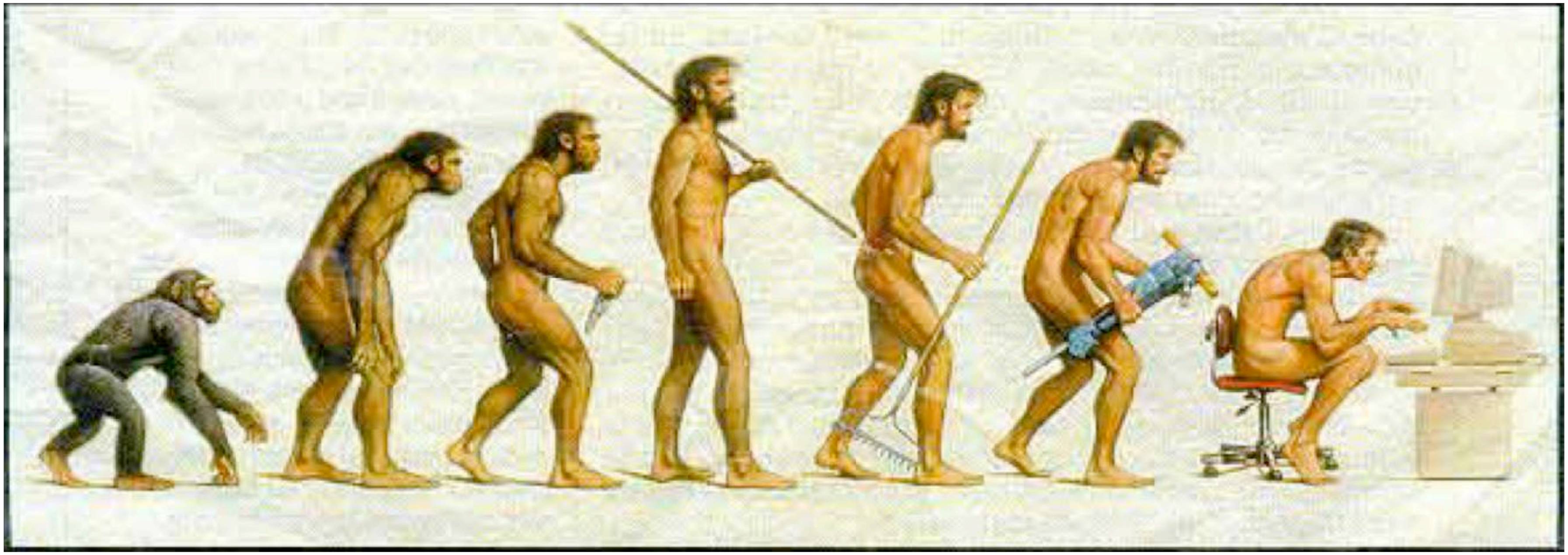
14 (TS)
+0.3 kcal/mol

The Mononuclear Mechanism is now in disfavor



The Evolution of Models for Carbonyl Addition

Mengel, A. and O. Reiser, "Around and Beyond Cram's Rule."
Chem. Rev. **1999**, 1191-1223



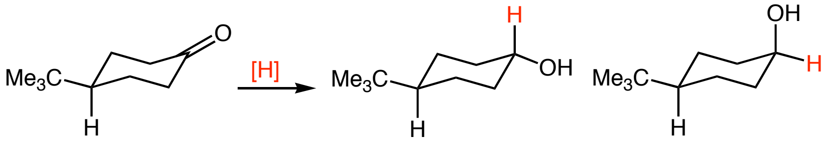
Fischer Cram Cornforth Felkin Anh/Eisenstein Cieplak Tomoda

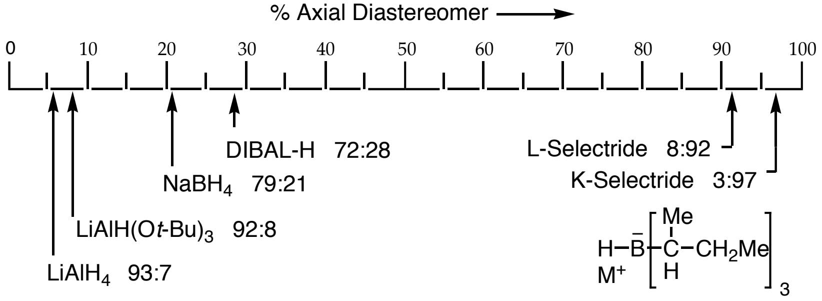
Humor provided by Sarah Siska

Evolution of a Model for C=O Addition

■ Product Development & Steric Approach Control:

Dauben, *JACS* **1956**, *78*, 2579



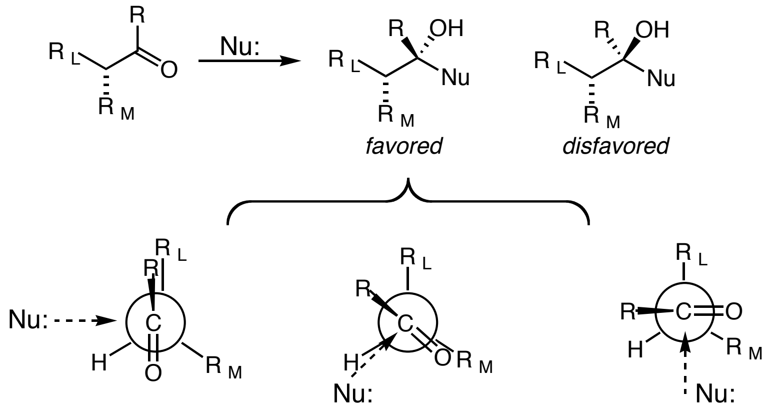


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

Assumption: Hindered reagents react through more highly developed transition states than unhindered reagents

Recall discussion in Lecture 7.

Carbonyl Addition: Evolution of Acyclic Models



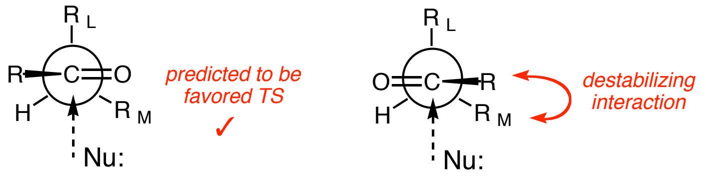
Cram
JACS **1952**, *74*, 5828

Karabatsos
JACS **1967**, *89*, 1367

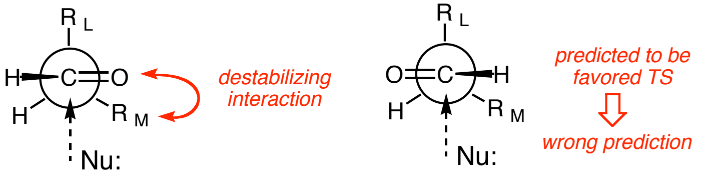
Felkin
TL. **1968**, 2199-2208

Assumptions in Felkin Model:

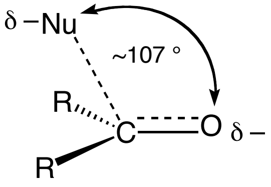
- ■ Transition states are all reactant-like rather than product-like.
- ■ Torsional strain considerations are dominant.
  Staggered TS conformations preferred
- ■ The principal steric interactions are between Nu & R.



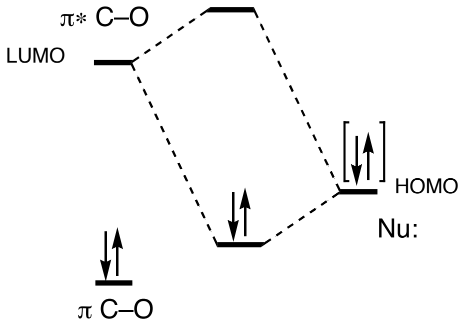
The flaw in the Felkin model: A problem with aldehydes!!



Stereoelectronic Effect: The HOMO-LUMO interaction dictates the following reaction geometry:



The Dunitz-Bürgi Angle

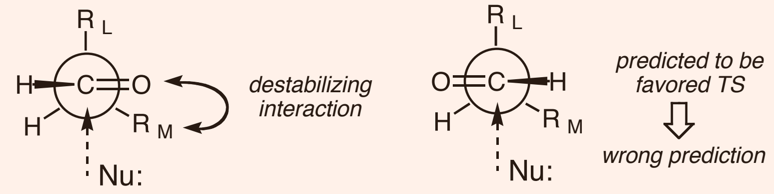


attack angle greater than 90 °; estimates place it in the 100–110 ° range

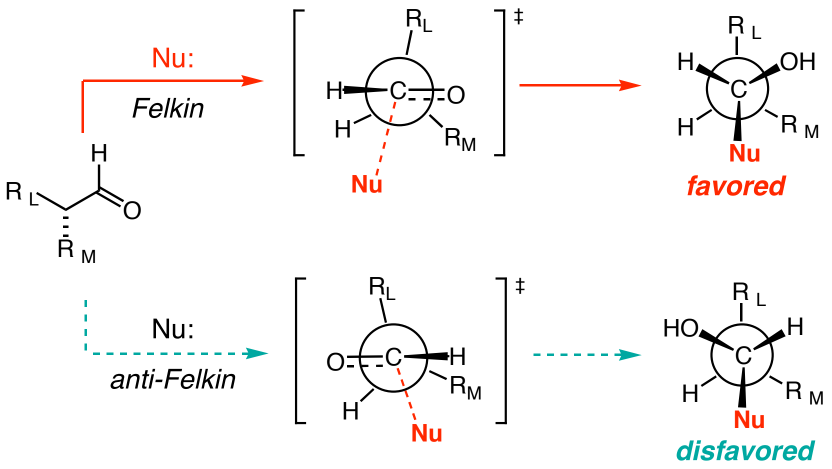
Burgi, Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153-161

The Felkin-Anh Eisenstein Model

The flaw in the Felkin model: A problem with aldehydes!!



Anh & Eisenstein *Noveau J. Chim.* **1977**, *1*, 61-70
Anh *Topics in Current Chemistry* **1980**, *88*, 146-162



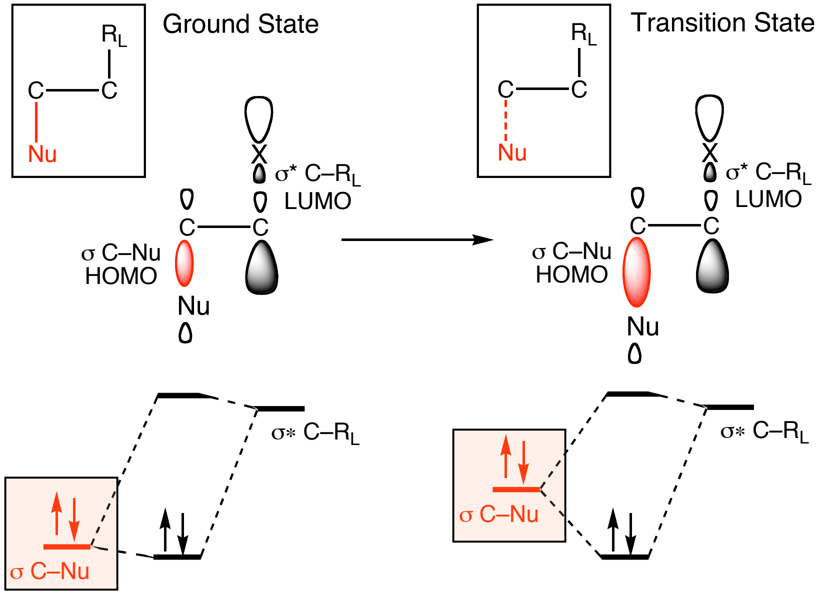
New Additions to Felkin Model:

- Dunitz-Bürgi C=O–Nu orientation applied to Felkin model.
- The antiperiplanar effect:
  Hyperconjugative interactions between C-R_L which will lower π*C=O will stabilize the transition state.

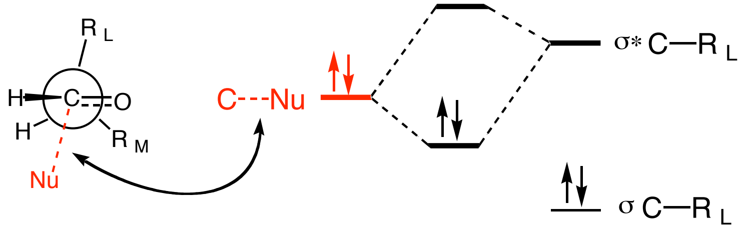
Theoretical Support for Staggered Transition states (Lecture 7)

(Read this) Houk, *JACS* **1982**, *104*, 7162-6
(Read this) Houk, *Science* **1986**, *231*, 1108-17

Houk: "The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds"
Lecture–7



Best acceptor σ* orbital is oriented anti periplanar to forming bond



■ Theoretical support:

Padden-Row, *Chem. Commun.* **1990**, 456; ibid **1991**, 327
Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5018
Frenking & Reetz, *Tetrahedron* **1991**, *47*, 8091

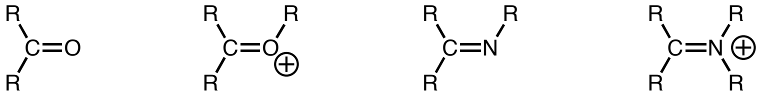
http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 22

Carbonyl and Azomethine Electrophiles-2



- Breakdown in the Felkin-Anh Model
- Cyclohexanone Revisited
- Diastereoselective Additions to Cyclic Ketones
- Chelate Controlled Carbonyl Additions

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

D. A. Evans

Wednesday
November 8, 2006

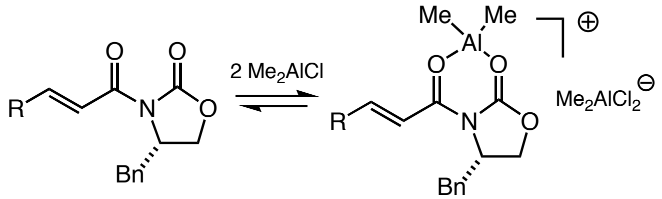
1. "Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chim.* **1977**, *1*, 61-70.

2. "Structural, mechanistic, and theoretical aspects of chelation controlled carbonyl addition reactions." Reetz, *Acc. Chem. Res.* **1993**, *26*, 462. **(pdf)**

3. "A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes." Evans, et al. *JACS* **1996**, *118*, 4322-4343. **(Handout)**

4. "The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride. The Merged Stereochemical Impact of α- and β-Stereocenters in Chelate-Controlled Carbonyl Addition Reactions with Enolsilane and Hydride Nucleophiles". Evans, Allison, Yang, Masse, *JACS* **2001**, *123*, 10840-10852. **(Handout)**

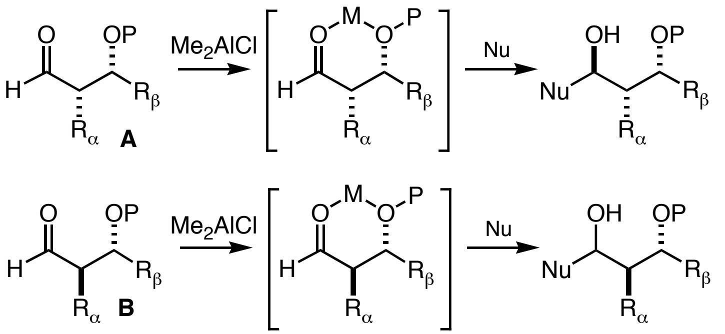
Me_2AlCl is the most powerful chelating Lewis acid yet documented



(1)

"Asymmetric Diels-Alder Cycloaddition Reactions with Chiral α,β-Unsaturated *N*-Acyloxazolidinones". Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

Syn Diastereomer: α & β Centers Reinforcing



(2)

(3)

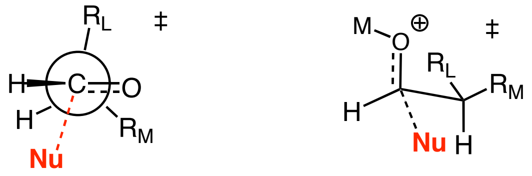
Anti Diastereomer: α & β Centers Opposing

The Felkin-Anh Eisenstein Model

So what is the dominant HOMO–LUMO interaction in the addition of nucleophiles to C=O's?

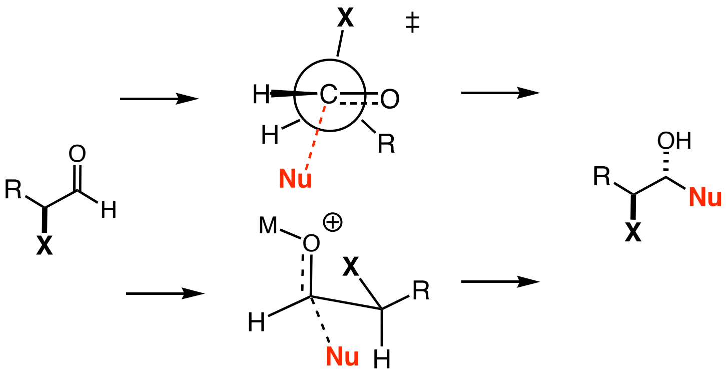
Felkin-Anh Hypothesis suggests:

This case suggests that the dominant HOMO–LUMO interaction is between the forming C–Nu bond (HOMO) and the π^*C=O LUMO. The LUMO associated with the resident *antibonding* C–R_L bond may further stabilize TS.



The HOMO: Forming C–Nu bond
The LUMO: π^* C=O
Additional transition state stabilization may be achieved by hyperconjugative stabilization of the forming bond through delocalization with the resident *antiperiplanar antibonding C–*R_L bond.

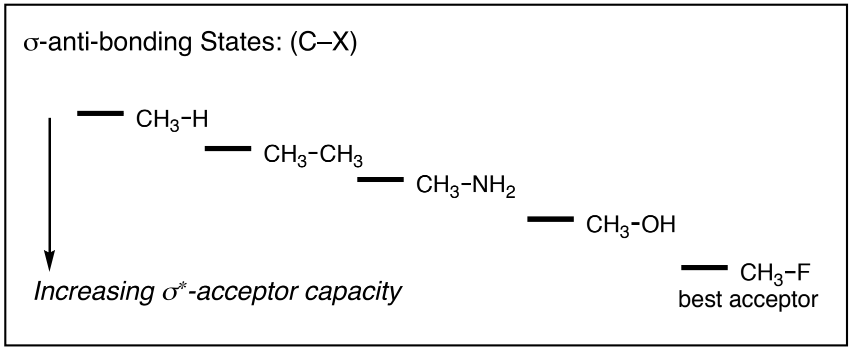
"Polar" Felkin-Anh Hypothesis suggests:



In the polar model, the substituent with the best acceptor antibonding orbital (σ^*C–X) is oriented antiperiplanar to the forming C–Nu bond.

Hierarchy of Donor & Acceptor States

The following trends are made on the basis of comparing the bonding and antibonding states for the molecule CH_3-X where X = C, N, O, F, and H.



σ-anti-bonding States: (C–X)

CH_3-H

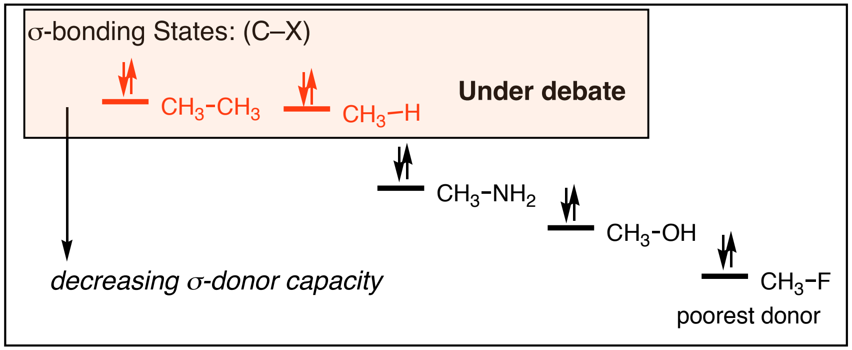
CH_3-CH_3

CH_3-NH_2

CH_3-OH

CH_3-F
best acceptor

Increasing σ^*-acceptor capacity



σ-bonding States: (C–X)

CH_3-CH_3

CH_3–H

Under debate

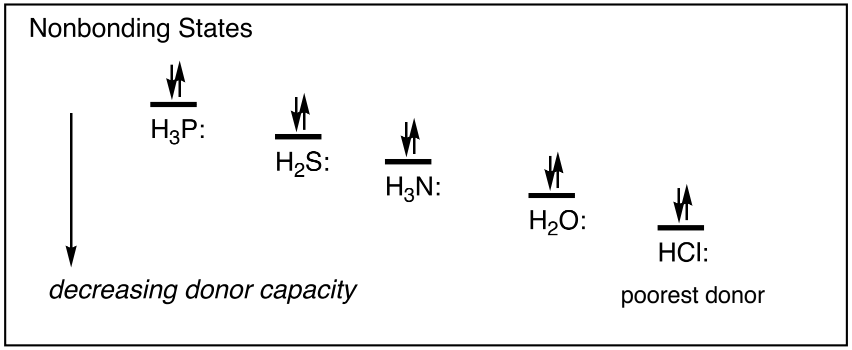
CH_3-NH_2

CH_3-OH

CH_3-F
poorest donor

decreasing σ-donor capacity

The following are trends for the energy levels of *nonbonding states* of several common molecules. The trend was established by photoelectron spectroscopy.



Nonbonding States

H_3P:

H_2S:

H_3N:

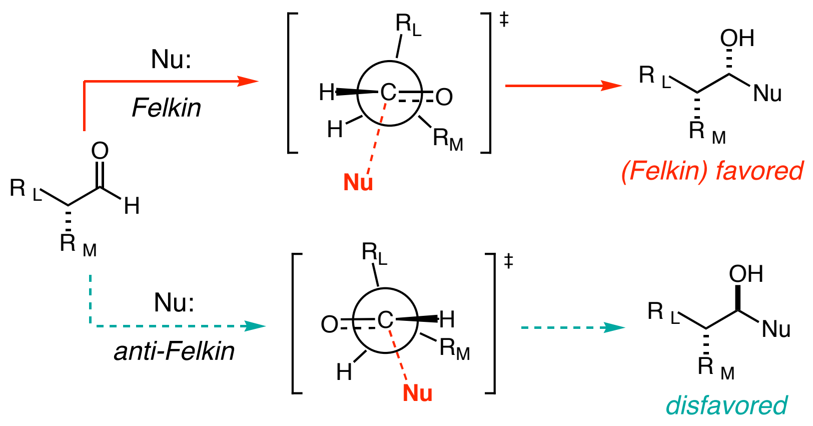
H_2O:

HCl:
poorest donor

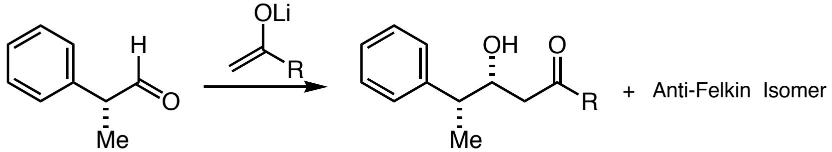
decreasing donor capacity

The Felkin-Anh Eisenstein Model: Verification

Addition of Enolate & Enol Nucleophiles

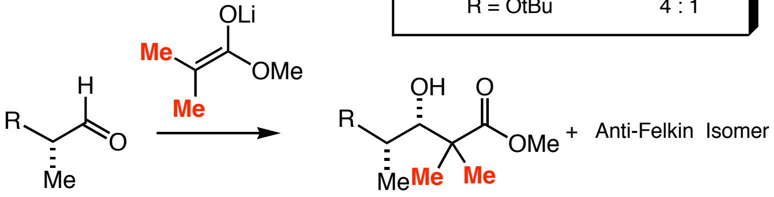


Trend-1: For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, *26*, 973.

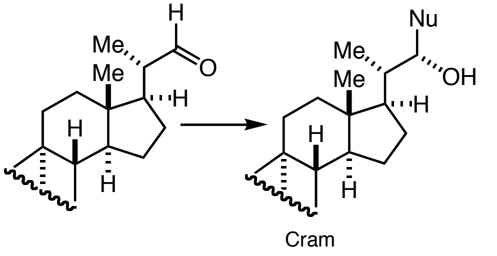
Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1



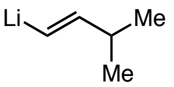
L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, *26*, 973.

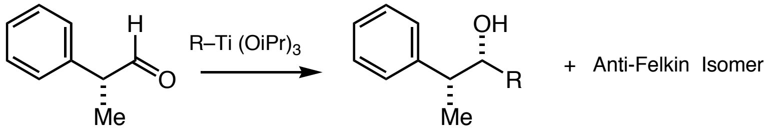
Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C_6H_{11}	9 : 1

■ This trend carries over to organometallic reagents as well



C. Djerassi & Co-workers,
J. Org. Chem. **1979**, *44*, 3374.

Reagent	Ratio
ClMg−C≡CEt	1 : 1
	5 : 1

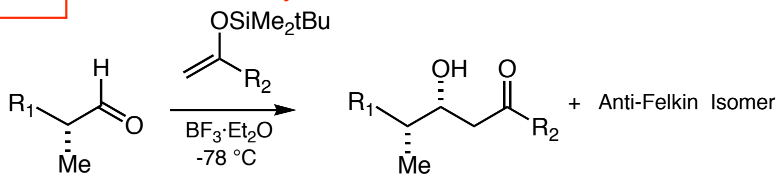


M. Reetz & Co-workers,
Angew. Chem. Int. Ed. **1982**, *21*, 135.

(R–MgX give ca 3:1 ratios)

R-Titanium	Ratio
R = Me	>90 : 10
R = n-Bu	>90 : 10

Trend-2: Lewis acid catalyzed reactions are more diastereoselective

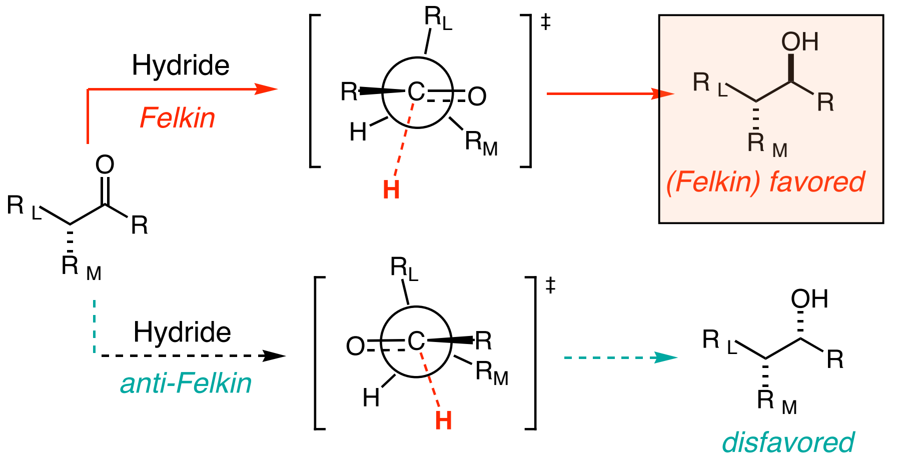


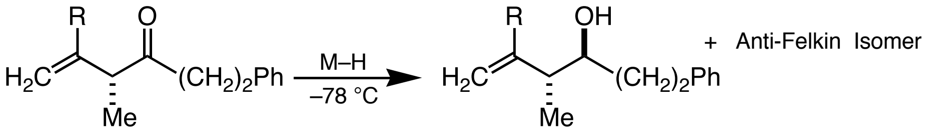
Ketone (R_1)	Enolate (R_2)	Ratio	Ratio Li enolate
R = Ph	R = Me	10 : 1	3 : 1
R = Ph	R = t-Bu	24 : 1	
R = Ph	R = OMe	15 : 1	
R = Ph	R = Ot-Bu	36 : 1	4 : 1
R = c-C_6H_{11}	R = Ot-Bu	16 : 1	

C. Heathcock & L. Flippin *J. Am. Chem. Soc.* **1983**, *105*, 1667.

The Felkin-Anh Eisenstein Model: Ketone Reduction

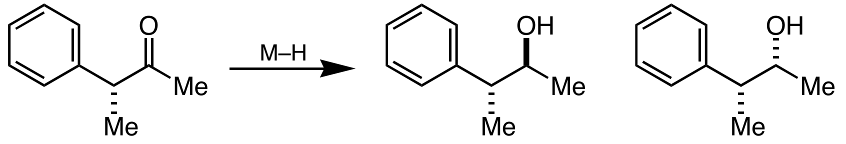
Addition of Hydride Nucleophiles





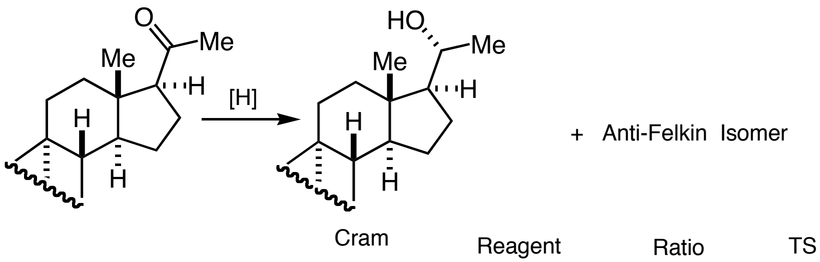
G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, *25*, 2479.

Ketone (R)	Reagent	Ratio
R = H	$\text{Li}^+\text{H–B}^-(\text{sec-Bu})_3$	96 : 4
R = H	DIBAL	47 : 53
R = Me	$\text{Li}^+\text{H–B}^-(\text{sec-Bu})_3$	>99 : 1
R = Me	DIBAL	88 : 12



M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

Reagent	Ratio	TS ‡
$\text{Li}^+\text{H–B}^-(\text{sec-Bu})_3$	22 : 1	Felkin
H–B(Sia)_2	1 : 4	Anti-Felkin

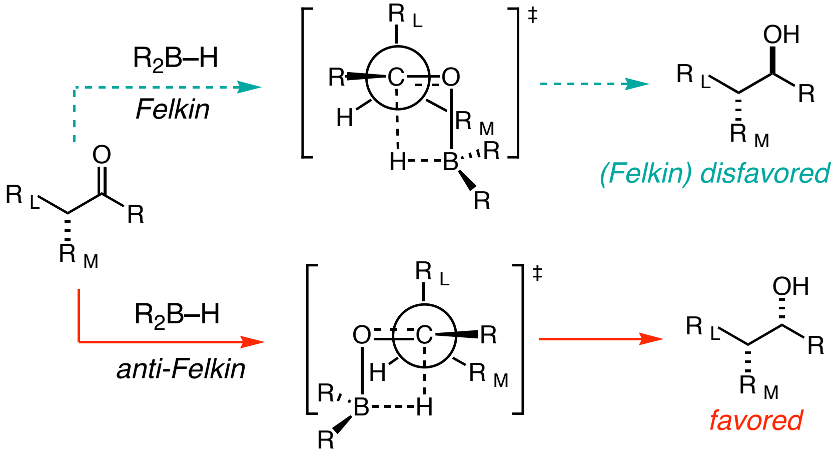


M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

Reagent	Ratio	TS ‡
$\text{Li}^+\text{H–B}^-(\text{sec-Bu})_3$	54 : 1	Felkin
NaBH_4	5 : 1	Felkin
LiAlH_4	3 : 1	Felkin
H–B(Sia)_2	1 : 10	Anti-Felkin

Note: Borane reducing agents do not follow the normal trend

Transition States for C=O-Borane Reductions



Nonspherical nucleophiles are unreliable in the Felkin Analysis

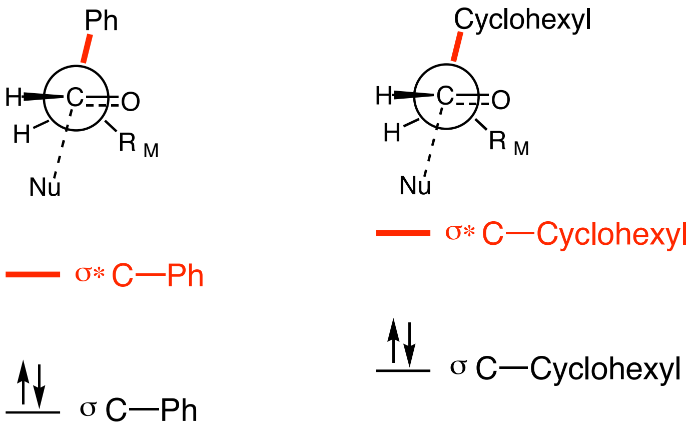
Exercise: Draw the analogous bis$(\text{R}_2\text{BH})_2$ transition structures

The Felkin-Anh Eisenstein Model: A Breakdown

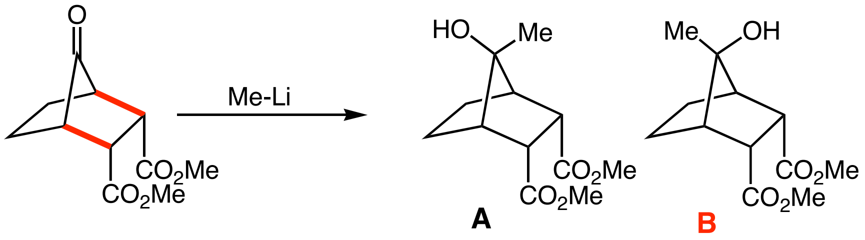
Are there cases not handled by the Anh-Eisenstein Model?

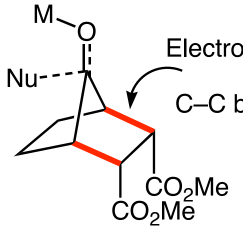
Anh-Eisenstein:
"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

σ* C_{SP3}–C_{SP2} is lower in energy than σ* C_{SP3}–C_{SP3} bond.



Case I:

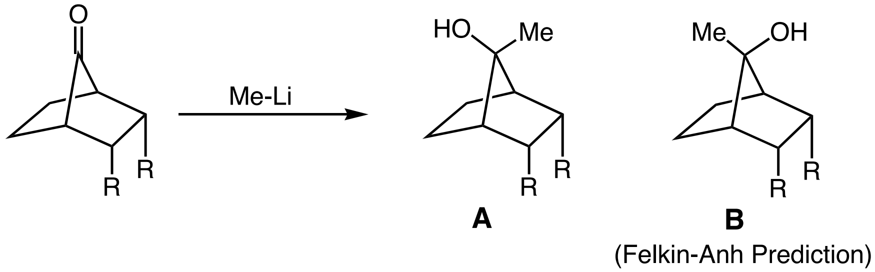




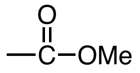
Electronegative -CO_2Me substituent will stabilize both C–C bonding & antibonding states

Felkin-Anh analysis predicts **B**

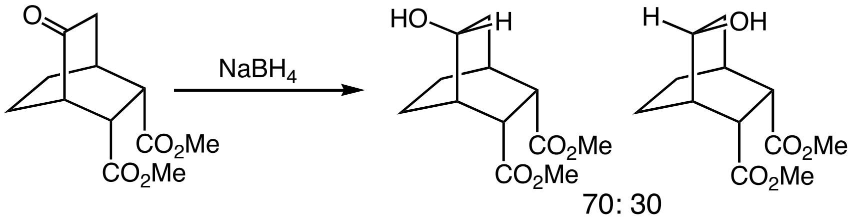
Felkin-Anh analysis predicts **B** for R = electronegative substituent.

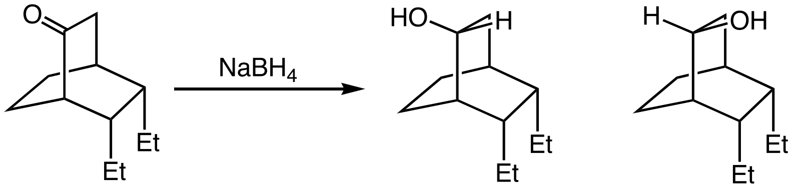


G. Mehta, *JACS* **1990**, *112*, 6140

(R) Substituent	A/B Ratio
 $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OMe}$	>90:10
—CH_2OMe	34:66
—$CH=CH_2$	27:73
—CH_2–CH_3	17:83

Felkin-Anh analysis predicts the wrong product!



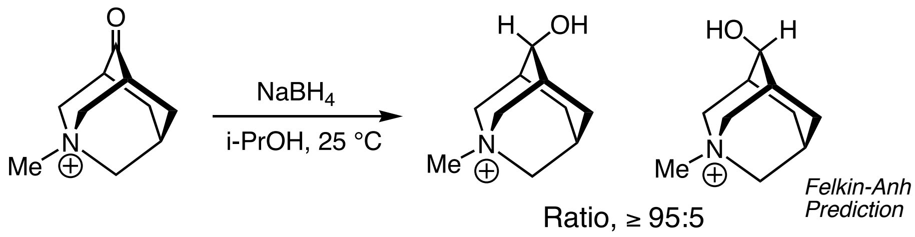


$NaBH_4$	39: 61
Me–Li	34: 66

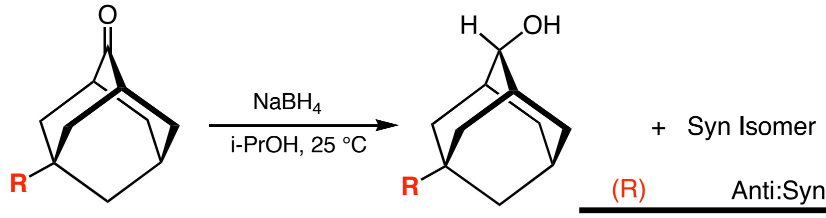
G. Mehta, *Chem. Commun.* **1992**, 1711-2:
"These results can be reconciled in terms of the Cieplak model."

The Felkin-Anh Eisenstein Model: A Breakdown

Case II: The Le Noble Examples **Le Noble, *JACS* 1992, *114*, 1916**

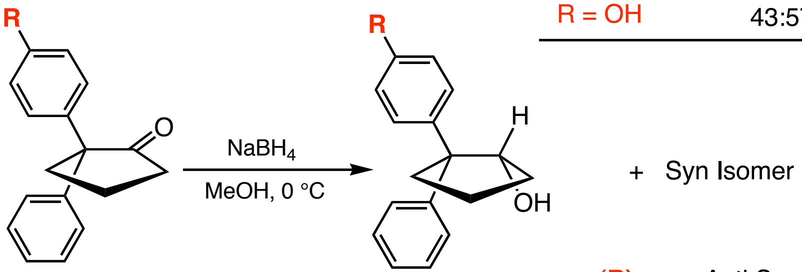


Pyramidally distorted C=O ruled out from inspection of X-ray structures.



(R)	Anti:Syn Ratio
R = F	62:38
R = CO_2Me	61:39
R = $SiMe_3$	45:55
R = OH	43:57

Le Noble, *J. Org. Chem.* **1989**, *54*, 3836



(R)	Anti:Syn Ratio
R = NO_2	79:21
R = Cl	63:37
R = OMe	43:57
R = NH_2	36:64

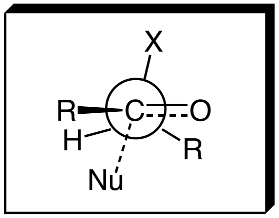
Halterman, *JACS* **1990**, *112*, 6690

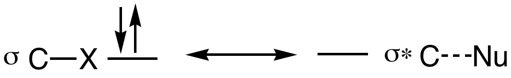
Cieplak Model for C=O Addition

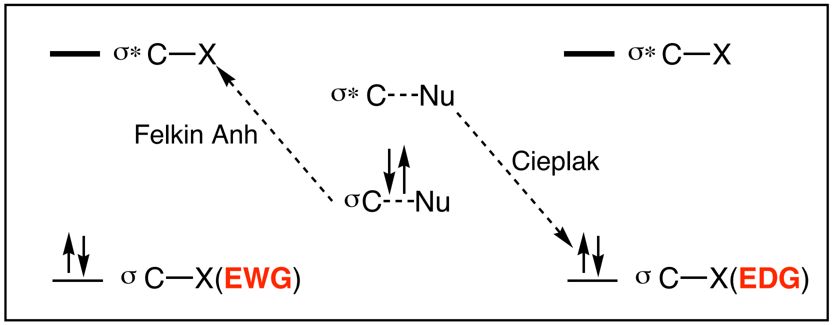
Cieplak, *JACS* **1981**, *103*, 4540; Cieplak/Johnson, *JACS* **1989**, *111*, 8447

Point A: TS is stabilized by antiperiplanar allylic bond, but....

Point B: Nature of the stabilizing secondary orbital interactions differ:







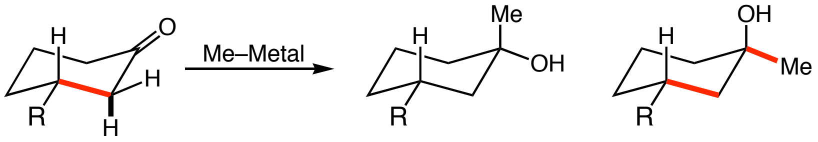
Point C: C–X Electron donating ability follows the order:
C–H > C–C > C–N > C–O
(Houk disputes the ordering of C–H, C–C)

Point D: Importance of torsional effects
(Felkin, Anh, Houk, Padden-Row) disputed.

> "Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamendal assumptions in frontier molecular orbital theory." "The Cieplak hypothesis is nonsense." "Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."
>
> *The management*

The Cyclohexanone Case Revisited: Frencking & Houk

Observation As R becomes more electronegative, percentage of axial attack increases.



(R) Substituent	% Axial Attack Me-Li	 Me_2Cu-Li
R = H	21%	6%
R = C_6F_5	34%	21%
R = CF_3	50%	42%

Felkin-Anh predicts opposite trend.

Cieplak argument consistent with results.

The Frencking Position:

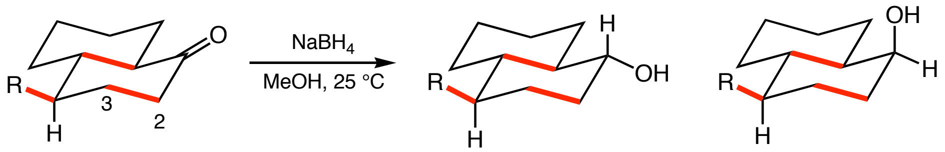
- Cieplak stabilizing interaction is "dubious." Why not stabilize the forming sigma bond?
- Enhanced rate of axial Nu attack on cyclohexanone is caused by better electrostatic interactions of the ketone with the attacking reagent and not by torsional considerations.
- Nonequivalence of the π^*C=O LUMO with a greater extension on the axial face dictates stereoselection (Klein, 1973).

"Since interactions between the π C=O & π^* C=O and the bonding & anti-bonding (β) C–H & (β) C–C orbitals are all symmetry allowed, it is difficult to predict a priori which interactions are dominant without carrying out quantum mechanical calculations."

Frencking & Reetz, *Angew. Chem.* Int. Ed. **1991**, *30*, 1146

Houk: Electrostatic rather than covalent considerations may be dominant.

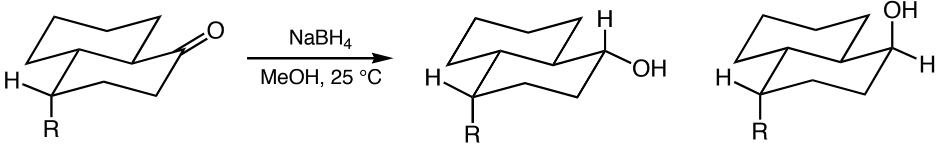
Houk: If hyperconjugative interactions are important, equatorial electronegative substituents should interact more strongly with the C(2-3) and C(9-10) bonds than axial substituents.



Since there seems to be little effect from the equatorial R substituent, hyperconjugation may not be a major contributor to TS stabilization.

(R) Substituent	Product Ratio
R = H	60:40
R = OAc	71:29
R = Cl	71:29

"**Cieplak:** If nucleophilic addition occurs anti to the better donor bond, the equatorial isomers should have considerably more axial attack than the parent while the axial isomers should have only a slight increase in axial attack."

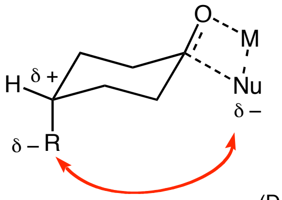


"Nevertheless, exactly the opposite is observed."

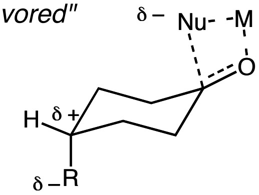
(R) Substituent	Product Ratio
R = OAc	83:17
R = Cl	88:12

Houk, "Axial 4-substituents favor axial attack for electrostatic reasons"

"Disfavored"



"Favored"



(DAE: Bimetallic transition states were not considered)

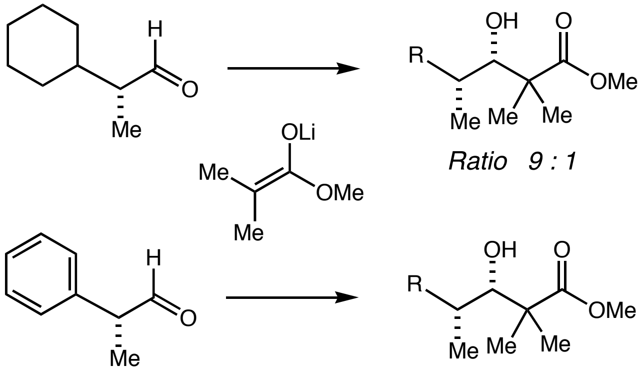
K. Houk & Co-workers, *J. Am. Chem. Soc.* **1991**, *113*, 5018

The Felkin-Anh Eisenstein Model: Electronic Effects

Are there electronic effects in the reaction?

Several cases have already been presented which may be relevant

L. Flippin & Co-workers, *Tetrahedron Lett.*. **1985**, *26*, 973.



+ Anti-Felkin Isomer

Ratio 9 : 1

+ Anti-Felkin Isomer

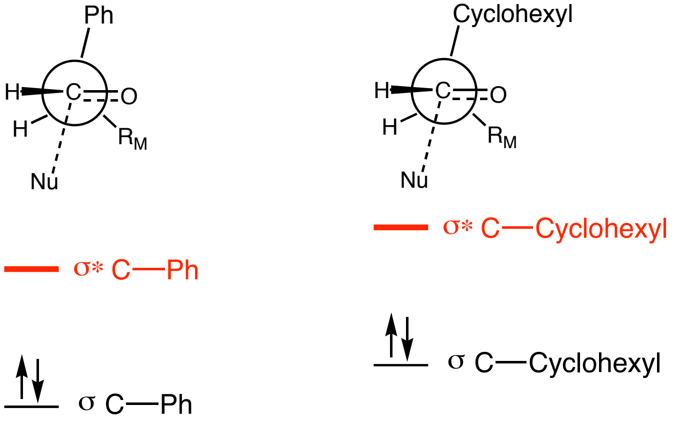
Ratio > 200 : 1

The molecular volume occupied by cyclohexyl acknowledged to be larger than that for phenyl. Because of shape phenyl "can get out of the way."

■ Anh-Eisenstein Explanation based on HOMO-LUMO Analysis:

"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

$\sigma*$ C_{SP3}–C_{SP2} is lower in energy than $\sigma*$ C_{SP3}–C_{SP3} bond.



σ* C—Cyclohexyl

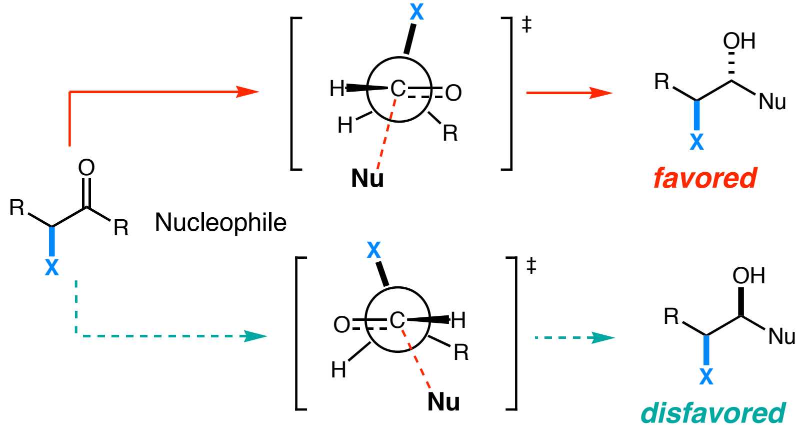
σ* C—Ph

↑↓ σ C—Cyclohexyl

↑↓ σ C—Ph

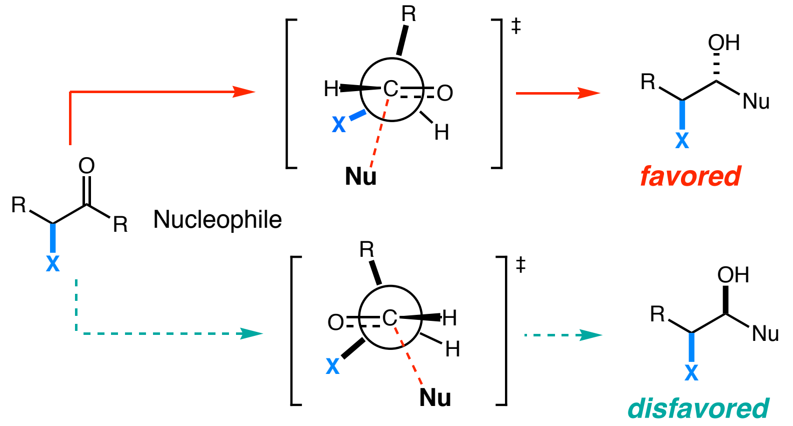
The Polar Felkin-Anh Model

Premise: Transition state **hyperconjugation** between forming bond (HOMO) and best antiperiplanar acceptor (σ* C–**X**, LUMO). Steric effects alre also considered; X = Halogen, OR, SR etc



Modified Cornforth Model

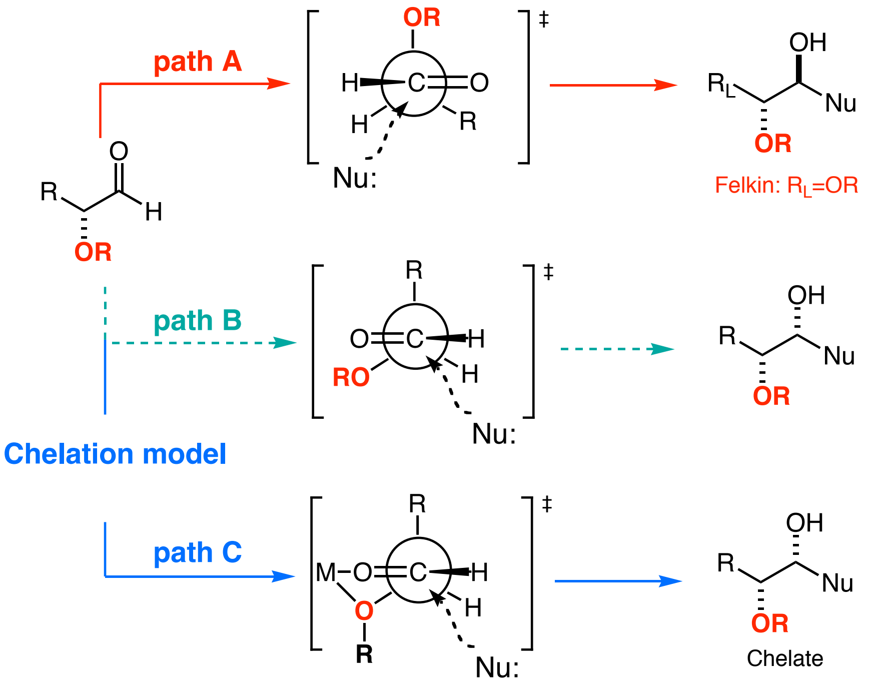
Premise: Transition State **dipole minimization** between polar C–X substituent and the transforming carbonyl function dictate preferred TS geometrics. Steric effects are also considered; X = Halogen, OR, SR etc



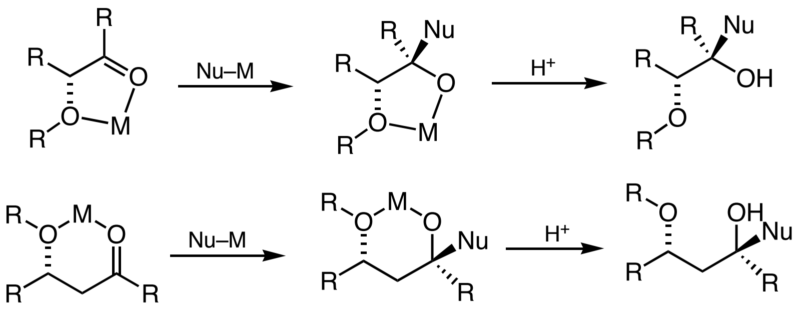
Both models lead to the same stereochemical prediction.

Carbonyl Addition Reactions: Chelate Organization

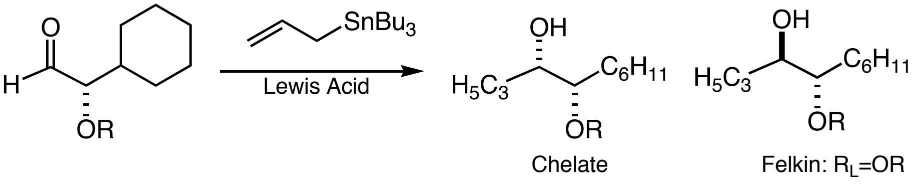
Addition of Carbon Nucleopiles



Chelate organization also provides a powerful control element in carbonyl addition reactions

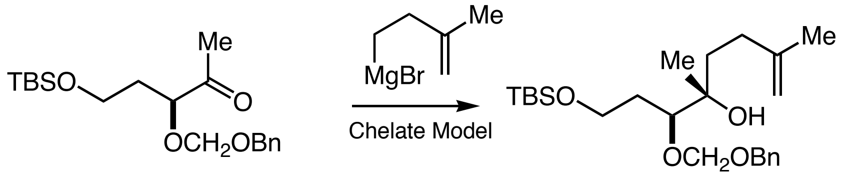


Reviews Reetz, *Acc. Chem. Res*. **1993**, *26*, 462-468 **(pdf)**
Reetz, *Angew. Chem. Int. Ed*. **1984**, *23*, 556-569

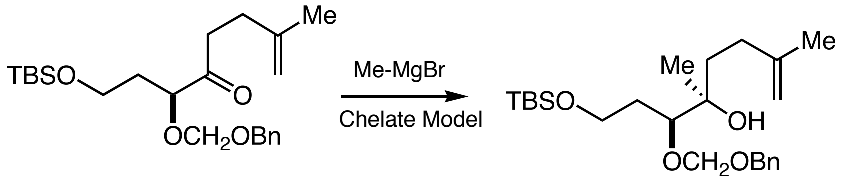


(OR)	Acid	Solv.	Ratio
R = CH_2OBn	$MgBr_2$	THF (0°)	20 : 80
R = CH_2OBn	$MgBr_2$	CH_2Cl_2 (-20°)	>99 : 1
R = CH_2OBn	$TiCl_4$	CH_2Cl_2 (-78°)	>99 : 1
R = $SiMe_2(t)Bu$	BF_3-Et_2O	CH_2Cl_2 (-78°)	5 : 95

G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 265

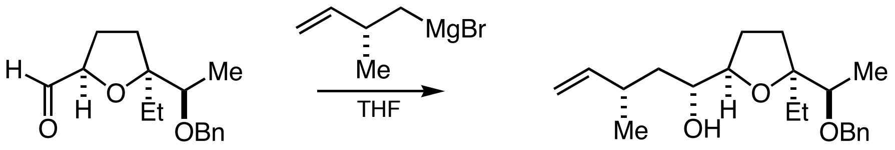


diastereoselection 50 : 1



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

diastereoselection >100 : 1

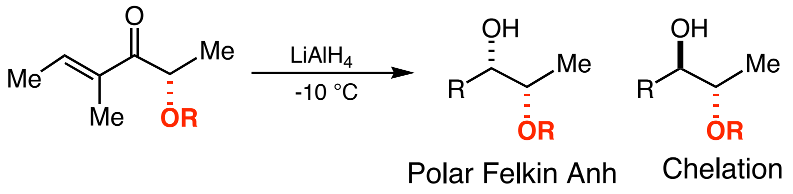


Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, *19*, 2745

"only one isomer"
Chelate Model

Chelate Organization in C=O Addition

Chelate organization provides a powerful control element in carbonyl addition reactions

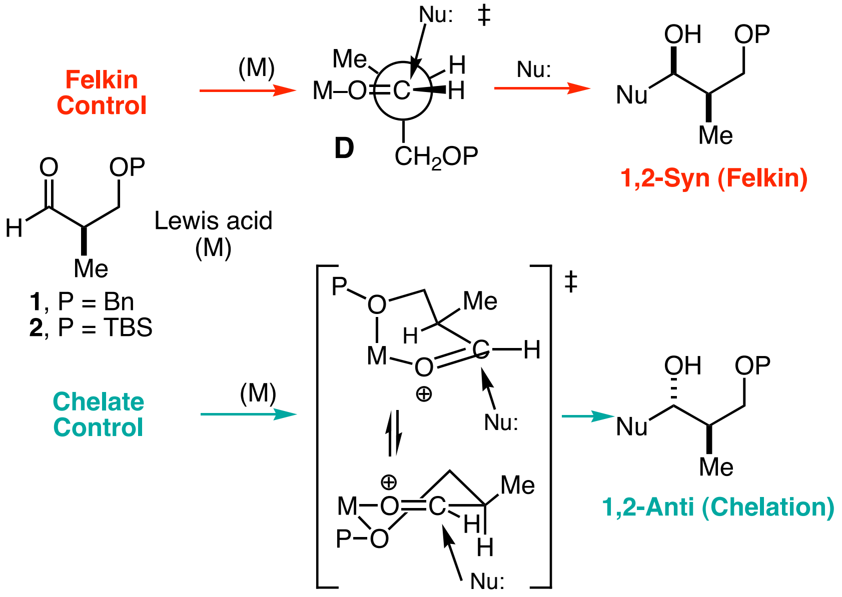


Overman
Tet Lett. **1982**, *23*, *2355*

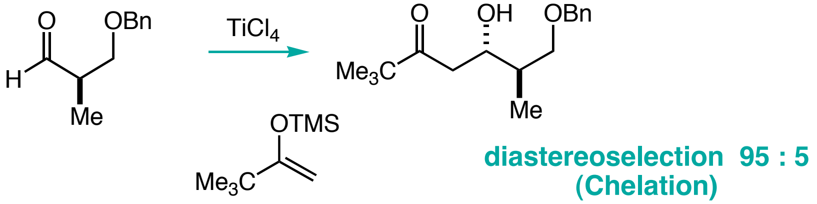
(OR)	Solv.	Ratio	Model
R = CH$_2$OBn	THF	30 : 70	Chelate
R = CH$_2$OBn	Et$_2$O	2 : 98	Chelate
R = SiPh$_2$(t)Bu	**THF**	**95 : 5**	**F–A: R$_L$=OR**

Degree of chelate organization may be regulated by choice of solvent and protecting group. Note that SiPh$_2$(t)Bu group prevents chelation.

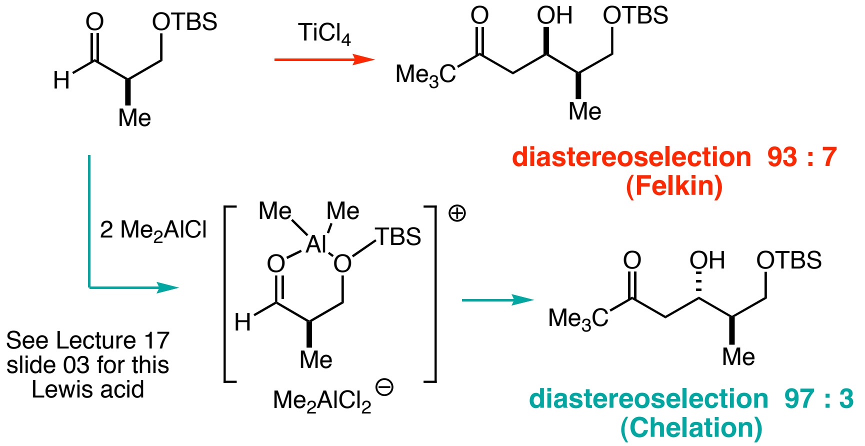
Case Study



1, P = Bn
2, P = TBS



diastereoselection 95 : 5
(Chelation)

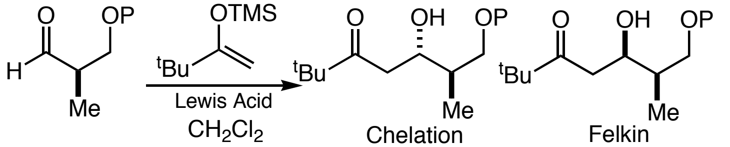


diastereoselection 93 : 7
(Felkin)

See Lecture 17
slide 03 for this
Lewis acid

diastereoselection 97 : 3
(Chelation)

Me$_2$AlCl & MeAlCl$_2$ only Lewis acids that will chelate strongly to OSiR$_3$ Groups.
Evans, Allison, Yang, Masse, *JACS* **2001**, *123,* 10840–10852



1 P = Bn
2 P = TBS

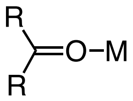
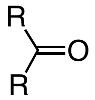
Chelation **9** **11**

Felkin **10** **12**

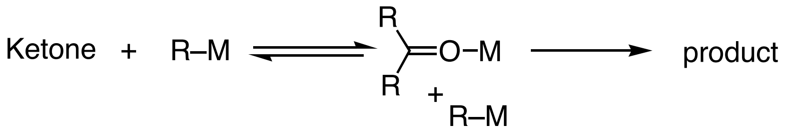
entry	Lewis acid[b]	**1** P = Bn **9** : **10**	(%)	**2** P = TBS **11** : **12**	(%)
A	BF$_3$•OEt$_2$	26 : 74	(76)	09 : 91	(55)
B	SnCl$_4$	50 : 50	(87)	07 : 93	(41)
C	TiCl$_4$	**97 : 03**	(74)	07 : 93	(55)
D	Me$_2$AlCl	90 : 10	(45)	**97 : 03**	(62)[c]
E	MeAlCl$_2$	78 : 22	(70)	77 : 23	(55)

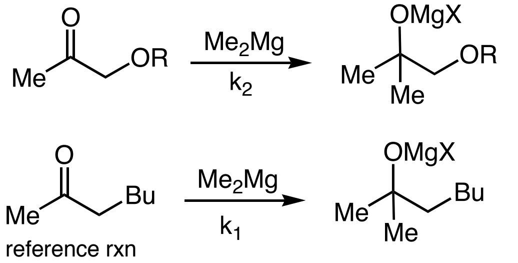
Carbonyl Addition Reactions: Chelate Organization

Kinetic Evidence for Chelate-Controlled C=O Additon

Since  much more reactive than 

Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.





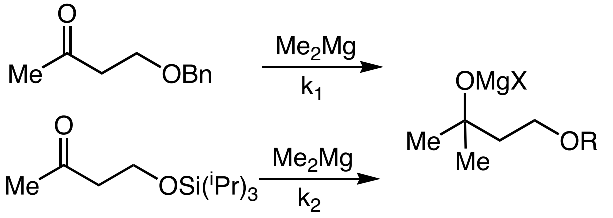
reference rxn

R	rel rate
–Me	213
–Bn	174
$–CMe_3$	9
$–SiMe_3$	7
$–Si\text{-}i\text{-}Pr_3$	1

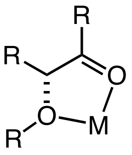
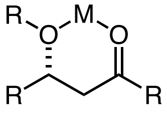
rxn run inTHF at - 78°C

Eliel, Frye, *JACS* **1992**, *114*, 1778-84 (read)

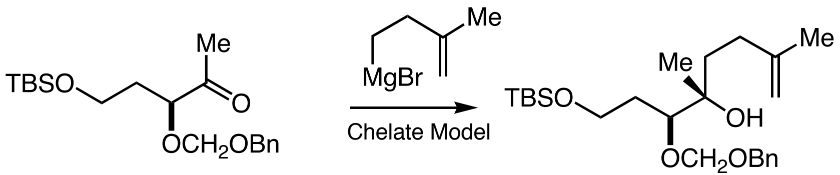
However, these trends are not transmitted strongly to β-chelation



$$\boxed{\frac{k_1}{k_2} = 2.5}$$

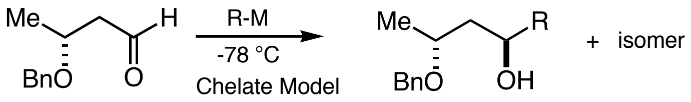
Hence, organization through  better than 

Alpha–Versus Beta-Chelation



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

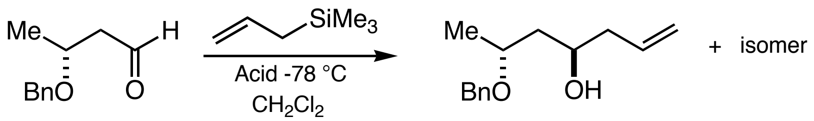
diastereoselection 50 : 1



M. T. Reetz & Co-workers
J. Am. Chem. Soc.. **1983**, 105, 4833.

Other nucleophiles reported

R-M	Solv.	Ratio
Me-MgCl	THF	40 : 60
$Me\text{-}TiCl_3$	CH_2Cl_2	90 : 10



Chelate Model

M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

Acid	Ratio
$TiCl_4$	95 : 5
$SnCl_4$	95 : 5
$BF_3\text{-}OEt_2$	85 : 15

- ■ Note that beta chelation can be developed as a control element by varying solvent & Nu.
- ■ Note BF_3 gives "apparent" chelate control

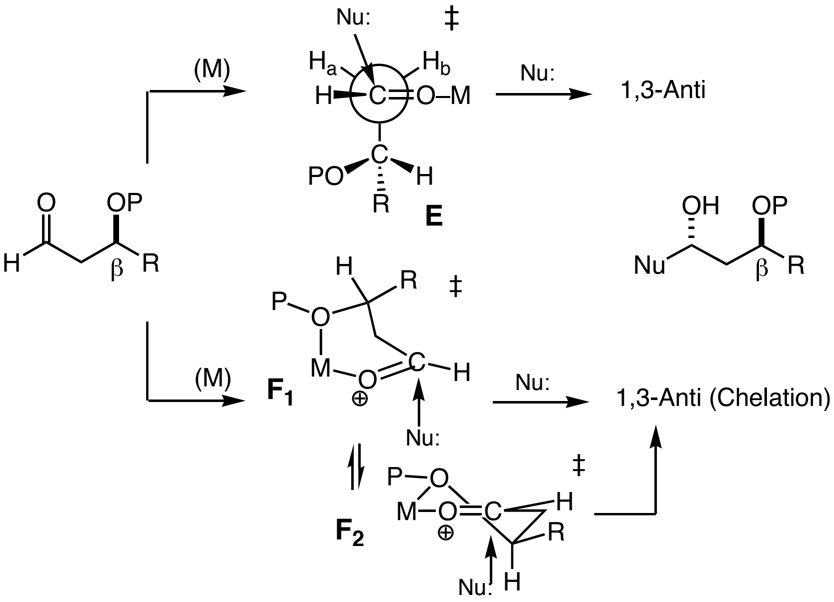
1,3-Stereoinduction Models for Chelate & non-Chelate Rxns

1,3-Stereoinduction Polar Model:

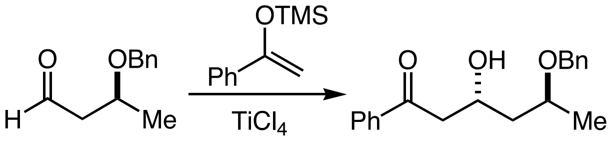
Evans, Dart, Duffy,Yang, *JACS* **1996**, *118,* 4322–4343

1,3-Stereoinduction Chelate Model:

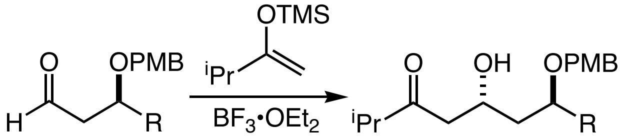
Evans, Allison, Yang,Masse, *JACS* **2001**, *123,* 10840–10852



1,3-Anti Relationship is favored by either polar or chelate models



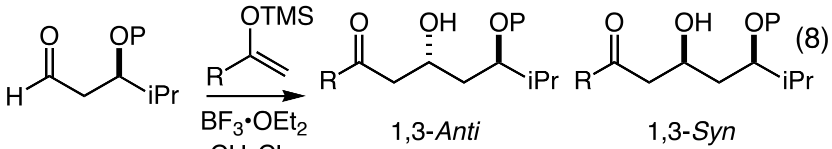
diastereoselection 92 : 8



R = (CH$_2$)$_2$Ph

diastereoselection 81 : 19

1,3-Stereoinduction Polar Model:



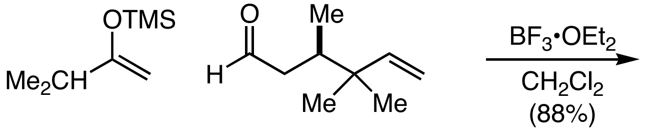
1 P = PMB
2 P = TBS

1,3-*Anti*
3
5

1,3-*Syn*
4
6

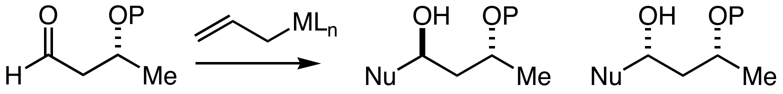
entry	R	**3** : **4** (P = PMB)	(%)	**5** : **6** (P = TBS)	(%)
A	t-Bu	89 : 11	(82)	84 : 16	(79)
B	i-Pr	92 : 08	(91)	80 : 20	(84)
C	Me	91 : 09	(89)	93 : 07	(87)

Steric effects appear to play a minor role in stereoinduction:



1,3-Anti (58%)

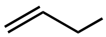
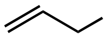
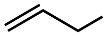
1,3-Syn (42%)



P = Bn (benzy)
P = MOM (methoxymethyl)

1,3-*Anti*

1,3-*Syn*

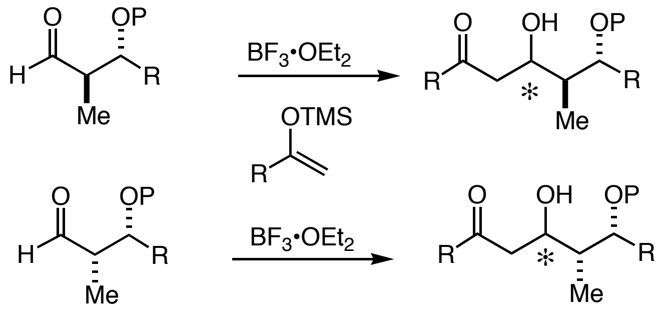
entry	conditions	(P = Bn) *anti* : *syn*	(P = MOM) *anti* : *syn*
A	SiMe$_3$ BF$_3$•OEt$_2$	85 : 15	—
B	SnPh$_3$ BF$_3$•OEt$_2$	79 : 29	—
C	SnMe$_3$ BF$_3$•OEt$_2$	—	70 : 30

Carbonyl Addition Reactions: Chelate Organization

1,3-Stereoinduction Polar Model

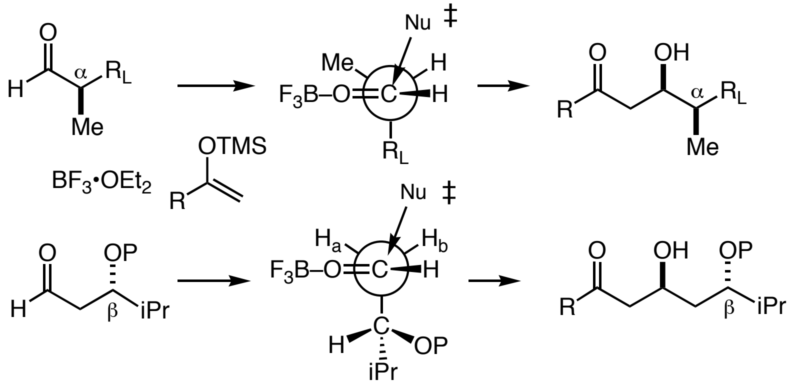
Evans, Dart, Duffy, Yang, *JACS* **1996**, *118,* 4322–4343

Can one develop a Rational model for α & β Stereocenters?

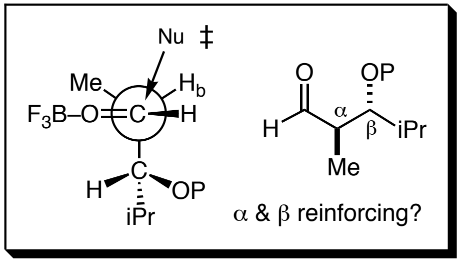


Which of the two stereochemical representations is reinforcing? Non-reinforcing?

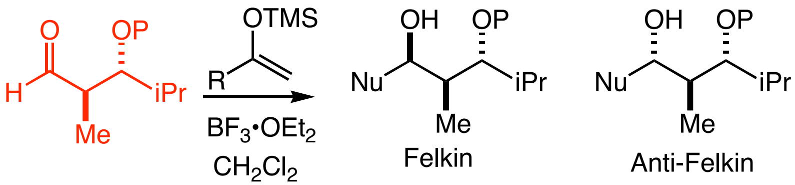
Integration of 1,3- Polar Model & Felkin-Anh Model



If both models are correct, they should **integrate** when the two stereocenters are **reinforcing**



The Anti Diastereomer



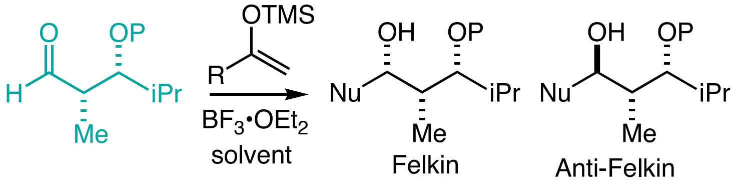
13 P = PMB
14 P = TBS

15
17

16
18

entry	R	**15** : **16** (P = PMB)	**17** : **18** (P = TBS)
A	t-Bu	99 : 01	99 : 01
B	i-Pr	98 : 02	95 : 05
C	Me	97 : 03	71 : 29

The Syn Diastereomer



19 P = PMB
20 P = TBS

21
23

22
24

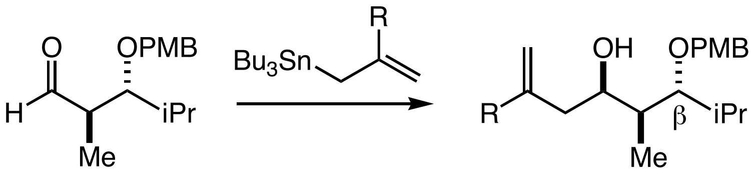
entry	R	Solvent	**21** : **22** (P = PMB)	**23** : **24** (P = TBS)
A	t-Bu	CH_2Cl_2	96 : 04	96 : 04
B	t-Bu	toluene	88 : 12	94 : 06
C	i-Pr	CH_2Cl_2	56 : 44	87 : 13
D	i-Pr	toluene	32 : 68	75 : 25
E	Me	CH_2Cl_2	17 : 83	58 : 42
F	Me	toluene	06 : 94	40 : 60

Conclusions

A: Anti diastereomer is reinforcing. Both models integrate.
B: Syn diastereomer transitions from Felkin control (Large Nu) to 1,3-control (Small Nu).

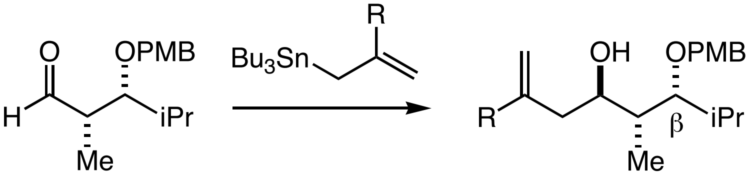
Reinforcing & Non-reinforcing Relationsips

The Anti Diastereomer: Both Centers Reinforcing



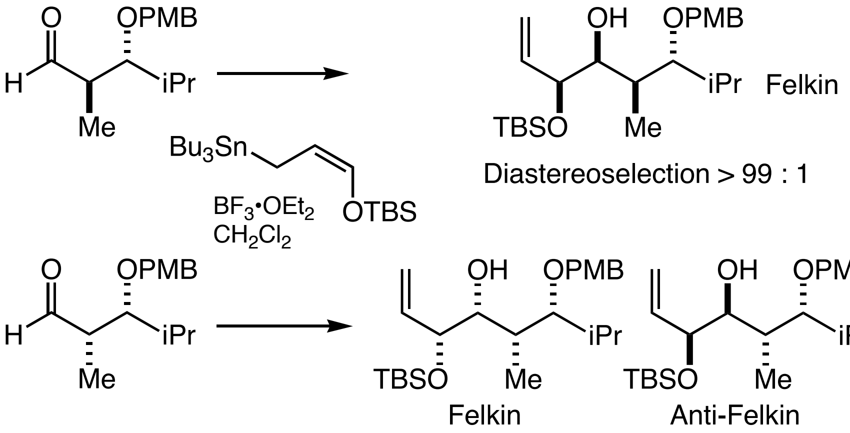
entry	Conditions	R	Felkin : anti-Felkin
A	BF_3•OEt_2, toluene	Me	>99 : 1
B	BF_3•OEt_2, toluene	H	>99 : 1
C	Ph_3CClO_4, CH_2Cl_2	H	>99 : 1

The Syn Diastereomer: Stereocenters are Non-reinforcing



entry	Conditions	R	Felkin : anti-Felkin
A	BF_3•OEt_2, toluene	Me	20 : 80
B	BF_3•OEt_2, toluene	H	13 : 87
C	Ph_3CClO_4, CH_2Cl_2	H	62 : 38

In this example, the OR substituent is the dominant stereo-control element

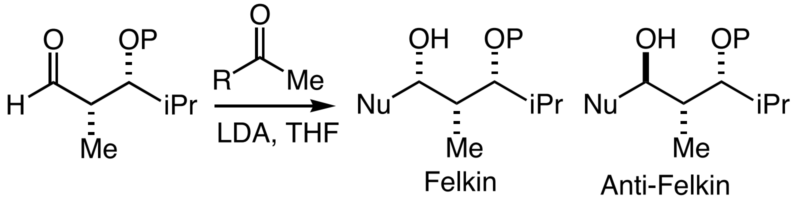


Diastereoselection > 99 : 1

Diastereoselection 59 : 32 : 9[a]

[a]The third unpictured product is the Felkin-3,4-*anti* diastereomer.

The Syn Diastereomer: Stereocenters are Non-reinforcing



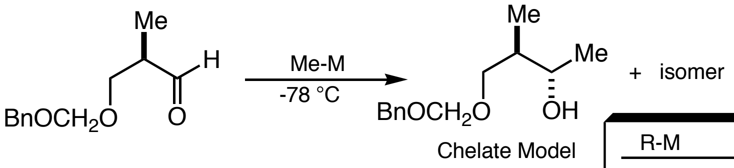
19 P = PMB **21** **22**

20 P = TBS **23** **24**

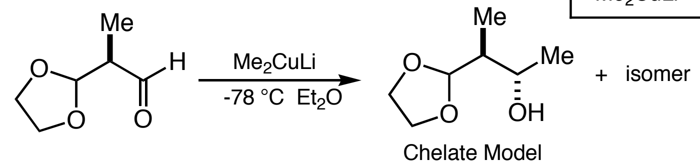
entry	R	**21** : **22** (P = PMB)	(%)	**23** : **24** (P = TBS)	(%)
A	t-Bu	11 : 89	(71)	08 : 92	(91)
B	i-Pr	14 : 86	(95)	13 : 87	(64)
C	Me	22 : 78	(73)	14 : 86	(88)

Carbonyl Addition Reactions: Chelate Organization

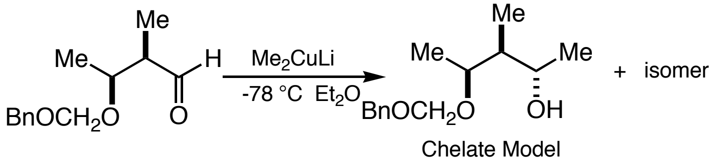
Beta Chelation with Organometals



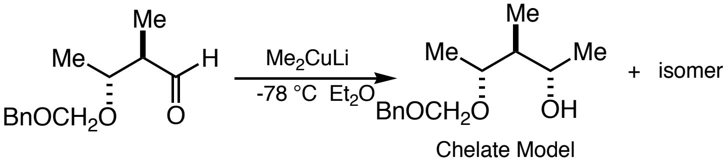
R-M	Ratio
MeMgBr	50 : 50
Me$_2$CuLi	97 : 3



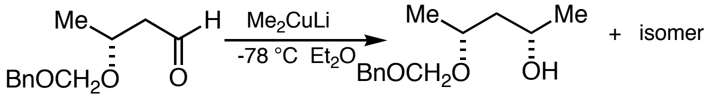
***diastereoselection* > 95 : 5**



***diastereoselection* > 95 : 5**

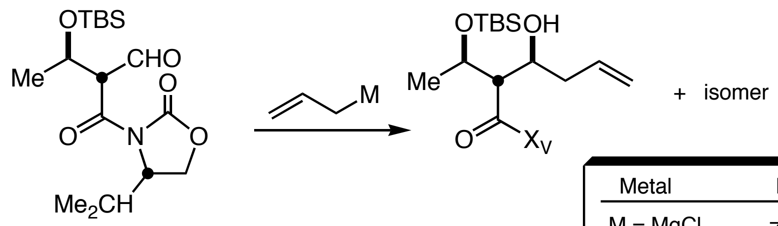


***diastereoselection* 70 : 30**



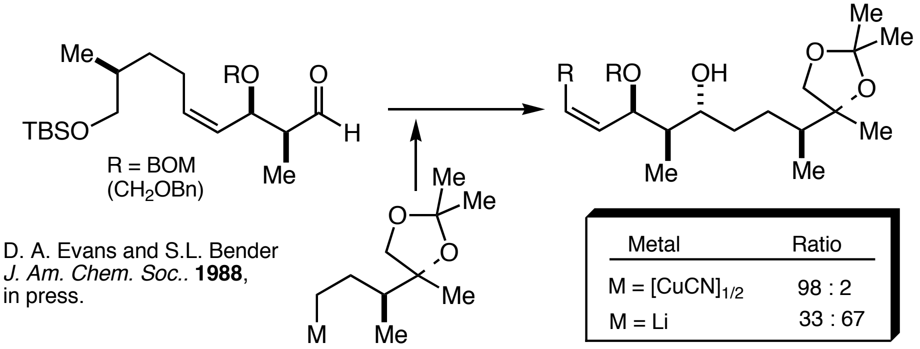
W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1035.

***diastereoselection* 50 : 50**



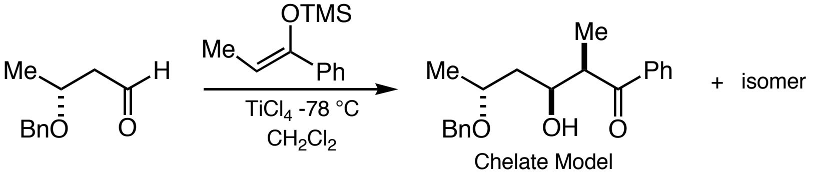
D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, *27*, 4961.

Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3



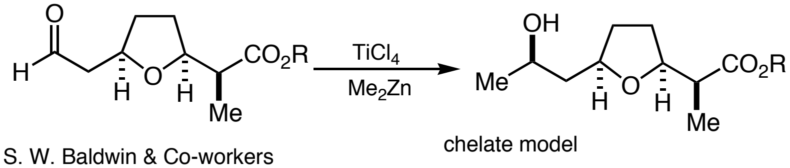
D. A. Evans and S.L. Bender
J. Am. Chem. Soc.. **1988**,
in press.

Metal	Ratio
M = [CuCN]$_{1/2}$	98 : 2
M = Li	33 : 67



M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

***diastereoselection* >92 %**

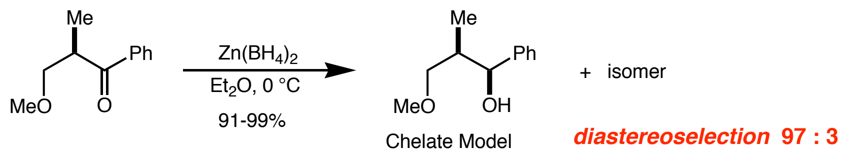


S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, *52*, 320.

***diastereoselection* 96 : 4**

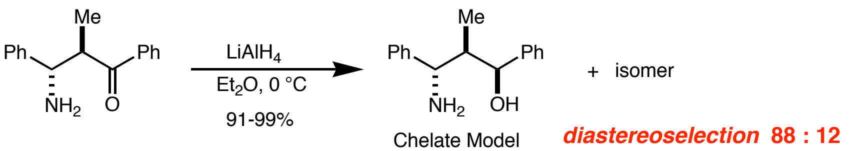
Carbonyl Addition Reactions: Chelate Organization

Beta Chelate-Controlled Reduction



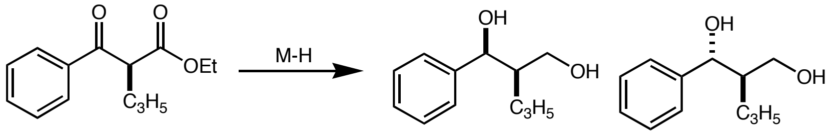
***diastereoselection* 97 : 3**

T. Oishi & Co-workers
Chem. Pharm Bull. **1984**, *32*, 1411.



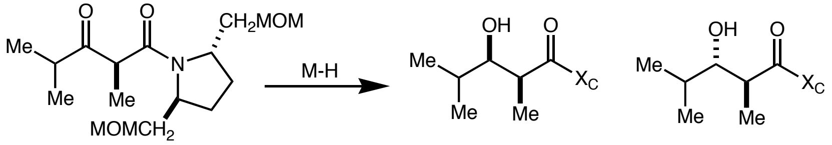
***diastereoselection* 88 : 12**

J. Barluenga & Co-workers
J. Org. Chem. **1985**, *50*, 4052.



G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

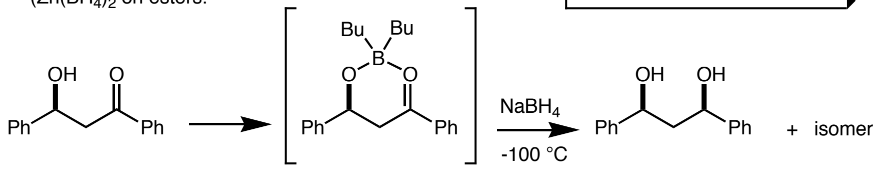
M-H	Ratio
$Zn(BH_4)_2$ Et_2O	100 : 0
$LiAlH_4$ THF	0 : 100



M. Yamaguchi & Co-workers
Tetrahedron Lett. **1985**, *26*, 4643.

T. Oishi & Co-workers
Tetrahedron Lett. **1980**, *21*, 1641
$(Zn(BH_4)_2$ on esters.

M-H	Ratio
$Zn(BH_4)_2$ Et_2O	100 : 0
KBH_3H THF	0 : 100

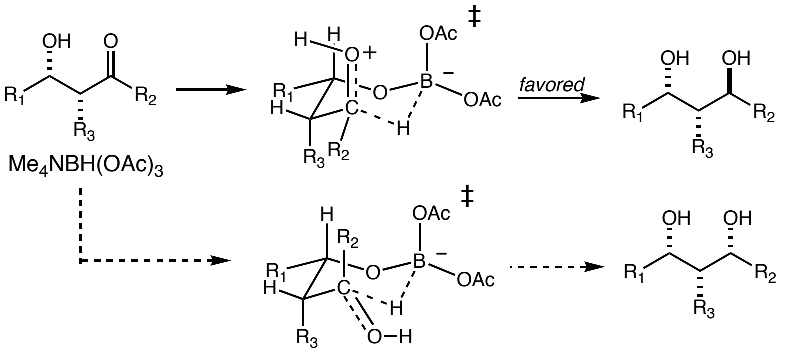


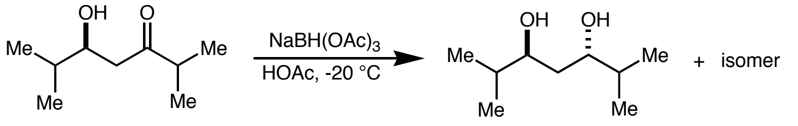
K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

***diastereoselection* 96 : 4**

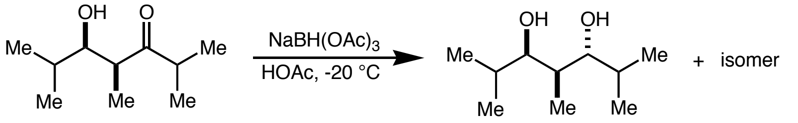
Directed reductions of β-hydroxyketones

Evans, Chapman, Carreira, JACS **110**, 3560 (1988)

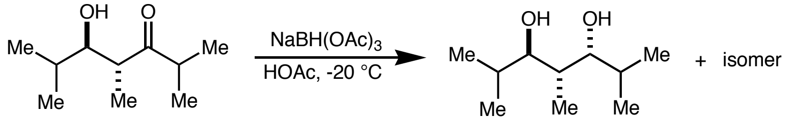




***diastereoselection* 96 : 4**

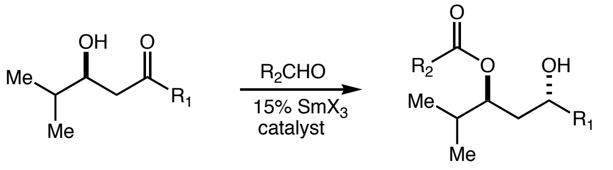


***diastereoselection* 98 : 2**



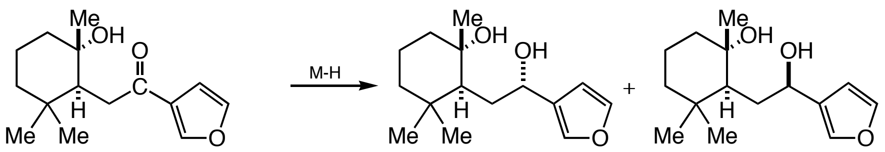
***diastereoselection* 98 : 2**

Propose a mechanism for this highly diastereoselective transformation,
Evans, Hoveyda, JACS **1990**, *112*, 6447.



diastereoselection
> 100:1

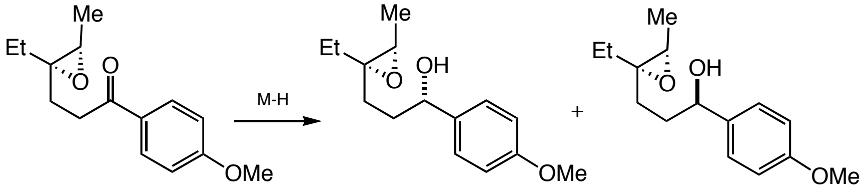
Remote Heteroatom Effects in Carbonyl Addition



Temp. & Solvent not specified in this study in first three cases

R. Baker & Co-workers
Chem. Commun. **1984,** 74

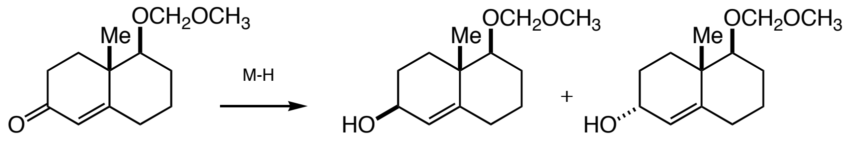
Reagent	Ratio
Li-AlH_4	40 : 60
Na-BH_4	50 : 50
Zn-BH_4	60 : 40
Li-$BHEt_3$, (THF, -78˚C)	100 : 0



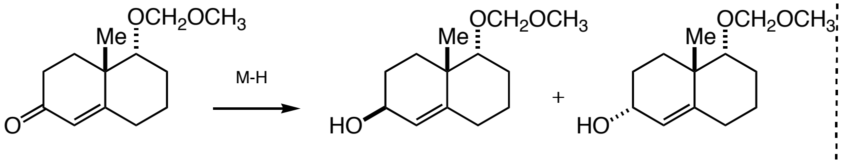
Y. Kishi & Co-workers
Tetrahedron Lett. **1978**, 2741.

Li-BH(R)$_3$, Et_2O, 25˚C	1 : 1
$LiAlH_4$, Et_2O, 25˚C	3 : 1
$LiAlH_4$-diamine,* -78˚C	11 : 1

** di-2-(o-toluidinomethyl)pyrrolidine*

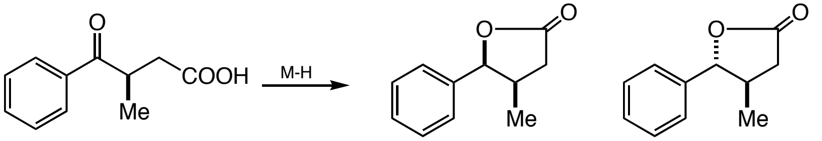


Li-BH(R)$_3$,	73 : 27
$LiAlH_4$	76 : 24



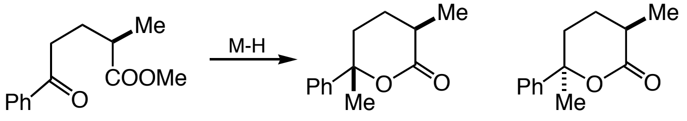
Li-BH(R)$_3$,	28 : 72
$LiAlH_4$	72 : 28

W. G. Dauben & Co-workers
Tetrahedron Lett. **1978**, 2741.



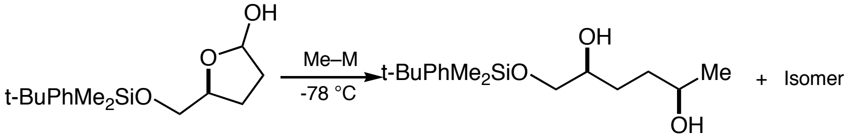
R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

Reagent	Ratio
$NaBH_2(OR)_2$	50 : 50
$NaBH_4$	70 : 30
DIBAL (2.4 equiv)	95 : 5
DIBAL (2.4 equiv) with ZnCl2	99 : 1



R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

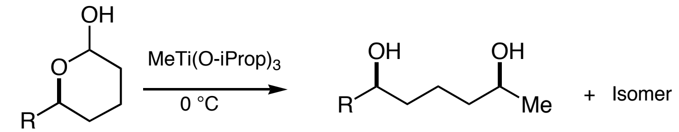
Solvent	Ratio
THF	50 : 50
C_6H_6	70 : 30



67-87% yields

G. Tsuchihashi & Co-workers
Tetrahedron Lett. **1987**,*28*, 6335.

Reagent	Solvent	Ratio
MeLi	Et_2O	1.7 : 1
MeMgBr	THF	1.3 : 1
Me_3Al	CH_2Cl_2	1.1 : 1
$MeTiCl_3$	CH_2Cl_2	8.4 : 1
MeTi(O-iProp)$_3$	CH_2Cl_2	12 : 1



R = Me, Ph(CH$_2$)$_2$

Ratio 4-5.5 : 1

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 23

The Evolution of Stereochemical Models for C=O Addition

■ Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

1. "Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, *1*, 61-70. **(handout)**

D. A. Evans

Friday
November 10, 2006

Additional Electronic handouts

2. "Structural, mechanistic, and theoretical aspects of chelation controlled carbonyl addition reactions."Reetz, Acc. Chem. Res. **1993** *26*: 462. **(pdf)**

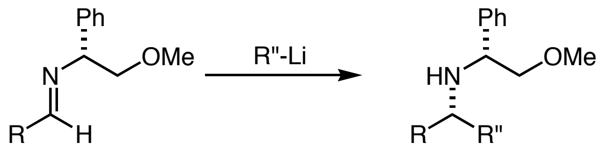
3. "A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes." Evans, et. al. *JACS* **1996**, *118*, 4322-4343. **(pdf)**

4. "The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride. The Merged Stereochemical Impact of α- and β- Stereocenters in Chelate-Controlled Carbonyl Addition Reactions with Enolsilane and Hydride Nucleophiles". Evans, Allison,Yang, Masse, *JACS* **2001**, *123*, 10840-10852. **(pdf)**

5. "Resurrecting the Cornforth Model for Carbonyl Addition: Studies on the Origin of 1,2-Asymmetric Induction in Enolate Additions to Heteroatom-Substituted Aldehydes," Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chemie Int. Ed.* **2003,** *42*, 1761-1765 **(pdf)**

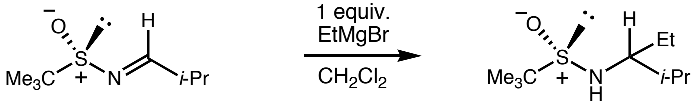
5. "Theoretical Investigation of Enolborane Addition to Alpha Heteroatom-Substituted Aldehydes. Relevance of the Cornforth and Polar Felkin-Anh Models for Asymmetric Induction" Cee, V. J.; Cramer, C. C.; Evans, D. A. *JACS* **2006**, *128*, 2920-2930. **(pdf)**

Problem 69. The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the stereochemistry of the product, rationalize the stereochemical outcome of the indicated reaction.



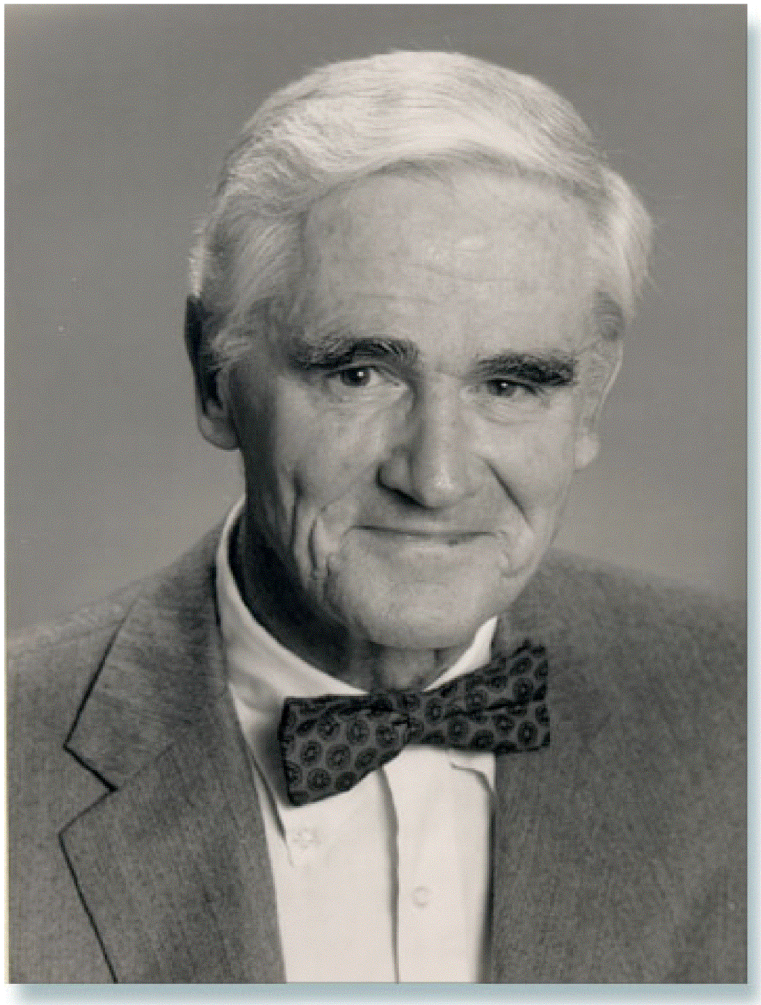
Diastereoselection >97:3

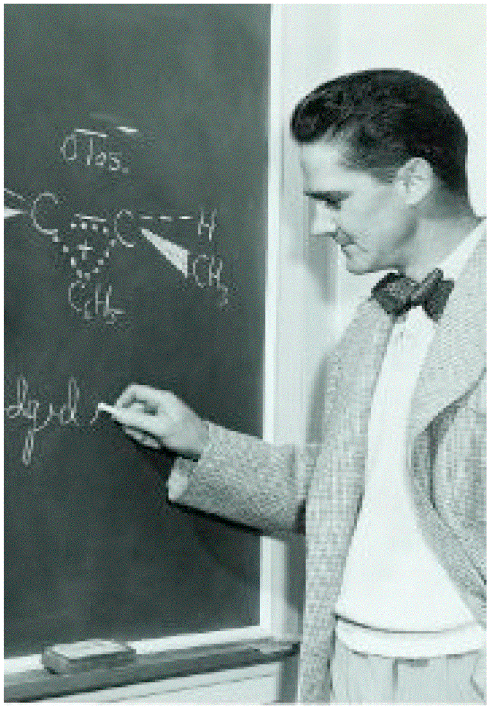
Problem 196. Part A. Provide a mechanism for the following reaction (*Tetrahedron*, **1999**, 8883). Include a clear transition state representation that predicts the major product diastereomer.
Part B. When the reaction is performed in diethyl ether or THF, the diastereoselectivity is significantly lowered. Propose an explanantion for this observation.



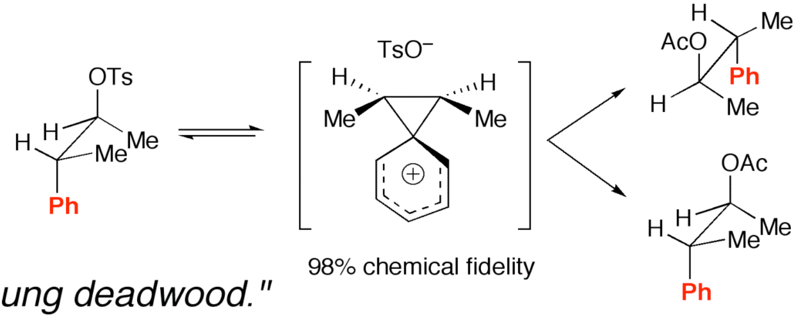
Diastereoselection >90:10

Donald J.Cram (1919–2001)





Phenonium Ion Experiments: Cram, *JACS* **1949**, *71*, 3865

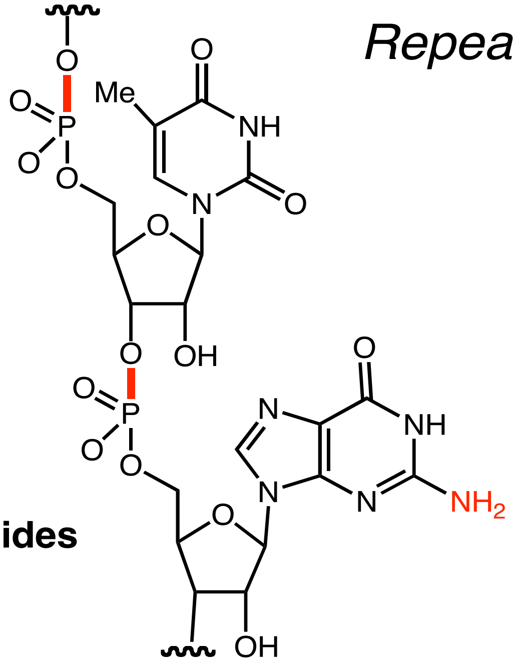


98% chemical fidelity

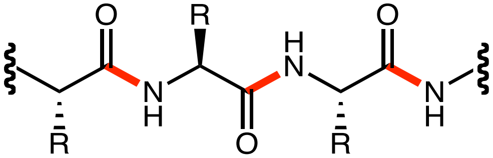
Cram: *"Just remember Dave, old deadwood is better than young deadwood."*

"A View from the Far Side. Memorable Characters and Interesting Places." Evans, D. A. *Tetrahedron* **1999**, *55*, 8589-8608.

Repeating Structural Motifs in Biomolecules



Polynucleotides

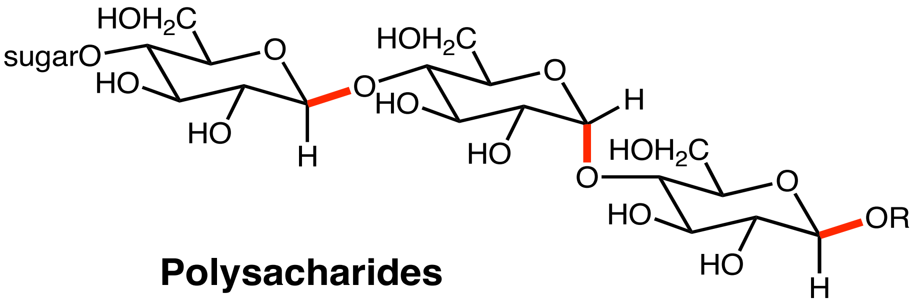


Polypeptides

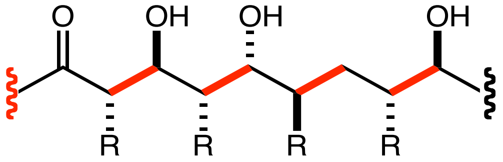
Coupling occurs at a
nonstereogenic center

greater complexity

The Diastereomer Problem!!



Polysacharides

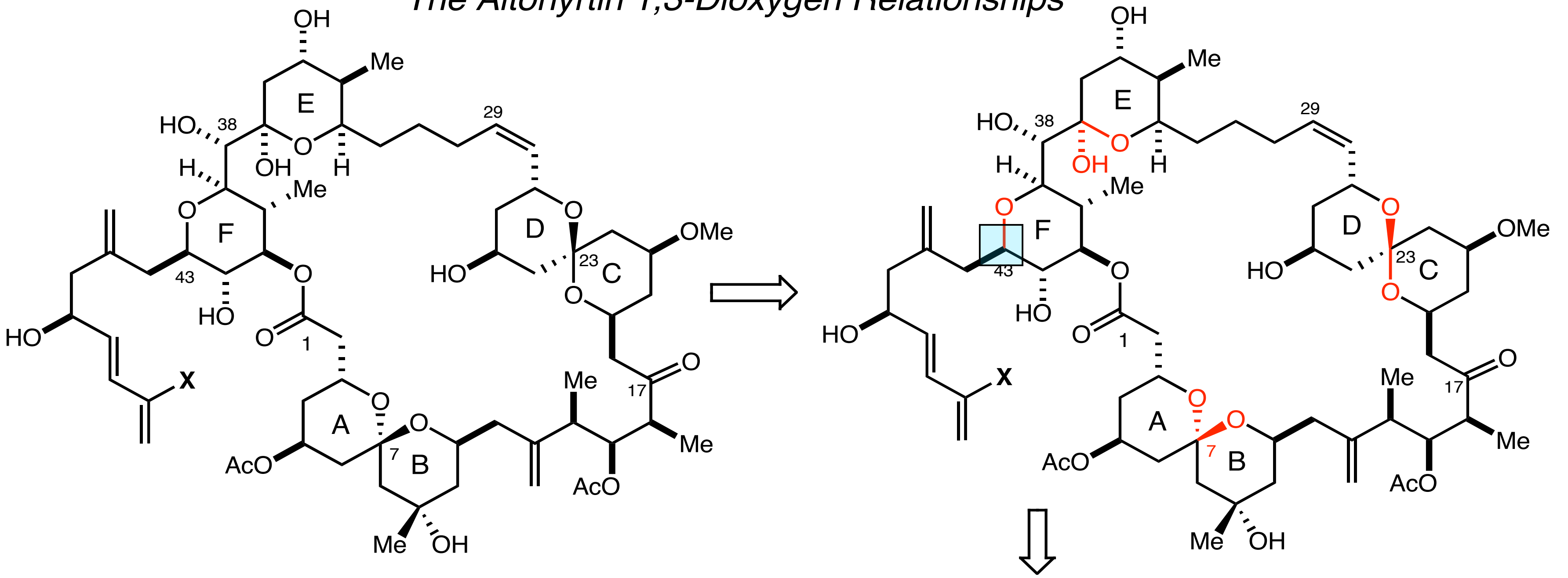


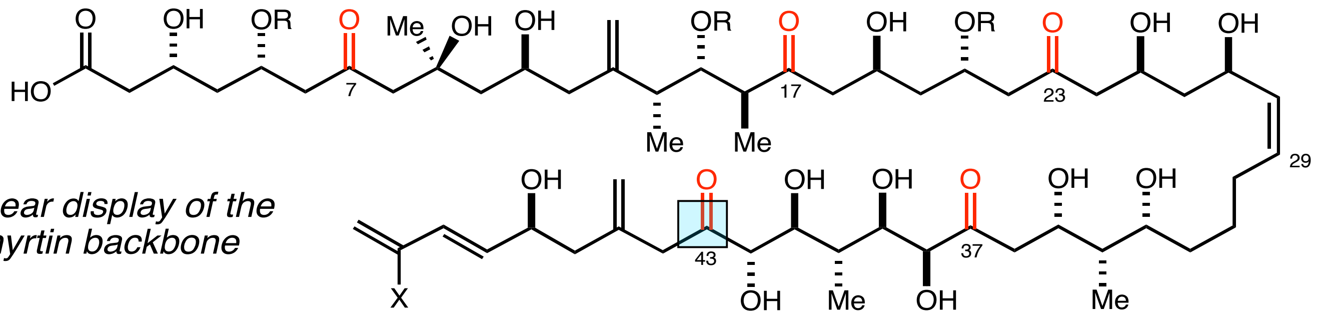
Polyacetates (R = H)
Polypropionates (R = Me)
Carbohydrates (R = OH)

Coupling produces a **new**
stereogenic center

Polyketide synthesis via enolate-based bond constructions

The Altohyrtin 1,3-Dioxygen Relationships

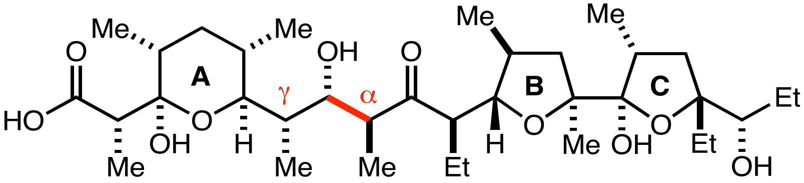




The linear display of the altohyrtin backbone

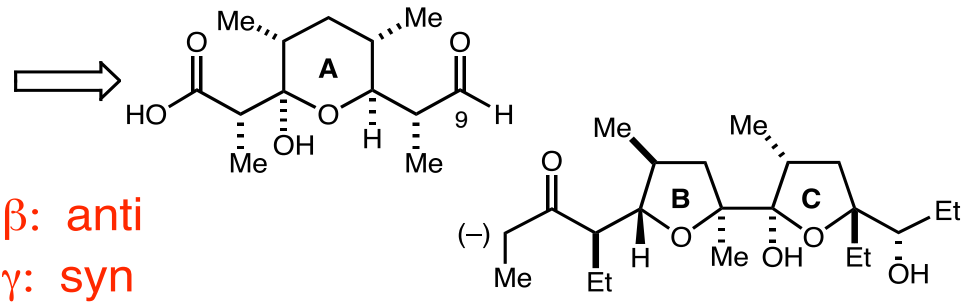
Tetrahedron **1999**, *55*, 8671

The aldol reaction is valuable in the coupling of complex fragments but....



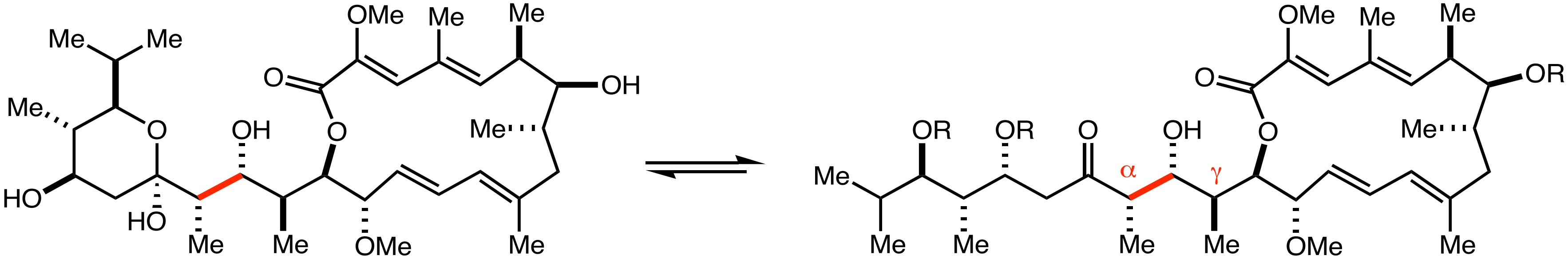
Ferensimycin B

JACS **1991**, *113*, 7613-7630



α–β: anti

β–γ: syn



Bafilomycin A$_1$

Tetrahedron Lett. **1993**, *34*, 6871-6874.

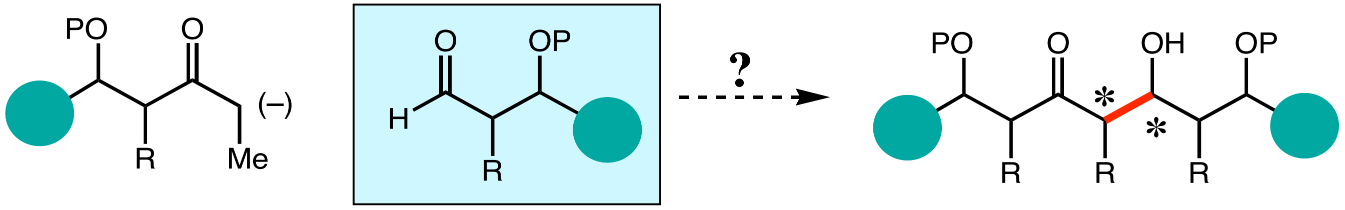
α–β: syn

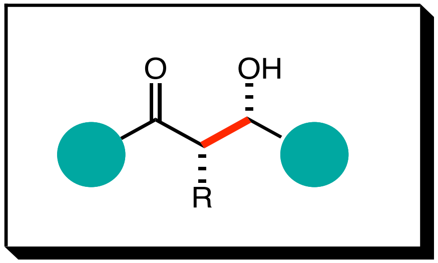
β–γ: anti

The challenge

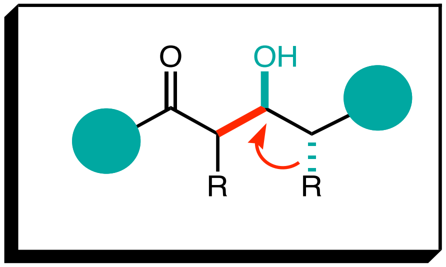
To predict how the stereogenic elements in reacting partners might influence the bond construction

Stereochemical Control Elements for Double Stereodifferentiating Aldol Additions

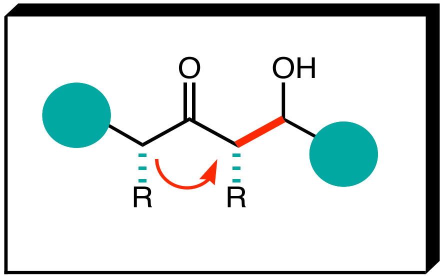




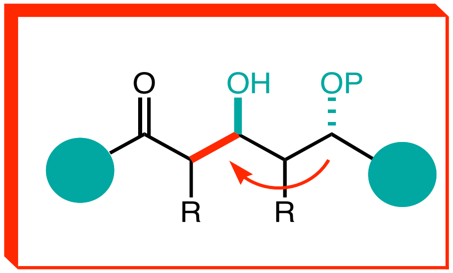
simple diastereocontrol
(enolate geometry)



1,2-induction R = Me (Felkin)
R = OR (Polar Felkin)



enolate facial bias



1,3-induction

The Aldehyde Fragment

Effects Governing Face Selectivity at Trigonal Carbon

- Steric Effects: Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules

- Electronic Effects (Inductive Effects): The effect of bond and through-space polarization by heteroatom substituents on reaction rates and selectivities

  Inductive Effects: Through-bond polarization
  Field Effects: Through-space polarization

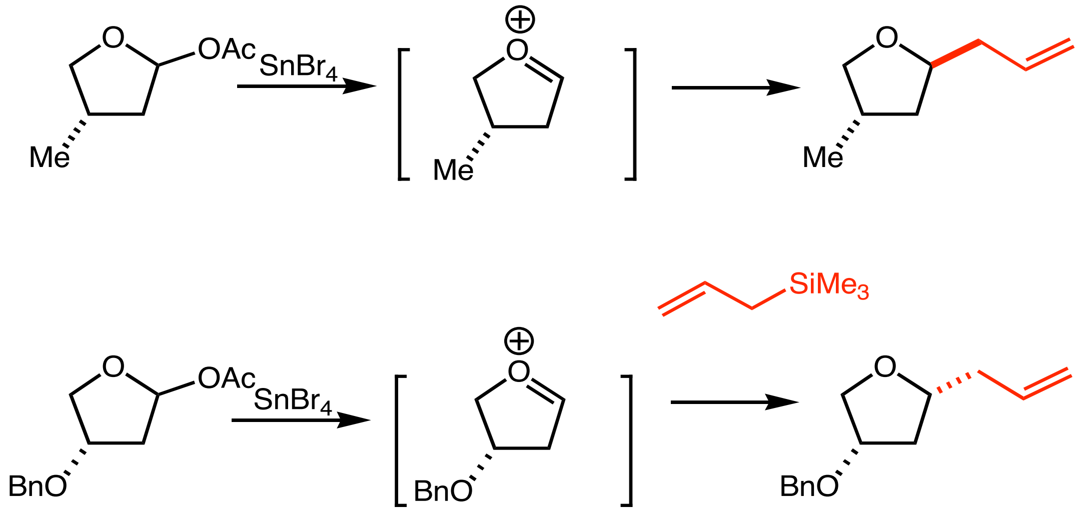
- Stereoelectronic Effects: Geometrical constraints placed upon **ground** and **transition states** by orbital overlap considerations.

"Organic chemists are proficient in the analysis of steric effects."

"Organic chemists are frequently unaware of the impact of electronic effects on the stereochemical outcome of reactions."

When steric and electronic (stereoelectronic) effects lead to differing stereochemical consequences

5-Membered oxocarbenium Ions: Woerpel etal. *JACS* **1999**, 121, 12208.



stereoselection 99:1

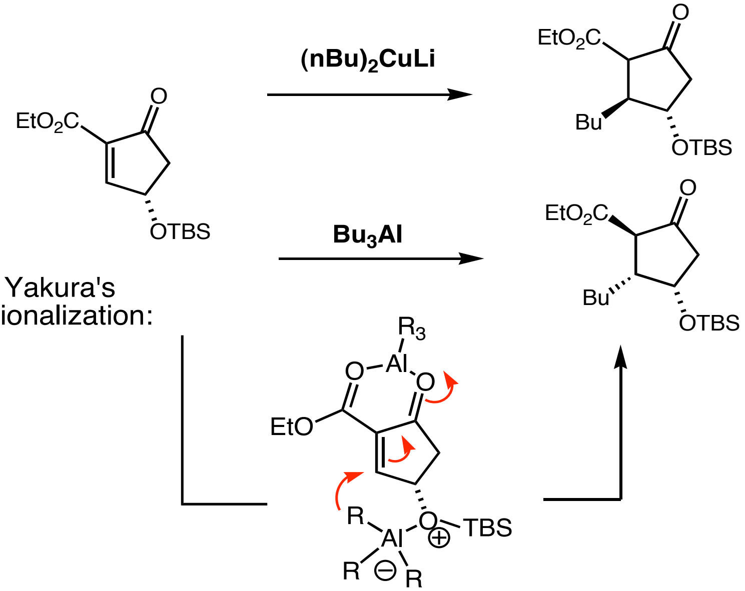
stereoselection >95:5

Dramatic evidence of the importance of electrostatic effects in controlling face selecticity.

Effects Governing Face Selectivity at Trigonal Carbon

When steric and electronic (stereoelectronic) effects lead to differing stereochemical consequences

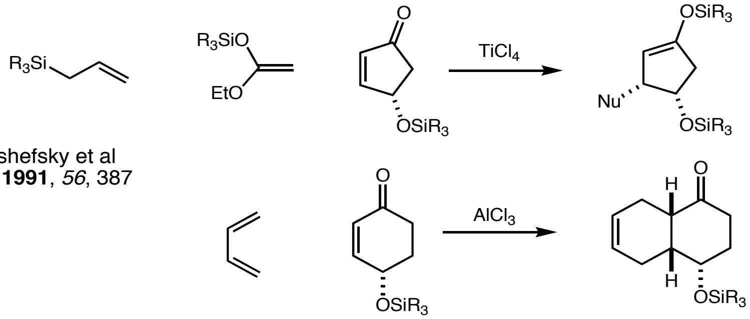
Yakura et al *Tet* **2000**,
56, 7715-7721



diastereoselection
8:1

only diastereomer

Yakura's
rationalization:



Danishefsky et al
JOC **1991**, *56*, 387

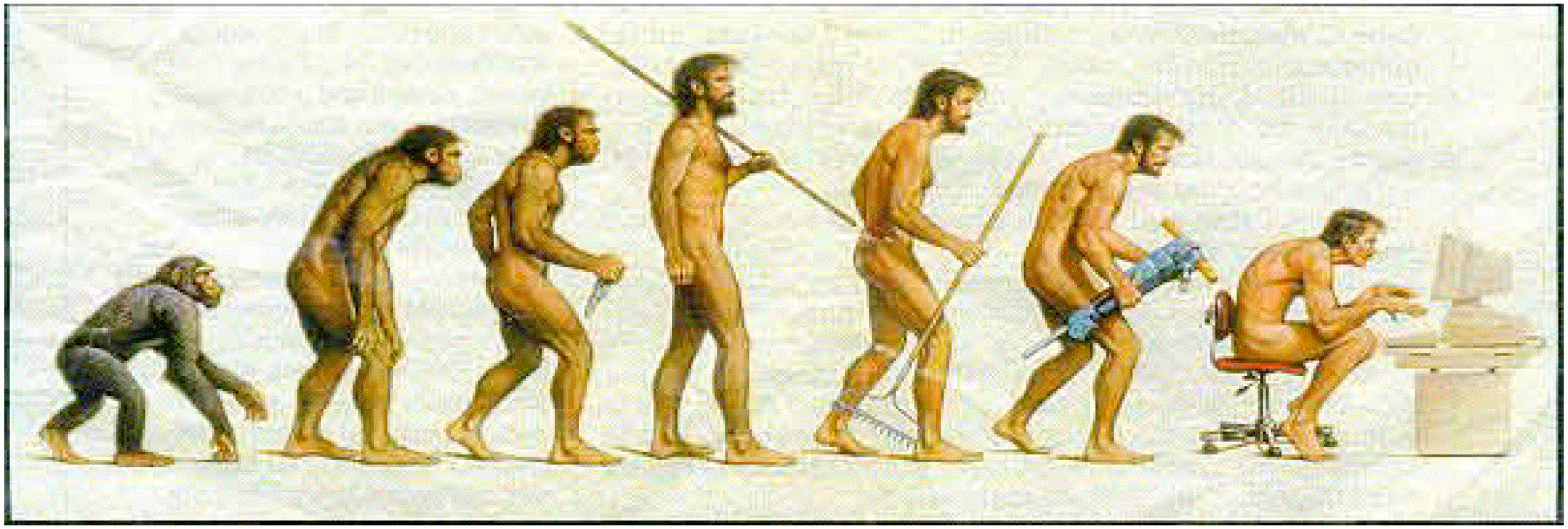
diastereoselection
>94:6

diastereoselection
93:7

Danishfesky rationalizes the indicated face selectivities on the basis of the "Cieplak Model".

Reaction face selectivities are frequently analyzed incorrectly!

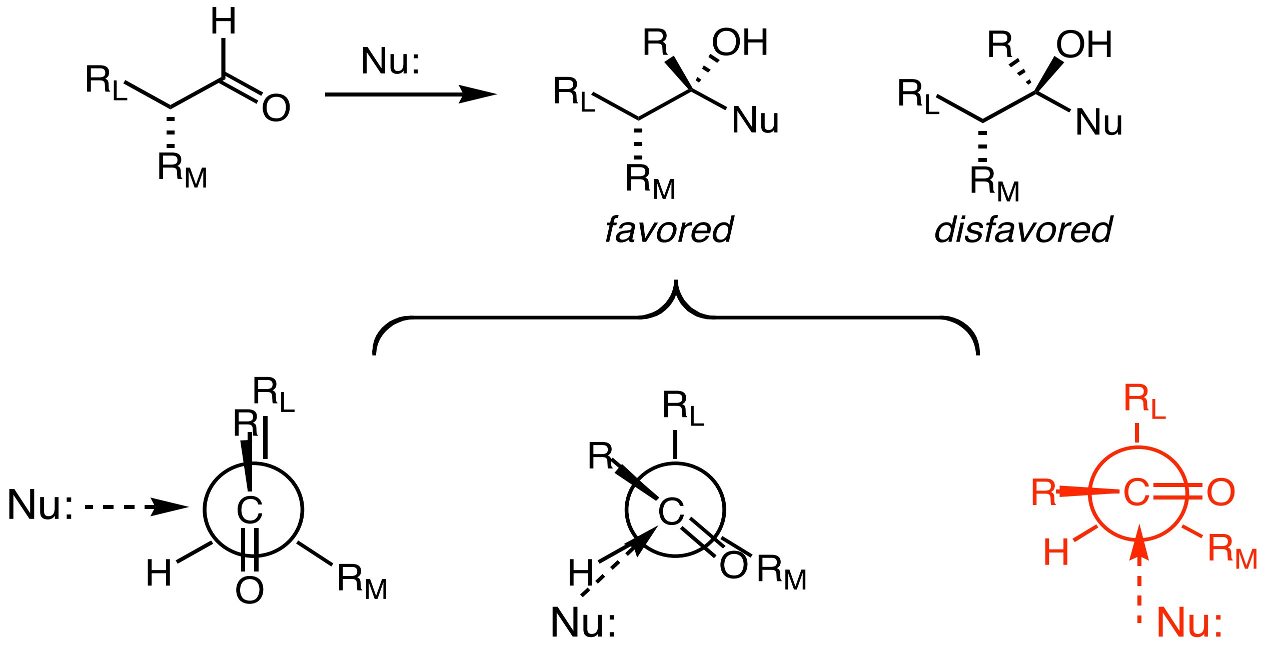
The Evolution of Models for Carbonyl Addition



Fischer Cram Cornforth Felkin Anh/Eisenstein Cieplak Tomoda

Humor provided by Sarah Siska

Carbonyl Addition: Evolution of Acyclic Models



Cram
JACS **1952**, *74*, 5828

Karabatsos
JACS **1967**, *89*, 1367

Felkin
TL. **1968**, 2199-2208

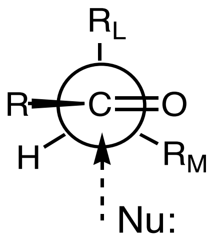
(a) “Torsional strain involving partial bonds. The stereochemistry of the lithium aluminium hydride reduction of some simple open-chain ketones.” Felkin, et al. *Tetrahedron Lett*. **1968**, 2199-2204.

(b) “Torsional strain involving partial bonds. The steric course of the reaction between allylmagnesium bromide and 4-t-butylcyclohexanone” *Tetrahedron Lett*. **1968**, 2204-2208.

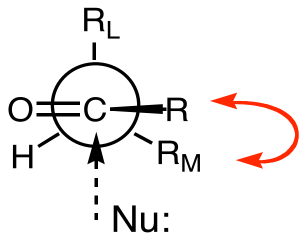
Assumptions in the Felkin Model:

- Transition states are all reactant-like rather than product-like.
- Torsional strain considerations are dominant.
  Staggered TS conformations preferred.

Houk, *JACS* **1982**, *104*, 7162-6

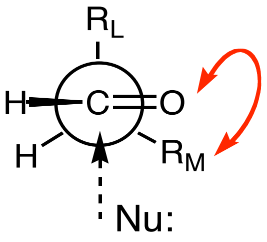


predicted to be favored TS
✓

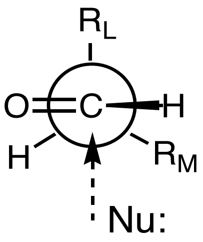


destabilizing interaction

The flaw in the Felkin model: A problem with aldehydes!!

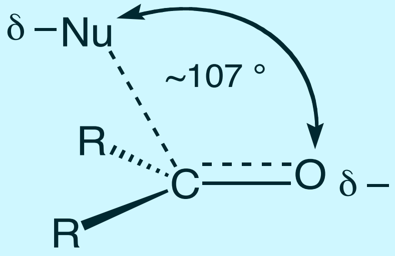


predicted to be disfavored TS



predicted to be favored TS
⇩
wrong prediction

Anh, Eisenstein:
Consider the Dunitz-Bürgi angle



The Dunitz-Bürgi Angle

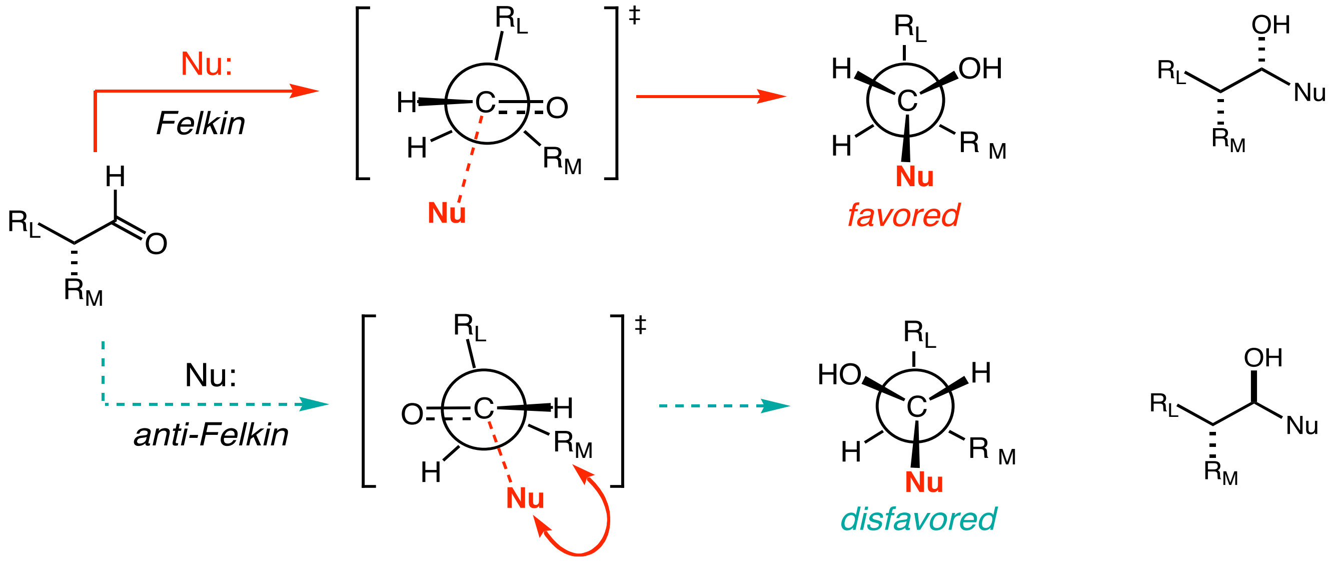
The Felkin–Anh Model

Anh & Eisenstein *Noveau J. Chim.* **1977**, *1*, 61-70

New Additions to Felkin Model:

- Dunitz-Bürgi C=O–Nu orientation applied to Felkin model.
- The antiperiplanar effect:

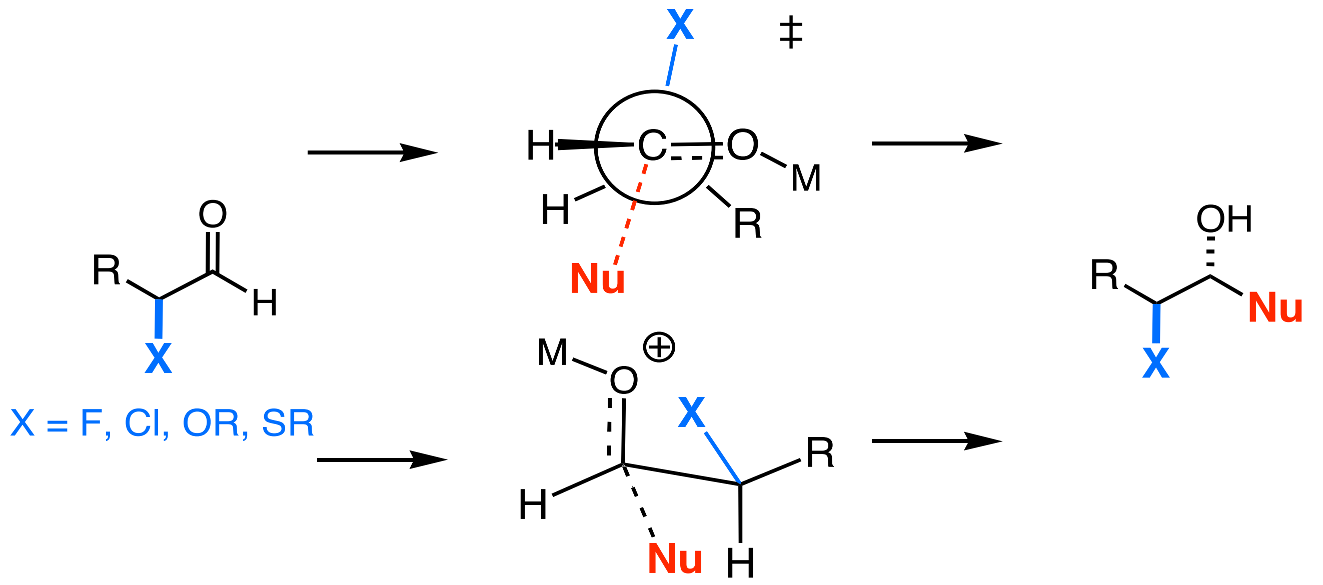
Hyperconjugative interactions between σ* C-R_L and forming σ C–N bond which will lower will stablize the transition state.



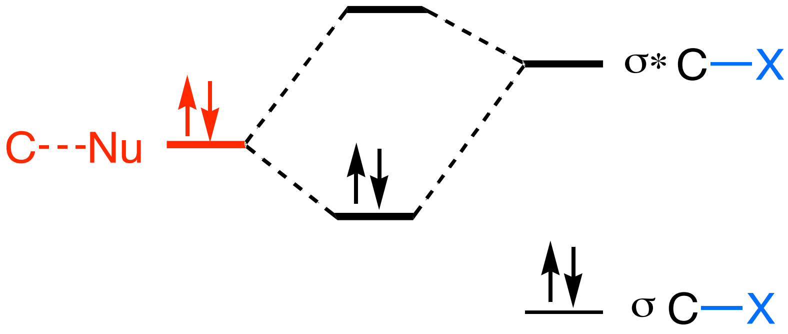
(Felkin): *“Transition state eclipsing interactions are greater than their ground state counterparts.”*

(Anh, Eisenstein): *Hyperconjugative interactions between C–R^*_L & C–Nu will stabilize the transition state.*

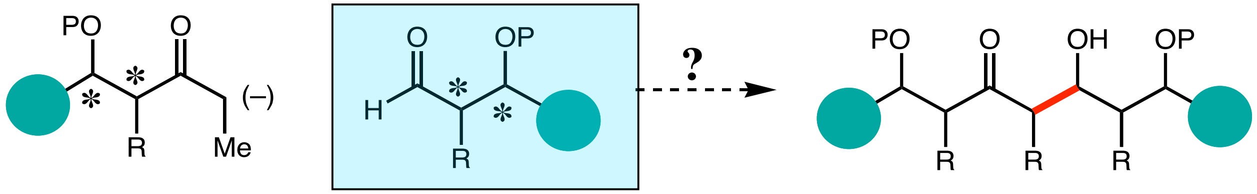
The Polar Felkin–Anh Model

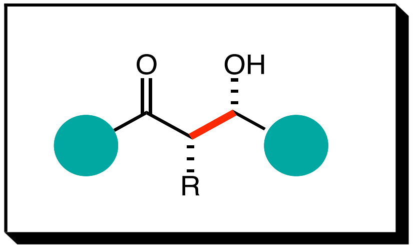


In the polar model, the substituent with the best acceptor antibonding orbital (σ*C–X) is oriented antiperiplanar to the forming C–Nu bond.

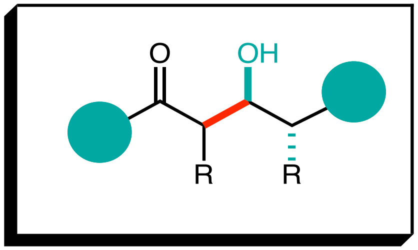


Stereochemical Control Elements for Double Stereodifferentiating Aldol Additions

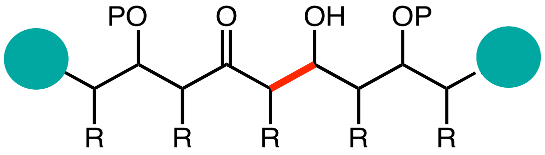




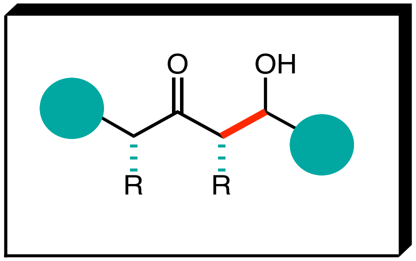
simple diastereocontrol
(enolate geometry)



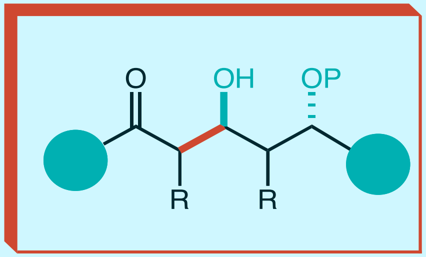
1,2-induction R = Me (Felkin)
R = OR (Polar Felkin)



R = H, Me, OR



enolate facial bias



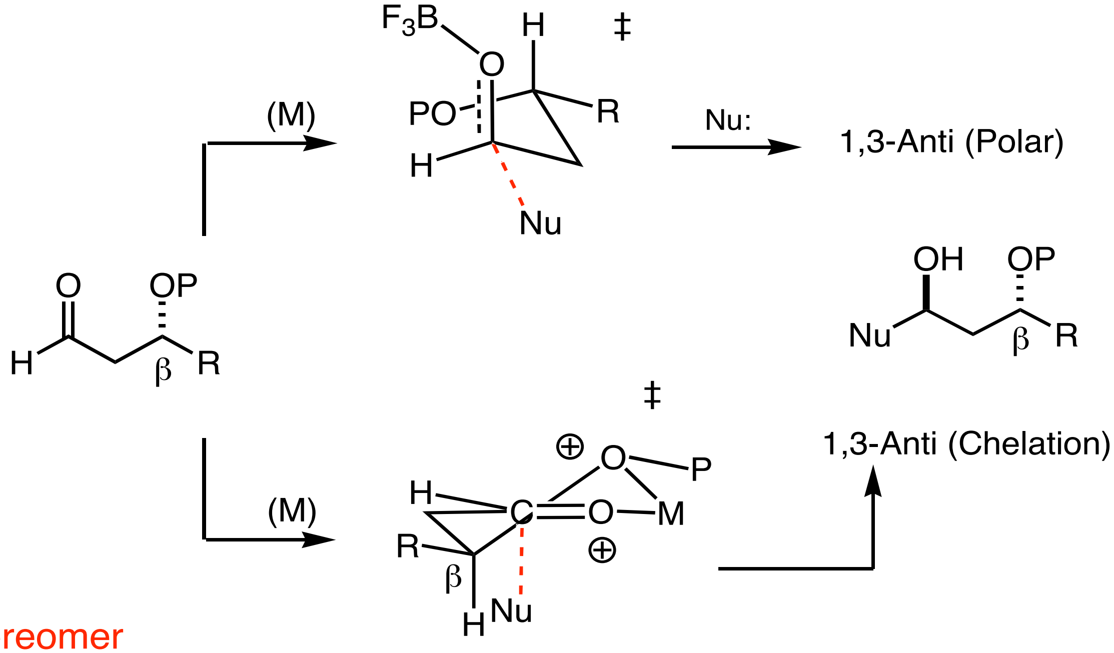
1,3-induction

The Aldehyde Fragment

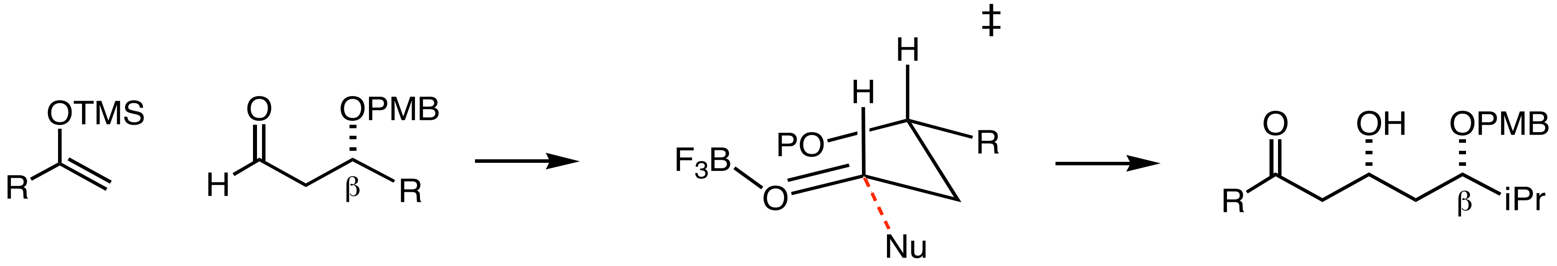
1,3-Stereoinduction Model

1,3-Stereoinduction Polar Model:
Evans, Dart, Duffy,Yang, *JACS* **1996**, *118,* 4322–4343

1,3-Stereoinduction Chelate Model:
Evans, Allison, Yang,Masse, *JACS* **2001**, *123,* 10840–10852



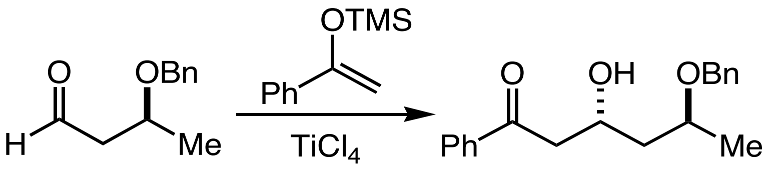
The minor diastereomer



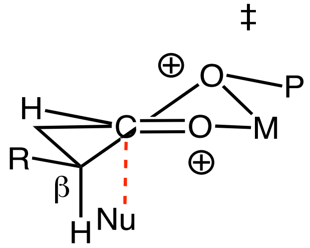
Dipole Destabilization

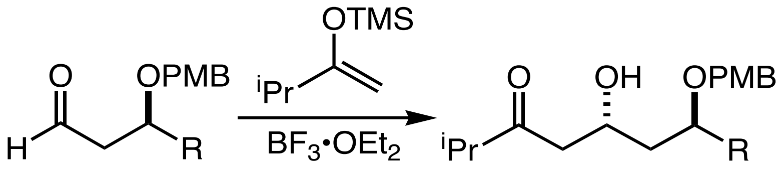
1,3-Stereoinduction Model

1,3-Anti Relationship is favored by either polar or chelate models



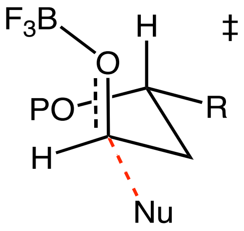
diastereoselection 92 : 8



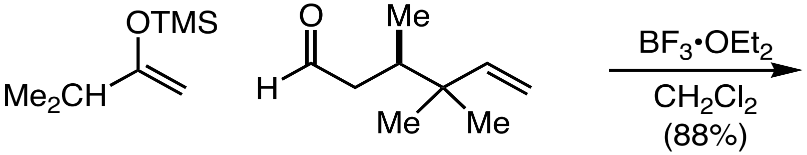


R = $(CH_2)_2Ph$

diastereoselection 81 : 19



Steric effects appear to play a minor role in stereoinduction:



1,3-Anti (58%)

1,3-Syn (42%)

Evans, *JACS* **1996**, *118,* 4322; *JACS* **2001**, *123,* 10840

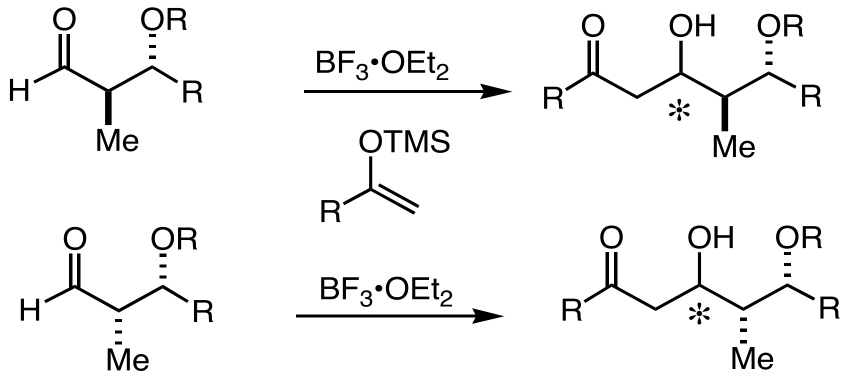
Electronic rather than steric effects control face selectivity!

A Merged Stereoinduction Model

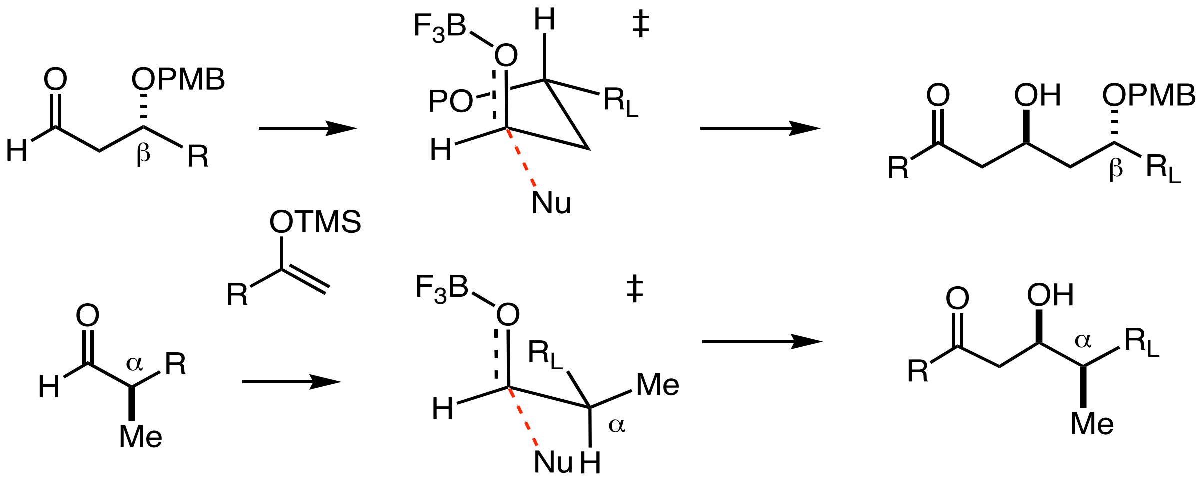
Can one develop a Rational model for α & β Stereocenters?

α & β reinforcing

α & β nonreinforcing



Which of the two stereochemical representations is reinforcing? Non-reinforcing?

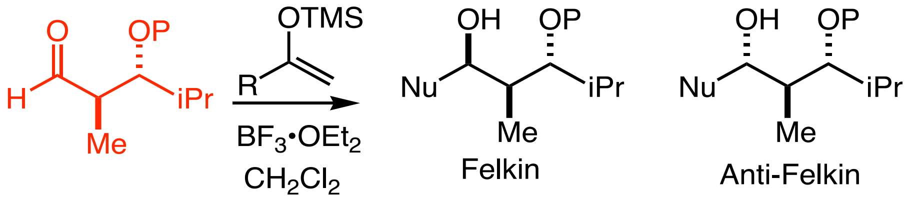


Evans, *JACS* **1996**, *118,* 4322; *JACS* **2001**, *123,* 10840

A Merged Stereoinduction Model

The Anti Diastereomer

α & β reinforcing



13 P = PMB
14 P = TBS

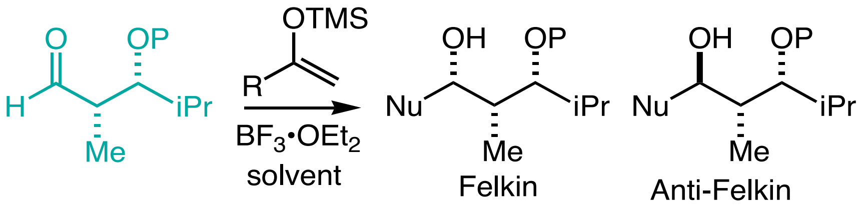
15
17

16
18

entry	R	**15** : **16** (P = PMB)	**17** : **18** (P = TBS)
A	t-Bu	99 : 01	99 : 01
B	i-Pr	98 : 02	95 : 05
C	Me	97 : 03	71 : 29

The Syn Diastereomer

α & β non reinforcing



19 P = PMB
20 P = TBS

21
23

22
24

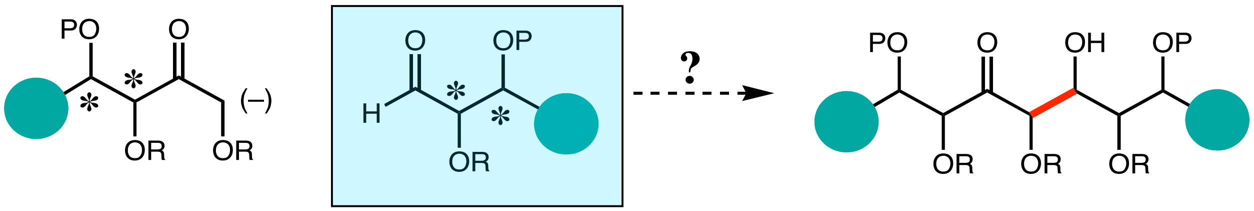
entry	R	Solvent	**21** : **22** (P = PMB)	**23** : **24** (P = TBS)
A	t-Bu	CH_2Cl_2	96 : 04	96 : 04
B	t-Bu	toluene	88 : 12	94 : 06
C	i-Pr	CH_2Cl_2	56 : 44	87 : 13
D	i-Pr	toluene	32 : 68	75 : 25
E	Me	CH_2Cl_2	17 : 83	58 : 42
F	Me	toluene	06 : 94	40 : 60

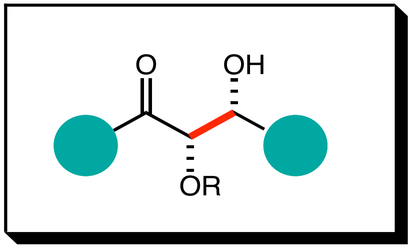
Conclusions

Both models integrate!!

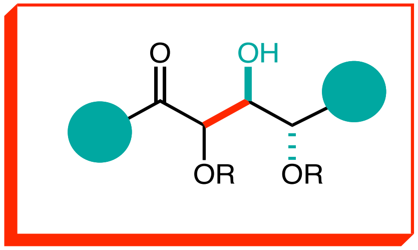
Syn diastereomer transitions from
Felkin control (Large Nu)
to
1,3-control (Small Nu).

Stereochemical Control Elements for Double Stereodifferentiating Aldol Additions:
Carbohydrate Polyols

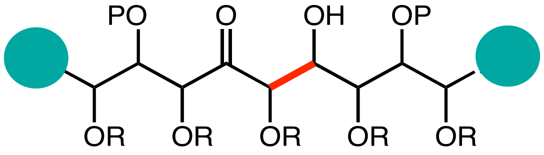




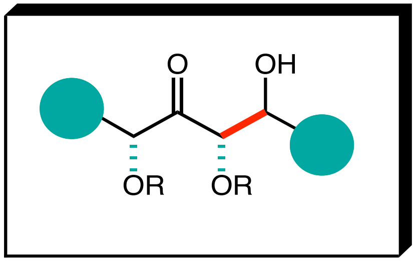
simple diastereocontrol
(enolate geometry)



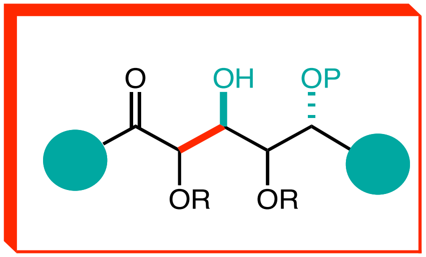
1,2-induction R = OR
(Polar Felkin-Anh)



R = H, Me, OR

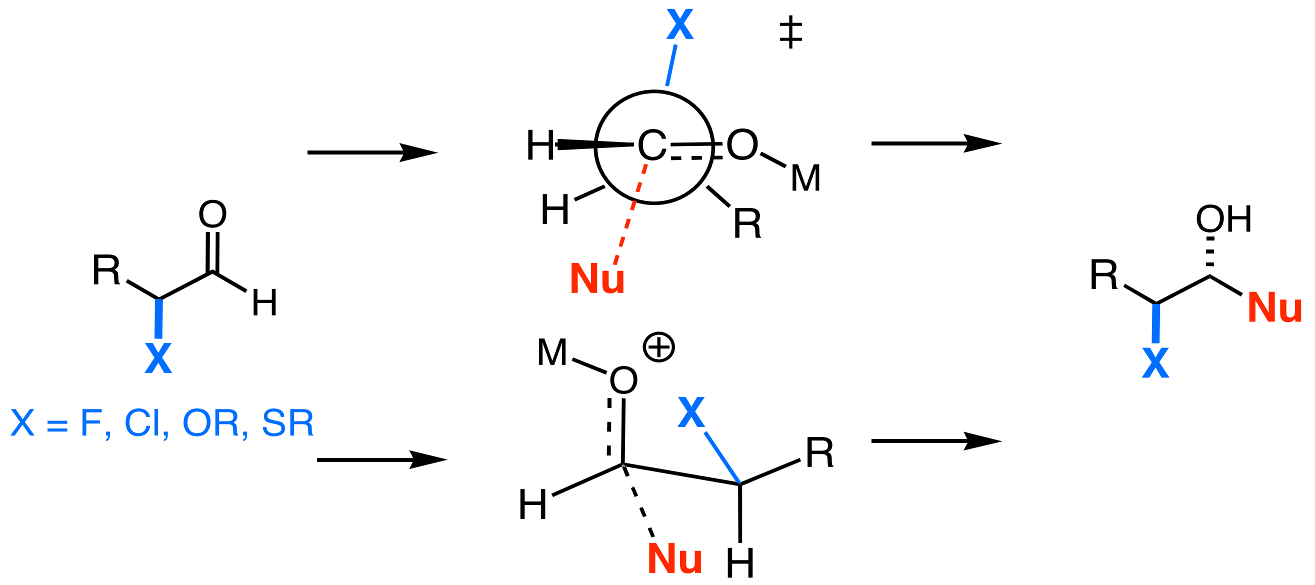


enolate facial bias

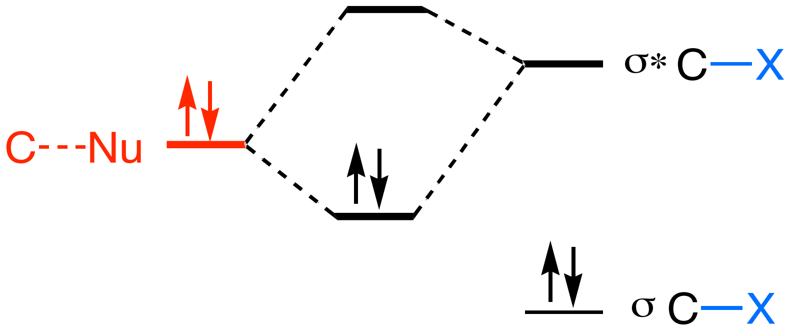


1,3-induction

The Polar Felkin–Anh Model



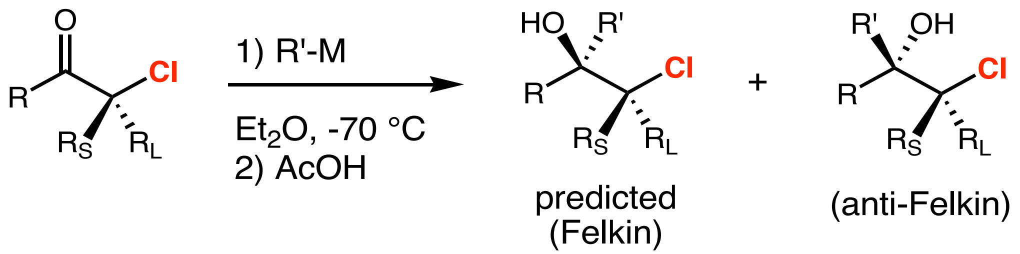
In the polar model, the substituent with the best acceptor antibonding orbital (σ^*C–X) is oriented antiperiplanar to the forming C–Nu bond.

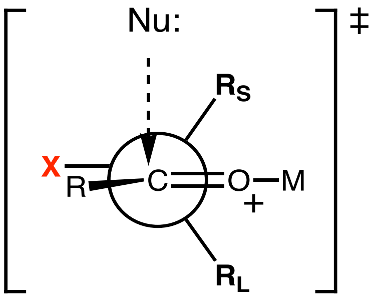


Cornforth Model for C=O Addition

Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112

Additions to α-Chloro Carbonyl Derivatives





Cornforth model

- argument based on importance of polarization in transition state, and evidence of selectivity in α-chlorocyclohexanone additions

- ". . . where the dipoles are antiparallel, the polarization of the carbonyl group would be easiest," thereby lowering transition state energy

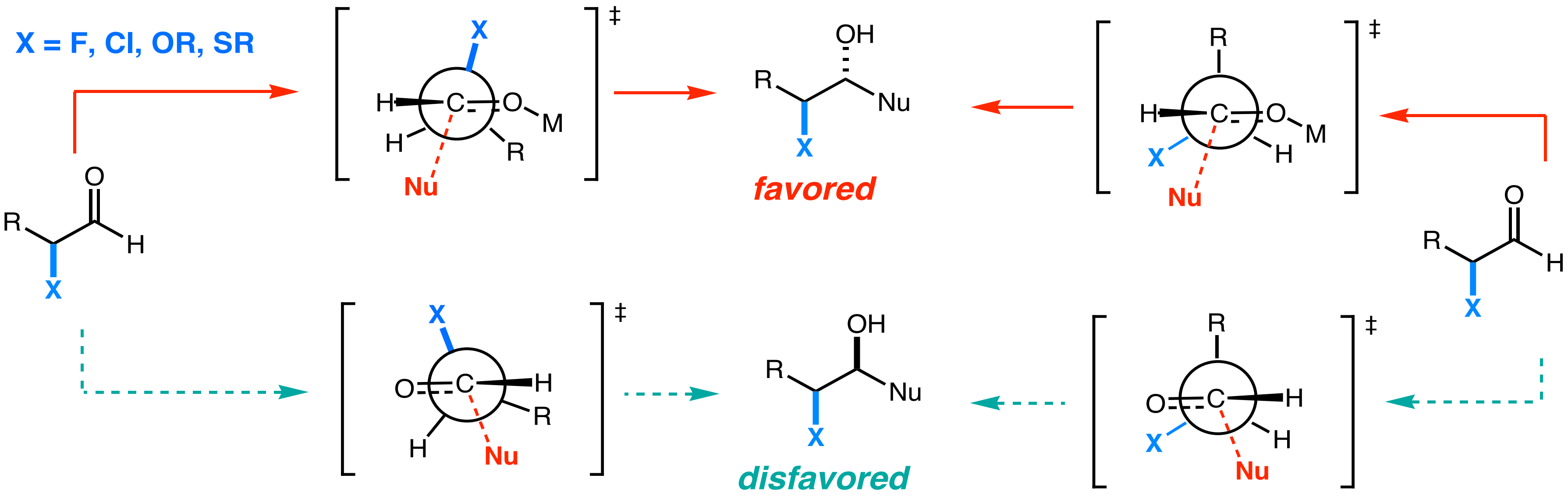
- a modification of Cram's rule for electronegative, non-chelating α-substituents X

How does one distinguish between the Cornforth & Felkin Anh Models for C=O Addition??

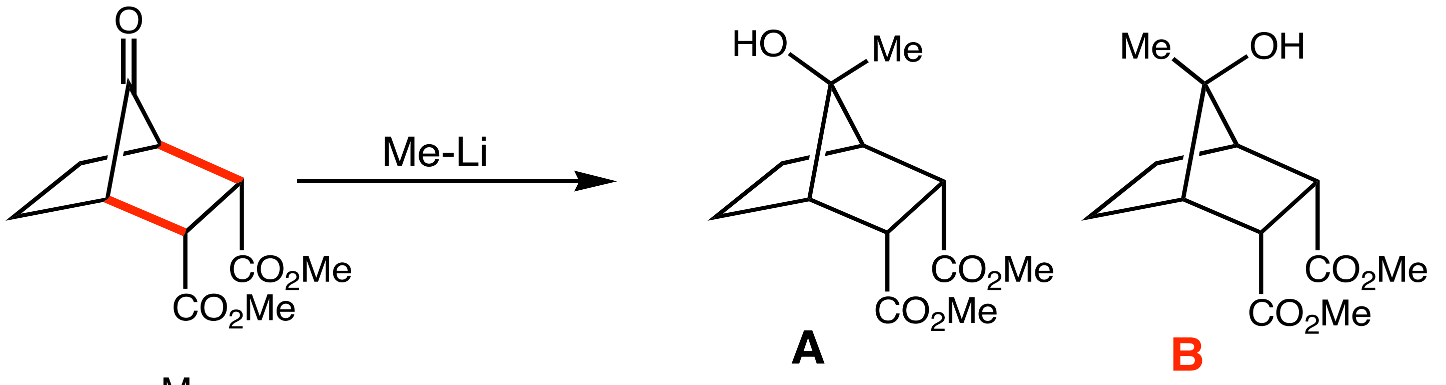
Ferlkin-Anh	Transition State Hyperconjugation
Cornforth	Transition State Electrostatic effects

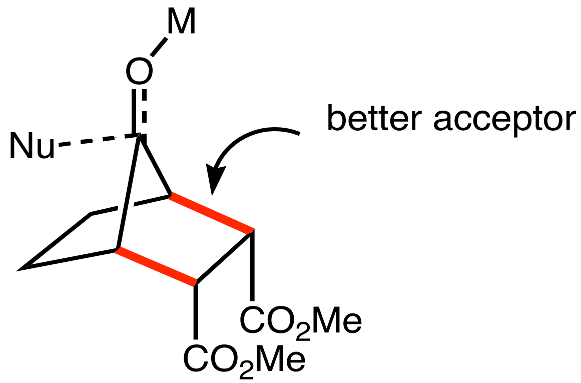
The Polar Felkin-Anh Model

The Cornforth Model



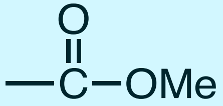
Cases Not Handled by the Felkin-Anh Model





Electronegative $-CO_2Me$ substituent
will stabilize both
C–C bonding & antibonding states

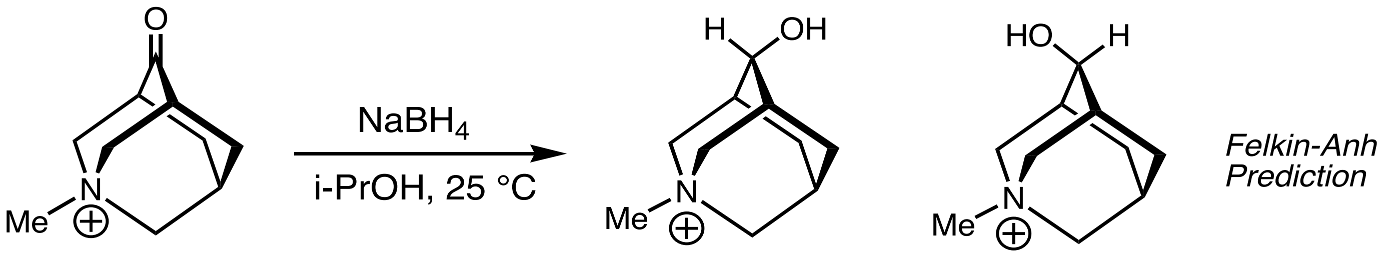
Felkin-Anh analysis
predicts **B**

(R) Substituent	A/B Ratio
 $-\overset{O}{\overset{\|}{C}}-OMe$	>90:10
$-CH_2OMe$	34:66
$-CH{=}CH_2$	27:73
$-CH_2-CH_3$	17:83

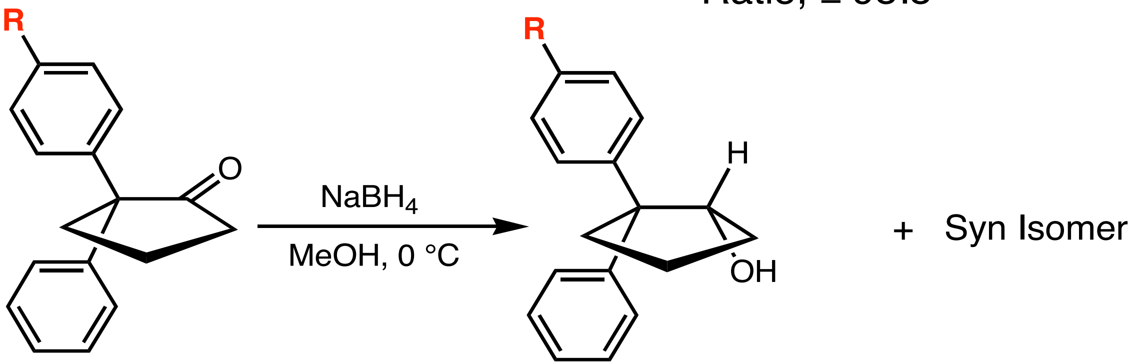
G. Mehta, *JACS* **1990**, *112*, 6140

Effects Governing Face Selectivity at Trigonal Carbon

Le Noble, *JACS* 1992, *114*, 1916



Ratio, ≥ 95:5



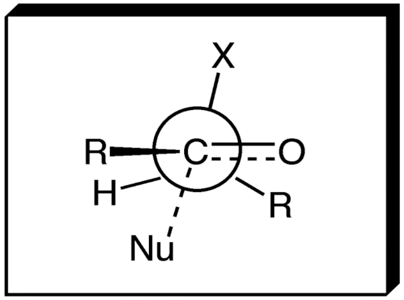
Halterman, *JACS* 1990, *112*, 6690

(R)	Anti:Syn Ratio
R = NO_2	79:21
R = Cl	63:37
R = OMe	43:57
R = NH_2	36:64

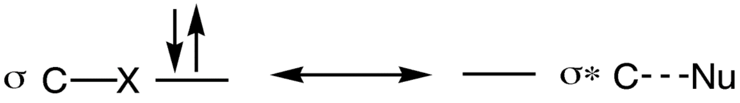
Cieplak Model for C=O Addition

Cieplak, *JACS* **1981**, *103*, 4540;   Cieplak/Johnson, *JACS* **1989**, *111*, 8447

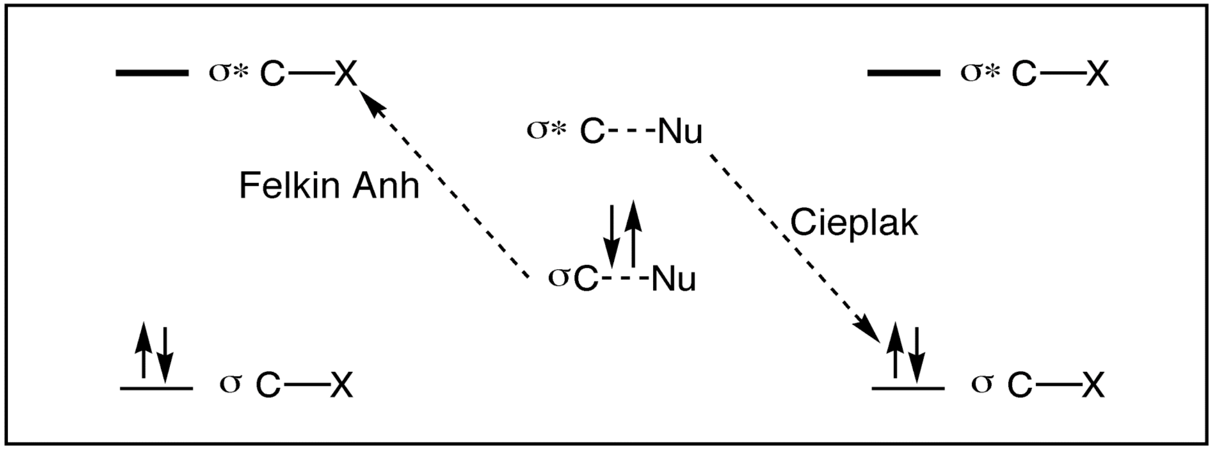
Point A: TS is stabilized by antiperiplanar allylic bond, but....



Point B: Nature of the stabilizing secondary orbital interactions differ:



σ C—X ⟷ σ^* C- - -Nu



σ^* C—X σ^* C—X

σ^* C- - -Nu

Felkin Anh

Cieplak

σC- - -Nu

σ C—X σ C—X

Point C: C–X Electron donating ability follows the order:

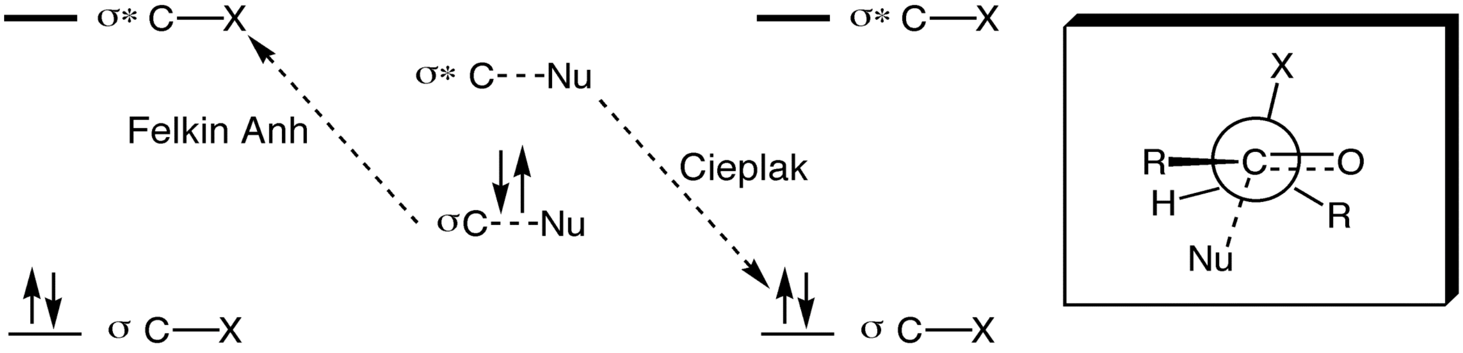
C–H > C–C > C–N > C–O

(Houk disputes the ordering of C–H, C–C)

Point D: Importance of torsional effects (Felkin, Anh, Houk, Padden-Row) disputed.

Cieplak Model for C=O Addition

Cieplak, *JACS* **1981**, *103*, 4540; Cieplak/Johnson, *JACS* **1989**, *111*, 8447



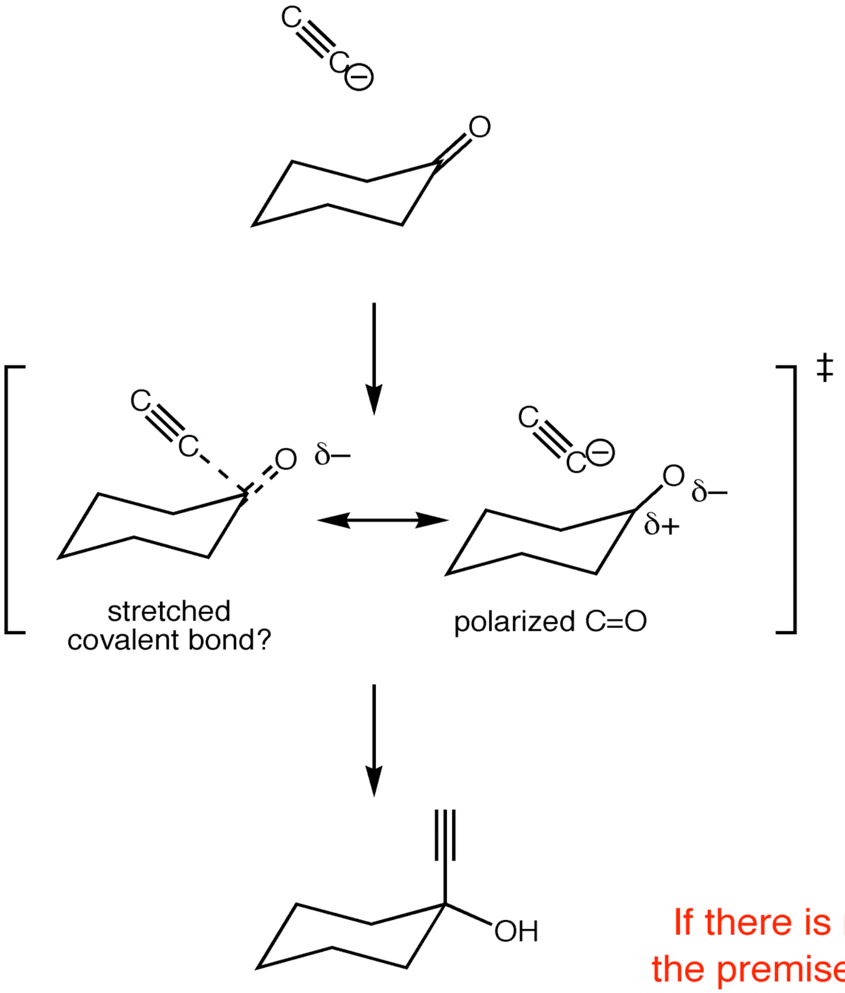
"Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamendal assumptions in frontier molecular orbital theory." The Cieplak hypothesis is nonsense."

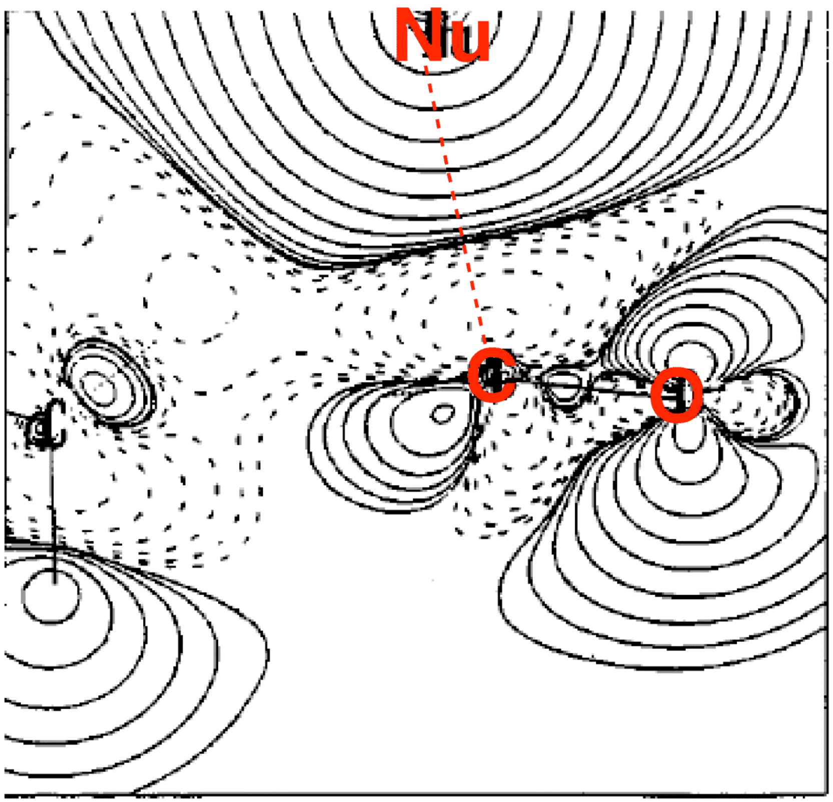
"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

The management

Theoretical Calculations for C=O

Cieplak J. Org. Chem. **1998,** *63,* 521-530

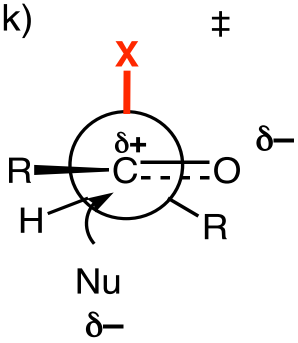




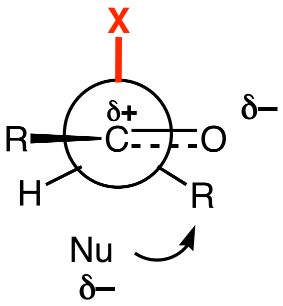
If there is no electron density along the internuclear axis the premise of the Felkin-Anh model has been invalidated.

Evans: Cieplak Ionic Model for C=O Addition

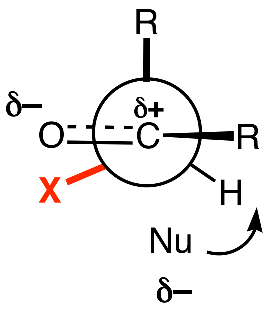
- There is little or no covalency along Nu....$^{\delta+}$C=O$^{\delta-}$ axis in the transition state (Cieplek)
- Eclipsed transition states are disfavored (Felkin, anh-Eisenstein, Houk)
- Transition state stabilization may be achieved by orienting the best σ-donor perpendicular to polarized C=O (Stereolectronic Effects)



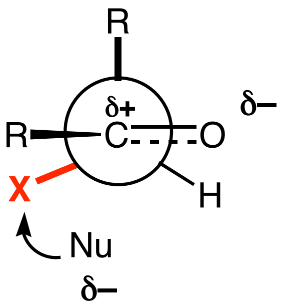
- Transition state stabilization may be achieved by orienting the largest substituent anti, rather than gauche to nucleophile (Steric Effects-1)



versus

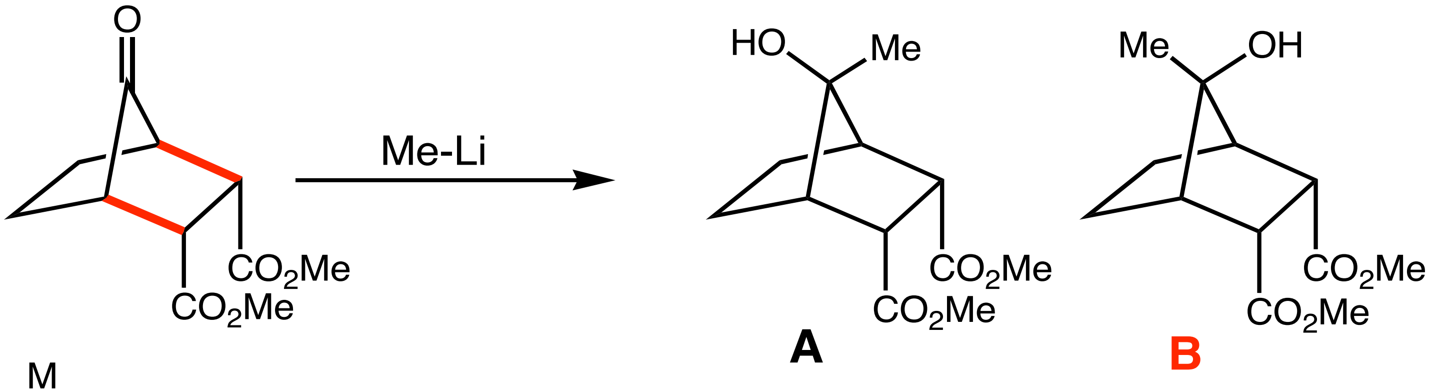


versus

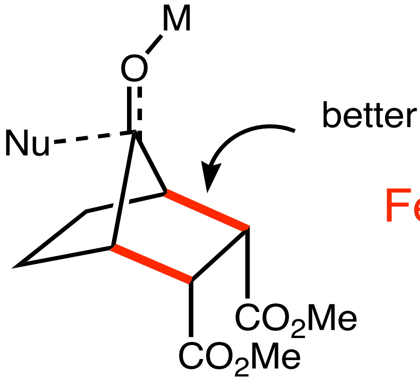


- If the C–X bond is very polar (**X** = F, Cl, OR), electrostatic (dipole) effects may be significant as noted by Cornforth

Cases Not Handled by the Felkin-Anh Model



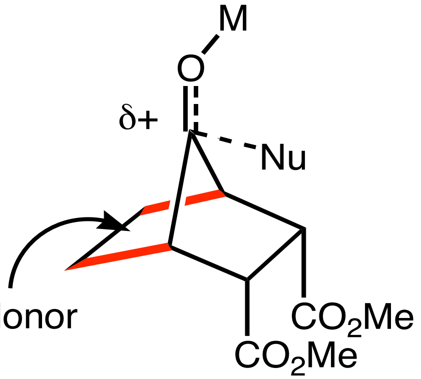
Felkin-Anh analysis predicts **B**



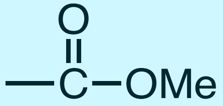
better acceptor

Felkin-Anh

Cieplak



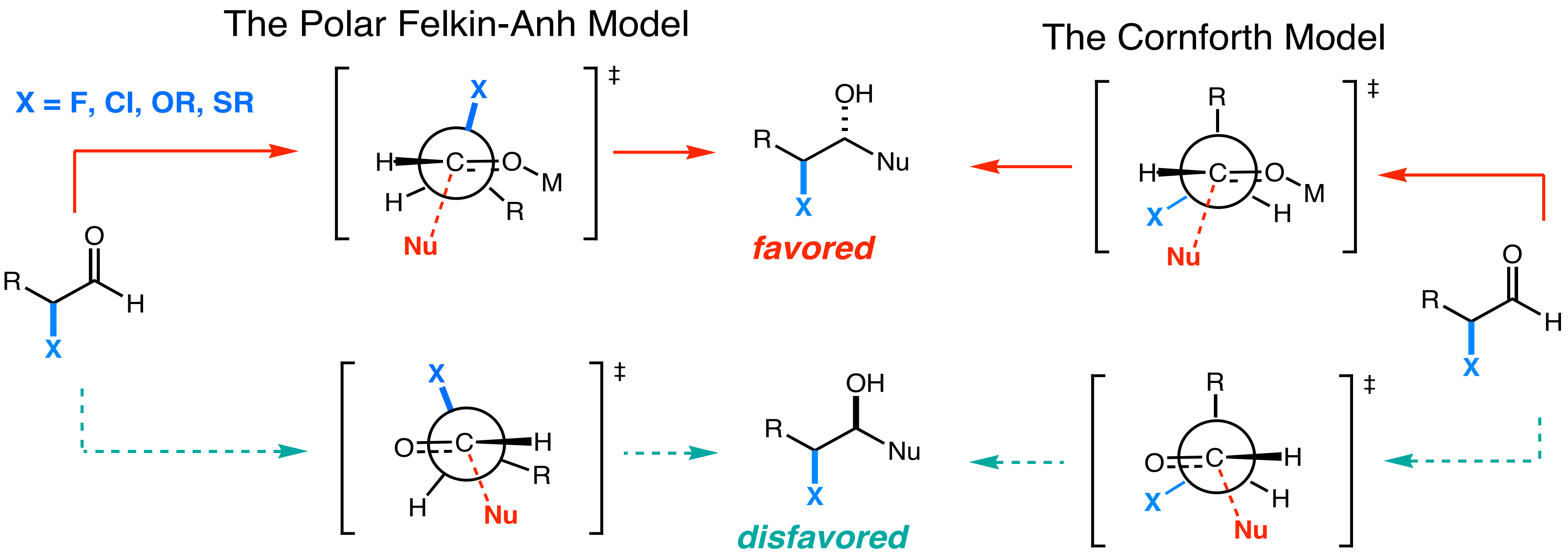
better donor

(R) Substituent	A/B Ratio
 $—\overset{\text{O}}{\overset{\|}{\text{C}}}\text{–OMe}$	>90:10
$—CH_2OMe$	34:66
$—CH=CH_2$	27:73
$—CH_2–CH_3$	17:83

G. Mehta, *JACS* **1990**, *112*, 6140

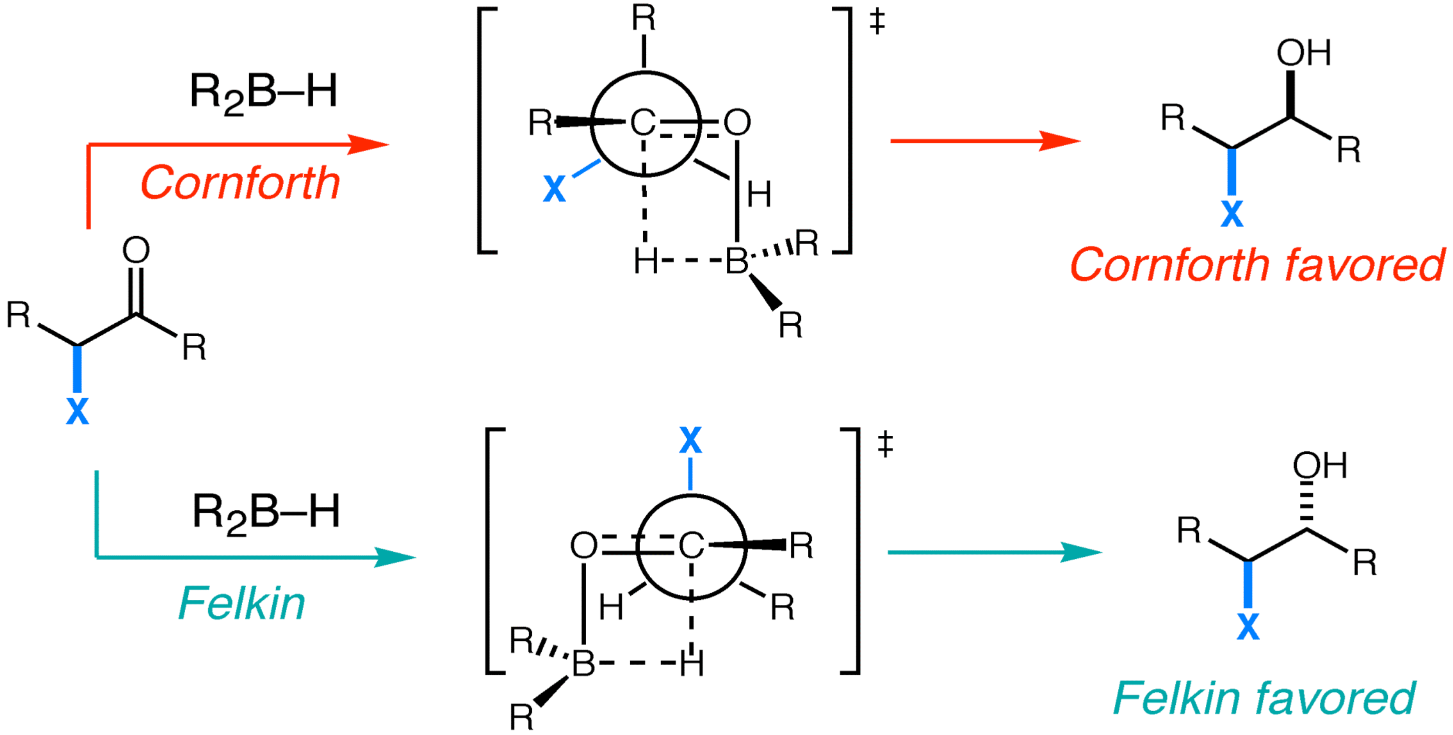
How does one distinguish between the Cornforth & Felkin Anh Models for C=O Addition??

Ferlkin-Anh	Transition State Hyperconjugation
Cornforth	Transition State Electrostatic effects

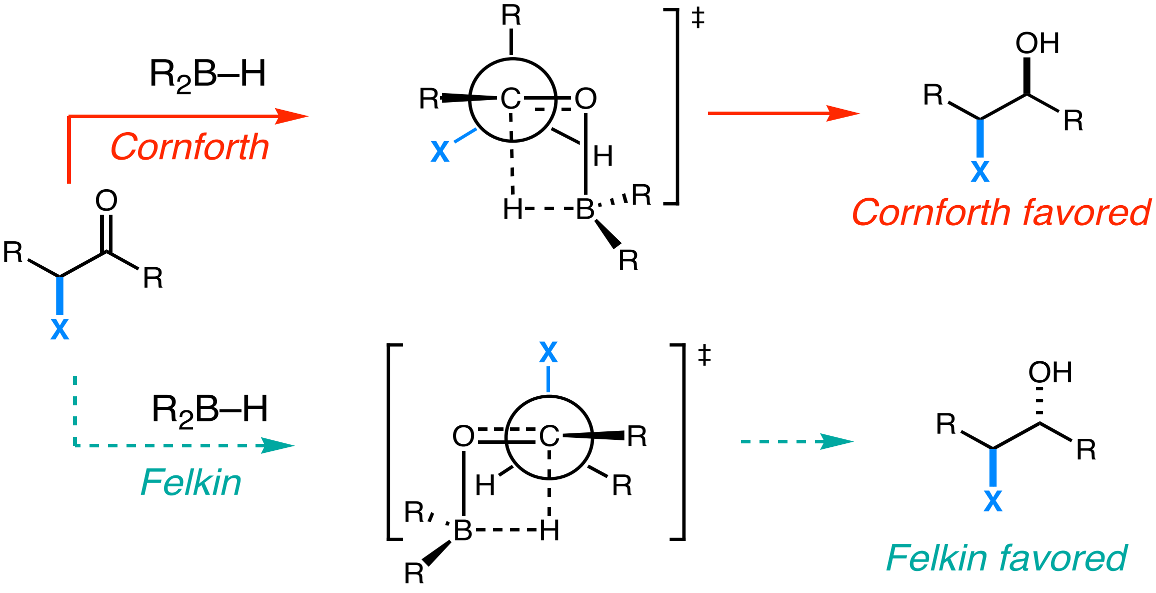


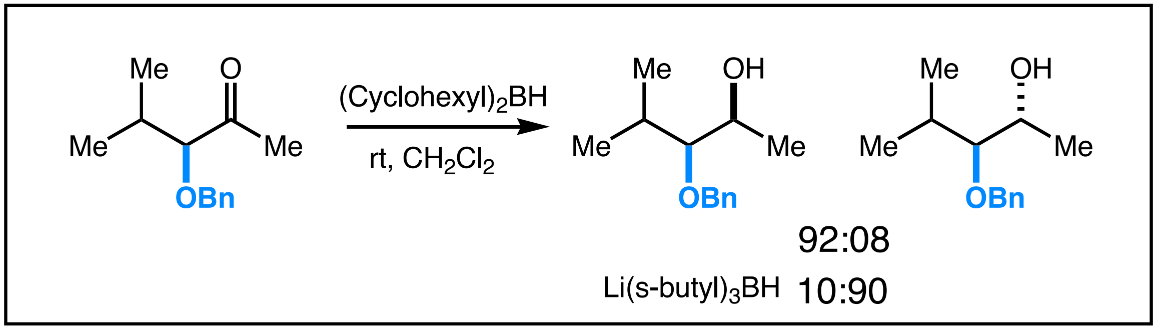
One needs a nucleophile that interacts with the vicinal stereocenter.

Dialkylborane reductions:
Individual models predict opposite stereochemical outcomes



The Cornforth Model Prevails!



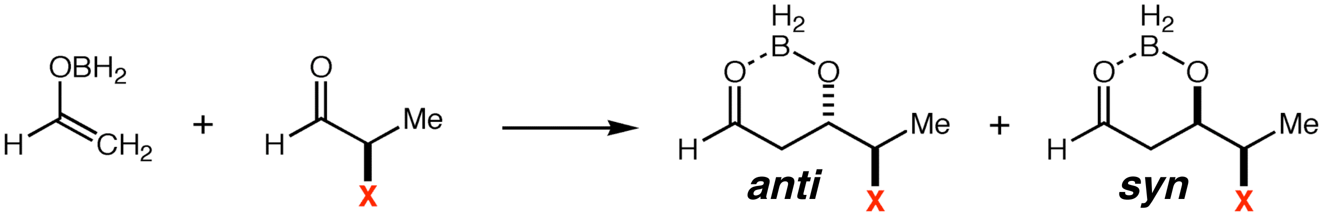


Siska, Cee, Young, *JACS* **2006,** *128,* 9433-9441

Ab Initio Investigation of Enolborane Aldol Reactions

Cee, Cramer, Evans, *JACS* **2006**, *128*, 2920-2930

Problem: Little theoretical support for the Cornforth model
Observation: Majority of prior theoretical studies: $^{-}$CN or $M^{+}H^{-}$

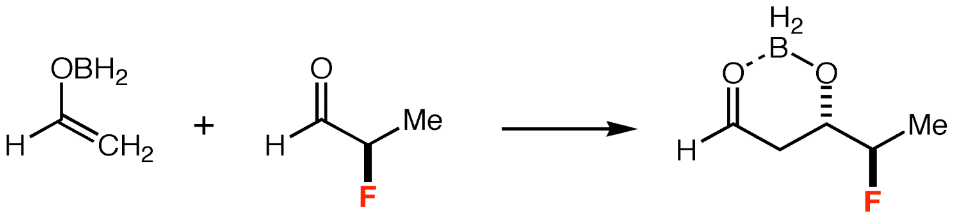


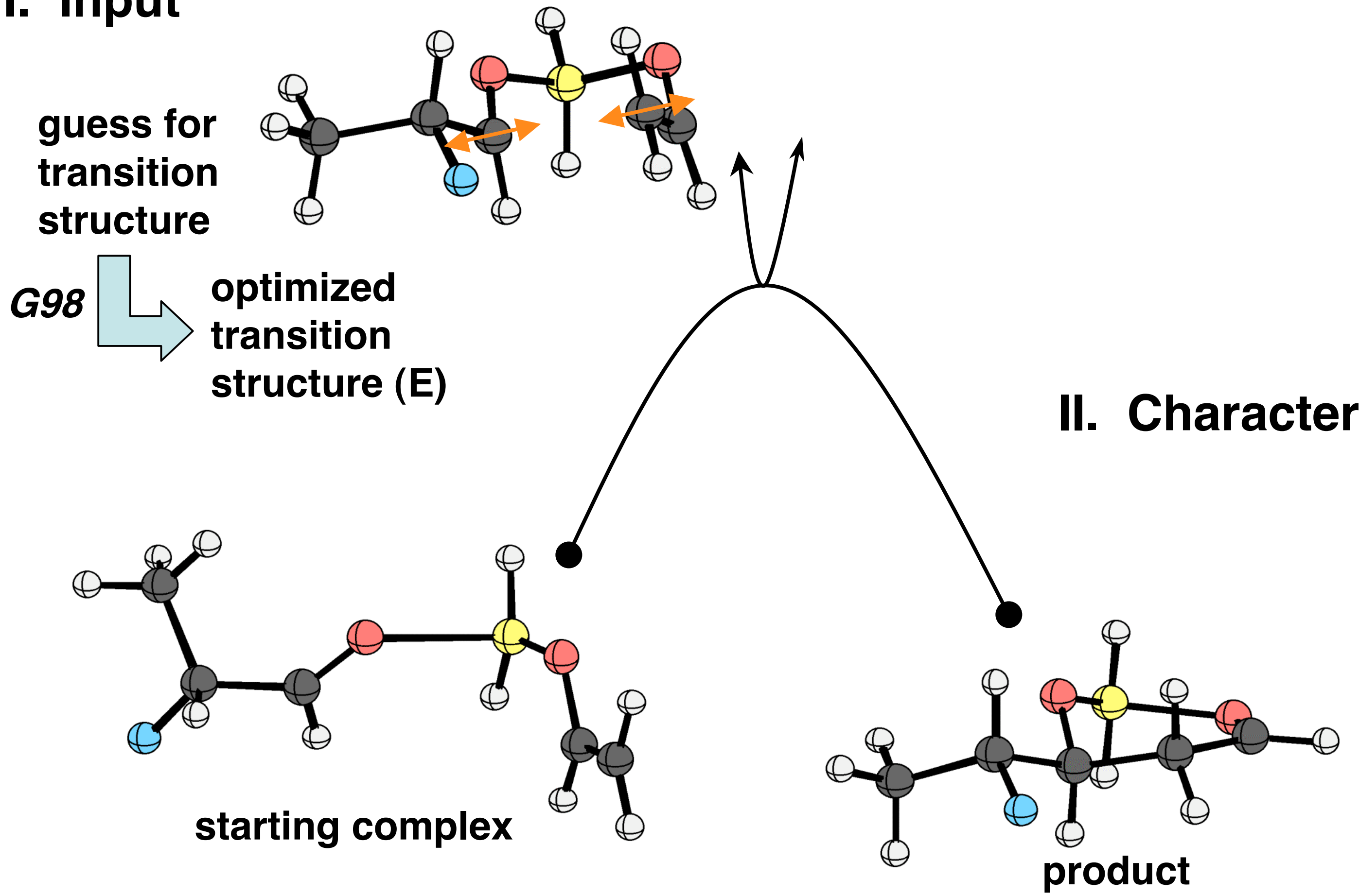
Full Study: X = F, Cl
Partial Study: X = OMe, SMe

1. **Theoretical Level: DFT (B3LYP/6-31G*)**
2. **Find all possible chair-like transition structures**
3. **Compare energies**

Allylation of 2-methoxypropanal: Gung and Xue *Tetrahedron: Asymmetry* **2001**, *12*, 2955-2959

Theoretical Investigation of Transition State Geometries





I. Input

guess for transition structure

G98

optimized transition structure (E)

II. Characterize

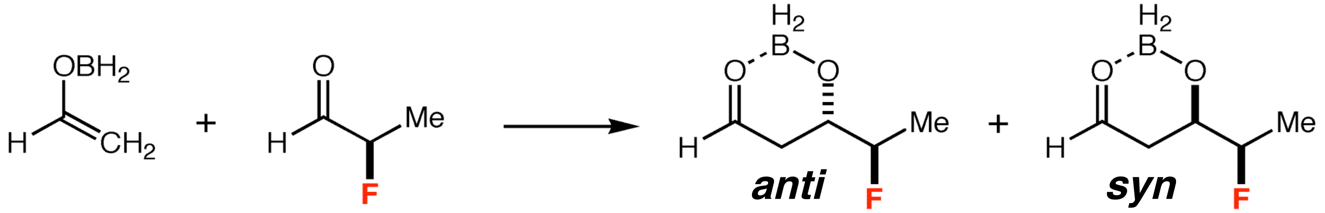
III. Rotate C–C, Repeat

starting complex

product

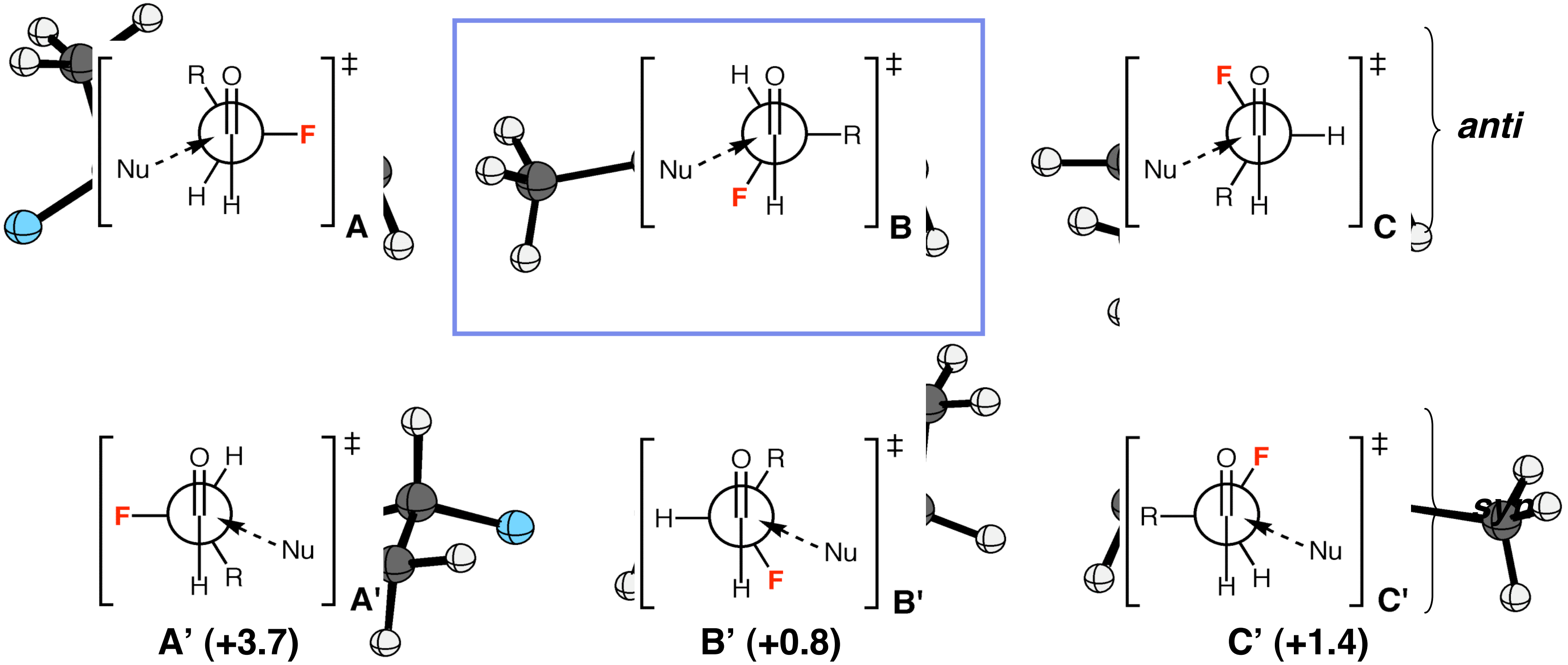
Acetaldehyde Enolborane + 2-Fluoropropanal
B3LYP/6-31G (kcal/mol)*

O	**F**
S	**Cl**



Polar Felkin-Anh

Cornforth



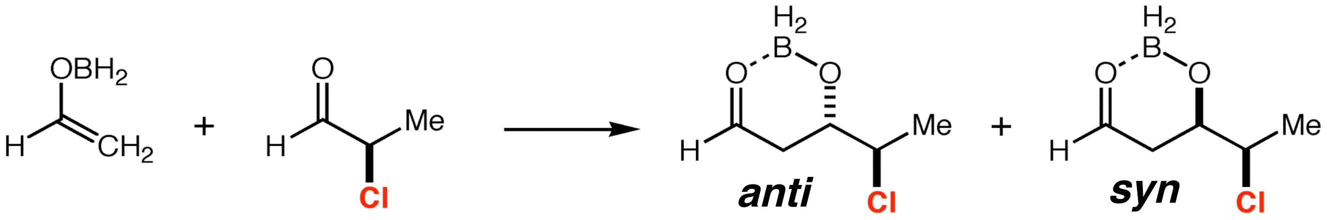
A’ (+3.7)

B’ (+0.8)

C’ (+1.4)

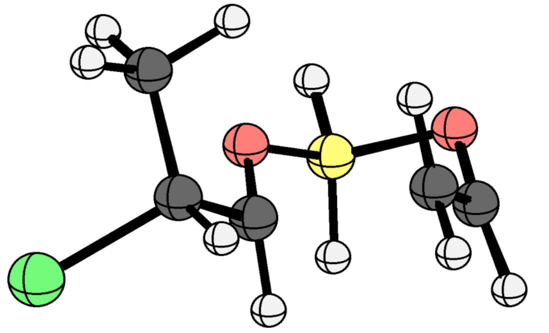
Acetaldehyde Enolborane + 2-Chloropropanal
B3LYP/6-31G (kcal/mol)*

O	**F**
S	**Cl**

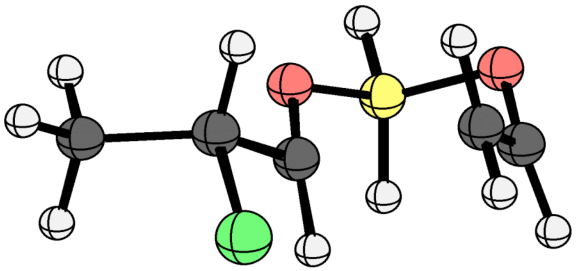


Polar Felkin-Anh

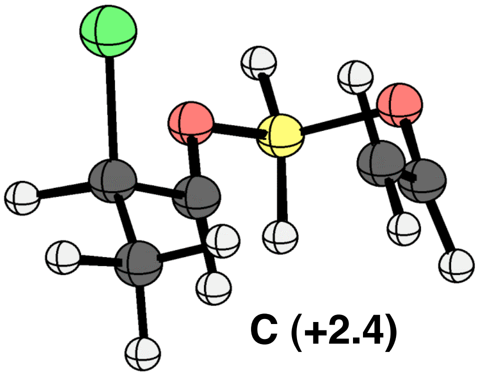
Cornforth



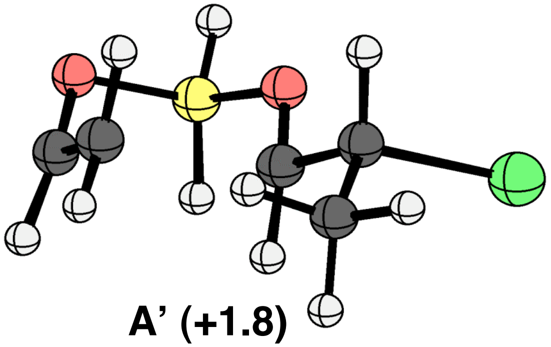
A (+0.3)



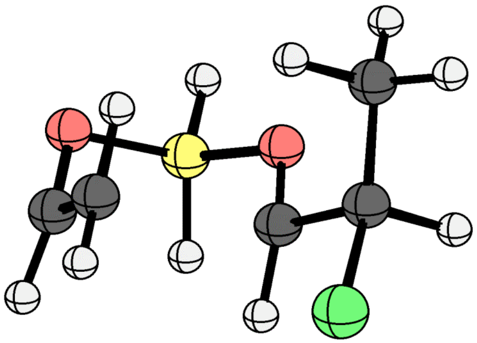
B (0)



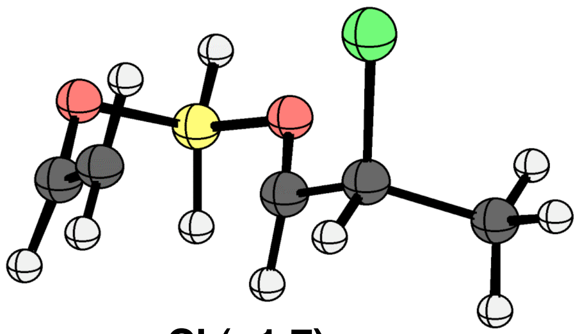
C (+2.4)



A’ (+1.8)



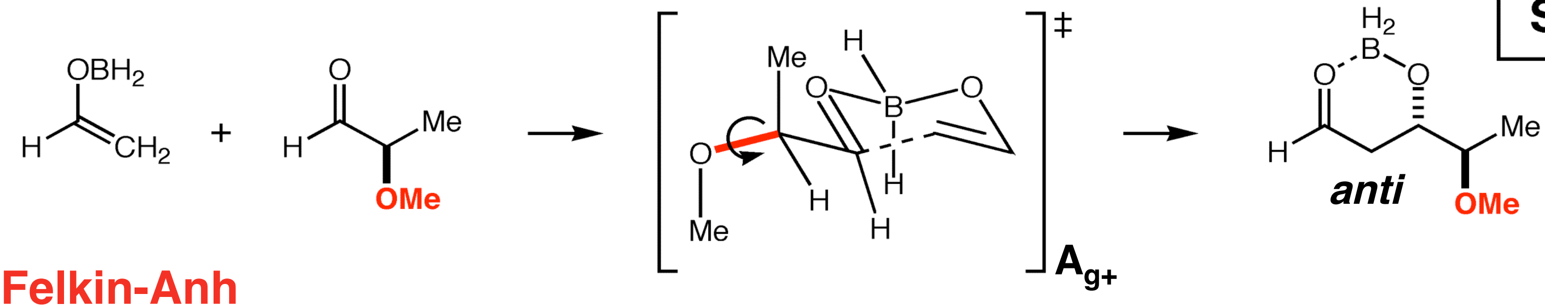
B’ (+0.6)



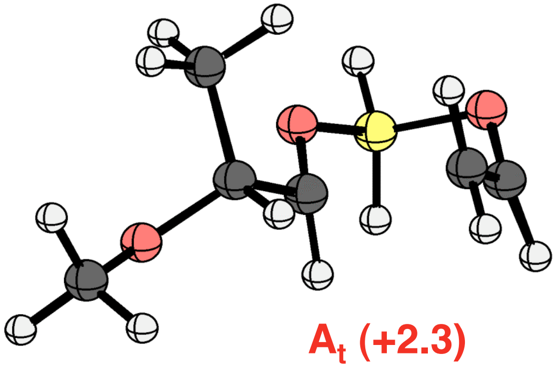
C’ (+1.7)

Generality: 2-Methoxypropanal

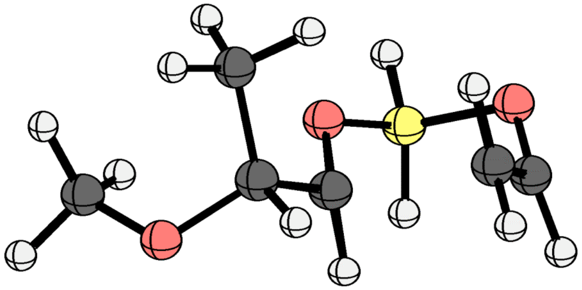
O	F
S	Cl



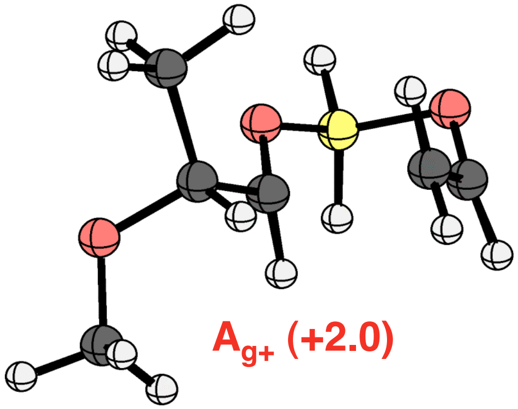
Polar Felkin-Anh



A$_t$ (+2.3)

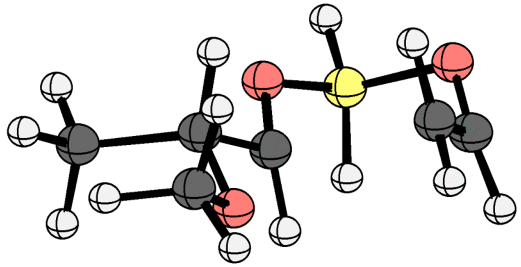


A$_{g-}$ (+2.0)

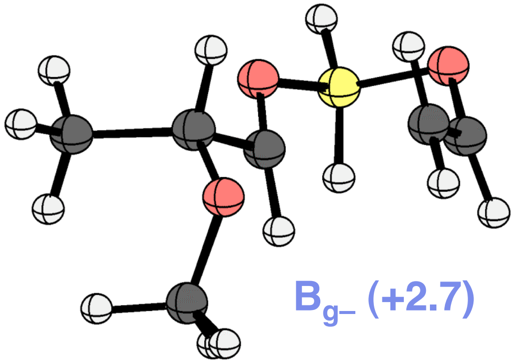


A$_{g+}$ (+2.0)

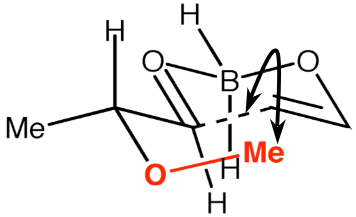
Cornforth



B$_t$ (0)



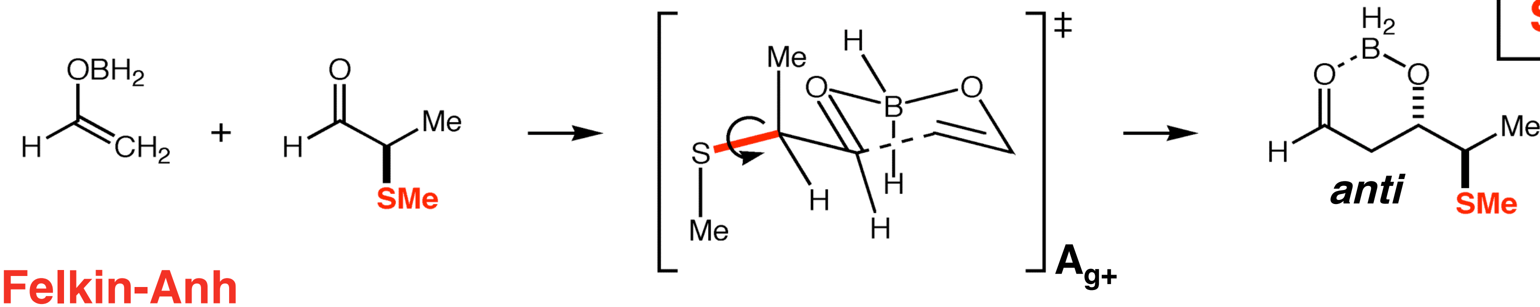
B$_{g-}$ (+2.7)



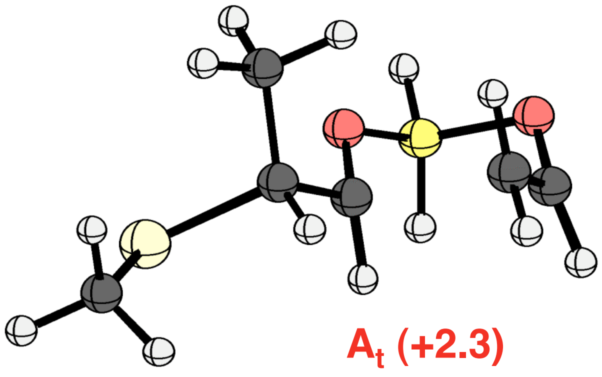
B$_{g+}$

Generality: 2-Thiomethylpropanal

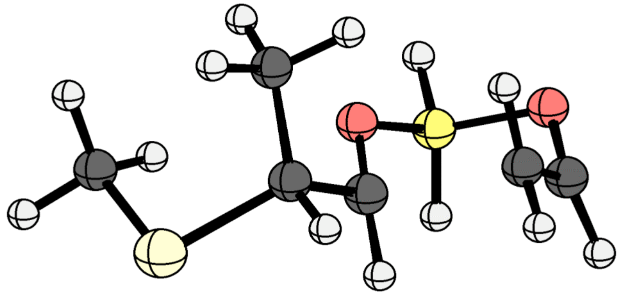
O	**F**
S	**Cl**



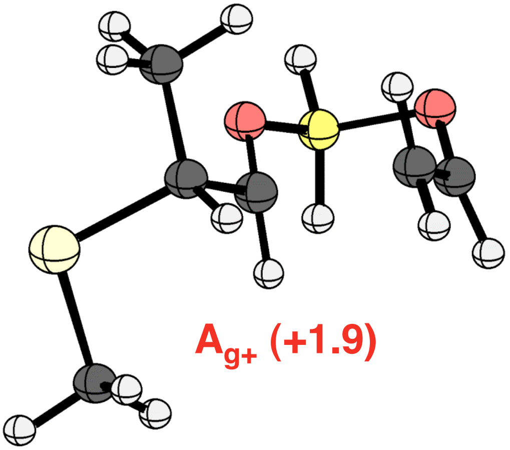
Polar Felkin-Anh



A_t (+2.3)

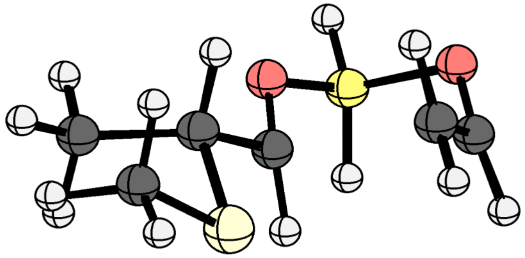


A_{g-} (0)

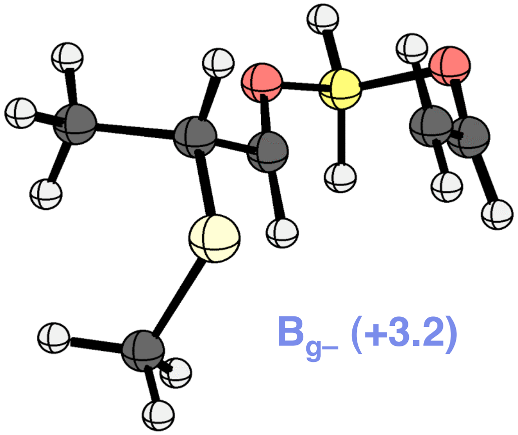


A_{g+} (+1.9)

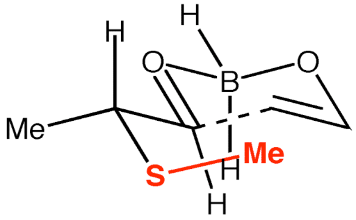
Cornforth



B_t (+3.2)



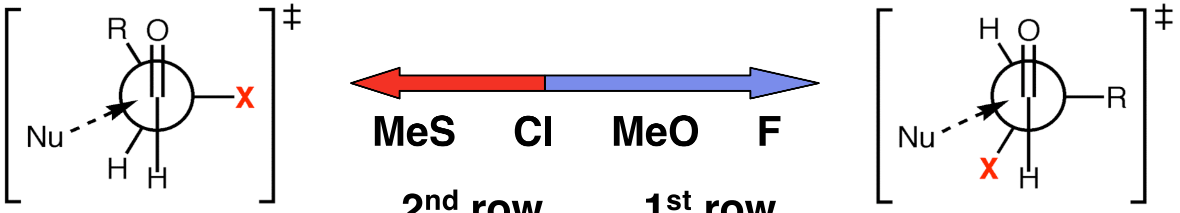
B_{g-} (+3.2)



B_{g+}

Periodic/Group Trends: $\sigma^*_{C\text{–}X}$ vs Electronegativity

Trends in C-X:



2nd row **1st row**

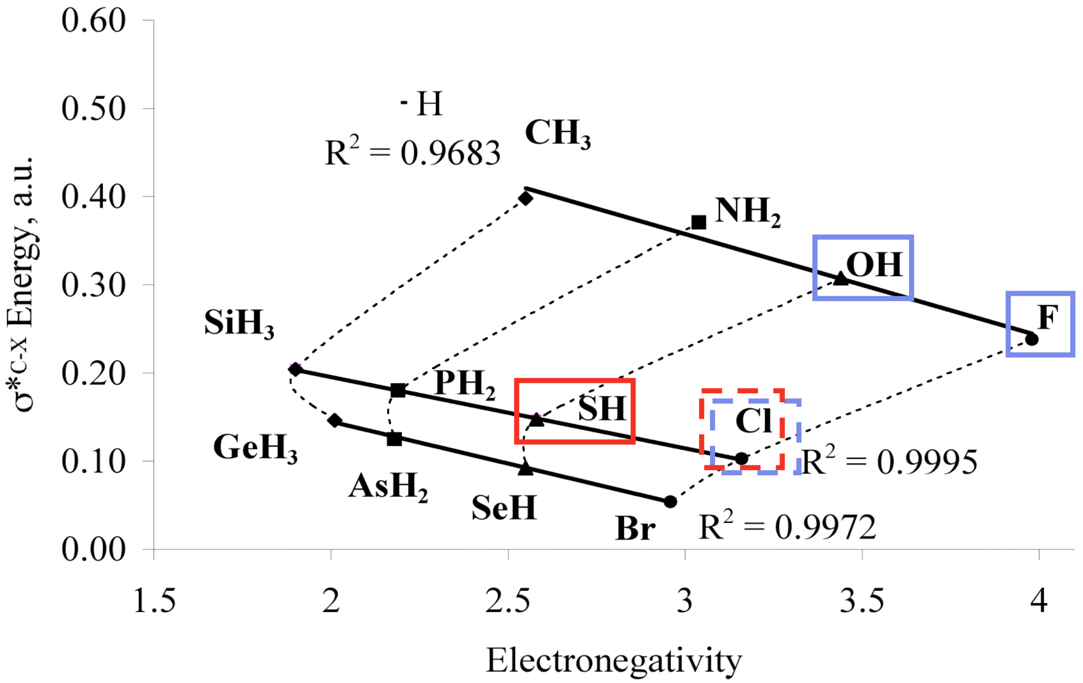
Polar Felkin-Anh

low energy $\sigma^*_{C\text{–}X}$

Cornforth

electronegative X

Calculated $\sigma^*_{C\text{–}X}$:



Polar Felkin-Anh

Cornforth Model

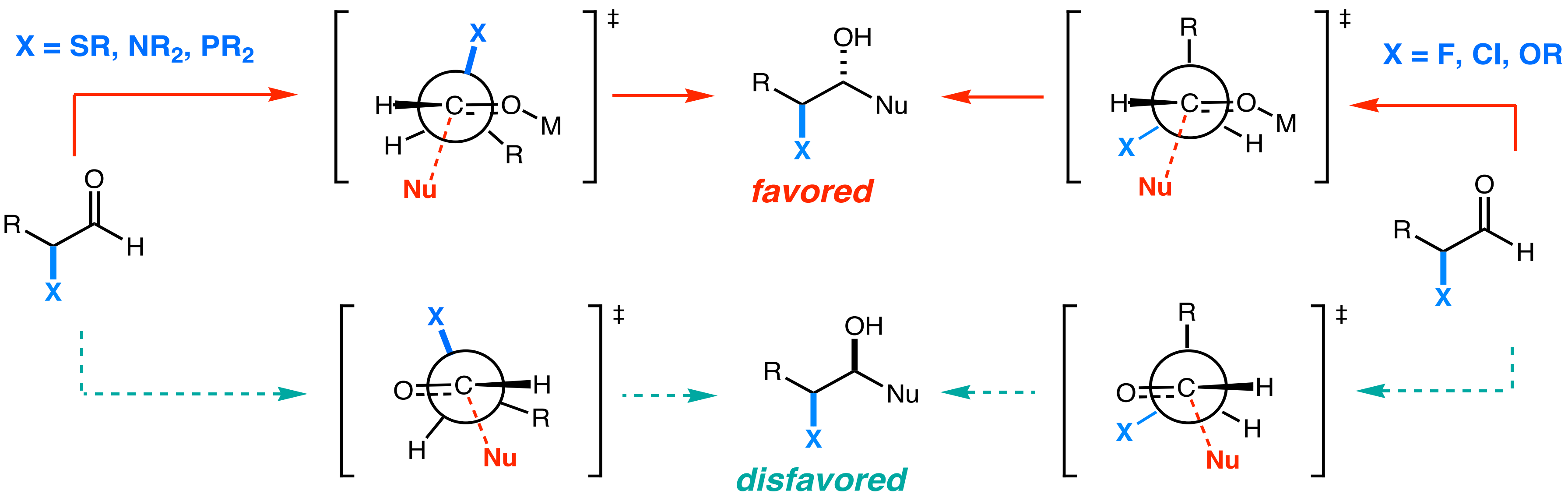
Alabugin and Zeidan *J. Am. Chem. Soc.* **2002**, *124*, 3175-3185

How does one distinguish between the Cornforth & Felkin Anh Models for C=O Addition??

Ferlkin-Anh	Transition State Hyperconjugation
Cornforth	Transition State Electrostatic effects

The Polar Felkin-Anh Model

The Cornforth Model

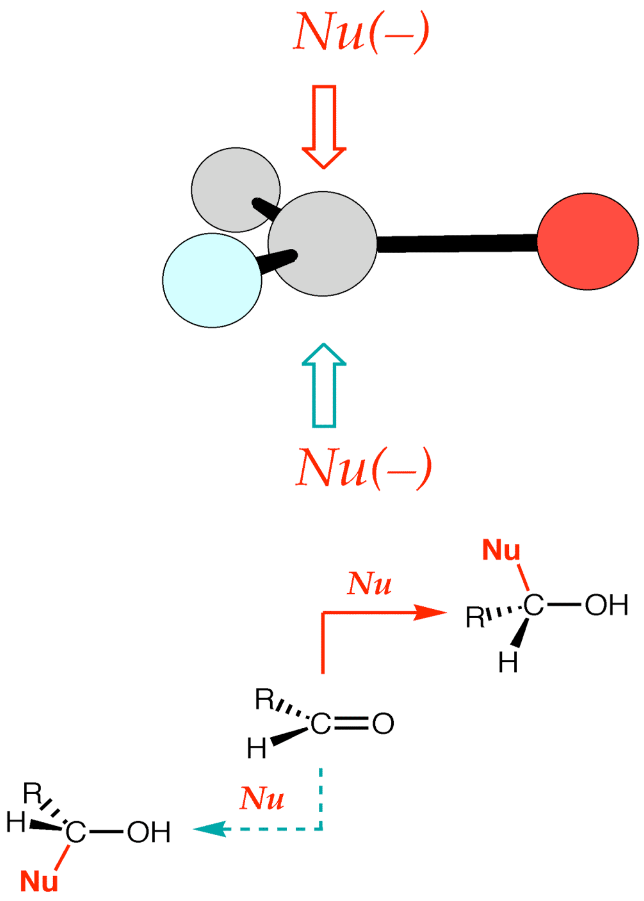


X: 2nd row heteroatoms

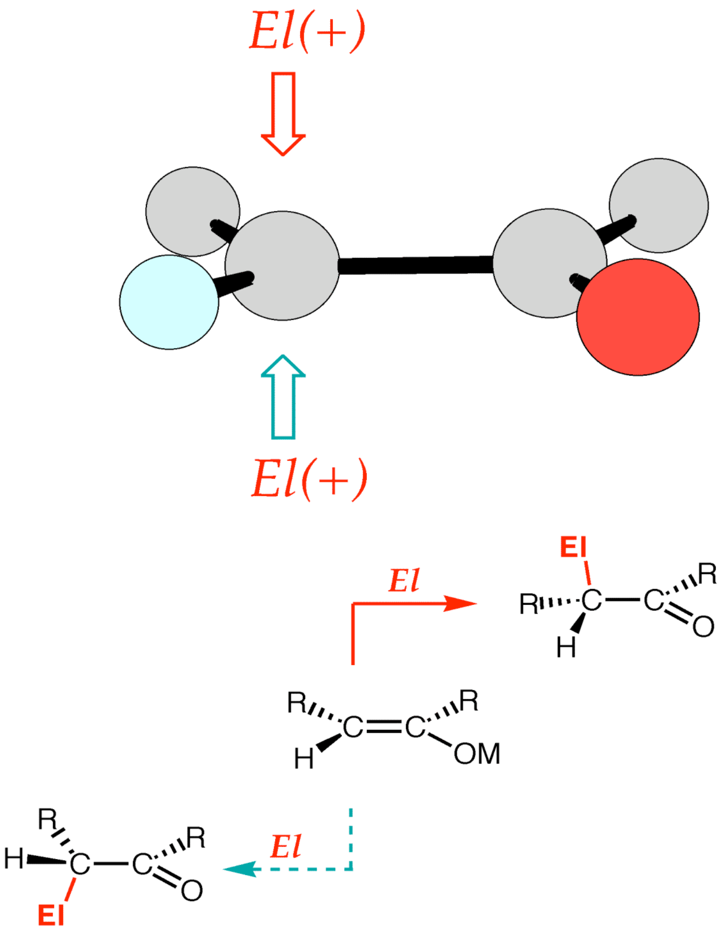
X: 1st row heteroatoms

The Stereochemical Demon:
Controlling the Reacting Enantioface in C–C Bond Constructions

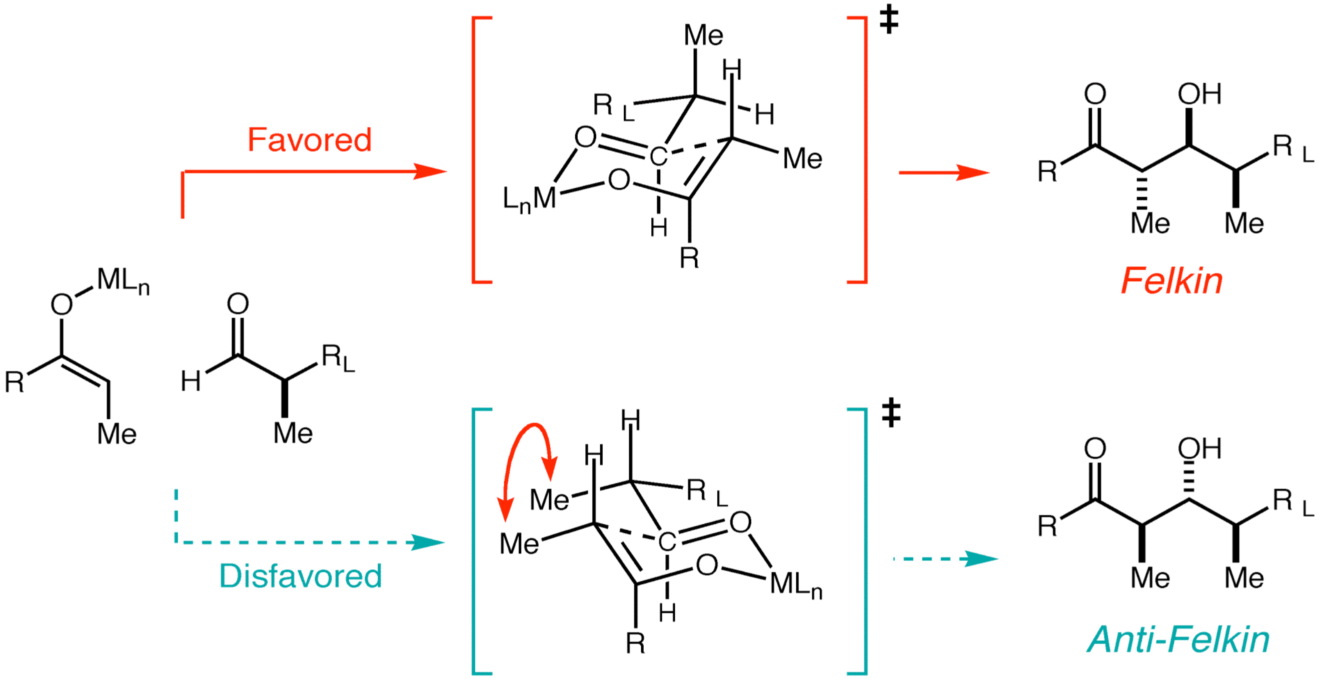
Electrophilic carbon



Nucleophilic carbon



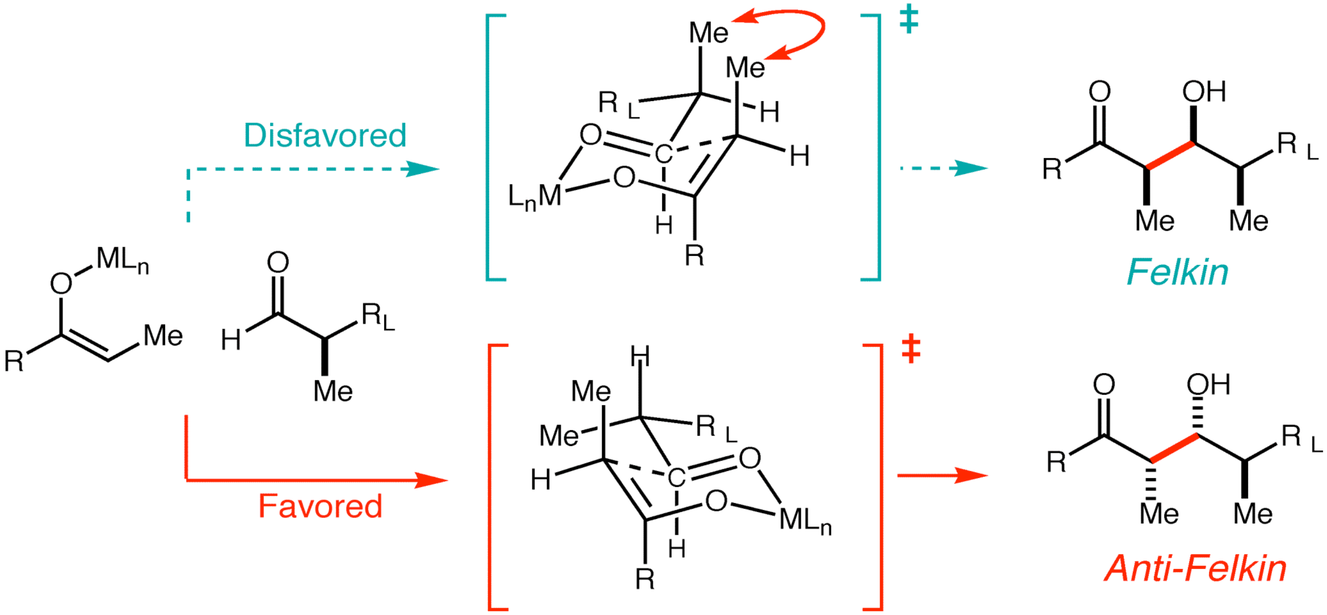
(E) Enolates Exhibit Felkin Aldehyde Diastereoface Selection



The illustrated syn-pentane interaction disfavors the anti-Felkin pathway.

Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157.

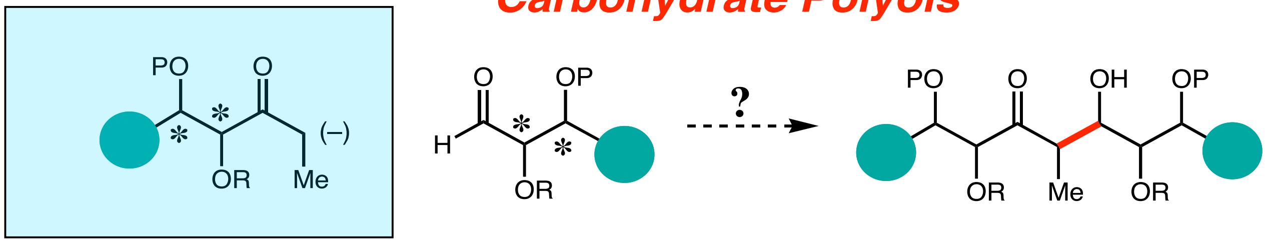
(Z) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection

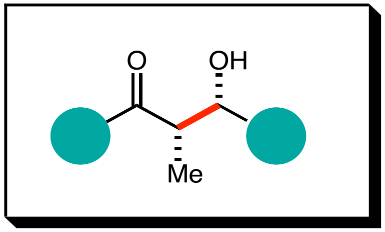


The illustrated syn-pentane interaction disfavors the Felkin pathway.

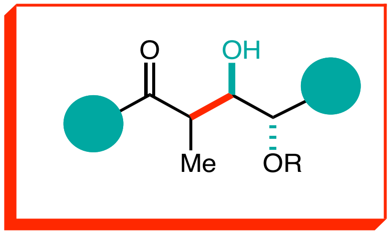
Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157.

Stereochemical Control Elements for Double Stereodifferentiating Aldol Additions:
Carbohydrate Polyols

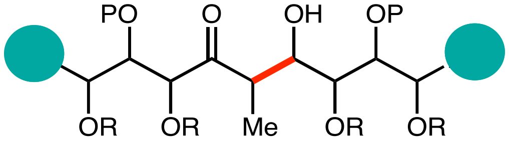




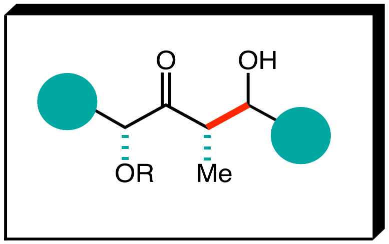
simple diastereocontrol
(enolate geometry)



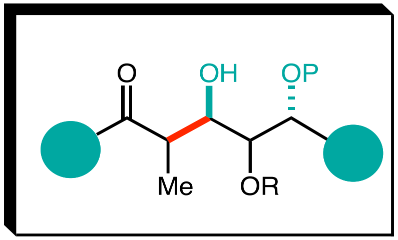
1,2-induction R = OR
(Polar Felkin-Anh)



R = H, Me, OR



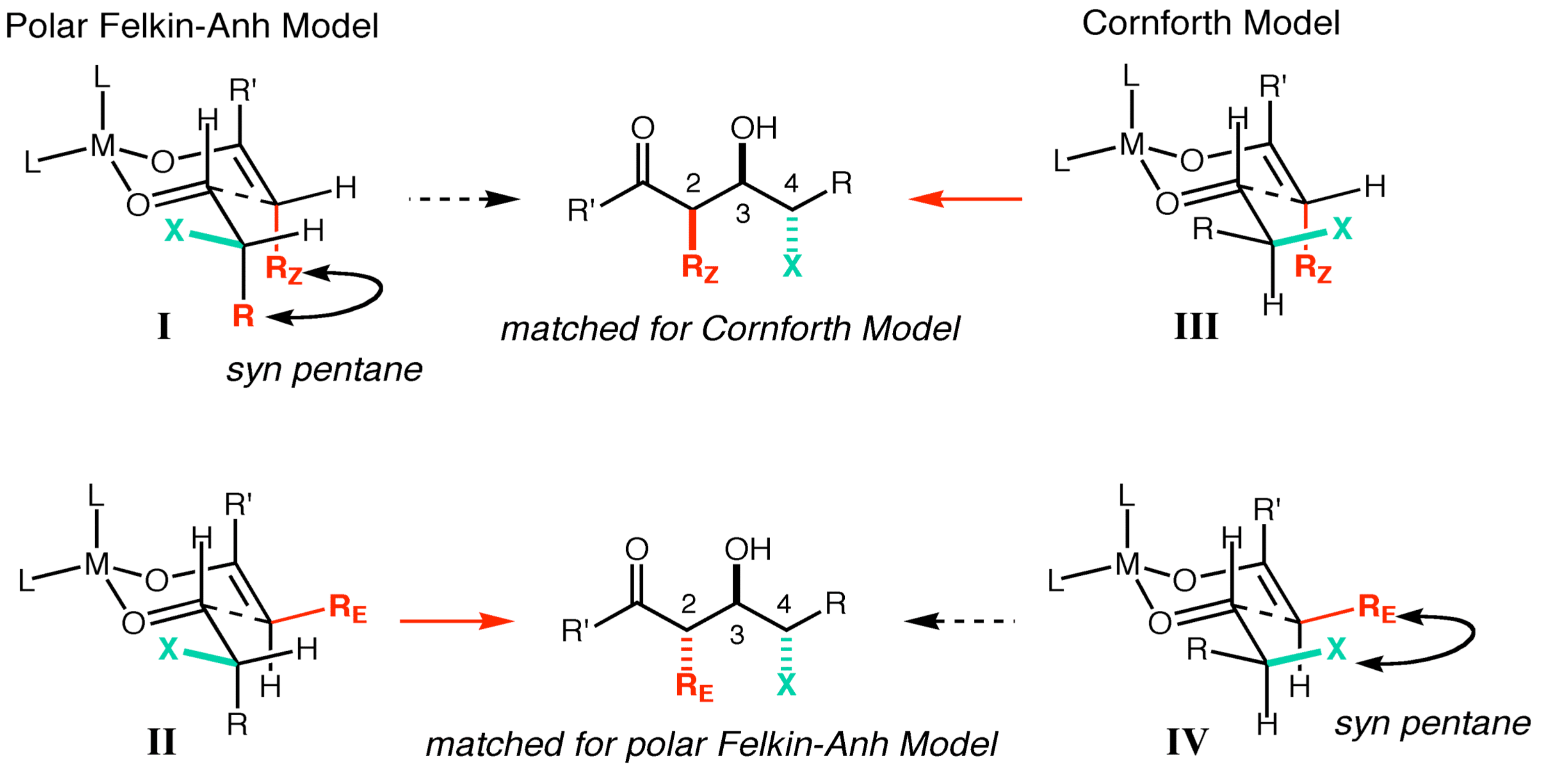
enolate facial bias



1,3-induction

Transition State Analyses: Polar Felkin-Anh & Cornforth Models.

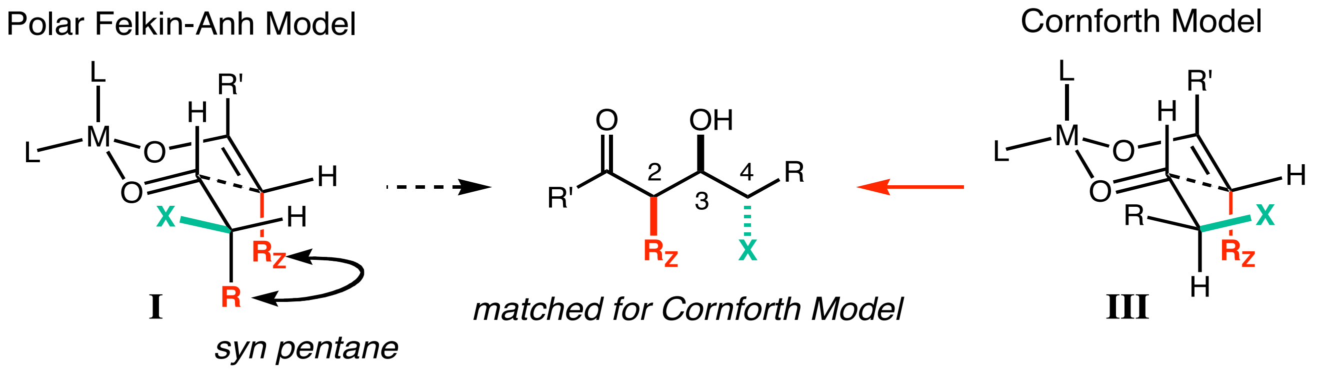
X = OR



Conforth Model Prediction: (*E*) enolates will exhibit diminished levels of 3,4-anti diastereoselection relative to (*Z*) enolates.

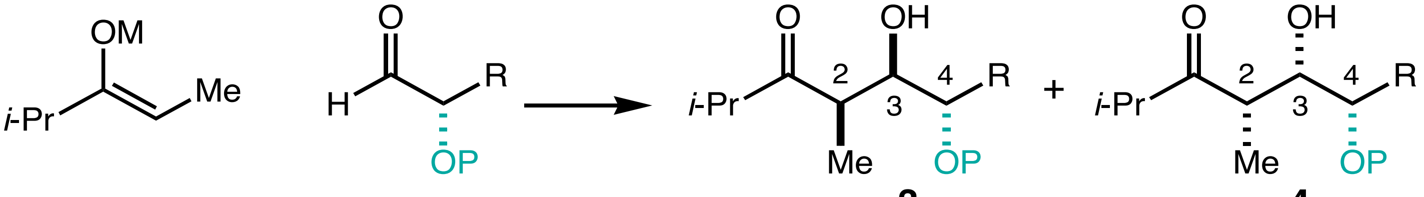
Polar Felkin Model Prediction: (*Z*) Enolates will exhibit diminished levels of 3,4-anti diastereoselection due to reactions through competing transition states relative to the analogous reactons of (*E*) enolates which encounter no such destabilizing syn-pentane interaction.

Evans, Cee, Siska, *Angew Chem Int Ed*. **2003**, *42*, 17661



Conforth Model Prediction: (*Z*) enolates will exhibit high levels of 3,4-anti diastereoselection relative to (*E)* enolates.

Polar Felkin Model Prediction: (*Z*) Enolates will exhibit diminished levels of 3,4-anti diastereoselection due to reactions through competing transition states relative to the analogous reactons of (*E*) enolates which encounter no such destabilizing syn-pentane interaction.

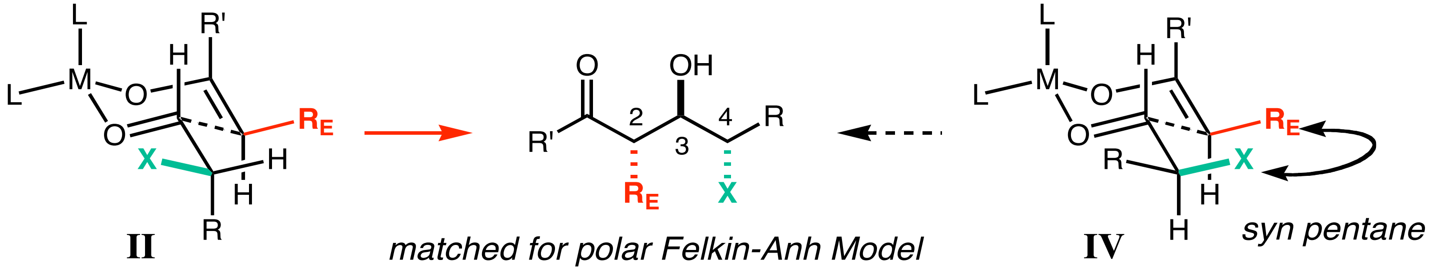


3 **4**

M	P	R	2,3-syn : 2,3-anti	**3** : **4**	yield, %^{c}
9-BBN	Bn	Me	95 : 05^b	89 : 11^b	95
	Bn	*i*-Pr	95 : 05	98 : 02	73
	TBS	Me	93 : 07	98 : 02	77
	TBS	*i*-Pr	94 : 06	98 : 02	72

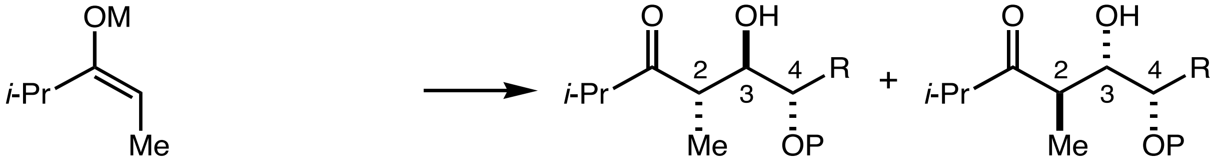
Polar Felkin-Anh Model

Cornforth Model



Conforth Model Prediction: (*E*) enolates will exhibit diminished levels of 3,4-anti diastereoselection relative to (*Z*) enolates.

Polar Felkin Model Prediction: (*E*) Enolates will exhibit high levels of 3,4-anti diastereoselection.



5 **6**

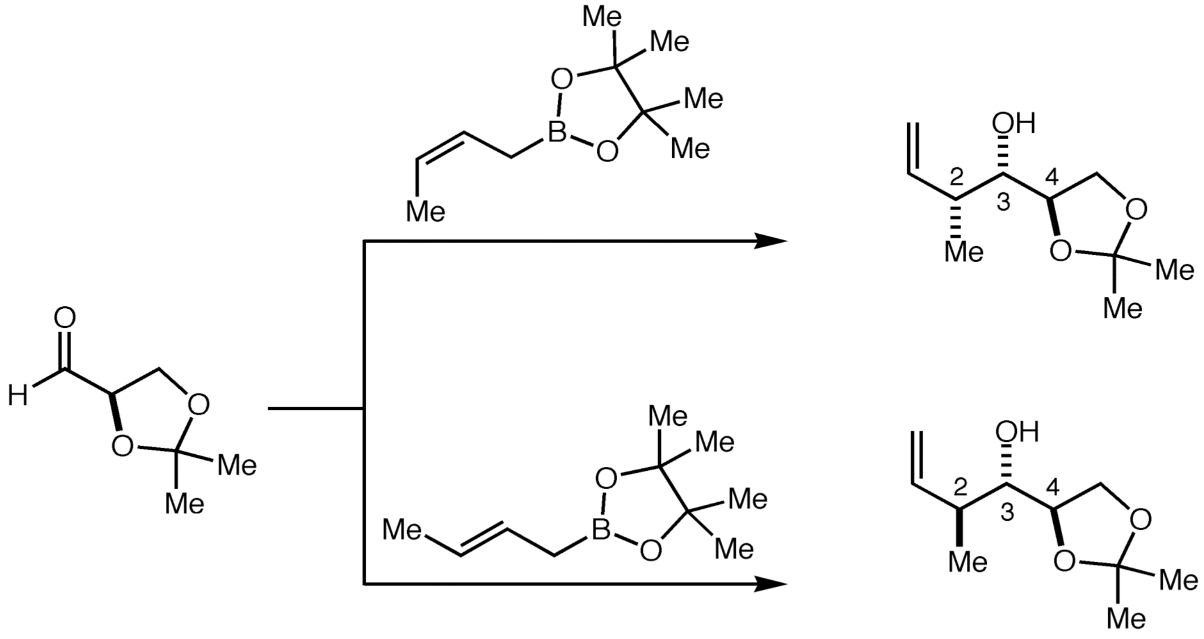
M	P	R	2,3-anti : 2,3-syn	**5** : **6**	yield, %[c]
(*c*-Hex)$_2$B	Bn	Me	>99 : 01[b]	33 : 67[b]	59
	Bn	*i*-Pr	>99 : 01	67 : 33	77
	TBS	Me	>99 : 01	21 : 79	77
	TBS	*i*-Pr	>99 : 01	43 : 57	85

Evans, Cee, Siska, *Angew Chem Int Ed*. **2003**, *42*, 17661

Cornforth model for C=O addition appears to be a reliable predictor

Conforth Model Prediction: (*E*) enolates will exhibit diminished levels of 3,4-anti diastereoselection relative to (*Z*) enolates.

Polar Felkin Model Prediction: (*Z*) Enolates will exhibit diminished levels of 3,4-anti diastereoselection due to reactions through competing transition states relative to the analogous reactons of (*E*) enolates which encounter no such destabilizing syn-pentane interaction.



3,4-anti : 3,4-syn 97:03

3,4-anti : 3,4-syn 55:45

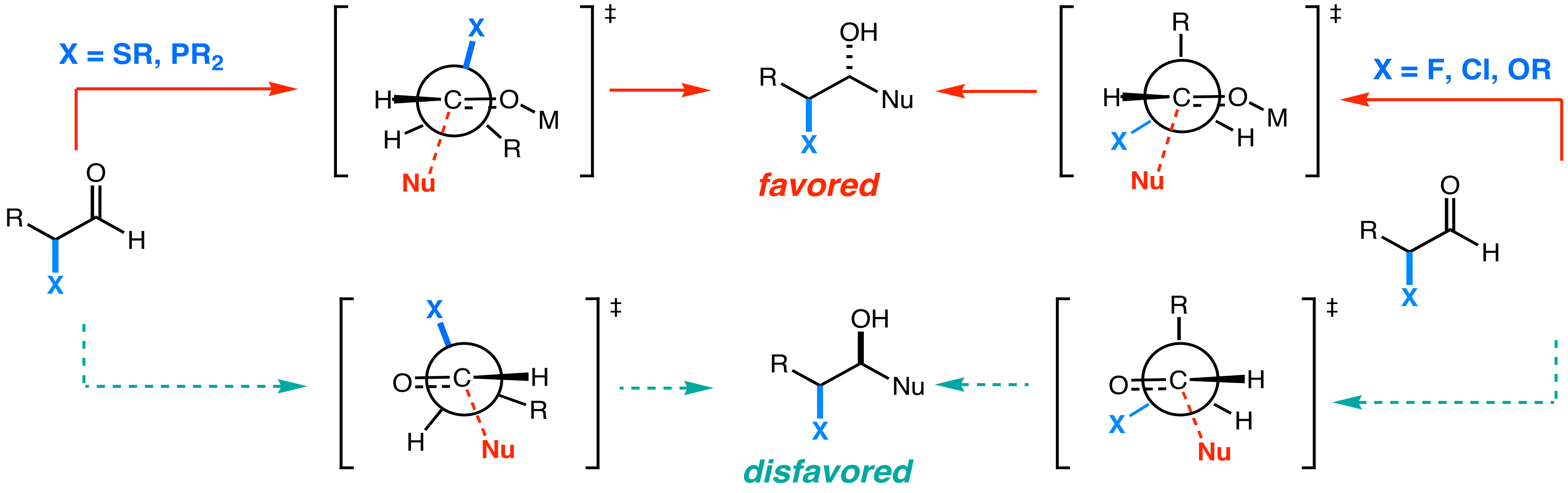
R. W. Hoffmann, *Chem. Scripta* **1985**, *25*, 53; b) R. W. Hoffmann, *Liebigs Ann. Chem.* **1987**, 881
W. R. Roush *J. Am. Chem. Soc.* **1986**, *108*, 3422-3434.

How does one distinguish between the Cornforth & Felkin Anh Models for C=O Addition??

Ferlkin-Anh	Transition State Hyperconjugation
Cornforth	Transition State Electrostatic effects

The Polar Felkin-Anh Model

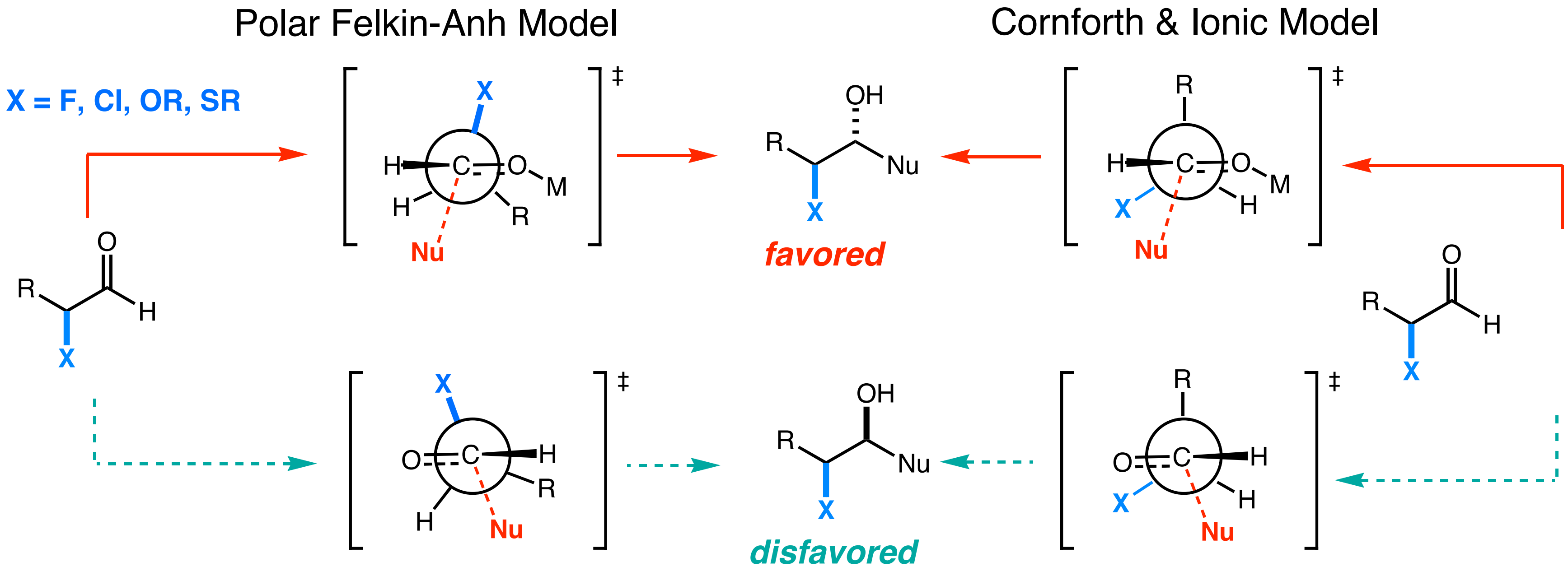
The Cornforth Model



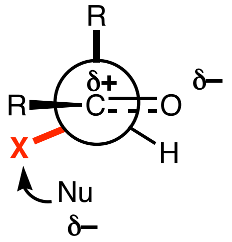
Both enolate and borane nucleophiles implicate the intervention of Cornforth geometries in additions to α-alkoxy aldehydes.

What is the current position for a stereochemical model for alpha alkoxy aldehydes substituted substrates?

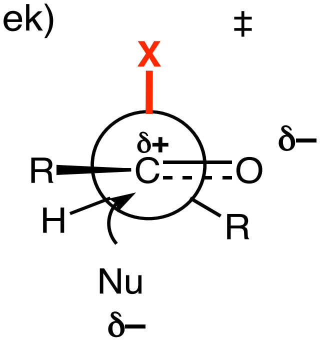
Ferlkin-Anh	Transition State Hyperconjugation is now in doubt.
Cornforth	Transition State Electrostatic effects are reasonable
Ionic Model	Best donor substituent perpendicular to pi framework in Cornforth geometry.



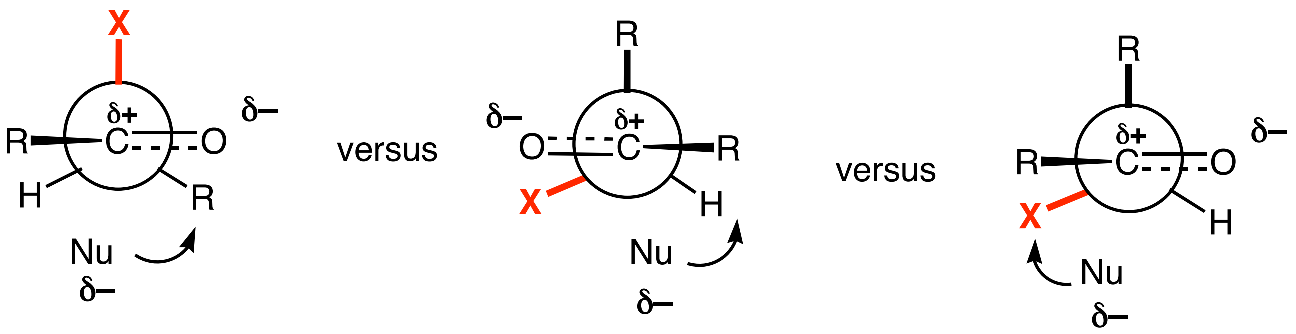
One needs to take seriously the Cieplak sugggestion that there might be any electron density between Nu and C=O in the transition state.



Evans: Cieplak Ionic Model for C=O Addition



- There is little or no covalency along Nu....$^{\delta+}$C=O$^{\delta-}$ axis in the transition state (Cieplek)
- Eclipsed transition states are disfavored (Felkin, anh-Eisenstein, Houk)
- Transition state stabilization may be achieved by orienting the best σ-donor perpendicular to polarized C=O (Stereolectronic Effects)
- Transition state stabilization may be achieved by orienting the largest substituent anti, rather than gauche to nucleophile (Steric Effects-1)



- If the C–X bond is very polar (**X** = F, Cl, OR), electrostatic (dipole) effects may be significant as noted by Cornforth

Effects Governing Face Selectivity at Trigonal Carbon

- Steric Effects: Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules

- Electronic Effects (Inductive Effects): The effect of bond and through-space polarization by heteroatom substituents on reaction rates and selectivities

  Inductive Effects: Through-bond polarization
  Field Effects: Through-space polarization

- Stereoelectronic Effects: Geometrical constraints placed upon **ground** and **transition states** by orbital overlap considerations.

"Organic chemists are proficient in the analysis of steric effects."

"Organic chemists are frequently unaware of the impact of electronic effects on the stereochemical outcome of reactions."

Acknowledgements

Professor Chris Cramer Dept of Chemistry, Univ. of Minnesota

Jim Gage

Mick Dart

Mike Yang

Joseph Duffy

Joseph Young

Sarah Siska

Victor Cee

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 23 SUPPLEMENT

Enantioselective Carbonyl Addition

- Enantioselective addition of R_2Zn to aldehydes
- Enantioselective Reduction of Ketones & Imines

Reading Assignment:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int Ed.* **1998**, *37*, 1986-2012 **(handout)**

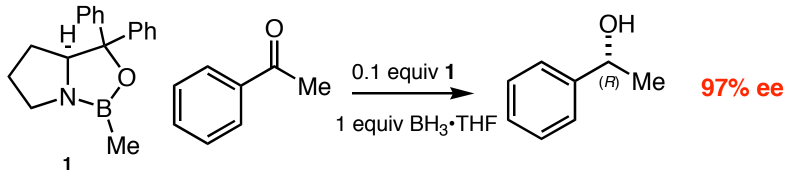
Enantioselective Carbonyl Addition (R_2Zn): Noyori *Angew. Chem. Int Ed.* **1991**, *30*, 49-69 **(handout)**

D. A. Evans

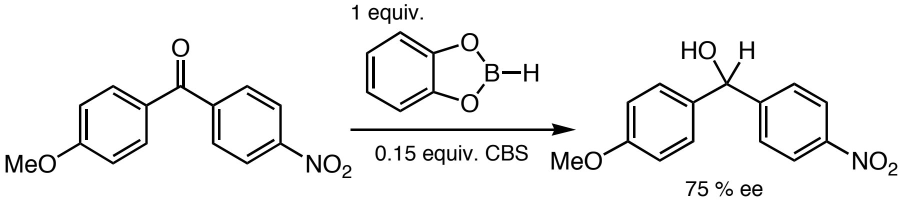
Monday
November 13, 2006

Relevant Problems:

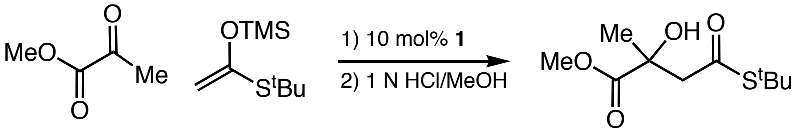
Cume Question, 2000: Corey's introduction of chiral oxazaborolidine catalysts **1** in the borane-mediated enantioselective reduction of ketones represents an important advance in asymmetric synthesis (Corey & Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012). Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



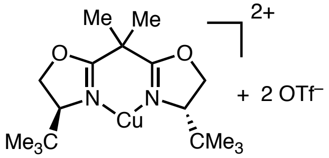
Problem 174: Corey's CBS catalyst for ketone reduction often delivers high yields of enantioenriched secondary alcohols (*ACIE*, **1998**, 1987). Provide a clear clear illustration of the transition state which predicts the absolute stereochemistry of the product obtained in the illustrated reaction. Include an explanation of why the reduction of this practically symmetric ketone is selective.



Problem 340: The C_2-symmetric Cu(II) complex is a ciral Lewis acidcatalyst that exhibits good chelating potential. The utilization of **1** in the catalyzed Mukaiyama aldol reaction is illustrated below (*JACS* **1999,** *121*, 686).



99%ee, 95% yield



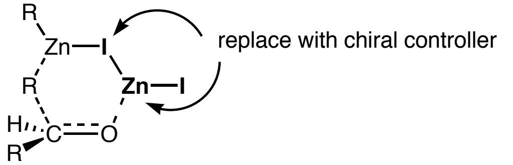
1

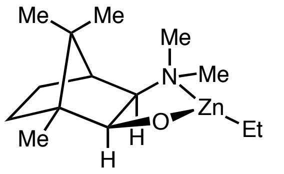
Hint; Remember that Cu(II) complexes strongly prefer a square planar geometry.

Provide the absolute stereochemistry of the product of this reaction. Provide a 3-dimensional drawing of the transition state for this reaction.

Enantioselective C=O Addition: Noyori Catalyst

Catalytic Asymmetric Carbonyl Addition

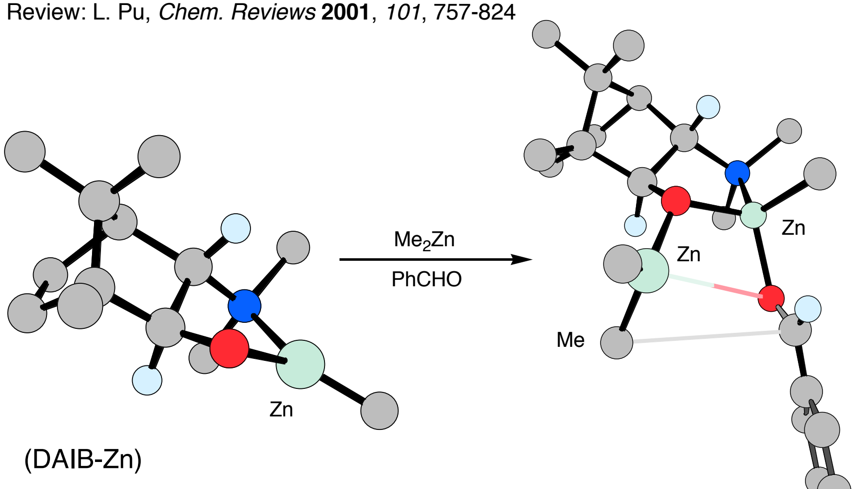




the catalyst

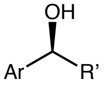
Noyori & co-workers, *J. Am. Chem. Soc.* **1986**, 108, 6072.
J. Am. Chem. Soc. **1989**, 111, 4028.

Review: Noyori *Angew. Chem. Int. Ed.* **1991**, *30*, 49
Review: L. Pu, *Chem. Reviews* **2001**, *101*, 757-824



(DAIB-Zn)

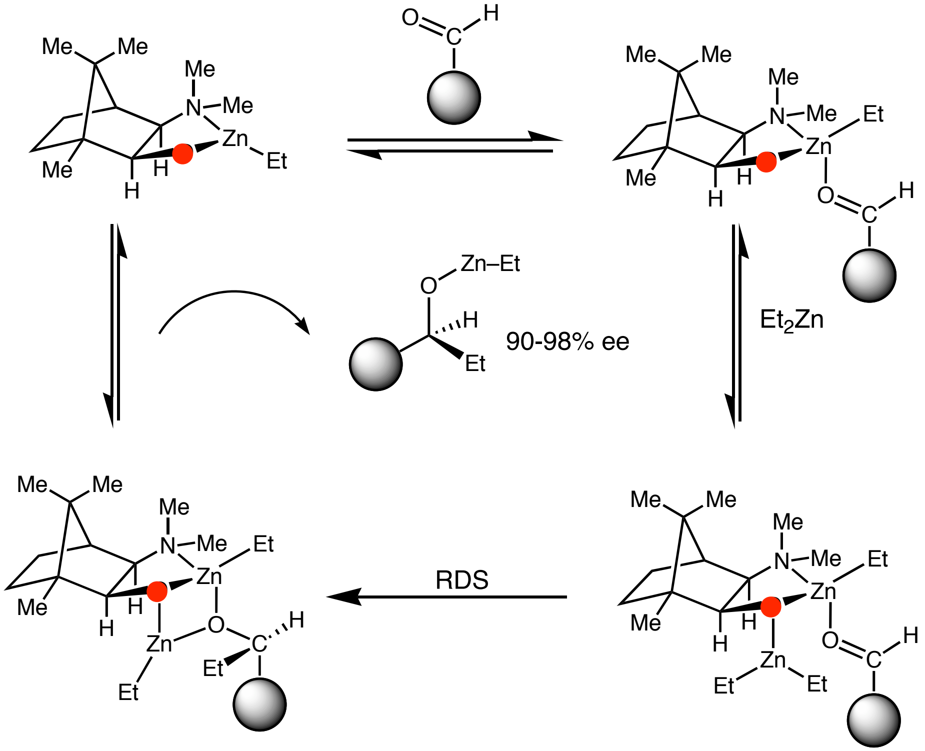
Ar–CHO + R$_2$'Zn $\xrightarrow[\text{0°C, toluene; 59 - 97\%}]{\textit{the catalyst}}$



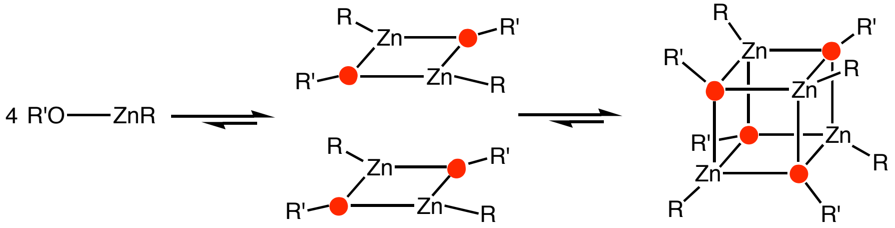
C_6H_5CHO	Et_2Zn	98% e.e.
"	Me_2Zn	91% e.e.
p-ClC_6H_4CHO	Et_2Zn	93% e.e.
p-$MeOC_6H_4CHO$	Et_2Zn	93% e.e.
Cinnamyl	Et_2Zn	96% e.e.
$PhCH_2CH_2CHO$	Et_2Zn	90% e.e.
n-$C_6H_{13}CHO$	Et_2Zn	61% e.e.

- *The method is catalytic in aminoalcohol.*
- *Two zinc species per aldehyde are involved in the alkylation step.*

The Catalytic Cycle



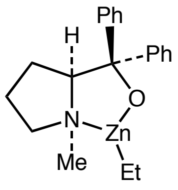
- *Catalyst must be sterically hindered so that association is precluded*



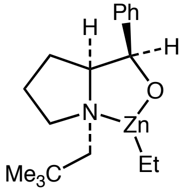
- *Product is taken out of the picture by aggregation*

Enantioselective C=O Addition: Noyori Catalyst-2

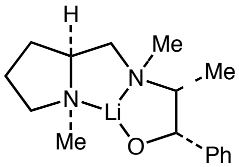
Other Catalysts for the R_2Zn Addition Process



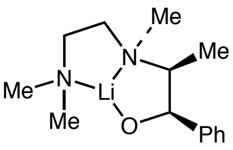
97% e.e. (S)



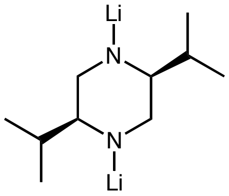
100% e.e. (R)



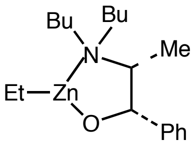
95% e.e. (S)



90% e.e. (R)



90% e.e. (R)



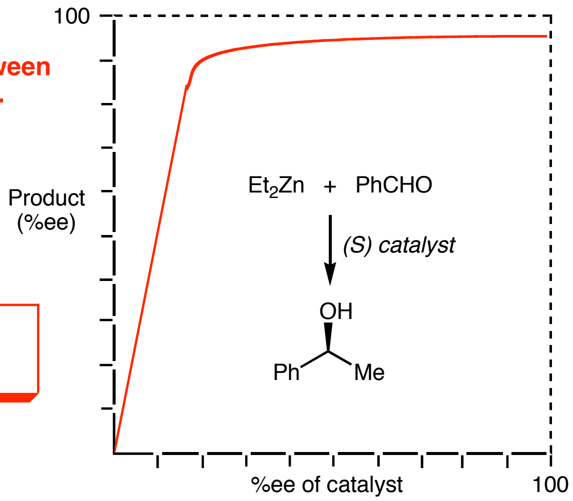
90% e.e. (R)

(Results are cited for the reaction of benzaldehyde and Et_2Zn)

Problem: Rationalize the stereochemical course of each of the catalysts

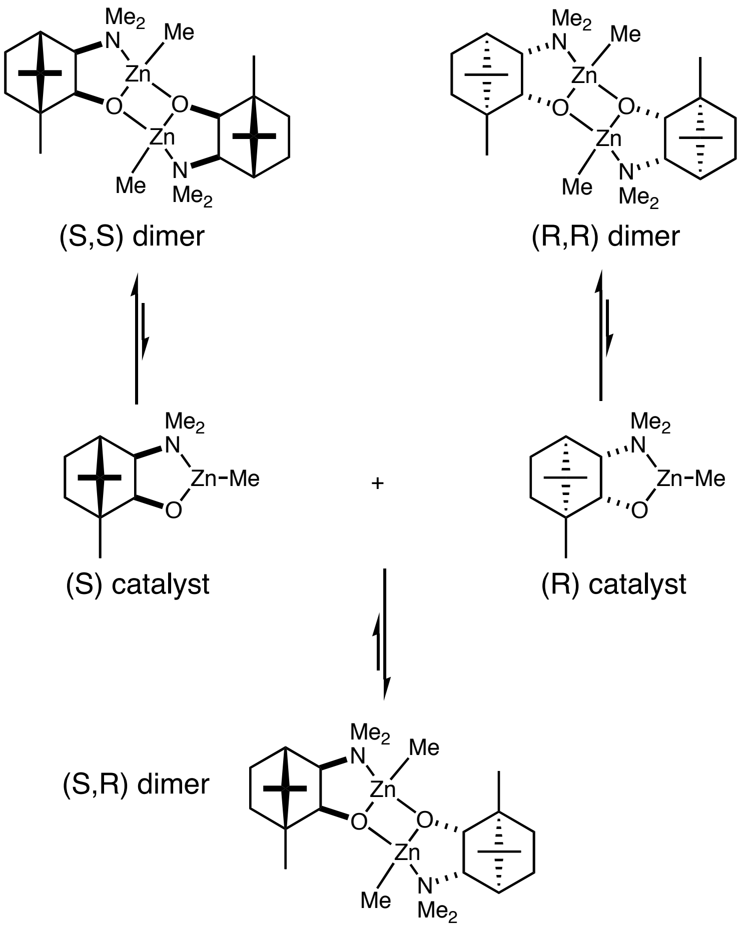
- ■ Non-linear effects observed with the Noyori Catalyst (DAIB-Zn)

There is no correlation between catalyst and product ee.



25% ee Catalyst affords product in 95% ee.

Explanation for Nonlinearity of DAIB Catalyst

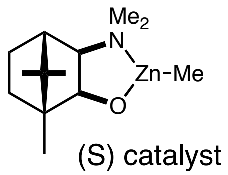


Observations

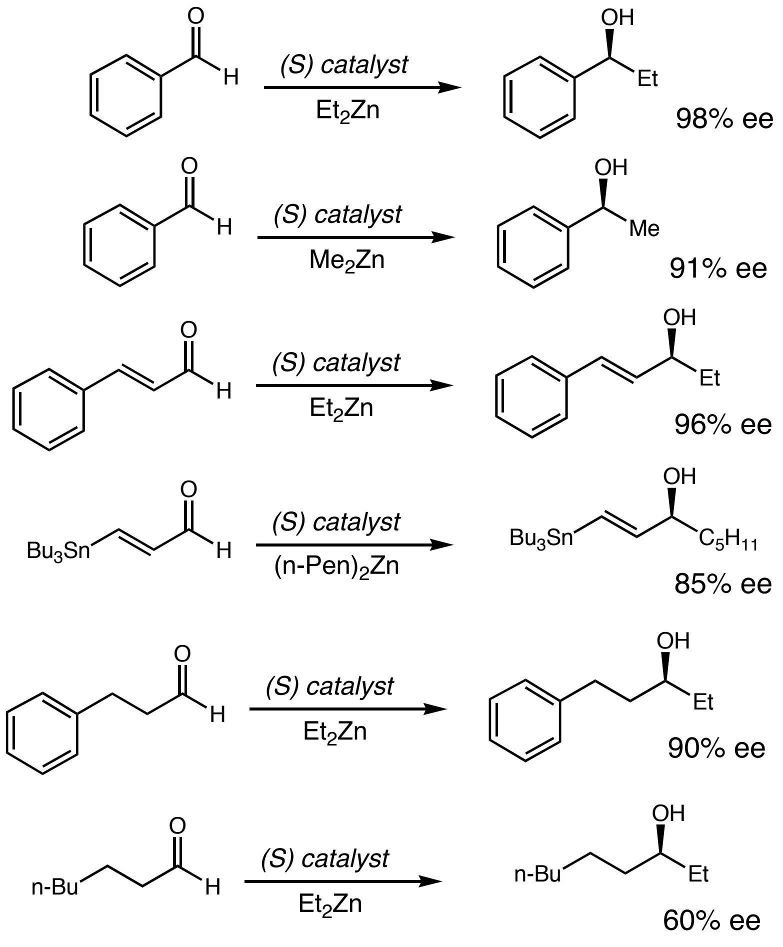
- ■ (S,S) dimer dissociates upon addition of RCHO & effects catalysis
- ■ (S,R) dimer is overwhelmingly more stable than (S,S) homodimer
- ■ (S,R) dimer is ineffective as a catalyst

Enantioselective C=O Addition: Dialkylzinc Addn Scope

Scope of the DAIB Catalyst



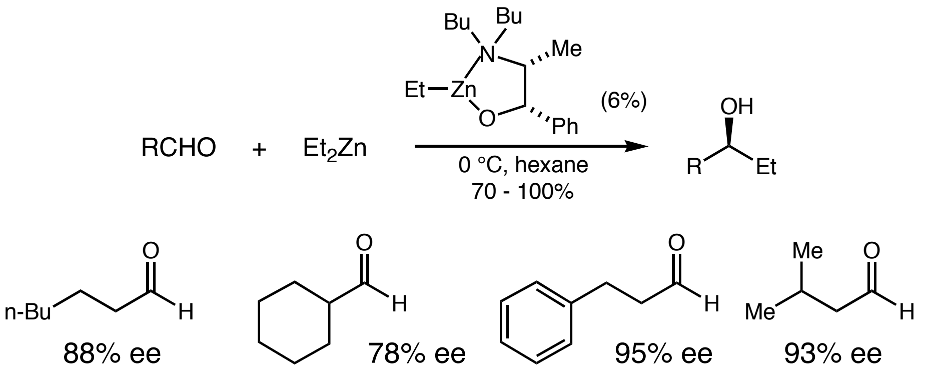
(S) catalyst



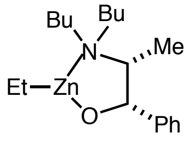
Review: Noyori *Angew. Chem. Int. Ed.* **1991**, *30*, 49

Improved Selectivity with Aliphatic Aldehydes

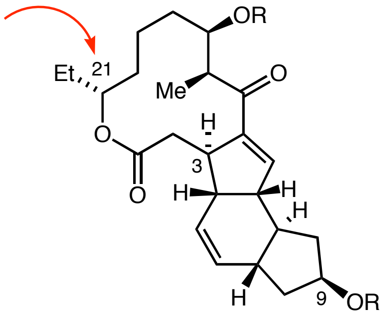
Soai, *J. Org. Chem.* **1991**, *56*, 4264



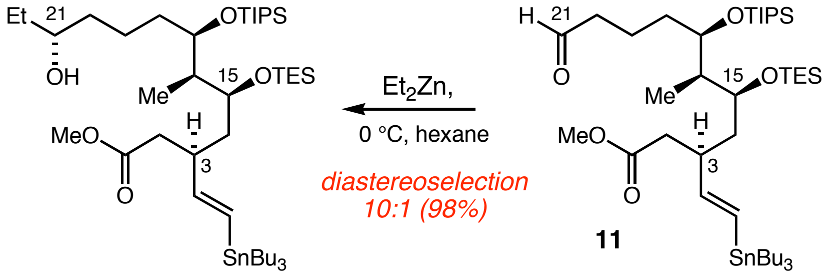
Lepicidin Application: The reaction functions in complex systems



the catalyst



Evans, Black, *JACS* **1993**, *115*, 44974513



diastereoselection 10:1 (98%)

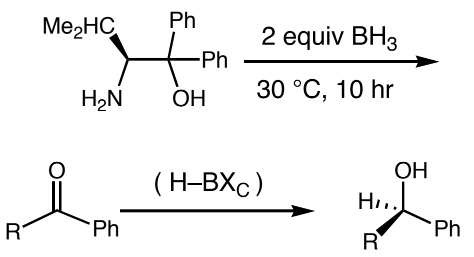
11

Enantioselective C=O Addition: Corey-Itsuno Catalyst

Discovery of a Catalytic Process

Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int Ed*. **1998**, *37*, 1986-2012 **(handout)**

- The Stoichiometric Process: Itsuno, 1983-1985



Chiral Boron Hydride (H–BX_C)

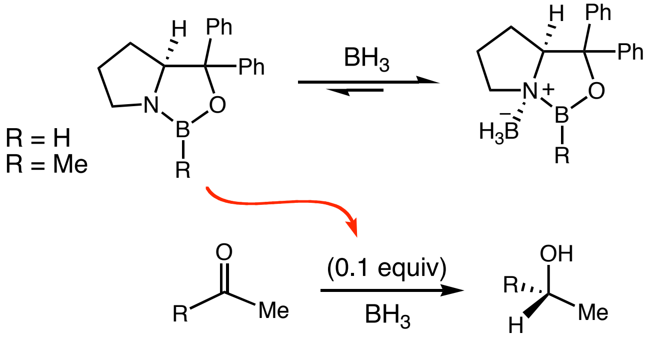
R = Me,	94 % ee
R = Et,	94 % ee
R = n-Bu	100 % ee

Itsuno, *Chem. Commun*. **1983**, 469

Itsuno, *J. Org. Chem.* **1984**, 49, 555

Itsuno, *J. Chem. Soc. Perkin Trans I*. **1985**, 2615

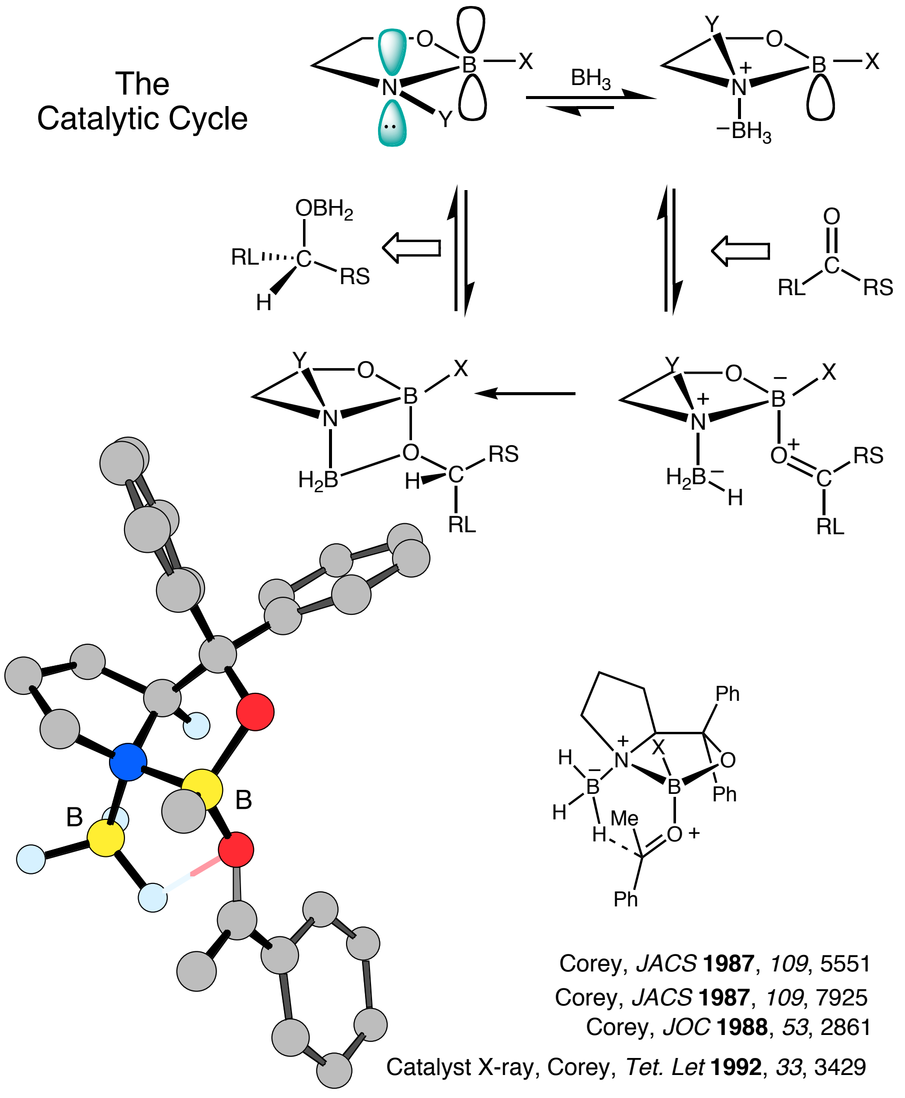
- The Catalytic Process: Corey, 1987



R = Ph,	97 % ee
R = t-Bu,	97 % ee
R = c-C_6H_{11}	91 % ee

But how does it really work ?

The Catalytic Cycle



Corey, *JACS* **1987**, *109*, 5551

Corey, *JACS* **1987**, *109*, 7925

Corey, *JOC* **1988**, *53*, 2861

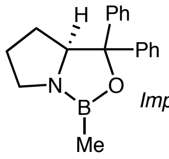
Catalyst X-ray, Corey, *Tet. Let* **1992**, *33*, 3429

Mathre, *JOC* **1993**, *58*, 2880

catalyst prep: Mathre, *JOC* **1993**, *58*, 799

Mathre, *JOC* **1991**, *56*, 751

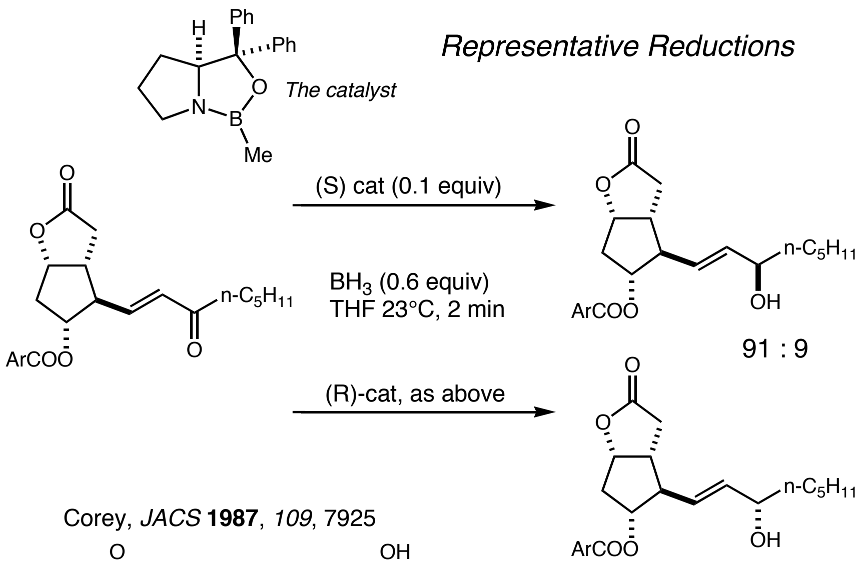
(Review) Martens, *Tertrahedron Asymmetry* **1992**, *3*, 1475



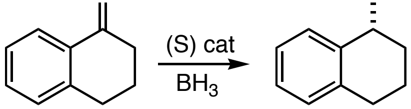
Improved version

Enantioselective C=O Addition: Catalyst Scope

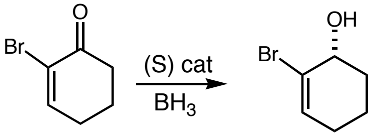
Representative Reductions



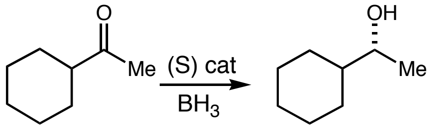
Corey, *JACS* **1987**, *109*, 7925



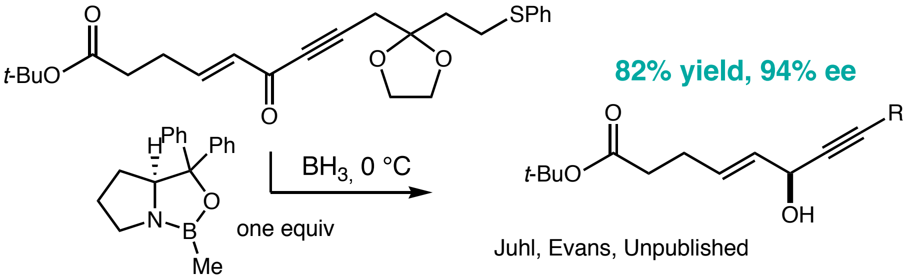
86% ee



91% ee

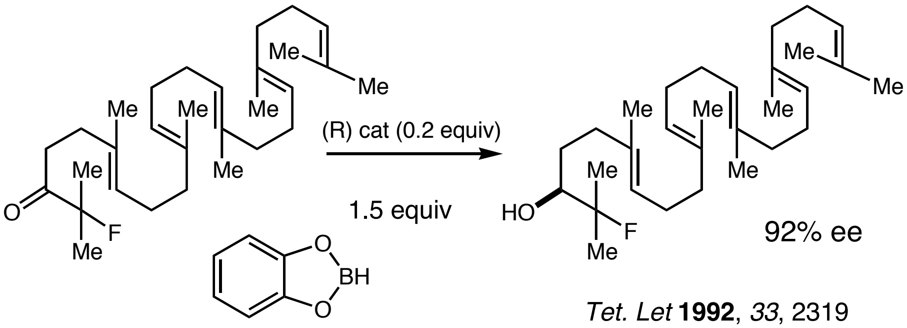


91% ee



82% yield, 94% ee

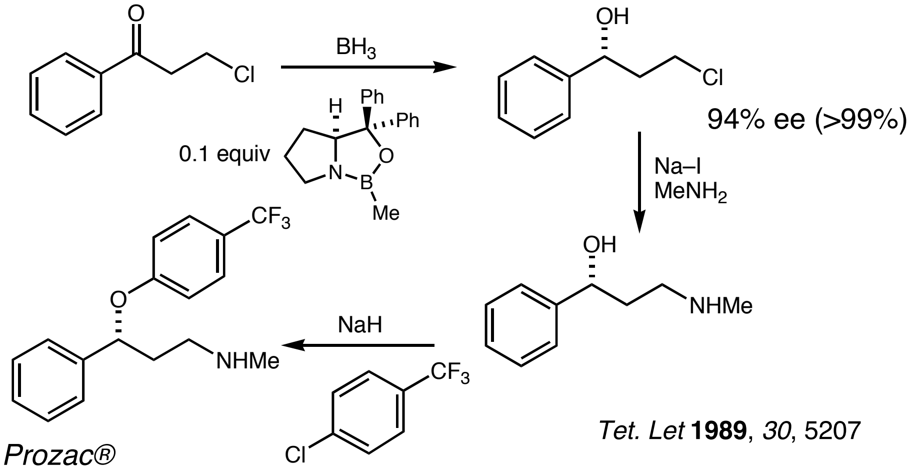
Juhl, Evans, Unpublished



92% ee

Tet. Let **1992**, *33*, 2319

Fluoxetine (Prozac®) Synthesis

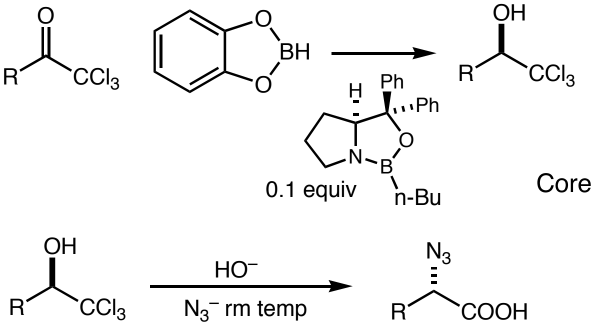


94% ee (>99%)

Tet. Let **1989**, *30*, 5207

Prozac®

An α-Amino Acid Synthesis

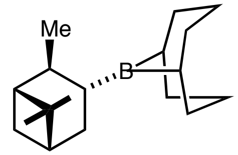


R	ee
n-C_5H_{11}	95%
c-C_6H_{11}	92%
t-C_4H_9	98%

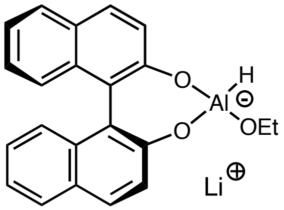
Corey, *JACS* **1992**, *114*, 1906
Tet. Let **1992**, *33*, 3435
Tet. Let **1992**, *33*, 3431

Enantioselective C=O Addition: Ketone Reduction

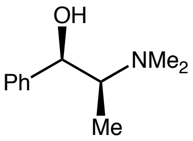
Enantioselective Reducing Agents



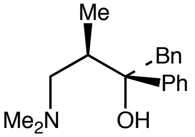
(R)-Alpine Borane



(S)-BINAL-H



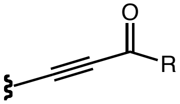
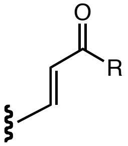
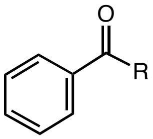
N-Methylephedrine, $LiAlH_4$, (3,5-xylenol)$_2$
[LiAl(lig)(OAr)$_2$H]



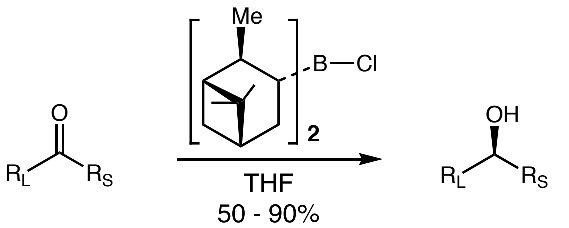
Darvon alcohol, $LiAlH_4$
[LiAl(lig)$_2$H]

Reviews:
Midland, *Asymmetric Synthesis*, *Vol 2*, p 45-
Granbois, *Asymmetric Synthesis*, *Vol 2*, p 71-
Brown, *Accts. Chem. Res.* **1992**, *25,* 16-24
Singh, *Synthesis* **1992**, 605-617

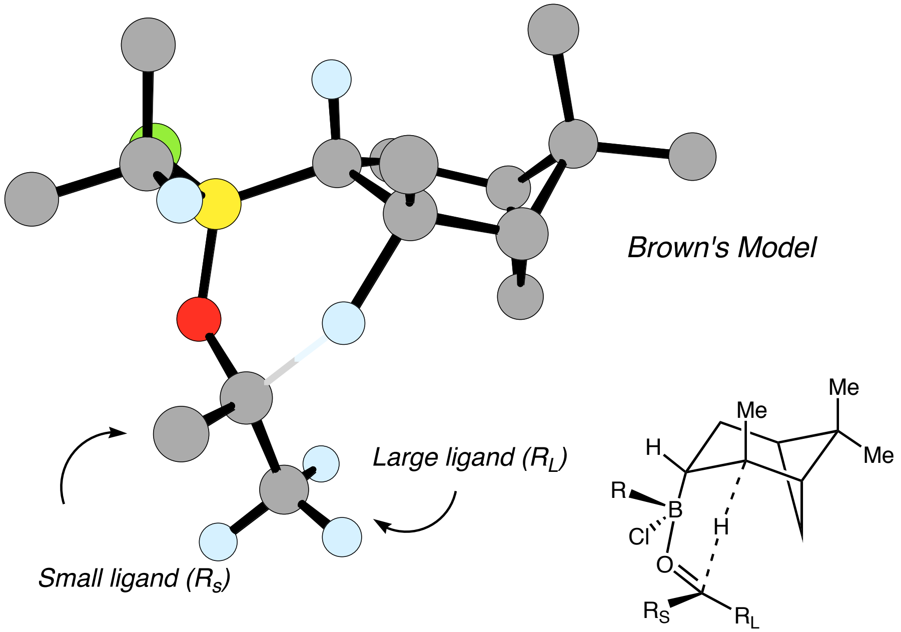
Reductions of Representative Carbonyl Compounds

Reagent			
Alpine-Borane	72 - 92% e.e.	59 - 89% e.e.	78% e.e. R=Me 90% e.e. R=CO_2Me
BINAL-H	84 - 96% e.e. (57% ee, R=i-Pr)	>95% e.e.	95 - 100% e.e. (71% ee, R=i-Pr)
Darvon-$LiAlH_4$	34 - 90% e.e.	25% e.e.	15 - 75% e.e.
N-Methylephedrine-$LiAlH_4$	75 - 90% e.e.	78 - 98% e.e. (cyclic ketones)	----

Stoichiometric Chloroborane Reducing Agents



Ketone	Reaction Conditions	% ee
acetophenone	–25 °C	98%
butyrophenone	–25 °C	98%
2,2-dimethylpropiophenone	–25 °C	79%
3,3-dimethyl-2-butanone	25°C, 12 days	95%
2,2-dimethylcyclohexanone	25°C, 2 days	91%



Brown's Model

Less hindered aliphatic ketones are not reduced with useful levels of enantioselectivity

Brown, *J. Org. Chem.* **1985**, *50*, 5446
Brown, *J. Org. Chem.* **1986**, *51*, 3394
Brown, *J. Org. Chem.* **1988**, *53*, 2916

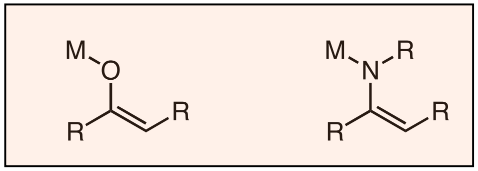
http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 24

Enolates & Metalloenamines-1



- Mild Methods for Enolate Generation
- Enolate Structure: A Survey of X-ray Structures
- Metallo-Enamine X-ray Structures

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Monday,
November 13, 2006

Assigned Journal Articles

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures"
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1988). **(handout)**

"Stereoselective Alkylation Reactions of Chiral Metal Enolates".
D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984). **(handout)**

"Soft Enolization: A Powerful Method for Diastereoselective Carbon-Carbon Bond Formation",
DA Evans & J. Shaw, Manuscript in preparation **(pdf)**

"Self-Regeneration of Stereocenters (SRS)-Applications, Limitations, & Abandonment of a Synthetic Principle",
D. Seebach et al. *Chem. Int. Ed. Engl.*, **35**, 2708 (1996). **(pdf)**

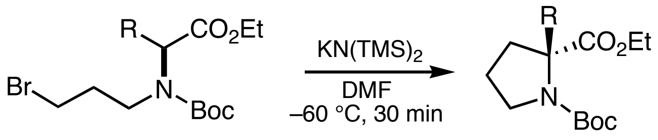
Other Useful References

"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res.* **21**, 121 (**1988**).

"Keto-Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution". Keeffe, Kresge, and Schepp *JACS*, 112, 4862 (**1990**).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (**1984**).

Database Problem 314. Kawabata and co-workers recently reported the remarkable enolate alkylation illustrated below (*JACS* **2003,** *125*, 13012). When the indicated α-aminoacid ester is treated with KHMDS in DMF at —60 °C, the derived cyclic amino acid ester is formed in high yield and enantioselectivity. The stereochemical outcome represents a formal retention of configuration. This reaction exhibits some generality as the 4- 5-, 6-, and 7-membered lactams may be obtained in high ee.

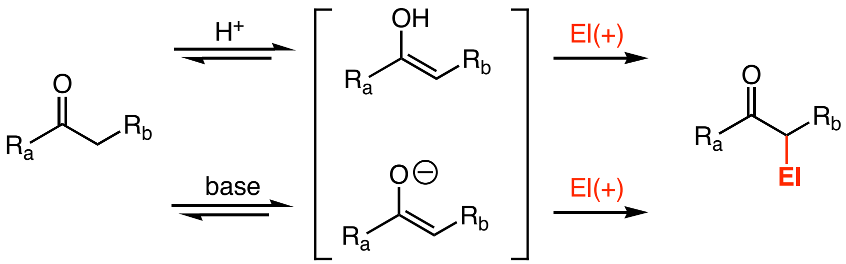


R	ee
Bn	98 (S)
Me_2CH	94 (S)

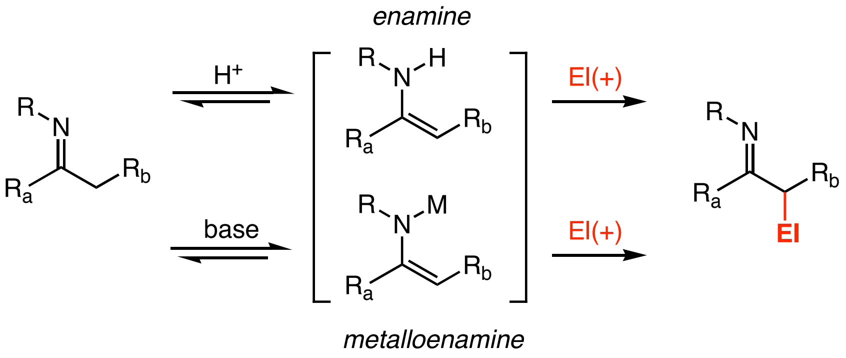
Provide a rationalization of these results. Three-dimensional drawings are recommended.

Enolates & Metalloenamines: Introduction

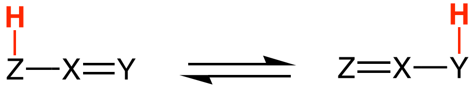
Enols & Enolates are the most important nucleophiles in organic & biological chemistry.



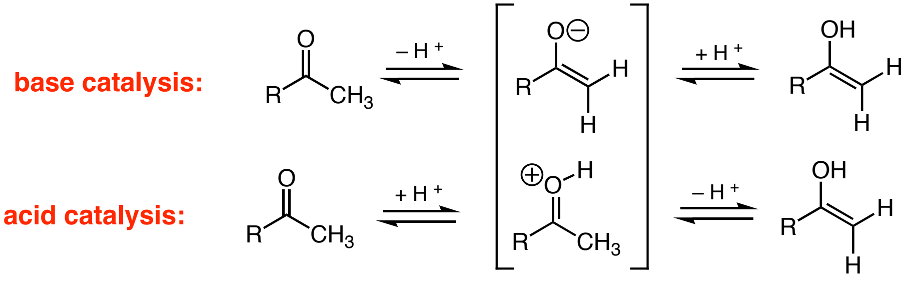
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



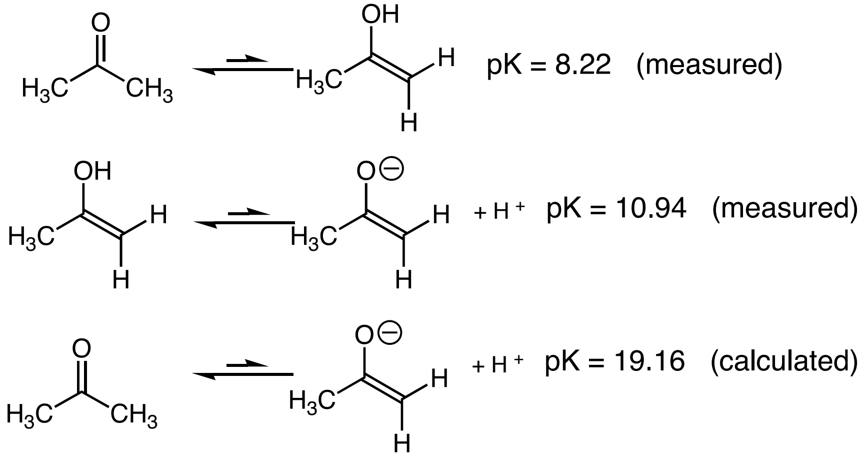
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



Acidity of Keto and Enol Tautomers: Consider Acetone:



pK = 8.22 (measured)

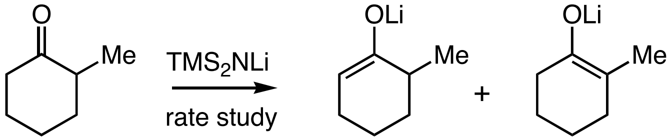
pK = 10.94 (measured)

pK = 19.16 (calculated)

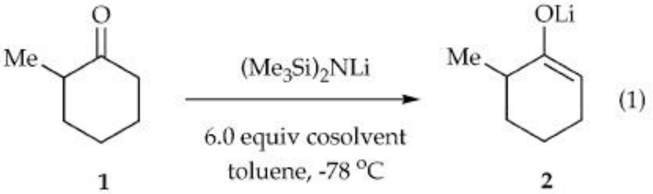
Kresge, *JACS* **1984**, *106*, 460

On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

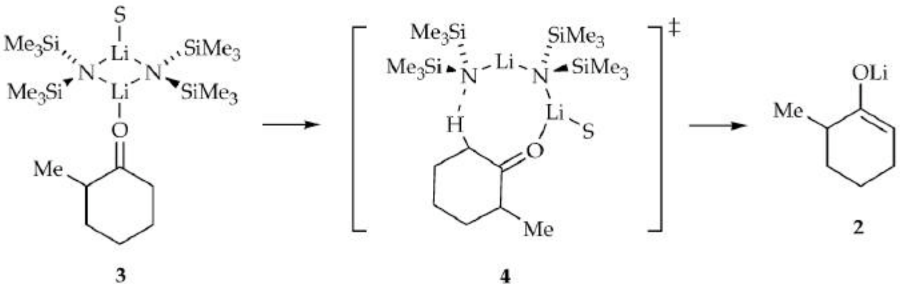
Enolization Kinetics Collum (*J. Org. Chem* **2004**, *69*, 242-249)



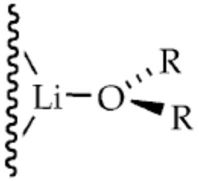
Kinetics suggest $(TMS_2NLi)_2(R_3N)(Ketone)^‡$



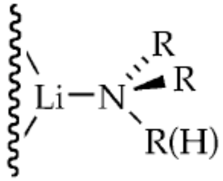
cosolvent:	none	THF	Et_3N
k_{rel}:	1.0	20	3,000



The correlation of high (enolization) rates with solvation of LiHMDS by hindered di- and trialklyamines was traced to steric relief that occurs when the reaction proceeds from the congested dimer-based LiHMDS-ketone complex **3** to the relatively less congested open-dimer-based transition structure **4**.



5



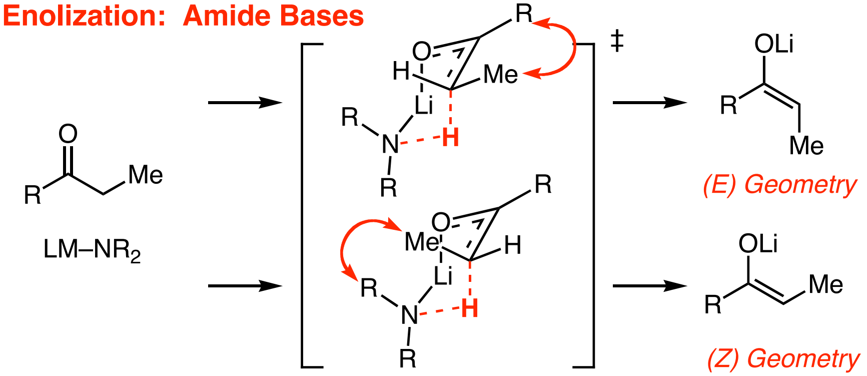
6

TABLE 2. Relative Rates (k_{rel}) for the Enolization by LiHMDS Solvated by Isostructural Dialkylamines (R_1NHR_2) and Dialkyl Ethers (R_1OR_2)

R_1XR_2	k_{amine}/k_{ether}
$R_1 = R_2 = i$-Bu	2
$R_1 = R_2 = i$-amyl	10
$R_1 = Et, R_2 = i$-Pr	35
$R_1 = R_2 = i$-Pr	170
$R_1 = R_2 = s$-Bu	60

In Comparison (Lecture 15)

Enolization: Amide Bases

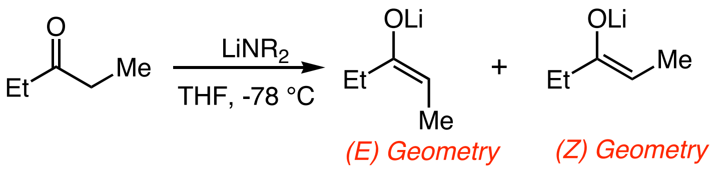


The Ireland Model (*J. Am. Chem. Soc.* **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650
For the latest word on this subject see: Xie, *JOC* 1997, *62*, 7516-9

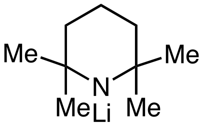
Enolization with Metal Amides bases

Base Structure

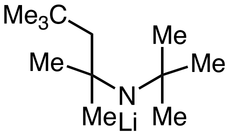
Corey & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 491, 495



$Li–N(i-Pr)_2$
(LDA) 77 : 23



(LiTMP) 86 : 14

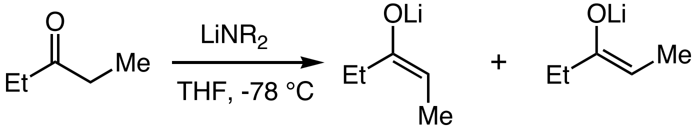


(LOBA) 98 : 2

Lithium Halide Effects

Collum (*J. Am. Chem. Soc.* **1991**, *113*, 9572)
Collum (*J. Am. Chem. Soc.* **1991**, *113*, 9575)
Collum (*J. Am. Chem. Soc.* **1991**, *113*, 5053)

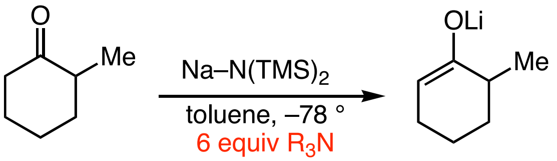
For the latest in the series of Column papers see: *JACS* **2000**, *122*, 2452-2458



	Ratio, (E):(Z)
LiTMP	86 : 14
LiTMP, 10% LiBr	98 : 2

Enolization in Non-Ethereal Solvents

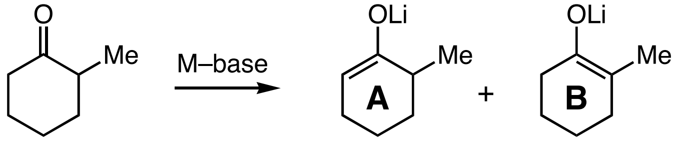
Collum (*JACS* **2003**, *125*, 14411)



R_3N	none	Me_2NEt	n-Bu_3N	1-Bu_3N
k_{rel}	1	200	3000	1

Reaction kinetics suggest $(TMS_2NLi)_2(R_3N)(Ketone)^{‡}$

Regioselective Enolization

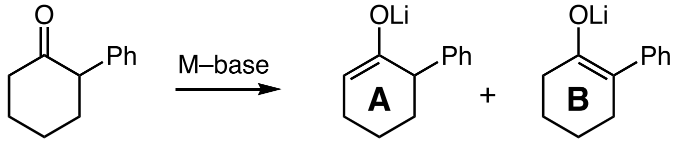


Base	temp	control	Ratio (A:B)
$LiN(i-Pr)_2$	–78 °	kinetic	99:1
$LiN(SiMe_3)_2$	–78 °	kinetic	95:5
$Ph_3C–Li$	–78 °	kinetic	90:10
$Ph_3C–Li$	heat	thermo	10:90
Na–H	heat	thermo	26:74
K–H	heat	thermo	38:62

A: Alkyl groups stabilize metal enolate

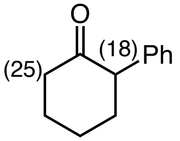
A: As M–O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure



ratio: 99:1

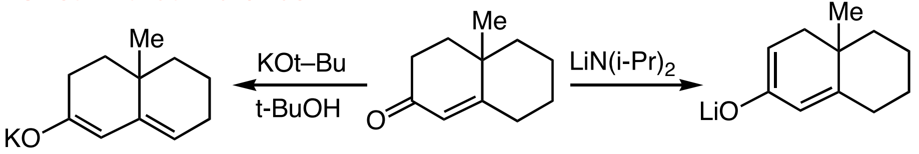
estimated pKa's (Bordwell)



$$A \rightleftharpoons B$$

pKeq est: 7 (10^{+7})

Unsaturated Ketones



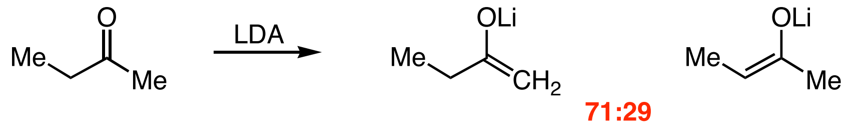
thermodynamic enolate

see kinetic acidity handout for an extensive compilation of cases.

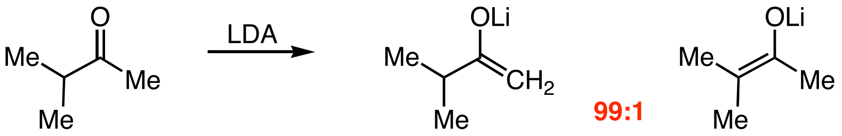
kinetic enolate

Enolization with Metal Amides bases

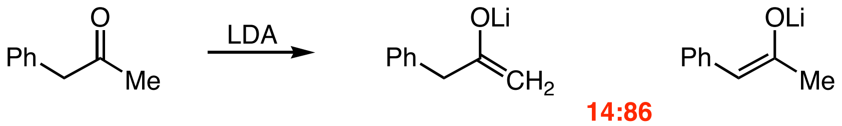
Kinetic Selection sensitive to structure



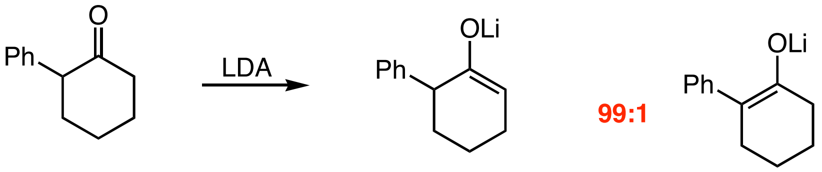
71:29



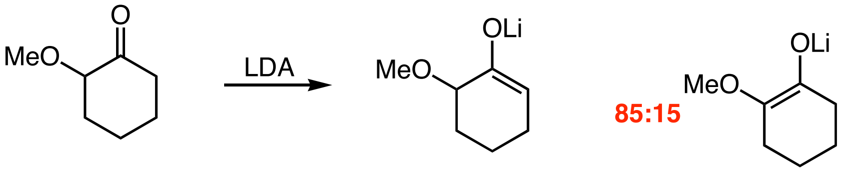
99:1



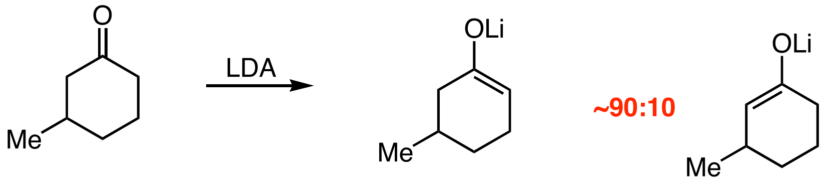
14:86



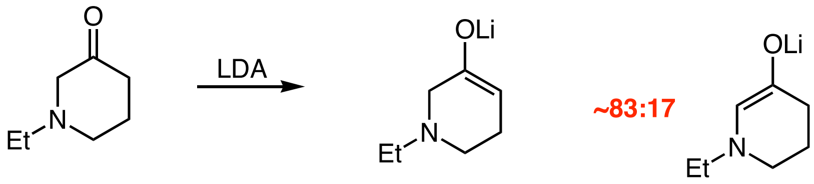
99:1



85:15

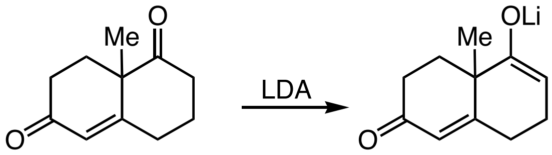


~90:10

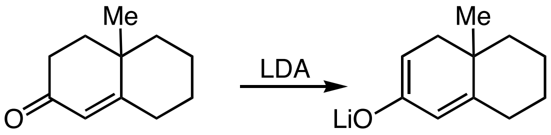


~83:17

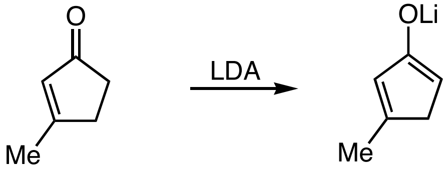
Kinetic Selection in Enolization of Unsaturated Ketones



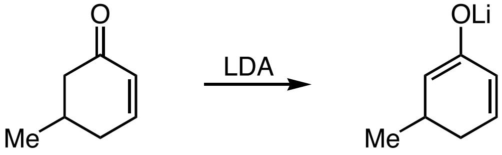
only enolate



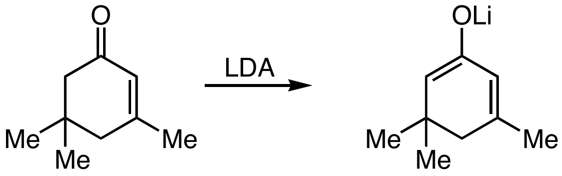
only enolate



only enolate



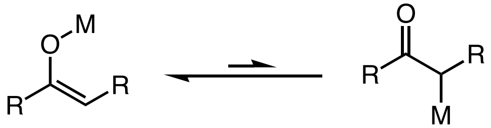
only enolate



only enolate

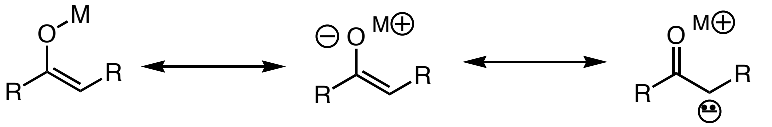
Enolate Structures from X-ray Diffraction

Metal Tautomerism



For alkali metal enolates (M = Li, Na, K etc.) the O-metal tautomer is strongly favored. This generalization holds for most alkaline earth enolates (Mg^{+2}) as well. These are the generally useful enolate nucleophiles

For certain metal enolates from heavy metals such as M = Hg^{+2} the C-metal tautomer is sometimes favored.



Resonance Structures

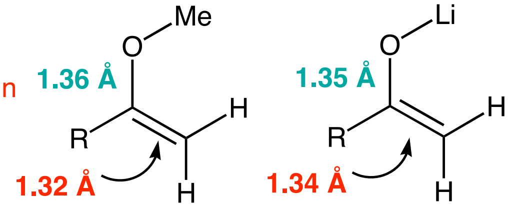
O^- resonance structure

C^- resonance structure

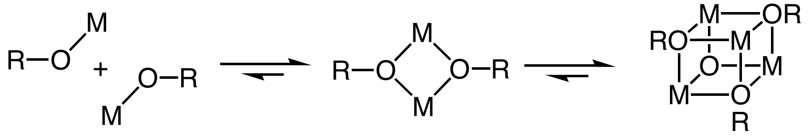
Since enolates usually function as carbon nucleophiles, it is therefore of some interest to assess the relative importance of the illustrated contributing polar resonance structures. Within the last decade good X-ray crystal structures of a number of metal enolates have been obtained.

One would predict that as the relative importance of the C^- structure increases, the C–O bond would shorten and the C–C bond would lengthen.

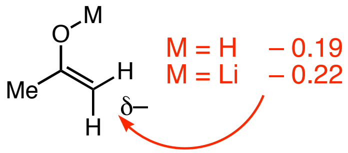
The prediction stated above does hold, but the net change in the C–C bond length is < 2 % !

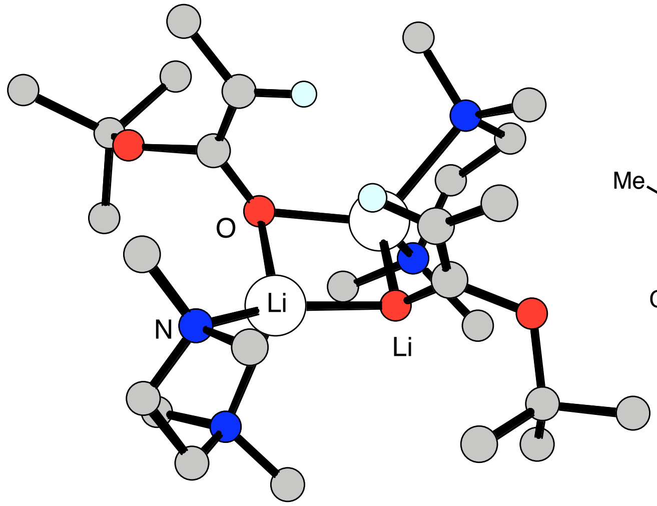


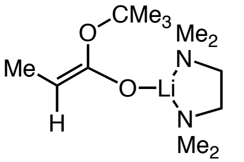
In solution and in the solid state metal enolates have a strong tendency to aggregate into dimers and tetramers to satisfy metal solvation requirements.



Ab initio calculations (Spartan) indicate that the partial negatilve charge on the alpha carbon is ~ – 0.22 for the Li enolate

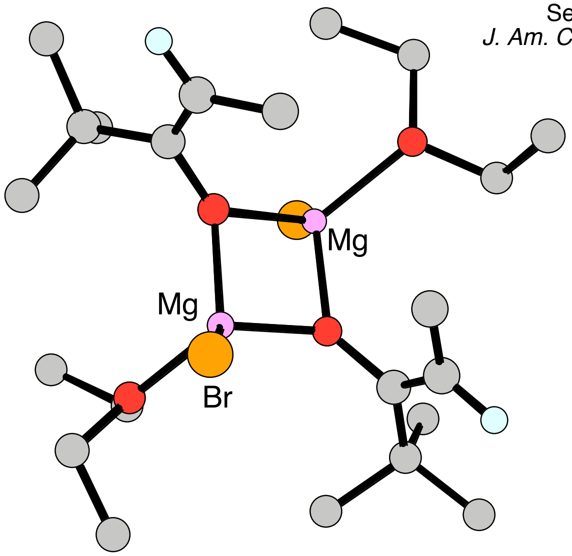


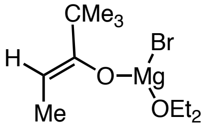




Crystallized as the dimer

Seebach & co-workers,
J. Am. Chem. Soc. **1985**, *107*, 5403.

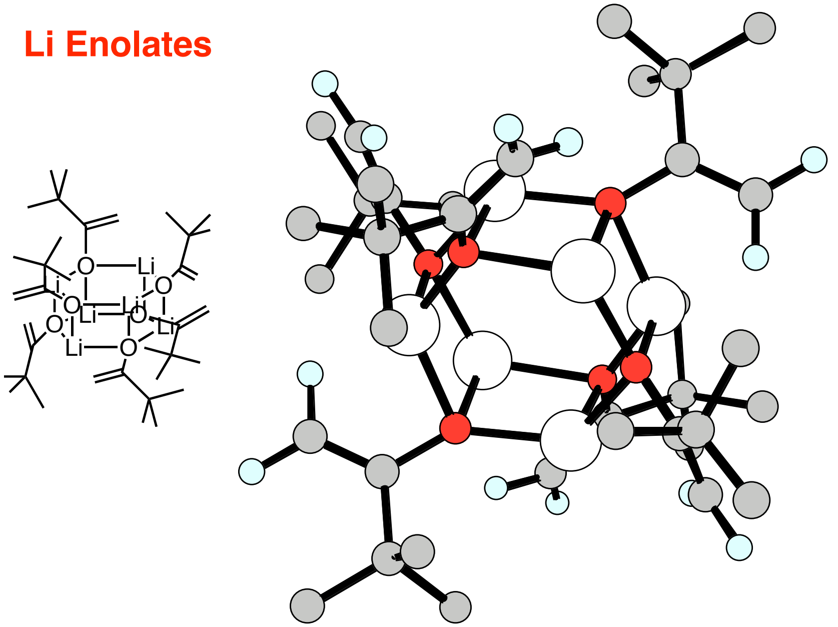


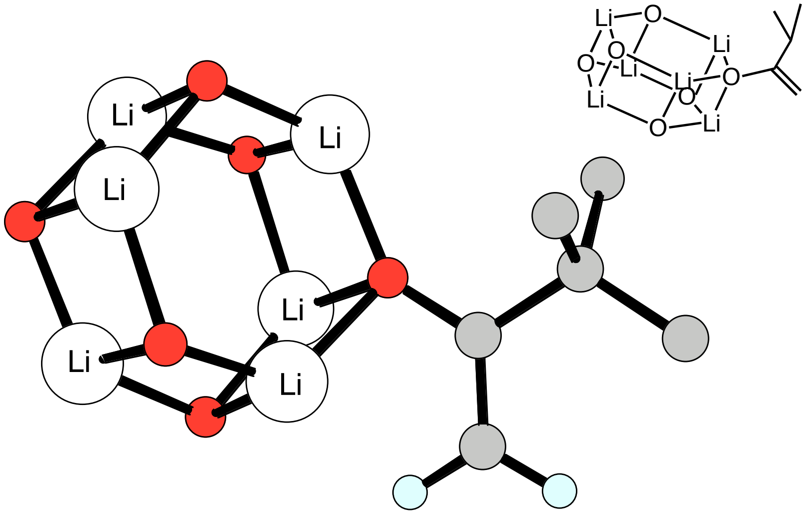


Crystallized as the dimer

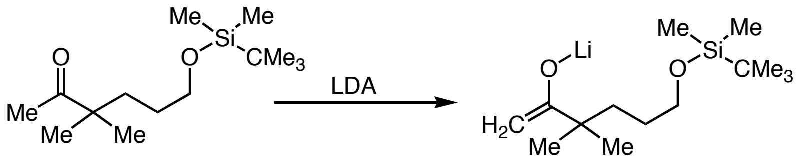
Enolate Structures: Lithiun Enolates

Li Enolates

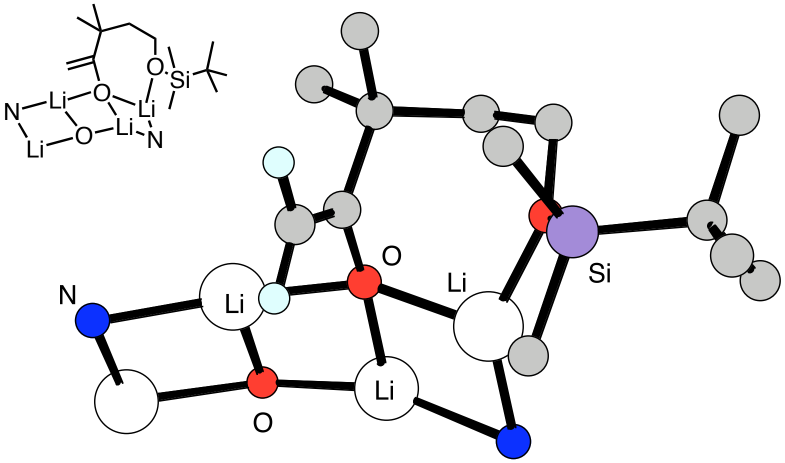


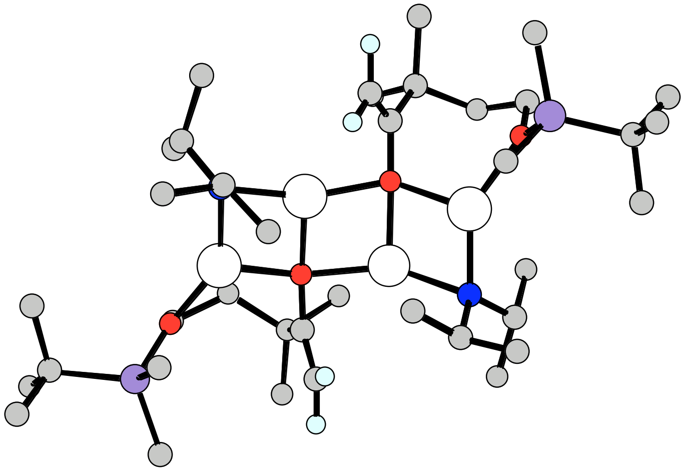


Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462-468.



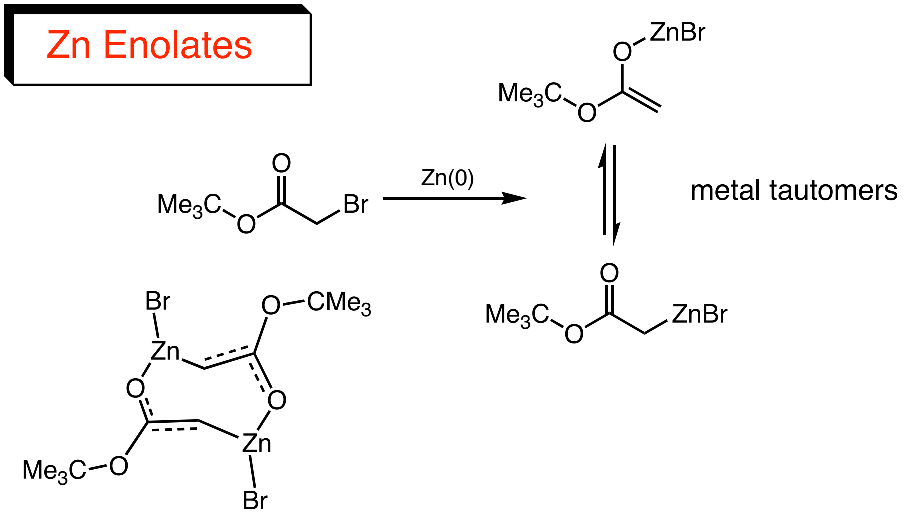
Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539-5541.

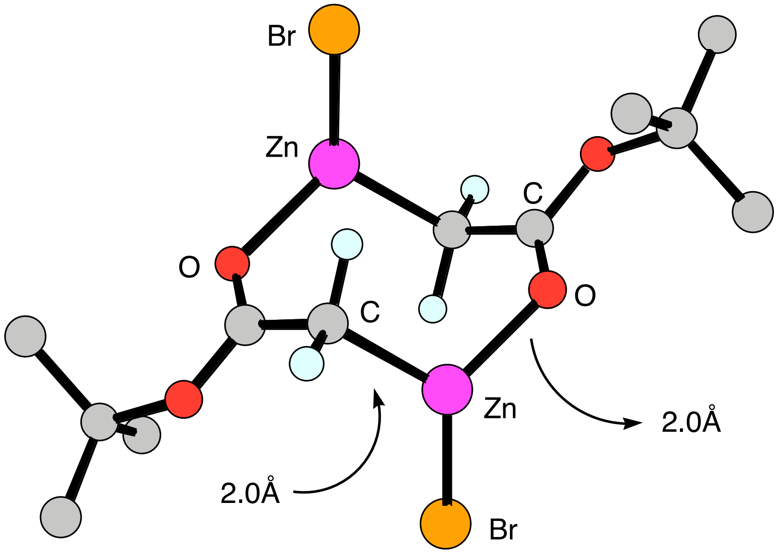




Enolate Structures: The Reformatsky Reagent

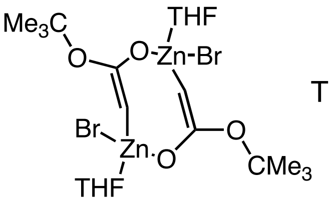
Zn Enolates



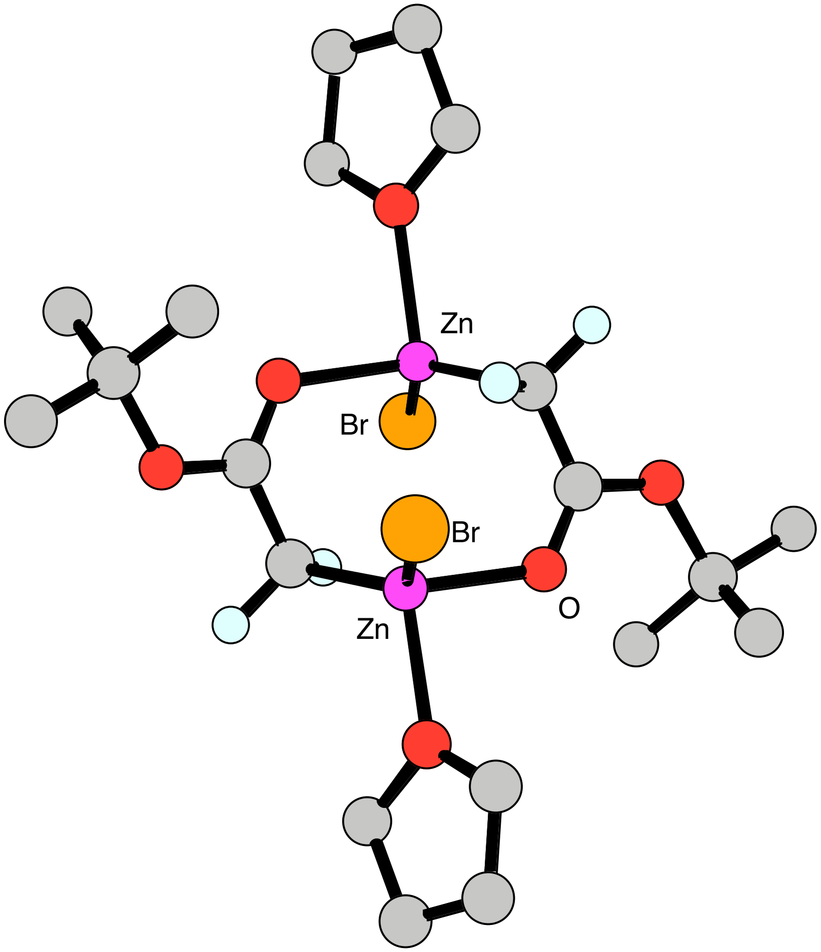


Dekker, J.; Boersma, J.; van der Kerk,
G. J. M. *J. Chem. Soc. Chem. Commun.* **1983**, 553.

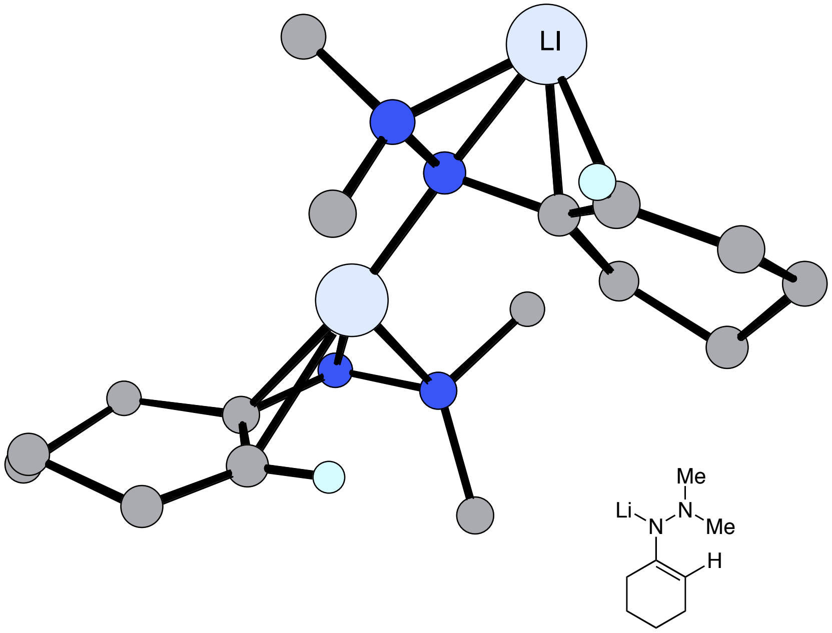
Dekker, J.; Budzelaar, J.; Boersma, J.; van der Kerk, G. J. M.
Organometallics **1984**, *3*, 1403.

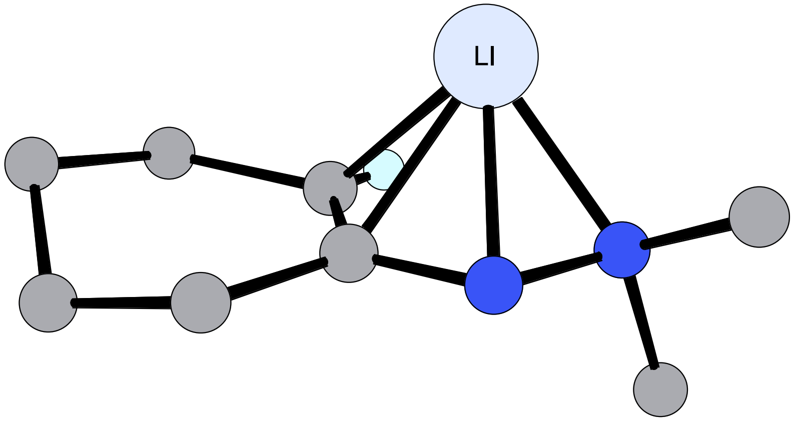


The THF Complex

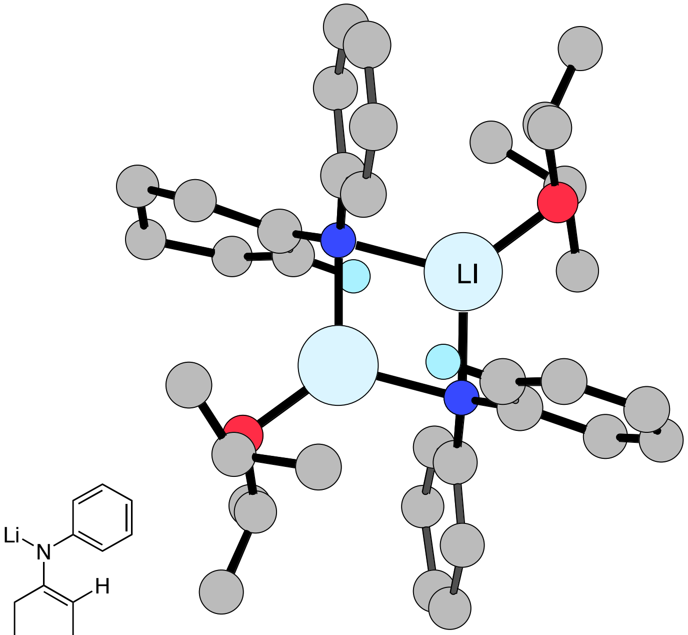


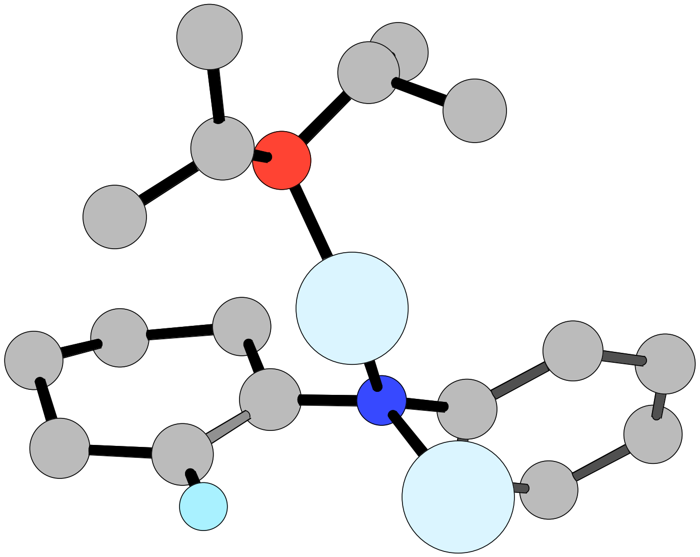
Metalloenamine X-ray Structures





Collum & Clardy, *JACS* **1984**, *106*, 4865

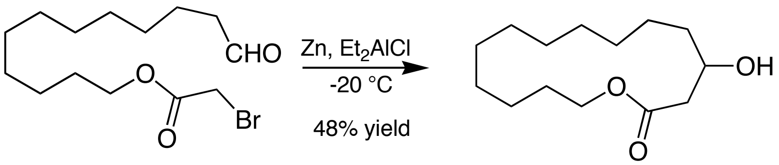




The Reformatsky Reaction

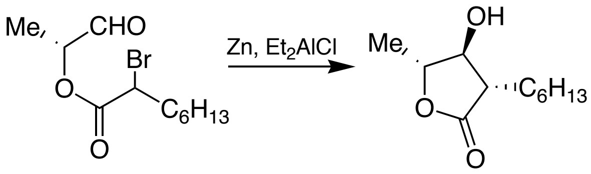
The "Classical" Reformatsky Process

Review: *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.8, pp 277-299
Fürstner, A. "Recent Advances in the Reformatsky Reaction." *Synthesis* **1989**, 571.



H. Nozaki & Co-workers,
J. Am. Chem. Soc. **197**, *99*, 7705

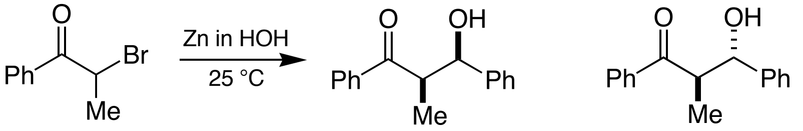
Both cyclic and acyclic cases studied (11 cases).



diastereoselection 10:1
55% yield

T. Nishida & Co-workers,
Tetrahedron **1991**, *47*, 6623.

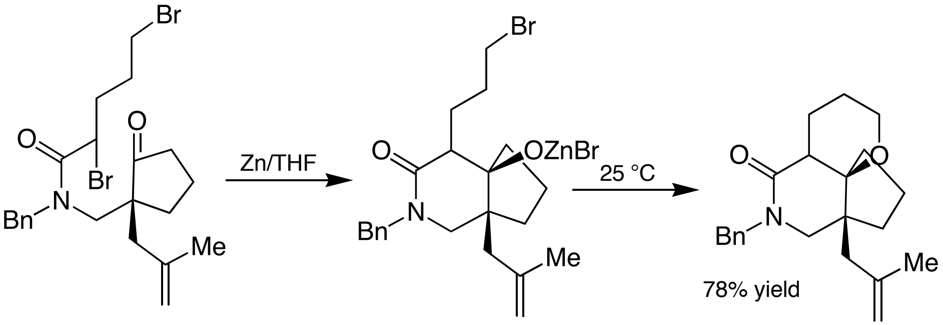
Based on the Nozaki recipe *JACS* **1977**, *99*, 7705



diastereoselection 60:40
87% yield

T. H. Chan & Co-workers,
Chem. Commun. **1990**, 505.

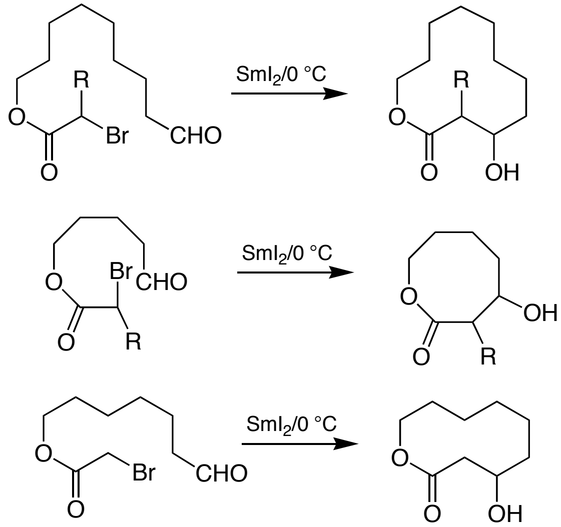
Rxns carried out in water with either activated Zn or Sn.
19 cases reported.



C. H. Heathcock & Co-workers,
J. Org. Chem. **1987**, *52*, 5745.

The Samarium(II) Variant

Molander, "Reductions with Samarium (II) Iodide." *Org. Reactions* 1994, *46*, 211-367.



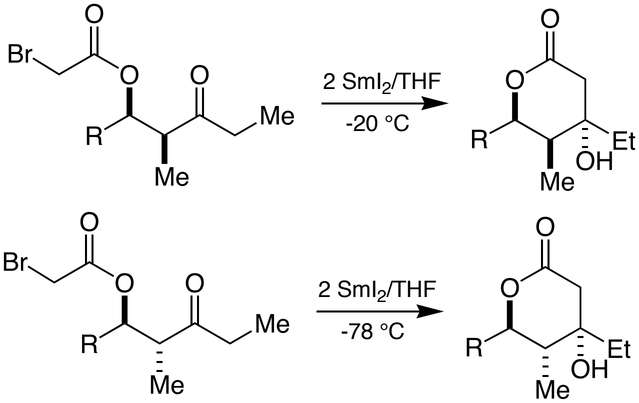
R = H: 85% yield
R = Me: 82% yield
aldol diastereoselection 70:30
no config assignment

R = H: 76% yield
R = Me: 82% yield
aldol diastereoselection 62:38
no config assignment

82% yield

Good entry into prior literature

T. Tabushi & Co-workers,
Tetrahedron Lett. **1986**, *27*, 3889.

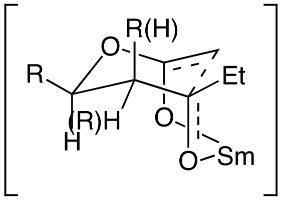


8: 1 diastereoselection
97% yield

one isomer? 86% yield

G. A. Molander & Co-workers,
J. Am. Chem. Soc. **1987**, *109*, 6556.

Proposed Transition structure



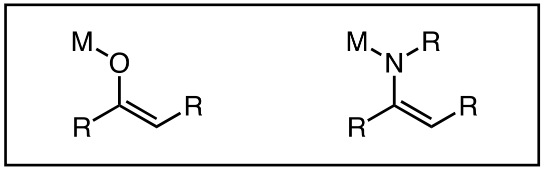
http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 25

Enolates & Metalloenamines-2



- Concept of Soft Enolization
- Introduction and General Trends
- Enolate Alkylation: Electronic & Steric Control Elements
- Enolate Alkylation: Unusual Cases
- Chiral Amide Enolates
- Chiral Ester Enolates
- Chiral Imide Enolates

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Wednesday
November 15, 2006

Assigned Journal Articles

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983). **(handout)**

"Self-Regeneration of Stereocenters (SRS)-Applications, Limitations, & Abandonment of a Synthetic Principle",
D. Seebach et al. *Chem. Int. Ed. Engl.*, **35**, 2708 (1996). **(handout)**

Other Useful References

"Advances in Asymmetric Enolate Methodology" Arya, Qin, *Tetrahedron* **2000**, *56*, 917-947 **(pdf)**

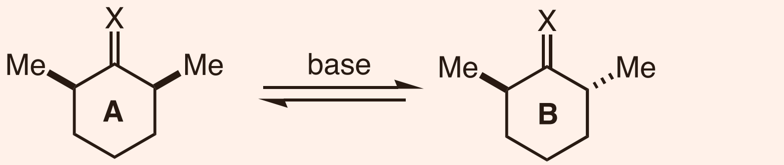
"Stereoselective Alkylation Reactions of Chiral Metal Enolates".
D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984).

"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"Keto-Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution". Keeffe, Kresge, and Schepp *JACS*, 112, 4862 (1990).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (1984).

Explain why **A** is favored for X = O while **B** is favored for X = NNHR



Manuscript for Submission to Angew. Chemie

Provided to you as an electronic handout

REVIEWS

Soft Enolization: A Powerful Method for Diastereoselective Carbon-Carbon Bond Formation

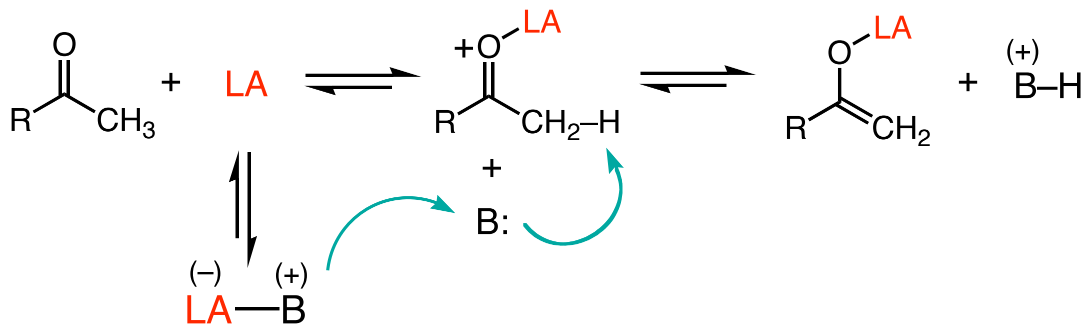
David A. Evans[*] and Jared T. Shaw[†]

Strategy

Choose Lewis Acid (LA) which can reversibly associate with amine base (B:).

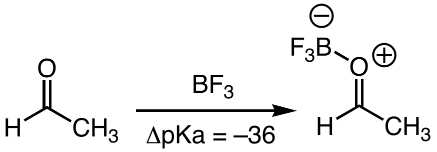
$$\mathrm{LA} + \mathrm{B:} \rightleftharpoons \overset{(-)}{\mathrm{LA}}\text{—}\overset{(+)}{\mathrm{B}}$$

This system has the potential to enolize carbonyl functional groups:



Mild Methods for Forming Enolates

Lewis Acid C=O Complexation Enhances C–H Acidity (Computation)



$\Delta H_{\text{gas phase}}$ **+366** **+316**

ΔH_{gp} H_2SO_4 = 304
ΔH_{gp} H–I = 314

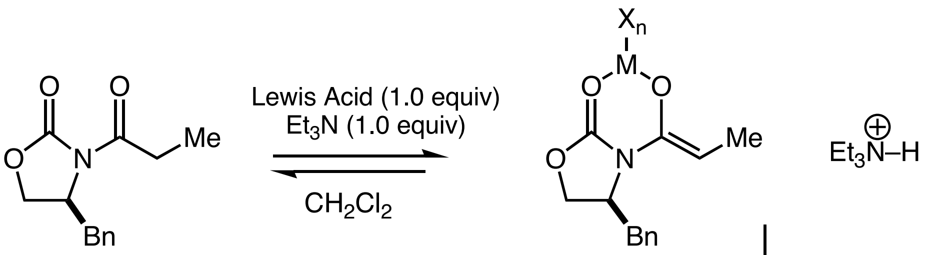
$\Delta\Delta H_{gp}$ = –50 kcal/mol
↓
$\Delta\Delta H_{HOH}$ = –24 kcal/mol

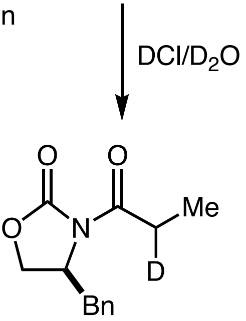
$$pK_{a\,HOH} \quad \mathbf{+17} \quad \xrightarrow[\mathbf{\Delta pKa = -24}]{BF_3} \quad \mathbf{-7}$$

BF_3 complexation generates a "superacid" comparable to the acidity of H_2SO_4

Ren et al, *JACS* **1999**, *121*, 2633-2634 **(pdf)**

Some qualitative observations (Evans Group, Unpublished))



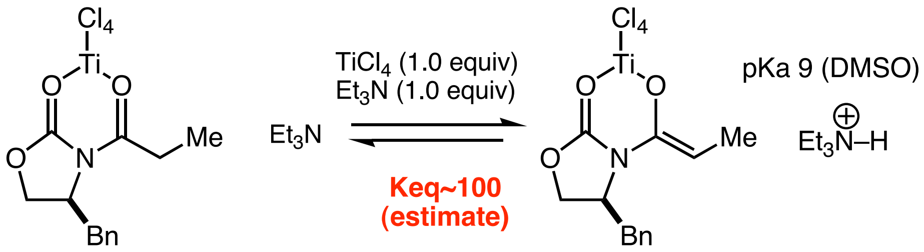


Lewis Acid (MX_n)	**% deuterium**
$TiCl_4$	100
$TiCl_3(Oi\text{-}Pr)$	100
$TiCl_4•(THF)_2$	80
$TiCl_2(Oi\text{-}Pr)_2$	70
$AlCl_3$	70
$MgBr_2•OEt_2$*	25
$TiCl(Oi\text{-}Pr)_3$	10
$SnCl_4$, Et_2AlCl, $ZrCl_4$	0

*2.0 equiv required

In these experiments, the Lewis acid was added first followed by the amine.

Some qualitative observations (Evans Group, Unpublished))

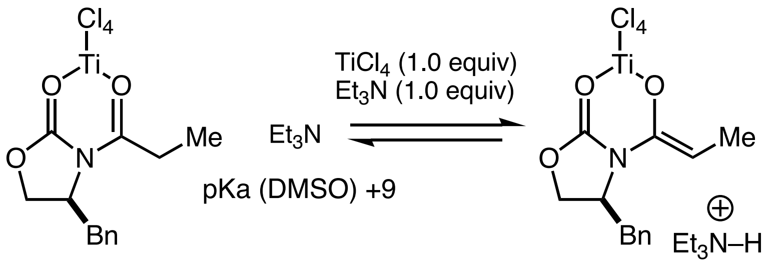


Keq~100 (estimate)

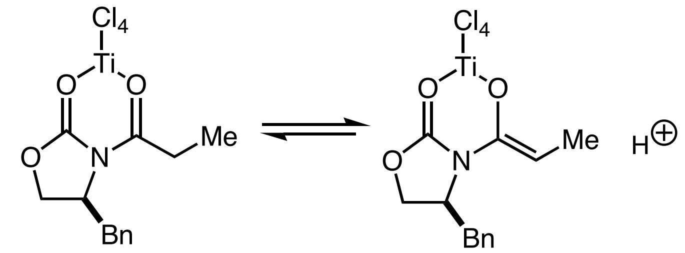
pKa 9 (DMSO)

estimated pKa (DMSO)???

	pK
$Et_3N^{\oplus}–H \rightleftharpoons H^{\oplus} + Et_3N$	**+9**



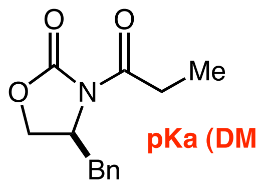
–2



pKa ~ +7

estimated pKa (DMSO) ~ +7

Hence $TiCl_4$ complexation lowers acidity by **~20 pka units.** this number is the same mgnitude as the BF_3–acetaldehyde case just discussed



pKa (DMSO)~ +27

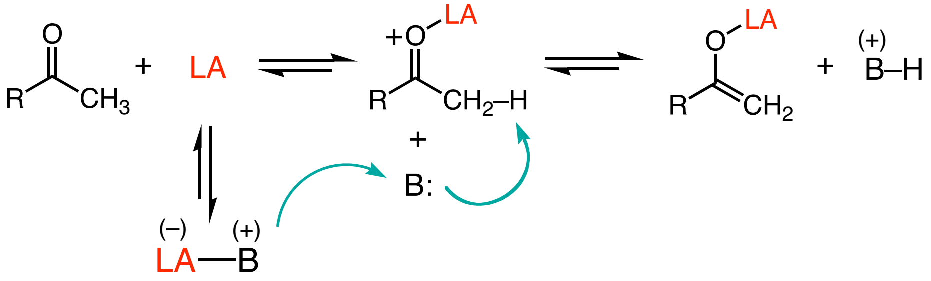
Design of Soft Enolization Systems

Strategy

Choose Lewis Acid (LA) which can reversibly associate with amine base (B:).

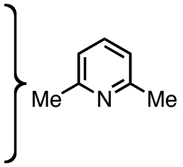
$$\mathrm{LA} + \mathrm{B:} \rightleftharpoons \overset{(-)}{\mathrm{LA}}\text{—}\overset{(+)}{\mathrm{B}}$$

This system has the potential to enolize carbonyl functional groups:

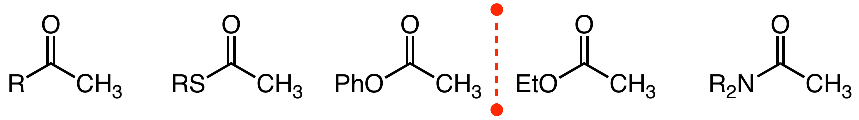


Useful Lewis Acid Pairs	Complexation
$MgBr_2$ + NEt_3	Reversible
$Li^{-}X$ + NR_3	Reversible
$Sn(OTf)_2$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$R_2B^{-}OTf$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
R_2BCl + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$PhBCl_2$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$TiCl_4$ + NR_3	Irreversible (Et_3N, $EtNi\text{-}Pr_2$)
$i^{-}PrOTiCl_3$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$(i^{-}PrO)_2TiCl_2$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$(i^{-}PrO)_3TiCl$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)

$^{-}OTf = {}^{-}OSO_2CF_3$



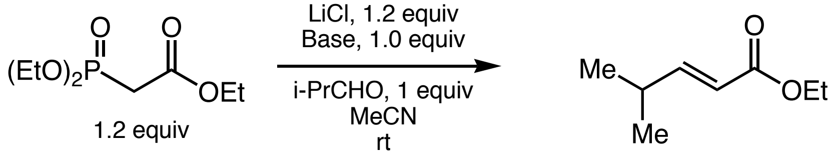
All of the above systems will enolize simple ketones to some extent.



100% enolization for B, Sn, Ti
partial enolization for Li, Mg

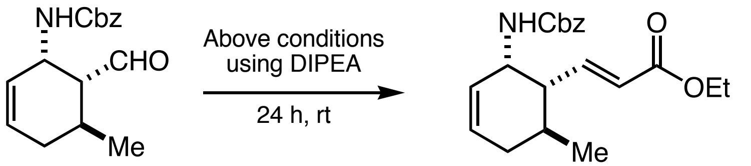
Lithium Enolates

Horner-Wadsworth-Emmons Reaction.



pKa 19.2 (DMSO), K^+ counterion
pKa 12.2 (Diglyme), Li^+ counterion

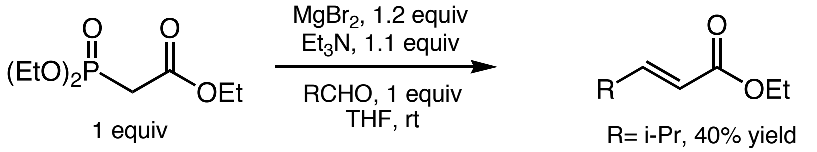
Roush & Masamune, Tet. Lett. 1984, 25, 2183-2186



85% + 10% recovered aldehyde

Conventional methods of deprotonation (NaH) resulted in epimerization (Overman *JACS* **1978**, 5179).

Magnesium Enolates



R= i-Pr, 40% yield
R= n-C_6H_{13}, 100% yield

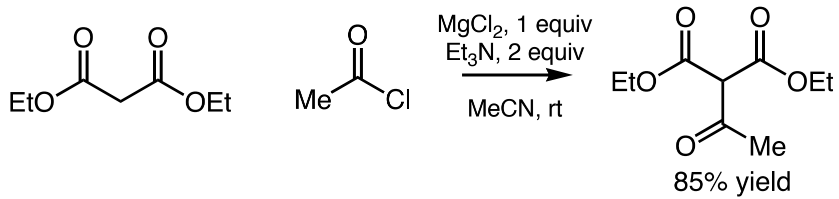
Rathke, Nowak *J. Org. Chem.* **1985**, *50*, 2624-2626.

A Survey of 'Soft' Enolization Techniques

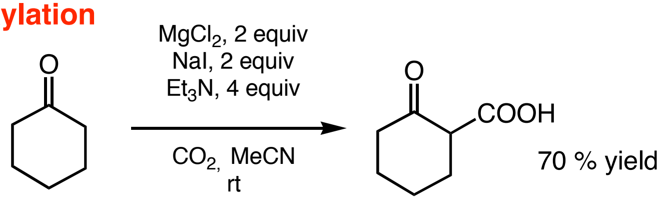
Magnesium Enolates

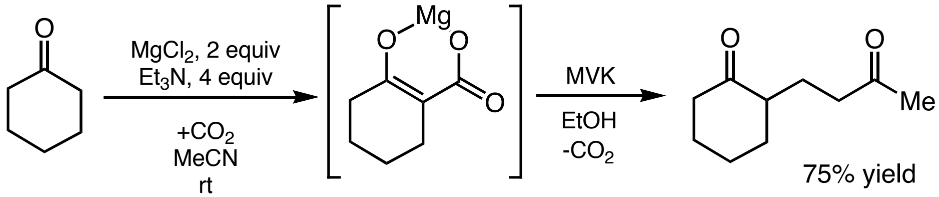
Rathke *J. Org. Chem.* **1985**, *50*, 2622-2624.
J. Org. Chem. **1985**, *50*, 4877-4879.
Syn. Comm. **1986**, *16*, 1133-1139.

Diethylmalonate acylations

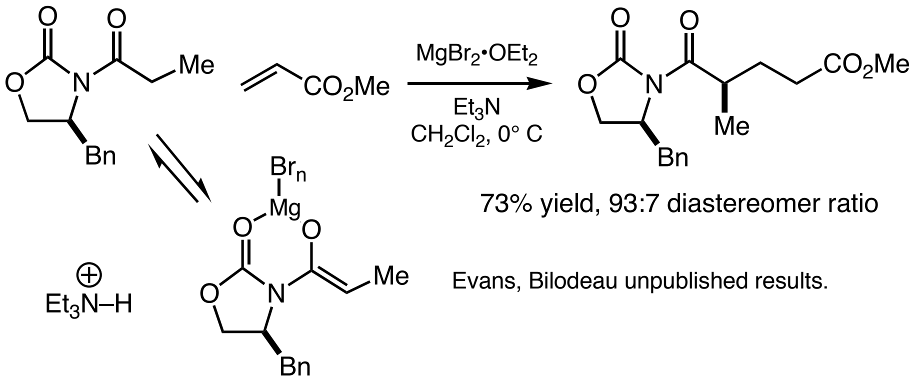


Ketone Carboxylation





Michael reaction



73% yield, 93:7 diastereomer ratio

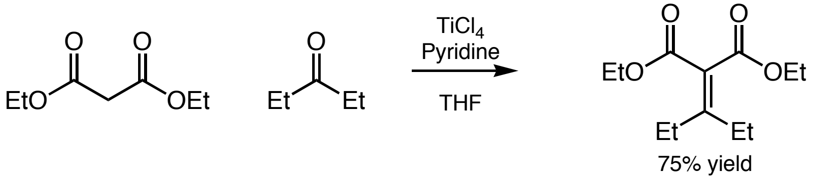
Evans, Bilodeau unpublished results.

Deuterium quench indicates 25% enolization of *N*-propionyloxazolidinone

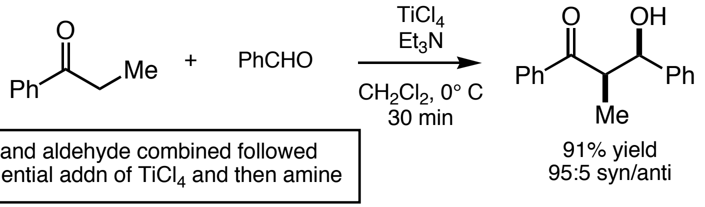
Titanium Enolates

The Early Literature

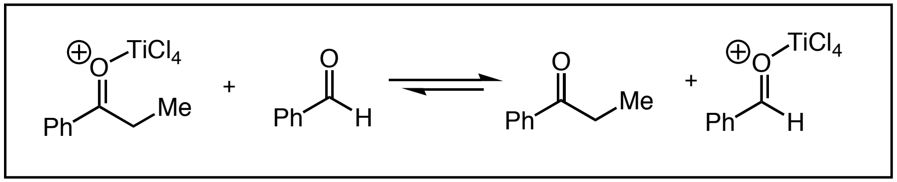
Lehnert, W. *Tetrahedron Lett.* 1970, 4723-4724.



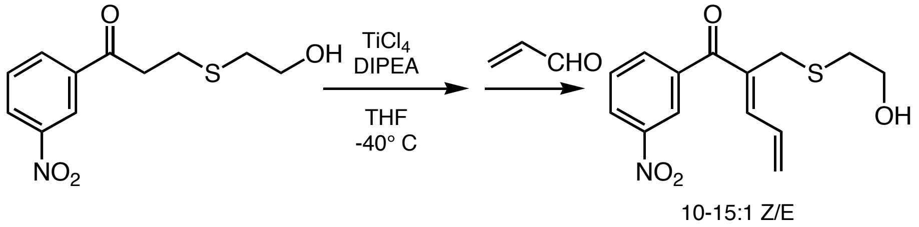
Harrison, C. R. *Tetrahedron Lett.* 1987, *28*, 4135-4138.



Ketone and aldehyde combined followed by sequential addn of $TiCl_4$ and then amine

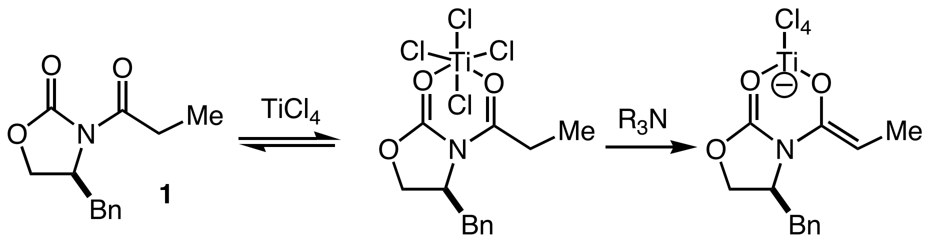


Brocchini, Eberle, Lawton *J. Am. Chem. Soc.* 1988, *110*, 5211-5212.



A Survey of 'Soft' Enolization Techniques

Titanium Enolates



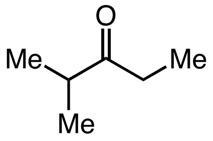
- Enolization process not responsive to tertiary amine structure
- DIPEA, Et_3N, N-Ethylpiperidine all suitable bases.
- DBU and tetramethylguanidine do not provide enolate.
- CH_2Cl_2 is the only suitable solvent for these enolizations.

N-Propionyloxazolidone (**1**)

Lewis Acid	% Enolization
$TiCl_4$	100
i-$PrOTiCl_3$	100
$TiCl_4$•2THF	80
(*i*-PrO)$_2$$TiCl_2$	70
(*i*-PrO)$_3$TiCl	~10

Ethylisopropylketone

Lewis Acid	% Enolization
$TiCl_4$	100
i-$PrOTiCl_3$	80
(*i*-PrO)$_2$$TiCl_2$	50



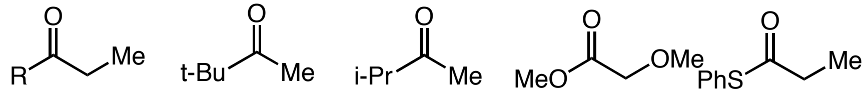
- Order of addition of reagents is important for $TiCl_4$.

R_3N + $TiCl_4$ → $R_3\overset{+}{N}\text{-}\overset{-}{Ti}Cl_4$ Irreversible Complexation

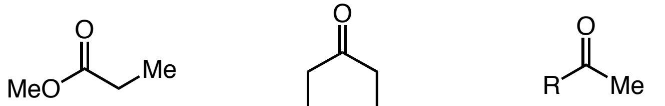
- Order of addition of reagents is not important for *i*-$PrOTiCl_3$ or (*i*-PrO)$_2$$TiCl_2$.

R_3N + *i*-$PrOTiCl_3$ ⇌ $R_3\overset{+}{N}\text{-}\overset{-}{Ti}Cl_3(O\textit{i}Pr)$ Reversible Complexation

- Enolizable substrates:



- Substrates Which present problems:

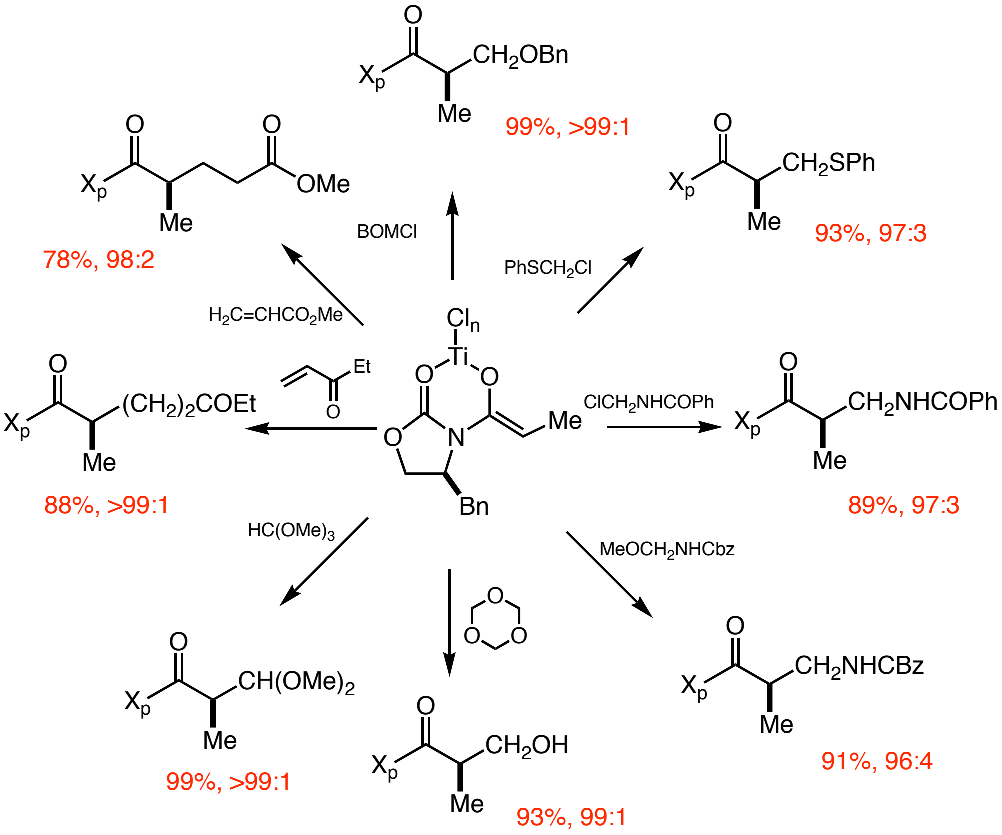


R=Ar, R<i-Pr

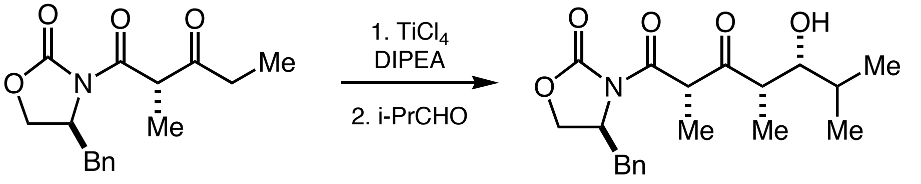
self condensation

self condensation

Reactions with Representative Electrophiles



J. Am. Chem. Soc. **1990**, *112*, 8215-8216.; *J. Org. Chem.* **1991**, *56*, 5750-5752.



86% yield, >99:1

Evans, Clark, Metternich, Novack, Sheppard *J. Am. Chem. Soc.* **1990**, *112*, 866.

A Survey of 'Soft' Enolization Techniques: Boron Enolates-1

Dialkylboron Triflates

Di-n-butylboron triflate

Mukaiyama, Inoue *Chem. Lett.* **1976**, 559-562.
Bull. Chem. Soc. Jpn. **1980**, *53*, 174-178.

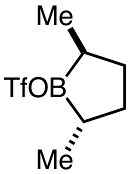
Enolizes ketones with 2,6-lutidine or DIPEA in ethereal solvents.

Diastereoselective Aldol Reactions of Boron Enolates.

Evans, Vogel, Nelson *J. Am. Chem. Soc.* **1979**, *101*, 6120.
Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
Evans, Bartroli, Shih *J. Am. Chem. Soc.* **1981**, *103*, 2127.
Masamune, S. et. al. *Tetrahedron Lett.* **1979**, 2225, 2229, 3937.
Masamune, S. et. al. *J. Am Chem. Soc.* **1981**, *103*, 1566-1568.

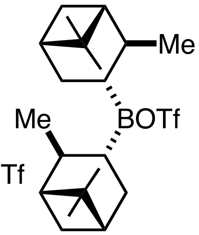
Chiral dialkylboron triflates

Masamune, Sato, Kim, Wollmann
J. Am. Chem. Soc. **1986**, *108*, 8279-8281.



Paterson, I. et. al.

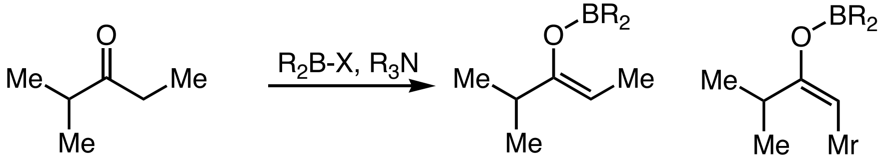
Tetrahedron **1990**, *46*, 4663-4684.
Tetrahedron Lett. **1989**, *30*, 997-1000.
Tetrahedron Lett. **1986**, *27*, 4787-4790.



(-)-(Ipc)$_2$BOTf

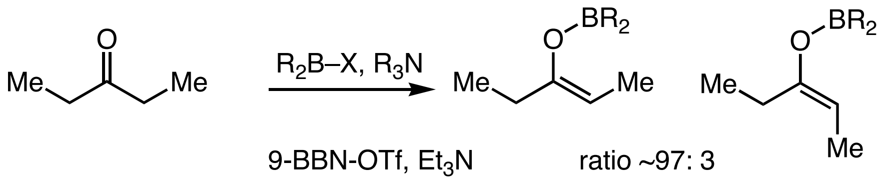
Enolate Stereochemistry

Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
Goodman, *Tetrahedron Lett.* **1992**, *33*, 7219.
Enolization Model: Paterson, *Tetrahedron Lett.* **1992**, *33*, 7223.



9-BBN-OTf, Et$_3$N	ratio ~ 88: 12
Cy$_2$B-Cl, Et$_3$N	ratio ~ 3: 97

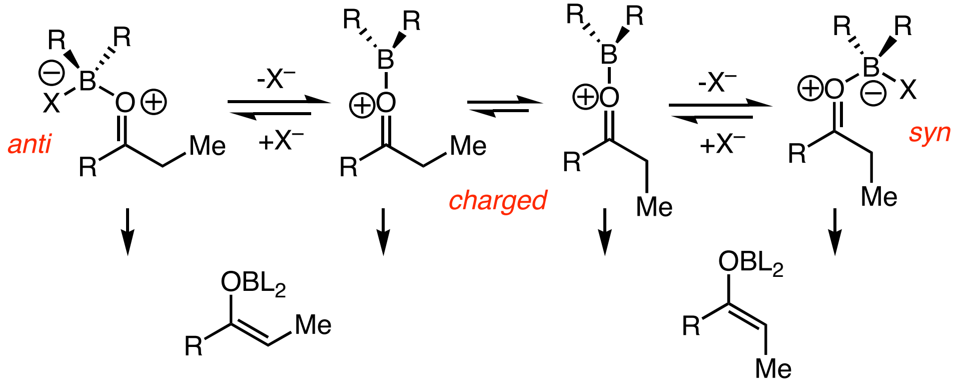
Brown, *J. Org. Chem.* **1993**, *58*, 147-153

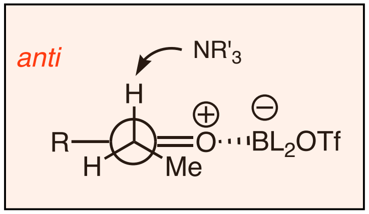


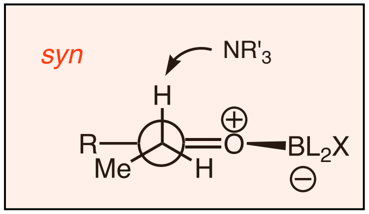
9-BBN-OTf, Et$_3$N	ratio ~97: 3
Cy$_2$B-Cl, Et$_3$N	ratio 21:79
Bu$_2$B-OTf, Et$_3$N	ratio ~97: 3

Borane and lutidine or DIPEA form 1:1 complex with L$_2$B-OTf. Complexation reversible as enolization will occur upon addition of ketone. Less hindered nitrogen bases - pyridine, Dabco, DBU, irreversibly complex with L$_2$B-OTf.

The Ketone-Boron Complexes as enolate precursors:







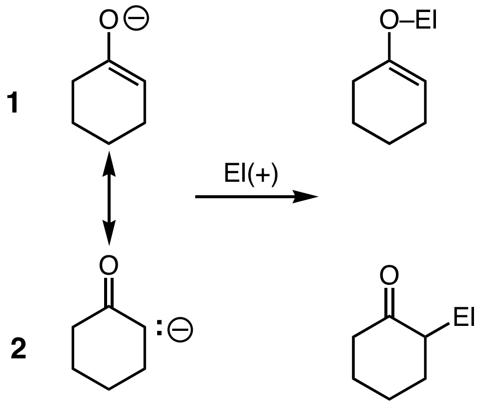
Cy$_2$BCl-ketone complex may deprotonate through syn complex

R$_2$BOTf-ketone complex may deprotonate through charged complex with (Z) preference

C versus O Enolate Reactivity & the Hammond Postulate

Question: Why do we generally show enolates reacting with electrophiles at carbon as opposed to oxygen ?? Let's begin the the discussion with an observation:

■ "As electrophile reactivity increases, the percentage of reaction at the enolate oxygen increases." For example, consider the reactions of cyclohexanone enolate with the two electrophiles, methyl iodide and the much more reactive acetyl chloride:



El(+)	C/O Rxn Ratio
$Me-\overset{O}{\overset{\|}{C}}-Cl$	<< 1
Me—I	>> 1

■ The very reactive acid chloride gives almost exclusively the O-acylation product while the less reactive methyl iodide affords the alternate C-alkylation product.

These results may be understood in the context of qualitative statements made by Hammond (**The Hammond Postulate**) and
Hine (**The Principle of Least Motion**)

The Principle of Least Motion:
"As reactions become more exothermic, the favored reaction becomes that path which results in the least structural (electronic) reorganization."

See Hine in *Advances in Phys. Org. Chem.* **1977**, *15*, 1-61

Since the X-ray data clearly support the picture that resonance structure **1** best represents the enolate structure, highly reactive electrophiles will favor O-attack according to Hine's generalization.

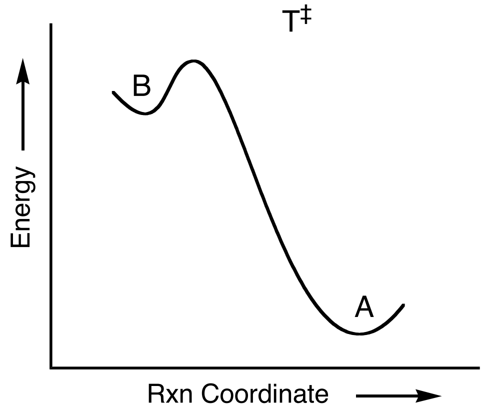
The Hammond Postulate is also relevant to this issue and is broadly used to make qualitative statements about transition state structure.

Hammond, *JACS* **1955**, *77*, 334 (handout)

■ In attempting to grasp the Hammond Postulate, let's consider two extreme reactions, one which is strongly endothermic and one which is strongly exothermic.

Strongly Exothermic Reactions
$\Delta H^\circ > 20$ kcal/mol

B ⟶ A

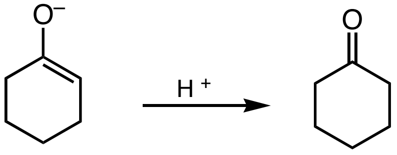


Hammond Postulate
"For strongly exothermic reactions, the transition state T‡ looks like reactant(s) e.g. B."

■ As applied to the enolate-electrophile reaction, for very exothermic reactions, e.g. the reaction with acetyl chloride, the transition state for the process will involve little enolate structural reorganization. Hence in this instance the electrophile heads for the site of highest electron density

Carey & Sundberg: **Part A**; Chapter 4, pp217-220
for discussion of Hammond's Postulate

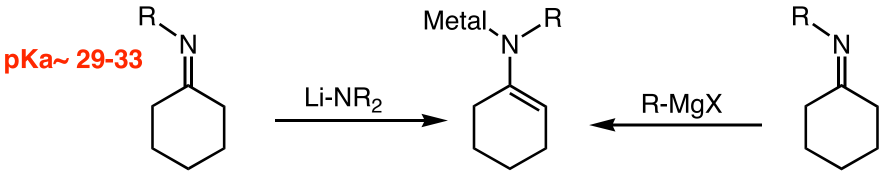
Based upon the above discussion draw a detailed mechanism for the protonation of cyclohexanone enolate.



Enols, Enolates, Enamines & Metalloenamines: Reactivity Hierarchy

■ Metalloenamines:

Imines may be transformed into their conjugate bases (enolate counterparts) with strong bases:

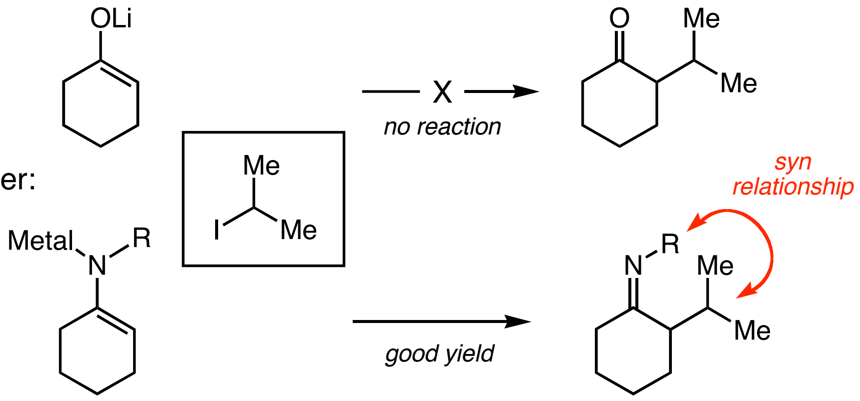


The usual bases employed are either lithium amides (LDA) or Grignard reagents. Note that Grignard reagents do not add to the C=N pi-bond due to the reduced dipole. With this functional group, deprotonation is observed to be the preferred reaction.

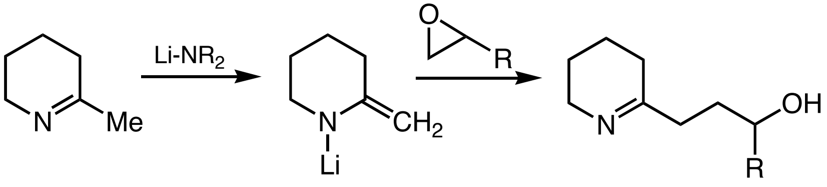
■ When to use a metalloenamine:

Metalloenamines are significantly more nucleophilic than ketone or aldehyde enolates. They are used when less reactive electrophiles are under consideration. For example:

However:

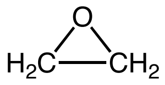


Metalloenamines are reactive enough to open epoxides in good yield. Ketone enolates are only marginally reactive enough for this family of electrophiles.



Decreasing Nucleophilicity →

Decreasing Electrophilicity ↓

Nucleophile / Electrophile	$C=C-{}^{\ominus}NR$	$C=C-{}^{\ominus}O$	$C=C-NR_2$	$C=C-OMe$
Br_2, O_3	+	+	+	+
H_3O^+	+	+	+	+
$R-\overset{O}{\overset{\|}{C}}-Cl$	+	+	+	■
$R-\overset{O}{\overset{\|}{C}}-H$	+	+	+	■
$R-\overset{O}{\overset{\|}{C}}-R$	+	+	▨	■
Me—I	+	+	▨	■
$R-\overset{O}{\overset{\|}{C}}-OR$	+	+	■	■
	+	▨	■	■
Me_2CH—I	+	▨	■	■
$R-\overset{O}{\overset{\|}{C}}-NR_2$	■	■	■	■

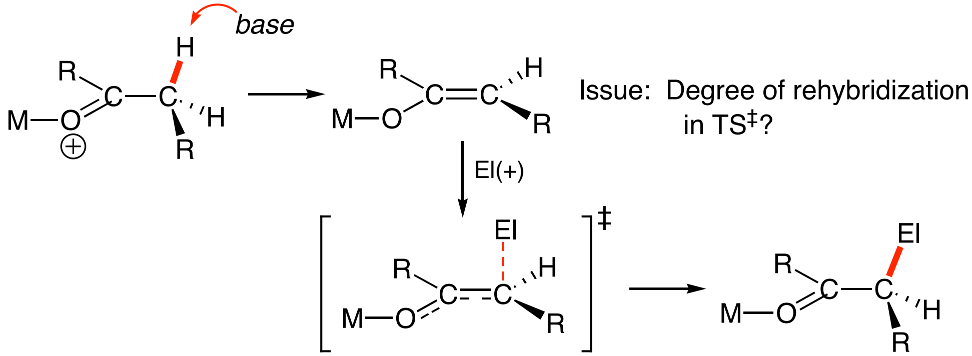
■ Nature uses enamines, "stabilized" enolates, and enol derivatives in C–C bond constructions extensively.

Enolate Alkylation: Stereoelectronic Control Elements

Review Evans, D. A. *Stereoselective Alkylation Reactions of Chiral Metal Enolates.*; Morrison, J. D., Ed.; AP: New York, 1984; Vol. 3, pp 1-110.

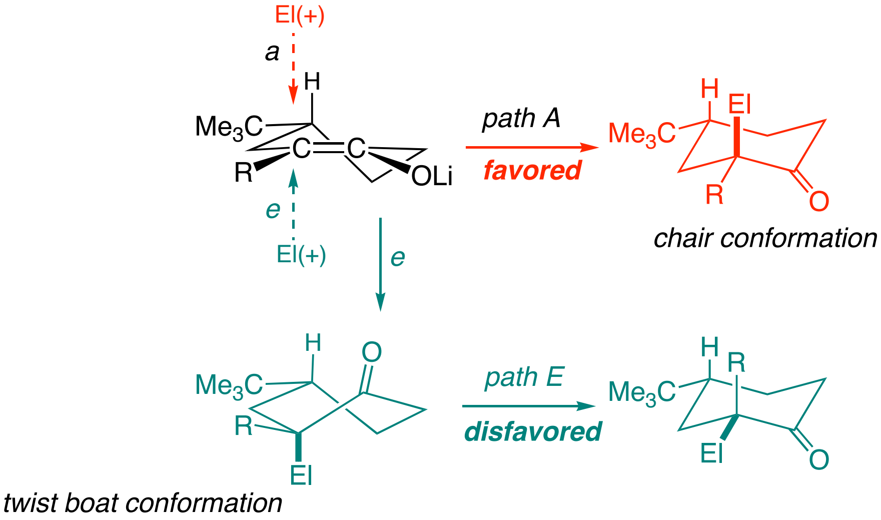
Stereoelectronic Issues

- Enolization: Breaking C–H bond must overlap with π* C–O in TS‡
- Alkylation: Forming C–El bond must overlap with π* C–O in TS‡



Issue: Degree of rehybridization in TS‡?

Cyclohexanone Enolate:



chair conformation

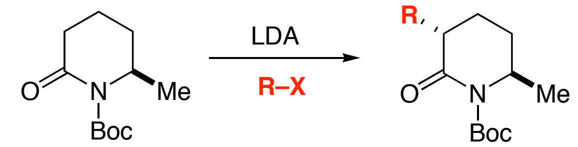
twist boat conformation

Metal	R-substituent	Electrophile	Ratio, a:e
Li	Me	CD_3I	70:30
Li	CO_2Me	Me-I	83:17

Chair vs boat geometries not stongly reflected in diastereomeric TS‡s. The transition states is early and enolate-like.

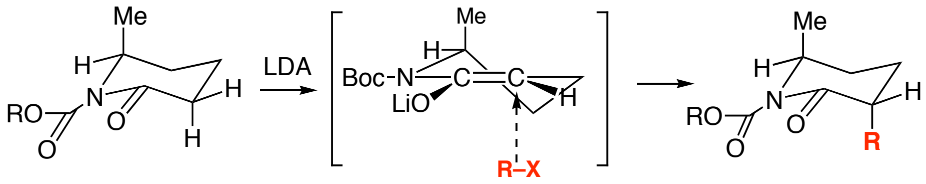
Examples where stereoelectronic factors are dominant

Pilli, *Tetrahedron*, **1999**, *55*, 13321

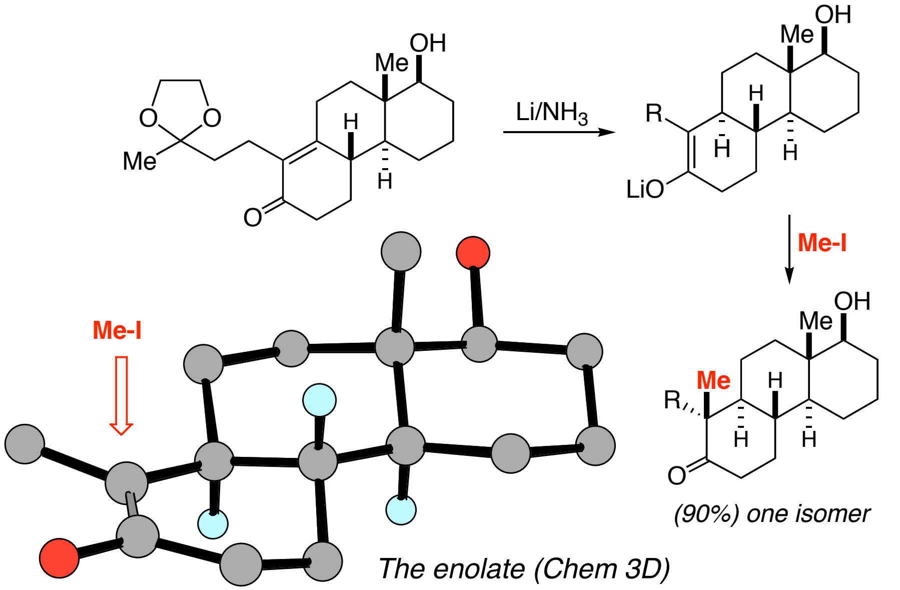


R–X	ratio
Bn–Br	>99:1
Allyl–Br	93:7

good illustration of the impact of allylic strain



The C_{19} Angular Methyl Group in the steroid nucleus



(90%) one isomer

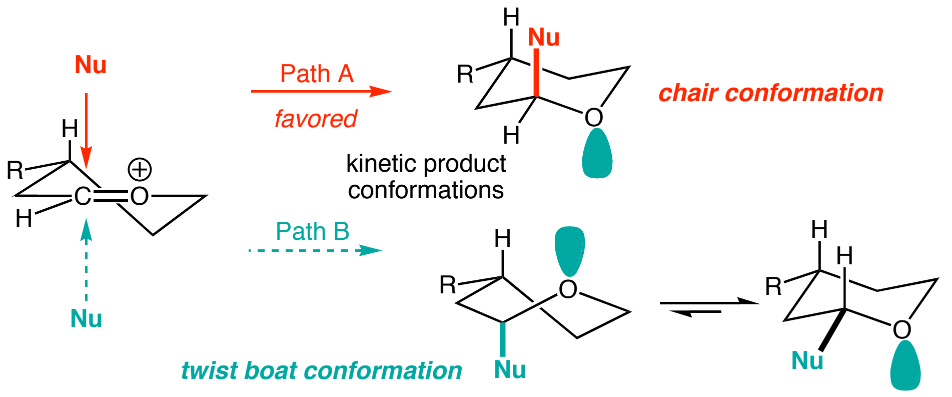
The enolate (Chem 3D)

Stereoelectronic Effects in 6-Membered Rings

As illustrated in this summary, there is a common thread to addition reactions to 6-membered, endocyclic pi-bonds as contained in oxo-carbenium ions, iminium ions, and enolates. In all instances, stereoelectronic considerations favor **"axial-chair"** transition states over the **"boat"** transition state alternatives. The stereoelectronic requirements for the SN2 reaction impose a related bias in the nucleopilic ring opening of epoxides and bromonium ions.The "diaxial" predisposition for the nucleophilic ring-opening of epoxides is known as the Furst-Plattner Rule.

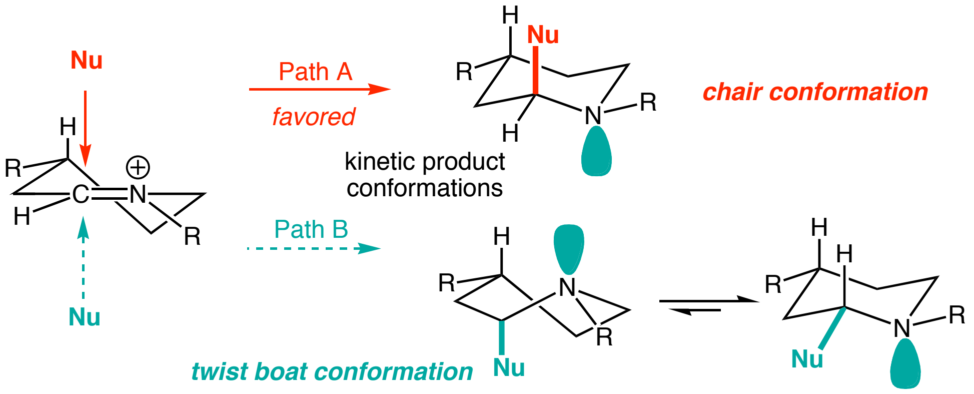
6-Membered Oxo-carbenium Ions

Stereoelectronic Effect: The geometrical constraint imposed by the forming bond and the obligatory antiperiplanar orientation of the developing lone pair



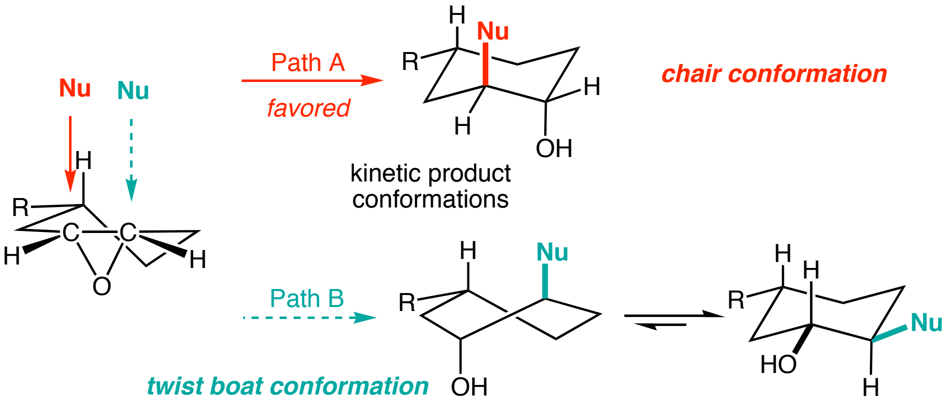
6-Membered Iminium Ions

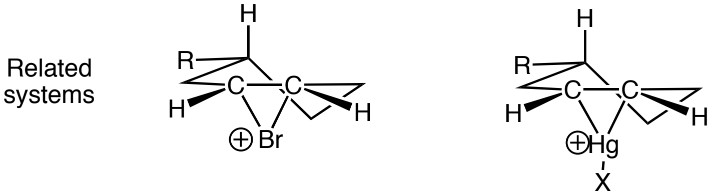
Stereoelectronic Effect: The geometrical constraint imposed by the forming bond and the obligatory antiperiplanar orientation of the developing lone pair



Cyclohexene Epoxides (*FÜRST-PLATTNER RULE*)

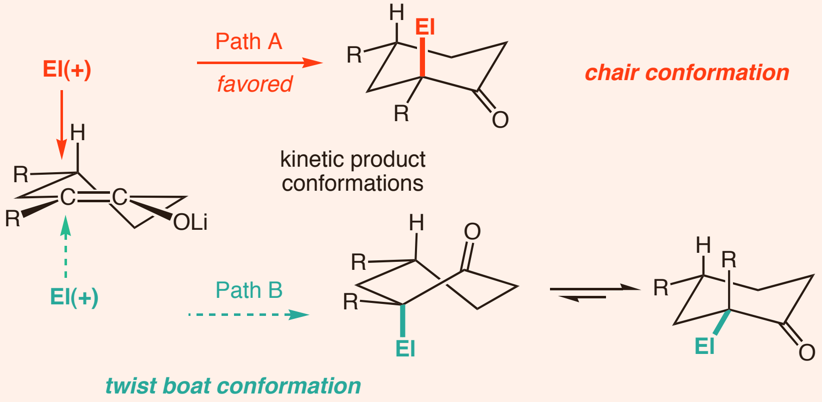
Stereoelectronic Effect: The anti geometrical constraint imposed by the forming bond and the leaving group in the indicated S_N2 reaction. The preference for "diaxial ring opening" preference of 6-membered epoxides also extends to bromonium ions and other olefin sigma complexes.





Cyclohexanone Enolates

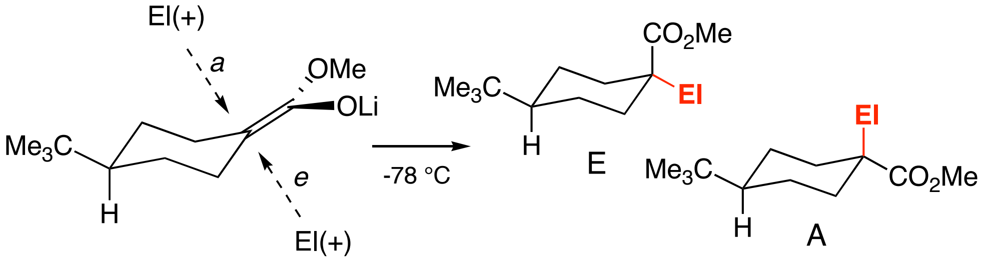
Stereoelectronic Effect: The geometrical constraint imposed by the forming bond and the obligatory overlap with the developing carbonyl.



Enolate Alkylation: Steric Control Elements

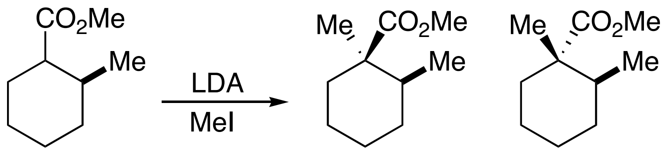
Steric Effects

In this case, both e and a paths are stereoelectronically equivalent. Diastereoselectivity is now determined by the differential steric effects encountered in the two TS‡s.

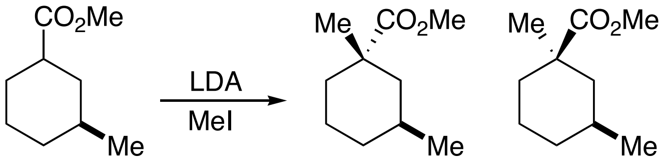


Electrophile	Ratio, E:A
Me-I	84:16
n-Bu-Br	87:13

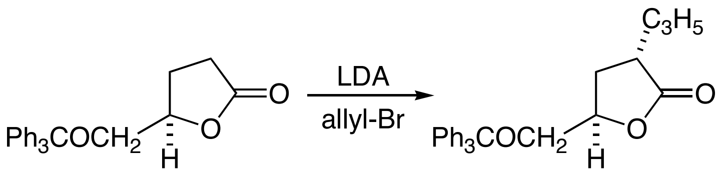
Representative cases



Ratio, 80 : 20

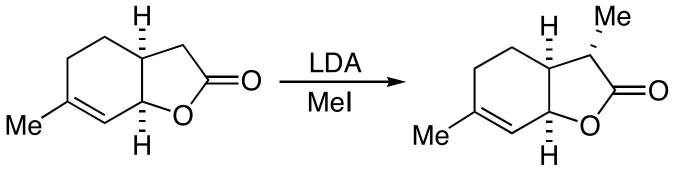


Ratio, 90 : 10



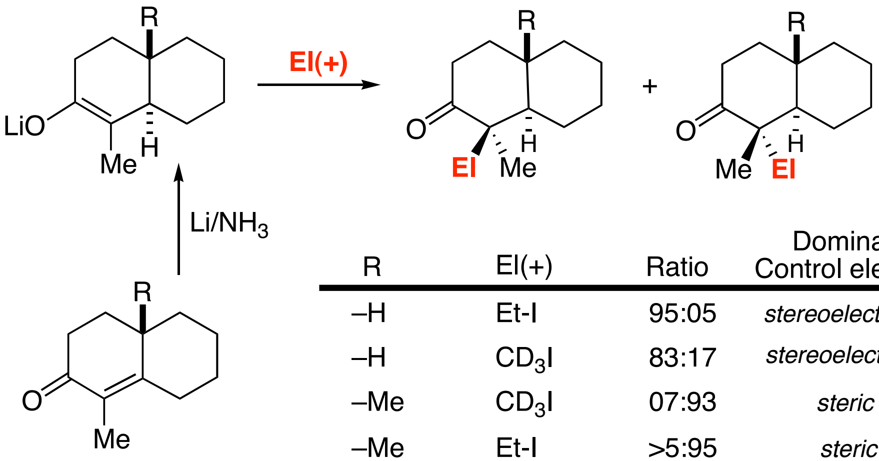
Ratio, >97 : 3

diastereoselectivity depends stongly on O-protecting group

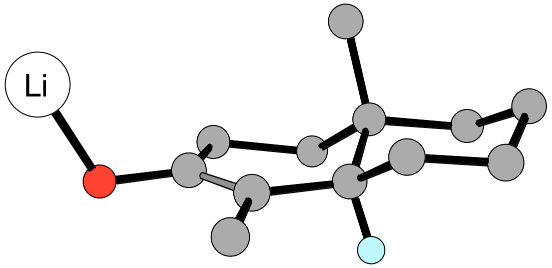


Ratio, >97 : 3

Cases with Opposed steric & electronic effects

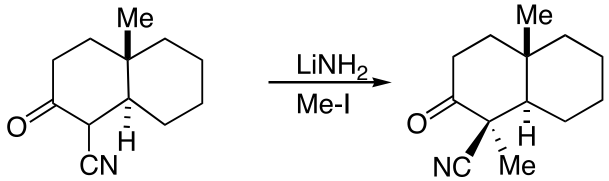


R	El(+)	Ratio	Dominant Control element
–H	Et-I	95:05	*stereoelectronic*
–H	CD_3I	83:17	*stereoelectronic*
–Me	CD_3I	07:93	*steric*
–Me	Et-I	>5:95	*steric*



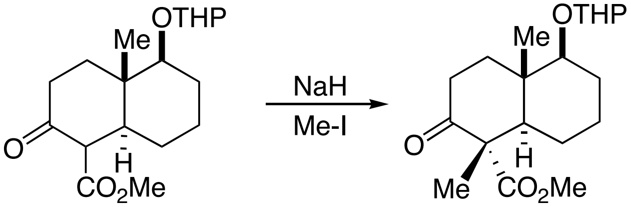
The enolate R = Me
(Chem 3D)

Based on above data, this case is reasonable:



(58%) >90 : 10

However



(67%) 93 : 7

Chiral Enolates & Enolate Acylation

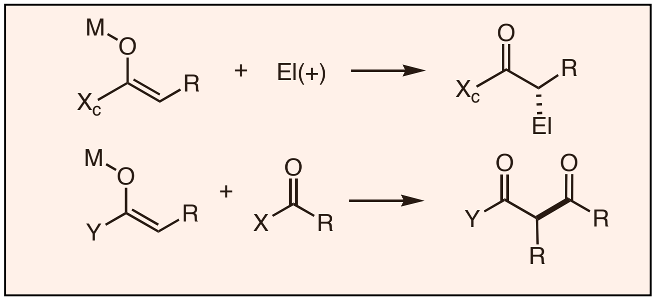
http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 26

Enolates-3



- Chiral Enolates
- Claisen Condenstaion
- Mander Reagent
- Weinreb Amides
- Dieckmann Cyclization

- Reading Assignment for this Week:

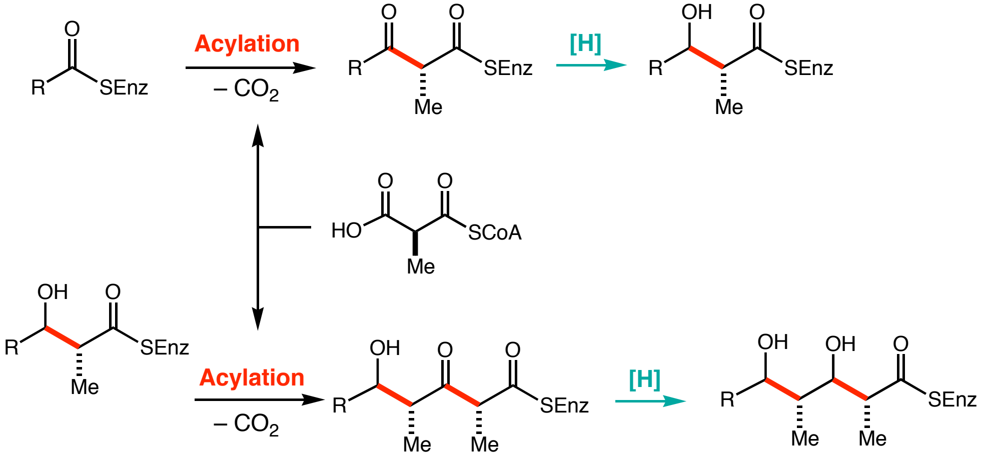
Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

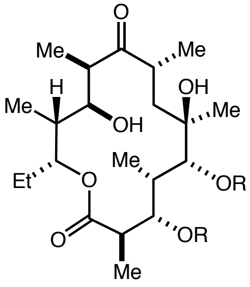
Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

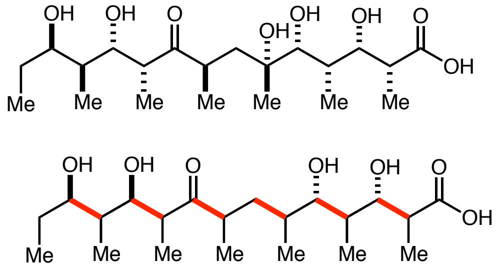
Friday
November 17, 2006

Polypropionate Biosynthesis





Erythromycin B



The 7 Propionate Subunits

"Erythromycin, with all of our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."

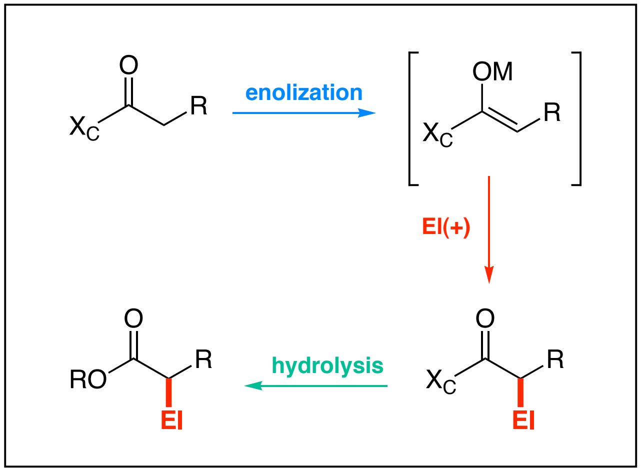
R. B. Woodward, 1956

Chiral Enolate Enolate Alkylation Circa 1978

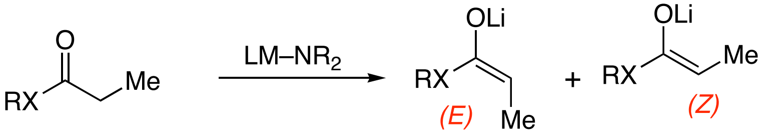
Chiral Enolate Design Requirements Circa 1978

Overall enantioselection will be the sum total of the defects introduced through:

- **Enolization selectivity**
- **Enolate-electrophile face selectivity**
- **Racemization attendant with X_c removal**

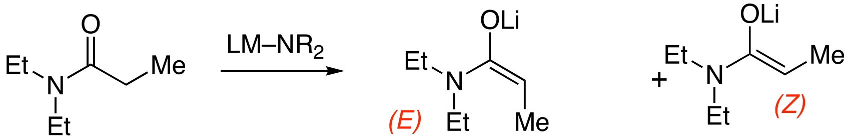


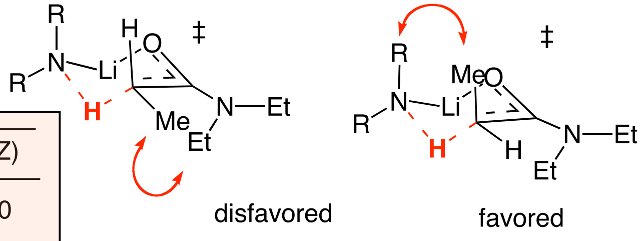
Enolization selectivity: Ester-based chiral controllers X_C limited by enolization selectivity (Lecture 23)



Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5

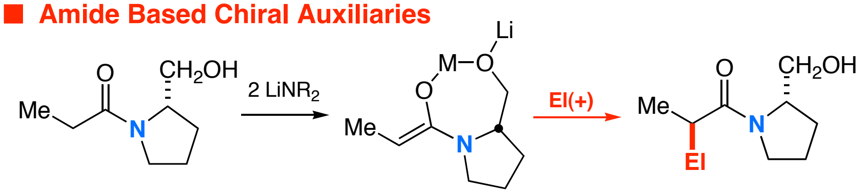
Enolization selectivity: Amide-based controllers X_C limited by enolization selectivity (Lecture 22)





Base	Ratio, (E):(Z)
LDA (THF)	0 : 100
s-BuLi (THF)	25 : 75

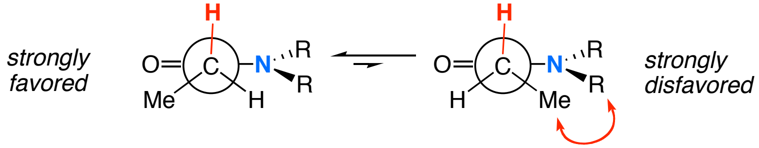
Amide Based Chiral Auxiliaries



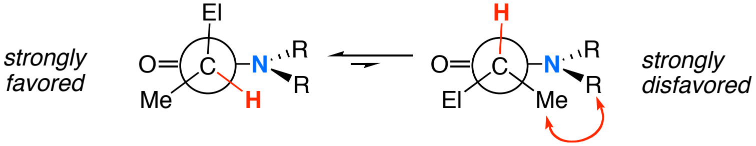
With Takacs, *Tetrahedron Lett.* **1980**, 4233

diastereoselection Ca 95 %

Allylic Strain controls Enolate Geometry:

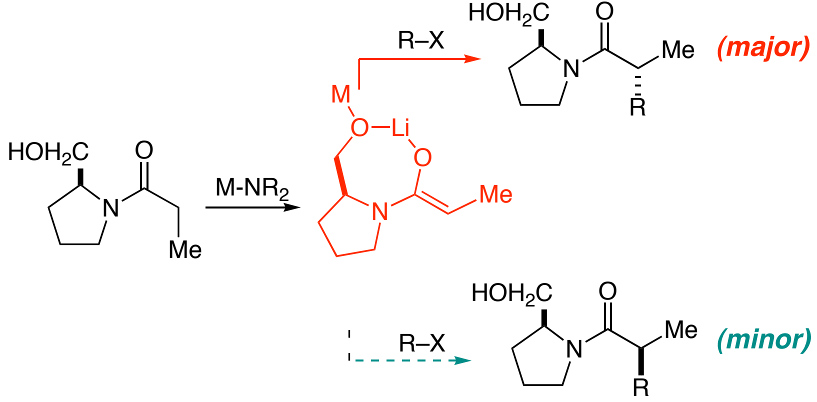


Allylic Strain Prevents Product Enolization:

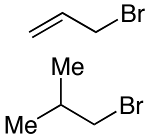


Enolate Alkylation: Chiral Amide Enolates

Chiral Amide Enolates



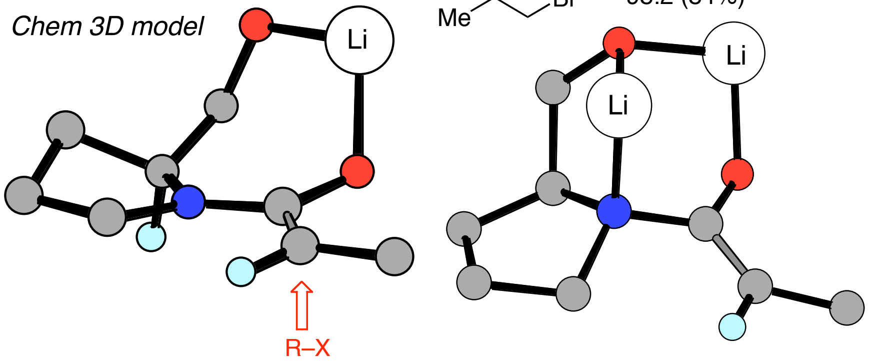
Evans, Takacs,
Tet. Lett. **1980**, *21*, 4233-4236



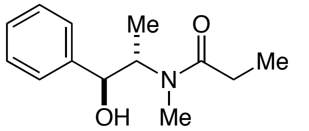
96:4 (98%)

98:2 (84%)

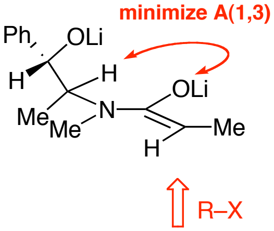
Chem 3D model



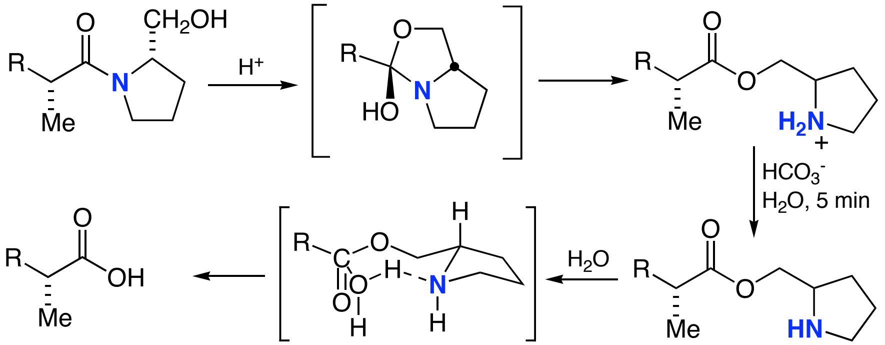
Nature of enolate chelation is ambiguous. Nitrogen chelation is a real possibility.



Myers, *JACS* **1997**, *119*, 6496



Amide Hydrolysis

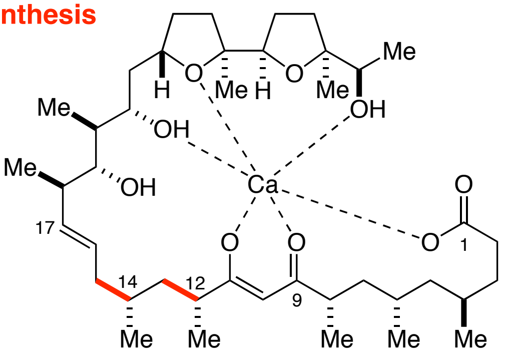


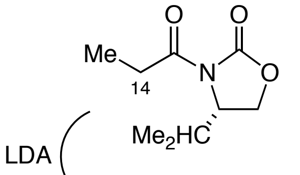
intramolecular general base catalysis

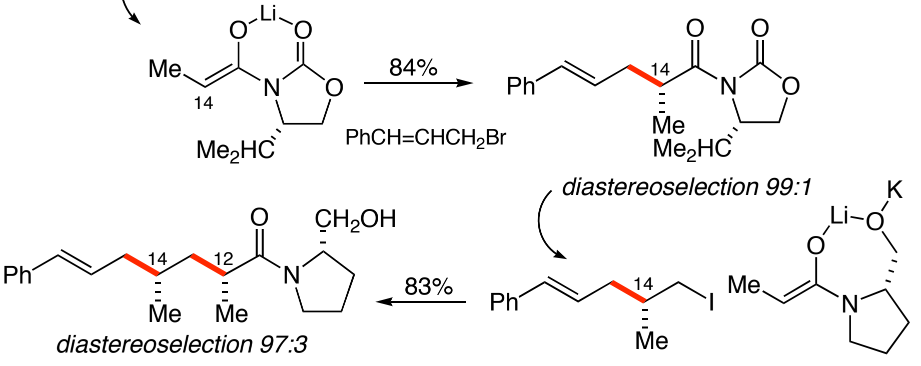
Applications in Ionomycin synthesis

Ionomycin Calcium Complex

JACS **1990,** *112*, 5290-5313





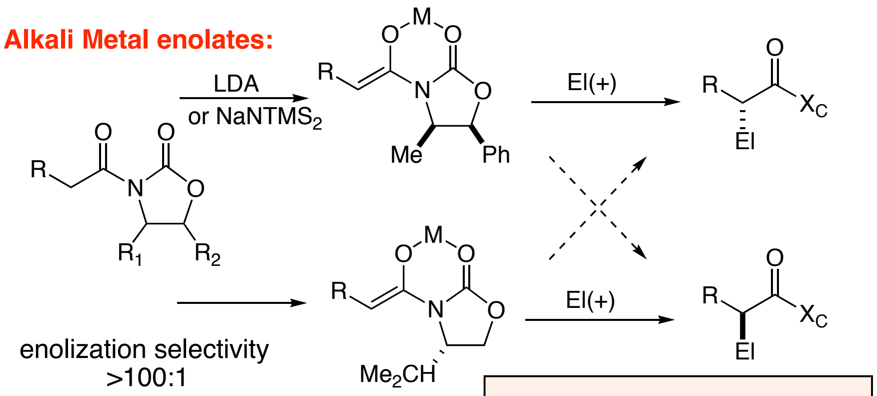


diastereoselection 99:1

diastereoselection 97:3

Enolate Alkylation: Chiral Imide Enolates

Alkali Metal enolates:



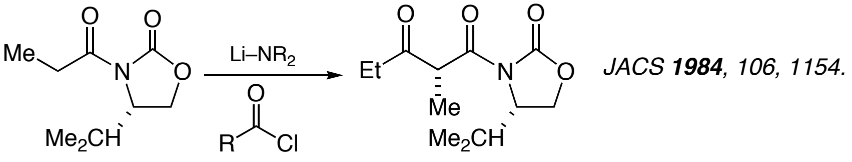
enolization selectivity
>100:1

M = Li, THF < 0 °C
M = Na, THF -78 to 0 °C

Alkyl Halide	Ratio
$ArCH_2Br$	50-120 : 1
$CH_2C{=}CHCH_2Br$	50 : 1
$ArCH_2OCH_2Br$	50 : 1
marginal reaction CH_3CH_2I	25 : 1
CH_3I	13 : 1

JACS. **1982**, *104*, 1737.

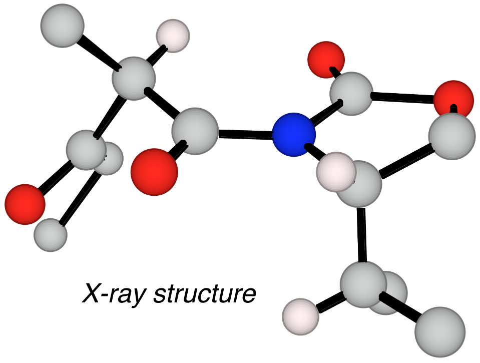
Enolate Acylation



*JACS **1984**, 106, 1154.*

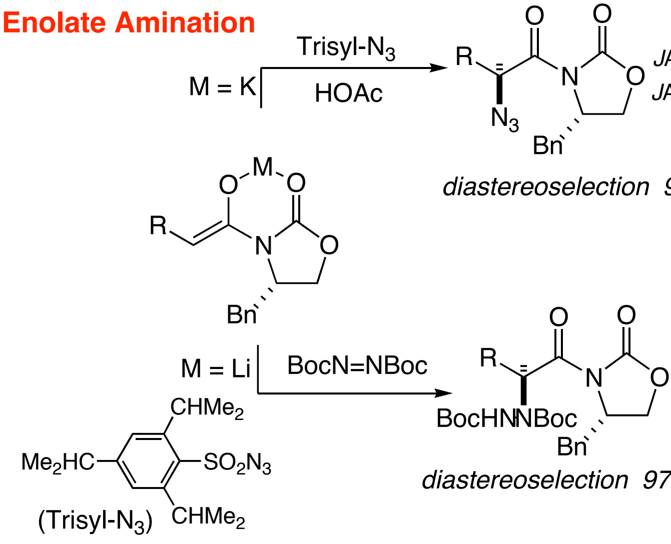
Diastereoselection ~ 97 : 3

New stereocenter not lost through enolization



X-ray structure

Enolate Amination



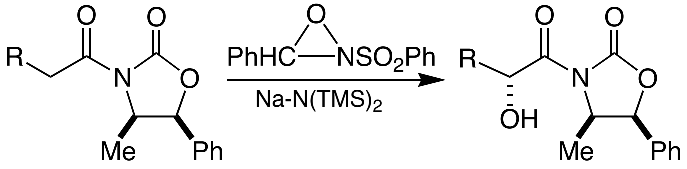
JACS **1987**, *109*, 6881.
JACS **1990**, *112*, 4012-4030

diastereoselection 91-99+ %

JACS **1986**, *108*, 3695.
Tet. **1988**, *44*, 5525-40

diastereoselection 97-99$^+$ %

Enolate Hydroxylation



Na enolate is required.
Why?

Imide (R)	Ratio	Yield *
$PhCH_2$-	94 : 6	86 %
$CH_2{=}CHCH_2$-	95 : 5	91 %
$MeO_2CCH_2CH_2CH_2$-	96 : 4	68 %
Ph-	90 : 10	77 %
Me_3C-	>99 : 1	94 %

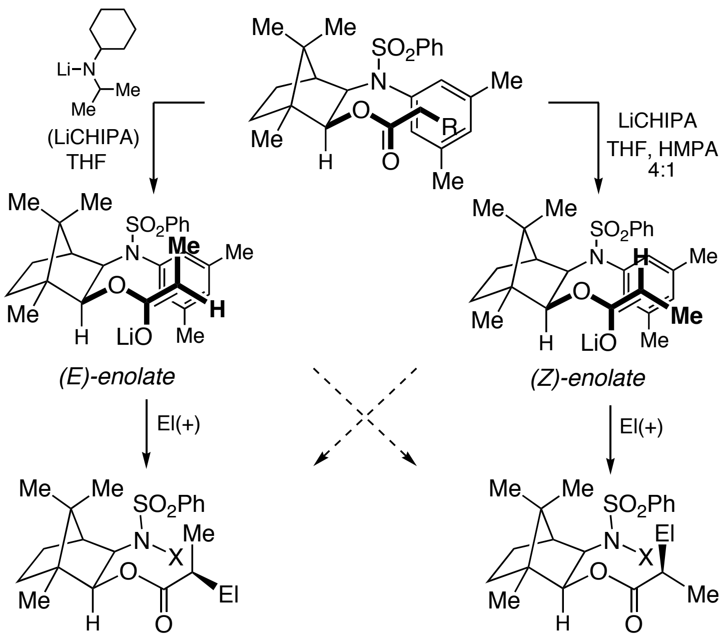
JACS. **1985**, *107*, 4346.

For all indicated rxns, as the R on the enolate grp increases in size enolate-El face selectivity increases. Explain.

Enolate Alkylation: Chiral Ester Enolates

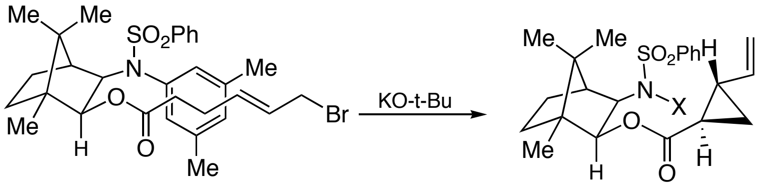
Chiral Ester Enolates

Helmchen, *Angew. Chem. Int.Ed.* **1981**, *20*, 207-208



enolate	El(+)	Ratio	
(E)	n-$C_{14}H_{29}$–I	98.5:1.5	
(Z)	n-$C_{14}H_{29}$–I	06:94	*enolate contamination*

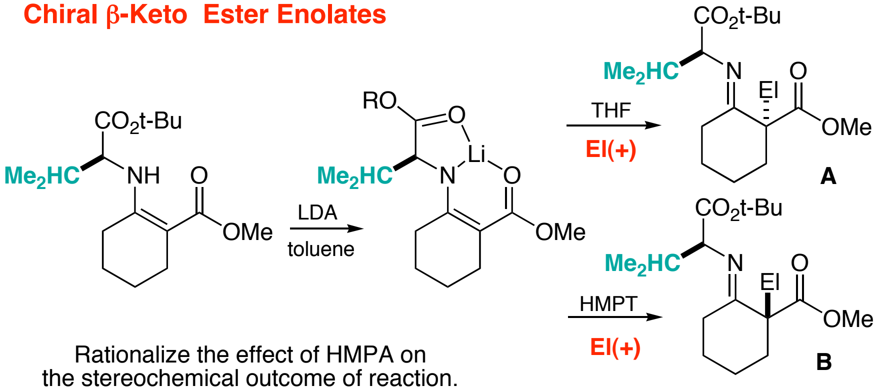
Helmchen, *Angew. Chem. Int.Ed.* **1984**, *23*, 60-61
Helmchen, *Tet. Lett.* **1983**, *24*, 1235-1238
Helmchen, *Tet. Lett.* **1983**, *24*, 3213-3216



Ratio, 93:7 (74%)

Helmchen, *Tet. Lett.* **1985**, *26*, 3319-3322

Chiral β-Keto Ester Enolates

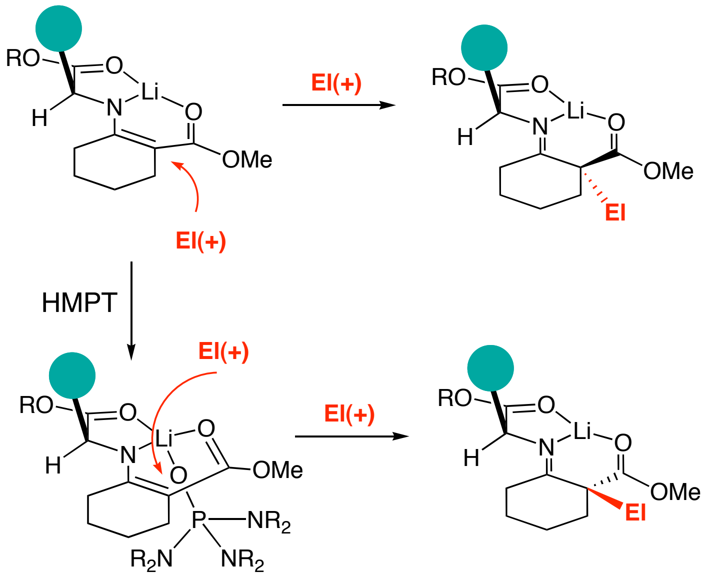


Rationalize the effect of HMPA on
the stereochemical outcome of reaction.

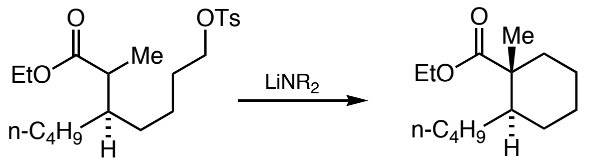
Koga, *JACS* **1984**, *106*, 2718-2719

El(+)	addend	Yield	Ratio (A:B)
Me–I	THF	63%	96:04
Me–I	HMPT	57%	01:99
Bn-Br	THF	48%	99:01
Bn-Br	HMPT	77%	15:85

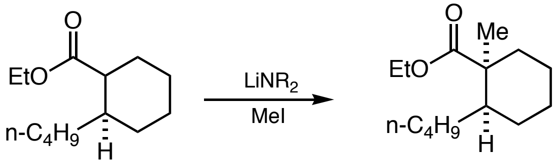
The Rationale:



Allylic Strain & Enolate Diastereoface Selection

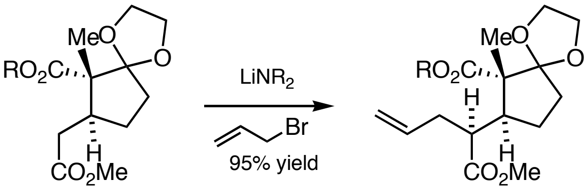


dr: 98:2



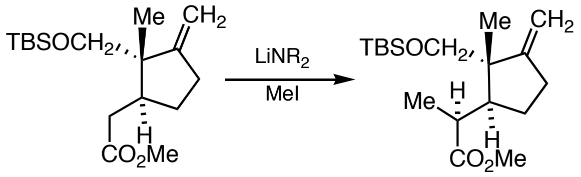
dr: 89:11

D. Kim, *Tetrahedron Lett.* **1986**, *27*, 943.



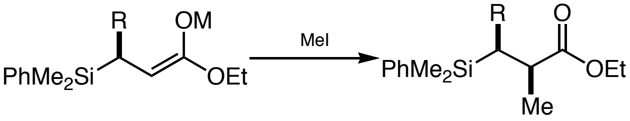
"one isomer"

G. Stork, *Tetrahedron Lett.* **1987**, *28*, 2088.



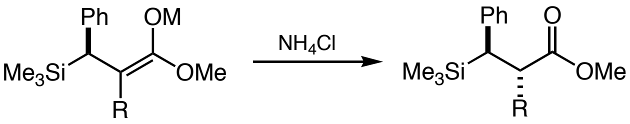
"one isomer"

T. Money, *Chem. Commun.* **1986**, 288.



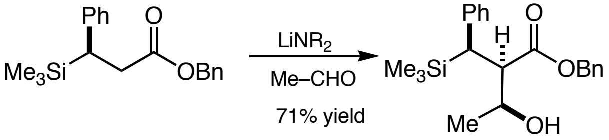
R = Me: dr: 99:1
R = Ph: dr: 97:3

I. Fleming, *Chem. Commun.* **1984**, 28.



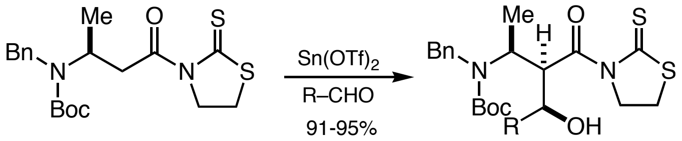
R-substituent	*diastereoselection*	
R = Me	87:13	
R = Et	80:20	
R = CHMe$_2$	40:60	major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun.* **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun.* **1984**, 904.



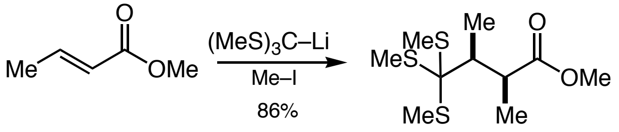
dr: 90:10 at C_3
one isomer at C_2

I. Fleming, *Chem. Commun.* **1986**, 1198.



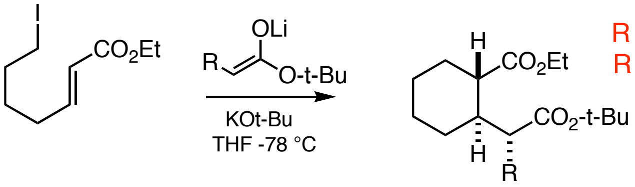
dr > 95:5

T. Mukaiyama, *Chem. Letters* **1986**, 637



dr > 99:1

K. Koga, *Tetrahedron Letters* **1985**, *26*, 3031.



R = H: one isomer
R = Me: > 15 :1

Y. Yamaguchi, *Tetrahedron Letters* **1985**, *26*,1723.

Metalloenamines-1

Seminal Paper: Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

Reviews:

Martin in *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.16, pp 475-502

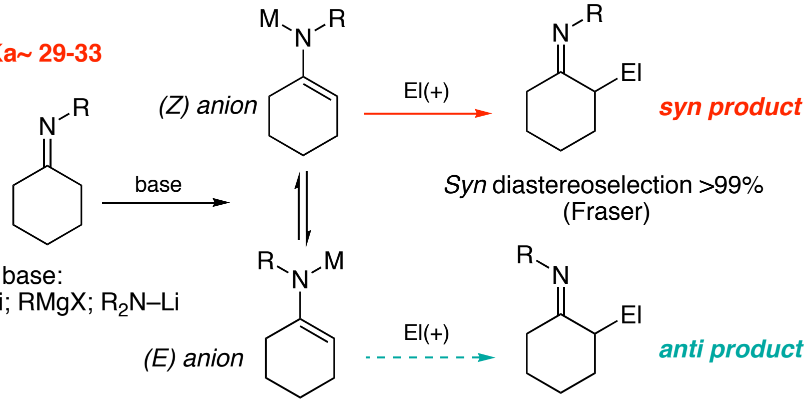
Whitesell *Synthesis*, **1983**, 517-535

Bregbreiter in *Asymmetric Synthesis*, **1983**; Vol 2, Chapter 9, pp 243-273

Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

Generation & Structure:

pKa~ 29-33



Syn diastereoselection >99% (Fraser)

The base:
R–Li; RMgX; R_2N–Li

Acidity Measurements: (Streitwiser, *JOC* **1991**, *56*, 1989; Fraser, *ibid.* **1985**, *50*, 3234):

Kinetic product geometry strongly favored the *syn* isomer (>99%) (Fraser)

Fraser, *JACS* ***1978***, *100*, 7999
Fraser, *Chem. Commun.* ***1979***, 47

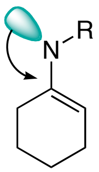
Solid State & Solution Structure:

X-ray structure reveals the following:

- ❐ Anion geometry is (Z)
- ❐ For M = Li, anion is delocalized rather than localized as pictured

Collum, *JACS* ***1984***, *106*, 4865-4869
Collum, *JACS* ***1985***, *107*, 2078-2082
Collum, *JACS* ***1986***, *108*, 3415-3422
Collum, *JACS* ***1993***, *115*, 789-790

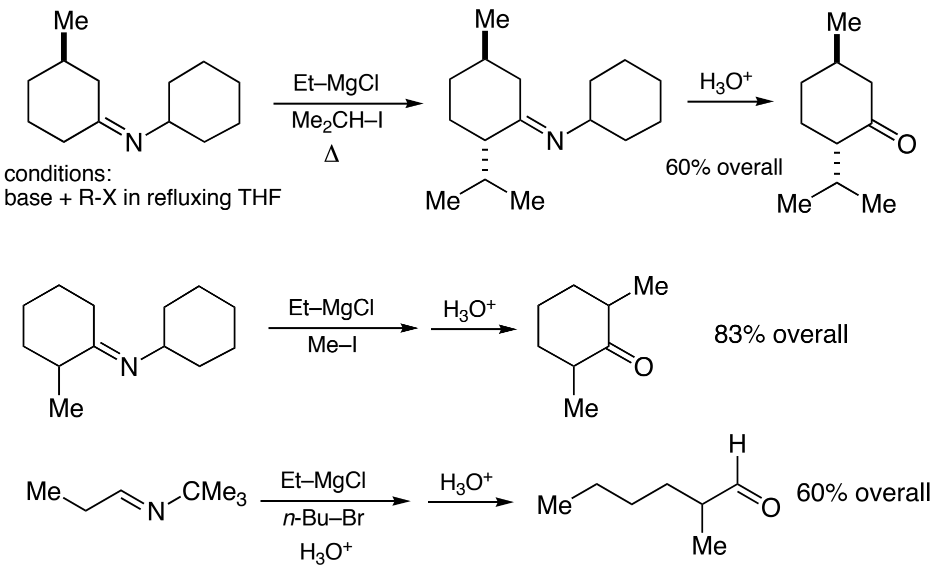
Geometry Rationalization:



nonbonding N-lone pair may be stabilized by delocalization into antibonding orbital of C=C.

Remember, (Z) geometry also favored for enol ethers

Representative Reactions:



conditions:
base + R-X in refluxing THF

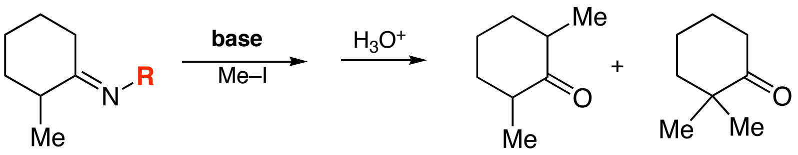
60% overall

83% overall

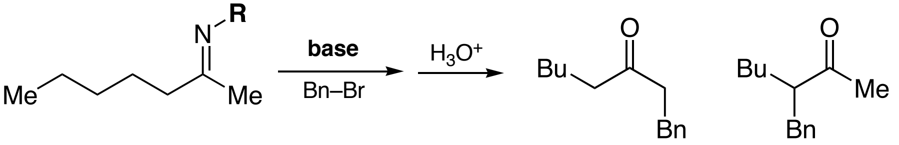
60% overall

Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

Nature of N-substituent, base, and solvent additive can play a role in deprotonation regioselectivity: Hosomi, JACS, 1982, 104, 2081-2082



R	base	ratio
–cyclohexyl	*s*-BuLi	10:90
$–NMe_2$	*s*-BuLi	100:0

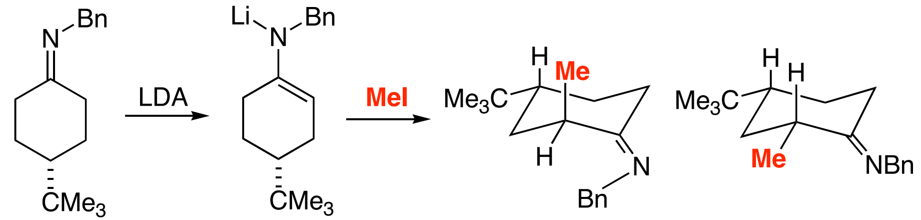


R	base	ratio
–cyclohexyl	*s*-BuLi	74:26
–cyclohexyl	*s*-BuLi	100:0

+ 1 equiv HMPA

Metalloenamines-2

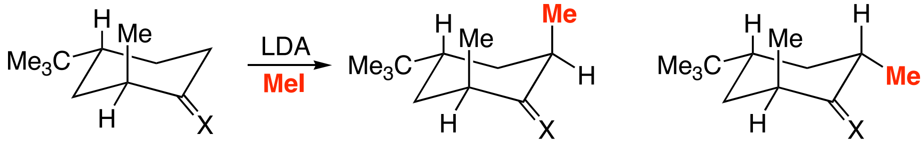
Stereoelectronic Issues:



Ratio, 97:3

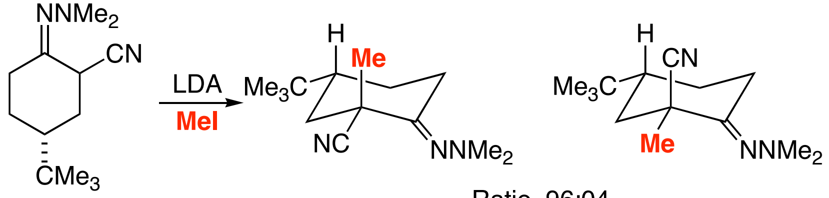
Fraser, *JACS* ***1978***, *100*, 7999 **(handout)**

Tendency for axial-chair alkylation is significantly greater that for ketones

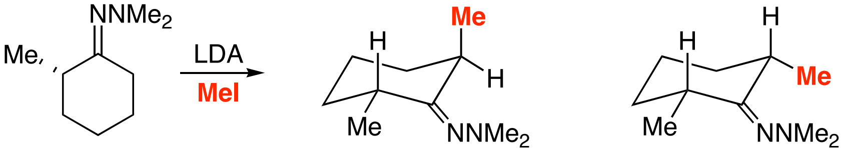


Fraser, *JACS* ***1978***, *100*, 7999 **(handout)**

X	Ratio
X = N-Bn	94:06
X = O	60:40



Ratio, 96:04



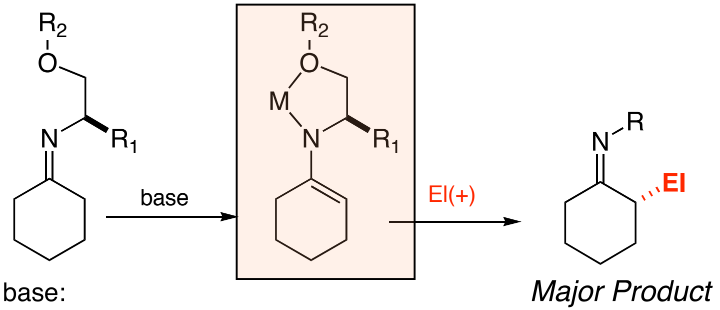
Ratio, 90:10

Collum, *JACS* ***1984***, *106*, 4865-4869 **(handout)**

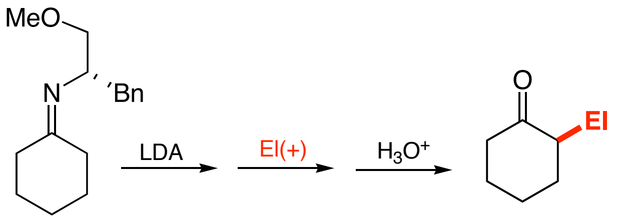
Chiral Metalloenamines:

early papers:
Meyers, *J. Am. Chem. Soc* ***1976***, *98*, 3032
Whitesell, *J. Org. Chem.* ***1978***, *42*, 377-378

full papers:
Meyers, *J. Org. Chem* ***1978***, *43*, 892
Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3081
Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3088



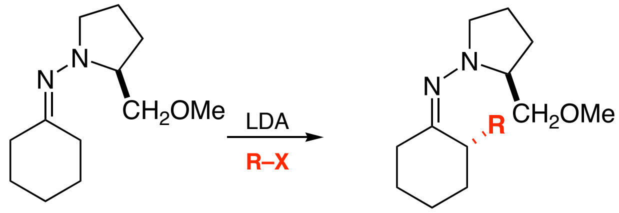
The base:
R–Li; RMgX; R$_2$N–Li



Meyers, *J. Am. Chem. Soc* ***1981***, *103*, 3081

R–X	ee
Me–I	87
Et–I	94
n-Pr–I	99

Chiral Metallated Hydrazones



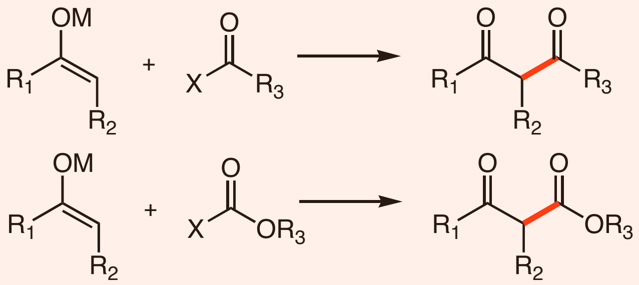
Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

Enolate Acylation & Carboxylation

The Reaction:

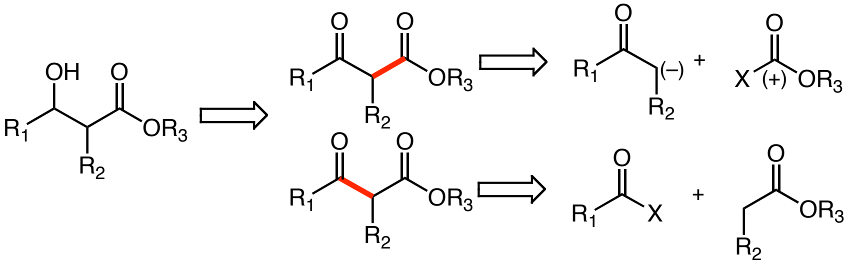
Acylation

Carboalkoxylation

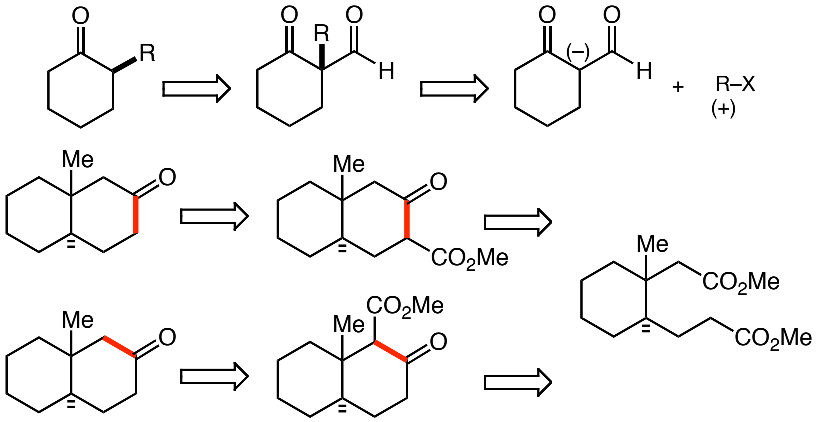


Situations where the reaction is employed:

- Acyl moiety is a constituent of the target structure:

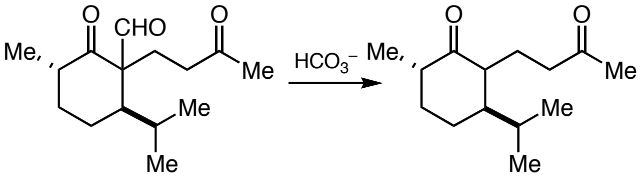


- Acyl moiety employed in assisting bond construction but not part of the target structure:



Deacylation: When an acyl residue is employed in the one of the illustrated bond constructions, it may then be removed by nucleophilic deacylation: Several examples are provided.

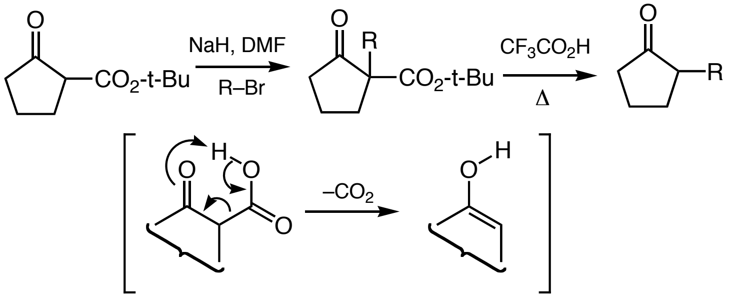
Deformylation:



competitive ring cleavage not a problem due to more electrophilic formyl C=O

Decarboxylation:

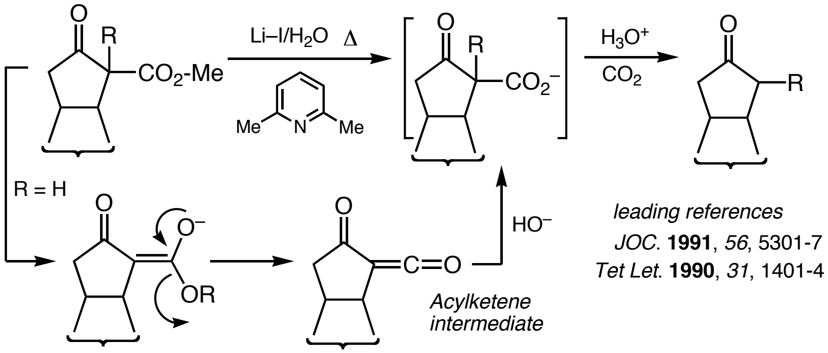
- Alkyl-Oxygen Cleavage: *tert*-butyl esters



Decarboxylation in this system is a sigmatropic rearrangement involving C=O participation

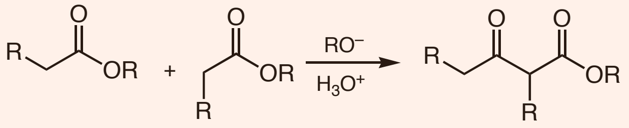
representative procedure: Henderson, *Synthesis* **1983**, 996

- Alkyl-Oxygen Cleavage: Methyl esters

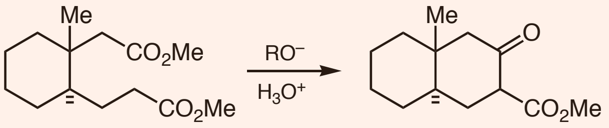


leading references
JOC. **1991**, *56*, 5301-7
Tet Let. **1990**, *31*, 1401-4

Claisen Condensation: Condensation of 2 esters

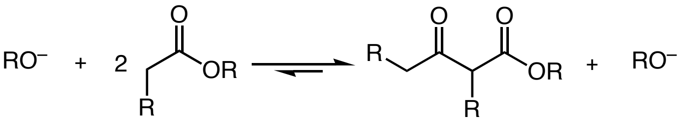


Intramolecular Variant: Dieckmann Condensation

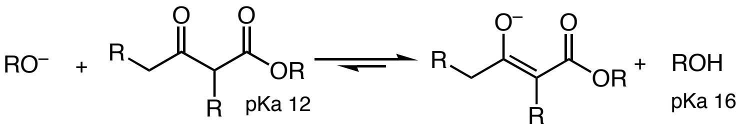


Strictly speaking, the Claisen and Dieckmann condensations are defined as condensations between ester enolates & ester electrophiles.
In this discussion, we choose to liberalize the classifcation to include ketone enolates as well.

Reaction Thermodynamics: Overall Keq ~ 1

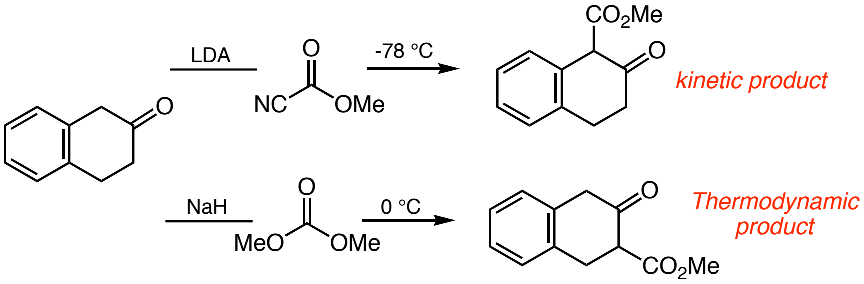


Final enolization Step: Keq ~ 10^{+4}



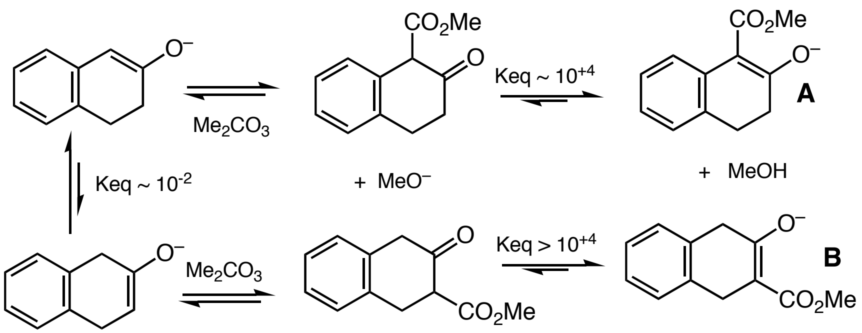
Contrary to popular belief, final enolization step does not render the process irreversible

Reaction Control Elements: These reactions can be manipulated to give either kinetic or thermodynamic control:

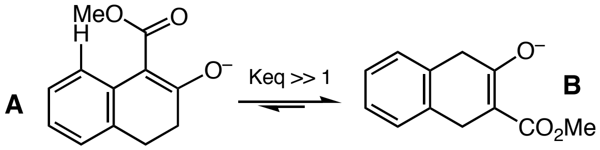


Analysis of the two processes:

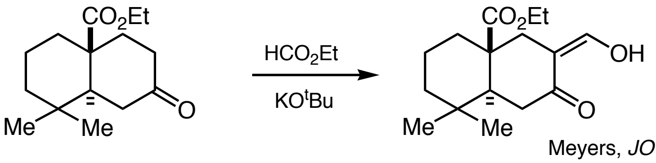
Conventional Carbomethoxylation: Equilibrium achieved between all species



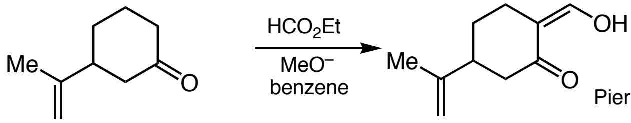
Critical issue: Product enolate **A** is significantly destabilized by peri-interaction with aromatic ring disrupting the required planarity of the delocalized enolate. Hence, the greater stability of **B** dictates the product.



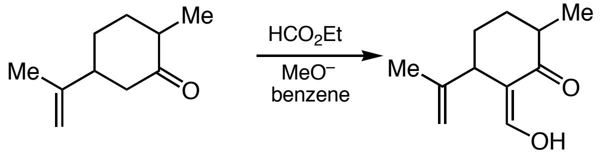
This type of control is general:



Meyers, *JOC* **1976**, *41*, 1976



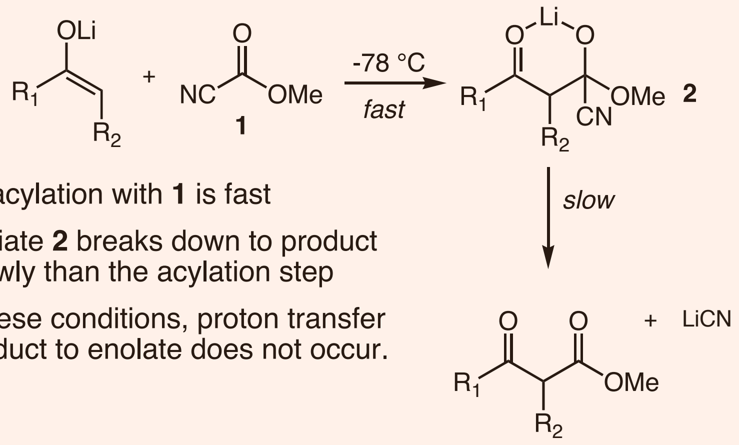
Piers, *Tet. Let* **1968**, 583



JACS **1965**, 87, 5728

Kinetic Enolate Acylation: The Mander Reagent

Kinetic Acylation: Methyl Cyanoformate (1):

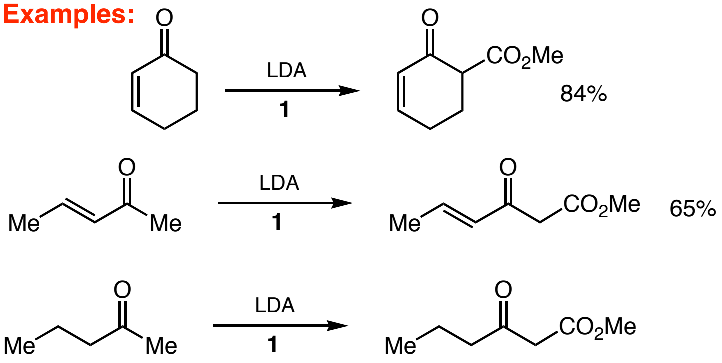


Enolate acylation with **1** is fast

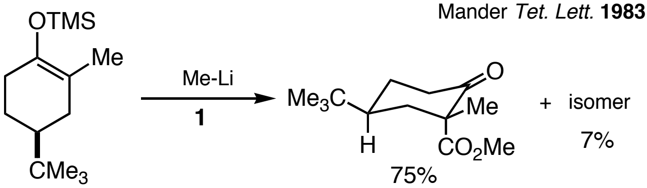
Intermediate **2** breaks down to product more slowly than the acylation step

Under these conditions, proton transfer from product to enolate does not occur.

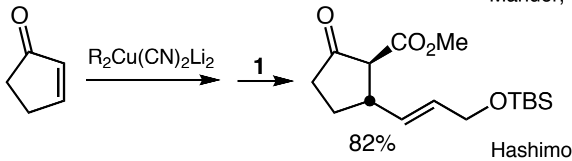
Examples:



Mander *Tet. Lett.* **1983**, *24*, 5425

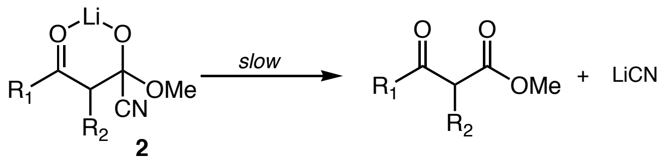


Mander, *SynLett.* **1990**, 169



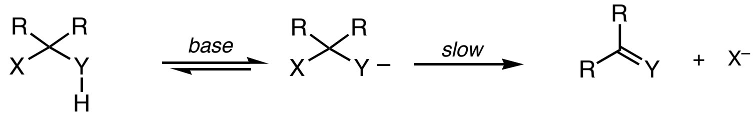
Hashimoto, *Chem. Lett.* **1989**, 1063

The Tetrahedral Intermediate 2; Why is it so stable?



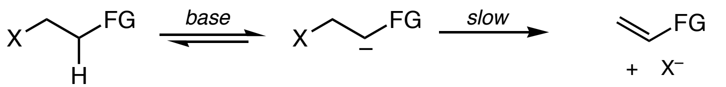
Consider this process in the broader context of elimination reactions of the E1cb classification where:

Y might be either C or some heteroatom
X might be various leaving groups such as CN, OR etc.



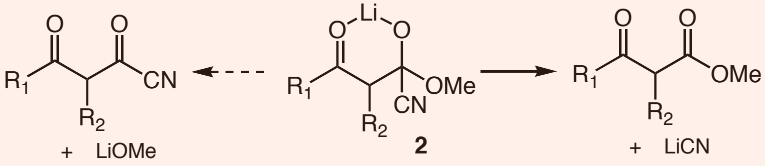
Data is available for the case where X = CN, OR & Y = carbanion:

Stirling, *Chem. Commun.* **1975**, 940-941



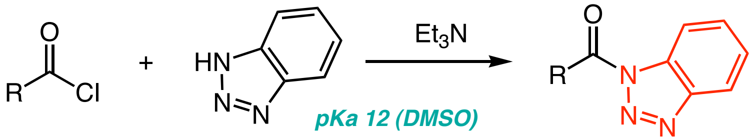
leaving grp (X)	pKa H–X	$\log \left[\frac{k_X}{k_{OPh}}\right]$
–OPh	10	1
–CN	9.5	<-7
$–C(Me)_2-NO_2$	~10	<-9
–OMe	16	-3.9

Above data makes the point that CN is a poor LG but it also leads one to the faulty conclusion that **2** should partition to acyl cyanide rather than methyl ester!



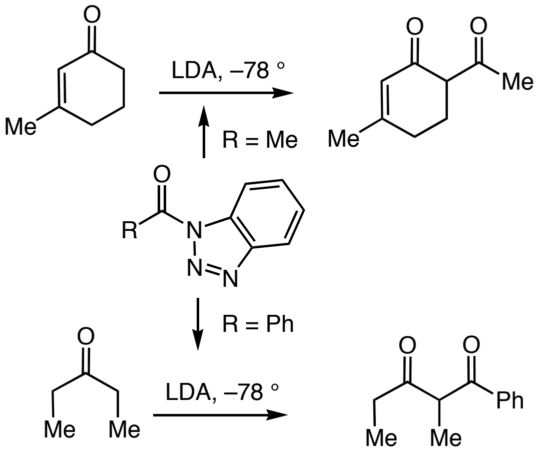
Kinetic Enolate Acylation: Acyl-Benztriazoles

N-Acylbenztriazoles: Excellent Acylating Agents

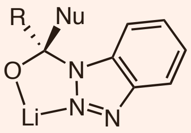


A. Katritzky, *SynLett* **2005,** 1656-1665
Chem. Eur. J. **2003,** *9*, 4586-4593

Compounds nicely crystalline & bench stable



94% yield
Ideal stoichiometry employed

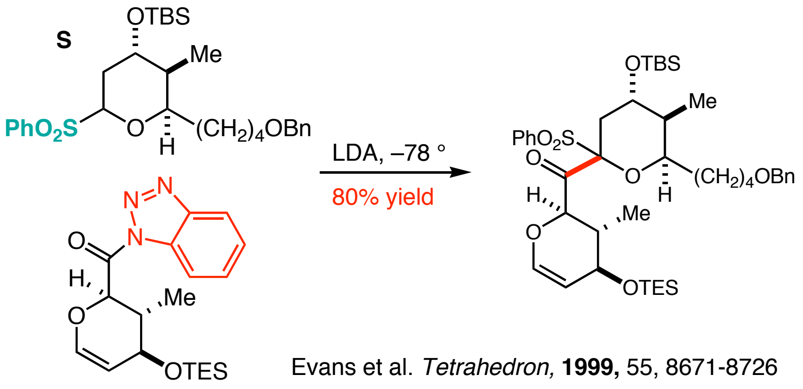


stabilized tetrahedral intermediate

86% yield

Katritzky, *J. Org. Chem.* **2000,** 65, 3679

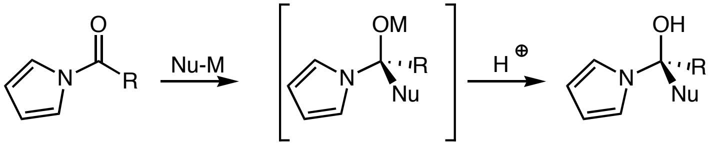
The only complex application to date



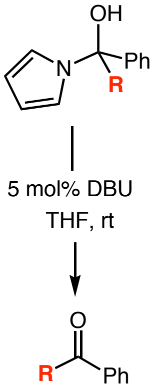
Evans et al. *Tetrahedron,* **1999,** 55, 8671-8726

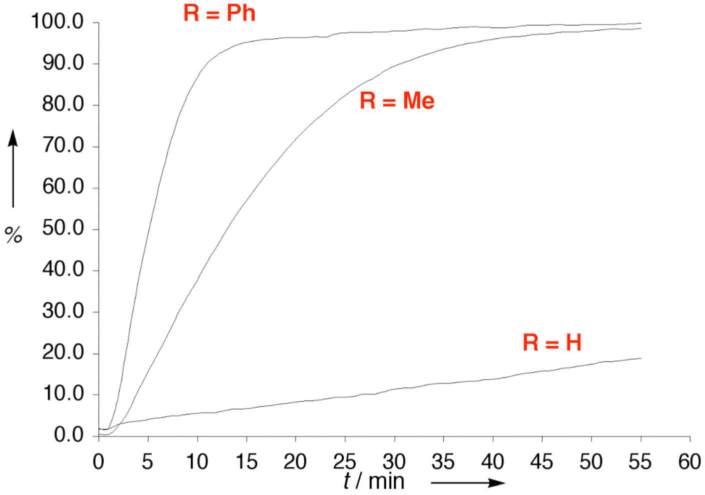
N-AcylPyrroles: Exceptionally Stable Tetrahedral Intermediates

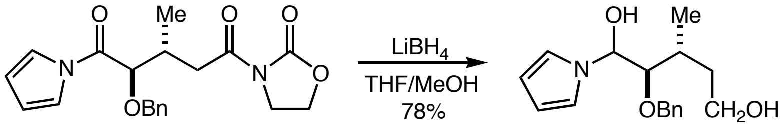
Evans et al. *Angew. Chem. Int. Ed.*, **2002,** *41*, 3188.

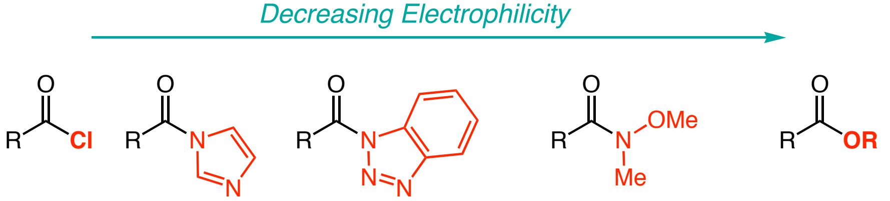


Tetrahedral Intermediates may be Isolated



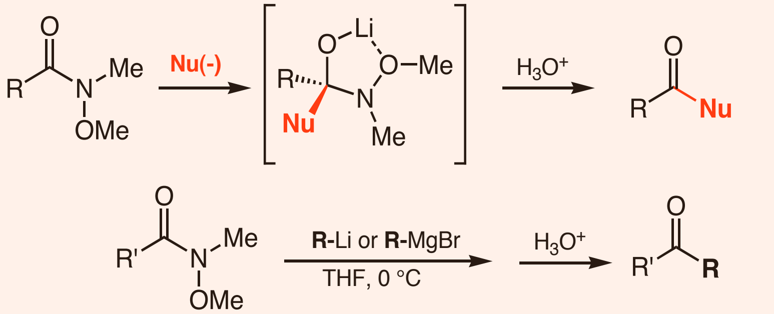






Carbon Acylation with *N*-Methoxy-*N*-methylamides

Acylating agents can be desiged where the tetrahedral intermediate exhibits exceptional stability:



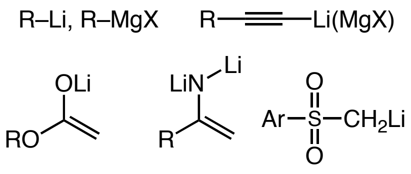
R = Me, n-Bu, or Ph; yields > 90%

Weinreb *Tet. Lett.* **1981**, *22*, 3815.

Nucleophiles:

Acceptable

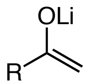
R–Li, R–MgX



DIBAL LiAlH$_4$ LiB(R)$_3$H

Unacceptable

R–ZnX & other colalent metal alkyls

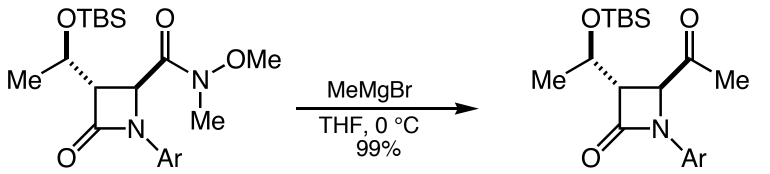


other colalent metal enolates

Weak hydride reagents: NaBH$_4$

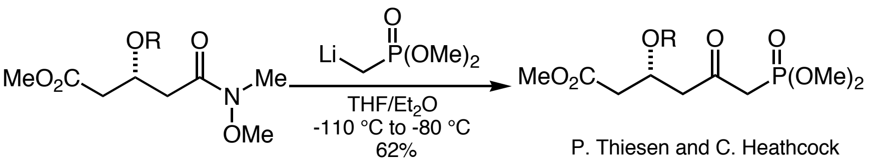
An excellent review on all aspects of Weinreb amide chemistry:
M. Sibi, *Organic Preparations and Procedures Int.*, **1993**, *25 (1)*, 15-40.

Representative Organometals:

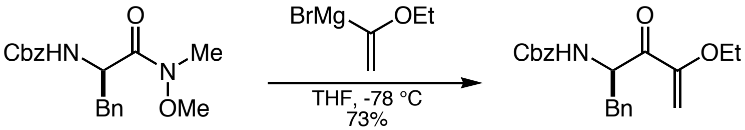


Several other examples reported.

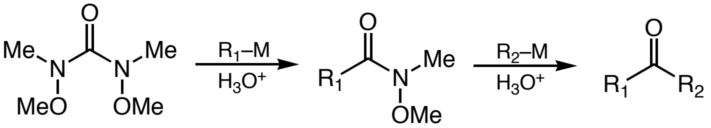
J. Prasad and L. Liebeskind
Tetrahedron Lett. **1987**, *28*, 1857.



P. Thiesen and C. Heathcock
J. Org. Chem. **1988**, *53*, 2374.

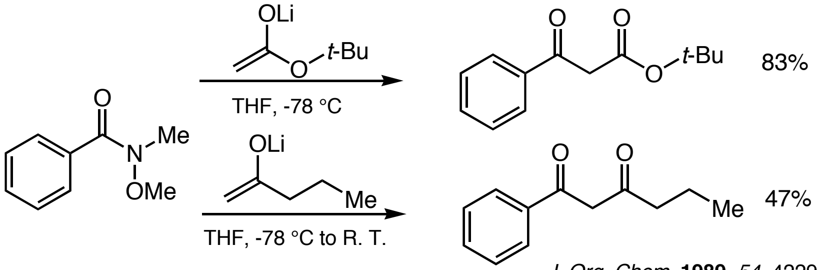


M. Angelastro, N. Peet and P. Bey
J. Org. Chem. **1989**, *54*, 3913.



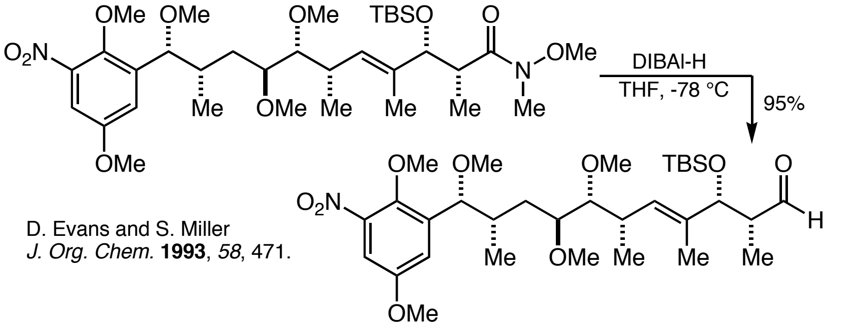
W. Wipple, H. Reich
J. Org. Chem. **1991**, *56*, 2911-2.

Enolates and Metalloenamines:



J. Org. Chem. **1989**, *54*, 4229.

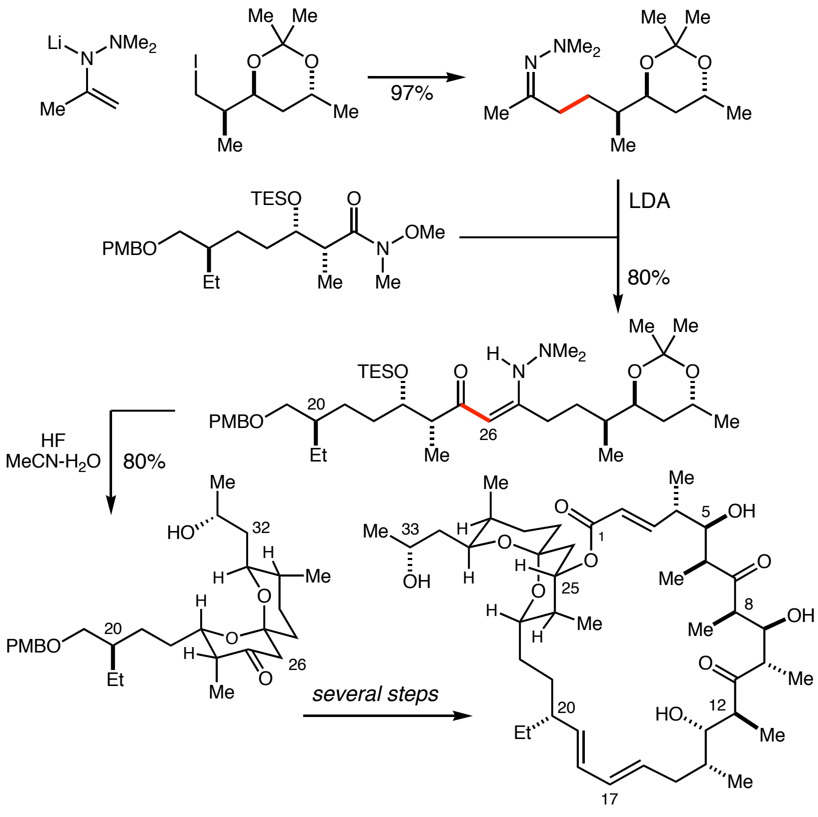
Hydride Reductions:



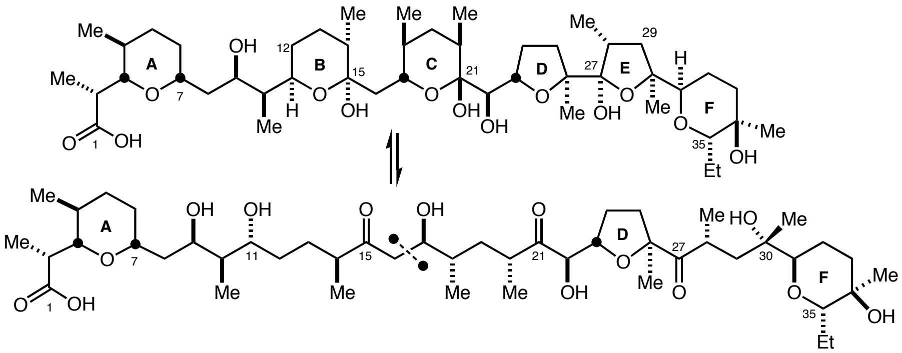
D. Evans and S. Miller
J. Org. Chem. **1993**, *58*, 471.

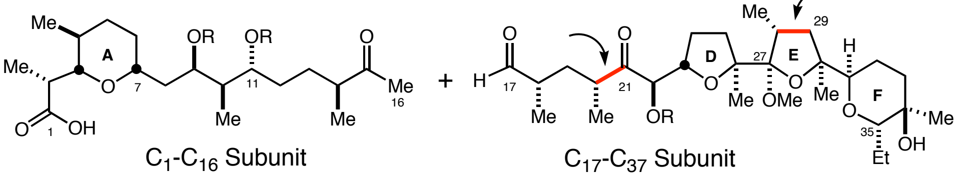
Carbon Acylation with *N*-Methoxy-*N*-methylamides-2

The Rutamycin B Synthesis, . *JACS.* **1993**, *115*, 11446-11459

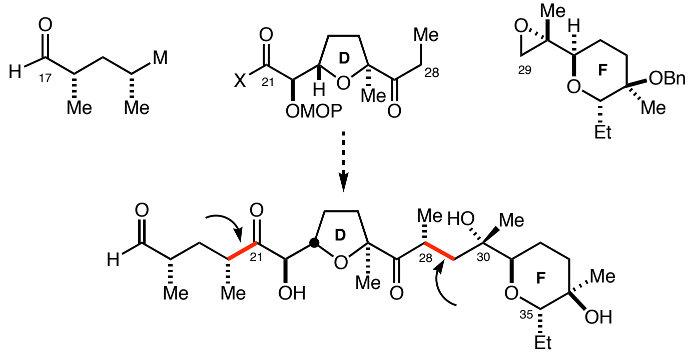


The X-206 Synthesis, *S. L. Bender, Ph. D. Thesis, Harvard University, 1986*

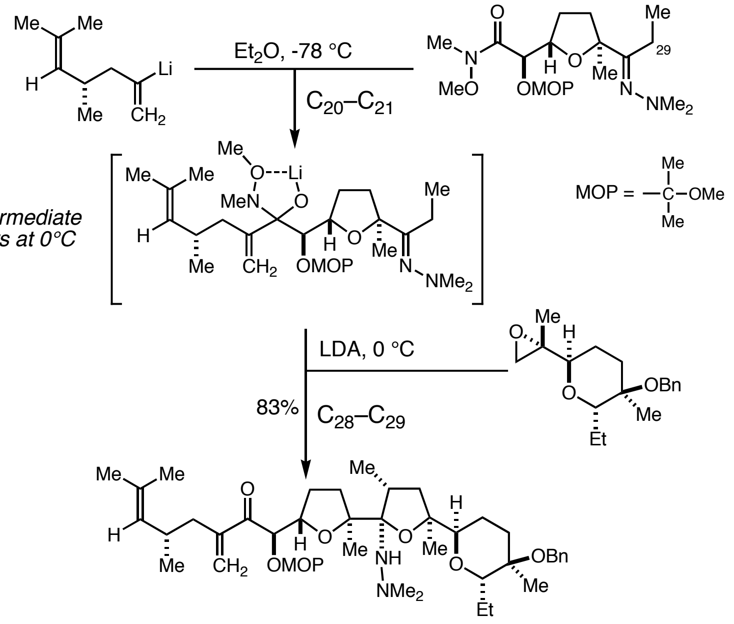




Problem is to control C=O reactivity on central D-fragment



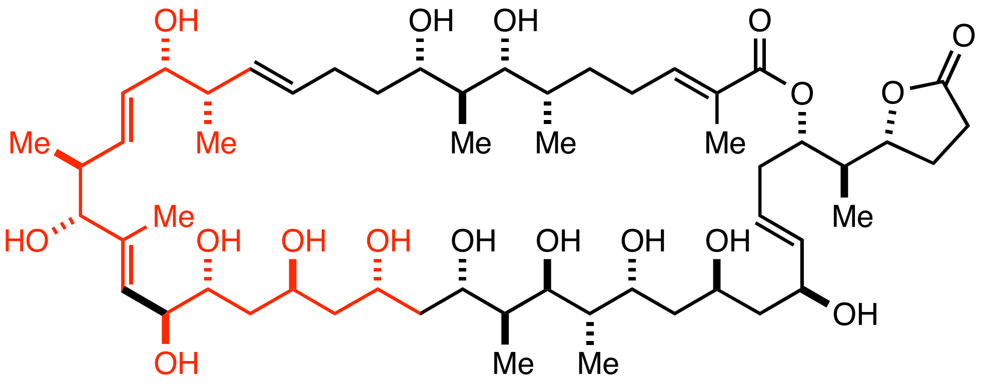
The Solution:



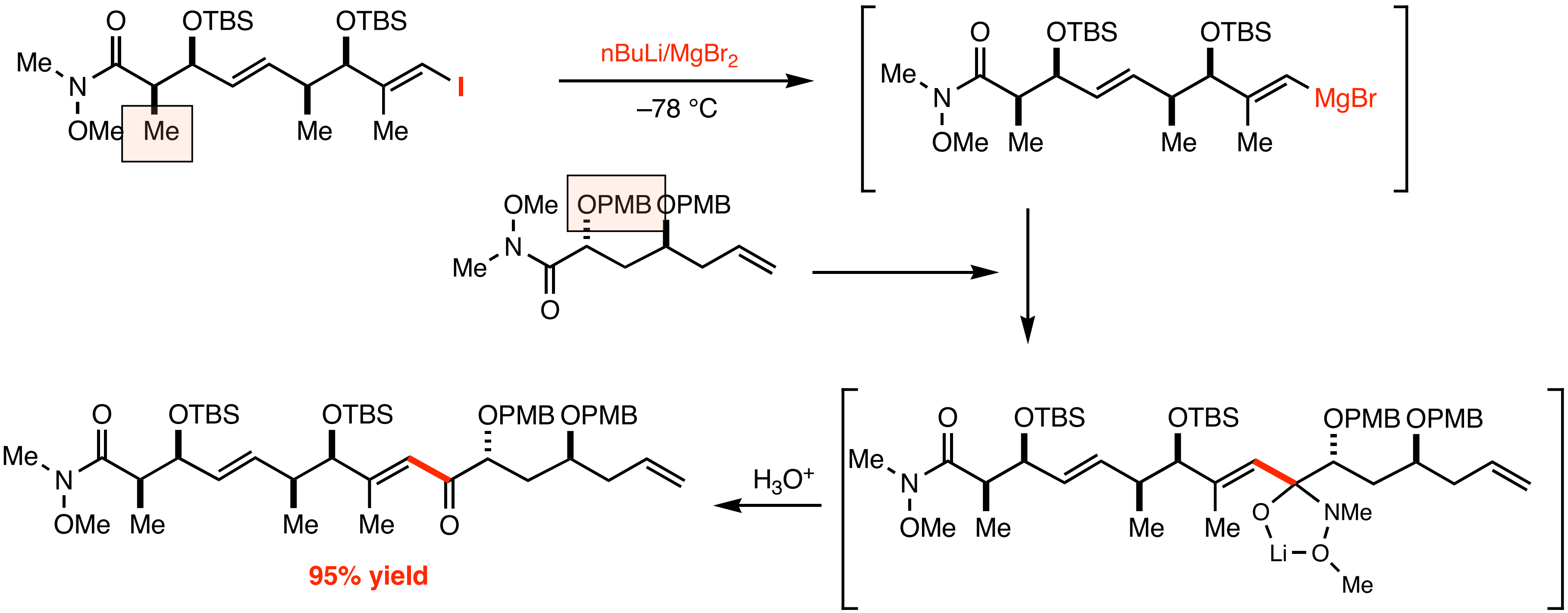
tetrahedral intermediate stable for hours at 0°C

Evans, Bender, Morris J. Am. Chem. Soc. **1988**, *110*, 2506.

Weinreb Amide Coupling Studies



Oasomycin

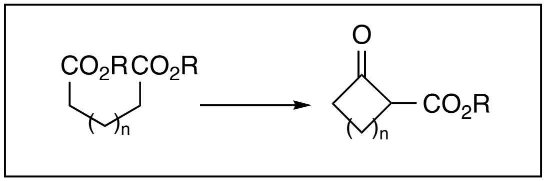


Pavel Nagorny, Angew. Chem. Int Ed, in Press

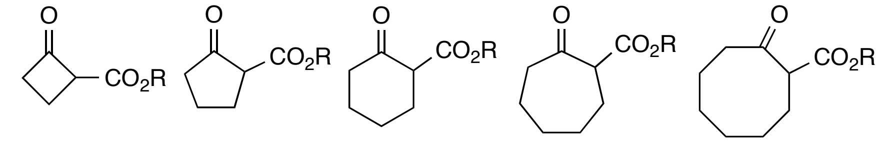
Intramolecular Enolate Acylation–Dieckmann Condensation

The Dieckmann Condensation

Reviews: Schaefer, Bloomfield, *Organic Reactions* **1967**, *15*, 1.
Davis & Garratt, *Comprehensive Organic Synthesis* **1991**, *2*, 806-829



Accesible Ring Sizes



not viable

excellent

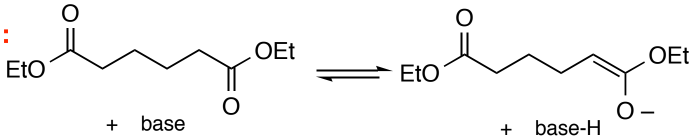
excellent

acceptable

situation dependent
high dilution required

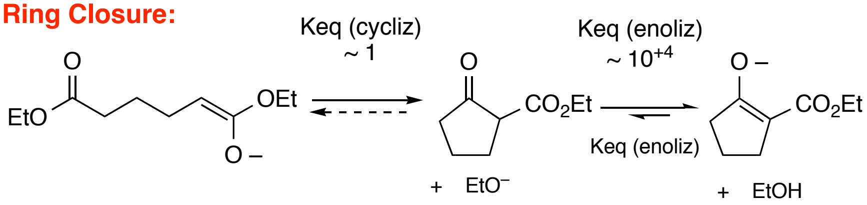
The individual steps:

Enolization:



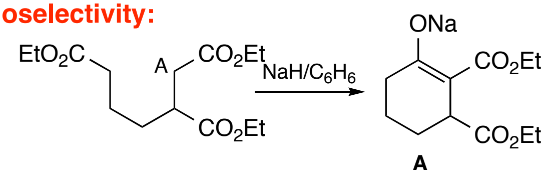
A variety of bases may be considered for the enolization step.
Either alkoxide or a non-nucleophilic base such as NaH are commonly used.
Choice of base can be important (Vide infra).

Ring Closure:

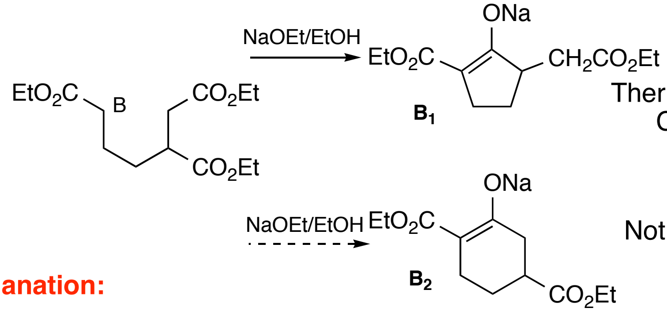


Statements claiming that the final enolization step renders the process irreversible are simply incorrect.

Regioselectivity:



Kinetic Control?



Thermodynamic
Control?

Not observed

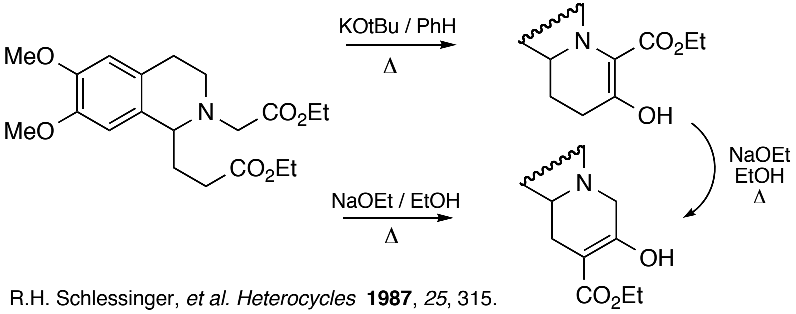
Explanation:

Enolization at (A) preferred on basis of inductive effects. Hence, Path A preferred in kinetically controlled situation

Enolates (B1) and (B2) both more stable than enolate (A)

Under equilibrating conditions (B1) appears to be preferred over (B2)

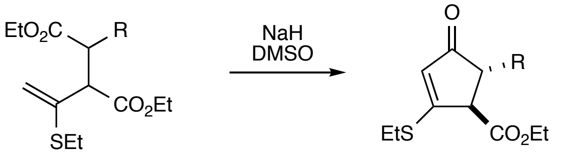
The effect of beta heteroatoms: classical kinetic vs. thermodynamic control



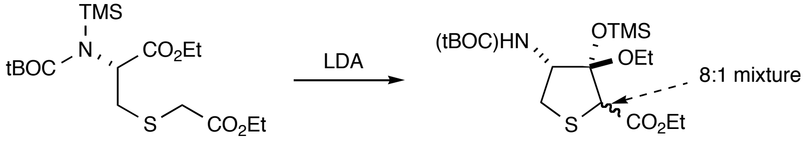
R.H. Schlessinger, *et al. Heterocycles* **1987**, *25*, 315.

Intramolecular Enolate Acylation–Dieckmann Condensation

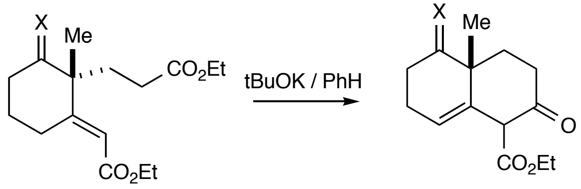
Miscellaneous Dieckmann Reactions of Potential Interest



R.Danieli, *J.Org.Chem.* **1983**, *48*, 123.

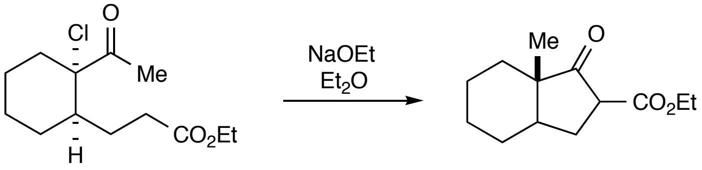


J.L. Adams, *J.Org.Chem.* **1985**, *50*, 2730.



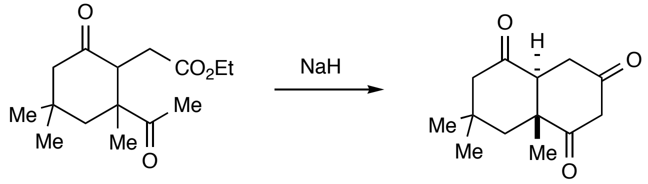
Peterset, *Recl.Trav.Chim.Pays-Bas* **1977**, *96*, 219.

Deduce the mechanism of this multistep process.

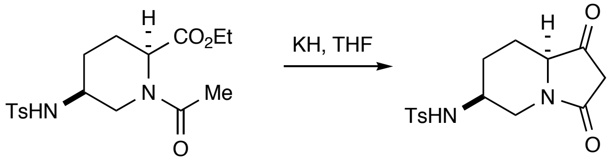


G.Stork and Co-workers, *J.Am.Chem.Soc.* **1960**, *82*, 4315.

Intramolecular Ketone Acylation

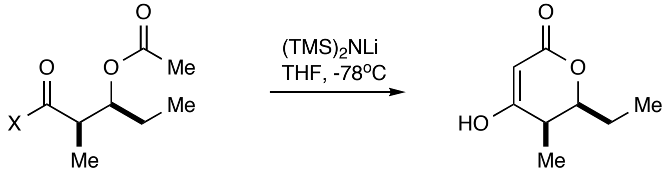


H.-J. Liu and Co-workers, *Tet.Lett.* **1982**, *23*, 295.



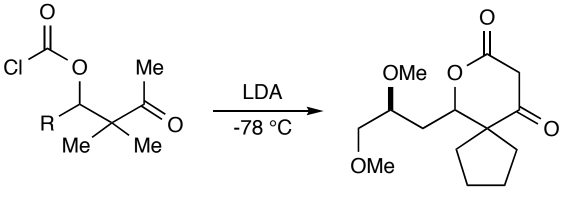
no loss of stereochemical integrity

T.M. Harris and Co-workers, *J.Org.Chem.* **1984**, *49*, 3681.



When X = NR$_2$, this is a good reaction, but when X = OR, it is a poor reaction.

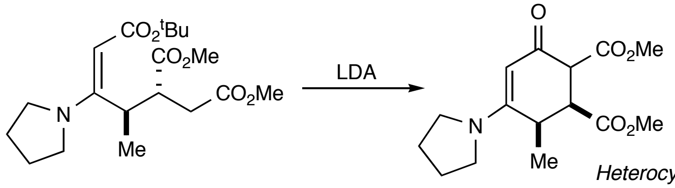
S.Brandawge and Co-workers, *Tet.Lett.* **1992**, *33*, 3025.



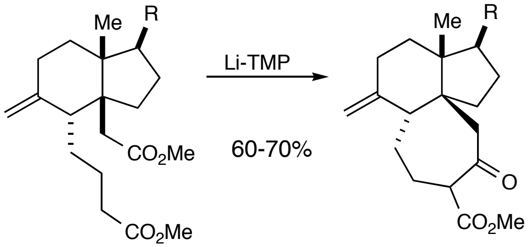
Kocienski and Co-workers, *Tet.* **1990**, *46*, 1716

Intramolecular Enolate Acylation–Dieckmann Condensation

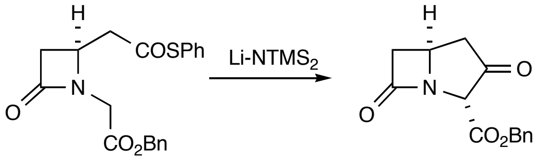
Kinetically controlled Cyclizations



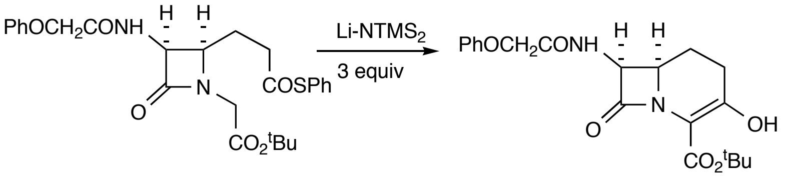
Heterocycles, **1987**, *25*, 315



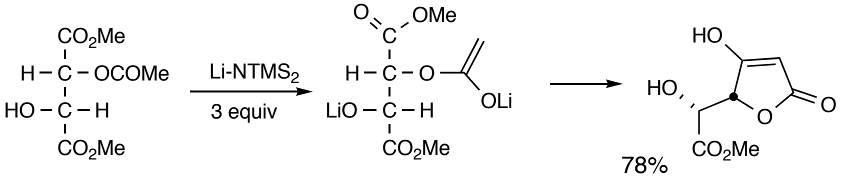
JACS, **1979**, *101*, 5060



Tet. Let, **1981**, *22*, 3883

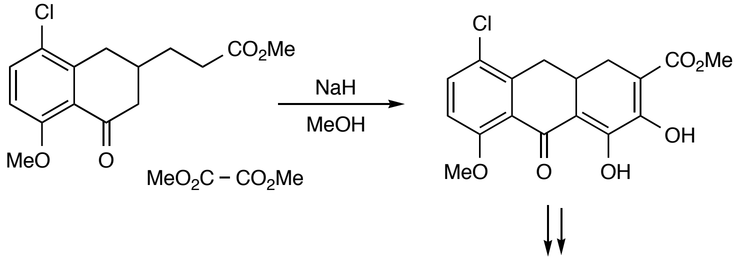


Hatanaka, *Tet. Let*, **1983**, *24*, 4837

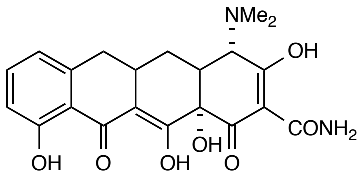


Brandange, *JOC*, **1984**, *49*, 927

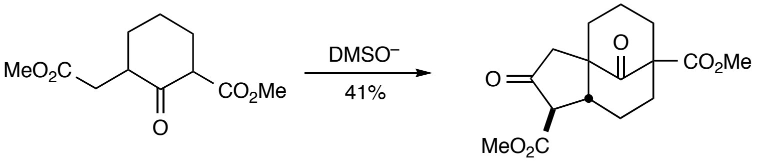
Multistep Condensations

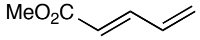


Woodward, *JACS*, **1962**, *84*, 3222

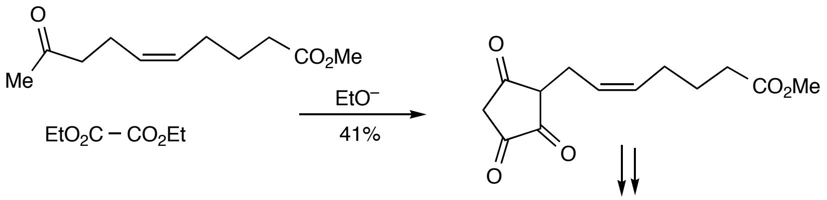


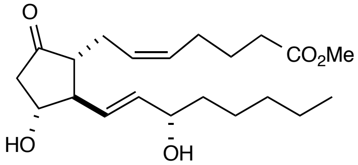
6-demethyl-6-deoxy-tetracycline





Danishefsky, *JACS*, **1973**, *95*, 2410





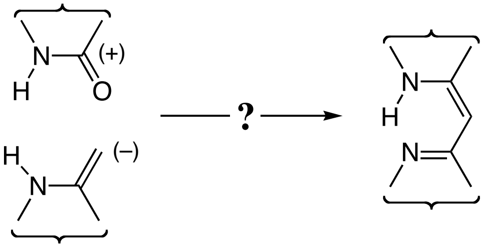
Prostaglandin E2

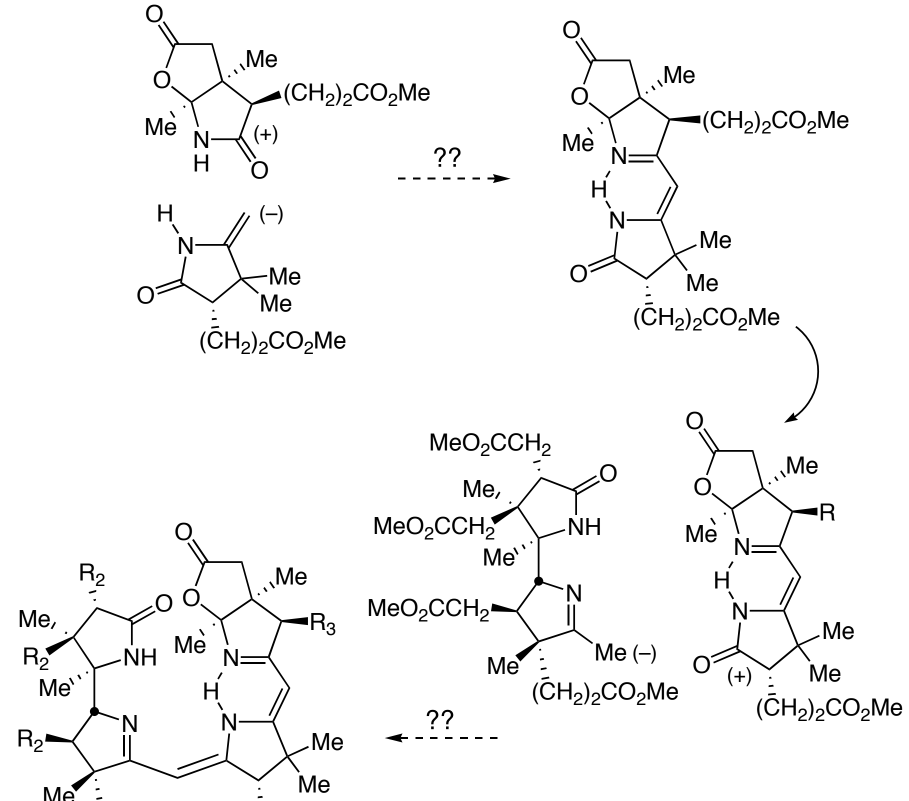
Sih, *JACS*, **1975**, *97*, 865

The Eschenmoser Coupling Reaction

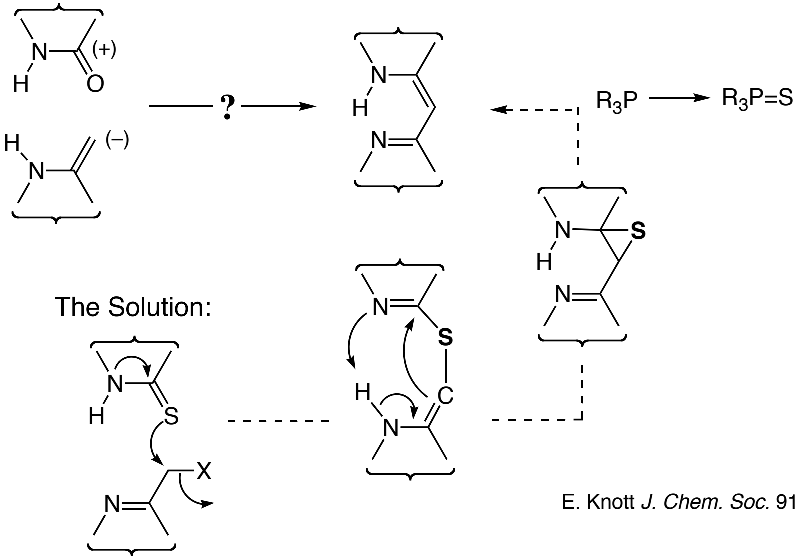
Key Bond Construction Needed for the B12 Synthesis:

The Problem:



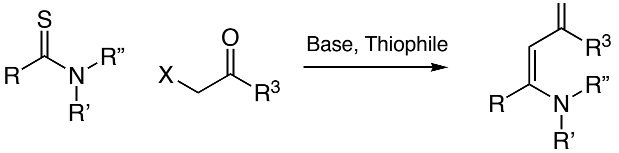


A. Eschenmoser *Science* **196**, 1410 (1977)



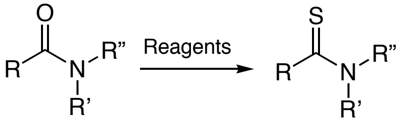
E. Knott *J. Chem. Soc.* 916 (1955)

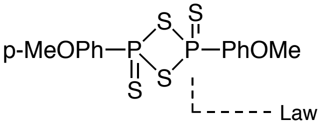
The General Reaction: Acylation of an Amide C=O



Key papers:
A. Eschenmoser *Helv. Chim. Acta.* **54**, 710 (1971)
A. Eschenmoser *Angew. Chem., Int. Ed. Engl.* **6**, 866 (1967)
A. Eschenmoser *Angew. Chem., Int. Ed. Engl.* **8**, 343 (1969)
Review: Trost *Comp. Org. Synth.* Vol. 2, Ch. 3.7 (1991)

The Thioamide component:





P_4S_{10}	JOC 46, 3558 (1981), Synthesis 149 (1973)
Lawesson's Reagent	Bull. Chim. Soc. Belg. 87, 229 & 293 (1978)
P_4S_{10}, Et_3N or $NaHCO_3$	Indian J. Chem., Sect. B 14, 999, (1976) JACS 102, 2392 (1980)
$RCS_2R' + R_2NH$ → Thioamide	Chem. Ind. (London) 803 (1974)
Imidate $+H_2S$ → Thioamide	Angew. Chem. 79, 865 (1967)

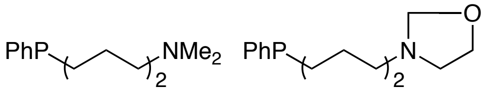
The Eschenmoser Coupling Reaction-2

Reagents for the Reaction:

Bases:
Inorganic: $MHCO_3$, MOH, MH, MOR
Organic: R_3N, N-methylmorpholine, buffered solutions

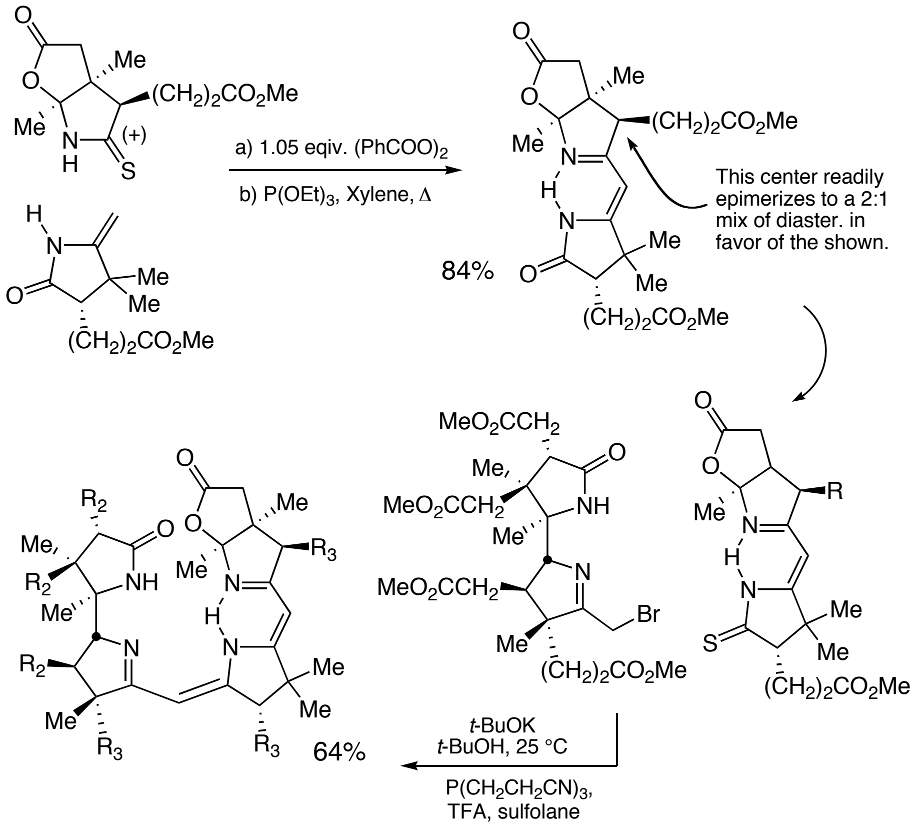
Thiophiles: Ar_3P, R_3P, $(RO)_3P$

Combination:

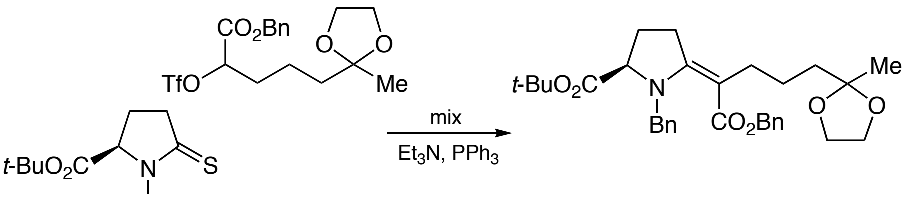


H. Rapoport *J. Org. Chem.* **46**, 3230 (1981)
A. Eschenmoser *Helv. Chim. Acta.* **54**, 710 (1971)

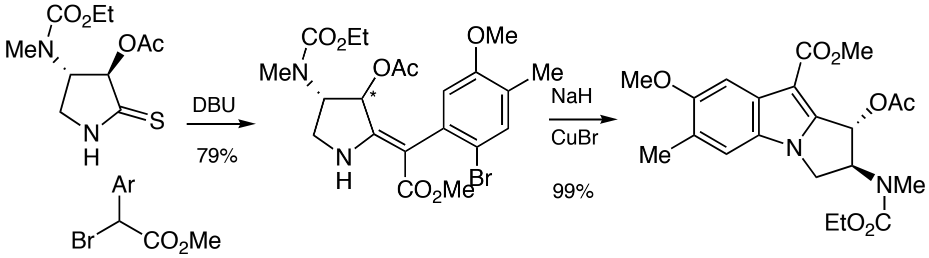
A. Eschenmoser *Science* **196**, 1410 (1977)



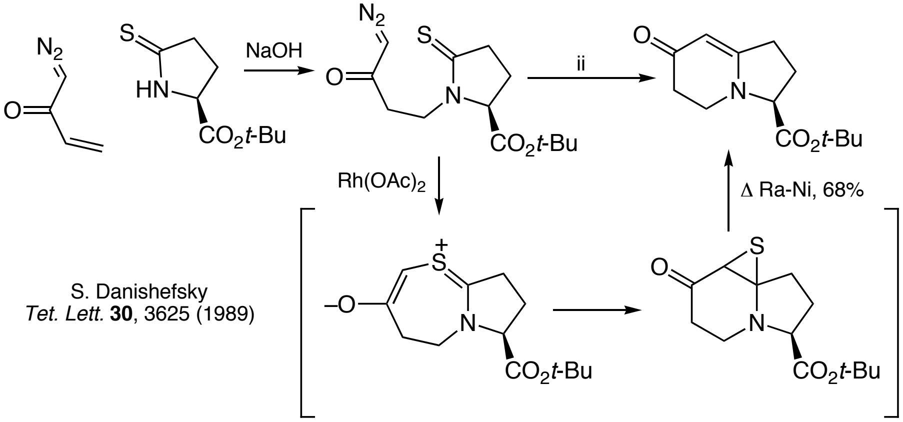
This center readily epimerizes to a 2:1 mix of diaster. in favor of the shown.



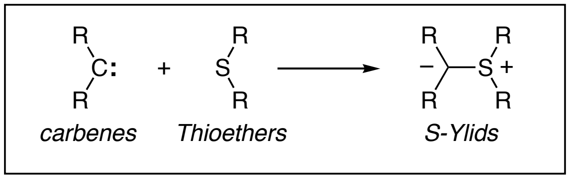
H. Rapoport *J. Org. Chem.* **46**, 3230 (1981)



T. Kametani *J. Chem. Soc., Perkin Trans. I* 1607 (1980)



S. Danishefsky
Tet. Lett. **30**, 3625 (1989)



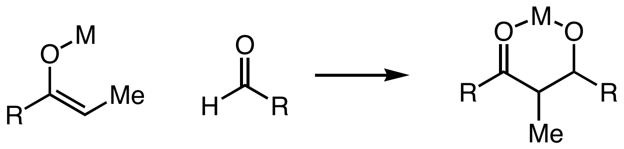
http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 27

The Aldol Reaction–1



- Polyketide Biosynthesis
- Historical Perspective on the Aldol Reaction
- Aldol Diastereoselectivity
- Enolate Diastereoface Selectivity
- Absolute Control in the Aldol Process

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Monday
November 27, 2006

Suggested Reading

Stereoselective Aldol Reactionsw in the Synthesis of Polyketide natural Products, I. Paterson et al. in Modern Carbonyl Chemistry, pp 249-297, J. Otera, Ed. Wiley VCH, **2000**

Ager, D. J., I. Prakash, et al. (**1997**). “Chiral oxazolidinones in asymmetric synthesis.” Aldrichimica Acta 30(1): 3-12

Other Useful References

Evans, D. A., J. V. Nelson, et al. (**1982**). “Stereoselective Aldol Condensations.” Top. Stereochem. 13: 1.

Heathcock, C. H. (**1984**). The Aldol Addition Reaction. Asymmetric Synthesis. Stereodifferentiating Reactions, Part B. J. D. Morrison. New York, AP. 3: 111.

Oppolzer, W. (**1987**). “Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis.” Tetrahedron **43**: 1969.

Heathcock, C. H. (**1991**). The Aldol Reaction: Acid and General Base Catalysis. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 133.

Heathcock, C. H. (**1991**). The Aldol Reaction: Group I and Group II Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 181.

Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

Franklin, A. S. and I. Paterson (**1994**). “Recent Developments in Asymmetric Aldol Methodology.” Contemporary Organic Synthesis 1: 317-338.

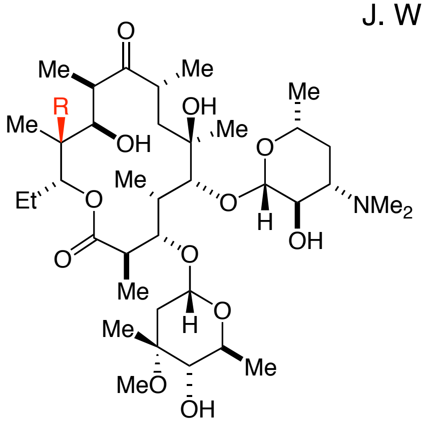
Cowden, C. J. and I. Paterson (**1997**). “Asymmetric aldol reactions using boron enolates.” Org. React. (N.Y.) 51: 1-200.

Nelson, S. G. (**1998**). “Catalyzed enantioselective aldol additions of latent enolate equivalents.” Tetrahedron: Asymmetry 9(3): 357-389.

Mahrwald, R. (**1999**). “Diastereoselection in Lewis-acid-mediated aldol additions.” Chem. Rev. 99(5): 1095-1120.

The Aldol Reaction: Polypropionate Biosynthesis

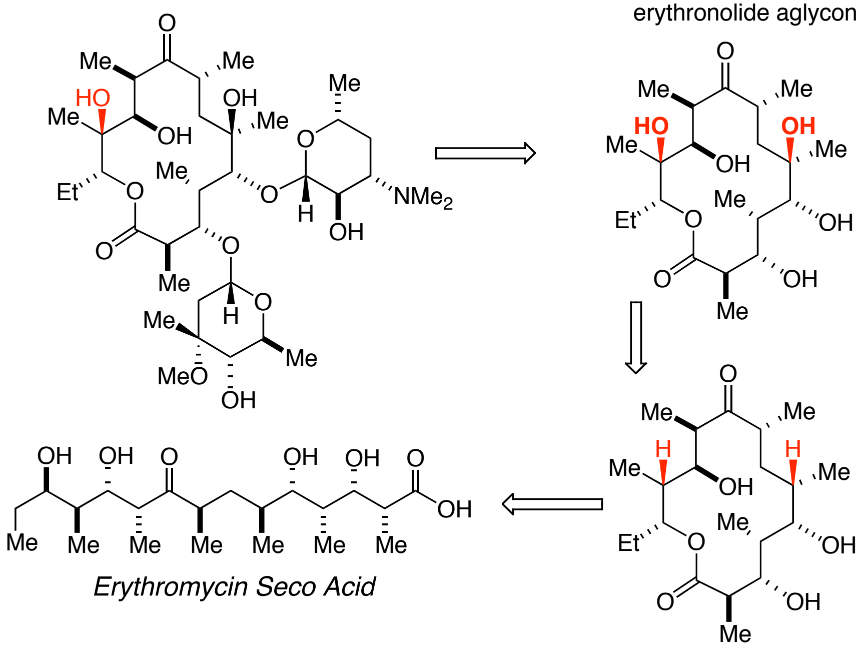
"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations."
J. W. Cornforth



J. W. Cornforth
Nobel Prize, 1975

Erythromycin A, R = OH
Erythromycin B, R = H

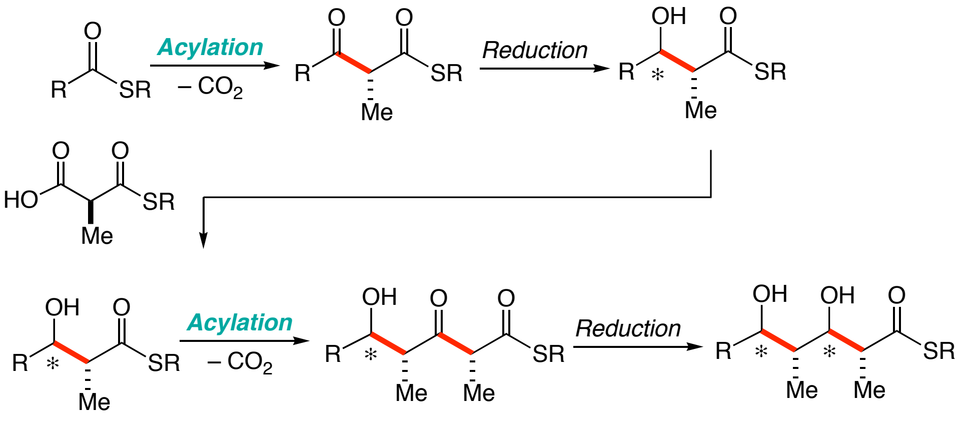
Retro-biosynthesis: Erythromycin A

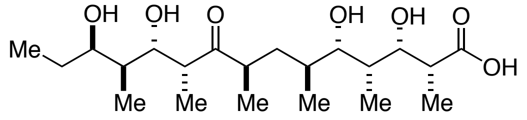


Erythromycin Seco Acid

Recent overview: Staunton, "Polyketide biosynthesis: a millennium review." *Nat. Prod. Rep.* **2001**, *18*, 380-416.

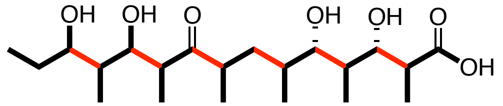
Polypropionate Biosynthesis: The Elementary Steps





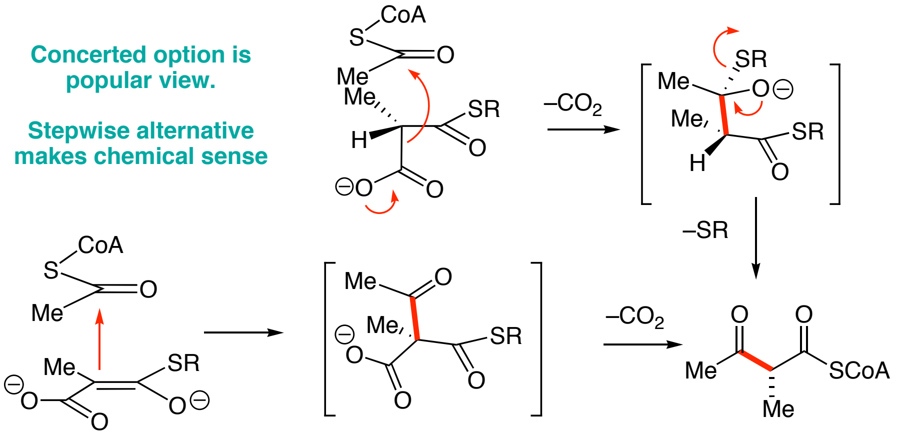
Erythromycin Seco Acid

The 7 Propionate Subunits



Acylation Event

The timing of the decarboxylation event is not yet known



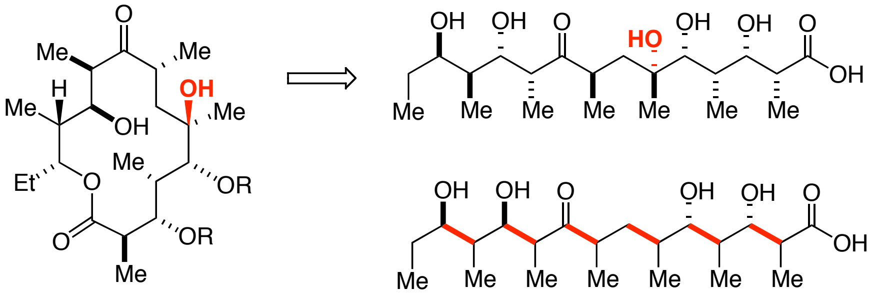
Concerted option is popular view.

Stepwise alternative makes chemical sense

See Lecture 24; page 24-08 for first laboratory example

Polypropionate Biosynthesis: A Laboratory Simulation

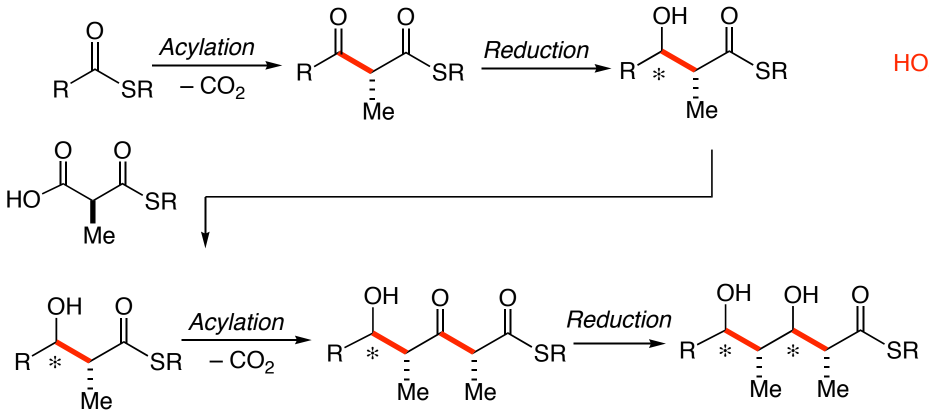
Polypropionate & Polyacetate Biosynthesis: Develop a Laboratory Simulation



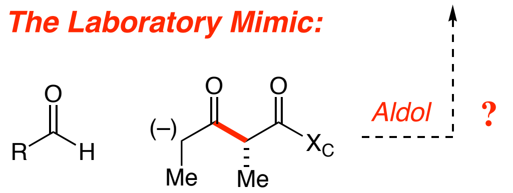
Erythrolide B

The 7 Propionate Subunits

Polypropionate Biosynthesis: The Elementary Steps

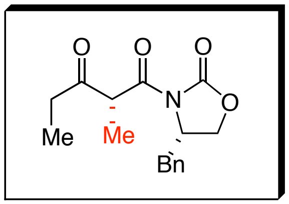


The Laboratory Mimic:

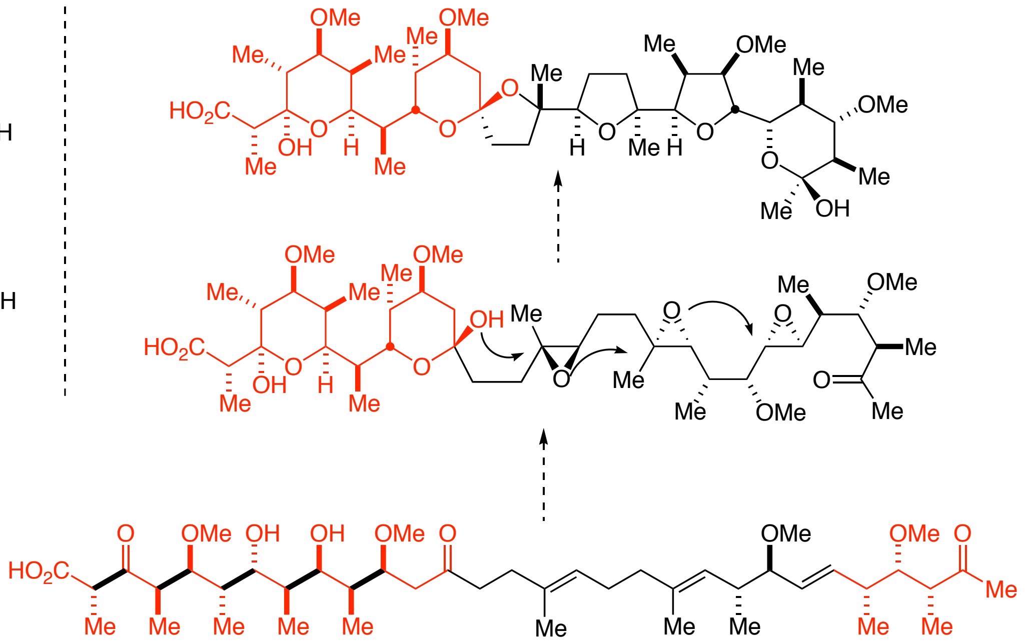


See Lecture 26; page 4:
*with M. Ennis JACS **1984**, 106, 1154.*

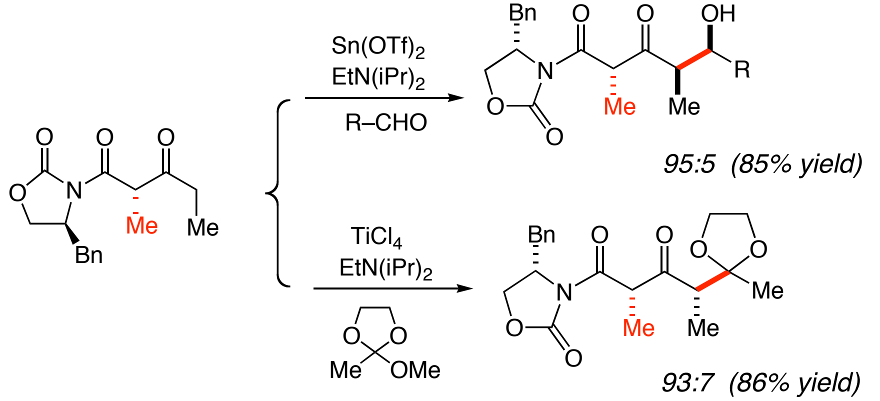
Dipropionyl Synthon



Latter Stages of Lonomycin Biosynthesis



Cane, Celmer, Westley *JACS* **1983**, *105*, 3594



with Ratz, Huff, & Sheppard, *JACS* **1995**, *117*, 3448

The Aldol Reaction: Early Contributions

General Reviews of the Aldol Literature:

Mukaiyama in *Organic Reactions*, **1982**; Vol 28, pp 203-331
Evans in *Topics in Stereochemistry*, **1982**; Vol 13, pp 1-115
Heathcock in *Asymmetric Synthesis*, **1984**; Vol 3, pp 111-212

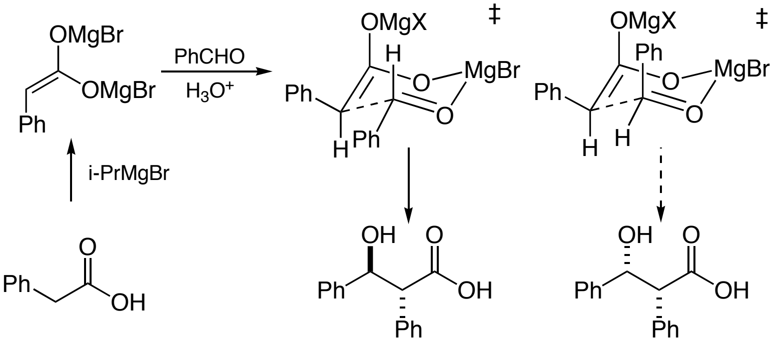
Comprehensive Organic Synthesis, **1991**; Vol 2

Group **I** & **II** metal enolates: Heathcock; Chapter 1.6, pp 181
Group **III** metal enolates: Masamune; Chapter 1.7, pp 239
Transition metal enolates: Paterson; Chapter 1.9, pp 301

Control relative stereochemical relationships

Zimmerman 1957:

Proposed chair-like geometry for the Ivanov Reaction



ratio, 75:25

Zimmerman recognized that diastereoselection should be a function of the relative sizes of the substituents on the carbonyl component.

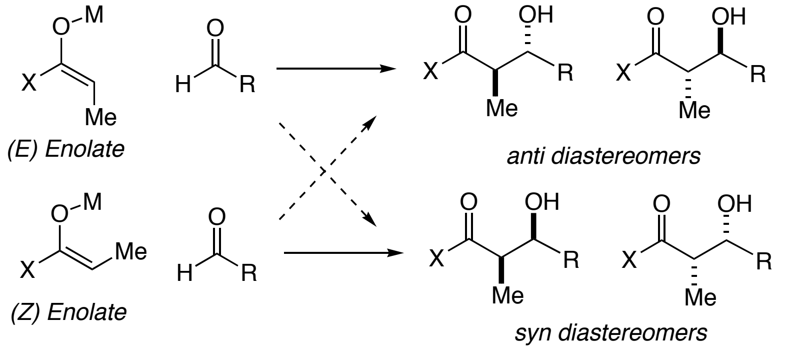
He also speculated on the role that the metal center might play in controlling the process.

The only flaw in the study was that he failed to determine whether the aldol adducts were stable to the reaction conditions.

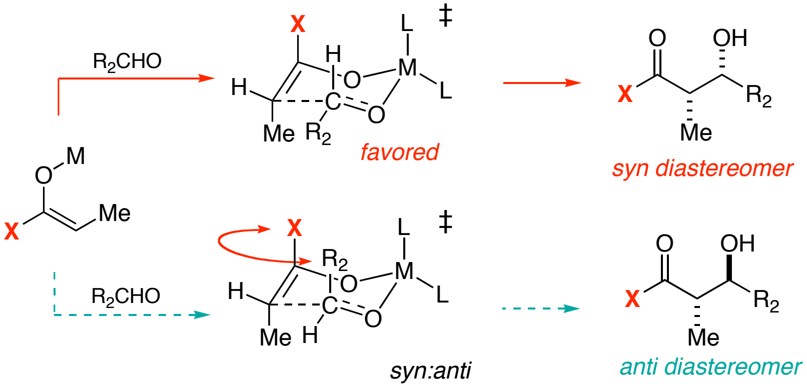
Zimmerman, *J. Am. Chem. Soc* ***1956****, 79,* 1920 **(handout)**

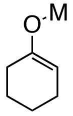
DuBois 1965-67:

Rough correlation between enolate stucture & product stereochemistry for alkali and alkaline earth enolates



Zimmerman-Traxler Model for *(Z)* Enolates



		syn:anti	
X = CMe_3	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972
X = C_6H_5	M = Li	80 : 20	
	M = Li	48 : 52	
	M = $AlEt_2$	50 : 50	House 1971

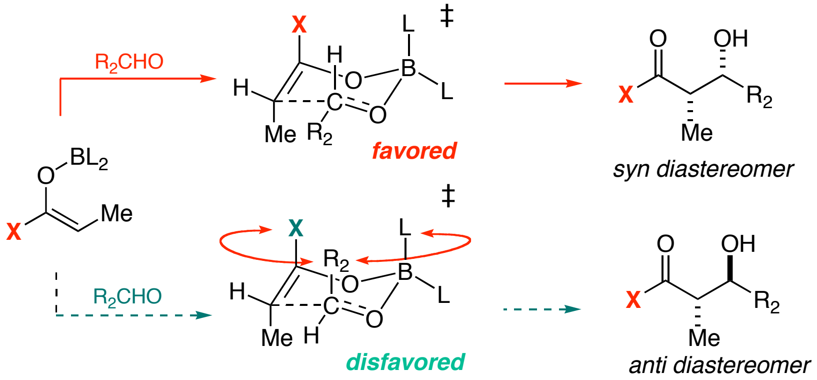
Stereocontrol optimal for "large" X; the reaction is not general.

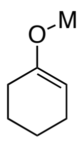
The Aldol Reaction: Boron Enolates

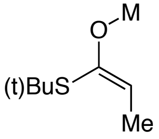
Why Boron?

To tighten up the transition state.
Design TS where control can come exclusively from metal center

M–O ⟶ B–O   M–C ⟶ B–C
1.9-2.2 Å   1.4-1.5 Å   2.0-2.2 Å   1.5-1.6 Å







		syn:anti	
X = CMe$_3$	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972
	M = BBu$_2$	> 97 : 3	DuBois 1972
X = C$_6$H$_5$	M = Li	80 : 20	Evans, Masamune 1979-81
	M = BBu$_2$	> 97 : 3	
X = Et	M = Li	80 : 20	
	M = BBu$_2$	> 97 : 3	
	M = Li	48 : 52	House 1971
	M = AlEt$_2$	50 : 50	Yamamoto 1977
	M = BBu$_2$	33 : 67 (ether)	
	M = BBu$_2$	17 : 83 (pentane)	Evans, Masamune 1979-81
	M = BCy(thex)	6 : 94 (CH$_2$Cl$_2$)	
	M = B(Cyp)$_2$	<5 : 95 (pentane)	

Evans et al. *JACS* ***1979***, *101*, 6120-6123; *JACS* ***1981***, *103*, 3099-3111

Masamune, *Tet. Lett* ***1979***, 1665, 2225, 2229, 3937

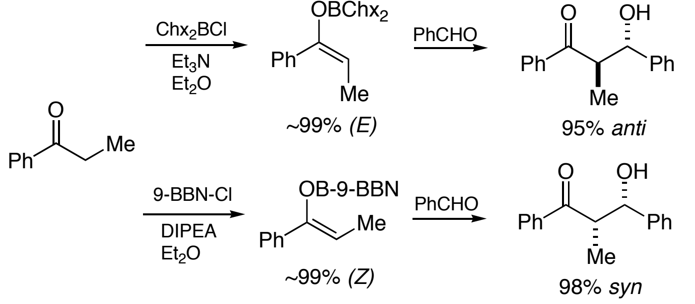
Are (E) enolates intrinsically less diastereoselective?

Now that there are good methods for preparing (E) enolates, it appears that both enolate geometries are nearly equivalent.

Dialkylboron chlorides (Brown)
JACS. **1989**, *111*, 3441-3442.
J. Org. Chem. **1992**, *57*, 499-504.

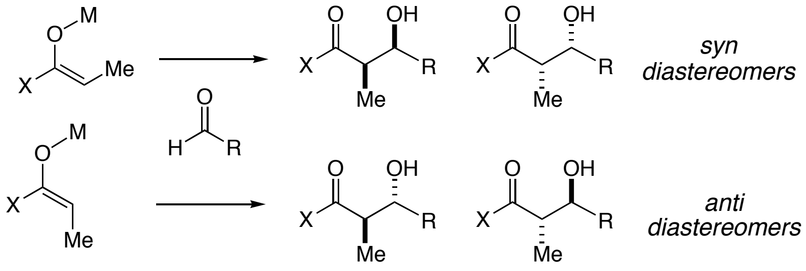
J. Org. Chem. **1992**, *57*, 2716-2721.
J. Org. Chem. **1992**, *57*, 3767-3772.
J. Org. Chem. **1993**, *58*, 147-153.

JACS. **1989**, *111*, 3441-3442.

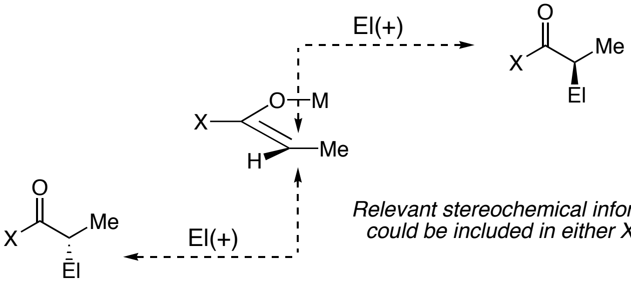


It appears that there is not a great difference in aldol diastereoselectivity

Dissection of the Aldol Problem: Select for one product diastereomer



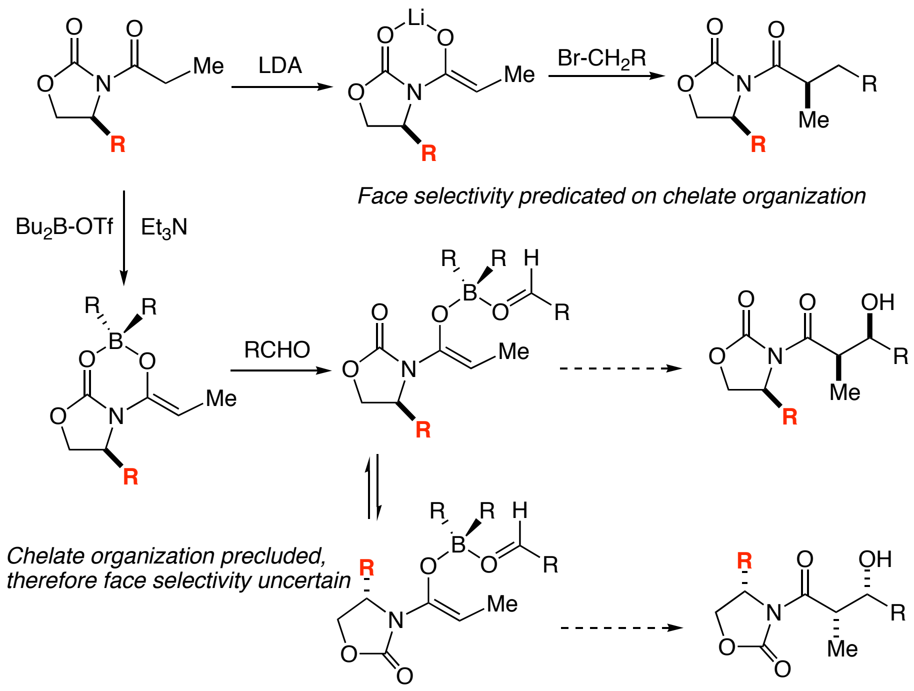
Control attack on the two enolate enantiofaces



Relevant stereochemical information could be included in either X or M

The Aldol Reaction: Boron Imide Enolates

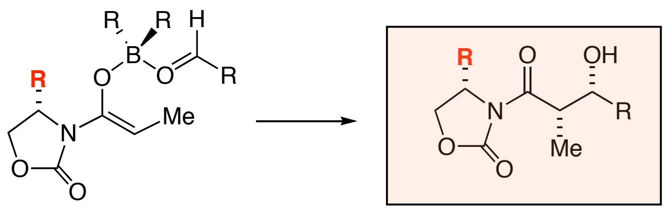
Imide Enolates: The problem of enolate face selectivity



Face selectivity predicated on chelate organization

Chelate organization precluded, therefore face selectivity uncertain

The aldol reaction selects for the opposite enolate diastereoface

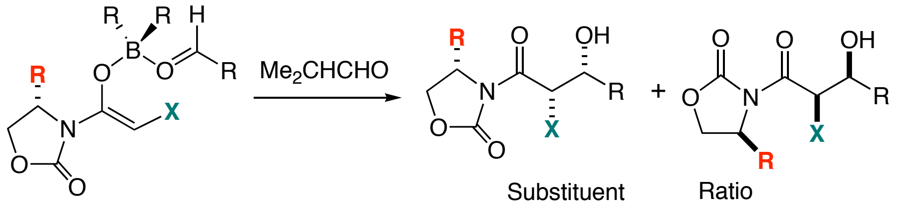


Result discovered but not predicted

diastereoselection > 98%

J. Am. Chem. Soc ***1981****, 103,* 2127-2129 **(Handout)**

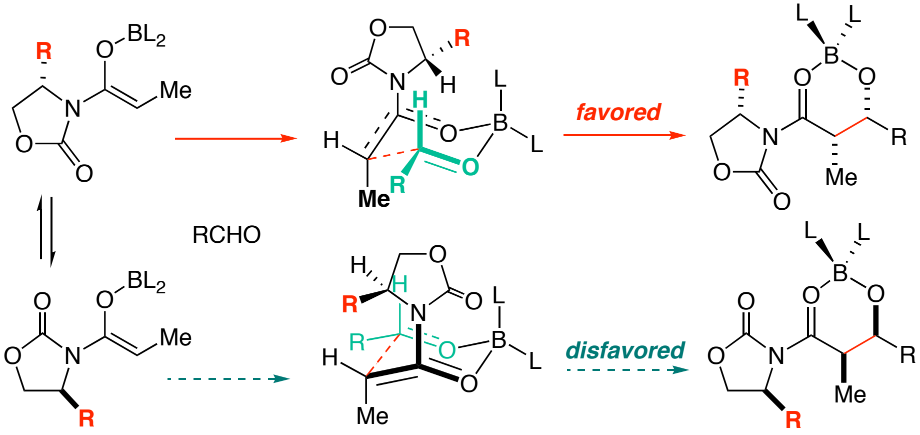
The Alpha substituent, X, plays pivotal role in aldol diastereoselection



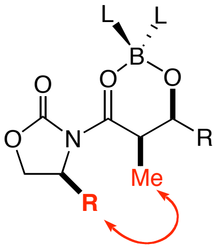
Substituent	Ratio
X = Me	> 300 : 1
X = SMe	60 : 1
X = H	1 : 1

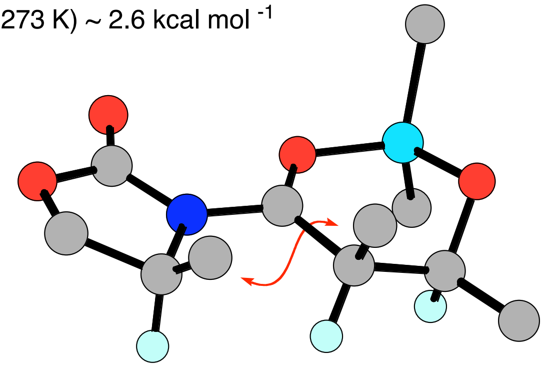
How can we rationalize these data ?

Model for Asymmetric Induction (unpublished)



$\Delta\Delta G^{\ddagger}$ (273 K) ~ 2.6 kcal mol $^{-1}$

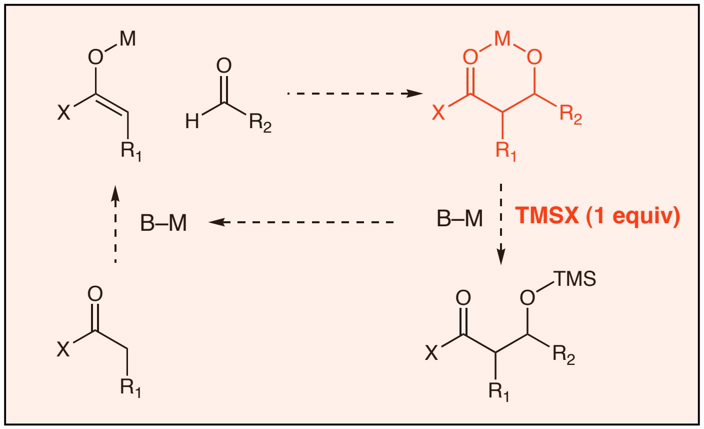




disfavored product diastereomer: The destabilizing interaction?

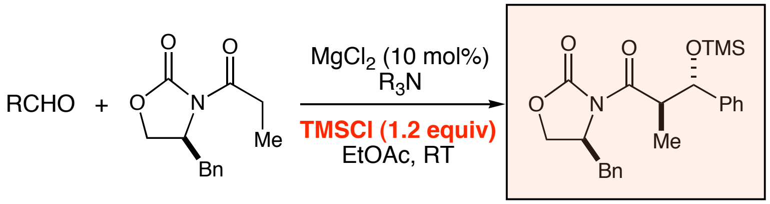
The Aldol Reaction: Magnesium Imide Enolates

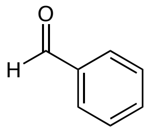
Aldol Reactions: A Third Reaction Variant



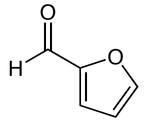
Requirement: **TMS–X must silylate aldolate but not enolate**

Anti Aldol Reactions from (Z) Enolates

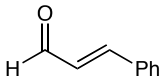




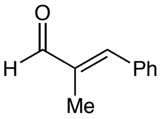
dr = 44:1 (91%)



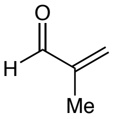
dr = 6:1 (80%)



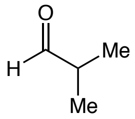
dr = 21:1 (92%)



dr = 28:1 (92%)

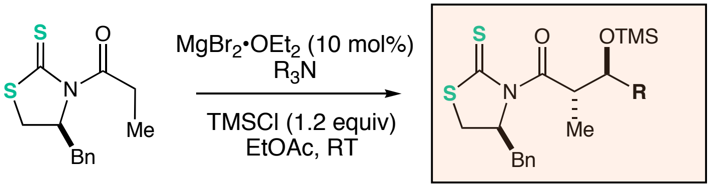


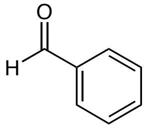
dr = 16:1 (77%)



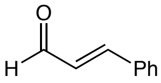
dr = 30:1 (65%)

Magnesium Enolates: with Tedrow, Shaw, Downey, *JACS* **2001**, *124*, 392

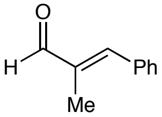




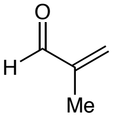
dr = 19:1 (85%)



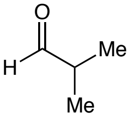
dr = 10:1 (87%)



dr = 19:1 (90%)

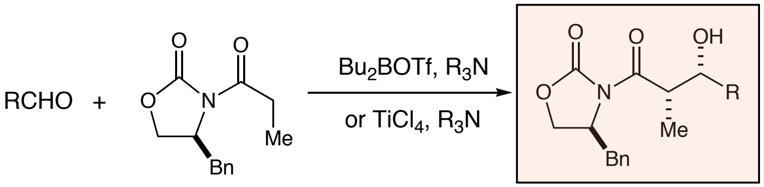


dr = 7:1 (56%)



dr = 16:1 (77%)

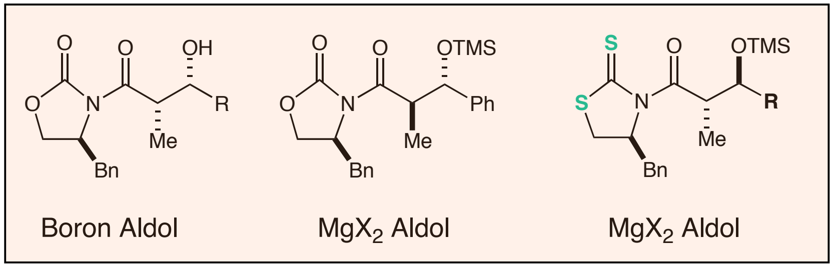
Magnesium Enolates: with Tedrow, Shaw, Downey, *Org. Lett.* **2002**, *4*, 1127



Boron with Bartroli & Shih *JACS* **1981**, *103*, 2127

Titanium *JACS* **1990**, *112*, 8215

Summary of Aldol Diastereoselection



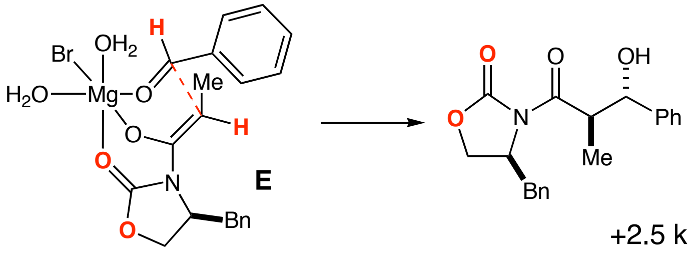
Boron Aldol

MgX_2 Aldol

MgX_2 Aldol

The Aldol Reaction: Magnesium Imide Enolate Transition States

Proposed Boat-Preferred Aldol Transition States



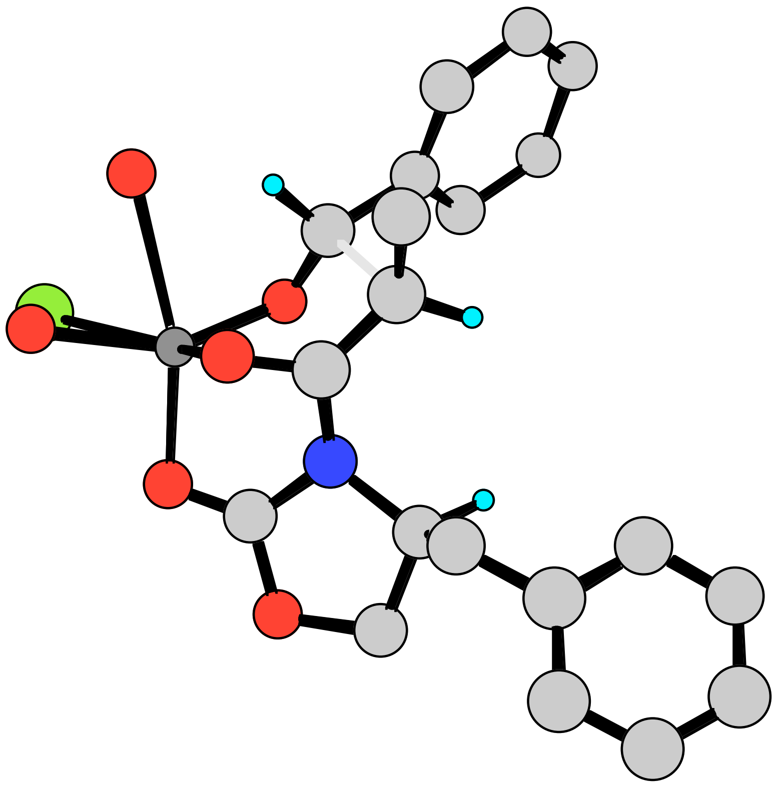
E

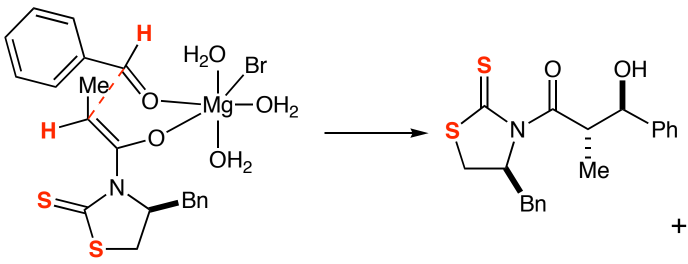
Tedrow, Shaw, Downey *Org. Lett.* **2002**, *4*, 1127

+2.5 kcal/mol (chair)

↑

0 kcal/mol (boat)



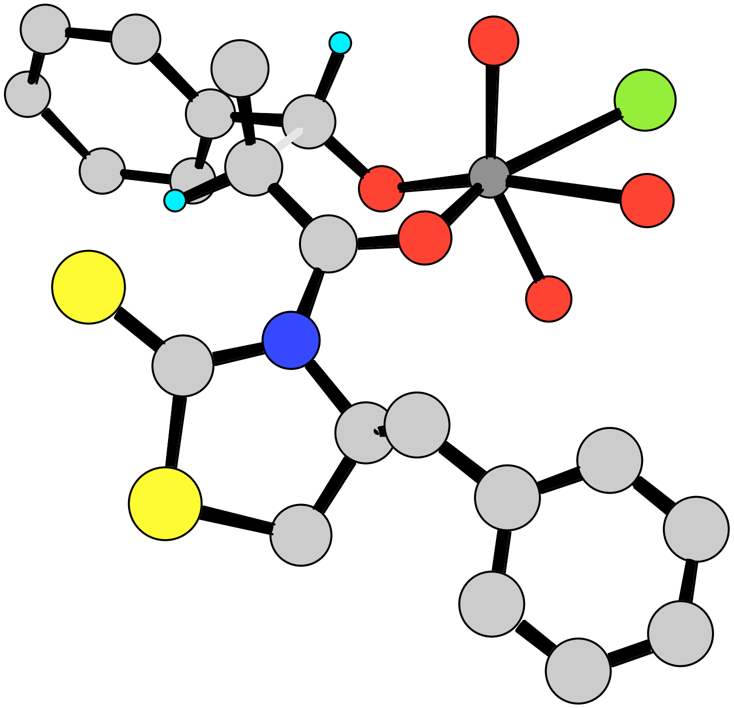


Tedrow, Shaw, Downey *Org. Lett.* **2002**, *4*, 1127

+2.8 kcal/mol (chair)

↑

0 kcal/mol (boat)

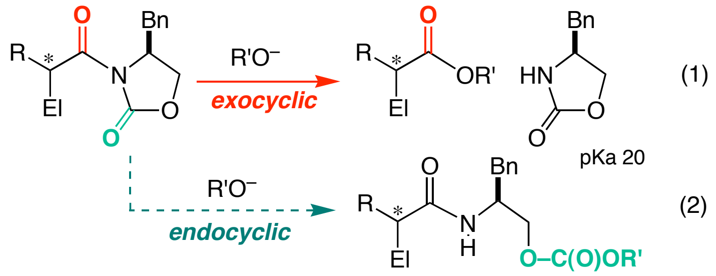


Boat transition states preferred for octahedral metals?

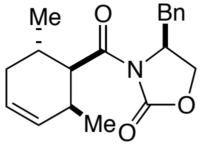
The Aldol Reaction: Imide Transformations

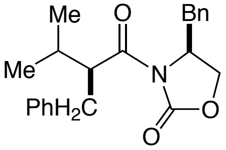
Imide Hydrolysis

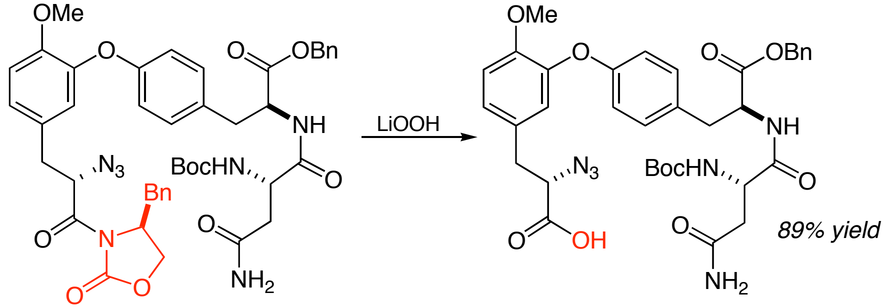
Imides may suffer attack at either of the two C=O functions (eq 1, eq 2)



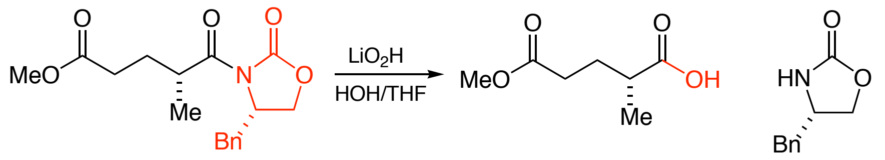
Product distribution a function of attacking nucleophile (*Tet. Lett.* ***1987***, *28*, 6141)

Substrate	Reagent	Exo:Endo Ratio
	LiOH	0 : 100
	LiOOH	76 : 16

Substrate	Reagent	Exo:Endo Ratio
	LiOH	06 : 89
	LiOOH	96 : 04



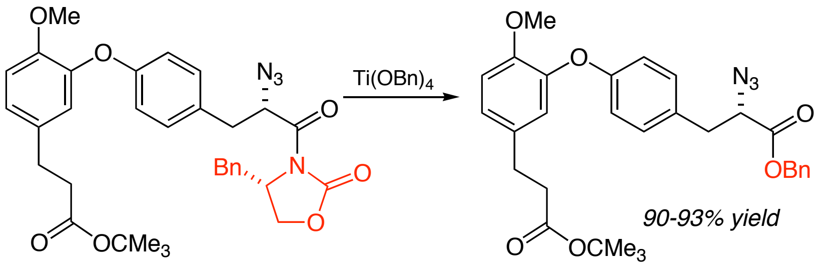
(OF-4949 Synthesis) JACS ***1989***, *111*, 1063



M. Bilodeau, unpublished results

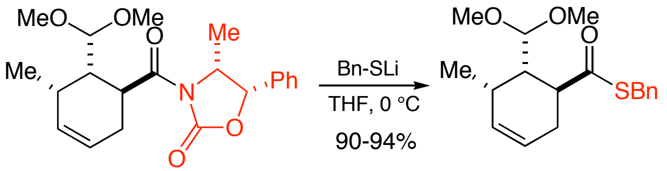
complete hydroytic selectivity possible

Trans-esterification

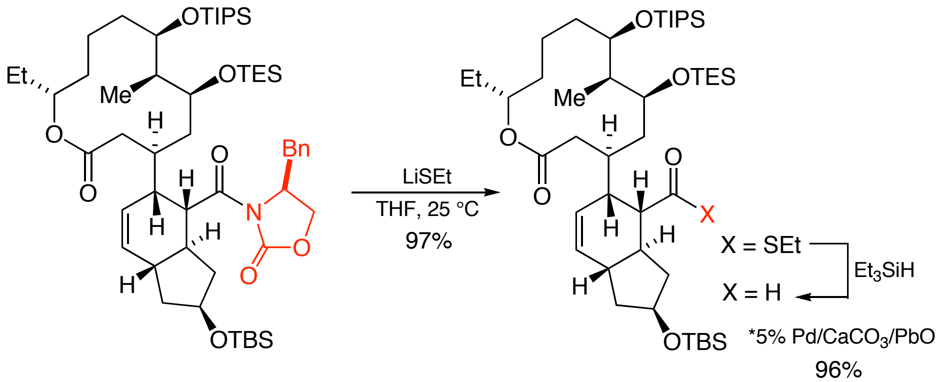


*(OF-4949 Synthesis) JACS****1989***, *111*, 1063

Trans-thioesterification:



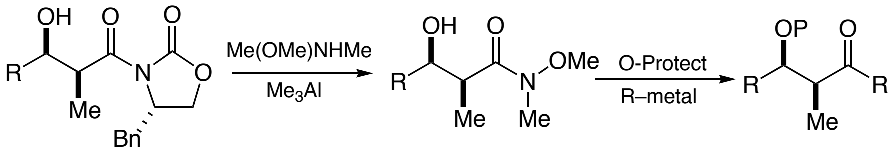
Damon, *Tet. Lett.* ***1990***, *31*, 2849-2852



(Lepicidin Synthesis) J. Am. Chem. Soc ***1993***, *115*, 4497-4513

$RCOSR \longrightarrow RCHO$ Fukuyama, *J. Am. Chem. Soc* ***1990***, *112*, 7050-7051

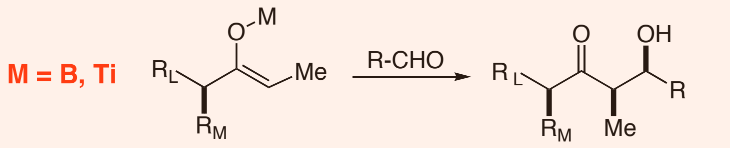
Transamination to Weinreb Amides (see Handout 24A)



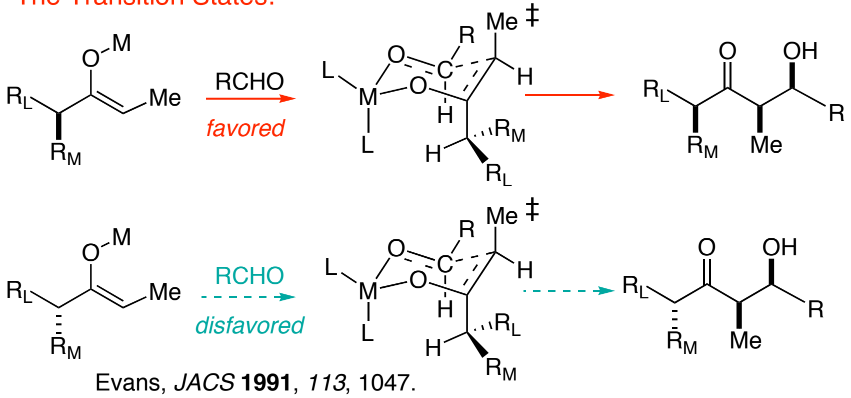
for recent examples see, *J. Am. Chem. Soc* ***1992***, *114*, 9434-9453

The Aldol Reaction: Syn Aldol Rxns of Chiral Ethyl Ketones

General Reaction for Syn Aldols: M = B, Ti

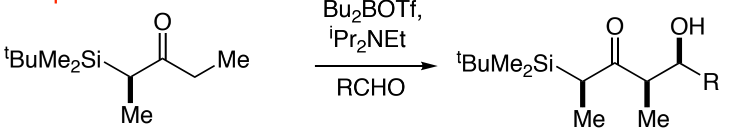


The Transition States:



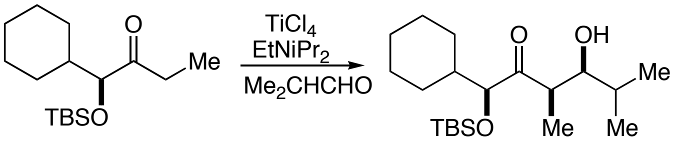
Evans, *JACS* **1991**, *113*, 1047.

Examples:



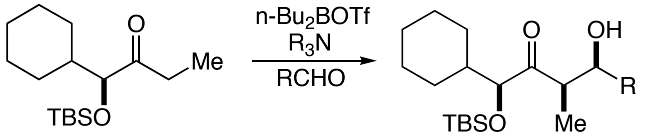
Enders *ACIEE* **1988**, *27*, 581.

Diastereoselection = 96-98%



Evans, *JACS* **1991**, *113*, 1047.

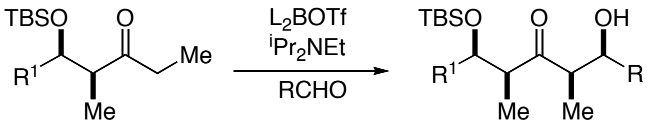
Diastereoselection: 99:1 (81%)



TBS = $SiMe_2{}^tBu$

Masamune, *JACS* **1981**, *103*, 1566.

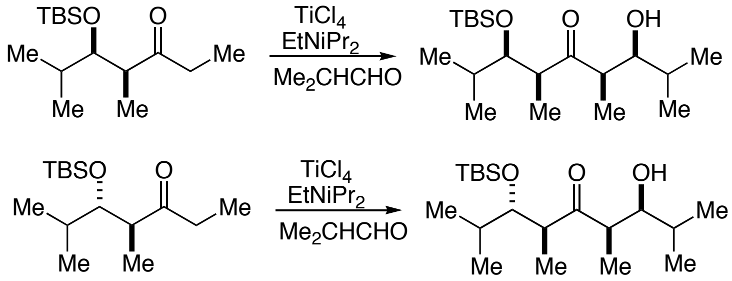
R	Diastereoselection
Ph	97:3
Et	98:2
$BnOCH_2CH_2$	96:4
Me_2CH	>99:<1



L	Diastereoselection
Bu	63:37 - 84:16
9-BBN	83:17 - 85:15
(-)-Ipc	72:28
(+)-Ipc	91:9 - 94:6

This system does not give a completely clean (Z) enolate

Paterson, McClure, *Tet.Lett.* **1987**, *28*, 1229.

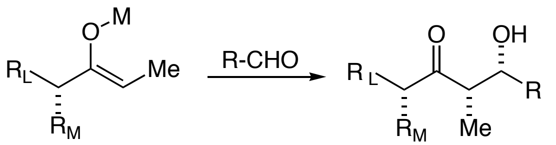


Evans, *JACS* **1991**, *113*, 1047.

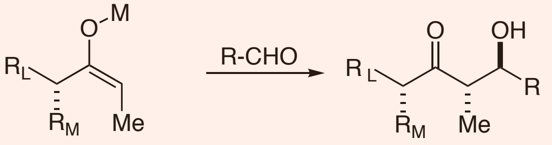
Diastereoselection: 95:5 (80-90%)

The Aldol Reaction: Anti Aldol Rxns of Chiral Ethyl Ketones

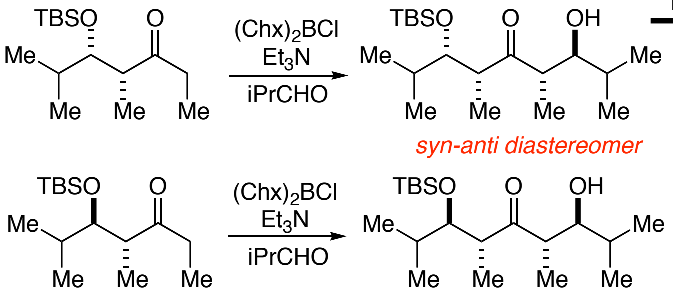
General Reaction for Syn Aldols:



General Reaction for Anti Aldols:



Examples:



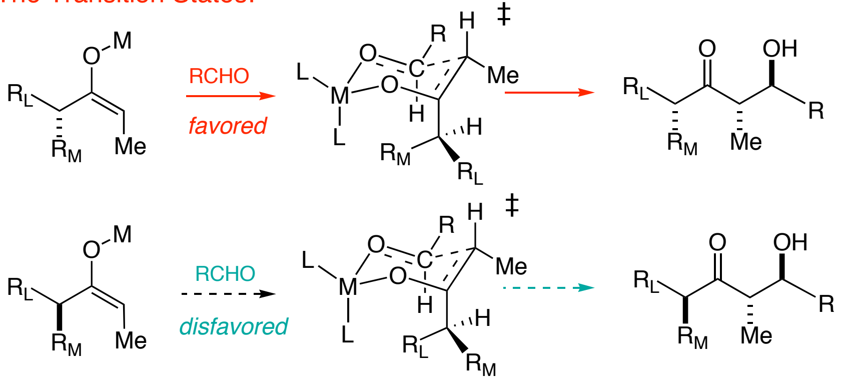
syn-anti diastereomer

Diastereoselection
major : Σ others

94:6 (90%)

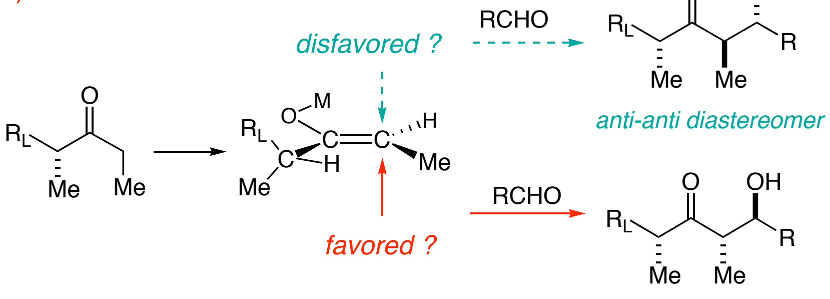
96:4 (75%)

The Transition States:



Evans, *JACS* **1991**, *113*, 1047.

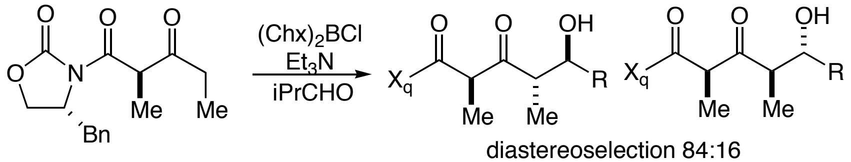
(E) Enolate Facial Bias



anti-anti diastereomer

syn-anti diastereomer

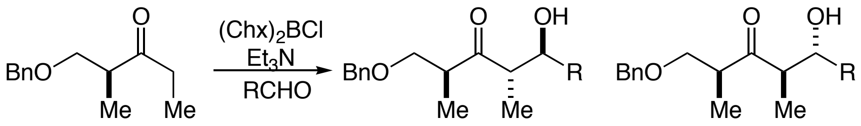
However, the preceding precedent does not extend to these systems:



diastereoselection 84:16

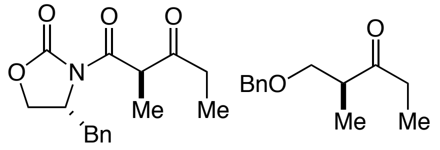
D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger *Tetrahedron*, **1992**, *48*, 2127-2142.

An analogous case:



diastereoselection 95:5

I. Patterson, J. M. Goodman, M. Isaka *Tetrahedron Lett.* **1989**, *30*, 7121-7124

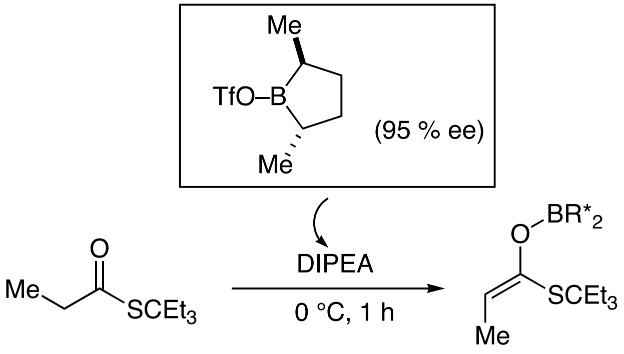


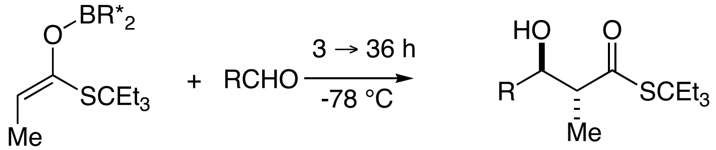
These enolates do not comply with steric analysis: → electronic effects?

Tetrahedron, **1992**, *48*, 2127-2142.

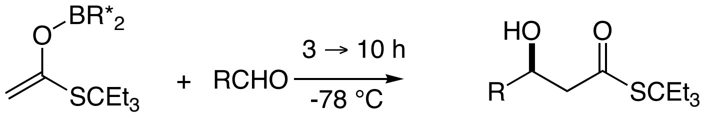
The Aldol Reaction: Metal-Centered Chirality

Masamune, Sato, Kim, Wollmann *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281.





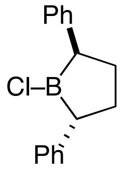
RCHO	Yield, %	anti/syn	ee % (corrected)
n-PrCHO	91	33:1	93 (98)
i-PrCHO	85	30:1	95 (99)
t-BuCHO	95	30:1	96 (99.9)
c-C_6H_{11}CHO	82	32:1	93 (98)
PhCHO	(71)	33:1	96 (99.8)

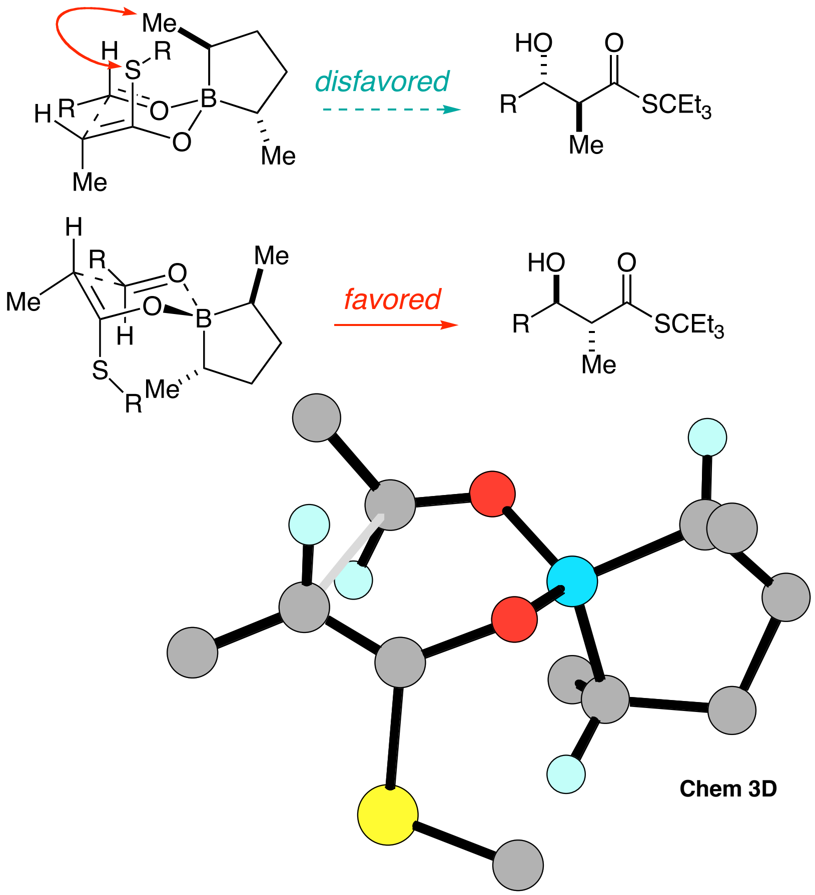


RCHO	Yield, %	ee % (corrected)
n-PrCHO	82	87 (91)
i-PrCHO	81	87 (92)
t-BuCHO	71	94 (98)
c-C_6H_{11}CHO	95	86 (90)
PhCHO	78	88 (92)

See analogous study by Reetz

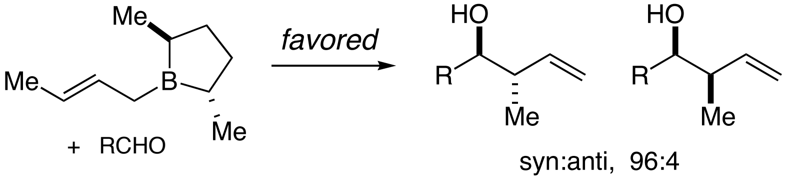
Reetz *Tetrahedron Lett.* **1986**, 4721





Analogous Carbonyl Allylation

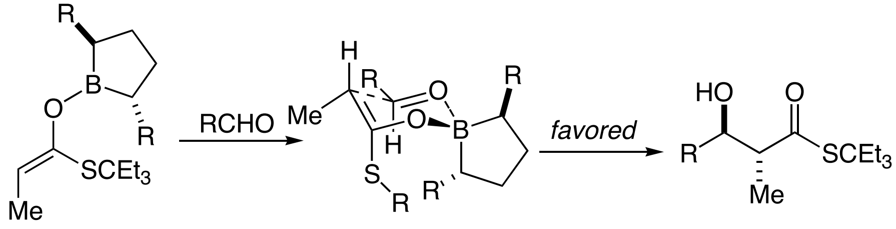
Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831



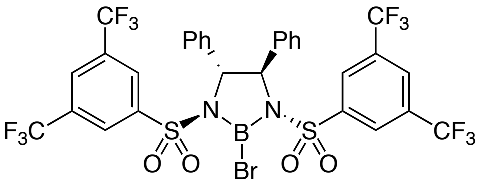
syn:anti, 96:4
enantioselection: 95-97%

The Aldol Reaction: Metal-Centered Chirality

Masamune-Reetz Analogy:



Metal-Based Chiral Auxilliary:



1

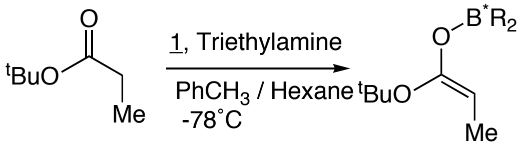
References:

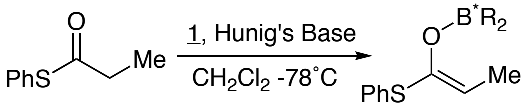
(Corey) *JACS*. **1989**, *111*, 5494
(Corey) *JACS*. **1990**, *112*, 4977
(Corey) *TL*. **1991**, *32*, 2857
(Corey) *TL*. **1993**, *34*, 1737.

Does this reagent perform in accord with the Masamune-Reetz analogy?
Note: The sulfonamide nitrogens are pseudo-tetrahedral

Enolization:

Either enolate geometry possible with proper choice of base, solvent, and substrate.

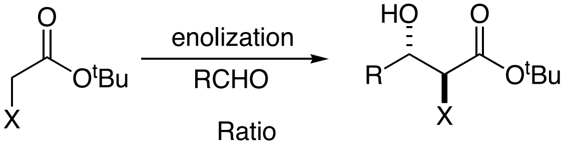




A mechanistic proposal for enolization control is presented in paper

(Corey) *JACS*. **1989**, *111*, 5494

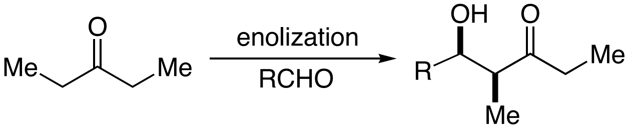
Chiral Anti Aldol Reaction: *JACS* **1990**, *112*, 4977; *TL* **1991**, *32*, 2857.



(R)	(X)	Ratio syn:anti	% ee	Yield
Ph-	Me	2 : 98	94	93 %
chex-	Me	6 : 94	75	82 %

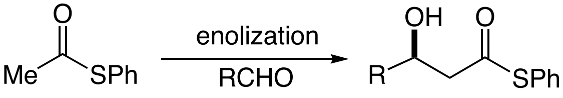
(R)	(X)	Ratio syn:anti	% ee	Yield
Ph-	Br	2 : 98	96	86 %
chex-	Br	2 : 98	91	65 %

Chiral Syn Aldol Reaction *JACS* **1989**, *111*, 5494.



(R)	Ratio syn:anti	% ee	Yield
Ph-	94 : 6	97	86 %
Me_2CH-	98 : 2	95	91 %
$MeCH_2$-	>98 : 2	>98	68 %

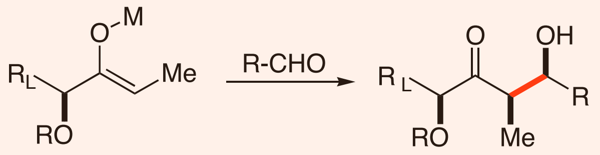
Chiral Acetate Aldol Reaction *JACS* **1989**, *111*, 5494.



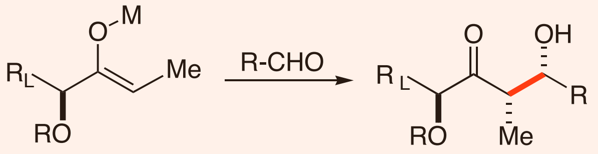
(R)	% ee	Yield
Ph-	91	84 %
Me_2CH-	83	82 %

The Aldol Reaction: Chelate vs Steric Control

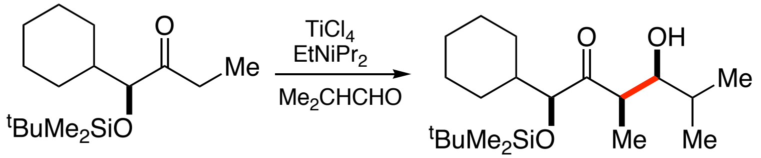
Reference Rxn



Chelate-Organized Variant

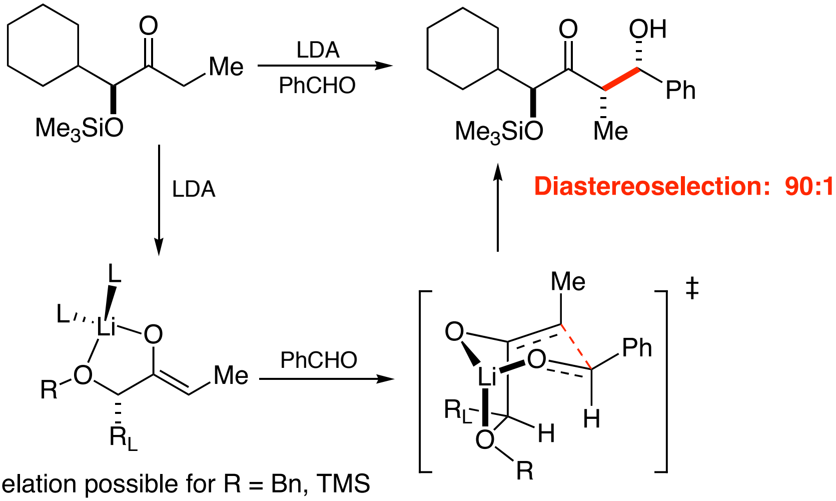


Nonchelate Reaction



Masamune, *JACS* **1981**, *103*, 1566 (boron enolate)
Evans, *JACS* **1991**, *113*, 1047 (titanium enolate)

Diastereoselection: 99:1

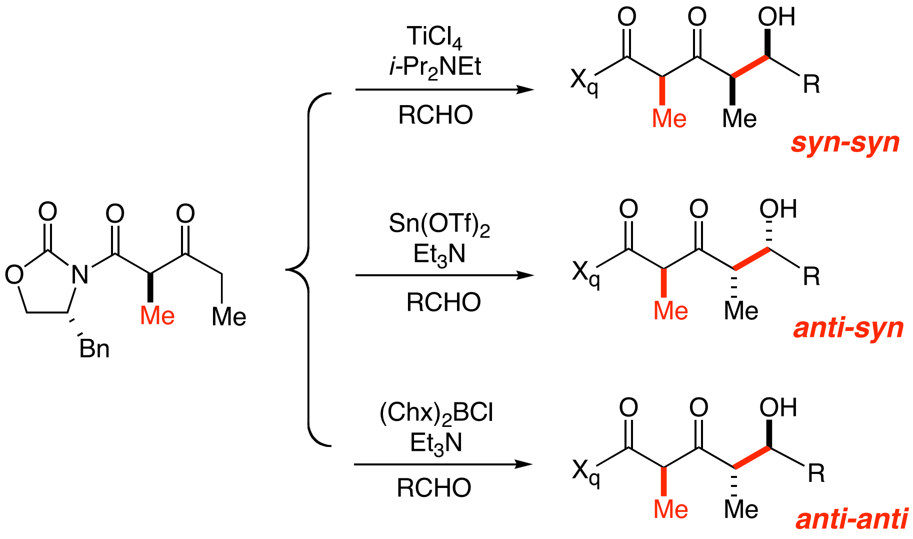


Diastereoselection: 90:10

Chelation possible for R = Bn, TMS
but marginal for TBS

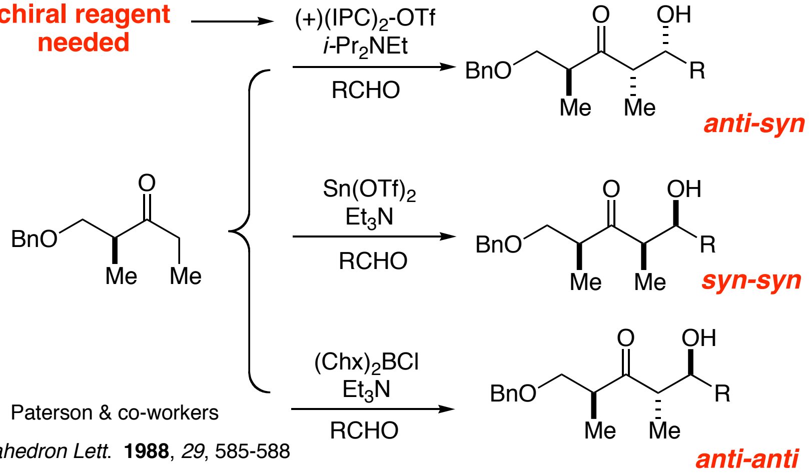
Thorton, *Tet. Let.* **1990**, *31*, 6001

Complimentary aldol reactions may be obtained by changing metal as well as enolate geometry



JACS, **1990**, *112*, 866; *Tetrahedron*, **1992**, *48*, 2127-2142.

chiral reagent needed



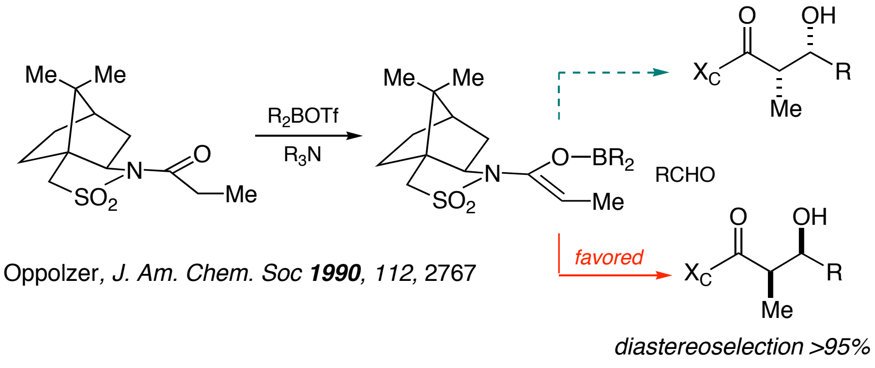
Paterson & co-workers

Tetrahedron Lett. **1988**, *29*, 585-588
Tetrahedron Lett. **1989**, *30*, 7121-7124
Tetrahedron Lett. **1992**, *33*, 4233-4236

The Aldol Reaction: Oppolzer Sultam Auxiliaries

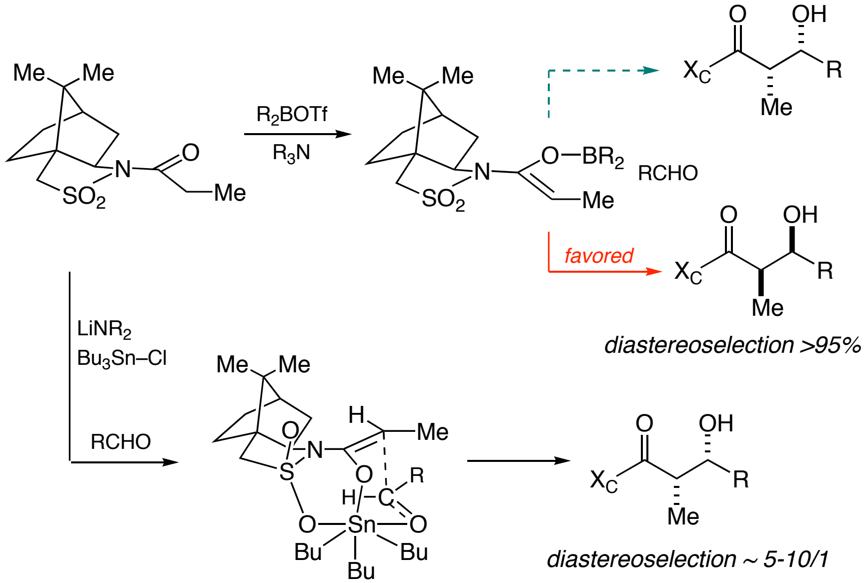
Reviews: Oppolzer, *Tetrahedron 1987, 43,* 1969-2004

Oppolzer, *J. Am. Chem. Soc* ***1990****, 112,* 2767

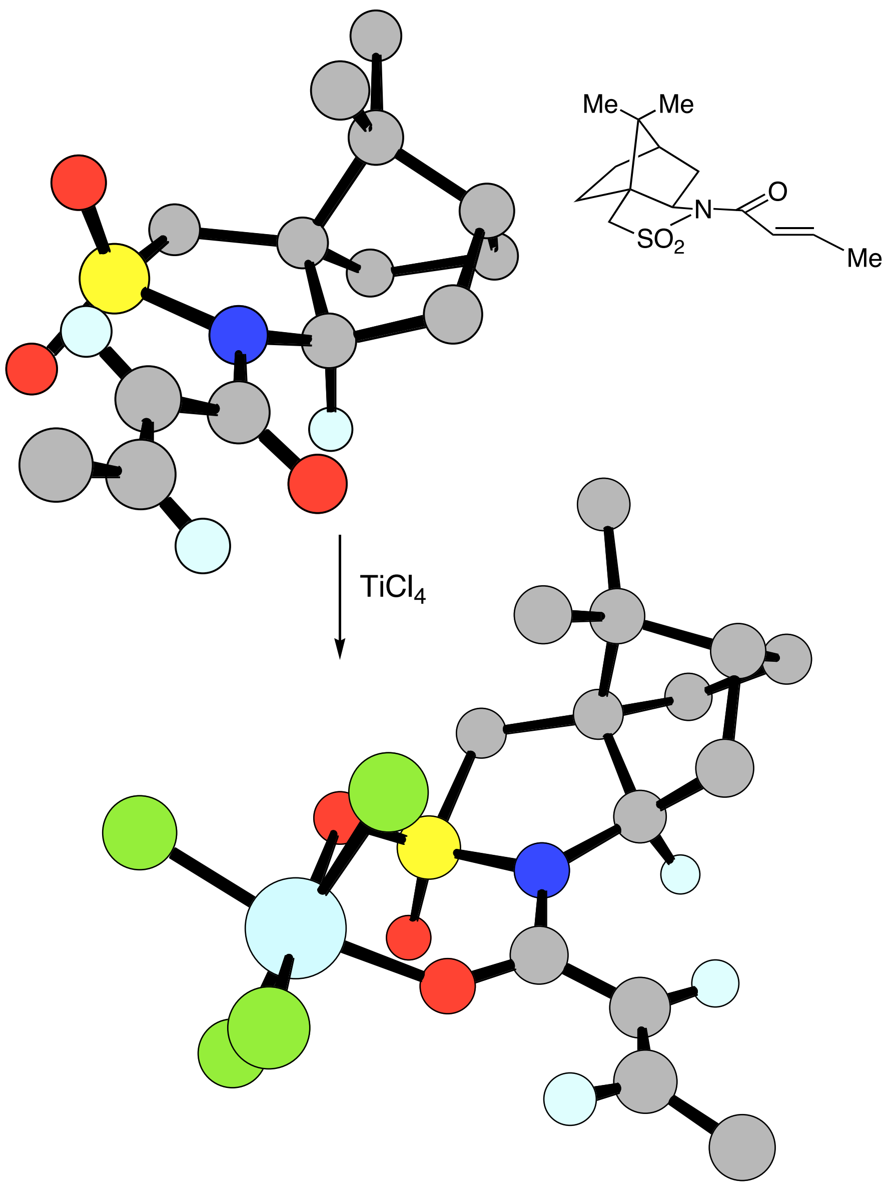


Oppolzer, *J. Am. Chem. Soc* ***1990****, 112,* 2767

Chelate-controlled alternative



X-ray Structures of the Sultam Auxiliary



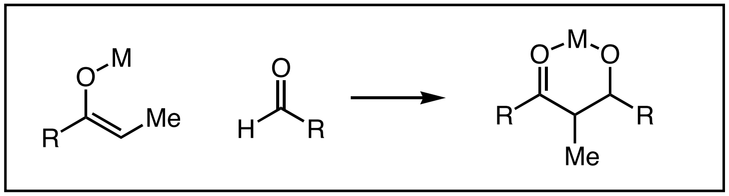
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 28

The Aldol Reaction–2



- (E) & (Z) Enolates: Felkin Selectivity
- Double Stereodifferentiating Aldol Reactions
- The Mukaiyama Aldol Reaction Variant
- Allylmetal Nucleophiles as Enolate Synthons

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

D. A. Evans

Wednesday
November 29, 2006

Assigned Reading

Concerning the Diastereofacial Selectivity of the Aldol Reactions of α-Methyl Chiral Aldehydes and Lithium and Boron Enolates
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157. **(handout)**

Other Useful References

Evans, D. A., J. V. Nelson, et al. (**1982**). “Stereoselective Aldol Condensations.” Top. Stereochem. 13: 1.

Heathcock, C. H. (**1984**). The Aldol Addition Reaction. Asymmetric Synthesis. Stereodifferentiating Reactions, Part B. J. D. Morrison. New York, AP. 3: 111.

Oppolzer, W. (**1987**). “Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis.” Tetrahedron **43**: 1969.

Heathcock, C. H. (**1991**). The Aldol Reaction: Acid and General Base Catalysis. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 133.

Heathcock, C. H. (**1991**). The Aldol Reaction: Group I and Group II Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 181.

Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

Franklin, A. S. and I. Paterson (**1994**). “Recent Developments in Asymmetric Aldol Methodology.” Contemporary Organic Synthesis 1: 317-338.

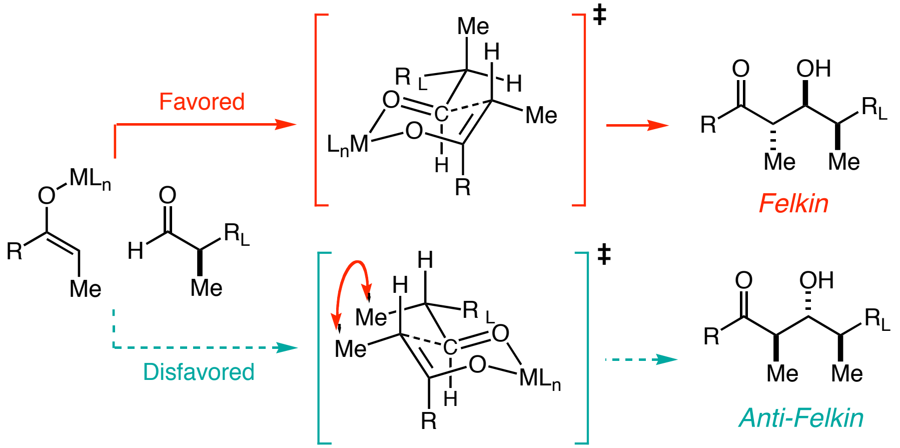
Cowden, C. J. and I. Paterson (**1997**). “Asymmetric aldol reactions using boron enolates.” Org. React. (N.Y.) 51: 1-200.

Nelson, S. G. (**1998**). “Catalyzed enantioselective aldol additions of latent enolate equivalents.” Tetrahedron: Asymmetry 9(3): 357-389.

Mahrwald, R. (**1999**). “Diastereoselection in Lewis-acid-mediated aldol additions.” Chem. Rev. 99(5): 1095-1120.

Carbonyl Addition Reactions: (E)-Enolate Nucleophiles

(E) Enolates Exhibit Felkin Aldehyde Diastereoface Selection

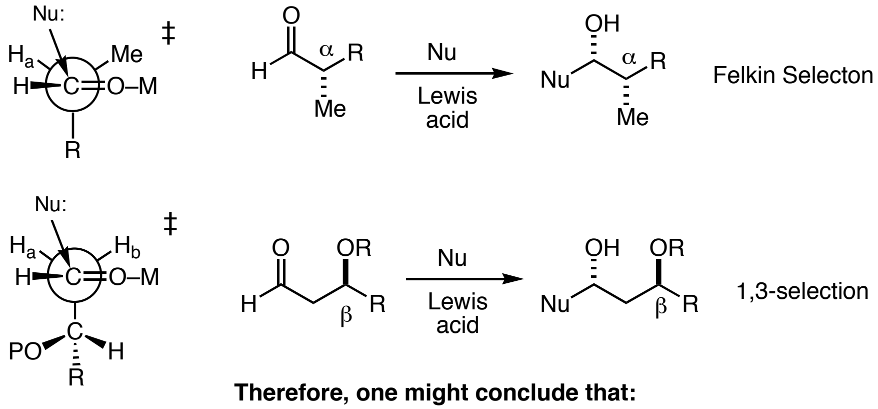


- ■ The illustrated syn-pentane interaction disfavors the anti-Felkin pathway.

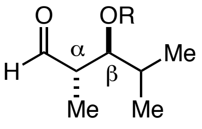
Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157 **(handout).**

Background Information: The influence of β-OR substituents on RCHO

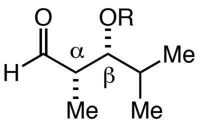
Evans, *JACS* **1996**, *118*, 4322-4343



Therefore, one might conclude that:

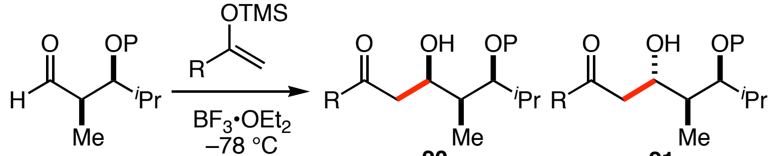


stereocenters reinforcing



stereocenters non-reinforcing

The Non-Reinforcing syn- RCHO is the most Interesting
Dependence of the Selectivity of Felkin-controlled Reactions on Nu Size



19 P = PMB
6 P = TBS

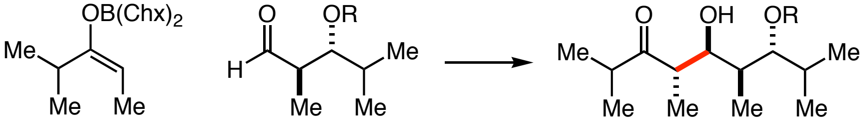
20 Felkin/1,3-*syn*

21 *anti*-Felkin/1,3-*anti*

α-substituent dominates for Large Nu

β-substituent dominates for small Nu

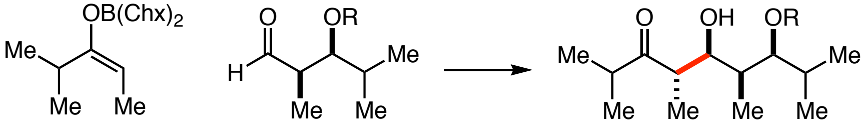
	P = PMB	P = TBS
R	**20** : **21**	**20** : **21**
t-Bu	96 : 04	94 : 06
i-Pr	56 : 44	75 : 25
Me	17 : 83	40 : 60



Felkin

both centers reinforcing

	major : Σ minors	
R = TBS	99 : 1	(77% yield)
R = PMB	93 : 7	(84% yield)



Felkin

centers non-reinforcing

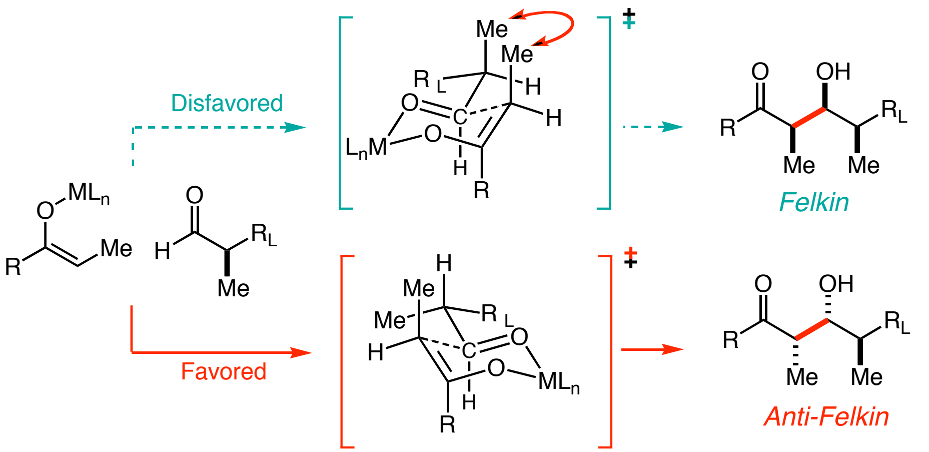
	major : Σ minors	
R = TBS	94 : 6	(79% yield)
R = PMB	74 : 26	(82% yield)

Achiral (*E*) enolates preferentially add to the Felkin diastereoface
High *anti*:*syn* diastereoselectivity (≥ 97 : 3) is observed in all cases

Evans etal. *JACS **1995**, 117,* 9073

Carbonyl Addition Reactions: (Z)-Enolate Nucleophiles

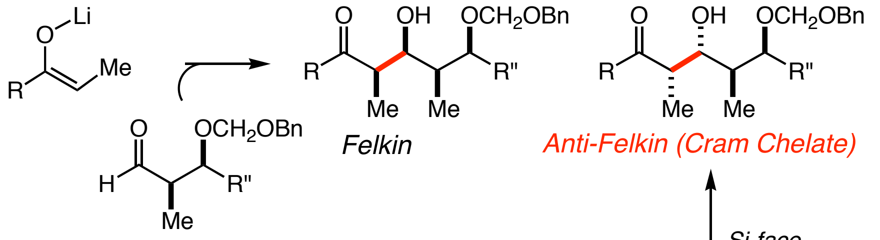
(Z) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection

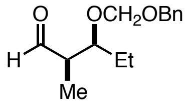
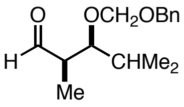


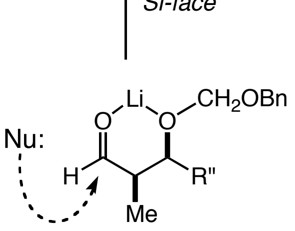
The illustrated syn-pentane interaction disfavors the Felkin pathway.

Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157 **(handout).**

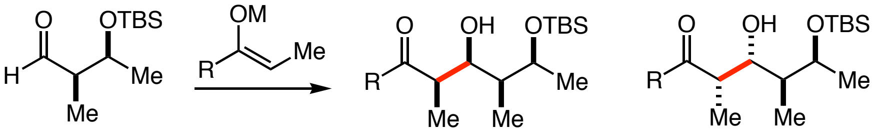
An Early study rationalized results through chelated transition states:



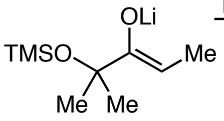
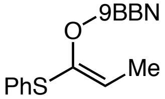
(R)	(R")	Felkin : Anti-Felkin
Et		17 : 83
C_6H_{11}		10 : 90
Et		13 : 87
C_6H_{11}		8 : 92



Masamune
JACS ***1982****, 104,* 5526

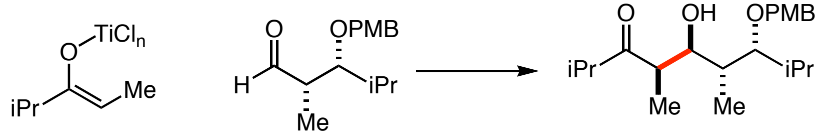


D. W. Brooks & Co-workers
Tetrahedron Lett. **1982**, *23*, 4991-4994.

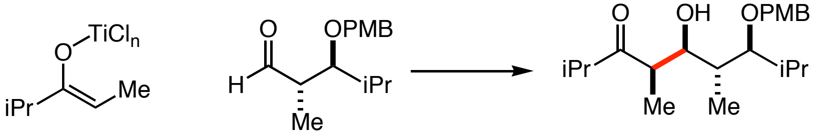
	Felkin : anti-Felkin
	**27 : 73**
	**29 : 71**

- The bulky OTBS group disfavors chelation. (see Keck, *JACS* **1986**, *108*, 3847.)
- The boron and lithium enolates display nearly equal levels of anti-Felkin selectivity.

Titanium enolates exhibit the same trend



anti-Felkin : Felkin 77 : 23 (78%)

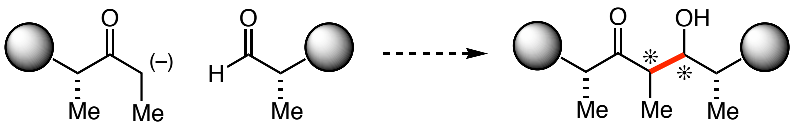


anti-Felkin : Felkin 56 : 44 (84%)

Evans etal. *JACS* ***1995****, 117,* 9073

Double Stereodifferentiating Bond Constructions-1

Double Stereodifferentiating Aldol Bond Constructions



Stereochemical Control Elements

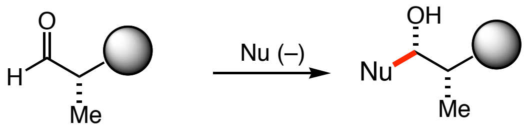
Enolate geometry

⇩

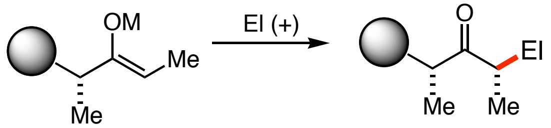
Enolate facial bias ⇨ Product Stereochemistry ⇦ **Aldehyde facial bias**

The Issue: Can one reliably take the diastereoselectivites of the individual reaction partners and use this information in the illustrated extrapolation:

The model reactions:

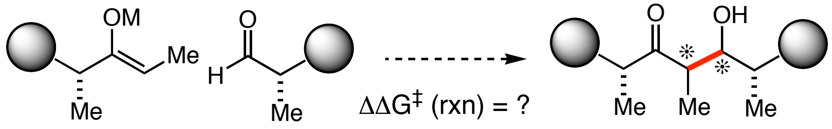


$\Delta\Delta G^{\ddagger}$ (aldehyde)



$\Delta\Delta G^{\ddagger}$ (enolate)

The extrapolation:

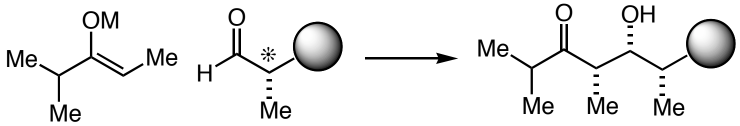


$\Delta\Delta G^{\ddagger}$ (rxn) = ?

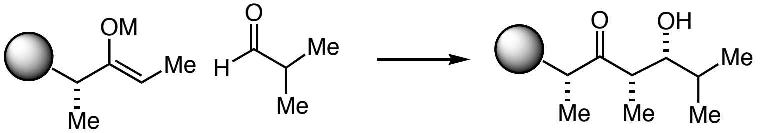
Masamune, *Angew. Chem. Int. Ed.* **1985**, *24*, 1-76

Matched reactant pair: Stereo-induction from both partners reinforcing

The reference reactions:

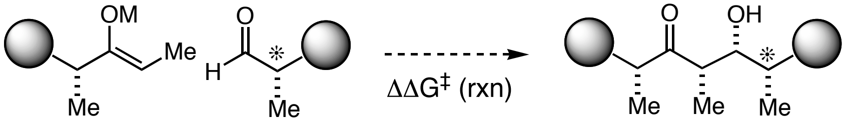


[aldehyde prod ratio] = 10/1



[enolate prod ratio] = 10/1

- ■ The double stereodifferentiating situation: Stereoselectivity?



$\Delta\Delta G^{\ddagger}$ (rxn)

- ■ The assumption: (Masamune, Heathcock)

It is presumed that useful information can be obtained from related achiral enolate & RCHO addition reactions and that the free energy contributions will be additive:

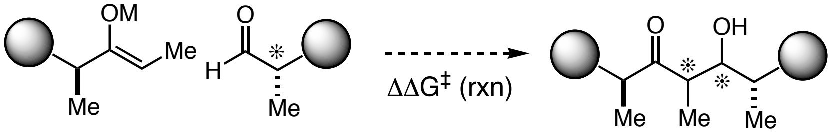
$$\Delta\Delta G^{\ddagger}\text{ (Rxn)} \sim \Delta\Delta G^{\ddagger}\text{ (enolate)} + \Delta\Delta G^{\ddagger}\text{ (RCHO)}$$

$$\log\text{ [Product ratio]} \sim \log\text{ [enolate ratio]} + \log\text{ [aldehyde ratio]}$$

$$\text{[Product ratio]} \sim \text{[enolate prod ratio]} \times \text{[aldehyde prod ratio]}$$

- ■ Hence, for the case at hand: [Product ratio] ~ [10] x [10] ~ 100

Mismatched reactant pair: Stereo-induction from partners nonreinforcing



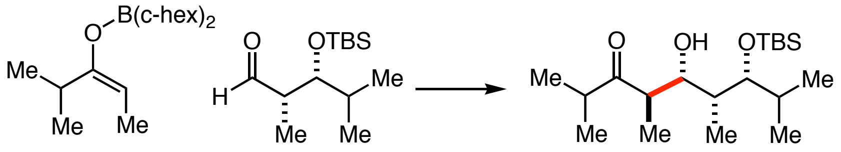
$\Delta\Delta G^{\ddagger}$ (rxn)

$$\Delta\Delta G^{\ddagger}\text{ (Rxn)} \sim \Delta\Delta G^{\ddagger}\text{ (enolate)} - \Delta\Delta G^{\ddagger}\text{ (RCHO)}$$

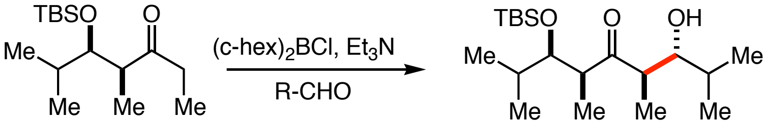
Double Stereodifferentiating Bond Constructions-2

The Masamune-Heathcock generalizations hold to a point:

(E)-Boron Enolates: The reference reactions

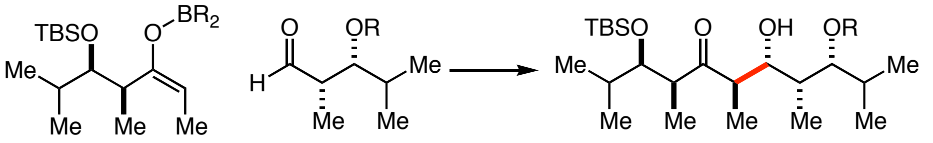


diastereoselection 94 : 6



diastereoselection 96 : 4

(E)-Boron Enolates: The matched cases

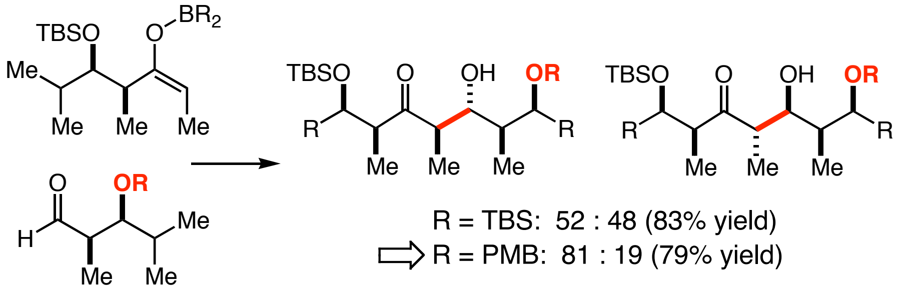


diastereoselection: anti : Σ others

R = TBS: >99 : 1 (85% yield)

R = PMB: >99 : 1 (84% yield)

(E)-Boron Enolates: The mismatched cases

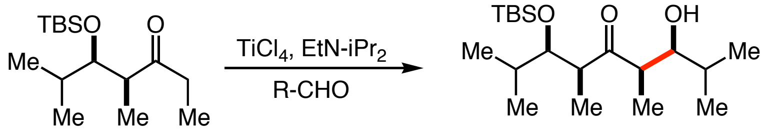


R = TBS: 52 : 48 (83% yield)

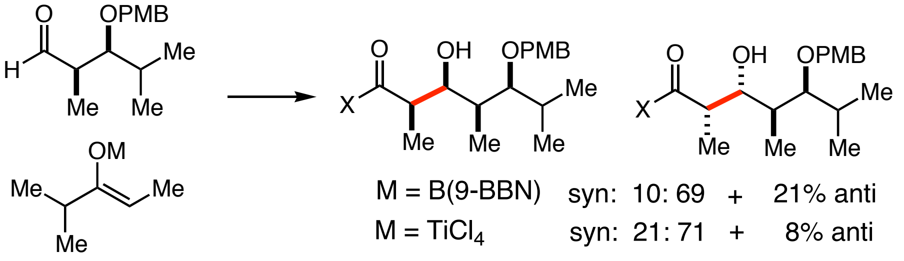
⇨ R = PMB: 81 : 19 (79% yield)

β-center on RCHO can play a significant role in this marginal situation

(Z)-Titanium Enolates: The reference reactions



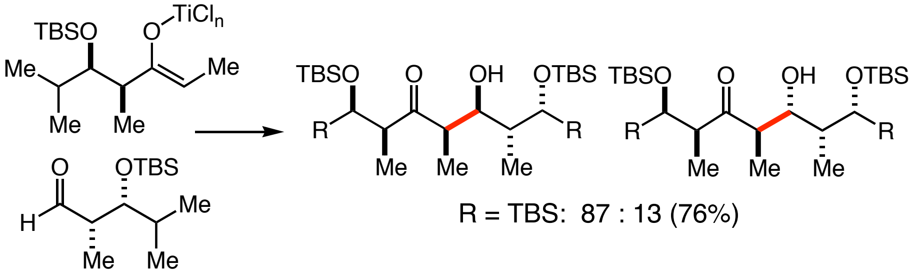
diastereoselection 96 : 4



M = B(9-BBN) syn: 10: 69 + 21% anti

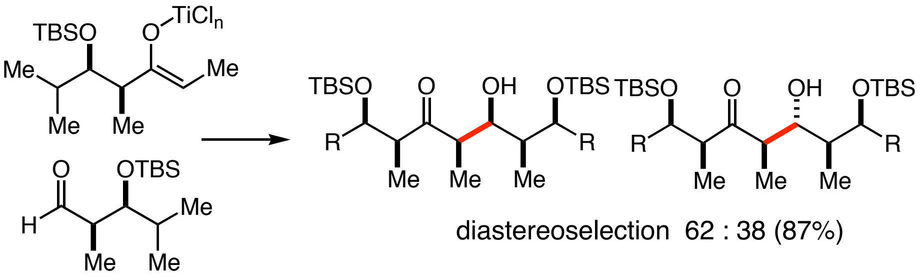
M = TiCl$_4$ syn: 21: 71 + 8% anti

(Z)-Titanium Enolates: The matched cases



R = TBS: 87 : 13 (76%)

(Z)-Titanium Enolates: The mismatched cases

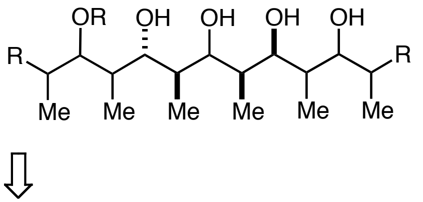


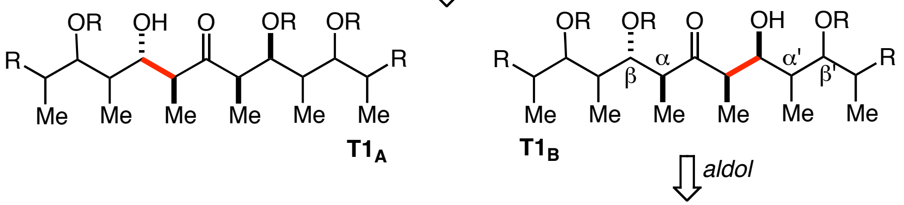
diastereoselection 62 : 38 (87%)

"Double Stereodifferentiating Aldol Reactions. The Documentation of "Partially Matched" Aldol Bond Constructions". Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *JACS* **1995**, *117*, 9073-9074.

Synthesis of Polyketide chains

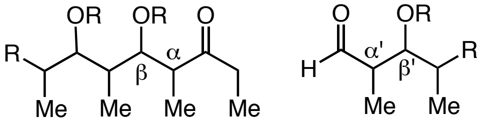
Given a polyprpionate chain of alternating Me & OH substitutents, select a disconnection point sectioning the fragments into subunits of comparable complexity by adding C=O as illustrated.





$T1_A$ **$T1_B$**

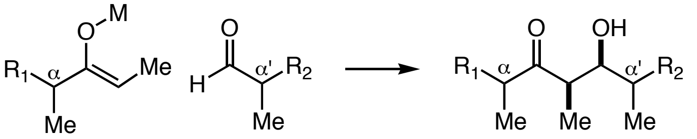
Focusing on the =O FG, there are 2 1st-order aldol disconnections highlighted. Let's proceed forward with **$T1_B$**. Carry out the dissconnection to subunits **2_K** and **2_A**.



2_K
α center important
β center ignore

2_A
Both centers important

For substituted enolate and enolsilane-based processes, there are at least three identifiable **stereochemical determinants** that influence reaction diastereoselectivity (eq 1). Two of these determinants are associated with the local chirality of the individual reaction partners. For example, enolate (enolsilane) chirality influences the absolute stereochemistry of the forming methyl-bearing stereocenter, and in a similar fashion, aldehyde chirality controls the absolute stereochemical outcome of the incipient hydroxyl-bearing stereocenter. The third determinant, the pericyclic transition state, imposes a relative stereochemical relationship between the developing stereocenters. This important control element is present in the aldol reactions of metal enolates (M = BR_2, TiX_3, Li, etc.), but is absent in the Lewis acid catalyzed (Mukaiyama) enolsilanes aldol variants that proceed via open transition states.

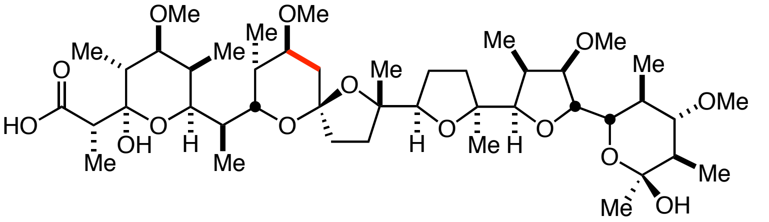


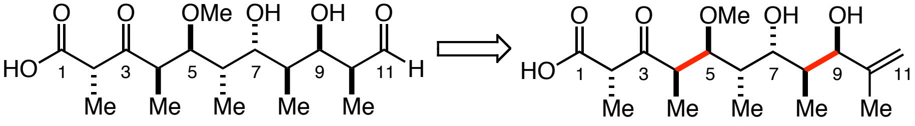
(1)

Stereochemical Determinants	M = BR_2	M = SiR_3
enolate facial bias	✔	✔
aldehyde facial bias	✔	✔
pericyclic transition state	✔	✘

The Lonomycin Synthesis: An example of polypropionate assembage

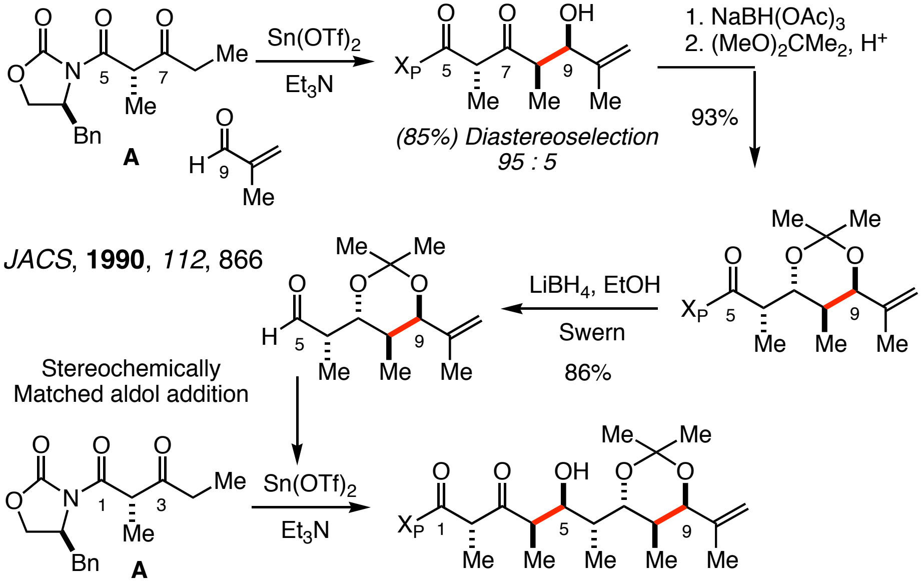
Evans, Ratz, Huff, Sheppard *JACS* **1995**, *117*, 3448





BH_3 Transform: See Lecture No. 8

C_1–C_{11} Assemblage

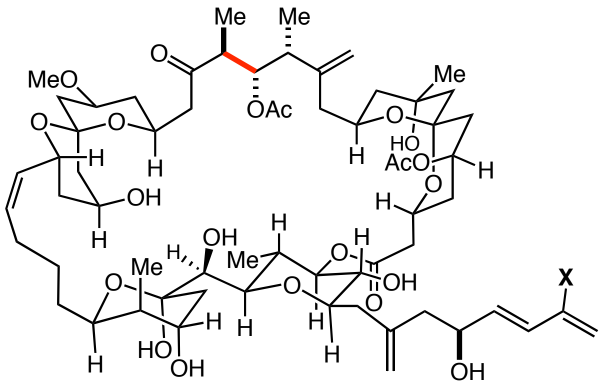


Anti-Felkin Adduct Diastereoselection >95 : 5 (86%)

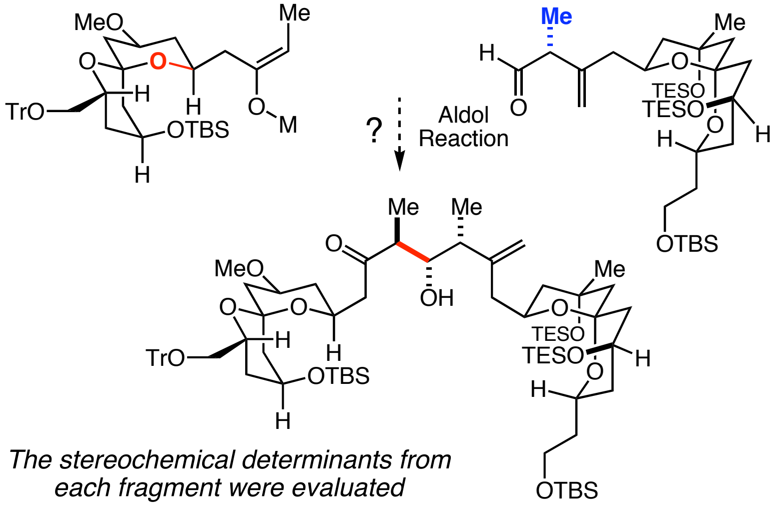
The $Sn(OTf)_2$ aldol reaction of A: see this lecture + *JACS*, **1990**, *112*, 866

Introduction to Complex Aldol Bond Constructions

The Altohyrtin Synthesis: An example of polypropionate assembage

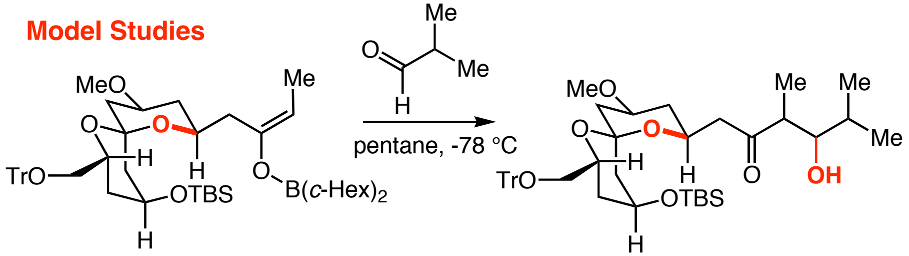


Evans, Trotter, Coleman, Côté, Dias, Rajapakse, *Tetrahedron* **1999**, *55*, 8671-8726.



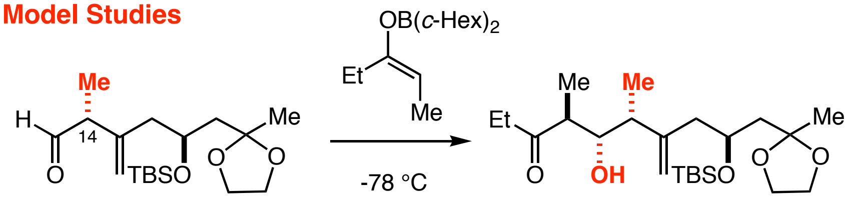
The stereochemical determinants from each fragment were evaluated

Model Studies



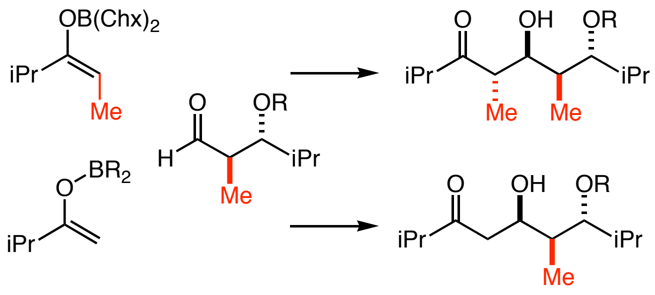
2:1 mixture of diastereomers

Model Studies



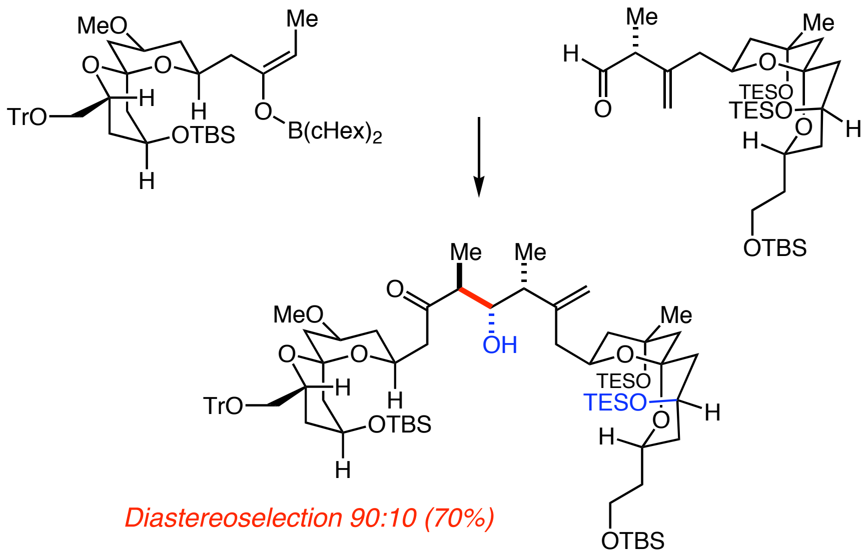
Diastereoselection 97:3

Background



major : Σ others	
R = TBS	99 : 1
R = PMB	93 : 7
R = PMB	69:31

The Aldol Fragment Coupling

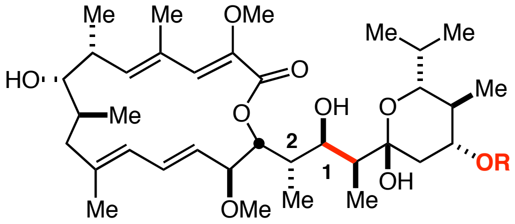


Diastereoselection 90:10 (70%)

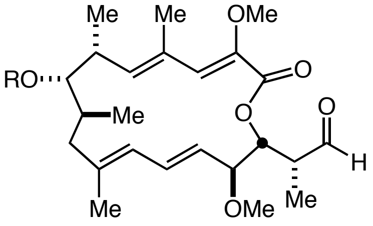
Bafilomycin A_1 Synthesis: An example of polypropionate assembage

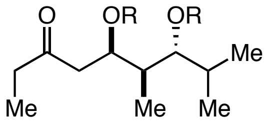
Evans, Calter, *Tetrahedron Lett.* **1993**, 34, 6871

Bafilomycin A_1



Critical Aldol Disconnection





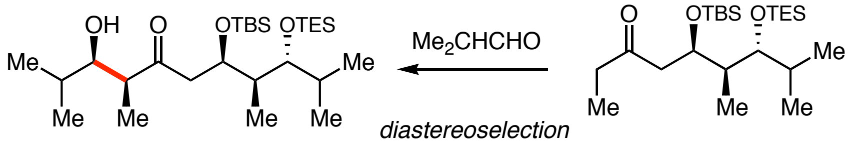
Required: Syn aldol addition

Aldehyde Frag: Target contains syn aldol retron wilth anti-Felkin relationship at 1 & 2

Enolate Frag: Can the needed enolate facial bias be built into the reaction??

Aldol Model Studies

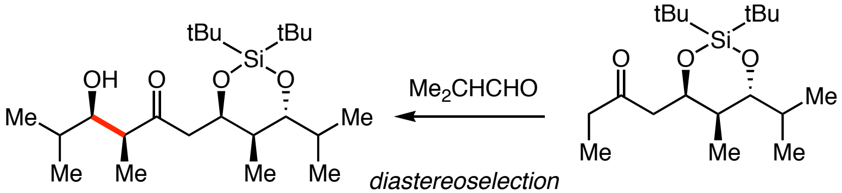
Enolization Conditions: $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78 °C.



Me_2CHCHO

diastereoselection 62:38[9]

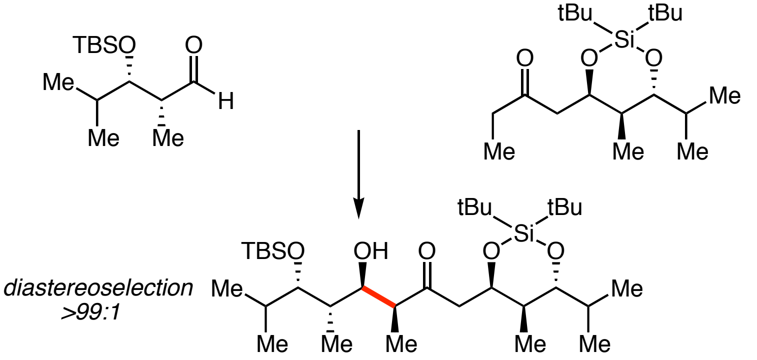
The Critical Observation



Me_2CHCHO

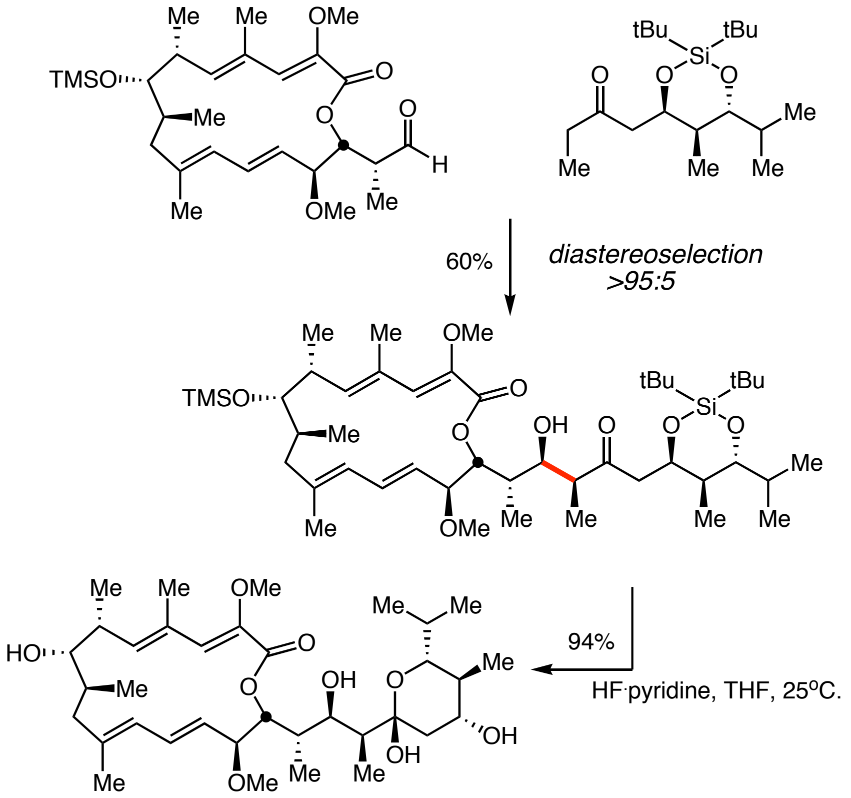
diastereoselection >99:1

Enolization Conditions: $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78°C.



diastereoselection >99:1

Critical Aldol Disconnection



60%

diastereoselection >95:5

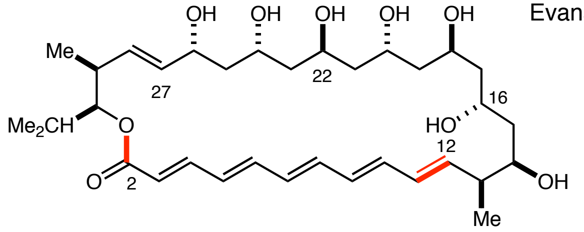
94%

HF·pyridine, THF, 25°C.

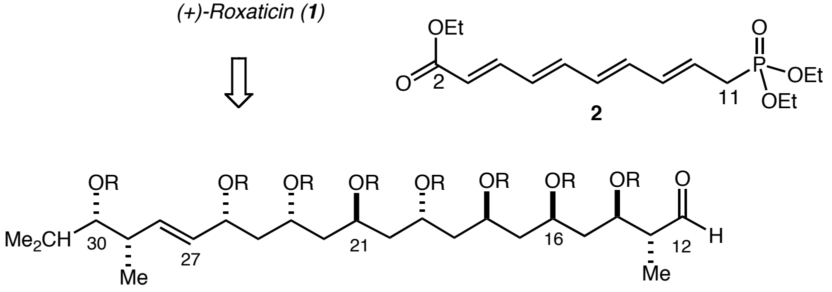
Bafilomycin A_1

Roxaticin, A Typical Polyacetate Natural Product

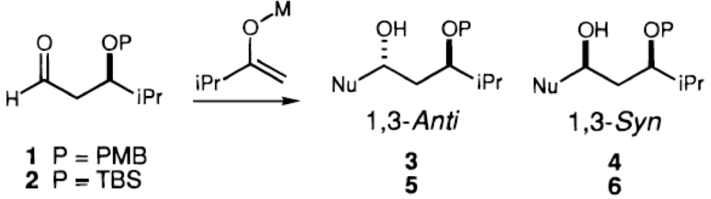
Evans et al. *JACS* **2003**, *125*, 10899



*(+)-Roxaticin (**1**)*



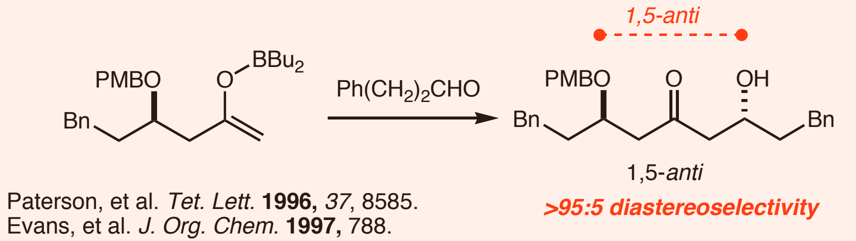
Relevant Chemistry



entry	metal	**3**:**4** (P = PMB) (yield, %)	**5**:**6**^{b} (P = TBS) (yield, %)
A	TMS/BF$_3$·OEt$_2$	92:08 (91)	80:20 (84)
B	Li	71:29 (99)	76:24 (91)
C	TiCl$_n$	60:40 (98)	58:42 (88)
D	9-BBN	42:58 (82)	52:48 (79)

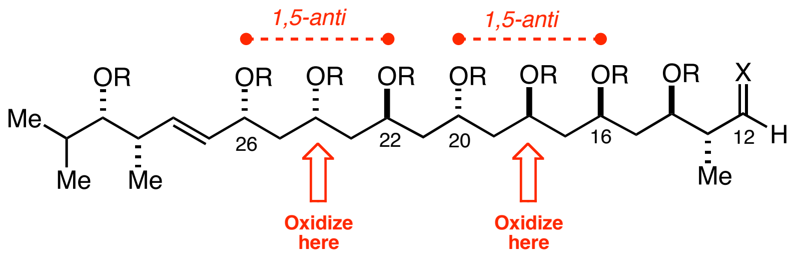
[a] Reactions were carried out in CH_2Cl_2 or THF (entry B) at −78

JACS **1996,** *118*, 4322-4343

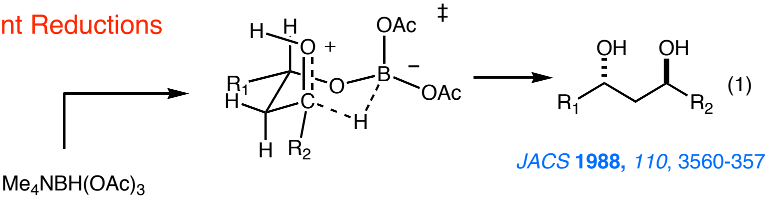


Paterson, et al. *Tet. Lett.* **1996,** *37*, 8585.
Evans, et al. *J. Org. Chem.* **1997,** 788.
Evans et al. *JACS* **2003**, *125*, 10893

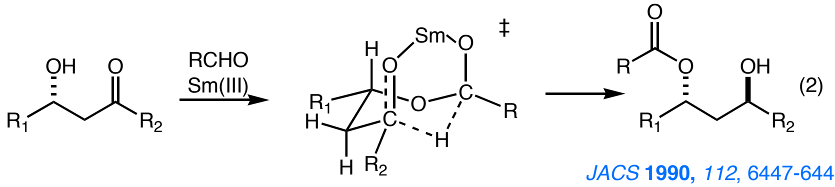
>95:5 diastereoselectivity



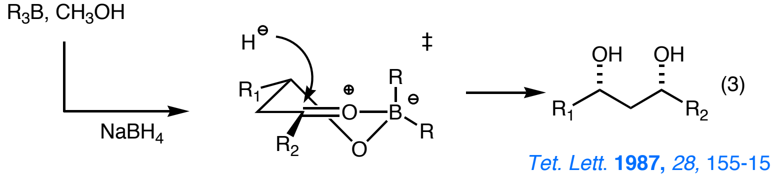
Relevant Reductions



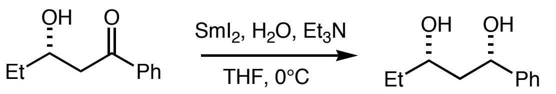
JACS **1988,** *110*, 3560-3578



JACS **1990,** *112*, 6447-6449



Tet. Lett. **1987,** *28*, 155-158



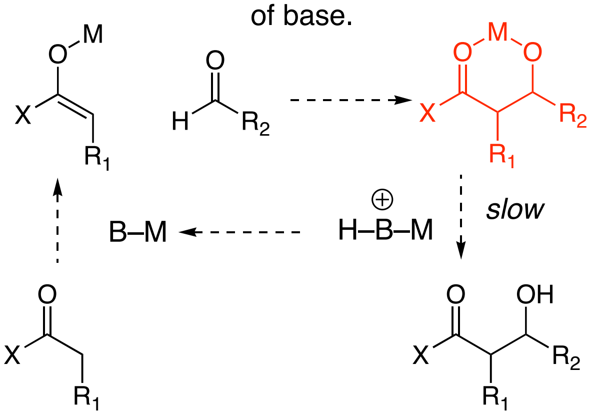
syn/anti ~ 100:1

Org. Lett. **2005,** *7*, 119

The Mukayama Aldol Reaction-1

Type I Aldol Reaction: Metal Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of base.

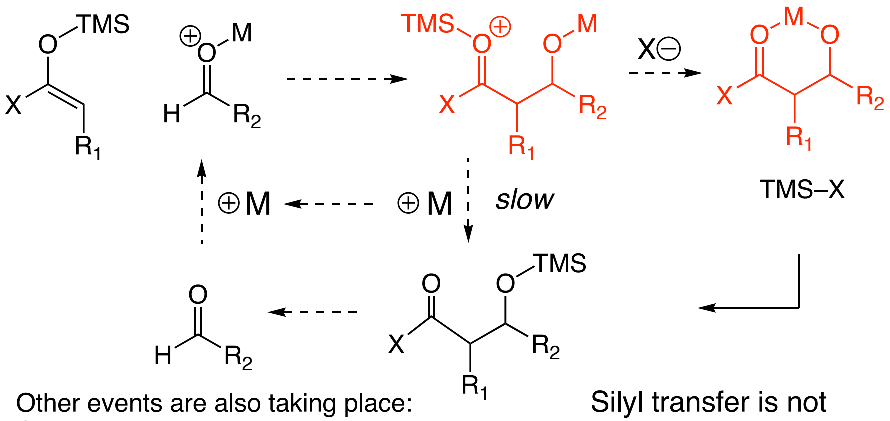


Catalytic Version: Slow step in the catalytic variant is protonation of the intermediate metal aldolate

Type II Aldol Reaction: Mukaiyama Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of Lewis acid.

The minimalist mechanism: MX = Lewis acid



Other events are also taking place:
Carreira *Tet. Lett* **1994**, *35*, 4323

Silyl transfer is not necessarily intramolecular

Recent Reviews

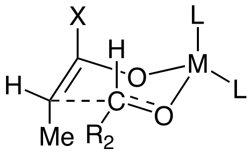
R. Mahrwald, *Diatereoselection in Lewis Acid Mediated Aldol Additions*, *Chem. Rev.* **1999**, *99*, 1095-1120

S. G. Nelson, *Catalyzed enantioselective aldol additions of latent enolate equivalents Tetrahedron: Asymmetry* **1998**, *9*, 357-389.

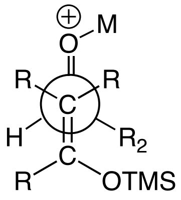
Mukaiyama Aldol Reaction, E. Carreira In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 998-1059.

Reaction Mechanism: "Closed" versus "Open" Transition States

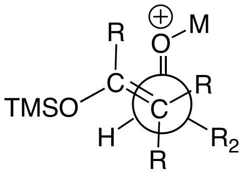
The Mukaiyama aldol reaction proceeds through an "open" transition state. The two illustrated competing TS orientations do not differ significantly in energy. For most reactions in this family there is not a good understanding of reactant-pair orientation. There is a prevalent view that the anti-periplanar TS is favored on the basis of electrostatic effects.



Metal aldolate TS
"Closed"



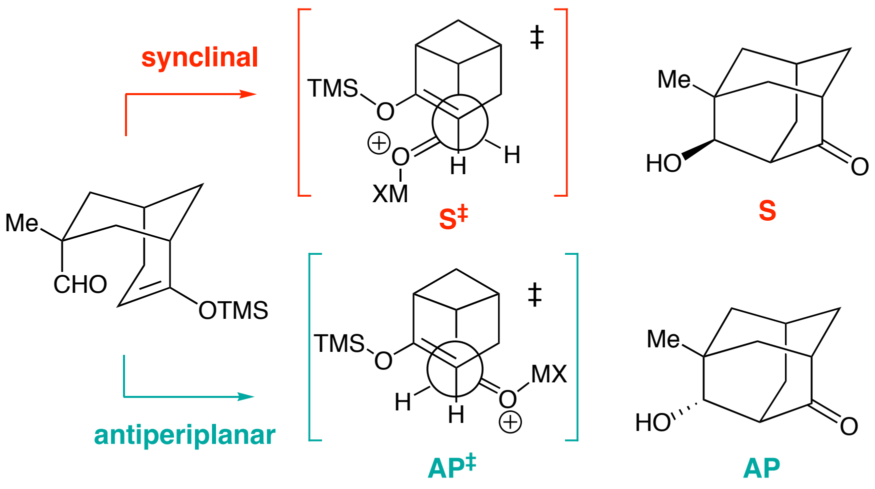
anti-periplanar TS
"Open"



synclinal TS
"Open"

The Mukayama Aldol Reaction-2

Denmark has designed a nice substrate to distinguish between synclinal and anntiperiplanar transition states:



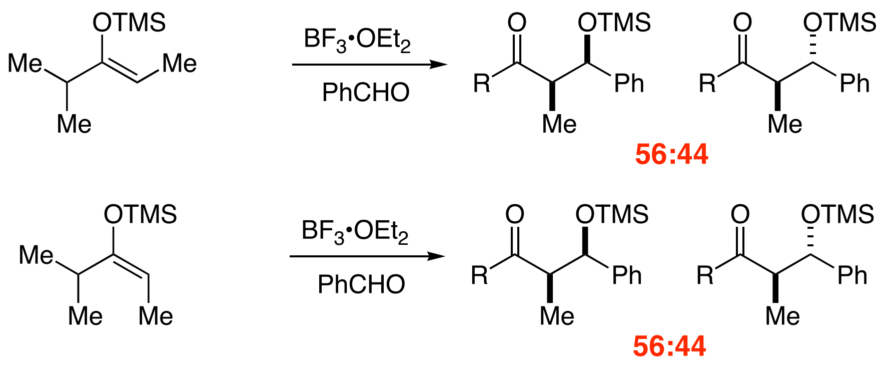
Lewis Acid	**S : AP**
$TiCl_4$	21:79
$SnCl_4$	18:82
$BF_3•OEt_2$	29:71
$TrClO_4$	27:73
$SnCl_2$	78:22

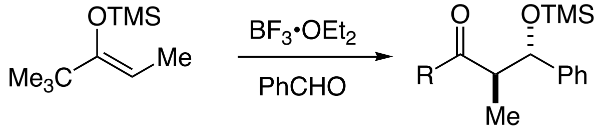
conclusion: there is a modest preference for the antiperiplanar TS

Denmark, *J. Org. Chem.* **1994**, *59*, 707-709

Syn-Anti Aldol Diastereoselection

Heathcock: *J. Org. Chem* **1986**, *51*, 3027

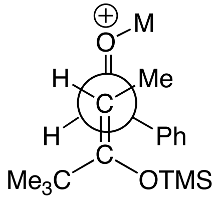




The effectice size of the enol substituents are probably dominant.

>95:5

The transition state?

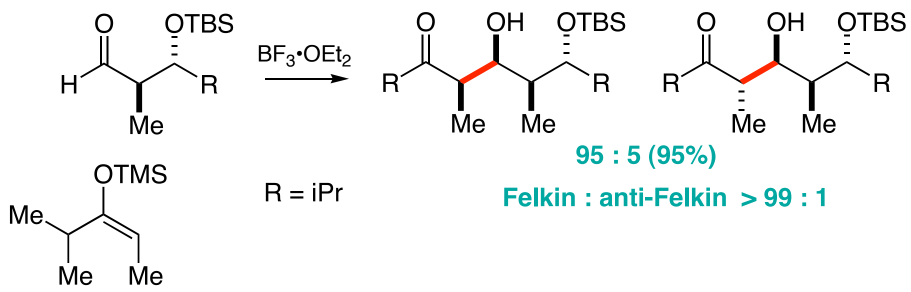


These reactions "exhibit little simple diastereoselection except in special cases."....Heathcock

The Mukayama Aldol Reaction-3

Merged Syn-Anti & Felkin Diastereoselection

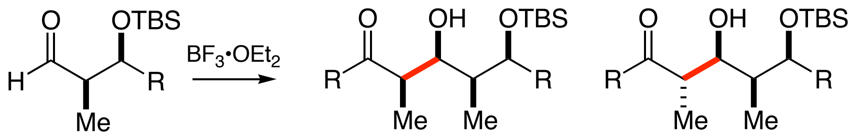
Evans: *JACS* **1995**, *117*, 9598



R = iPr

95 : 5 (95%)

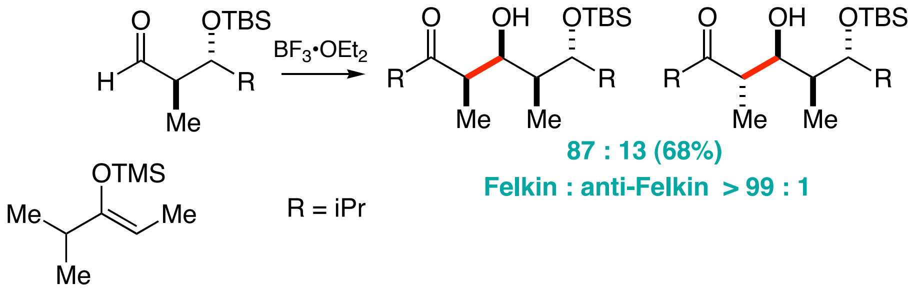
Felkin : anti-Felkin > 99 : 1



70 : 30 (89%)

Felkin : anti-Felkin 99 : 1

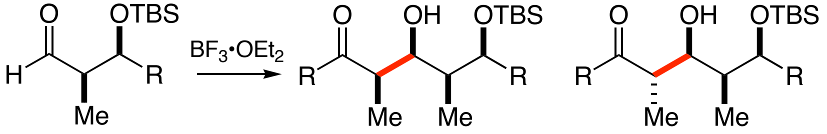
Conclusions:
Moderate to Good syn diastereoselectlion
Excellent Felkin diastereoselectlion



R = iPr

87 : 13 (68%)

Felkin : anti-Felkin > 99 : 1

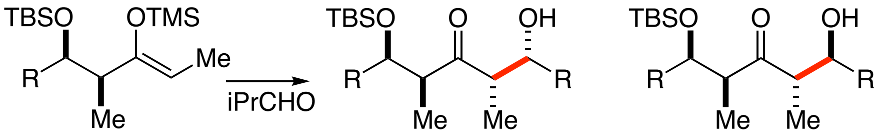


91 : 9 (75%)

Felkin : anti-Felkin 87 : 13

Conclusions:
Moderate to Good syn diastereoselectlion
Excellent Felkin diastereoselectlion

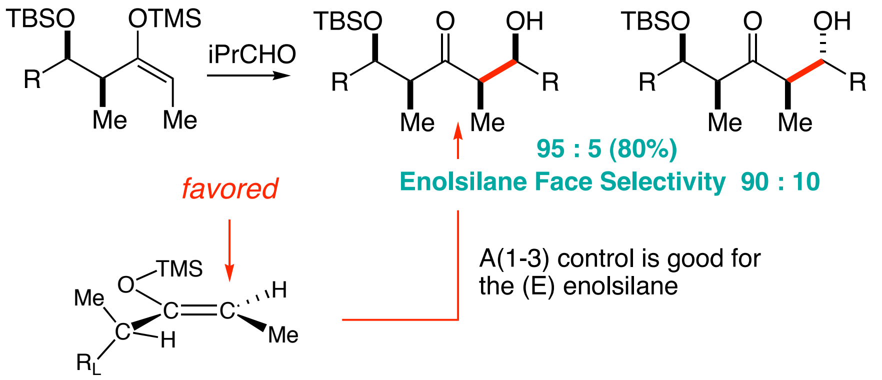
Enolslane Face Selection



R = iPr

59 : 41 (82%)

Enolsilane Face Selectivity 95 : 5

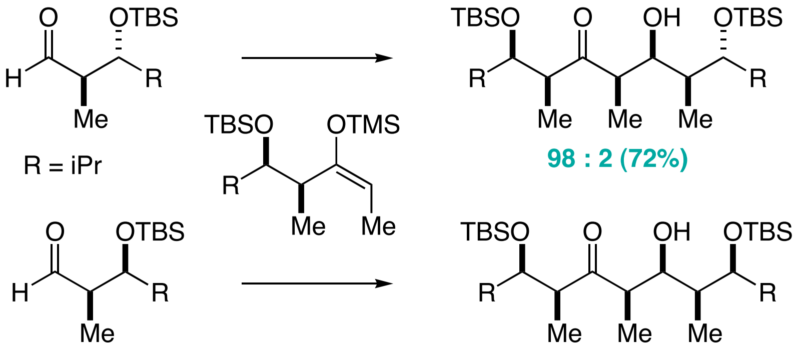


95 : 5 (80%)

Enolsilane Face Selectivity 90 : 10

A(1-3) control is good for
the (E) enolsilane

Double Stereodifferentiating *Syn* Aldol Rxns with Enolsilanes



R = iPr

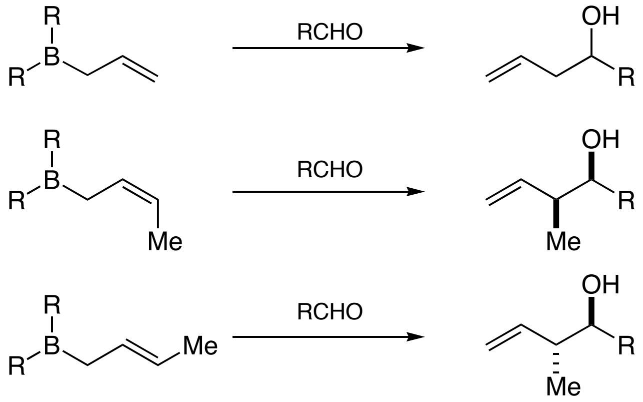
98 : 2 (72%)

98 : 2 (83%)

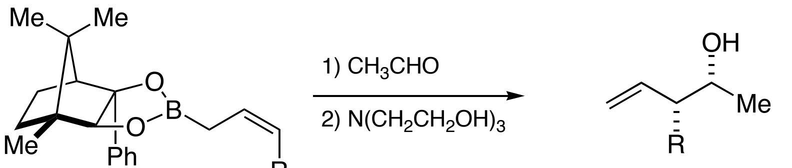
Allyl and Crotylmetal Species–1 : Boron

■ General Reviews of Allyl Metal Reagents: Comprehensive Organic Synthesis, **1991**;Vol. 2.

■ The General Reactions



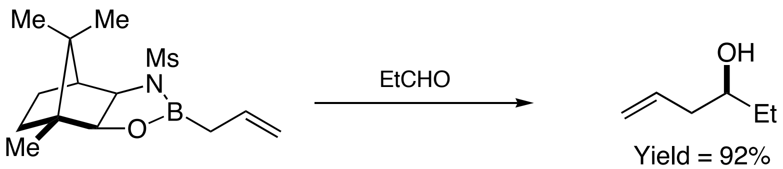
■ The Hoffman Chiral Allylboronic Esters



R = Me: Yield = 93%
ee = 60-70%

R = H: Yield = 92%
ee = 65%

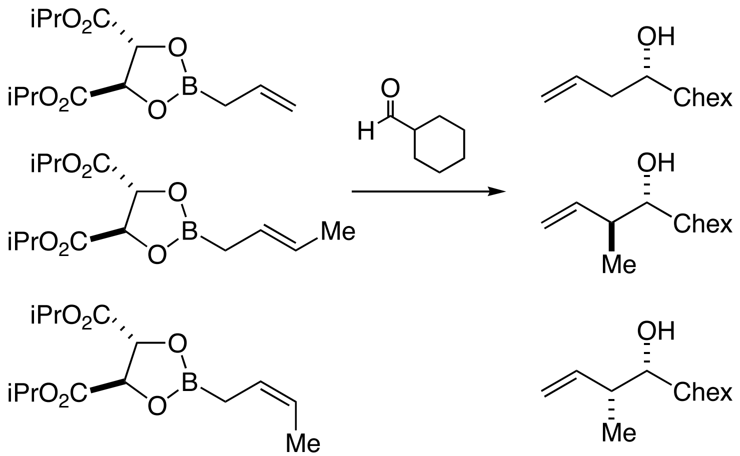
R. Hoffman *Tetrahedron Lett.* **1979**, 4653-4656.
ACIEE, **1978**, *17*, 768-769.



Yield = 92%
ee = 92%

M. Reetz *Chem. Ind. (London)* **1988**, 663-664.

■ The Tartrate-derived Allylboronic Esters

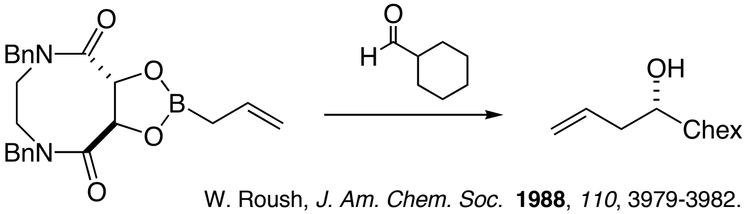


Yield = 72%
ee = 87%

Yield = 100%
ee = 91%

Yield = 90%
ee = 83%

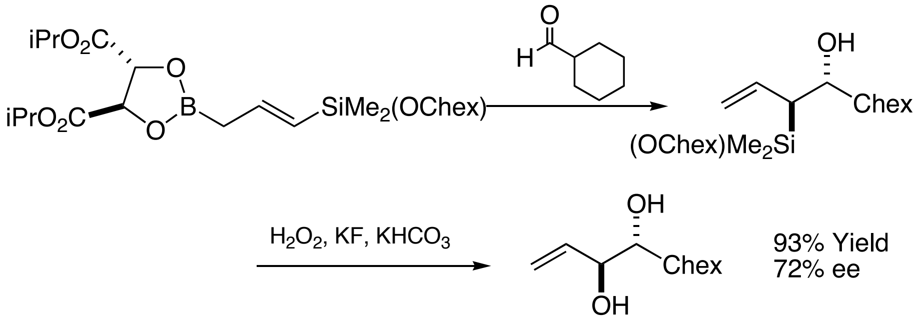
W. Roush, *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.
Tetrahedron Lett. **1988**, *29*, 5579-5582.



Yield = 40%
ee = 97%

W. Roush, *J. Am. Chem. Soc.* **1988**, *110*, 3979-3982.

■ A Reagent for the Generation of Anti-1,2-Diols

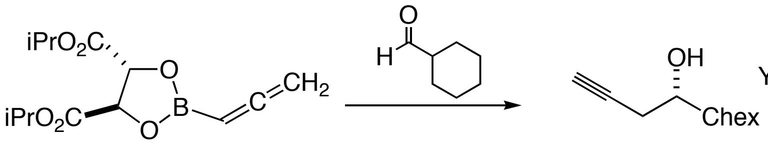


93% Yield
72% ee

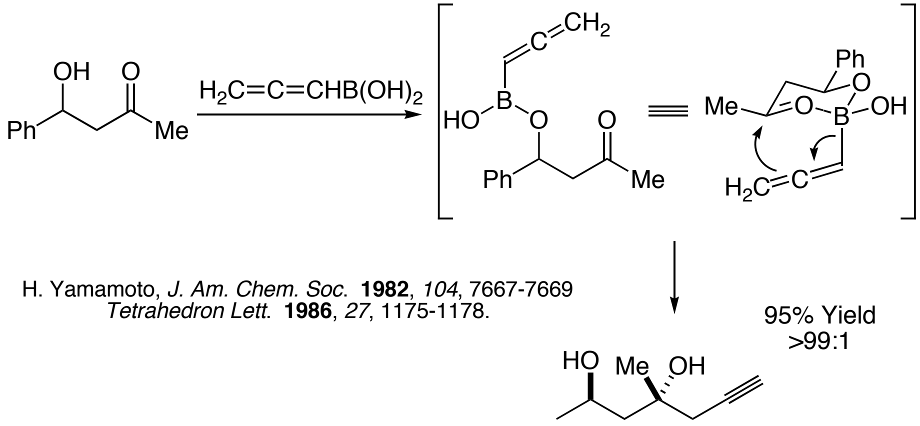
W. Roush, *Tetrahedron Lett.* **1990**, *31*, 7563-7566.

Allyl and Crotylmetal Species–2 : Boron

■ Allenylboronic Esters: Tartrate-derived Controllers and Internal Delivery



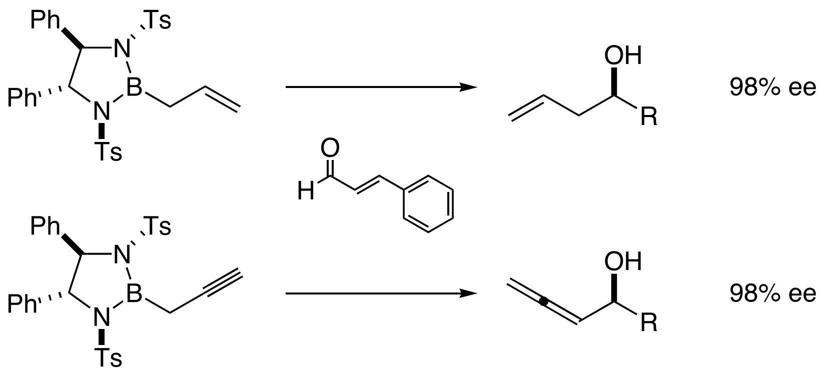
Yield = 56%
ee = 92%



95% Yield
>99:1

H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104*, 7667-7669
Tetrahedron Lett. **1986**, *27*, 1175-1178.

■ The Corey Stein Controller

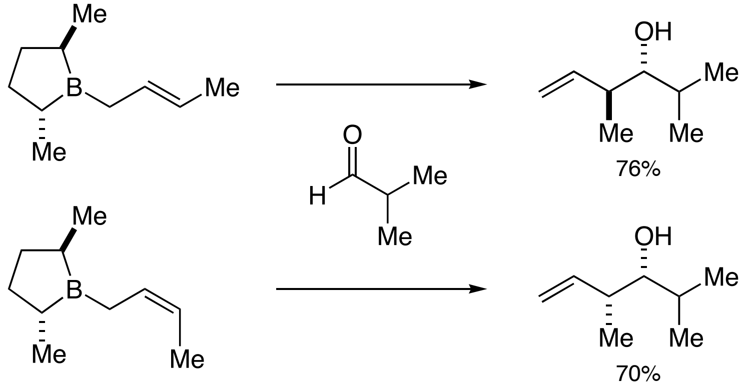


98% ee

98% ee

E. J. Corey, *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
J. Am. Chem. Soc. **1990**, *112*, 878-879.

■ The Masamune Borolane



96:4
97% ee

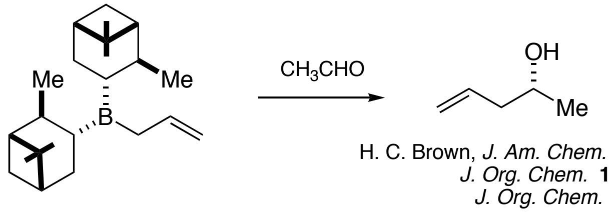
76%

96:4
93% ee

70%

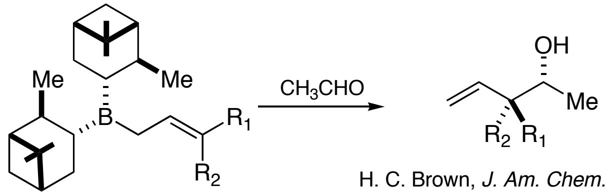
S. Masamune, *J. Org. Chem.* **1987**, *52*, 4831-4832.

■ The Brown IPC Controller



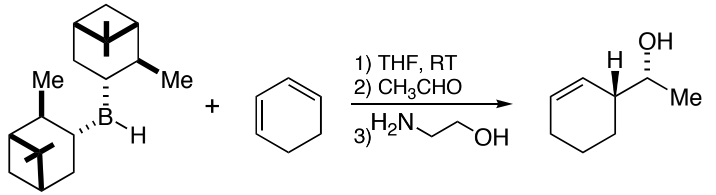
> 99% ee

H. C. Brown, *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093.
J. Org. Chem. **1991**, *56*, 401-404.
J. Org. Chem. **1992**, *57*, 6614.



R_1 = Me, R_2 = H: ee = 90%
R_1 = H, R_2 = Me: ee = 90%
R_1 = H, R_2 = OMe: ee = 90%

H. C. Brown, *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538.
See also: *Tetrahedron Lett.* **1990**, *31*, 455-458.



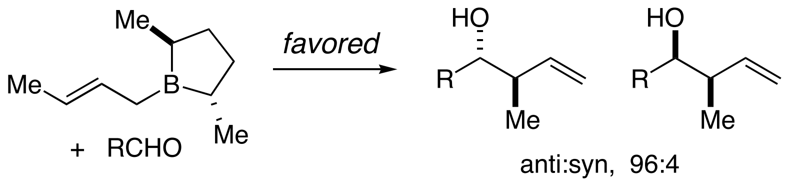
ee = 94%

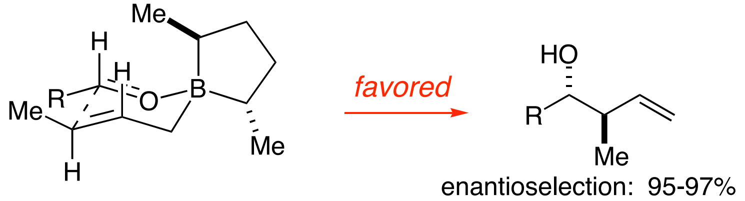
H. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2633.

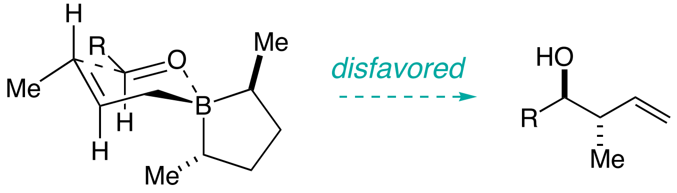
Allyl and Crotylmetal Species–3

The Allylboron Reagents Add to Carbonyl Compounds via a Zimmerman-Traxler Transition State

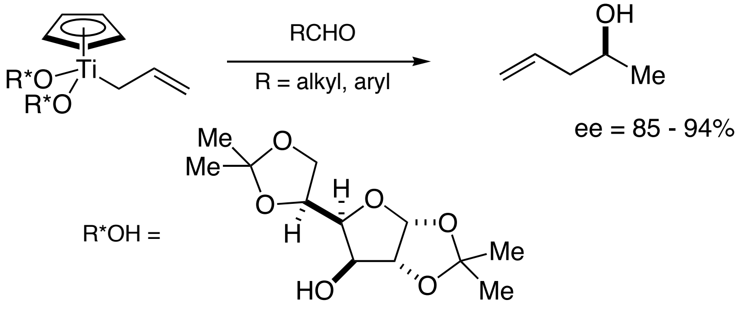
Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831







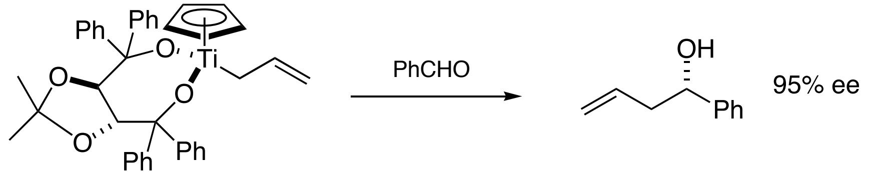
An Enantioselective Allyltitanium Reagent



M. Riediker, R. Duthaler, *ACIEE*, **1989**, *28*, 494-495.
In *Organic Synthesis via Organometallics*, **1991**, 285-309.
J. Am. Chem. Soc. **1992**, *114*, 2321-2336.

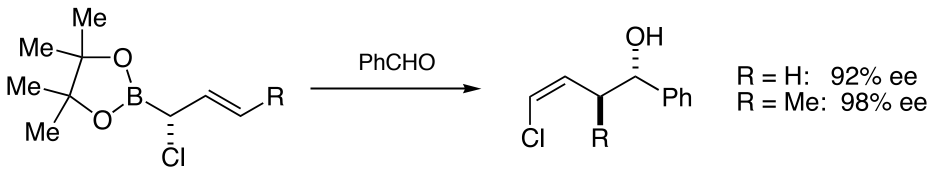
Duthaler *Chem. Rev.* **1992**, *92*, 807

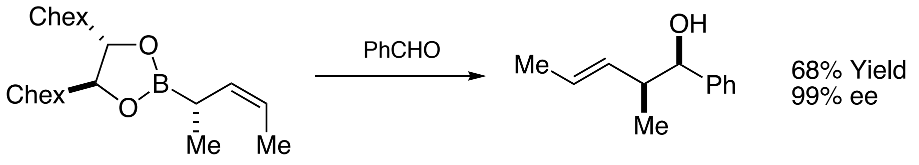
Another Enantioselective Allyltitanium Reagent



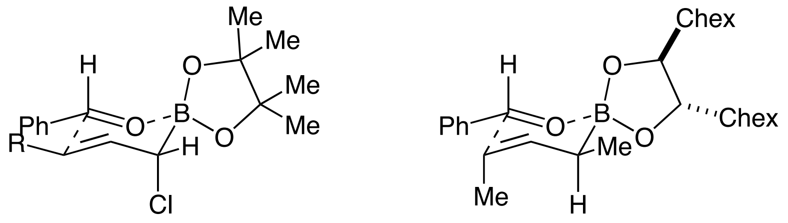
R. Duthaler, *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336.

Chiral α-Substituted Allyl Metal Reagents: Boron





R. Hoffman, *Chem. Ber.* **1986**, *119*, 2013-2024.
Chem. Ber. **1988**, *121*, 1501-1507.
ACIEE, **1986**, *25*, 1028-1030.



The favored transition states

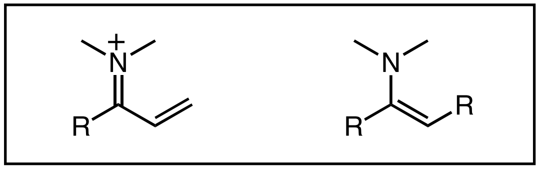
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 29

Enamines and Imminium Ions in Organocatalysis



- Introduction and General Trends
- Historical Backgound - The Hajos-Parrish Reaction
- Direct Asymmetric Aldol and Mannich Reactions
- α-Amination and Oxidation Reactions
- Michael Reactions
- Cascade Reactions

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Jonathan F. Lawrence

Friday, December 1, 2006

Assigned Journal Articles

"Theory of Asymmetric Organocatalysis of Aldol and Related Reactions: Rationalizations and Predictions."
K. N. Houk, et al. *Acc. Chem. Res.*, **37**, 558 (2004). **(handout)**

"Enantioselective Organocatalysis",
Dalko, Peter, *ACIEE*. **40**, 3726 (2001). **(electronic handout)**

Other Useful References

"Enamine Catalysis is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents." List, B. *Acc. Chem. Res.* **37**, 548 (2004).

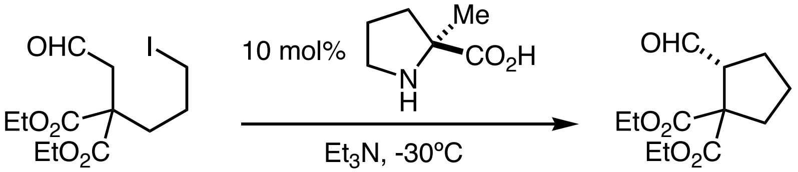
"Enamine-Based Organocatalysis with Proline and Diamines: The Development of Direct Catalytic Aymmetric Aldol, Mannich, Michael, and Diels-Alder Reactions." Barbas, C., *Acc. Chem. Res.* **37**, 580 (2004).

"Proline Catalyzed Asymmetric Reactions" List, Benjamin, *Tetrahedron,* **58**, 5573 (2002).

"Asymmetric Aminocatalysis", List, Benjamin,*Synlett*, **11**, 1675 (2001).

"Amino Acids and Peptides as Asymmetric Organocatalysts", Miller, Scott *Tetrahedron*, 58, 2481 (2002).

Provide a mechanism that accounts for enantiomerically enriched products.

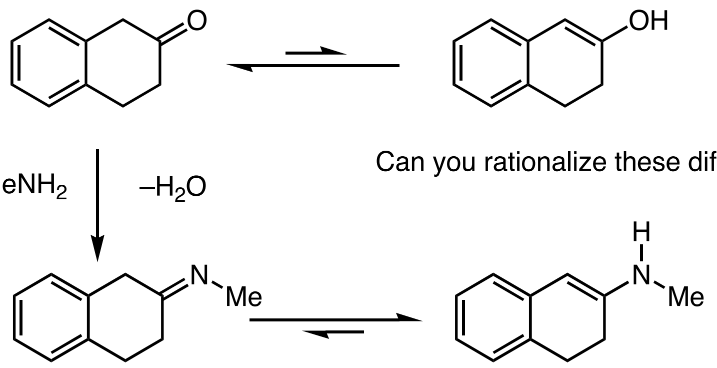


92% yield, 95% ee

List, B. *JACS* **2004**, 126, 450-451.

Properties and Reactivity of Enamines

Tautomeric Equilibria: Ketones vs. Imines



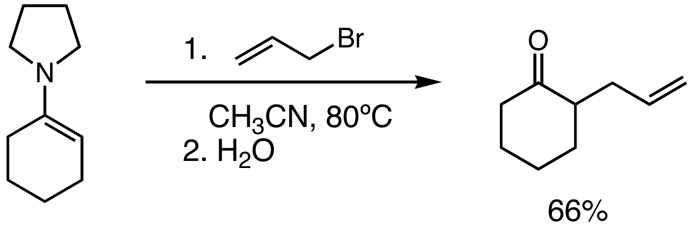
Keq ~ 10^{-3}

Can you rationalize these differences?

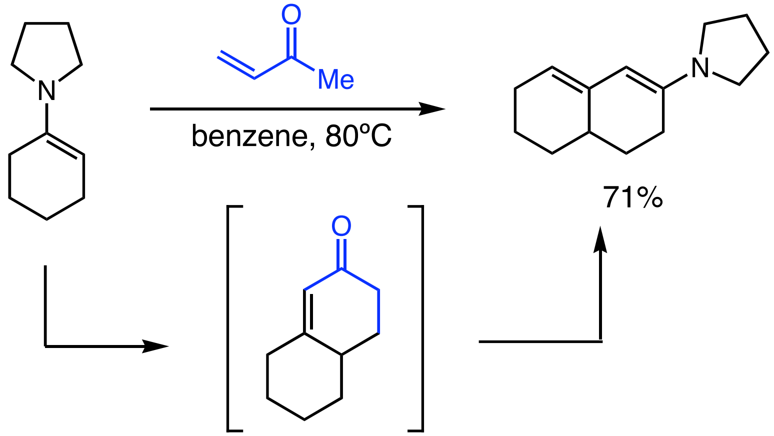
Keq > 10

The enamine content in an analogous imine is invariably higher than its carbonyl counterpart. In the case above, ring conjugation now stabilizes the enamine tautomer as the major tautomer in solution.

Representative akylation and acylation reactions of enamines



66%

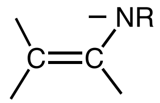
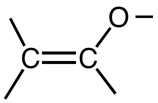
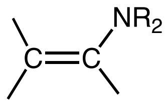
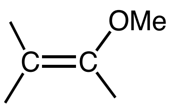
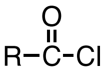
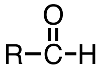
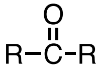
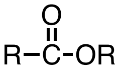
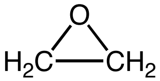
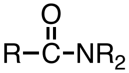


71%

Stork, G. *JACS* **1963**, 85, 207.

Decreasing Nucleophilicity - - - - - - ->

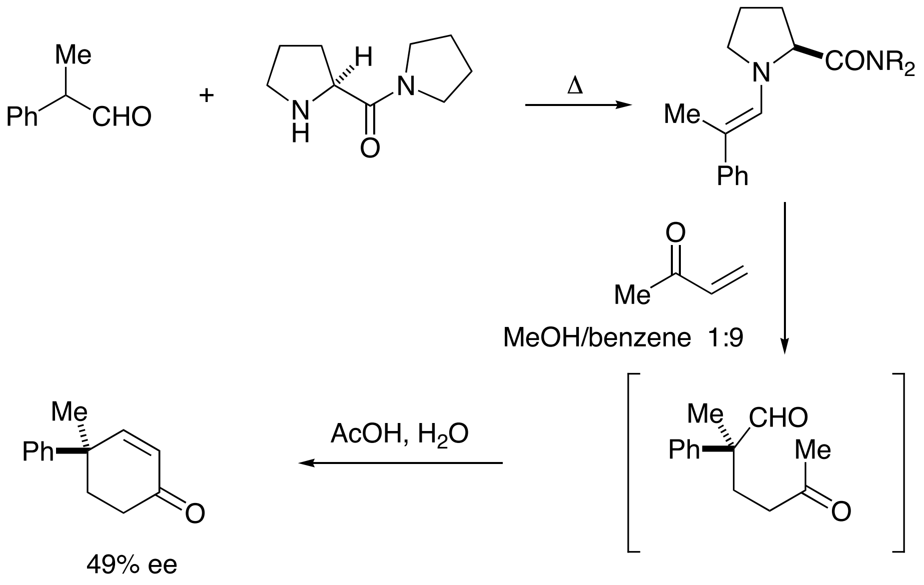
Decreasing Electrophilicity - - - - ->

Nucleophile Electrophile				
Br$_2$, O$_3$	+	+	+	+
H_3O^+	+	+	+	+
 $R-C(=O)-Cl$	+	+	+	■
 $R-C(=O)-H$	+	+	+	■
 $R-C(=O)-R$	+	+	▨	■
Me—I	+	+	▨	■
 $R-C(=O)-OR$	+	+	■	■
	+	▨	■	■
Me$_2$CH—I	+	▨	■	■
 $R-C(=O)-NR_2$	■	■	■	■

- Nature uses enamines, "stabilized" enolates, and enol derivatives in C–C bond constructions extensively.

The First Asymmetric Variant

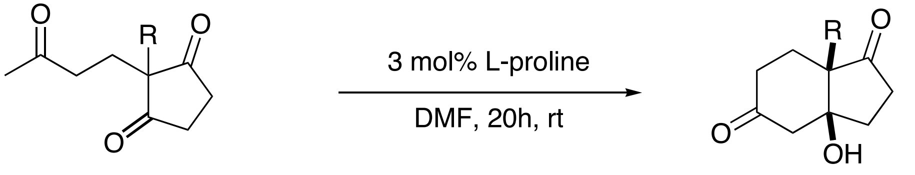
Yamada, 1969



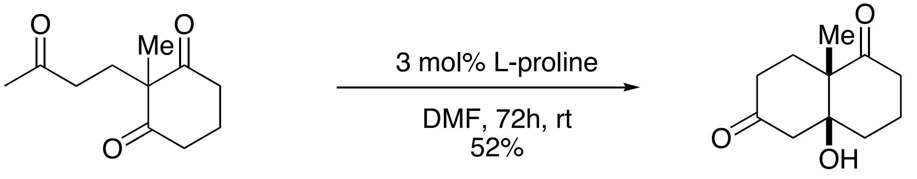
Yamada, S. *TL* **1969**, *10*, 4237.

The Seminal Experiments

Hajos and Parrish, 1974



R = Me 100%, 93% ee
R = Et 71%, 99% ee

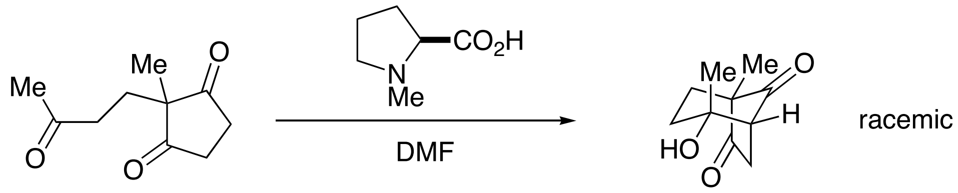


74% ee

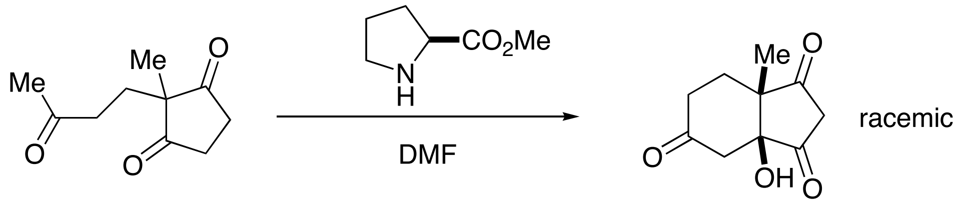
Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.
Eder, U., Sauer, G., Weichert, R. *ACIEE* **1971**, *10*, 496.

- the use of protic solvents severly diminished enantioselectivity
- other amino acids as catalysts lead to decreased chemical yield and enantioselectivity
- Eder, Sauer, and Weichert obtained the corresponding aldol condensation product in similar optical purity using 47 mol% L-proline and 1N $HClO_4$

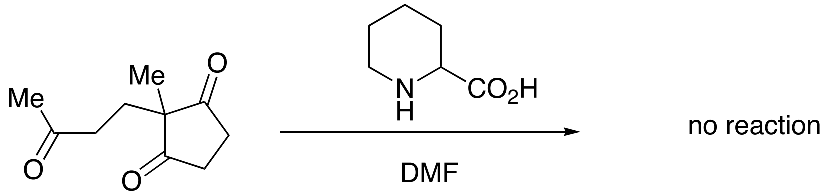
Effect of the Catalyst



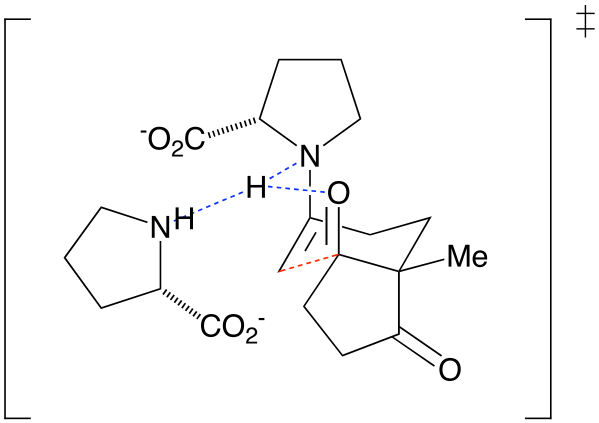
"major product"



"major product"



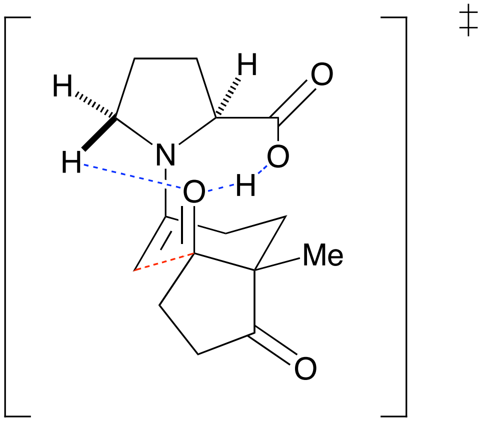
Agami, 1984 - 1986



- favorable (enamine) N-H---O hydrogen bond
- N-H *anti* to carboxylate electrostatically favored
- reaction is second-order in proline (non-linear effect observed)
- second proline acts as a proton shuttle, allowing enamine to be nucleophilic

Agami, C. *TL* **1986**, *13*, 1501.

Houk, 2001 - 2003



- N-H---O hydrogen bond does not lower energy of transition state
- favorable O-H---O hydrogen bond
- additional NC-H---O hydrogen bond further stabilizes system
- reaction is first order in proline (supported by kinetic data) and no non-linear effect observed

Houk, K. *JACS* **2001**, *123*, 12911.
Houk, K., List, B. *JACS* **2003**, *125*, 16.

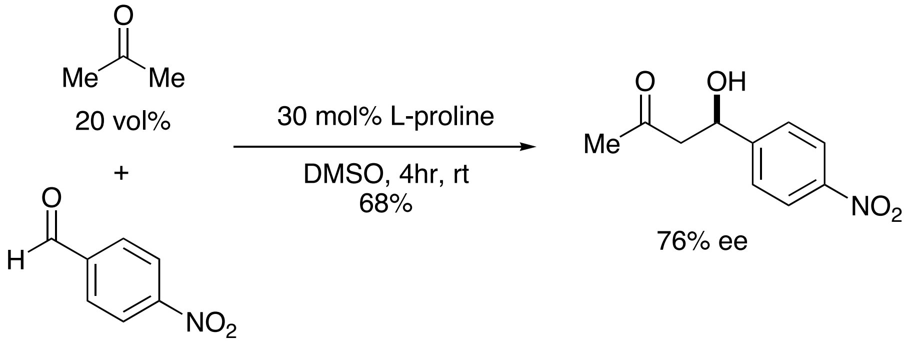
general hydrogen bond energies

O -H - - O	3.0-8.0 kcal
C -H - - O	0.5-3.8 kcal

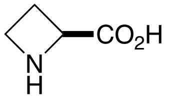
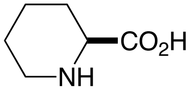
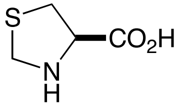
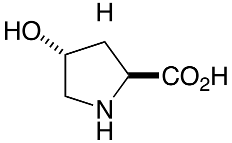
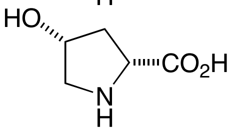
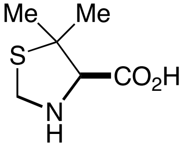
for a discussion on R_3N^+-C-H---O=C bonds, see:
Houk, K. *JACS*, **2002**, *124*, 7163.

The Direct Proline-Catalyzed Aldol Reaction

The initial reaction

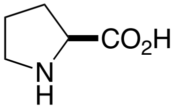


Catalyst Screen

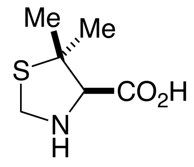
compound	% yield	% ee
(L)-His, (L)-Val (L)-Tyr, (L)-Phe	< 10	--
	55	40
	< 10	--
	67	73
	85	78
	> 50	- 62
	66	86

Aldehyde scope

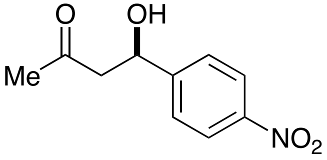
Catalyst:



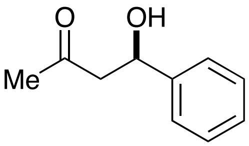
1



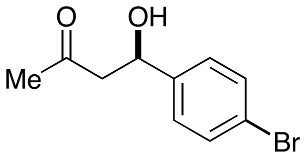
2



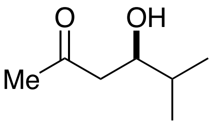
cat. **1**, 68% y., 76% ee
cat. **2**, 60% y., 86% ee



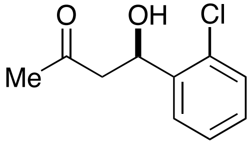
cat. **1**, 62% y., 60% ee
cat. **2**, 60% y., 89% ee



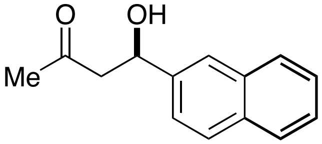
cat. **1**, 74% y., 65% ee
cat. **2**, 65% y., 67% ee



cat. **1**, 97% y., 96% ee
cat. **2**, 61% y., 94% ee



cat. **1**, 94% y., 69% ee
cat. **2**, 71% y., 74% ee



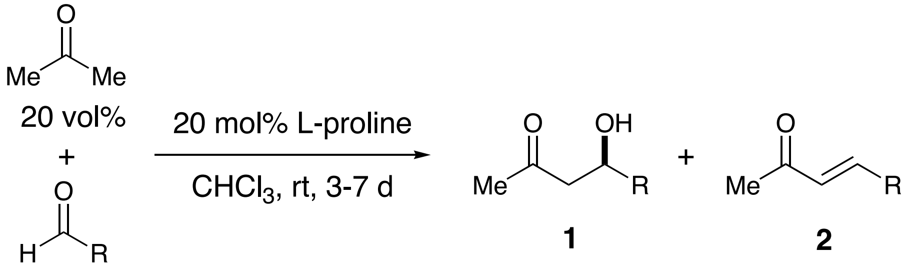
cat. **1**, 54% y., 77% ee
cat. **2**, 60% y., 88% ee

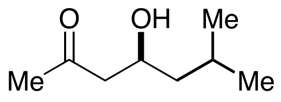
- ■ α–unbranched aldehydes unsuccessful due to self-aldolization

List, B. *JACS*, **2000**, *122*, 2395.
Barbas, C. *JACS*, **2001**, *123*, 5260.

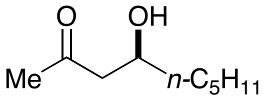
The Direct Proline-Catalyzed Aldol Reation

Conditions which tolerate α–unbranched aldehydes





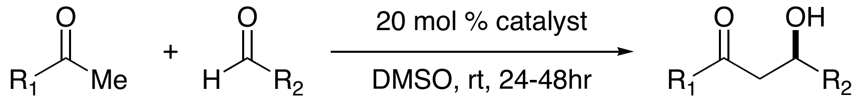
23% yield **1**, 61% ee, 46% yield **2**

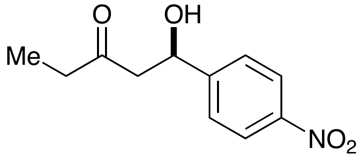


35% yield **1**, 73% ee, 40% yield **2**

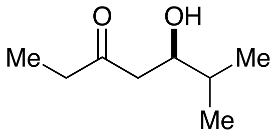
List, B. *OL* **2001**, *3*, 573.

Ketone scope





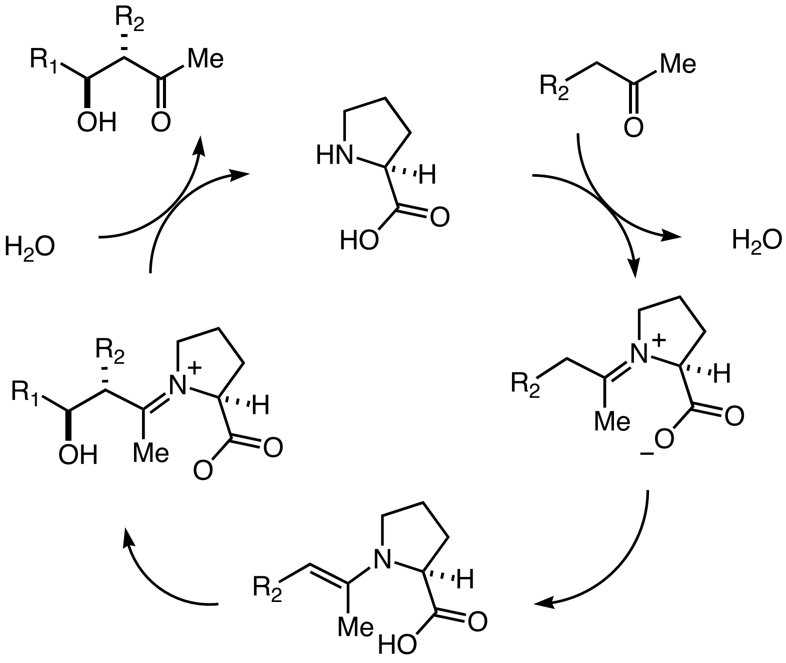
cat. **1**, 65% yield, 77% ee
cat. **2**, 57% yield, 74% ee



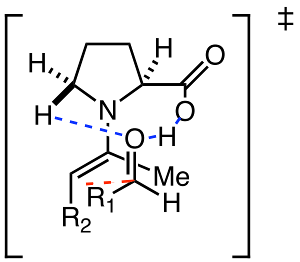
cat. **1**, 60% yield, 80% ee
cat. **2**, <5% yield, ---

Barbas, C. *JACS,* **2001**, *123*, 5260.

Direct Aldol Mechanism

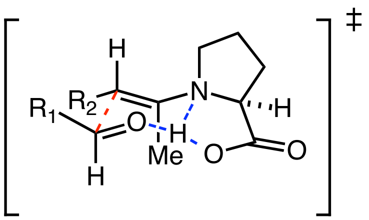


Houk's calculated T.S.:



- synclinal approach of aldehyde
- R_1 in pseudo-eqitorial position
- C-H - - O distance ~ 2.4 Å
- DFT calculations in DMSO

Previously Proposed T.S.:

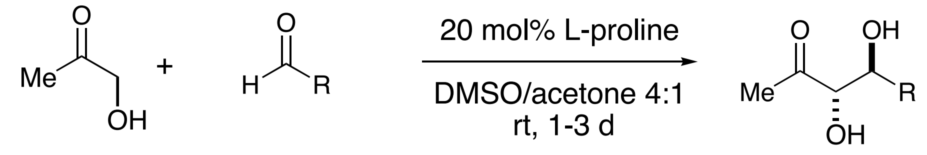


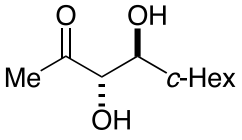
- metal-free Zimmerman-Traxler model

List, B. *JACS* **2000**, *122*, 2395.
List, B., Houk, K. *JACS* **2003**, *125*, 2475.

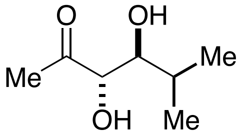
The Direct Aldol Reaction - Other Applications

Synthesis of 1,2-diols

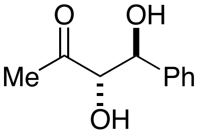




60% yield, >99% ee
>20:1 dr



62% yield, >99% ee
>20:1 dr



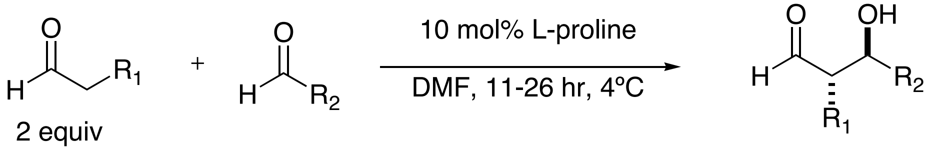
83% yield, 80% ee
1:1 dr
(DMTC cat. gives 95% ee)

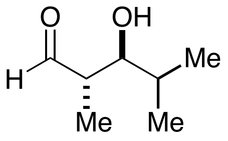
Generation of more substituted enamine due to:

- increased acidity of α–proton
- increased stability of enamine due to $O_{n.b.}$ --> π^* C=C

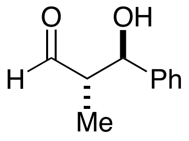
List, B. *JACS*, **2000**, *122*, 2395.
Barbas, C. *JACS,* **2001**, *123*, 5260.

Donor scope expanded to include aldehydes

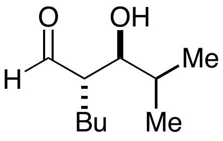




82% yield, >99% ee
24:1 dr



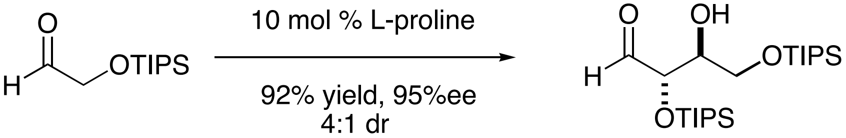
81% yield, 99% ee
3:1 dr

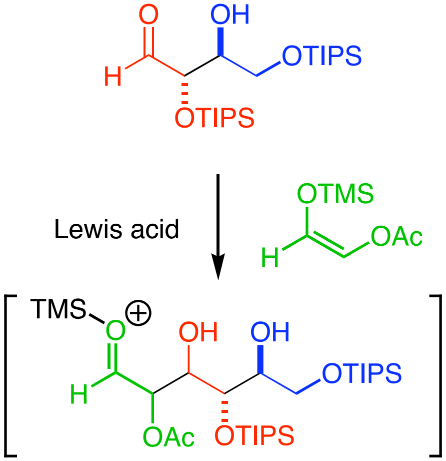


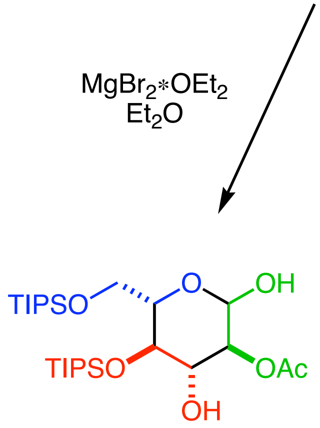
80% yield, 98% ee
3:1 dr

MacMillan, D. *JACS*, **2002**, *124*, 6798.

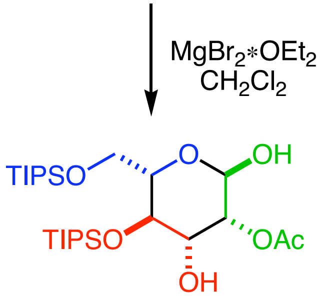
Synthesis of carbohydrates



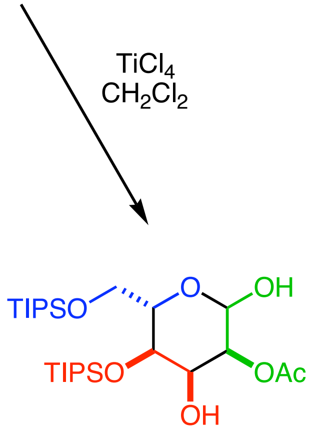




79% yield, 95% ee
10:1 dr
Glucose



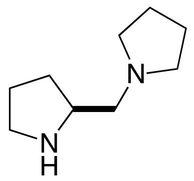
87% yield, 95% ee
>19:1 dr
Mannose



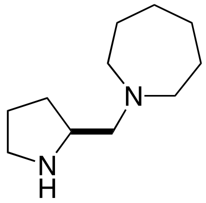
97% yield, 95% ee
>19:1 dr
Allose

MacMiillan, D. *Science*, **2004**, 305, 1752.

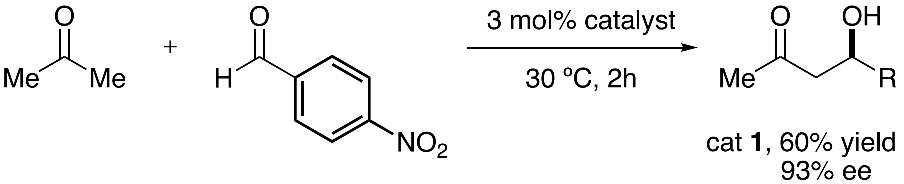
Other catalysts for the direct aldol reaction



1

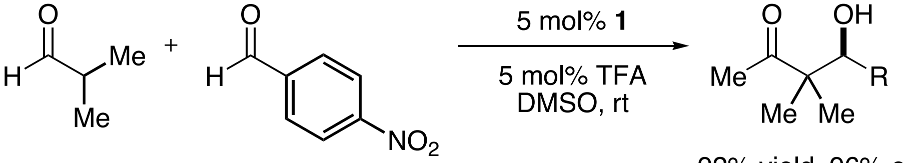


2



cat **1**, 60% yield
93% ee
cat **2**, 72% yield
93% ee

Yamamoto, *Tet.* **2002**, *58*, 8167.



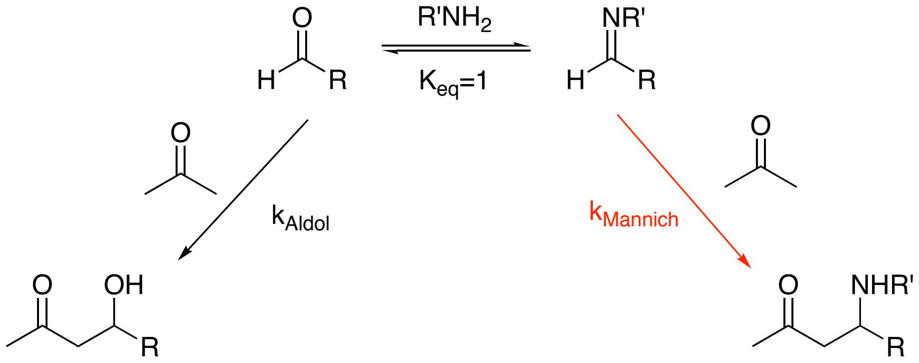
92% yield, 96% ee

- unsymmetrical α,α–disubstituted aldehydes give low diastereoselectivity

Barbas, C., *ACIEE* **2004**, *43*, 2420.

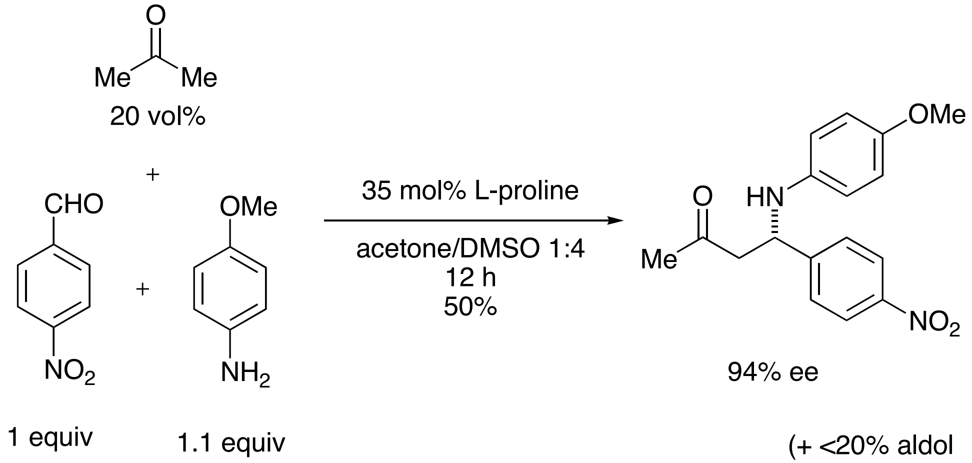
Mannich reaction: First report

Reaction rate considerations



- enamime addition must be faster to the imine than to the corresponding aldehyde ($k_{Mannich} > k_{Aldol}$)
- formation of the aldimine must be faster than aldol addition

Three-component coupling

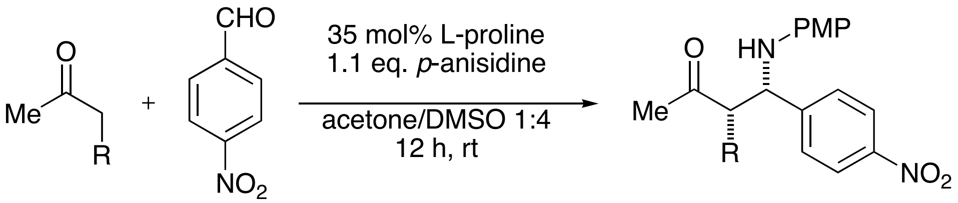


(+ <20% aldol product)

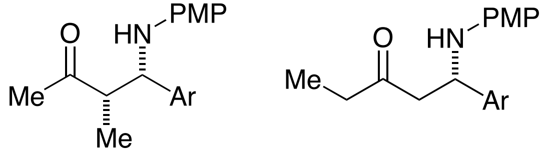
List, B. *JACS*, **2000**, *122,* 9336.

The Proline-Catalyzed Direct Mannich Reaction

Substrate Variation



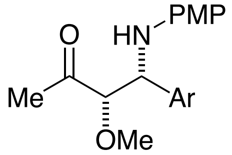
When R = Me



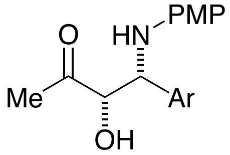
1 **2**

95% yield,
ratio **1**:**2** = 2.5:1
1 = 99% ee,
>20:1 dr
2 = 94% ee

When R = OMe, OH



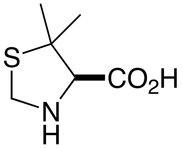
93% yield, 98% ee
>20:1 dr



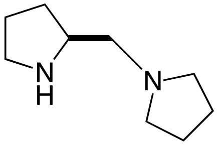
92% yield, >99% ee
>20:1 dr

List, B. *JACS*, **2000**, *122*, 9336.

- aliphatic and aromatic aldehydes are both good substrates
- as electron donationfrom aldehyde increases, enantioselectivity and diastereoselectivity decrease
- proline uniquely effective as Mannich reaction catalyst



60% y., 16% ee

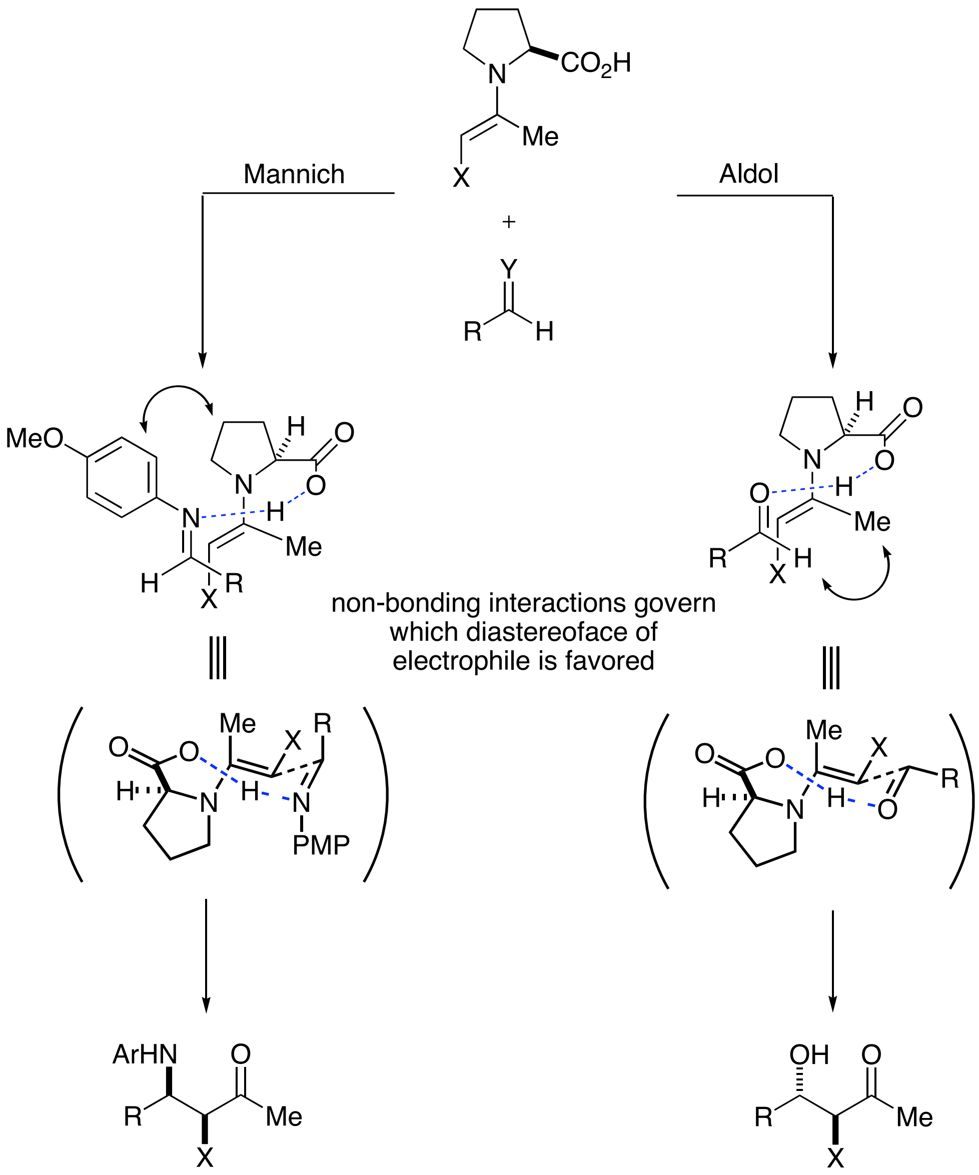


26% y., 0% ee

results for reaction
with isovalerylaldehyde

List, B. *JACS* **2002**, *124*, 827.

Transition State comparison

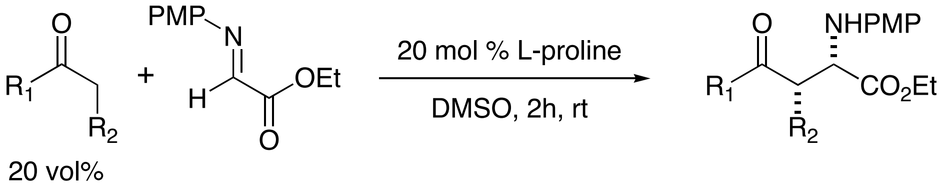


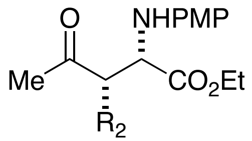
non-bonding interactions govern
which diastereoface of
electrophile is favored

List, B. *JACS* **2002**, *124*, 827.

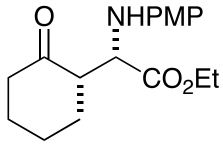
Other electrophiles can be used

α-imino ethyl glyoxylate with ketones:





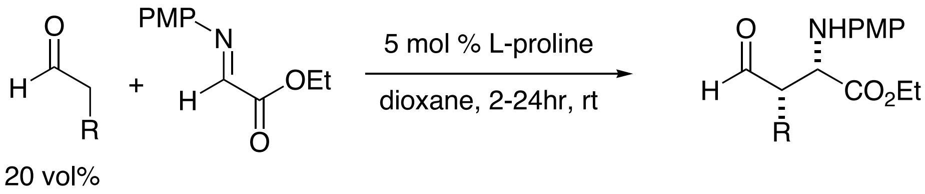
for R_2=Me, allyl, OH
62-79% yield, >99% ee,
>20:1 dr



81% yield, >99% ee,
>20:1 dr

Barbas, C. *JACS* **2002**, *124*, 1842

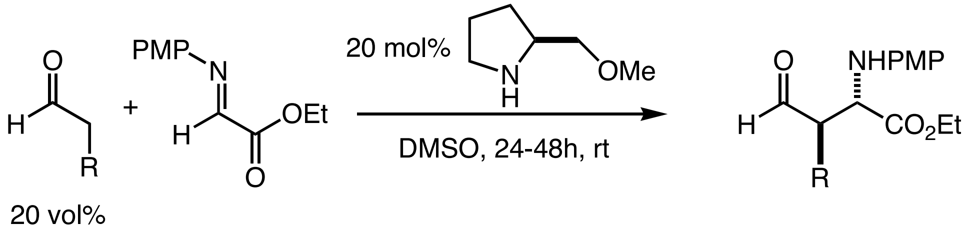
α-imino ethyl glyoxylate with aldehydes:



R =	% yield	dr	% ee
Me	72	1.1:1	99
Et	57	1.5:1	99
i-Pr	81	>10:1	93
n-Bu	81	3:1	99
n-Pent	89	>19:1	>99

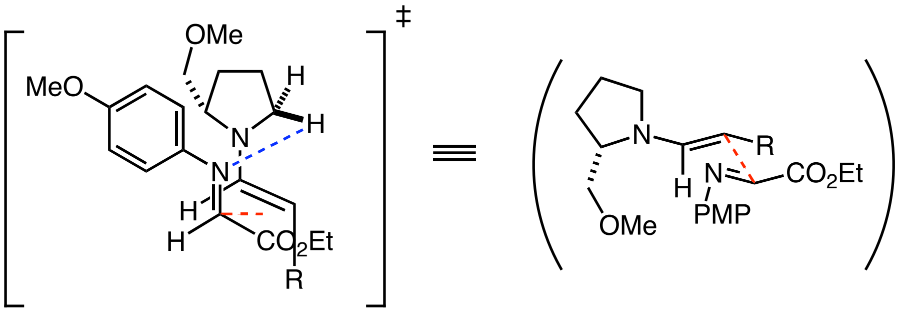
Barbas, C. *JACS* **2002**, *124*, 1866.

A fortuitous finding: an *anti*-selective Mannich catalyst



R =	% yield	dr	% ee
Et	44	1:1	75
i-Pr	52	10:1	82
n-Bu	54	10:1	74
t-Bu	57	>10:1	92
n-Pent	78	>10:1	76
n-Hex	68	>19:1	76

transition state:

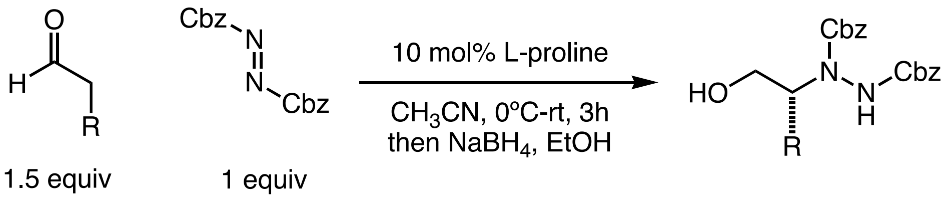


Barbas, C. *TL* **2002**, *43*, 7749.

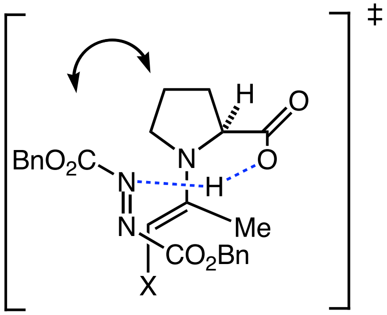
For a review of SMP use in asymmetric synthesis, see:
Enders, D. *Synthesis* **1996**, 1403.

Direct Amination and Oxidation Reactions

Amination: a route to α-amino alcohols and ketones

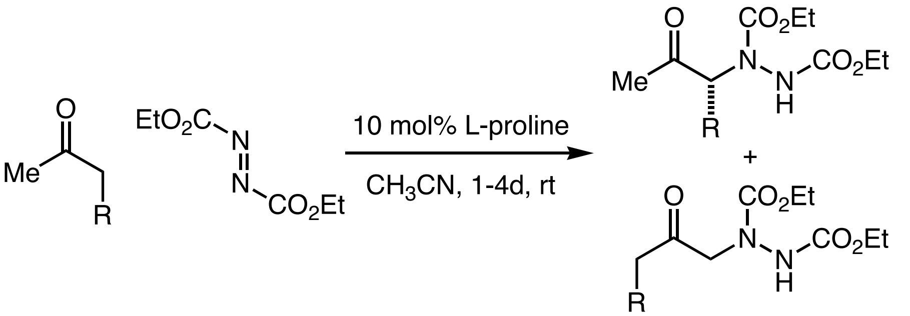


R =	% yield	% ee
Me	97	>95
n-Pr	93	>95
n-Bu	94	97
i-Pr	99	96
Bn	95	>95



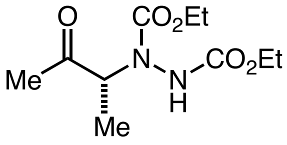
- longer reaction time leads to epimerization, so aldehyde is reduced *in situ*

List, B. *JACS* **2002**, 124, 5656.

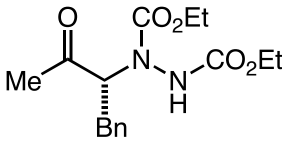


1

2



ratio **1**:**2** = 10:1
80% yield, 95% ee

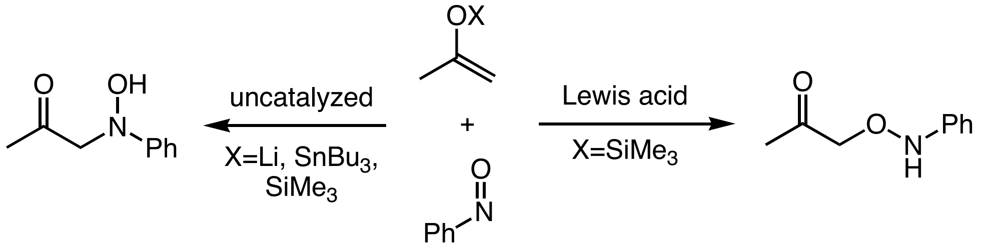


ratio **1**:**2** = 4.5:1
92% yield, 98% ee

Jorgensen, *JACS* **2002**, *124*, 6254.

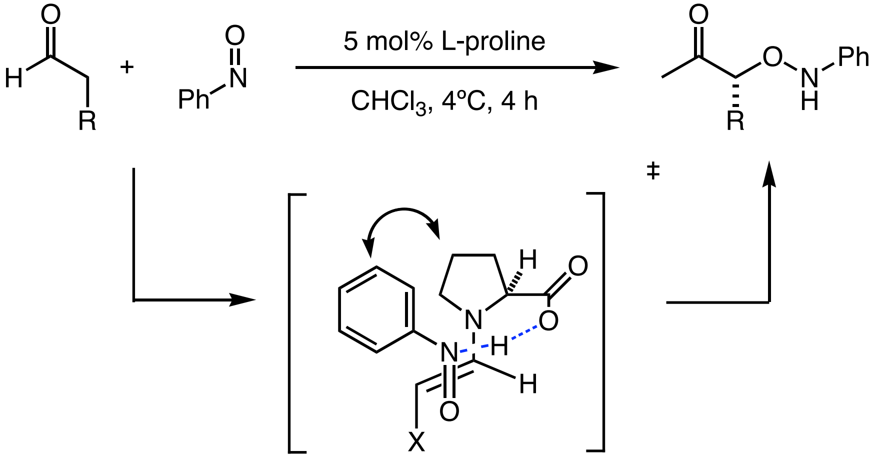
α-Oxidation of aldehydes with nitrosobenzene

The choice of reaction conditions determines N or O selelctive addition:



Yamamoto, H. *OL*, **2002**, *4*, 3579.

Larger basicity of nitrogen allows proline to catalyze O-nucleophilic addition:

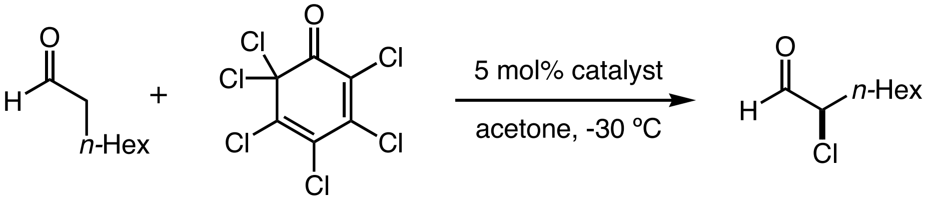


R =	% yield	% ee
Me	88	97
n-Bu	79	98
i-Pr	85	99
$CH_2CH=CH_2$	99	96
Bn	95	97
Ph	60	99
$(CH_2)_3OTIPS$	76	98
CH_2-(3'-N-methyl indole)	83	98

MacMillan, D. *JACS* **2003**, *125*, 10808.

Direct Halogenation Reactions

Chlorination

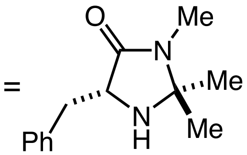


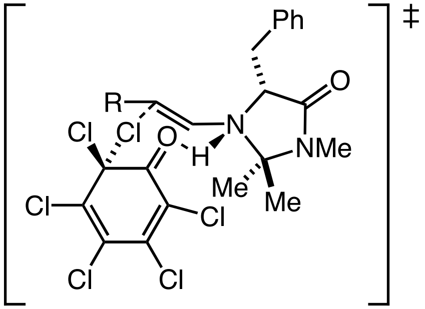
1 equiv

1.2 equiv

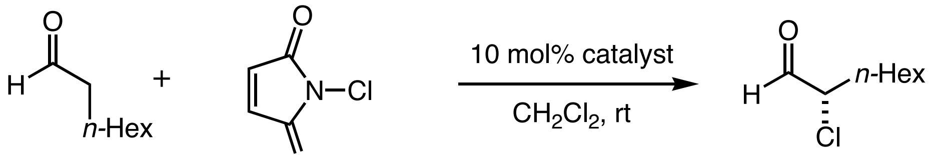
71% yield
92% ee

catalyst =





MacMillan, *JACS* **2004**, *126*, 4108.

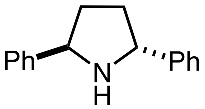


1 equiv

1.3 equiv

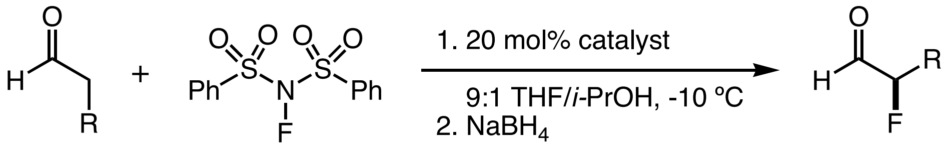
99% yield
95% ee

catalyst =



Jorgensen, *JACS* **2004**, *126*, 4790.

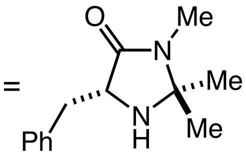
Fluorination

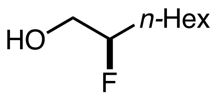


1 equiv

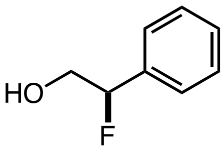
5 equiv

catalyst =

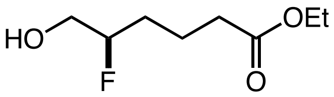




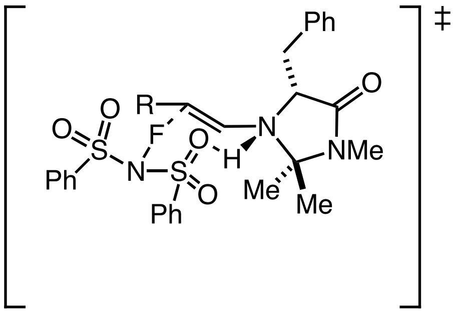
71% yield
92% ee



54% yield
99% ee



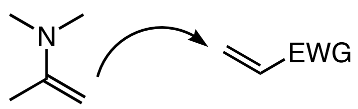
77% yield
91% ee



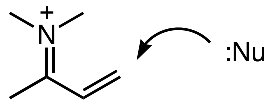
MacMillan, D. *JACS* **2005**, *127*, 8827.

Direct Organocatalytic Michael Reactions

There are two mechanistic possibilities:



additions to:
- alkylidene malonates
- α,β–unsaturated nitroalkenes

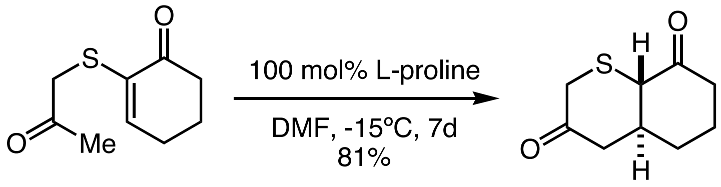


additions of:
- malonate esters
- nitroalkanes
- aromatics (Friedel-Crafts reactions)
- silyloxy furans

Diels-Alder reaction
Dipolar cycloaddition

Enamine examples:

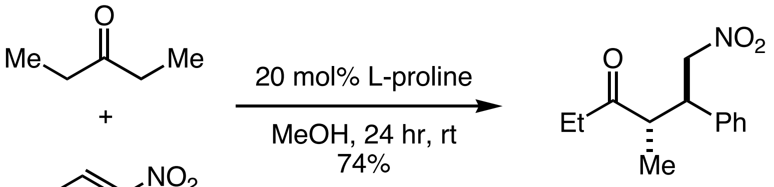
An early attempt:



28% ee

Kozikowski, A. *JOC*, **1989**, *54*, 2275.

More recent results with nitroolefins:

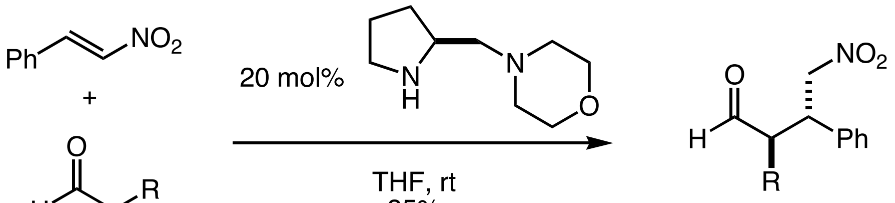


73% ee, dr=7.3:1

■ MeOH required as solvent to obtain high ee

Enders, *Synlett* **2002**, 26.

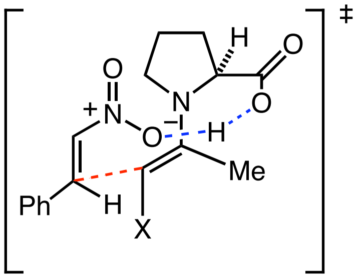
Use of a diamine catalyst

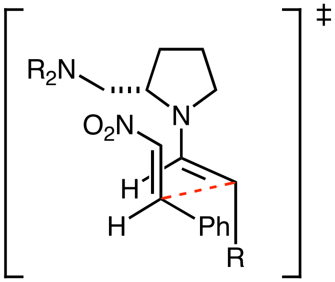


R = Me 56% ee, dr=9:1
R = *i*-Pr 72% ee, dr=11:1

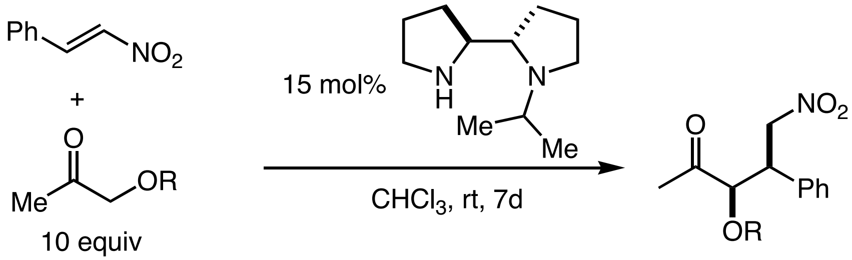
Barbas, C. *OL* **2001**, *3*, 3737.

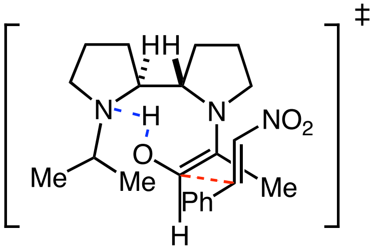
Contrasting transition states:





A highly enantioselective system:





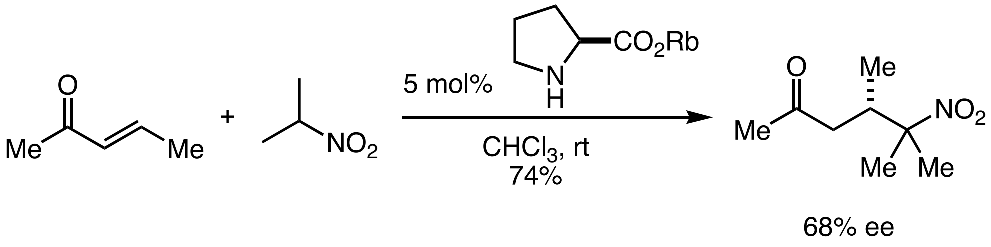
		syn/anti	
R	yield	dr	ee
Me	75	1:5	69
H	79	5:1	98

Alexakis, A. *OL*, **2003**, *5*, 2559.

Direct Organocatalytic Michael Reactions and Cycloadditons

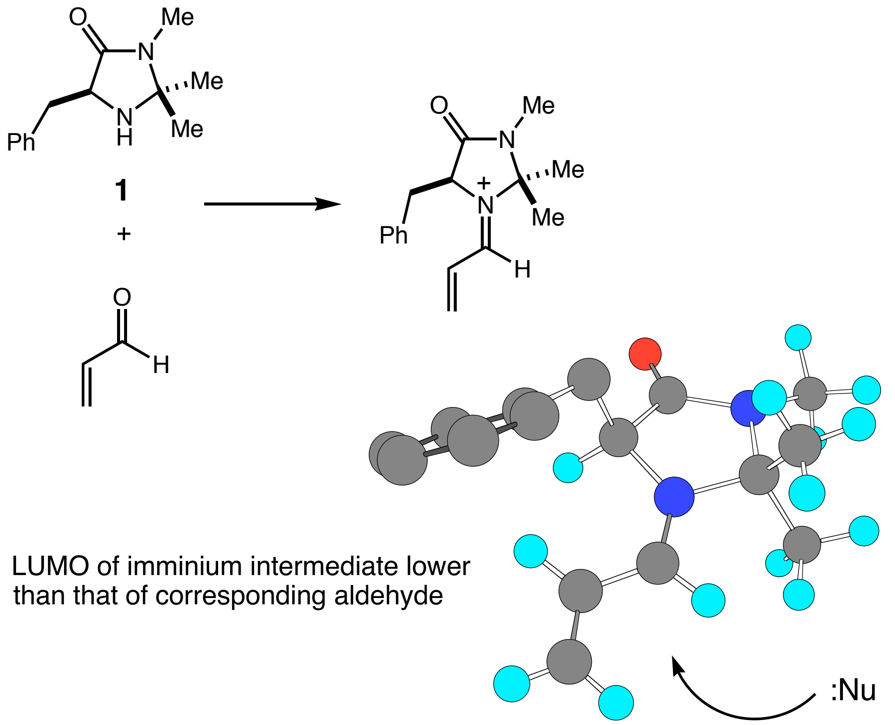
Imminium examples

Proline is only mildly successful:



Yamaguchi, *JOC* **1996**, *61*, 3520.

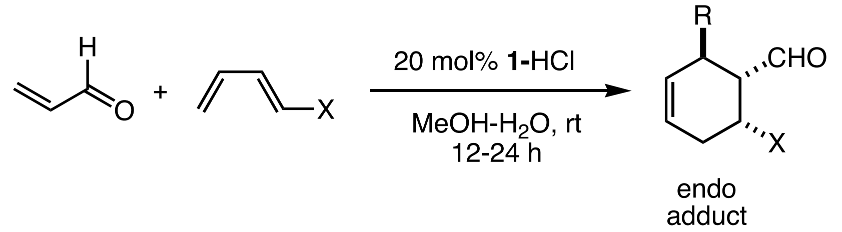
MacMillan introduces a new catalyst:

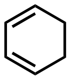
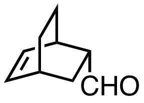
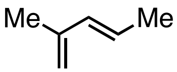
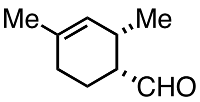


- LUMO of imminium intermediate lower than that of corresponding aldehyde

A listing of reactions catalyzed by MacMillan's imidazolidinone

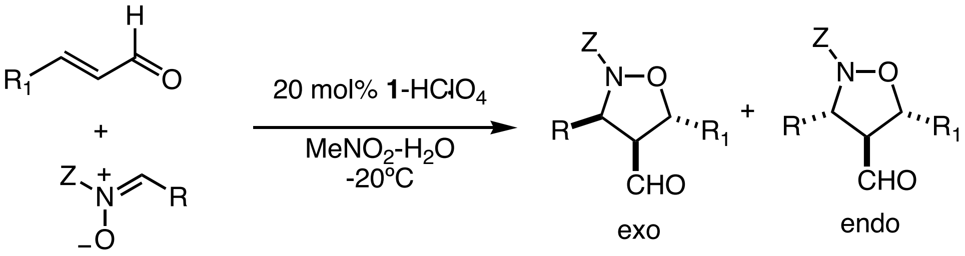
Diels-Alder reactions:

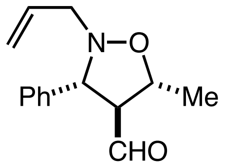


diene	product	
		82% yield, 94% ee, 14:1 endo/exo
		75% yield, 90% ee, 5:1 endo/exo

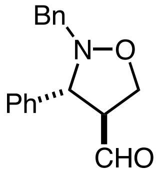
MacMillan, D. *JACS* **2000**, *122*, 4243.

Nitrone cycloadditons:

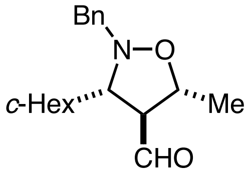




73% yield, 98% ee
13:1 endo/edo



72% yield, 90% ee
4:1 endo/edo

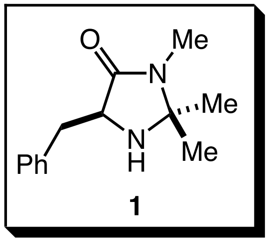


70% yield, 99% ee
>20:1 endo/edo

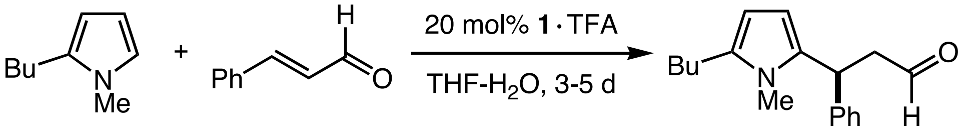
MacMillan, D. *JACS* **2000**, *122*, 9874

Direct Organocatalytic Michael Reaction

More chiral imidazolidinone catalyzed reactions

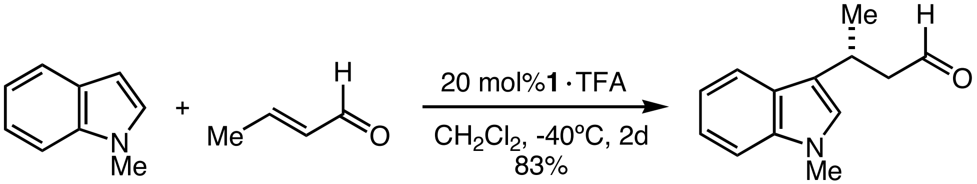


Friedel-Crafts reactions:



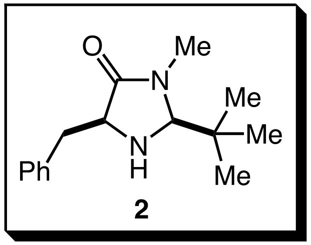
87% y, 90% ee

MacMillan, D. *JACS* **2001**, *123*, 4371.

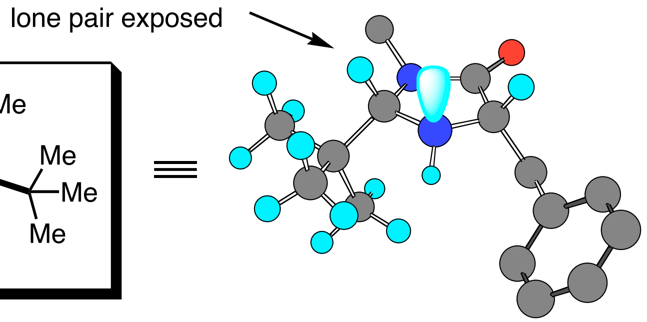


58% ee

- reaction was sluggish with **1**, so a new catalyst was developed

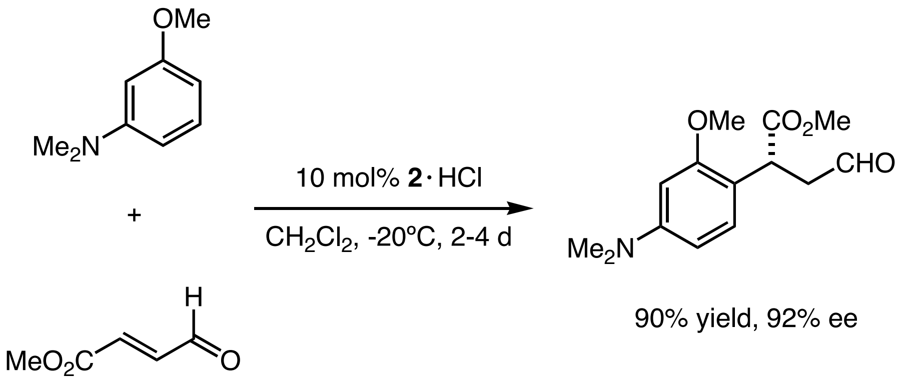


≡



- above reaction now gives 92% ee with **2** due to increased reaction rate and steric shielding from *tert*-butyl group

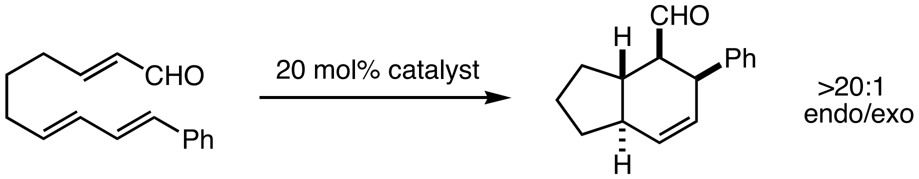
MacMillan, D. *JACS* **2002**, *124*, 1172.



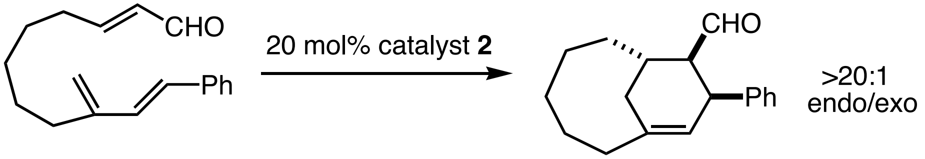
90% yield, 92% ee

MacMillan, D. *JACS* **2002**, *124,* 7894.

IMDA reactions:



catalyst **1**: 84%, 77% ee
2: 85%, 93% ee

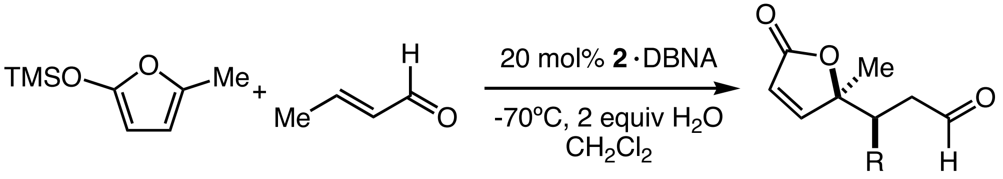


65% y, 98% ee

MacMillan, D. *JACS* **2005**, *127,* 11616.

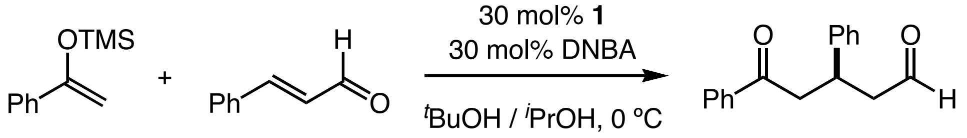
Organocatalytic Michael Reactions and Cascade Processes

Mukaiyama michael reactions:



81% yield, 92% ee
22:1 syn/anti

MacMillan, D. *JACS* **2003**, *125*, 1192.

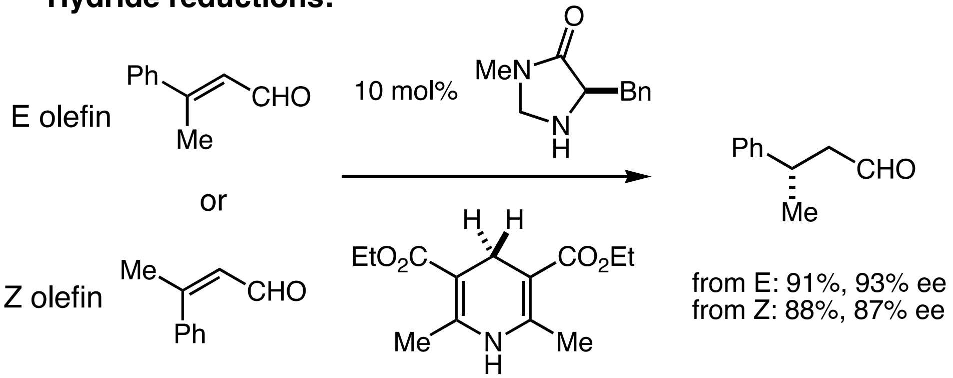


75% yield, 90% ee

Wang, W. *OL* **2005**, *7*, 1637.

- note that Lewis acid catalysis promotes 1,2 addition with enals

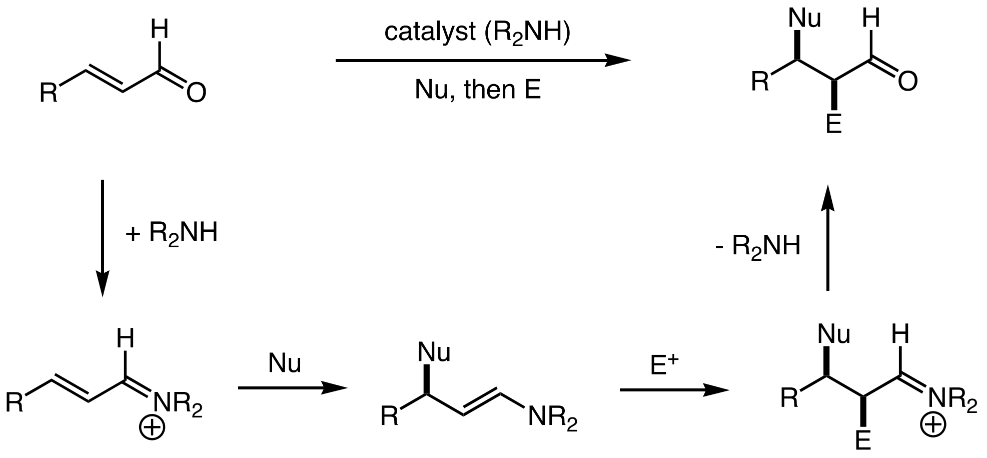
Hydride reductions:



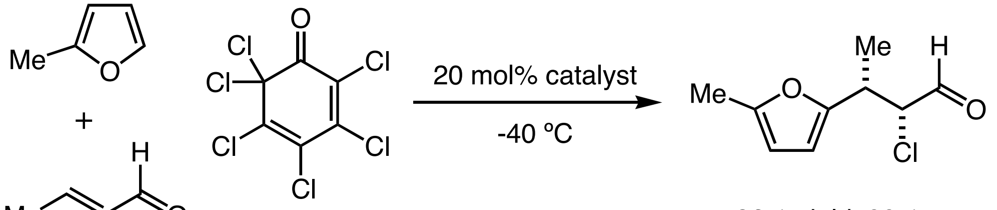
from E: 91%, 93% ee
from Z: 88%, 87% ee

MacMillan, D. *JACS* **2005**, *127*, 32.
see also: List, B. *ACIEE* **2004**, *43*, 6660.

Cascade reactions combine imminium and enamine catalysis

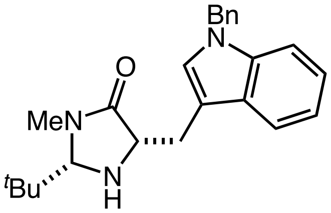


Friedel-Crafts plus chlorination:

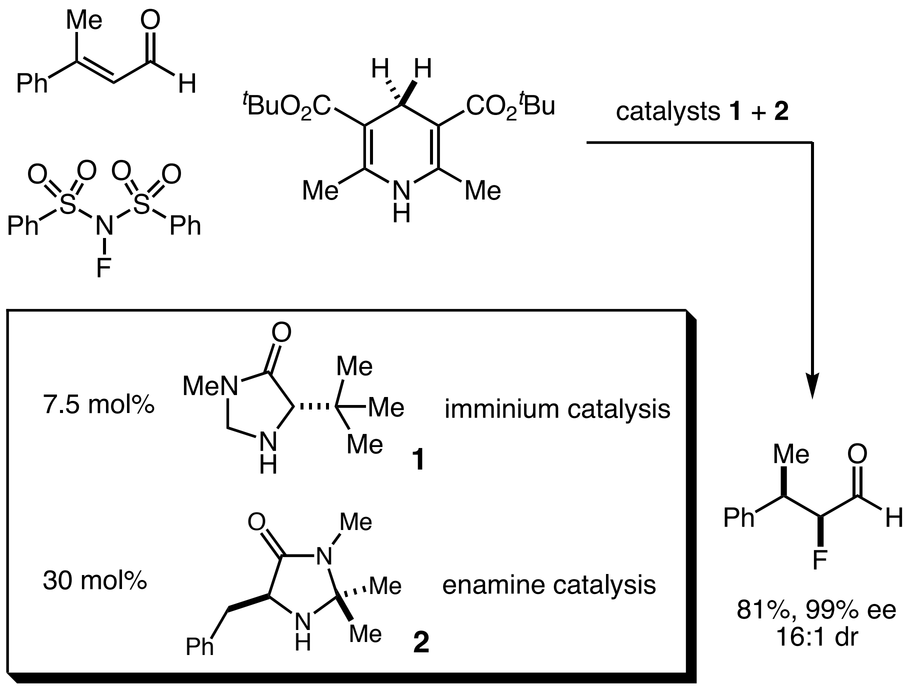


86% yield, 99% ee
14:1 dr

catalyst =

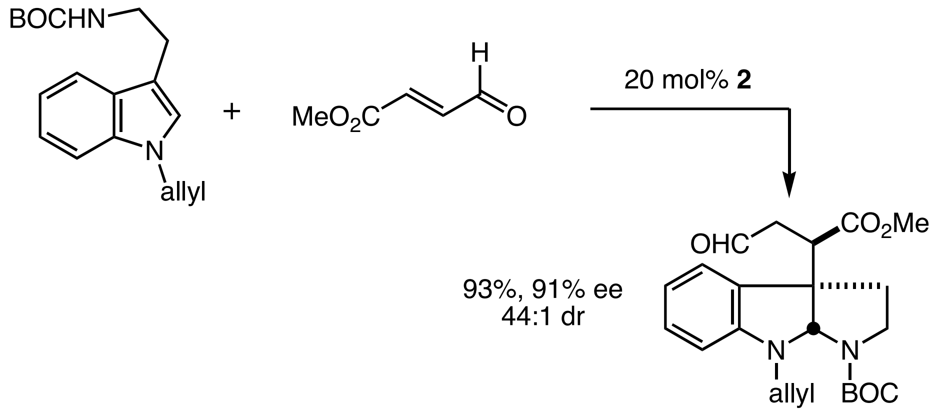


Hydride reduction plus fluorination:



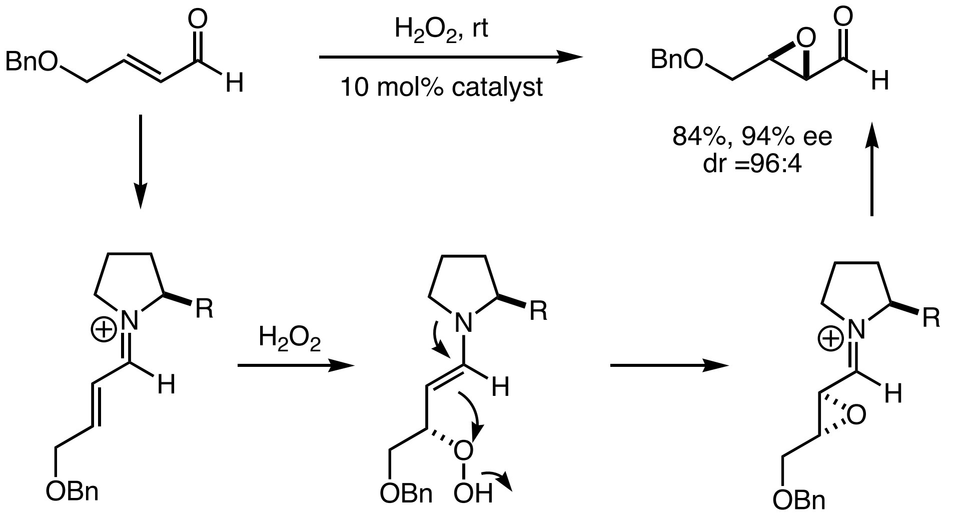
MacMillan, D. *JACS* **2005**, *127*, 15051.

Intramolecular cascade reactions



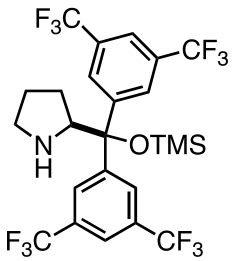
MacMillan, D. *PNAS* **2004**, *101*, 5482.

Epoxidation:



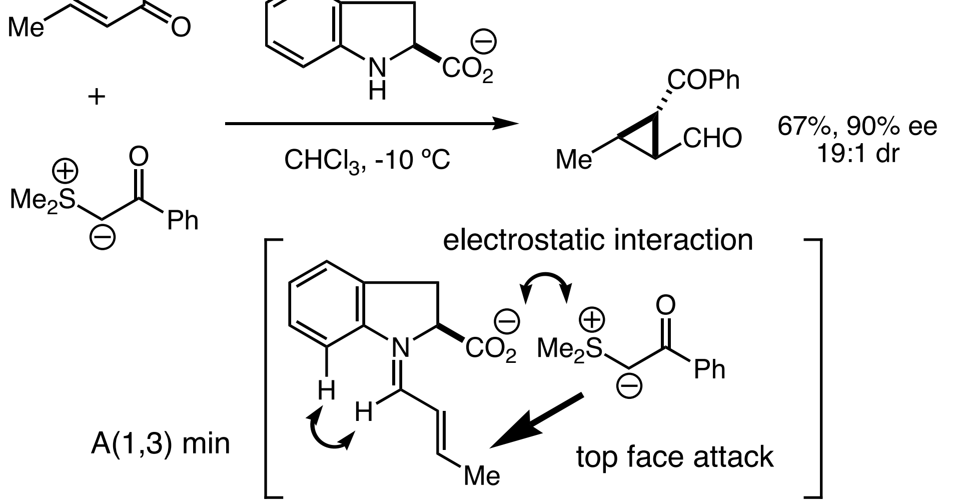
Jorgensen, K. *JACS* **2005**, *127*, 6964.

catalyst =



Cyclopropanation:

20 mol%



MacMillan, D. *JACS* **2005**, *127*, 3240.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 30

Functional Group Classification Scheme for Polar Bond Constructions

- Historical Perspective
- Charge Affinity Patterns
- Functional Group Classification Scheme
- The Chemistry of the $-NO_2$ Group
- The Chemistry of the $-N_2$ Group

Reading Assignment for this Week:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."
D. A. Evans *Unpublished manuscript.* ***(Handout)***

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239. ***(Handout)***

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis'"
Seebach, D. et. al, *Chimia*, **1979**, *33*, 1-18. ***(Handout)***

D. A. Evans

Monday
December 5, 2005

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."
M. Saltzman *J. Chem. Ed.* **1972**, *49*, 750. ***(Handout)***

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."
A. Lapworth *J. Chem. Soc.* **1922**, *121*, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, *44*, 1293.

Monographs:

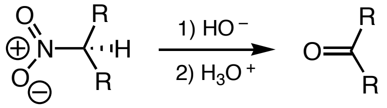
Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis".; John Wiley & Sons, Inc.: New York, 1987.

Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: NY, 1991.

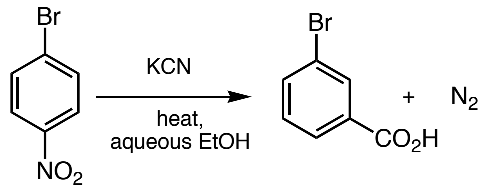
Ono, N., "The Nitro Group in Organic Synthesis", Wiley-VCH, 2001

Several Interesting Problems

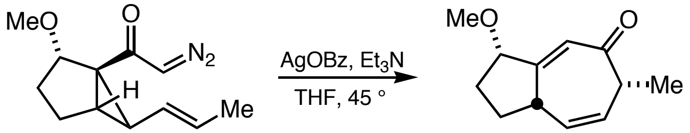
Provide a mechanism for the Nef reaction



The **von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If ^{15}N-labeled KCN is used, the N_2 formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.



Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, *125*, 13624). Please provide a mechanism for the illustrated transformation. Your answer should include clear 3-D drawings where relevant. the answer may be found in the database.



95% yield

Ambiphilic Functional Groups

Required Reading:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."
D. A. Evans *Unpublished manuscript.*

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis"'
Seebach, D. et. al, *Chimia*, **1979**, *33*, 1-18.

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A. Lapworth *J. Chem. Soc.* **1922**, *121*, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, *44*, 1293.

"Displacement of Aliphatic Nitro Groups by Carbon & Heteroatom Nucleophiles." R. Tamura, A. Kamimura, N. Ono *Synthesis* **1991**, 423.

"Functionalized Nitroalkanes as Useful Reagents for Alkyl Anion Synthons." G. Rosini, R. Ballini *Synthesis* **1988**, 833.

"Conjugated Nitroalkenes: Versatile Intermediates in Organic Synthesis."
A. G. M. Barrett, G. G. Graboski *Chem. Rev.* **1986**, *86*, 751.

Monographs:

Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis".; John Wiley & Sons, Inc.: New York, 1987.

Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: New York, 1991.

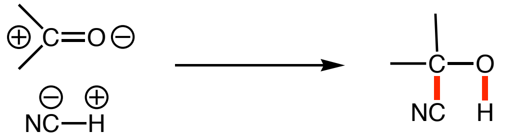
Arthur Lapworth (1872–1941)

Lapworth was among the first to understand and conceptualize the effect of heteroatomic substituents on the reactivity of individual carbon centers, and how this effect is propagated through the carbon framework of organic molecules.

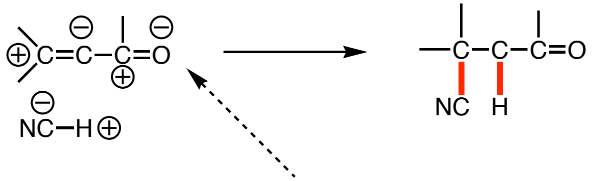
Lapworth's Theory of Alternating Polarities:

"Latent Polarities of Atoms and Mechanism of Reaction, with Special Reference to Carbonyl Compounds."
A. Lapworth *Mem. Manchester. Lit. Phil. Soc.* **1920**, *64 (3)*, 1.

"The addition of electrolytes to the carbonyl compound invariably proceeded as if the carbon were more positive than the oxygen atom, and invariably selected the negative ion; for example:"



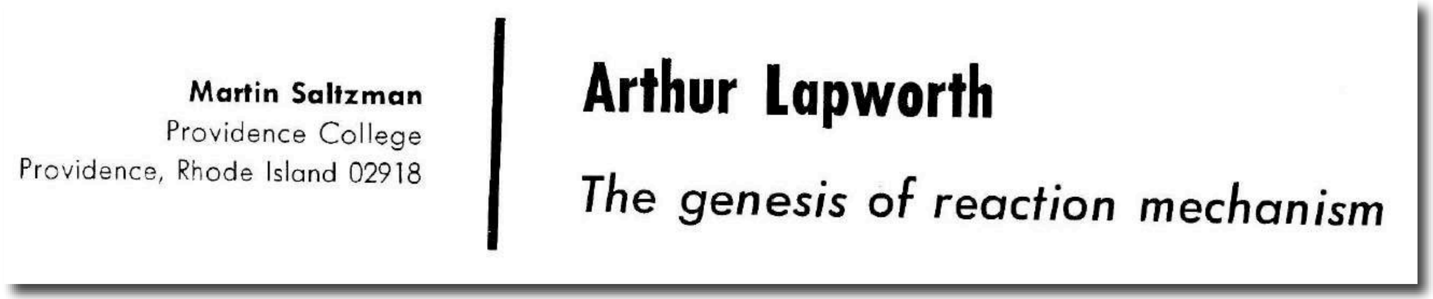
"The extension of the influence of the directing, or "key atom," over a long range seems to require for its fullest display the presence of double bonds, and usually in conjugated positions...."



The "key atom" is the one with the most electronegative character, in this case the carbonyl oxygen.

anionoid/cationoid --------------➤ nucleophilic/electrophilic

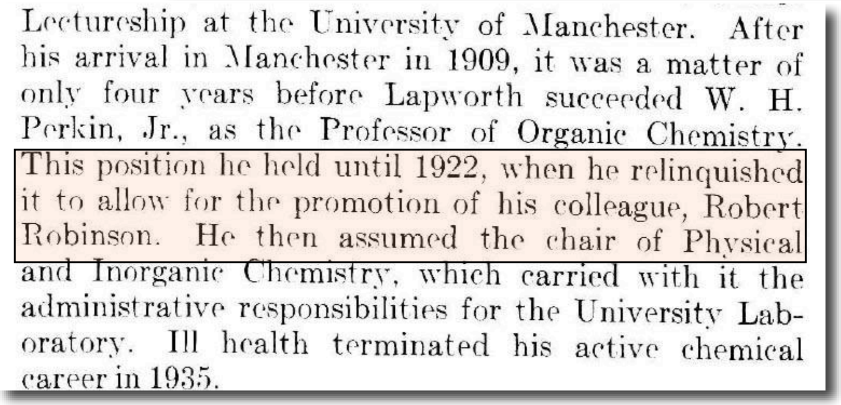
The Lapworth polarity designations can be used to form the basis of a functional group classification scheme.



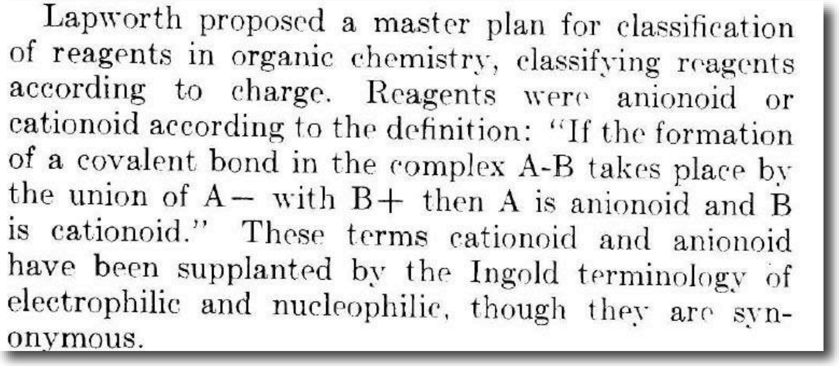
Martin Saltzman
Providence College
Providence, Rhode Island 02918

Arthur Lapworth

The genesis of reaction mechanism

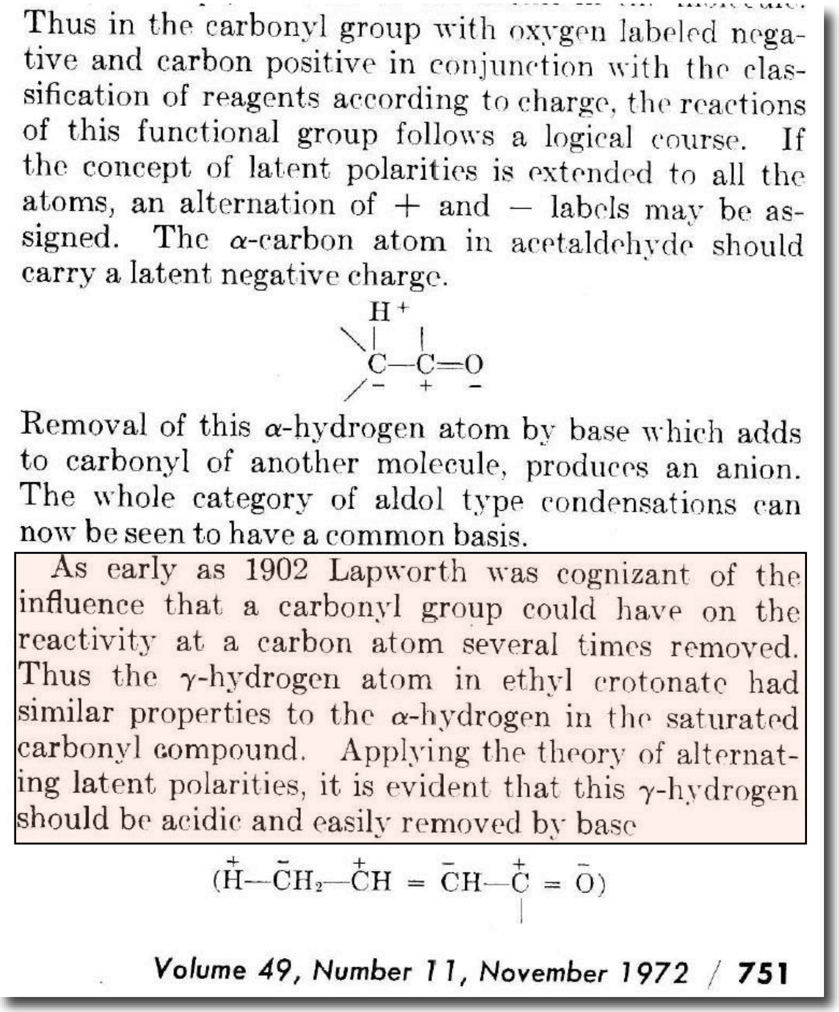


Lectureship at the University of Manchester. After his arrival in Manchester in 1909, it was a matter of only four years before Lapworth succeeded W. H. Perkin, Jr., as the Professor of Organic Chemistry. This position he held until 1922, when he relinquished it to allow for the promotion of his colleague, Robert Robinson. He then assumed the chair of Physical and Inorganic Chemistry, which carried with it the administrative responsibilities for the University Laboratory. Ill health terminated his active chemical career in 1935.



Lapworth proposed a master plan for classification of reagents in organic chemistry, classifying reagents according to charge. Reagents were anionoid or cationoid according to the definition: "If the formation of a covalent bond in the complex A-B takes place by the union of A− with B+ then A is anionoid and B is cationoid." These terms cationoid and anionoid have been supplanted by the Ingold terminology of electrophilic and nucleophilic, though they are synonymous.

An electronic handout will be provided



Thus in the carbonyl group with oxygen labeled negative and carbon positive in conjunction with the classification of reagents according to charge, the reactions of this functional group follows a logical course. If the concept of latent polarities is extended to all the atoms, an alternation of + and − labels may be assigned. The α-carbon atom in acetaldehyde should carry a latent negative charge.

$$\overset{H^{+}}{\underset{-}{C}}-\underset{+}{C}=\underset{-}{O}$$

Removal of this α-hydrogen atom by base which adds to carbonyl of another molecule, produces an anion. The whole category of aldol type condensations can now be seen to have a common basis.

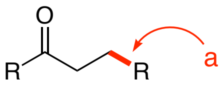
As early as 1902 Lapworth was cognizant of the influence that a carbonyl group could have on the reactivity at a carbon atom several times removed. Thus the γ-hydrogen atom in ethyl crotonate had similar properties to the α-hydrogen in the saturated carbonyl compound. Applying the theory of alternating latent polarities, it is evident that this γ-hydrogen should be acidic and easily removed by base

$$(\overset{+}{H}-\overset{-}{C}H_2-\overset{+}{C}H=\overset{-}{C}H-\overset{+}{C}=\overset{-}{O})$$

Reactivity Patterns of Functional Groups: Charge Affinity Patterns

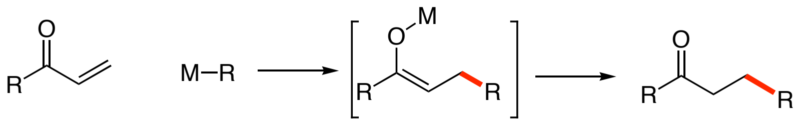
- Polar rxns form the basis set of bond constructions in synthesis
- Generalizations on conferred site reactivity will therefore be important

Given this target

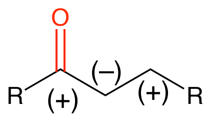


and the desire to form this bond

The functional group =O "dictates" the following bond construction



- Conferred site reactivity of =O



Charge Affinity Patterns

- Use the descriptors (+) and (–) to denote the polar disconnections shown.

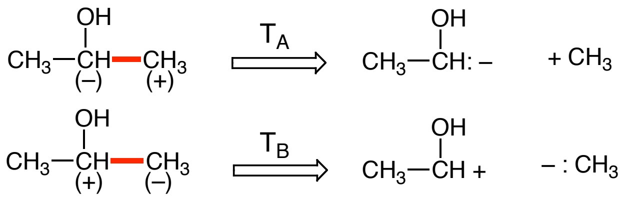
$\overset{(-)}{A}-\overset{(+)}{B} \Longrightarrow$ A: – B+

$\overset{(+)}{A}-\overset{(-)}{B} \Longrightarrow$ A: + B:–

- In the transforms illustrated above, symbols (+) & (–) are used to denote the particular polar transform illustrated.

In the present case there is NO INTRINSIC BIAS in favoring one transform over the other.

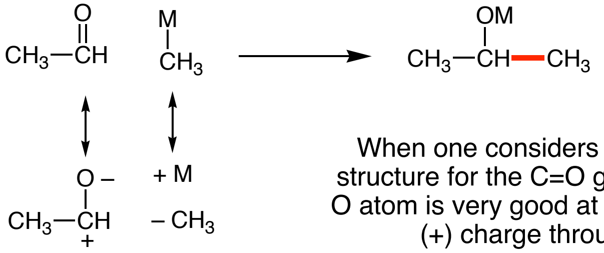
Let's now add an OH functional group (FG) to propane at C-2 and see whether one creates a bias in the favoring of one or the other transforms:



$CH_3-\underset{(-)}{\overset{OH}{CH}}-\underset{(+)}{CH_3} \xRightarrow{T_A} CH_3-\overset{OH}{CH}:^- \quad + CH_3$ *disfavored*

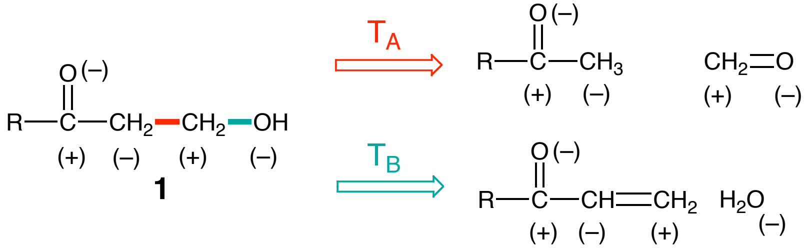
$CH_3-\underset{(+)}{\overset{OH}{CH}}-\underset{(-)}{CH_3} \xRightarrow{T_B} CH_3-\overset{OH}{CH}\,+ \quad -:CH_3$ *favored*

- The actual reaction associated with this transform is the addition of organometals to carbonyl substrates.



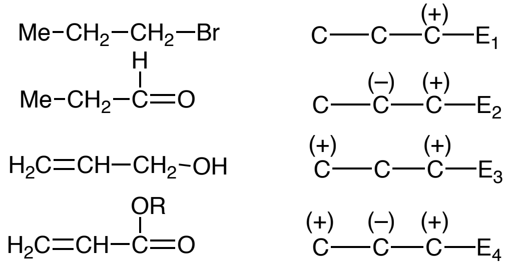
When one considers the polar resonance structure for the C=O group it is clear that an O atom is very good at stabilizing an adjacent (+) charge through resonance.

- Consider polar disconnections of the illustrated β-hydroxy ketone **1**:



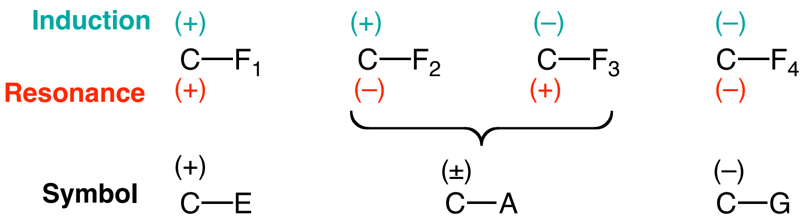
It is evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

Charge Affinity Patterns of Common Functional Groups



Classification of Functional Groups

Functional groups activate the carbon skeleton at the point of attachment by either induction & resonance.



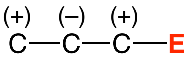
E = electrophilic at the point of attachment
A = ambiphilic at the pont of attachment
G = nucleophilic at the point of attachment

For simplicity, we will designate three FG classes according to the designations provided above.

E & G-Functions:

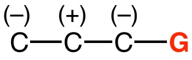
To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G, having the charge affinity patterns denoted below.

Hypothetical E-function



$\overset{(+)}{C}-\overset{(-)}{C}-\overset{(+)}{C}-E$

Hypothetical G-function

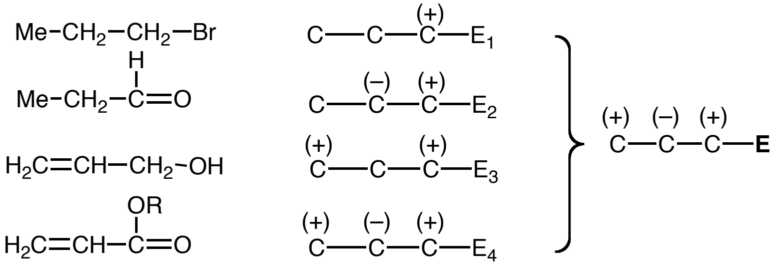


$\overset{(-)}{C}-\overset{(+)}{C}-\overset{(-)}{C}-G$

Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated polar site reactivity patterns toward both electrophiles and nucleophiles.

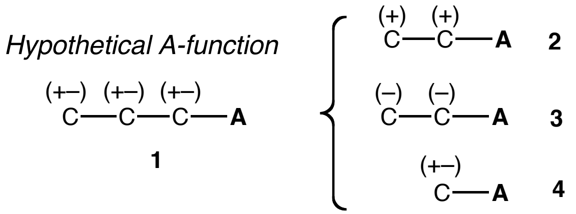
Any FG that conforms either to the ideal charge affinity parrern or a sub-pattern thereof will thus be classified as either an E- or G-function.

Representative E-functions:



A-Functions:

A 3rd hypothetical FG, designated as A, may be defined that has an unbiased charge affinity pattern as in **1**. Such an idealized FG's activates all sites to both nucleophilic and electrophilic reactions, and as such include those functions classifies as either E– or G–. The importance of introducing this third class designation is that it includes those functional groups having non-alternate charge affinity patterns such as **2–4**.



FG-Classification Rules

In the proposed classification scheme the following rules followed in the assignment of class designation of a given FG.

- Activating functions are to be considered as heteroatoms appended to or included within the carbon skeleton.
- Activating functions are inspected and classified according to their observed polar site reactivities.
- Since proton removal and addition processes are frequently an integral aspect of FG activation, the FG, its conjugate acid or base, and its proton tautomers are considered together in determining its class designation.
- The oxidation state of the FG is deemphasized since this is a subordinate strategic consideration.

Common E-Functions: Symbol: (+)C—E

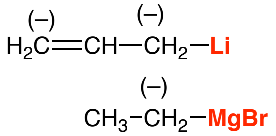
—OR ═O
—NR$_2$ ═NR
—X, X = halogen

exception: ≡O
exception: ≡N

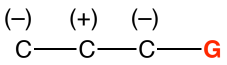
Also consider all combinations of of above FGs; e.g =O + OR

Common G-Functions: Symbol: (–)C—G

Typical G-class functions are the Group I-IV metals whose reactivity patterns, falls into a subset of the idealized G-FG **5**.


$\overset{(-)}{H_2C}{=}CH{-}\overset{(-)}{CH_2}{-}\mathbf{Li}$

$CH_3{-}\overset{(-)}{CH_2}{-}\mathbf{MgBr}$


$\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\mathbf{G}$

5

Common A-Functions: Symbol: (±)C—A

A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se).

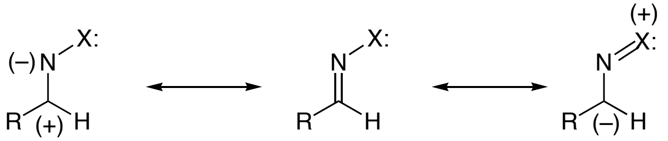
Typical A-functions, classified by inspection, are provided below

$—NO_2$ $=NOR$ $=NNR_2$ $=\underset{+}{N}(O)R$ $=N_2$ $\equiv N$

$—SR$ $—S(O)R$ $—SO_2R$ $—SR_2$

$—PR_2$ $—P(O)R_2$ $—\overset{+}{P}R_3$

■ These FG's are capable of conferring both (+) and (–) at point of attachment.



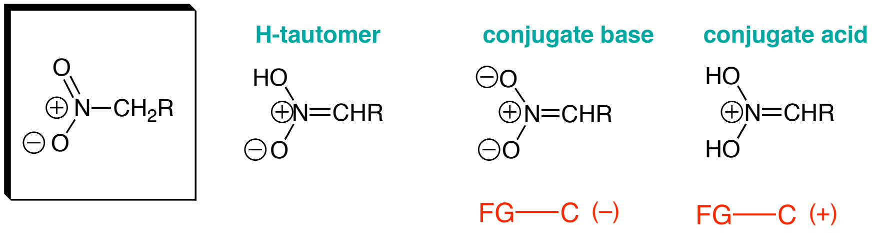
X = OR, NR_2

Remarkably, the dual electronic properties of oximes were first discussed by Lapworth in 1924 before the modern concepts of valence bond resonance were developed.

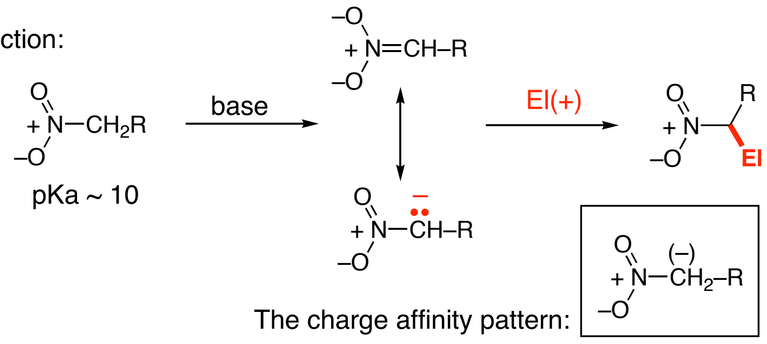
Lapworth, A. *Chemistry and Industry* **1924**, *43*, 1294-1295.

The Nitro Functional Group

As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base.



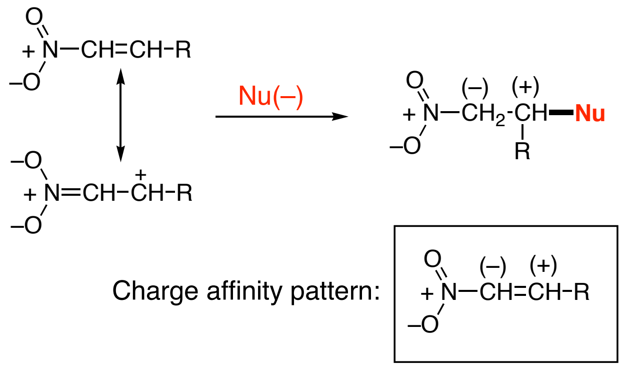
The Reaction:



The charge affinity pattern:

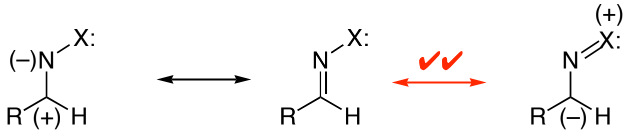
■ **This reactivity pattern may be extended via conjugation:**

The Reaction:



Charge affinity pattern:

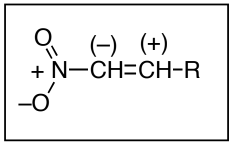
■ **The resonance feature which has been exploited:**

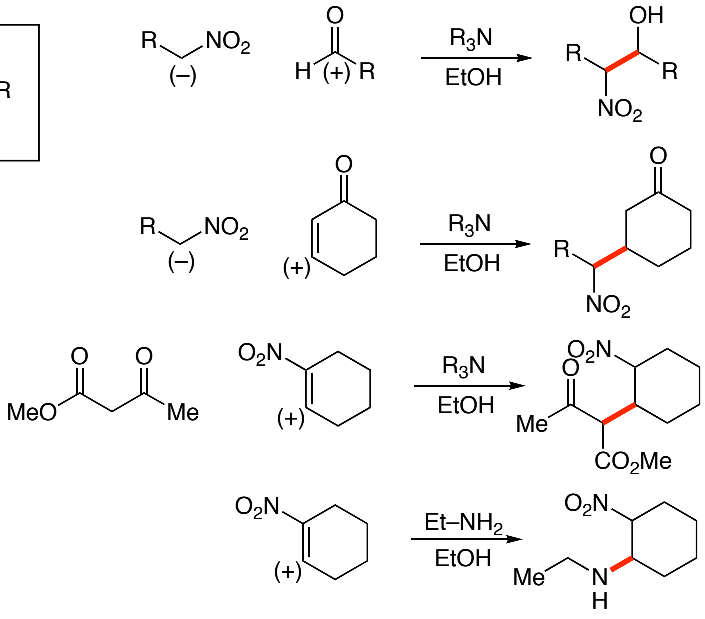


X = OR, NR_2

Charge Affinity Patterns & the Nitro Functional Group

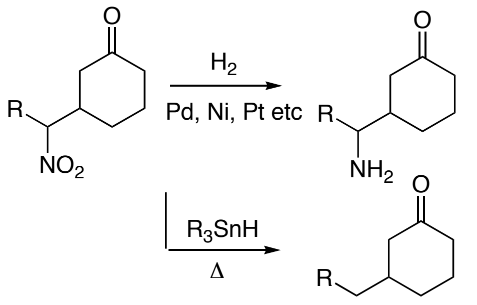
Some Reactions of the Nitro Functional Group





Important Transformations of the $–NO_2$ Functional Group

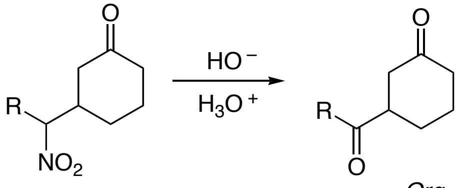
- **Reduction:**



rxn is quite facile

Ono, N.; Kaji, A. *Synthesis* **1986**, 693.

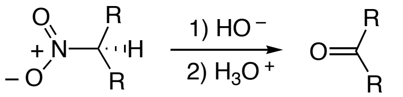
- **Nef Reaction:**



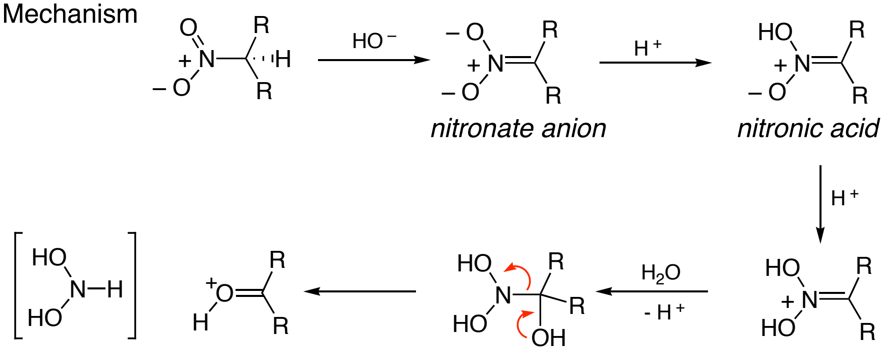
Pinnick, *Org. Reactions* **1990**, *38*, 655

The Nef Reaction

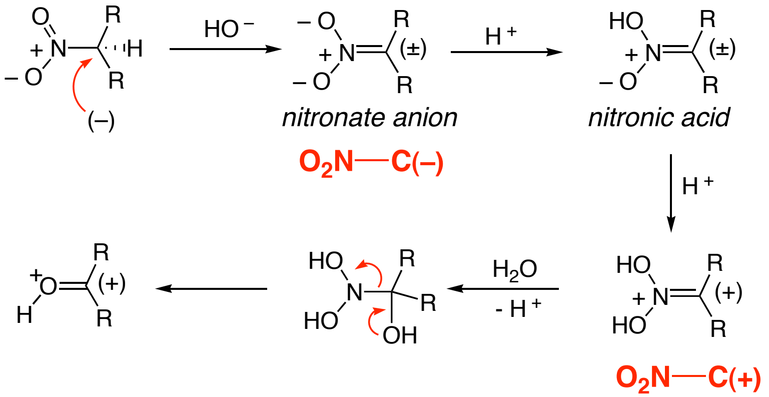
- **Overall Transformation:**



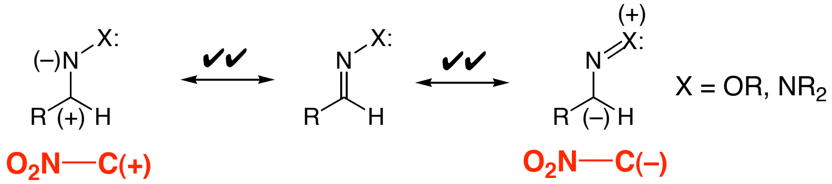
- Mechanism



The charge affinity patterns represented

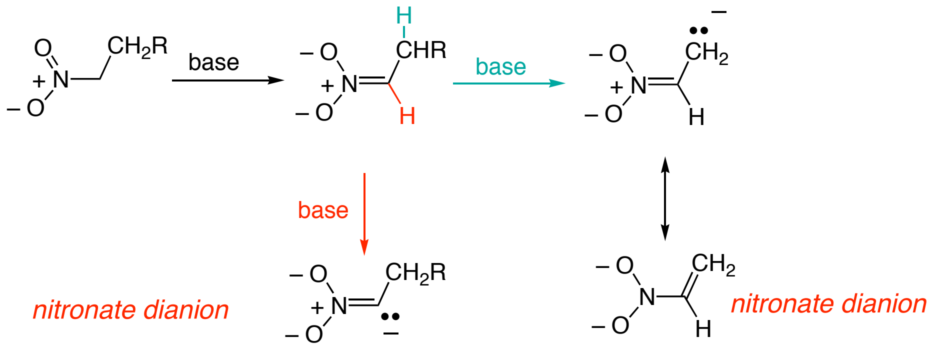


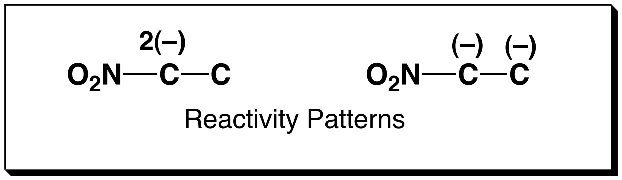
- **The resonance features which have been exploited:**



Charge Affinity Patterns & the Nitro Functional Group

Other Nonalternate Behavior of $–NO_2$ FG

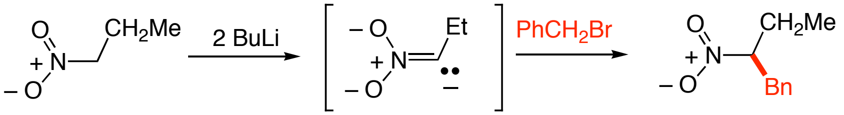



$$O_2N—\overset{2(-)}{C}—C \qquad O_2N—\overset{(-)}{C}—\overset{(-)}{C}$$

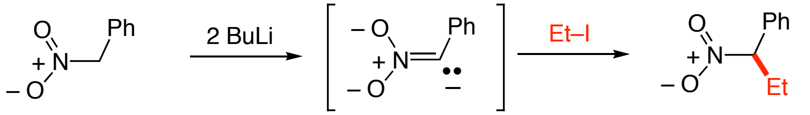
Reactivity Patterns

Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164

Representative examples: $O_2N—\overset{2(-)}{C}—C$

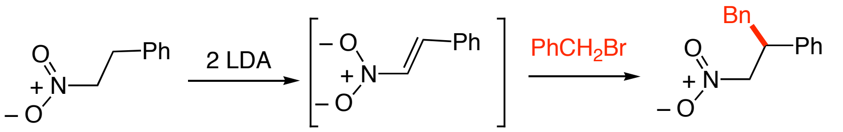


51% yield

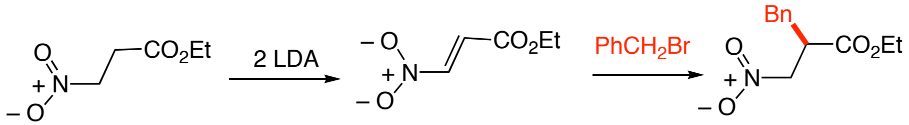


80% yield

Representative examples: $O_2N—\overset{(-)}{C}—\overset{(-)}{C}$



40% yield



Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164

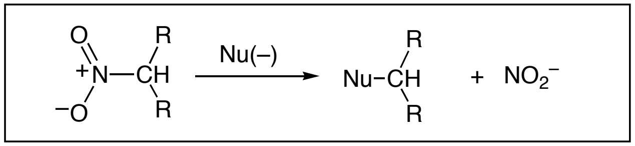
80% yield

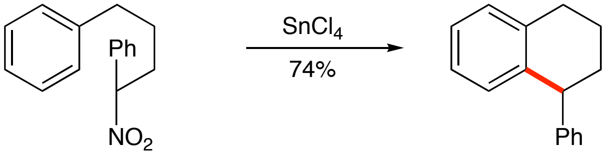
$–NO_2$ As a Leaving Group

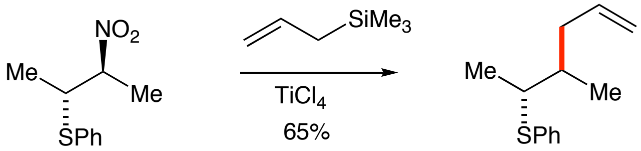
Review: Tamura et. al. *Synthesis* **1991**, 423-434.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis"' Seebach, D. etal, *Chimia*, **1979**, *33*, 1-18

Representative examples: $O_2N—C(+)$

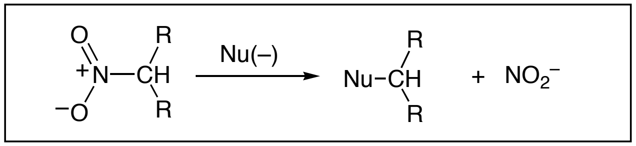


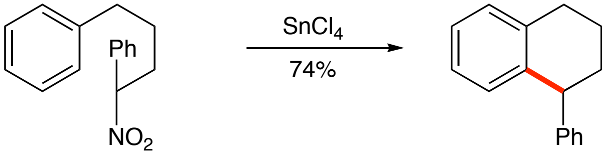


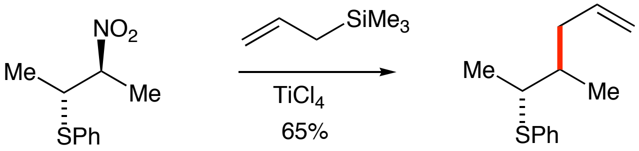


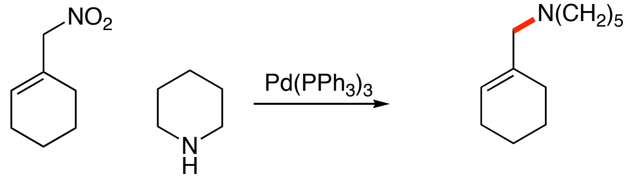
$-NO_2$ As a Leaving Group

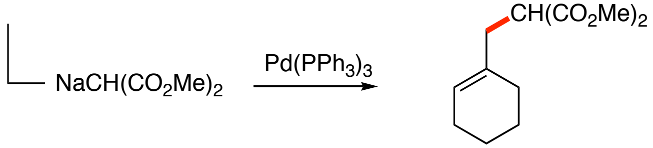
Representative examples: **O_2N—C (+)**

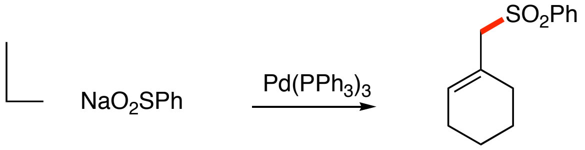


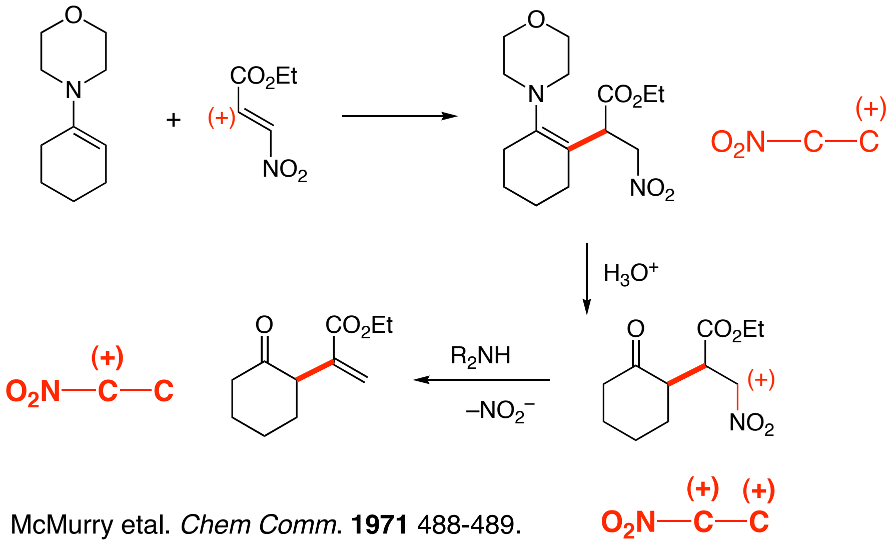






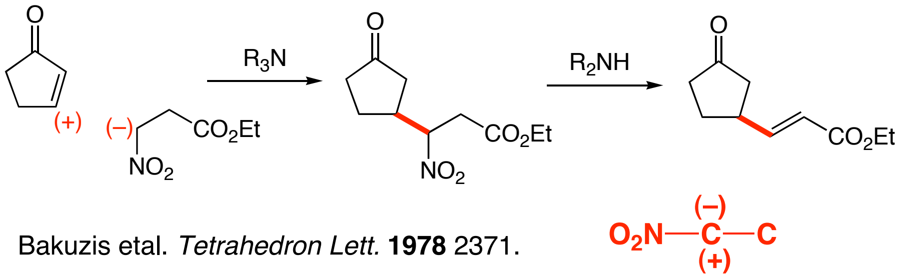






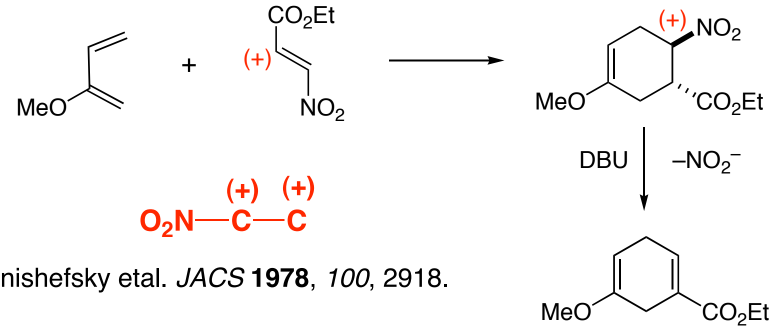
McMurry etal. *Chem Comm*. **1971** 488-489.

$$\overset{(+)}{}\overset{(+)}{}\;O_2N—\overset{(+)}{C}—\overset{(+)}{C}$$



Bakuzis etal. *Tetrahedron Lett.* **1978** 2371.

$$O_2N—\overset{(-)}{\underset{(+)}{C}}—C$$

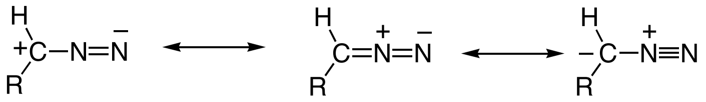


$$O_2N—\overset{(+)}{C}—\overset{(+)}{C}$$

Danishefsky etal. *JACS* **1978**, *100*, 2918.

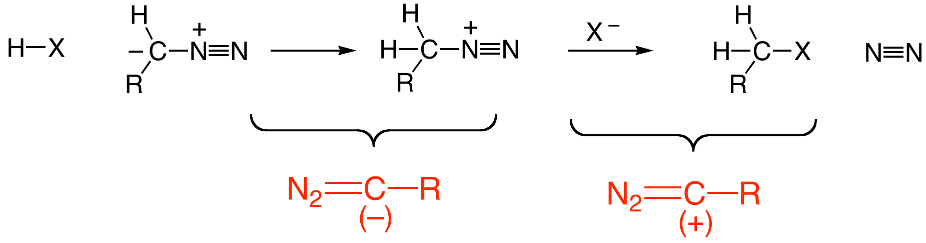
Nonalternate Reactivity Patterns of Diazo Functional Groups

The Diazo Functional Group



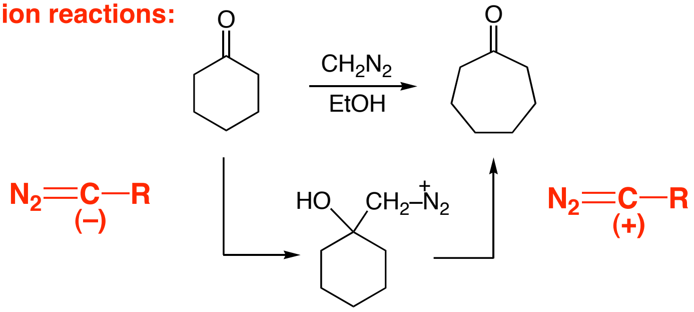
- Both (+) and (–) reactivity patterns suggested by resonance structures

- Rxns with acids:



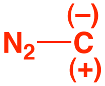
- **Initiating reactivity is (–); subsequent reactivity is (+)**

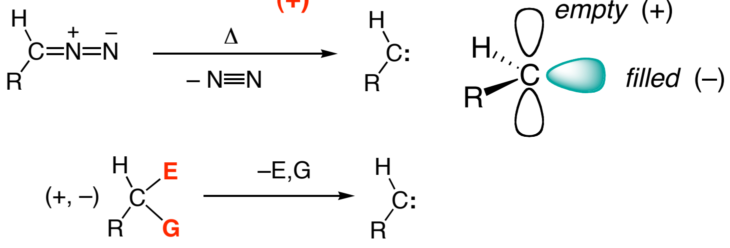
- **Ring expansion reactions:**



Restriction: Starting ketone must be more reactive than product ketone

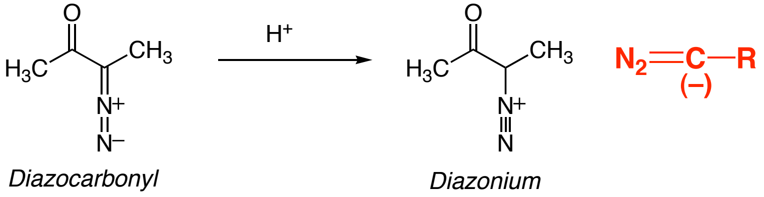
- **Precursors to Carbenes:**





Acid Catalyzed Reactions of Diazo Compounds

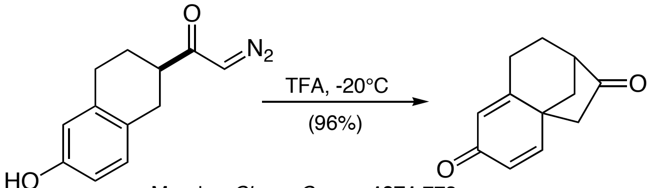
Review: Smith, Tet. 1981 2407



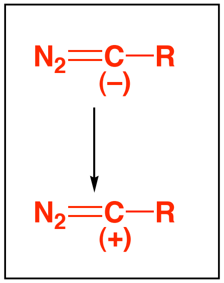
Common acids include BF_3•OEt_2, HBF_4, TFA, etc.

Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

Acid-Catalyzed Reactions

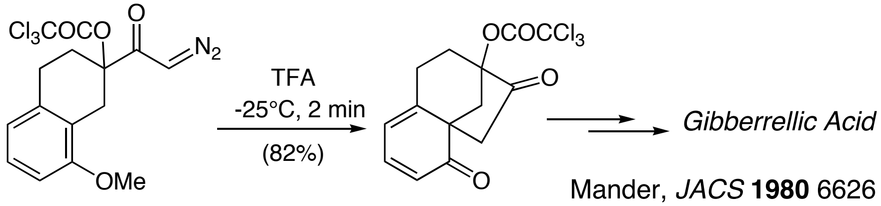


Mander, *Chem. Comm.* **1971** 773
Tet., **1991** 134



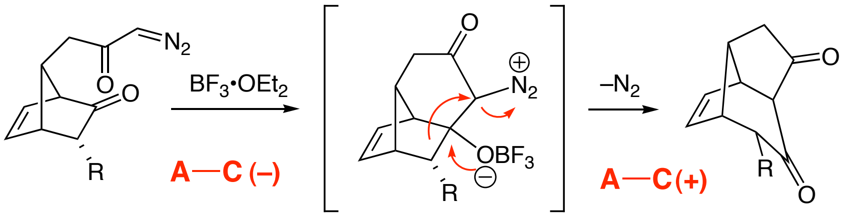
"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantites of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

Lewis Mander



Mander, *JACS* **1980** 6626

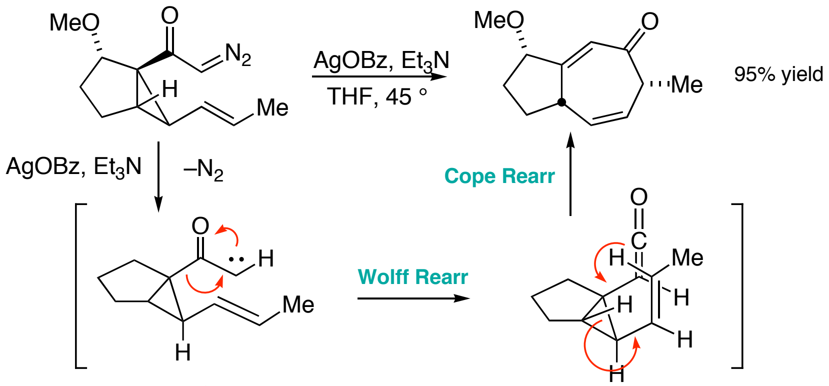
Diazo–Carbonyl Insertations:



Mander, *Aust. J. Chem.* **1979** 1975

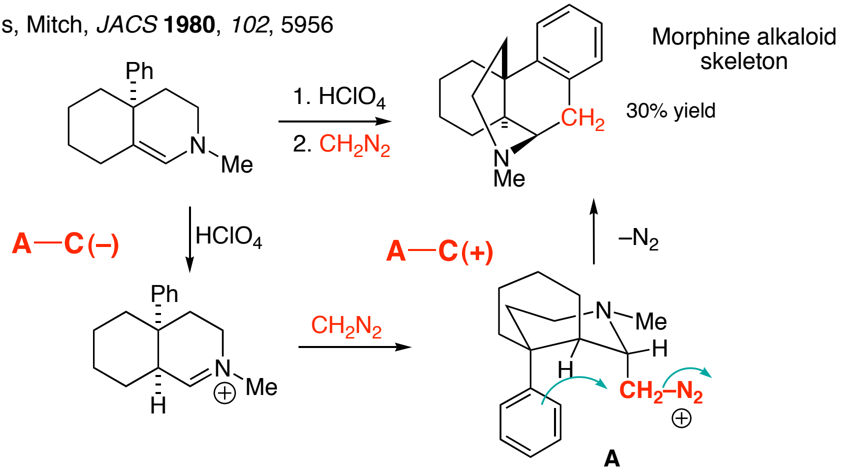
Wolff Rearrangements

Web Problem 332. Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, *125*, 13624).

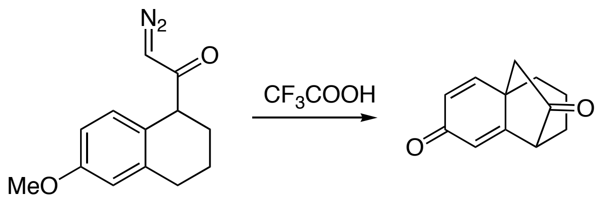


Diazo-mediated Ring Construction:

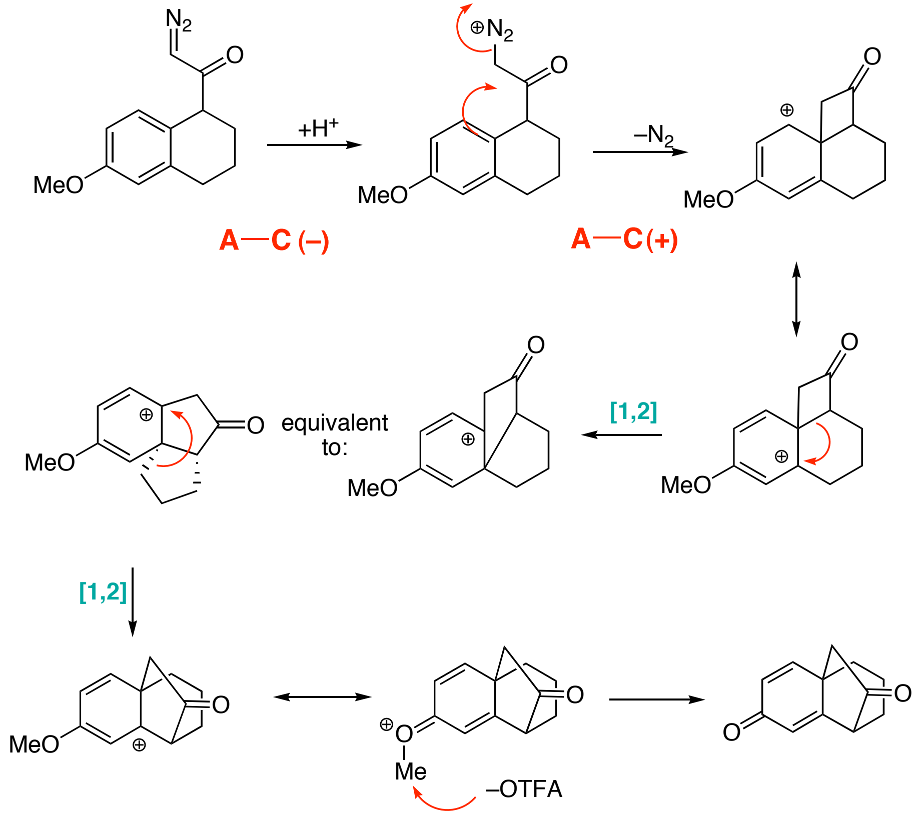
Evans, Mitch, *JACS* **1980**, *102*, 5956



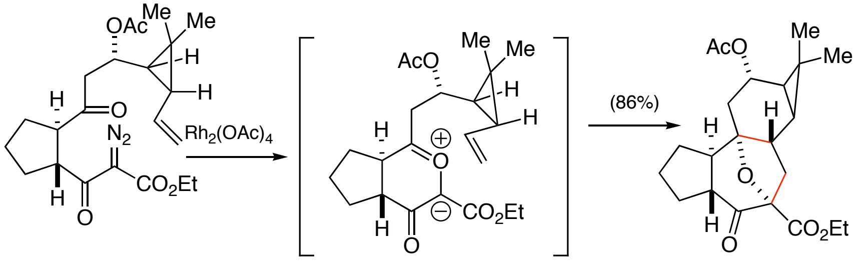
Web Problem 150. Provide a concise mechanism for the indicated reaction in the space below. Key descriptor for answer, "Carbene".



The Answer

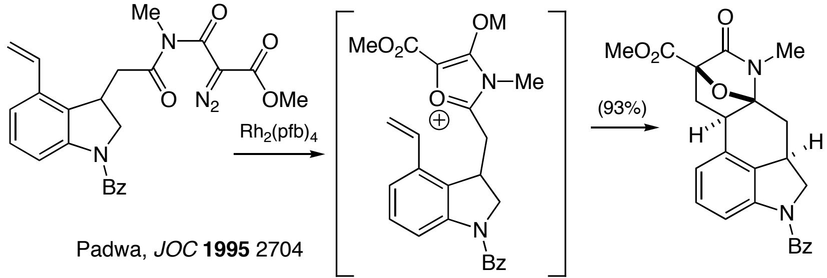


Dipolar Cycloadditions: Carbonyl Ylides



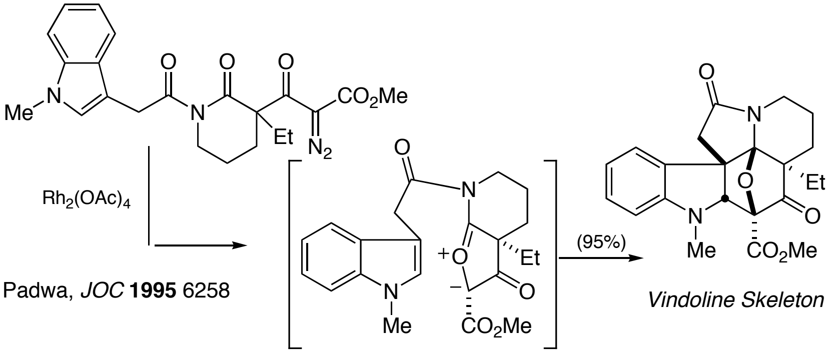
Dauben, *JOC* **1993** 7635

Tigilane Skeleton



Padwa, *JOC* **1995** 2704

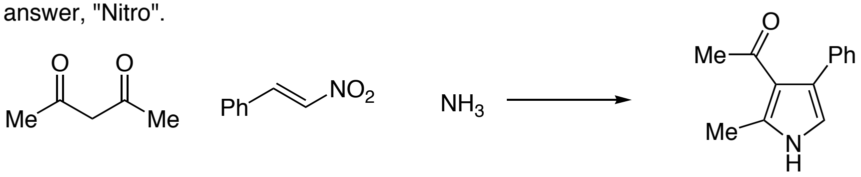
Lysergic Acid Skeleton



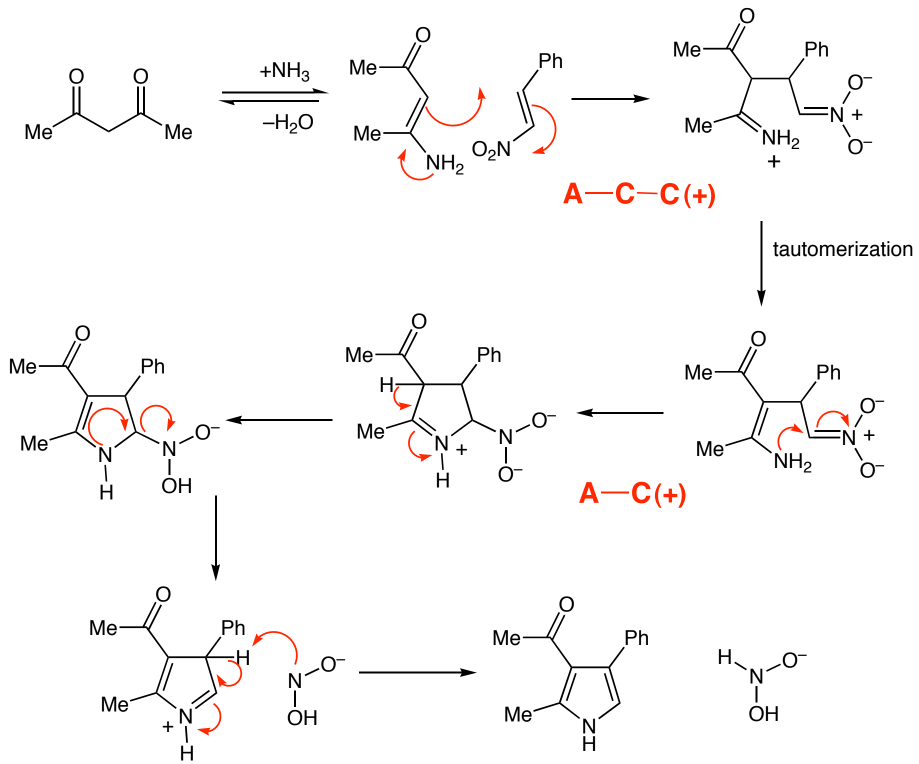
Padwa, *JOC* **1995** 6258

Vindoline Skeleton

Web Problem 109. The following is a general reaction for the formation of pyrroles. In this condensation, any of the three reaction constituents may be widely varied. (Ono, "The Nitro Group in Organic Synthesis" Wiley-VCH, **2001**. Chapter 10, pp 326-328). Siince it is not clear what the "inorganic" reaction product is, provide us with anything that is mechanistically sound using the reagents illustrated. Key descriptor for answer, "Nitro".



In the space below provide a plausible mechanism for this transformation.



Overall reactivity pattern: $A-\overset{(+)}{C}-\overset{(+)}{C}$

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 31

Ambiphilic Functional Groups–2
Hydrazone-Based Transformations

- Wolff-Kishner Reduction
- Wharton Rearrangement
- Eschenmoser-Tanabe Fragmentation
- Reduction of Tosyl Hydrazones: "The Alkene Walk"
- Tosyl Hydrazone-Based Fragment Coupling
- TBS-Hydrazones: Superior intermediates
- The Shapiro Reaction
- Bamford-Stevens Reaction

Reading Assignment for this Week:

"The Myers papers" **(handouts)**

Nitroso-Alkenes
T. L. Gilchrist, *Chem. Soc. Rev.* **1983**, *12*, 53-72 **(handout)**

The Synthetic Utility and Mechanism of the Rednctive Deoxygenation of α,β-Unsaturated p-Tosylhydrazones with Sodium Cyanoborohydride
R. O. Hutchins et al. *J. Org. Chem* **1975,** *40*, 923

David A. Evans

Wednesday
December 6, 2006

Relevant Background Reading

Hutchins, R. O. (**1991**). "Reduction of C=X to CH_2 by Wolff-Kishner and Other Hydrazone Methods". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 8: 327.

Shapiro, R. H. (**1976**). “Alkenes from Tosylhydrazones.” *Org. React.* (N.Y.) 23: 405.

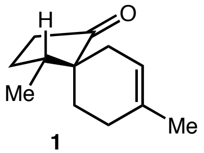
Addlington, R. M. and A. G. M. Barrett (**1983**). “Recent Applications of the Shapiro Reaction.” *Acc. Chem. Res.* 16: 55.

Chamberlin, and Bloom (**1990**). “Lithioalkenes from arylsulphonyl-hydrazones.” Org. React. (N.Y.) 39: 1.

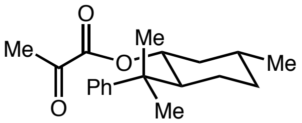
Bergbreiter, and Momongan (**1991**). "Hydrazone Anions". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 2: 503.

Cume Question, November, 2000 and current Problem Set

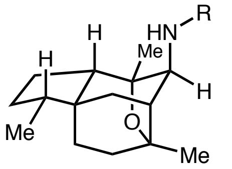
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS*. **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



1



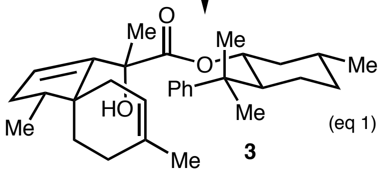
2



(–)-hispidospermidin

$$\mathbf{1}\ \xrightarrow[\text{HCl, CH}_3\text{CN, 75\%}]{\text{2,4,6-triisoproylbenzene-sulfonyl hydrazine,}}\ \text{Intermediate }\mathbf{A}\ \xrightarrow{n\text{-BuLi (2.05 equiv)}}\ \text{Intermediate }\mathbf{B}$$

55% $\downarrow$ $MgBr_2$, -78 °C then add **2**

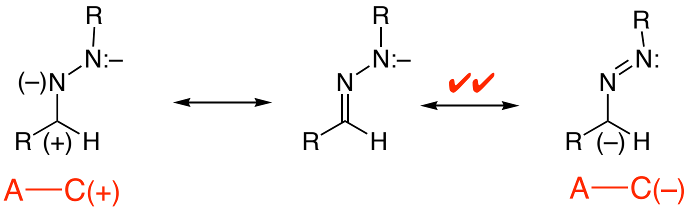


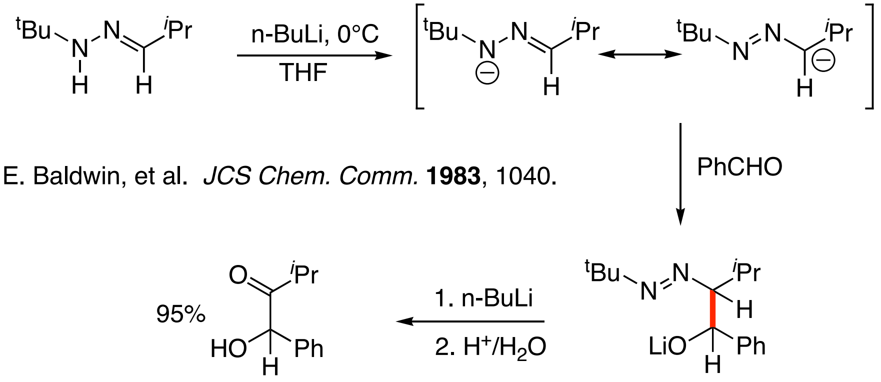
3

(eq 1)

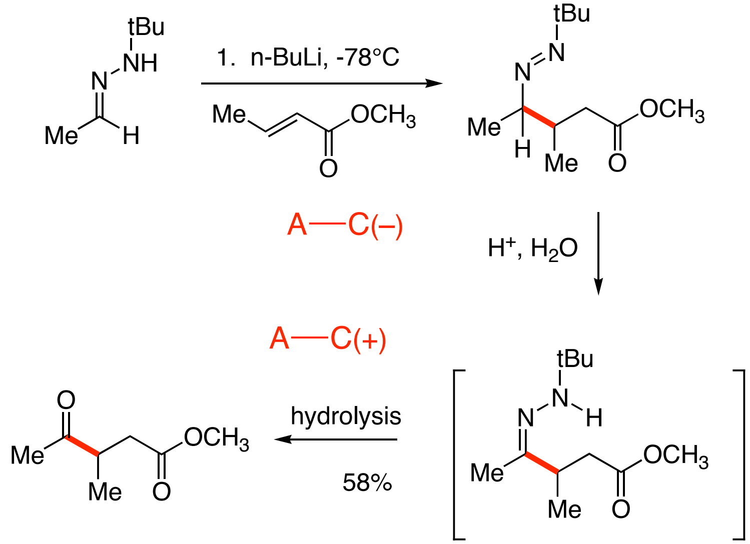
Hydrazone Transformations-1

Hydrazone Anions: A useful Reversed Polarity Equivalent

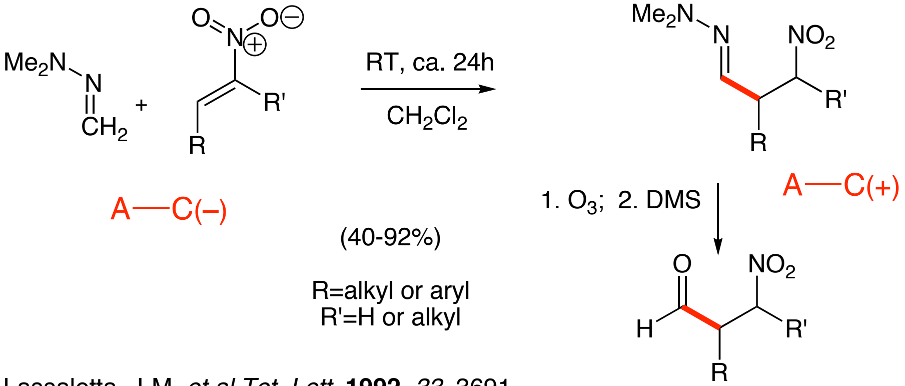




J. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.

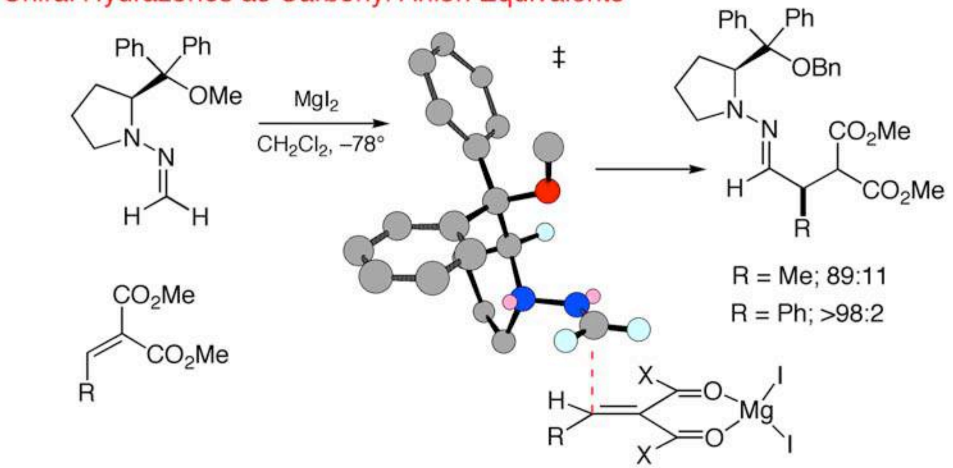


J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.

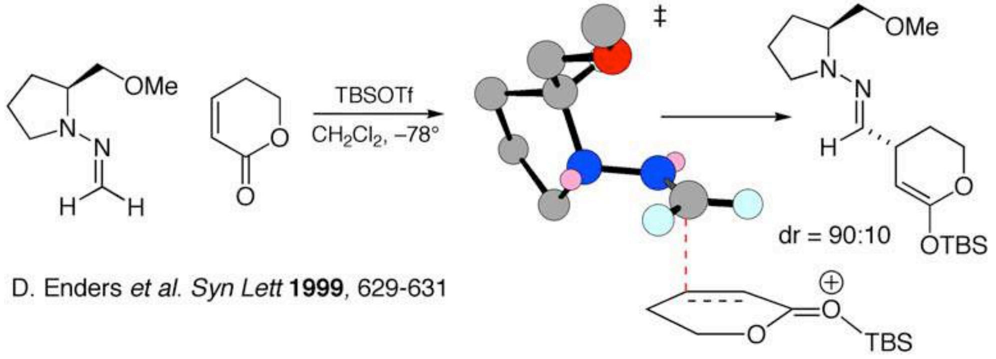


Lassaletta, J-M, *et al.Tet. Lett.* **1992**, *33*, 3691.

Chiral Hydrazones as Carbonyl Anion Equivalents

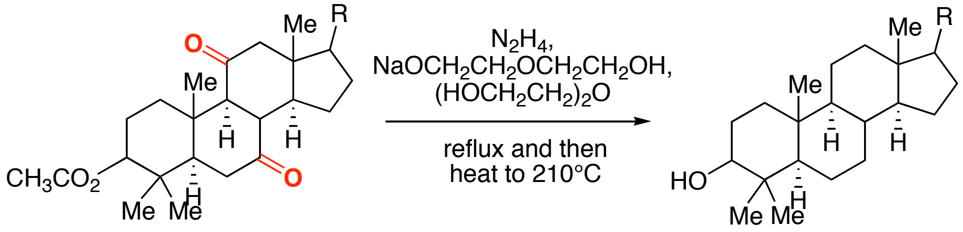


Lassaletta, J-M, *et al. Chem Commun* **2002**, 498-499



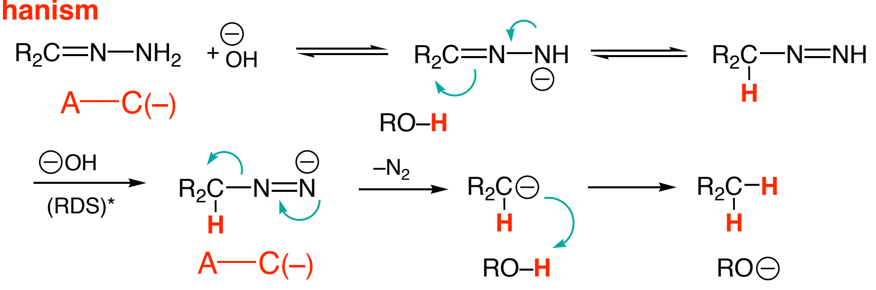
D. Enders *et al. Syn Lett* **1999**, 629-631

Wolff-Kishner Reduction

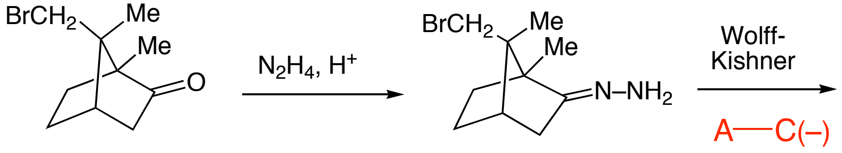


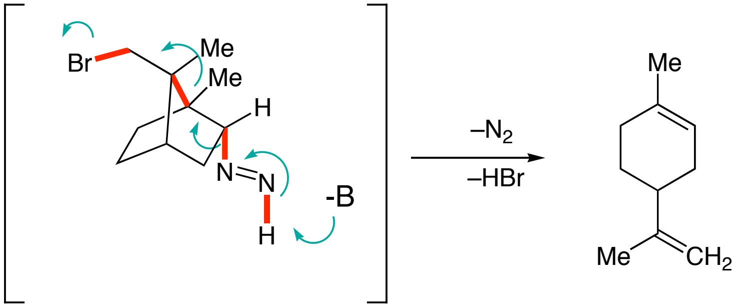
Barton, D. H. R., Ives, D. A. J., and Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.

Mechanism



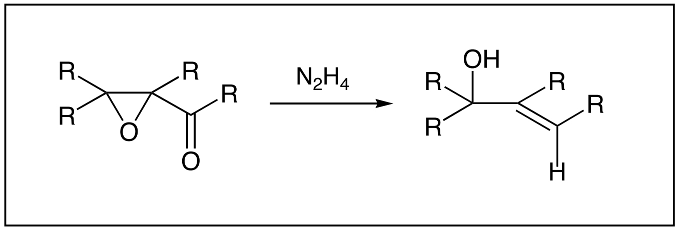
Elimination of α-Leaving Groups



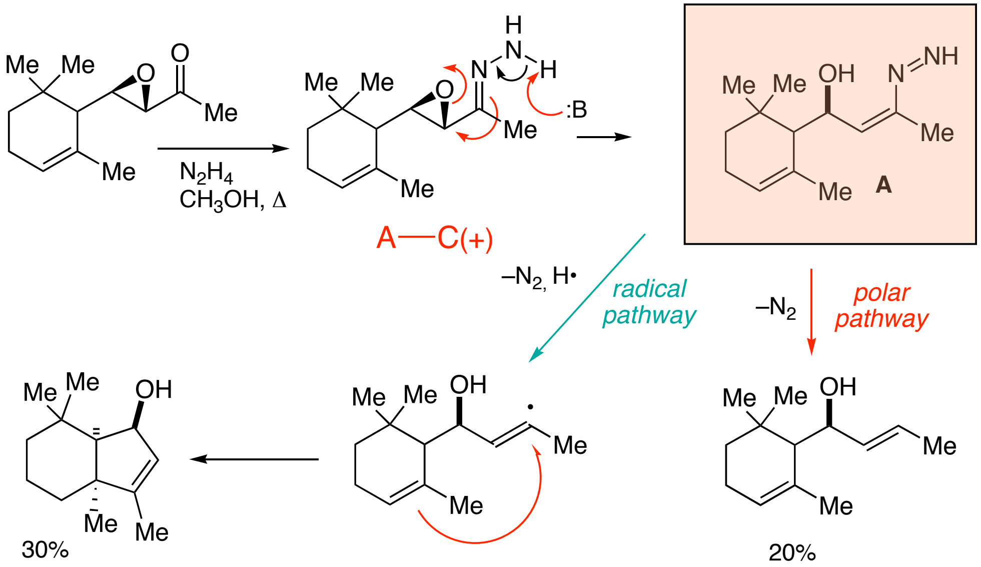


D. H. Gusyafson, W. F. Erman *J. Org. Chem.* **1965**, *30*, 1665.

The Wharton Rearrangement

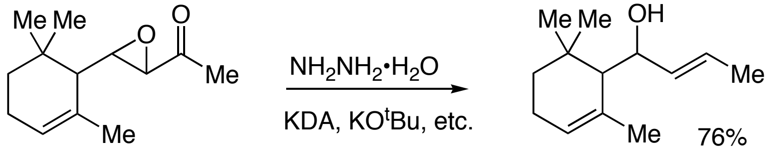


This example illustrates the 2 possible modes for the decomposition of **A**.



G. Stork et al. *JACS* **1977**, *99,* 7067.

Some procedural improvements:



For stable hydrazones, strongly basic conditions favor the ionic pathway.

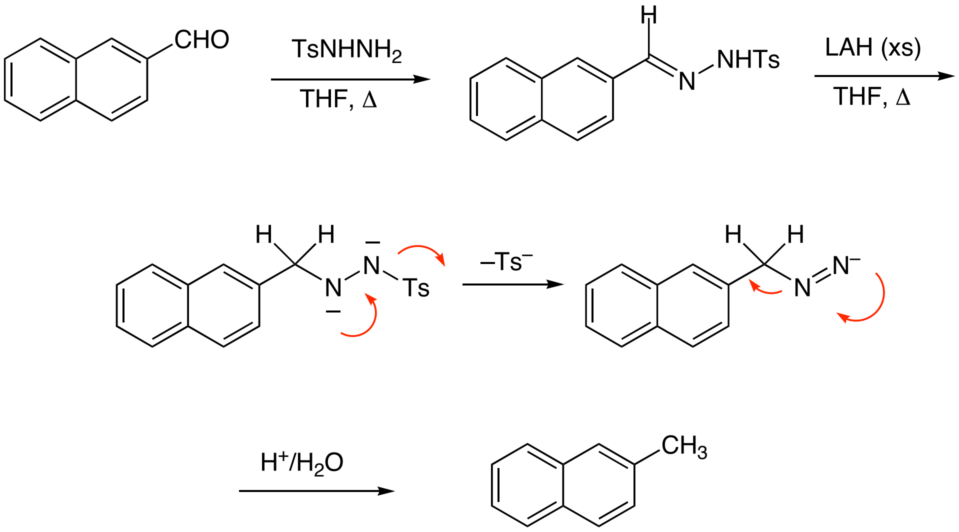
C. Dupuy, J. L. Luche *Tetrahedron Lett.* **1989**, *44,* 3437.

Hydrazone Transformations-3

Tosylhydrazones – Better Than Hydrazones

Tosylhydrazones are isolable, stable, and easily prepared.

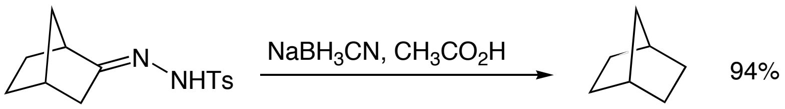
The presence of the tosyl leaving group strongly biases the system towards polar reaction pathways under hydridic reducing conditions.



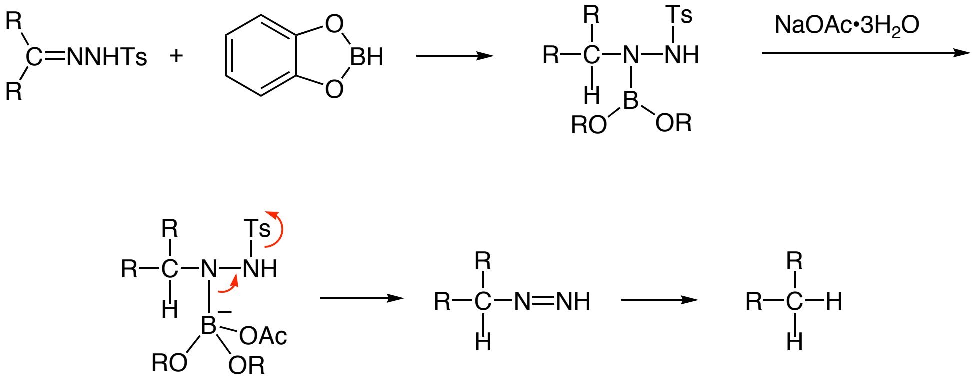
L. Caglioti, M. Magi *Tetrahedron* **1963**, *19*, 1127.

Further Refinements

Very mild reduction with $NaBH_3CN$ under slightly acidic conditions (pH 4-5).
No reduction in the absence of acid; carbonyl, nitro, nitrile FGs unaffected.
Aromatic, sterically hindered carbonyls very poor substrates.

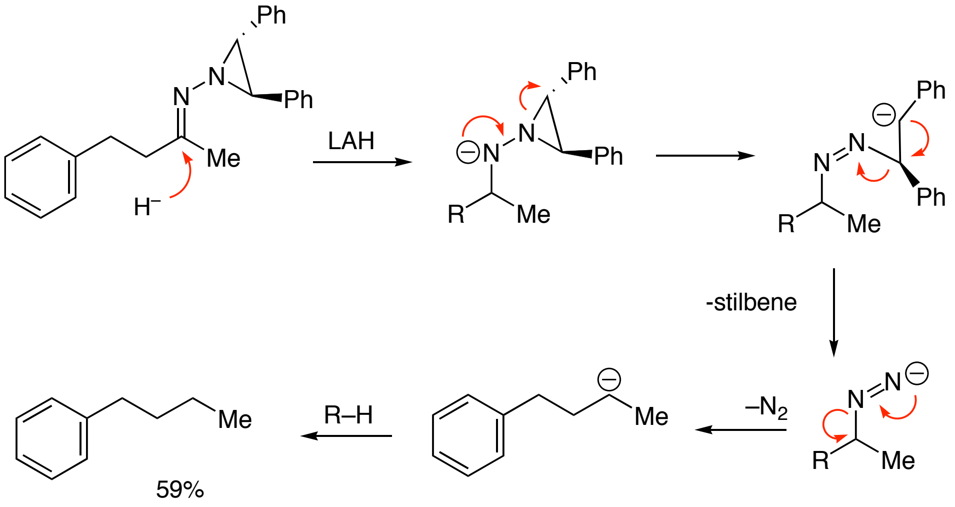


R. O. Hutchins, et al. *JACS* **1973**, *95,* 3662.



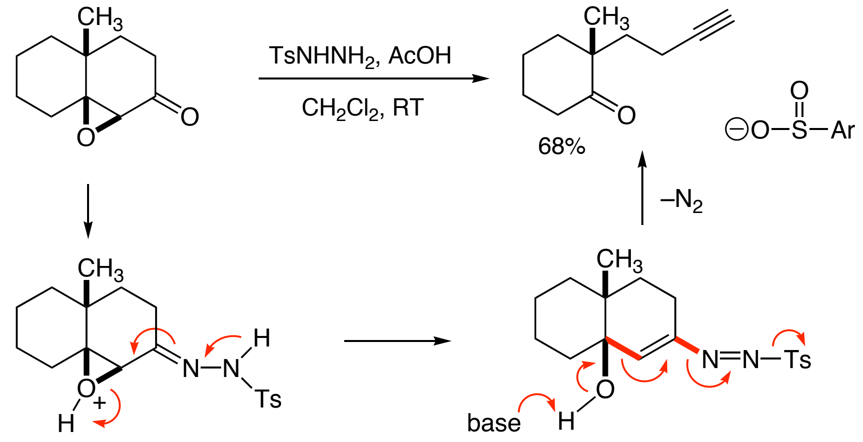
G. W. Kabalka, et al. *J. Org. Chem.* **1975**, *40,* 1834.

Another Interesting Leaving Group

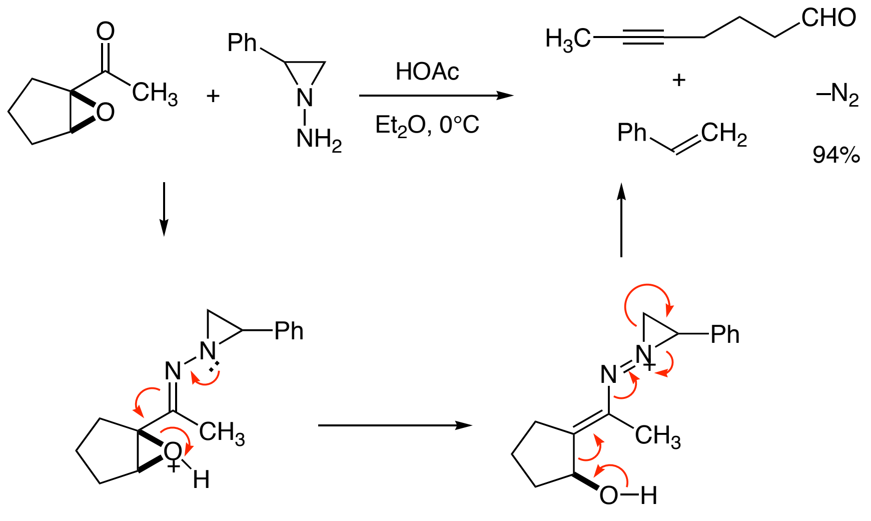


A. R. Chamberlin, et al. *Tetrahedron Lett.* **1991**, *32,* 1691.

The Eschenmoser–Tanabe Fragmentation

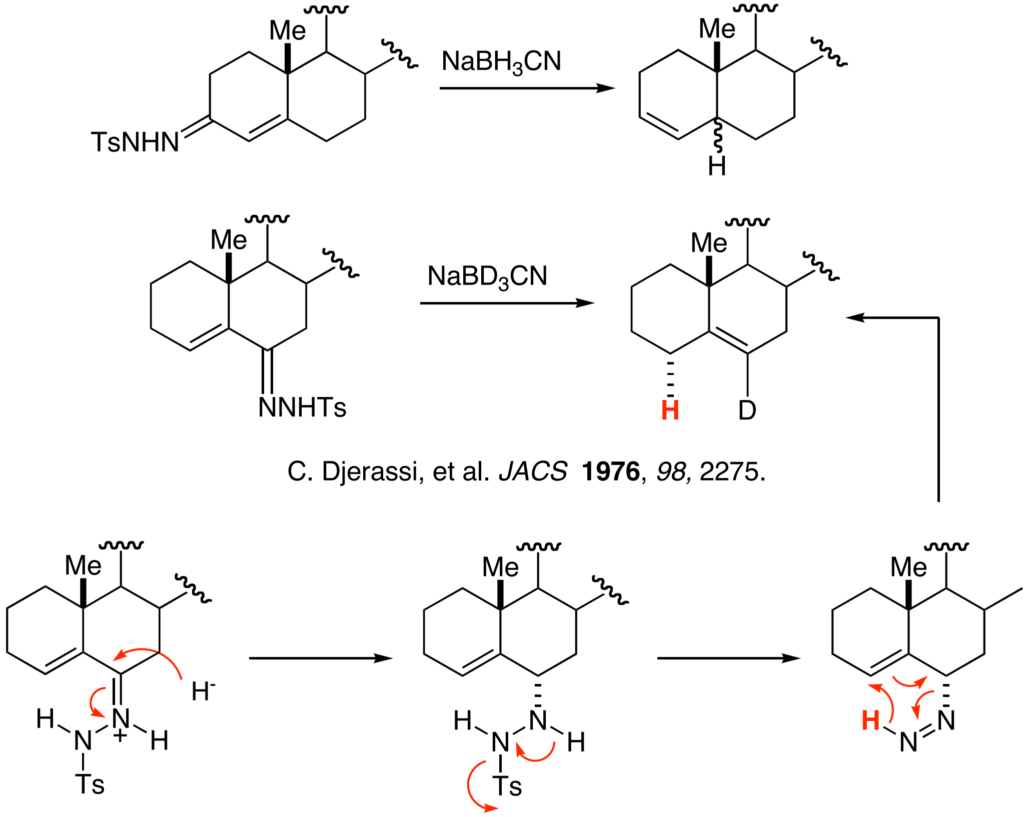


A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, *50*, 708.



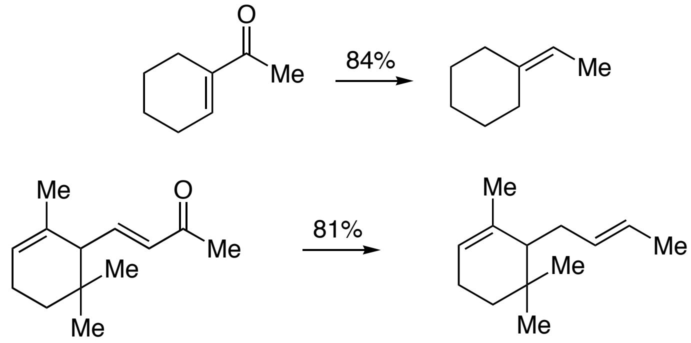
A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, *50*, 2108.

Tosylhydrazone Reductions: The Alkene Walk



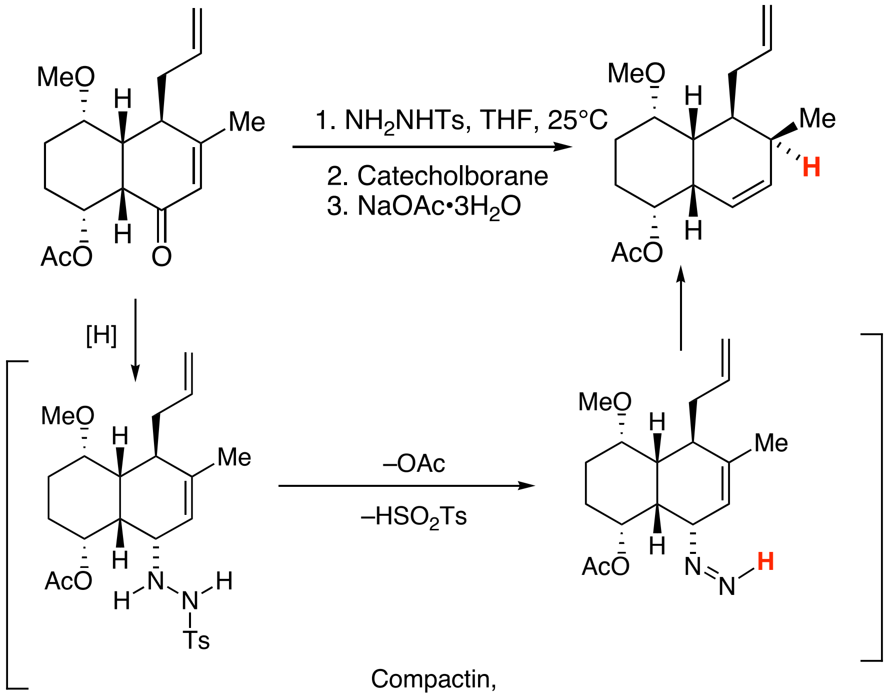
C. Djerassi, et al. *JACS* **1976**, *98*, 2275.

This has been developed into a reliable reduction



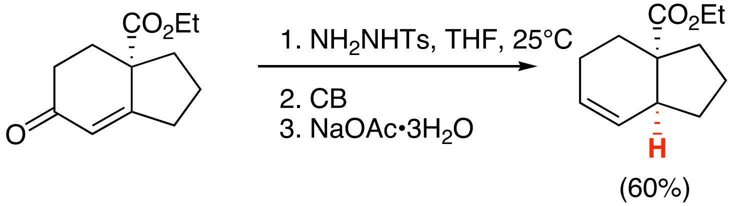
16 cases reported: Hutchins, et al. *JOC* **1975**, *40*, 923

Alkene Walk: Syntheses



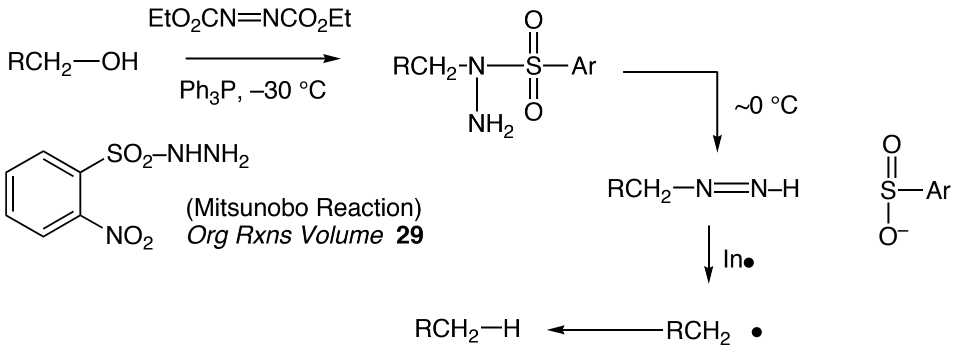
Compactin,
Wendler, N. L., *et al. Tet. Lett.* **1982**, *23,* 5501.

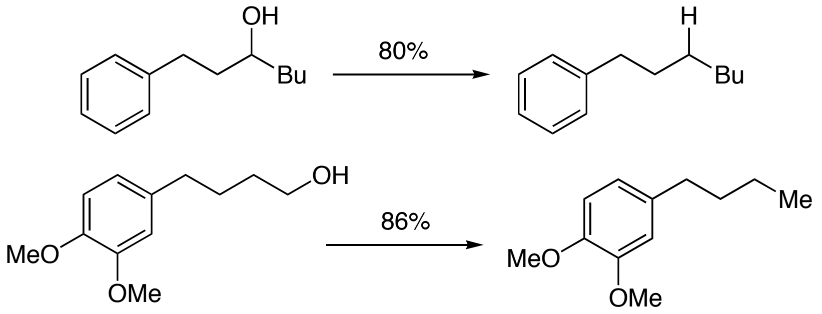
The stereochemical course of the hydrazone reduction may be stereospecifically transferred via the 1, 3-rearrangement



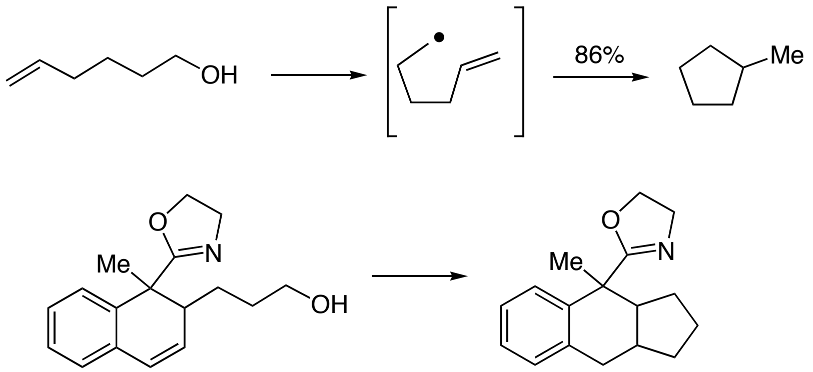
Topiramate,
Maryanoff, B. E., *et al. Tet. Lett.* **1992**, *33,* 5009.

Sulfonylhydrazone Reductions: Alcohol Deoxygenation





The intervention of radicals has been implicated (again):



10 cases reported: A. Myers, et al. *JACS* **1997**, *119,* 8572.

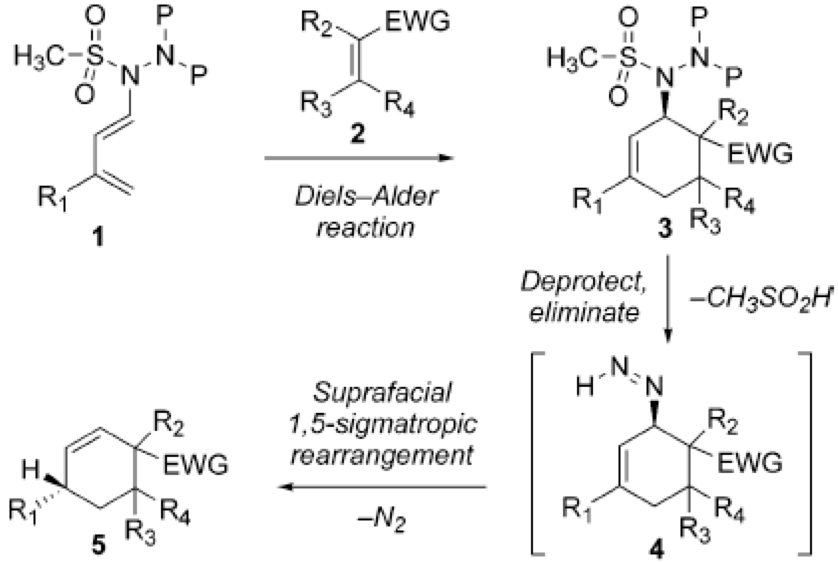
Design, Synthesis, and Reactivity of 1-Hydrazinodienes for Use in Organic Synthesis

Glenn M. Sammis, Eric M. Flamme, Hao Xie, Douglas M. Ho, and Erik J. Sorensen*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544-1009

8612 ■ **J. AM. CHEM. SOC. 2005**, *127*, 8612−8613

Scheme 1. A New Type of Hydrazine-Substituted Diene for Use in Organic Synthesis



P = Protecting group; EWG = Electron-withdrawing group

Scheme 2. Synthesis of 1-Hydrazinodiene **7**

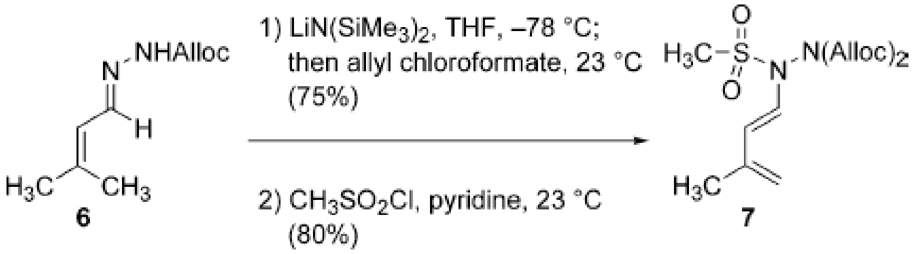
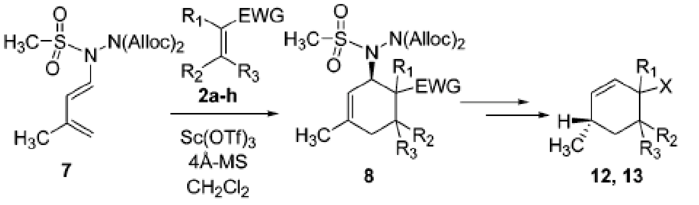
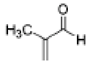
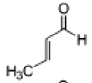
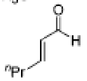
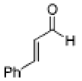
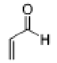
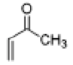
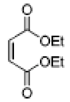
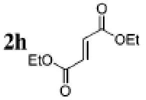

6
7
NHAlloc
N(Alloc)2
1) LiN(SiMe3)2, THF, –78 °C; then allyl chloroformate, 23 °C (75%)
2) CH3SO2Cl, pyridine, 23 °C (80%)

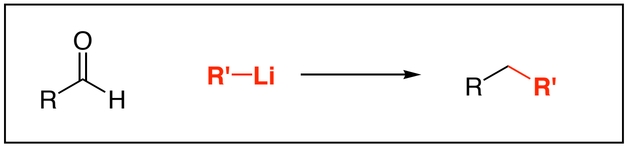
Table 1. Dienophile Scope for the Diels−Alder/1,5-Sigmatropic Rearrangement Process

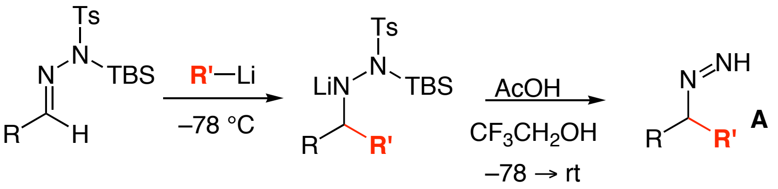


12a-f: X = CH(-OCH$_2$CH$_2$O-); **13a-b**: X = CO$_2$Et

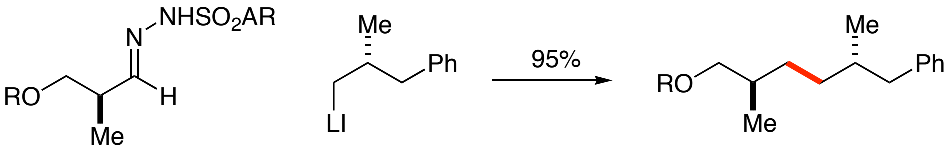
Dienophile		Sc(OTf)$_3$ (mol%)^a	dr (*endo*/*exo*)^b	Yield **8** (%)^c	Yield **12(13)** (%)
2a		10	83:17 (92:8)^d	89^e (81)^{d,e}	62^f
2b		10	25:75	65	60^f
2c		10	30:70	45	55^f
2d		10	7:93	72	68^e
2e		10	33:67	47	54^f
2f		10	20:80	66	57^f
2g		30	5:95	76	49^g
2h		30	10:90	30	13^g

Tosylhydrazone-Based Fragment Coupling



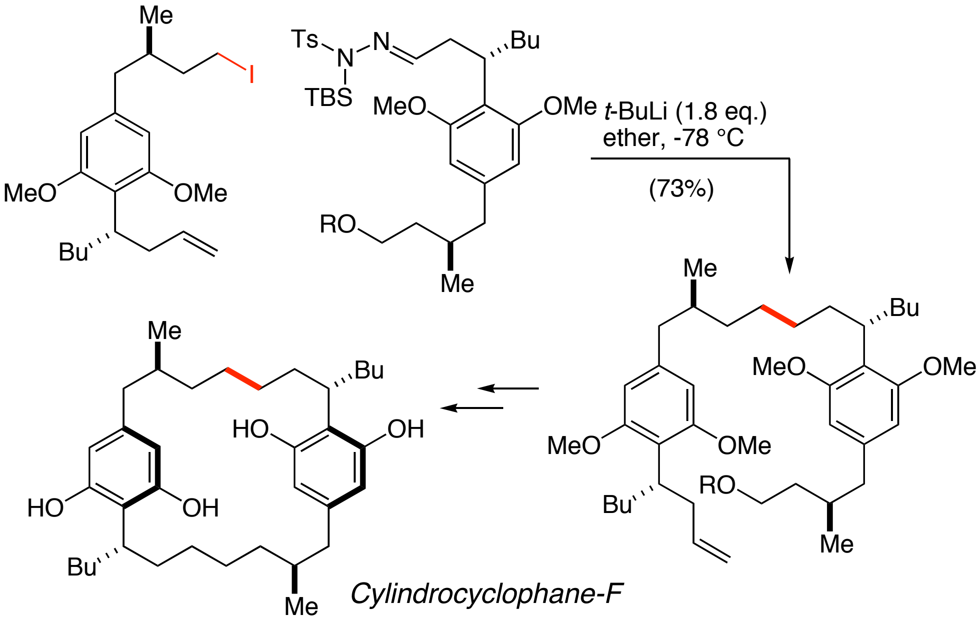


The monoalkyl azene **A** decomposes via a radical pathway



16 cases reported: A. G. Myers etal. *JACS*, **1998**, *120*, 8891.

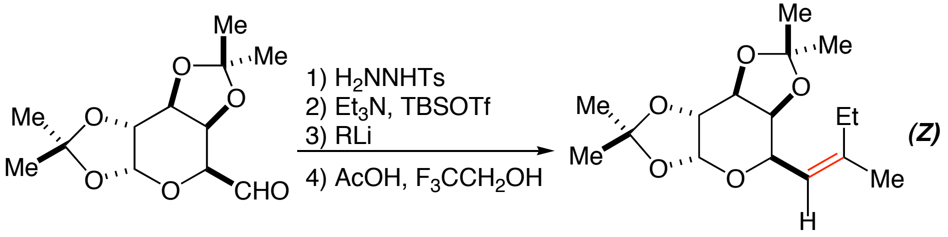
A Complex Application: A. Smith etal. *JACS* **1999**, *121*, 7423

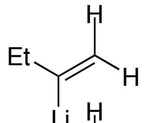
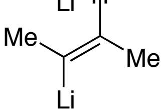


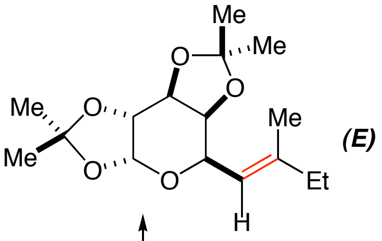
Cylindrocyclophane-F

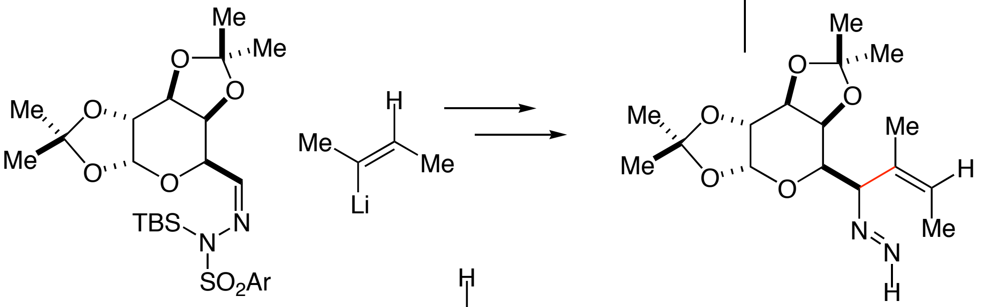
Stereoselective Construction of Trisubstituted Olefins

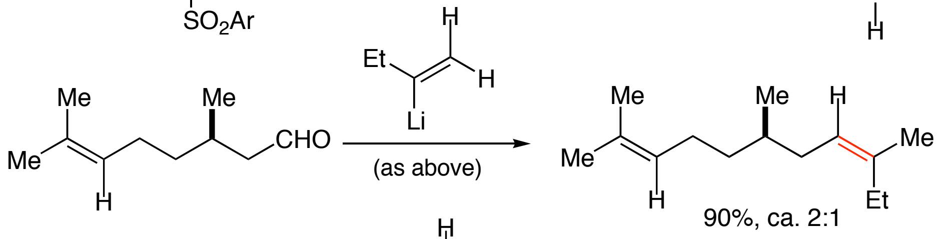
A. G. Myers, P. J. Kukkola *JACS*, **1990**, *112*, 8208.

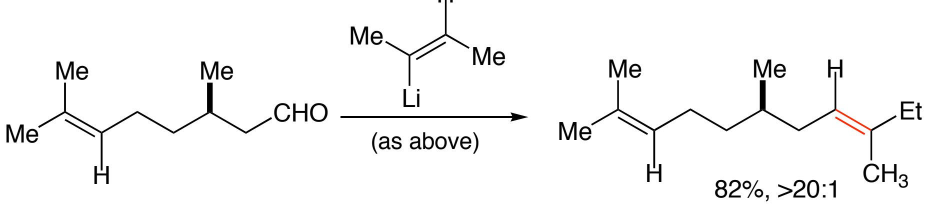


RLi	Ratio ***Z*:*E***	Yield
	50:50	79%
	<5:95	81%

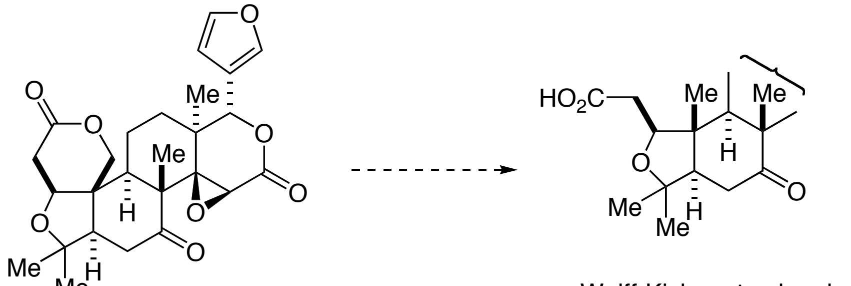








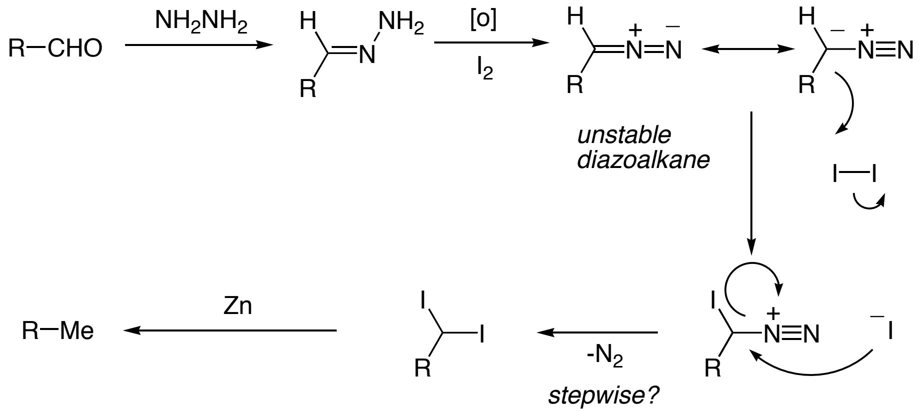
The Constitution of Limonin, Arigoni, Barton, Corey and Jeger, *Experietia*, **1960**, 41



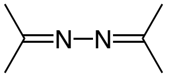
Limonin

Wolff-Kishner too harsh

Proposed reaction: Barton, *JCS*, **1962**, 470.

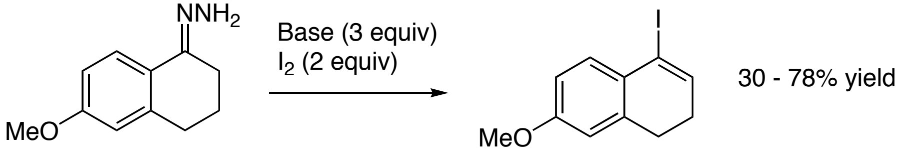


Not very general:



azine is often a major product

Ketones provide vinyl iodides

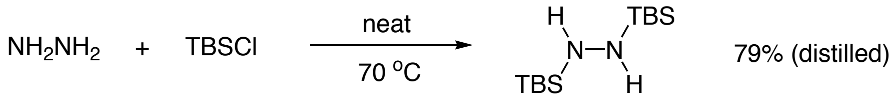


Barton, *Tetrahedron*, **1988**, *44*, 147-162

For a very recent application, see: Theodorakis, *Angew. Chemie Int. Ed.* **2004**, *43*, 793-742

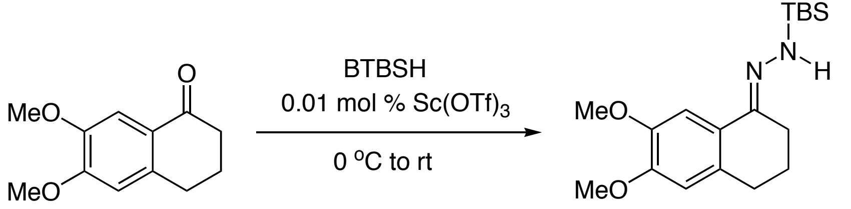
Recent Contributions from the Myers laboratory: bis-TBS Hydrazine : BTBSH

Preparation:

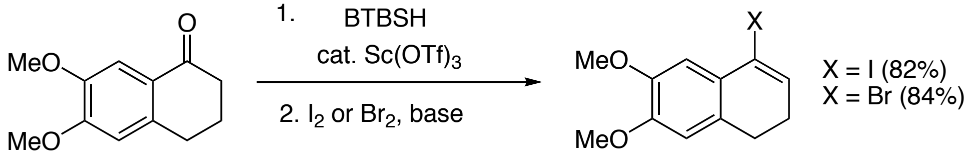


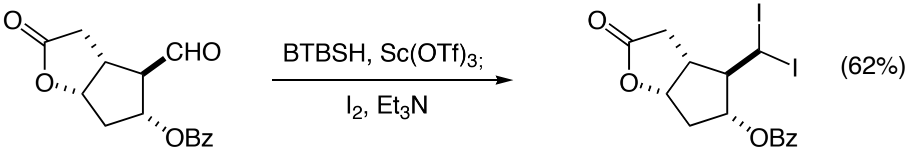
Furrow and Myers, *JACS*, **2004**, *126*, 5436

Straightforward condensation:

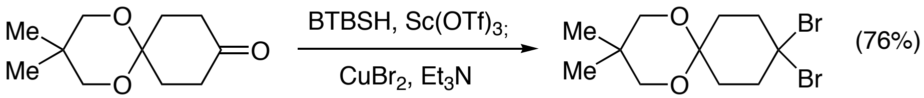


95% yield, 15 examples





The Corey Lactone

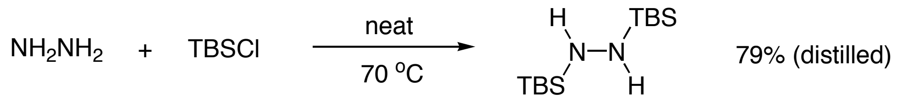


Furrow and Myers, *JACS*, **2004**, *126*, 5436

Hydrazone Transformations-8

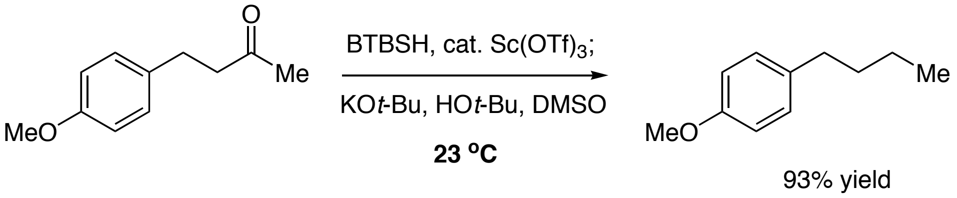
Recent Contributions from the Myers laboratory: bis-TBS Hydrazine : BTBSH

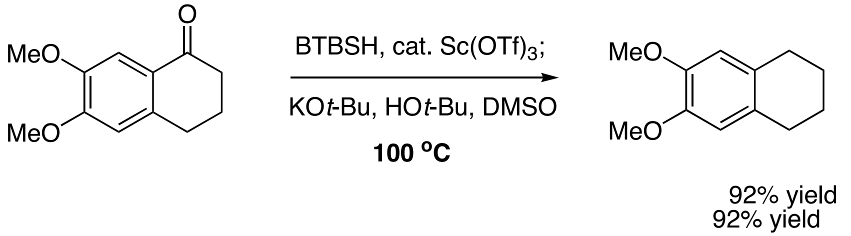
Preparation:



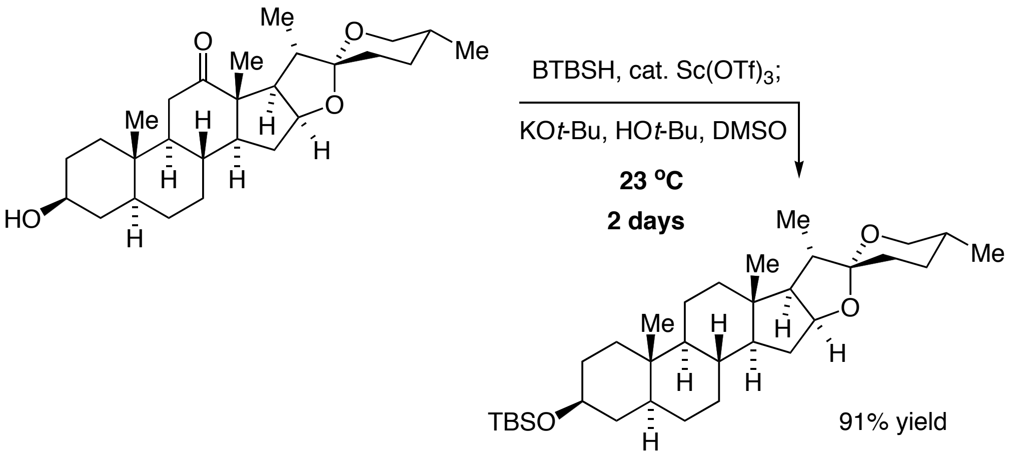
Furrow and Myers, *JACS*, **2004**, *126*, 5436

Modified Wolff-Kishner reductions: One-pot, two-step protocol



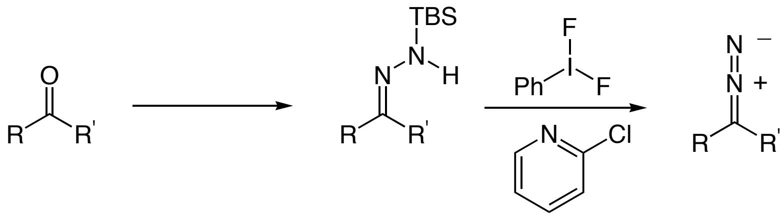


92% yield



7 examples, *JACS*, **2004**, *126*, 5436

The Generation of Diazoalkanes in Situ from TBS Hydrazones:

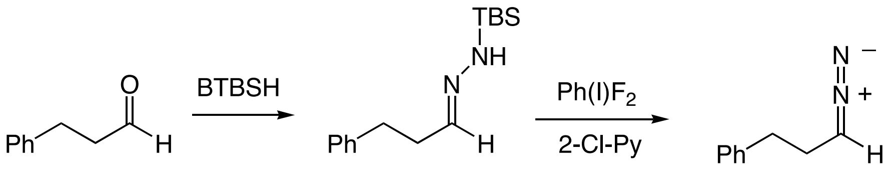


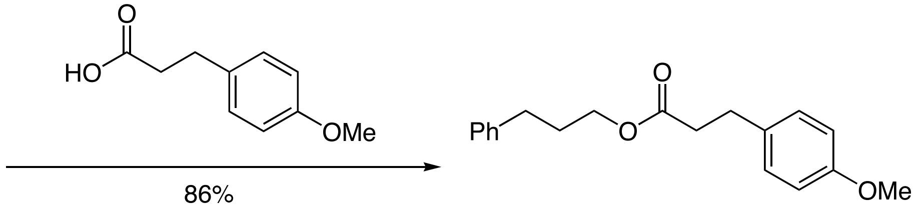
Furrow and Myers, *JACS*, **2004**, *126*, 12223

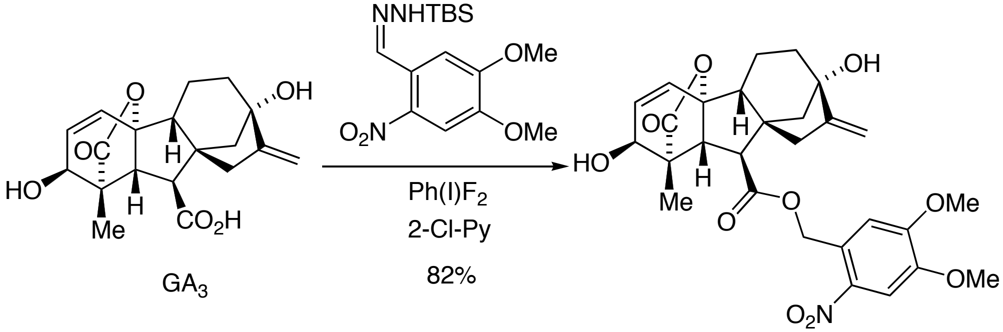
The generation of unstabilized diazoalkanes is very difficult as usually both the starting materials and products are unstable.

Methods such as the Bamford-Stevens reaction may be hazardous.

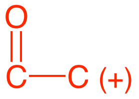
Esterification of Carboxylic Acids with Diazoalkanes generated in Situ



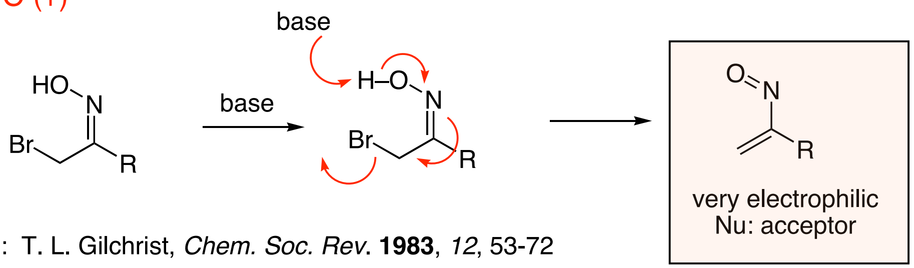




GA$_3$

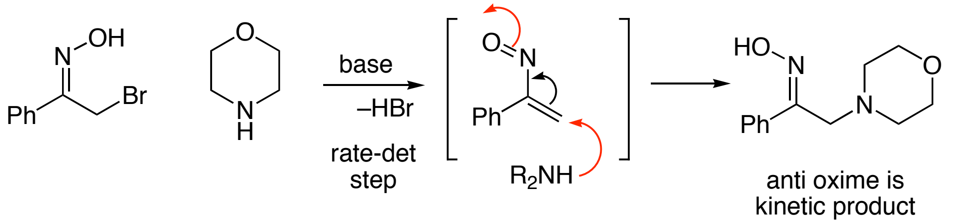


α-Keto Carbonium Ion Equivalents

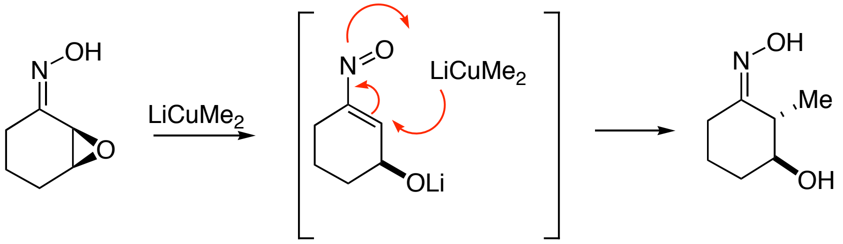


Review: T. L. Gilchrist, *Chem. Soc. Rev*. **1983**, *12*, 53-72

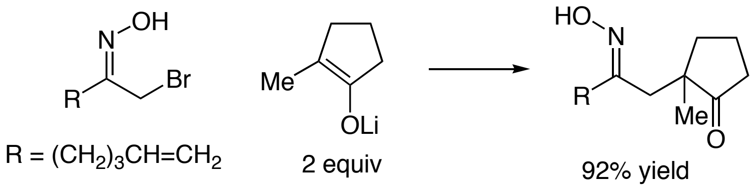
Reactions with Nucleophiles



T. Kaiser, *JACS*. **1972**, *94*, 9276-9277

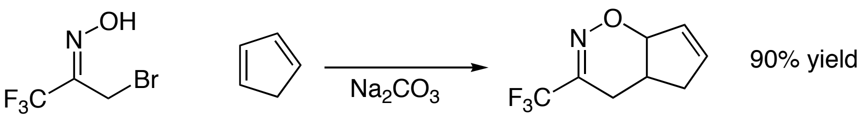


Corey, *Tetrahedron Lett*. **1975**, 3117



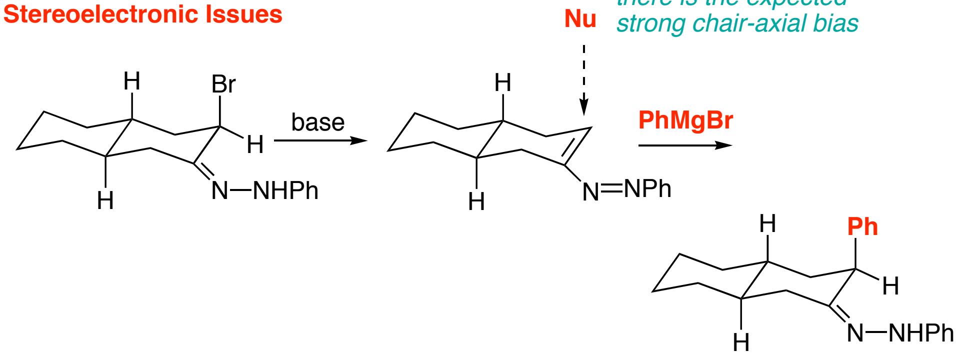
Corey, *Helv. Chem. Acta*. **1977**, *60*, 2964

Cycloadditions



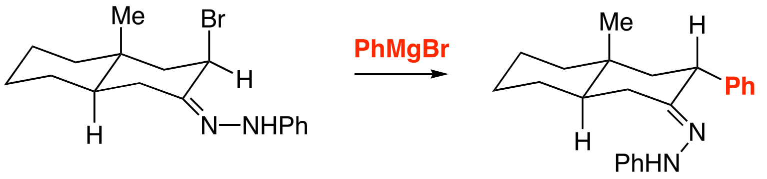
Ressig, *J. Org. Chem*. **1992**, *57*, 339

Stereoelectronic Issues

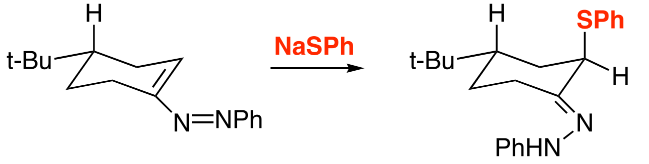


there is the expected strong chair-axial bias

Stereoelectronic vs Steric Issues



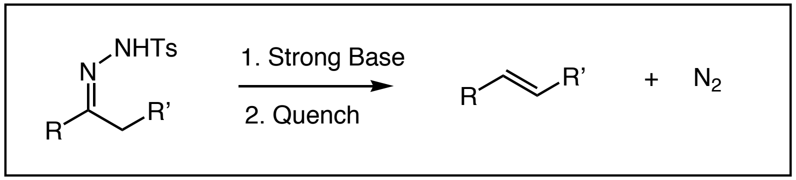
Bozzini, *Tetrahedron* **1982**, 38, 1459



there is the expected strong chair-axial bias

Bozzini, *Tetrahedron* **1982**, 39, 3413

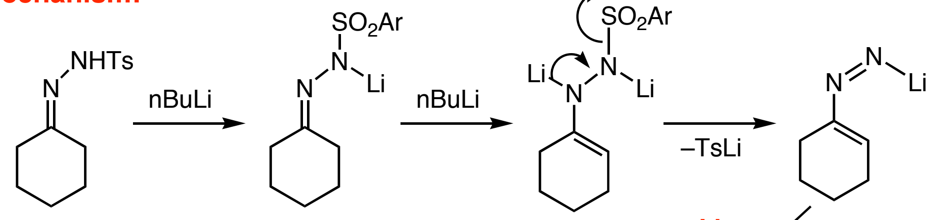
The Shapiro Reaction-1

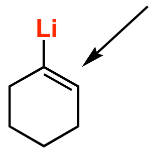


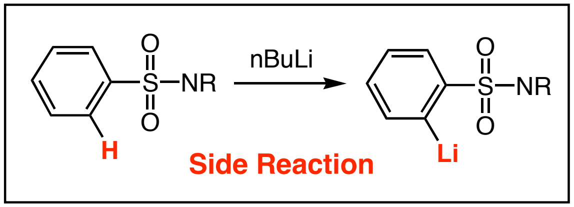
General Reviews:

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapters 4.3 .
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapters 4.6.
Shapiro, *Organic Reactions* **1976**, Vol 23, pp 405-507.

Mechanism:

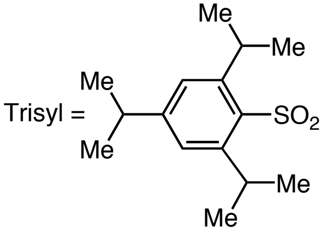




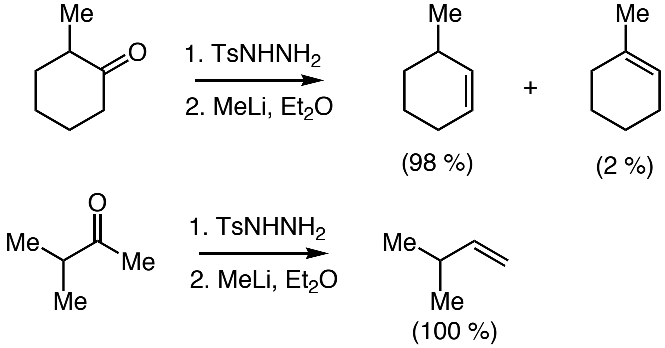


Side Reaction

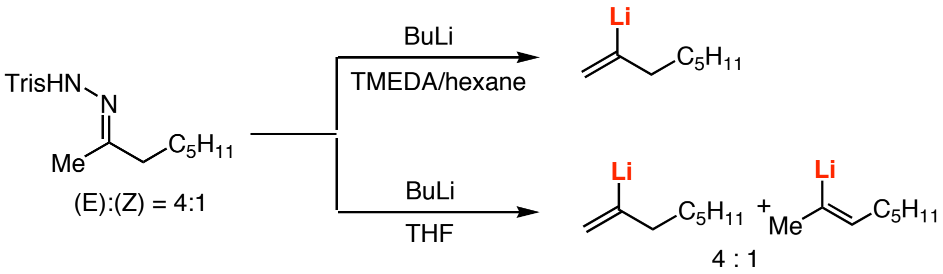
the Triisopropylsulfonyl (Trisyl) group is used (Roberts *Tet. Let.* **1981**, *22*, 4895).



Regiochemistry

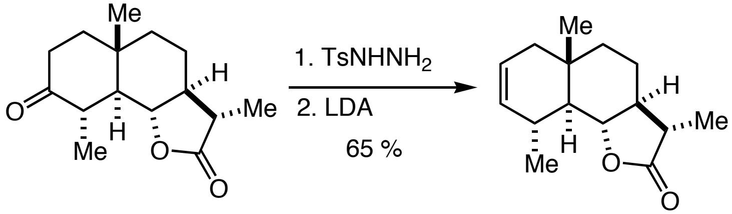


Deprotonation of the monoanion occurs predominantly at the kinetically more acidic site giving, after elimination, the less substituted alkene product.

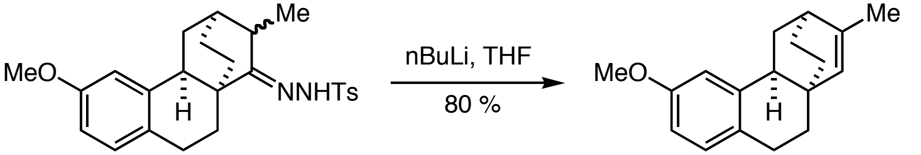


In THF solution regiochemical ratios generally reflect the starting hydrazone geometries

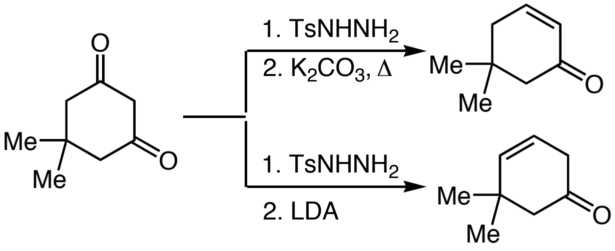
Bond *J. Org. Chem.* **1978**, *43,* 154.



Grieco *J. Org. Chem.* **1977**, *42*, 1717.

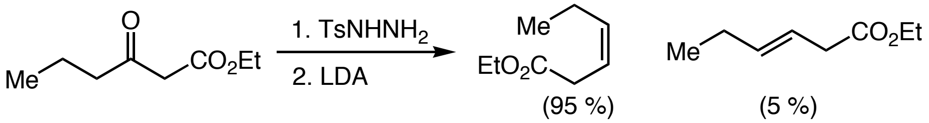


Nemoto *et. al. JCS, Perkin Trans. 1* **1985**, 927.



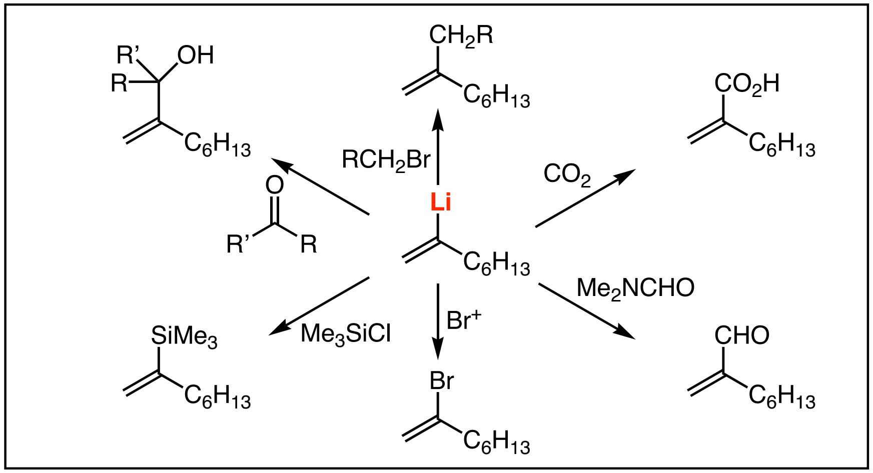
via dianion

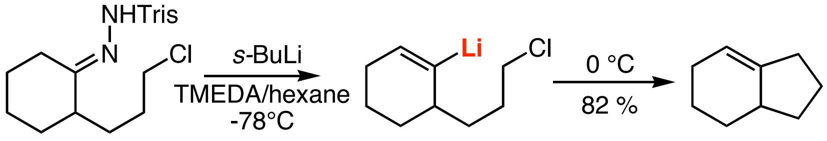
via trianion



The Shapiro Reaction-2

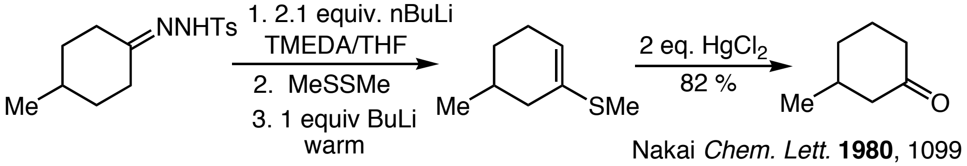
Trapping of the intermediate alkenyllithium





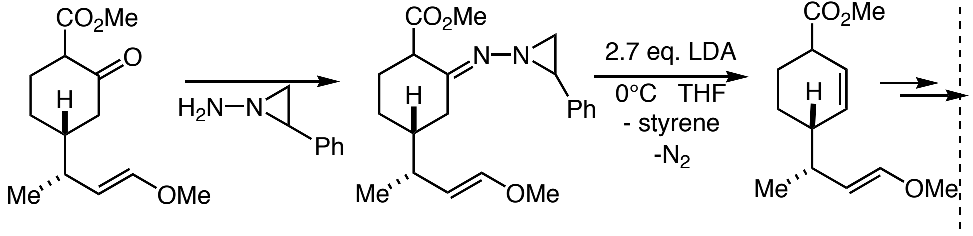
Bloom *Tet Lett.* ***1984***, *25*, 4901

Carbonyl Transposition

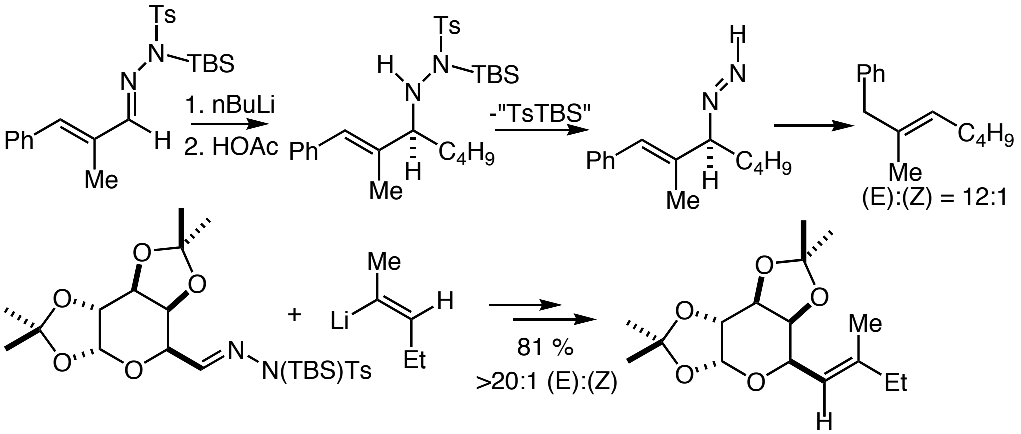


Nakai *Chem. Lett.* **1980**, 1099

Shapiro alternatives

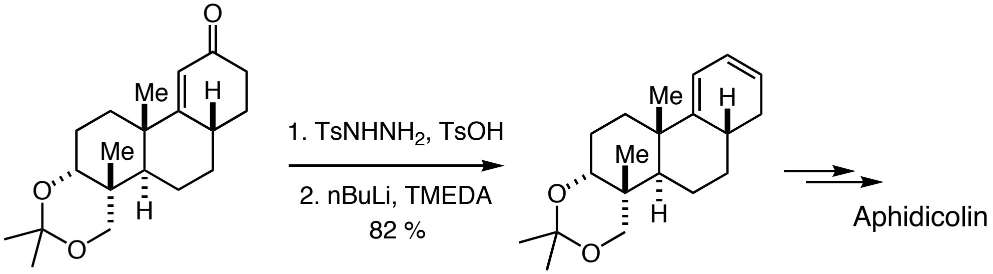


(Juvabione) Evans *J. Am. Chem. Soc.* **1980**, *102*, 774

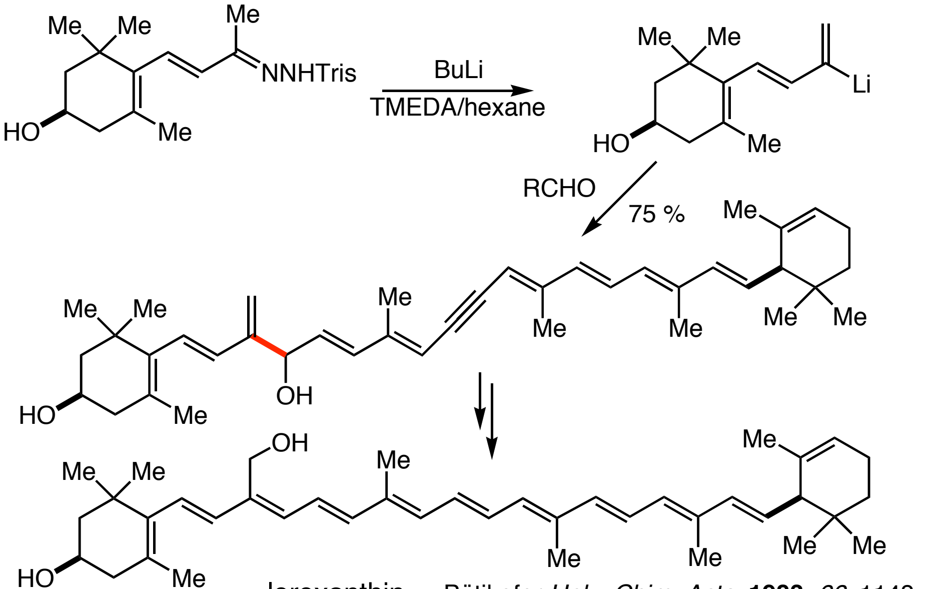


Applications

Myers, *J. Am. Chem. Soc.* **1990**, *112*, 8208



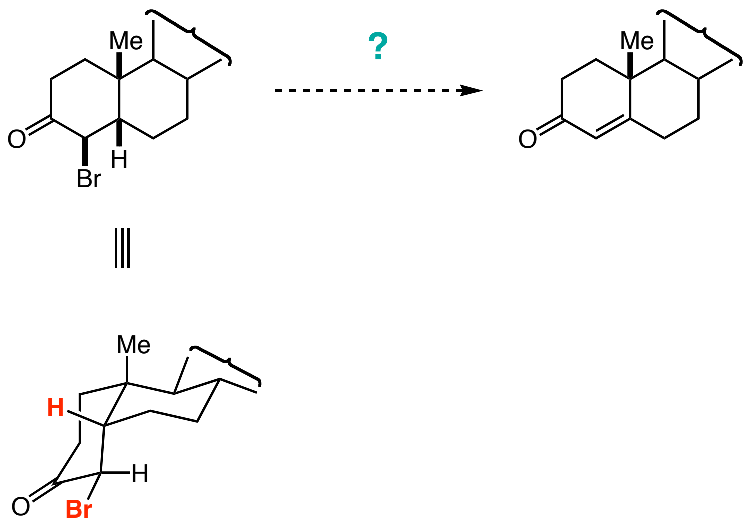
van Tamelen *J. Am. Chem. Soc.* **1983**, *105*, 142.



Ioroxanthin Bütikofer *Helv. Chim. Acta.* **1983**, *66*, 1148

Other uses of Hydrazones

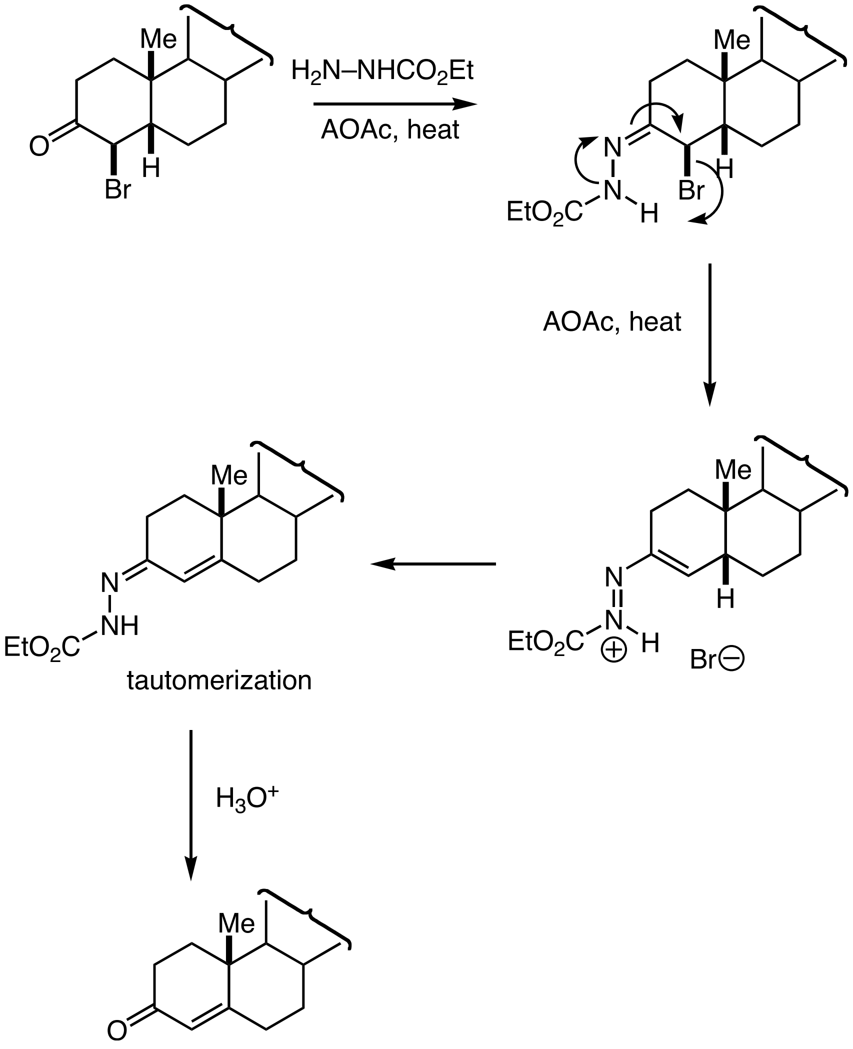
How would you convert A into B?



Problem: The syn relationship between Br and H renders the direct dehydrohalogenation with base unfavorable (relative to other potential reactions).

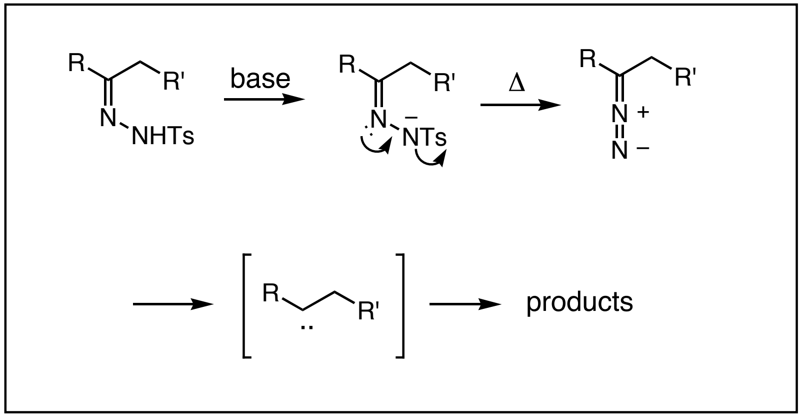
Solution: proceed via the hydrazone.

Mattox-Kendall Dehydrohalogenation (Paquette, *Reagents*, Vol 5, p 3509)

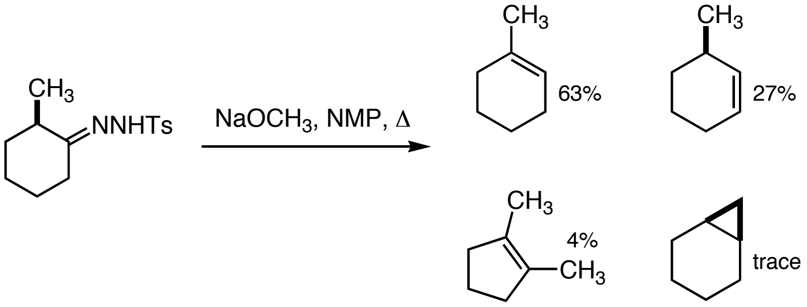


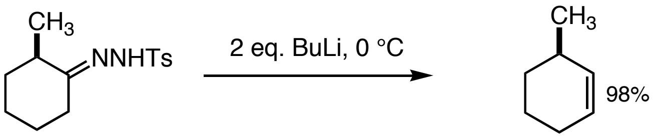
The Bamford-Stevens Reaction

An Alternative Decomposition Pathway for Tosyl Hydrazones

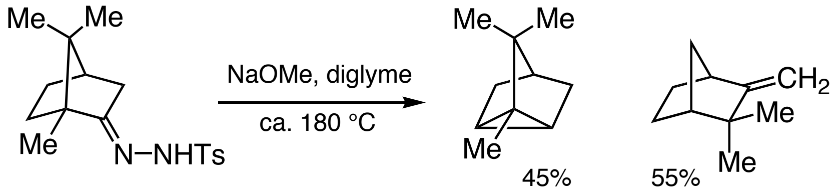


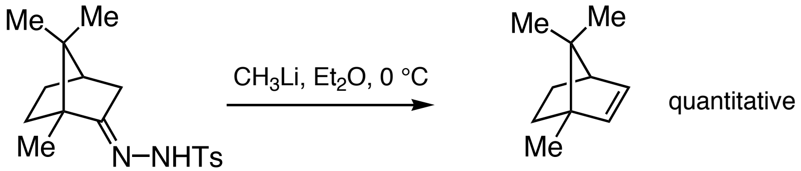
Bamford-Stevens vs. Shapiro



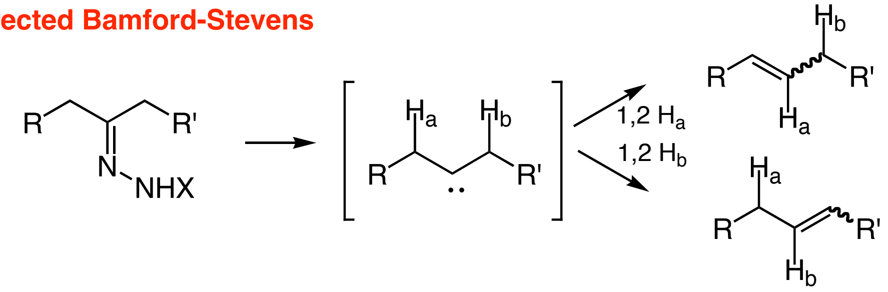


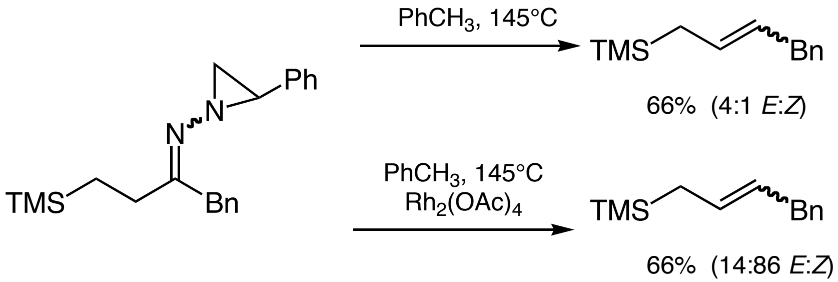
R. H. Shapiro *Org. React.* **1976**, *23*, 405.





Directed Bamford-Stevens





T. K. Sarkar, et al. *JCS Chem. Comm.* **1992**, 1184.

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 32

Ambiphilic Functional Groups–3
Sulfur-Based Activating Groups

- Sulfur-Ylides
- Sulfur-Stabilized Carbanions: Structure
- Sulfone-Based Transformations
- Pummerer Rearrangement

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

"Chemical Chameleons: Organosulfones as Synthetic Building Blocks"
B. M. Trost, *Bull. chem. Soc. Japan,* **1988**, *61*, 107-124 **(handout)**

"Evolution of Dithiane-Based Strategies for the Construction of Architecturally Complex Natural Products", *Accounts Chem. Res.* **2004,** *37,* 366-377 **(handout)**

Pummerer Review, A. Padwa, *Synthesis* **1997**, 1353-1377 **(handout)**

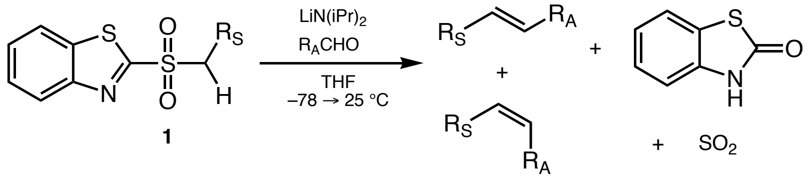
D. A. Evans

Friday
December 8, 2006

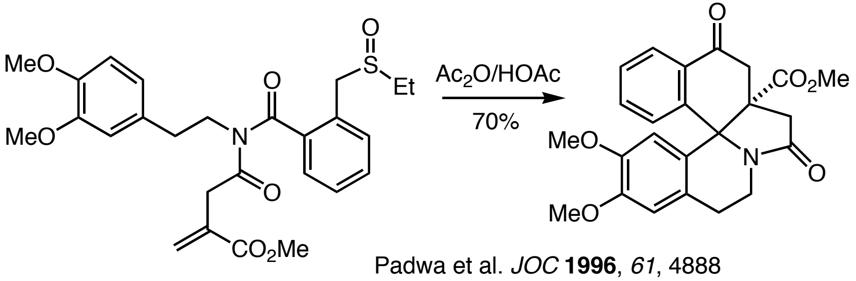
Relevant Background Reading

General:	Simpkins, N.S. *Sulphones in Organic Synthesis*, Pergamon Press, New York, 1993.
General:	Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019.
Julia:	Blakemore, *J. Chem. Soc. Perkin Trans I.* **2002**, 2563.
Electrophilic Properties:	Trost, B.M. *Bull.Chem. Soc. Jpn.* **1988**, *61*, 107.
SO_2 Extrusion:	Vogtle, F.; Rossa, L. *ACIEE* **1979**, *18*, 515.
Ramberg-Bäcklund Rxn:	Paquette, L.A. *Org. Reactions* **1977**, *25*, 1.
Triflones:	Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.
Sulfoximides:	Johnson, C.R. *Tetrahedron* **1984**, *40*, 1225

Problem 37: The stereoselective construction of trans olefins through carbanion-mediated condensation processes has still not been rendered general. One transformation that may be used in certain circumstances is the "one-step" Julia transformation illustrated below. Provide a mechanism for this transformation.



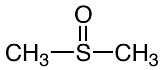
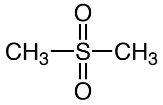
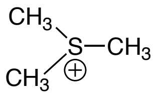
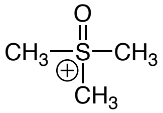
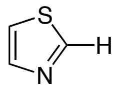
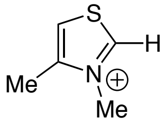
The cruel mechanistic problems that you should be prepared for in Chem 206
Six Pummerer Problems in database.

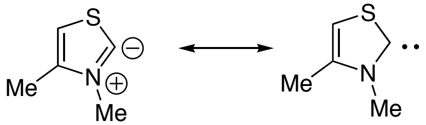


Padwa et al. *JOC* **1996**, *61*, 4888

Acidities of Sulfur-based Functional Groups

Bordwell, F. G.; Zhang, X.-M. *Acc. Chem. Res.* **1993**, *26*, 510-17.

		pKa (DMSO)	
CH_3-S-CH_3	Sulfide	**(45)**	← CH_4 pKa (~56)
			← NH_3 pKa (~41)
 $CH_3-\overset{O}{\overset{\|}{S}}-CH_3$	Sulfoxide	**~35**	
 $CH_3-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-CH_3$	Sulfone	**~ 31**	← HOH pKa 31
	Sulfonium Salt	**18.2**	pKa of Phenol
	Oxo-Sulfonium Salt	**< 18**	
	Thiazole	**29.4**	
	Thiazolium Salt	**16.5**	

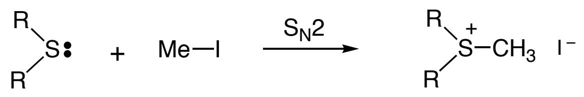

"carbenoid resonance structure

$R_2S-\overset{(-)}{\underset{(+)}{C}}$

Reactivity Pattern
Nonalternate

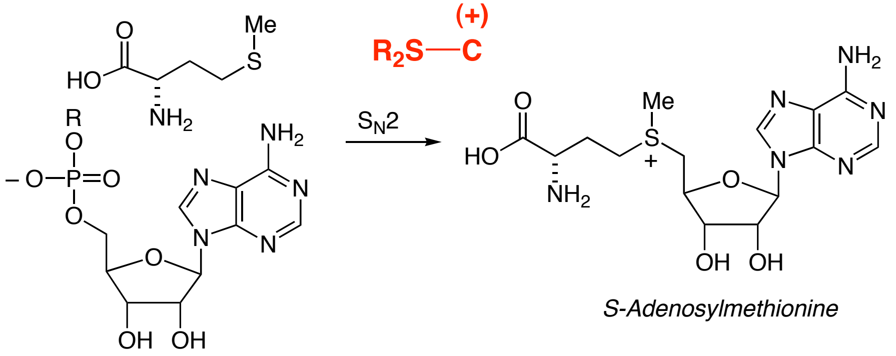
Reactions of Sulfonium Ylids

- **Synthesis:**



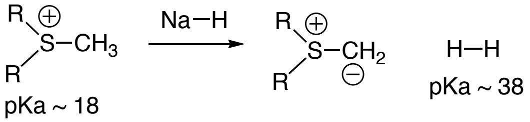
Sulfonium Salt: pKa ~ 18

$R_2S-\overset{(+)}{C}$

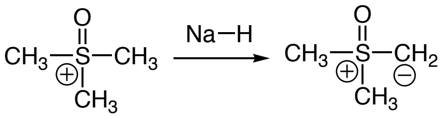


S-Adenosylmethionine

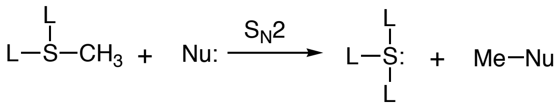
- Deprotonation:



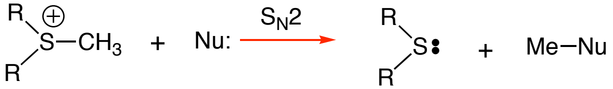
$R_2S-\overset{(-)}{C}$



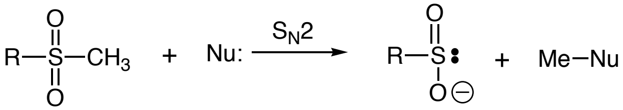
- **Leaving Group Potential:** $R_2S-C(+)$



Excellent LG



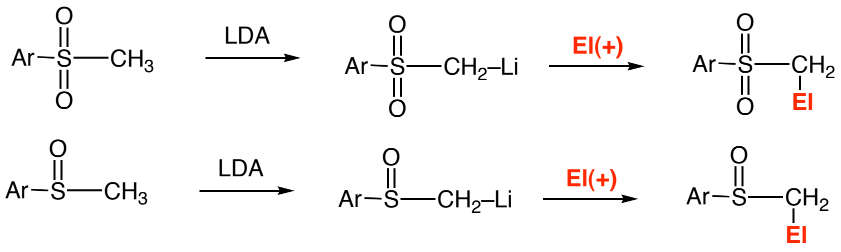
Good LG



X-ray Structures of Metallated Sulfones & Sulfoxides

Sulfone- & Sulfoxide Based Carbanions: Structure

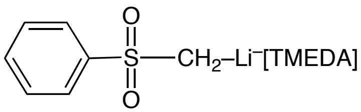
- Sulfone- and sulfoxide-stabilized carbanions are extremely useful carbon nucleophiles in organic synthesis.

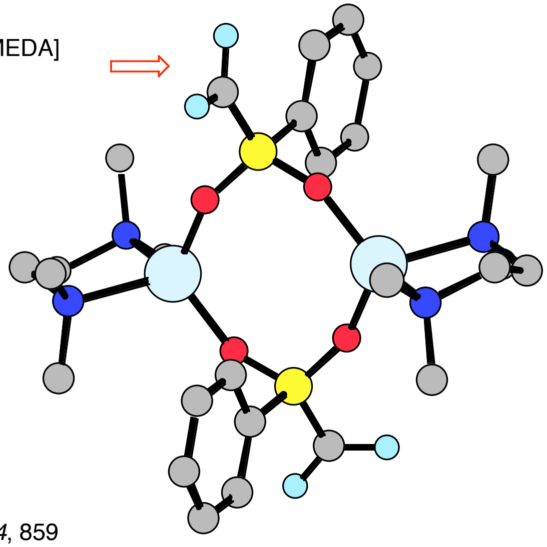


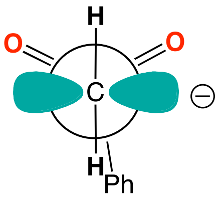
However, until recently little information was available on the solid state structures of these species:

> "The Structure of Lithium Coumpounds of Sulfones, Sulfoximides, Sulfoxides, Thioethers, 1,3 Dithianes, Nitriles, Nitro Compounds, and Hydrazones."
> Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

Here are several examples taken from the Boche review:

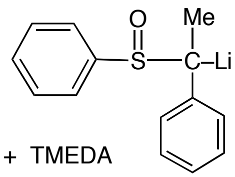




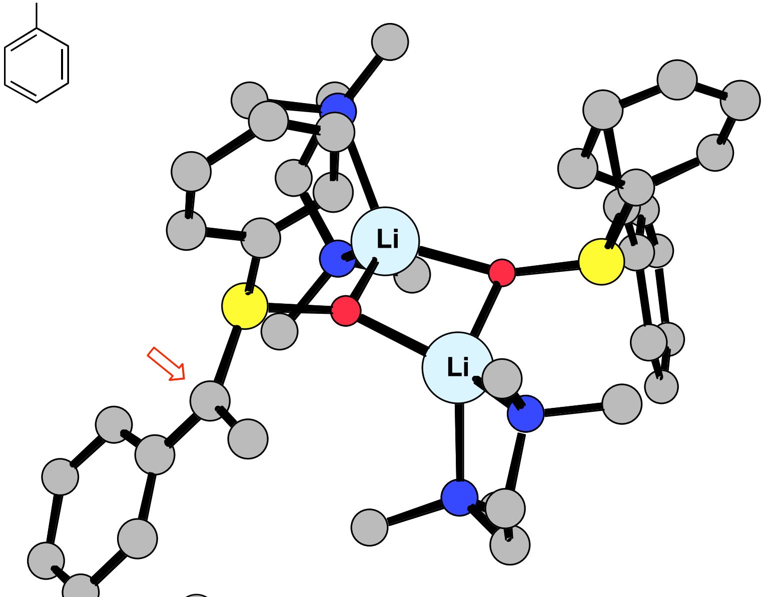


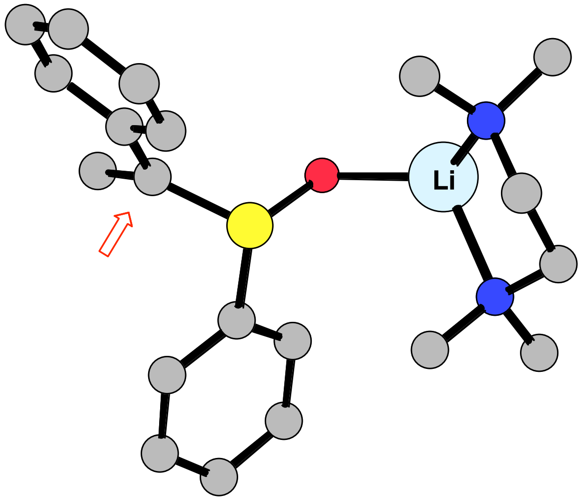
delocalization into sigma* S–O

Gais, etal.
Angew. Chem. Int. Ed. **1985**, *24*, 859



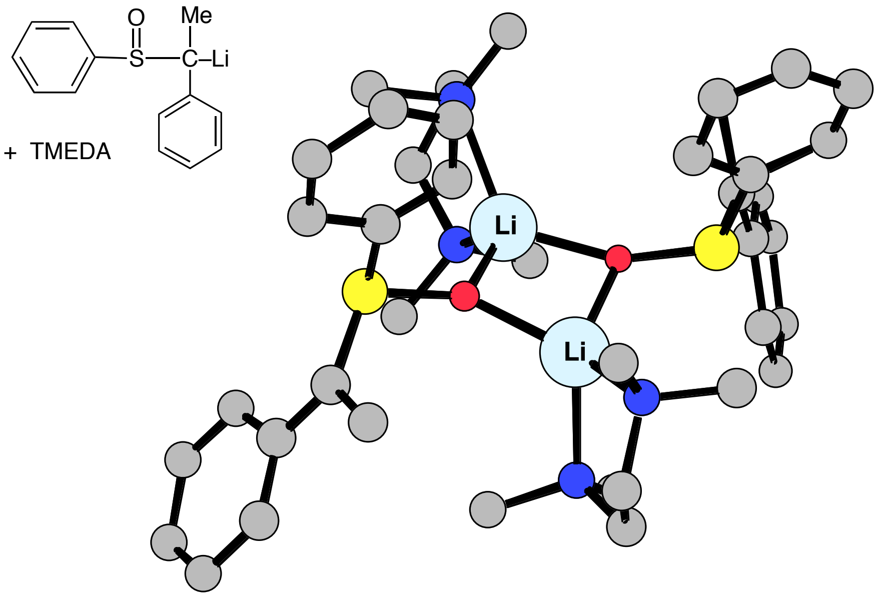
Boche, etal. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101



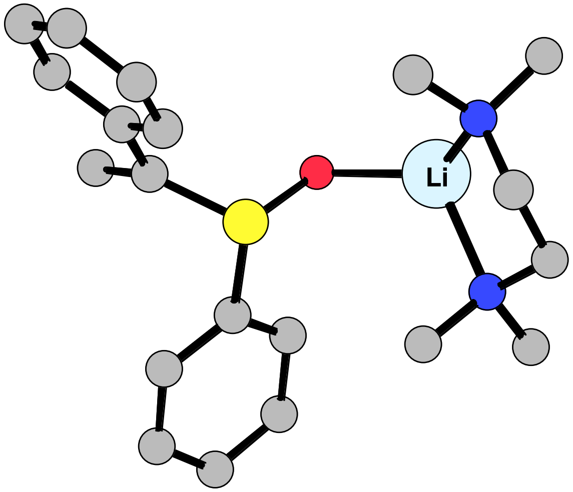


- The Li counterions are not associated with the charged carbon.
- The carbanions are largely trigonal.

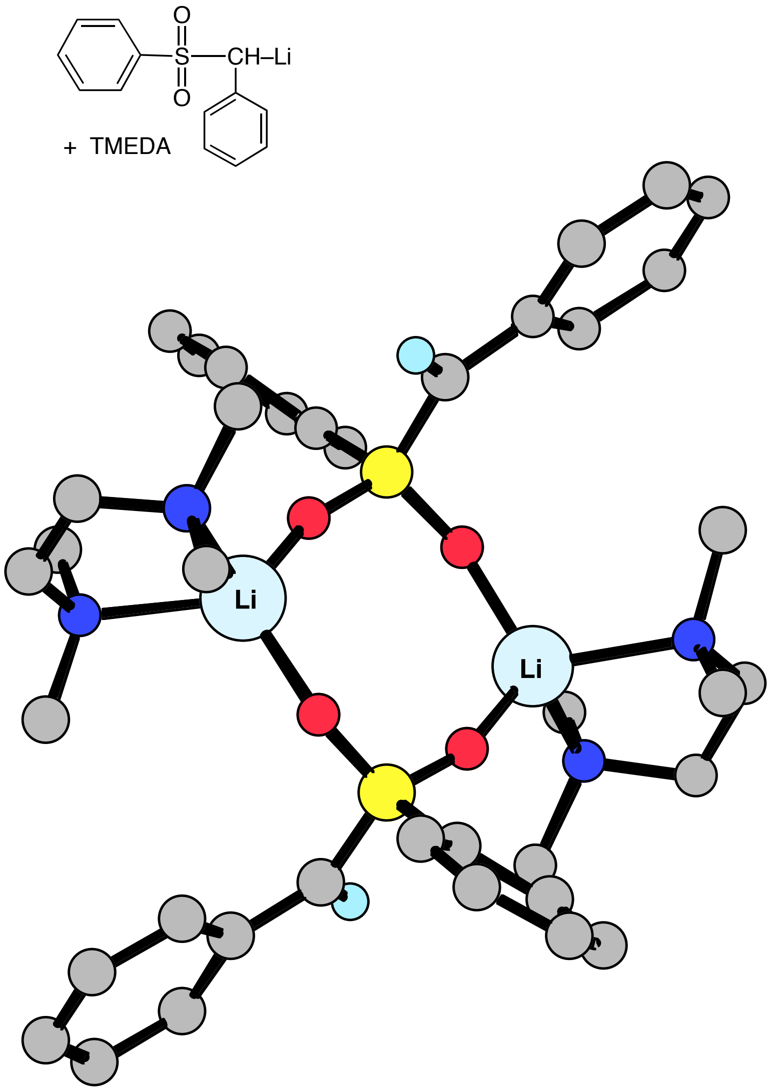
X-ray Structures of Phenylsulfinyl Carbanions



+ TMEDA



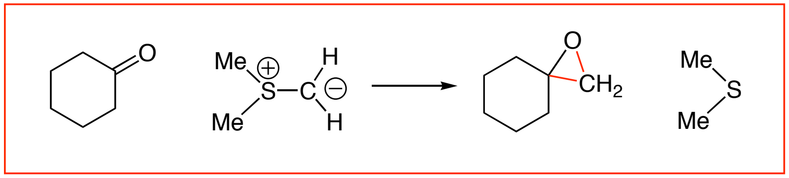
Boche, etal. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101



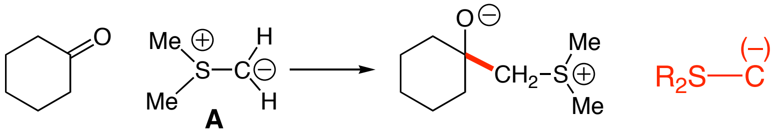
+ TMEDA

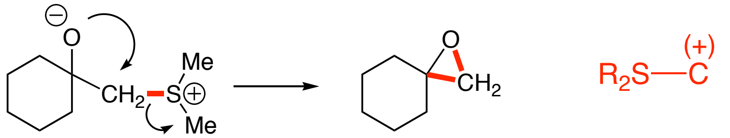
Boche, etal. *Angew. Chem. Int. Ed.* **1985**, *24*, 573

Reactions with ketones: $R_2S—\overset{(\mp)}{C}$ Reactivity Pattern: Nonalternate



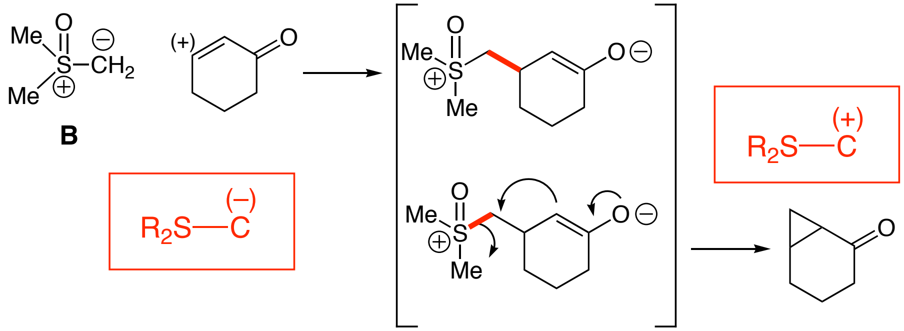
Corey & Chaycovski, *JACS* **1965**, *87*, 1353-1364. **(Handout)**



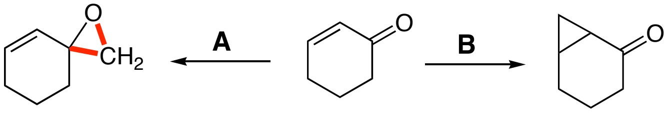


"Twenty-five Years of Dimethylsulfoxonium Methylide (Corey's Reagent).", Gololobov, Y. G.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* 1987, *43*, 2609. **(electronic handout)**

Reactions of OxoSulfonium Ylids: Conjugate Addition

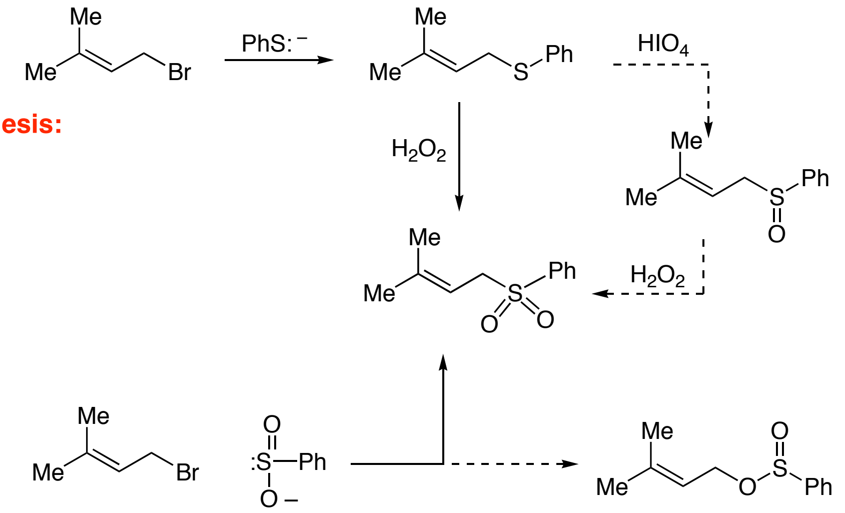


Nonalternate reactivity pattern revealed in consecutive reactions



Reactions of Sulfones

Synthesis:

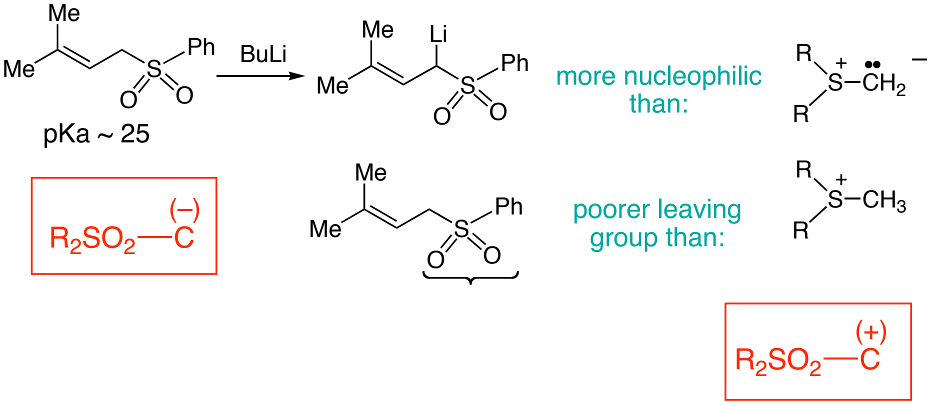


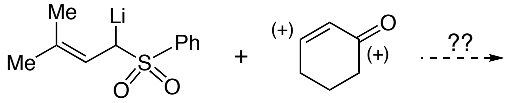
(Sulfinate anion)

Sulfinate ester
not observed

Good review article: Magnus, *Tetrahedron* **1977**, *33*, 2019-2045.

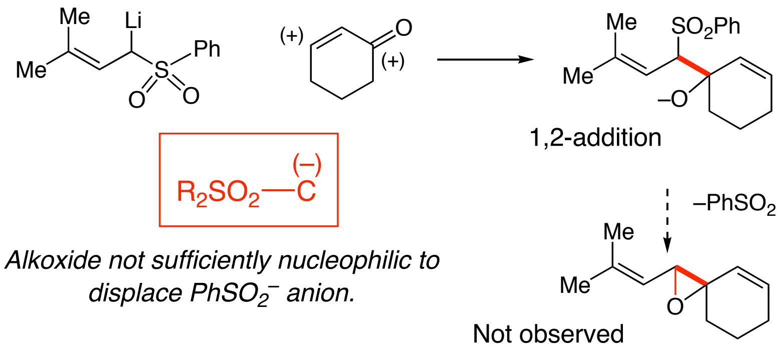
Reactions of Sulfones





1,2- vs 1,4-addition ??

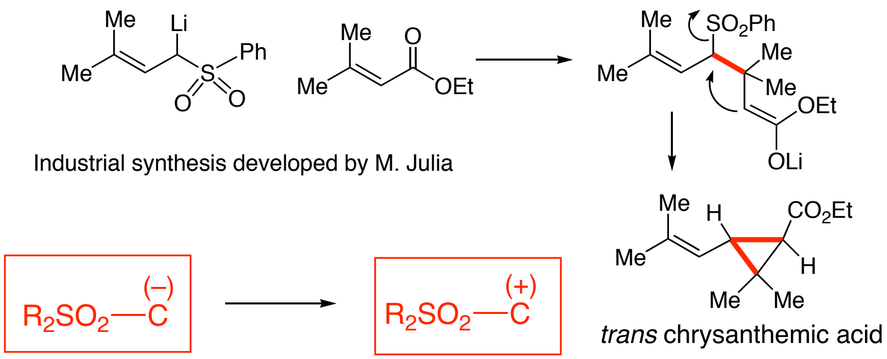
Will function as LG ??



$R_2SO_2—\overset{(-)}{C}$

Alkoxide not sufficiently nucleophilic to displace $PhSO_2^-$ anion.

However!!

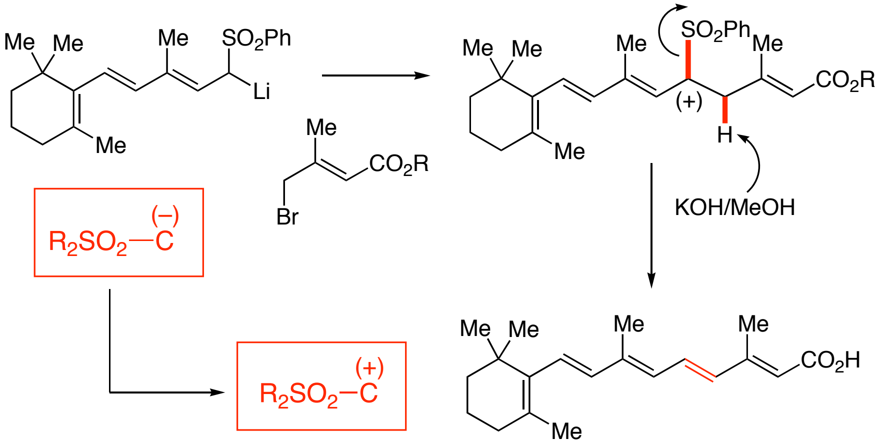


Industrial synthesis developed by M. Julia

$R_2SO_2—\overset{(-)}{C}$ → $R_2SO_2—\overset{(+)}{C}$

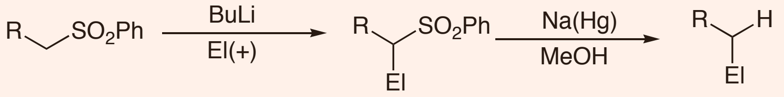
trans chrysanthemic acid

Synthesis of Vitamin A: Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130

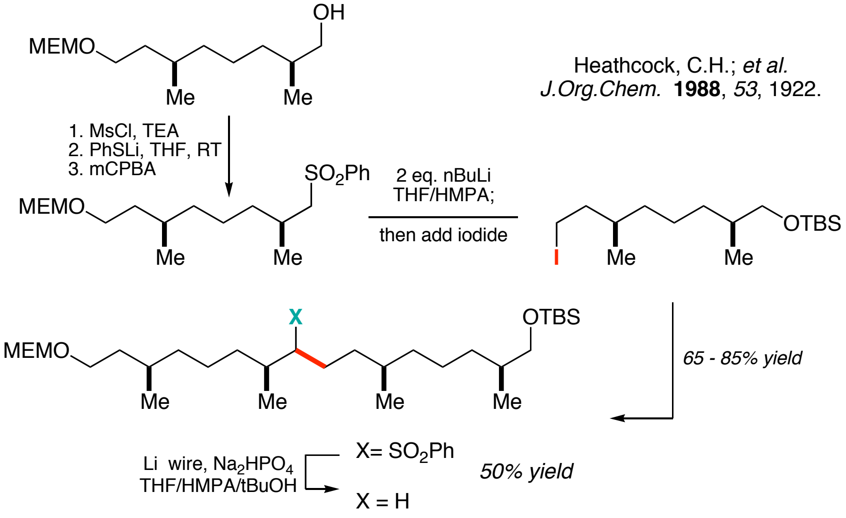


$R_2SO_2—\overset{(-)}{C}$ → $R_2SO_2—\overset{(+)}{C}$

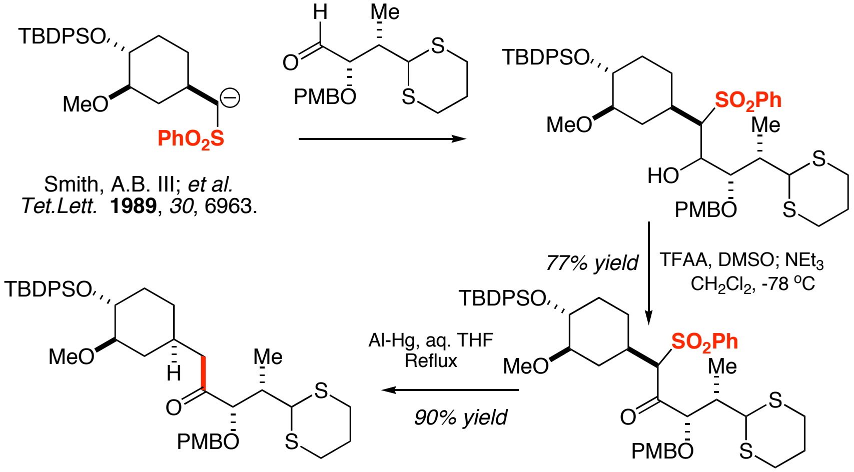
The Sulfone group may also be readily removed reductively:



Fragment Coupling with Sulfonyl Carbanions



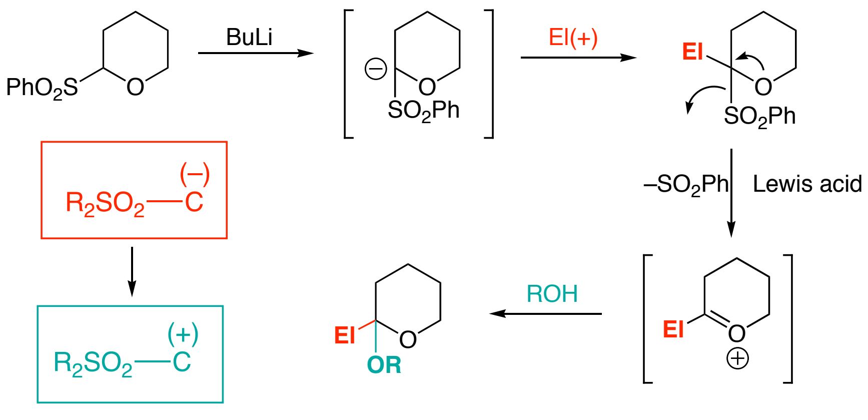
Heathcock, C.H.; *et al.* *J.Org.Chem.* **1988**, *53*, 1922.



Smith, A.B. III; *et al.* *Tet.Lett.* **1989**, *30*, 6963.

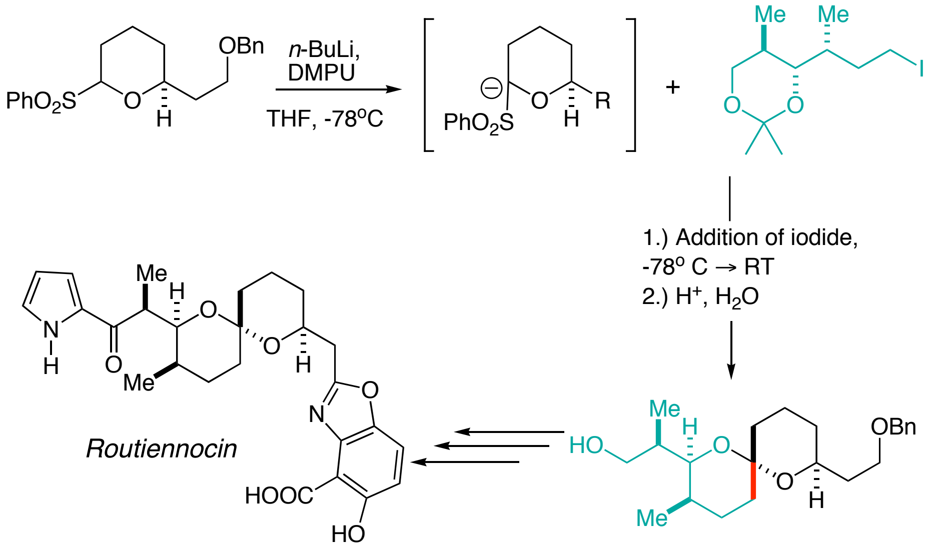
Sulfur-Based Functional Groups-4

Functionalization of cyclic Ethers

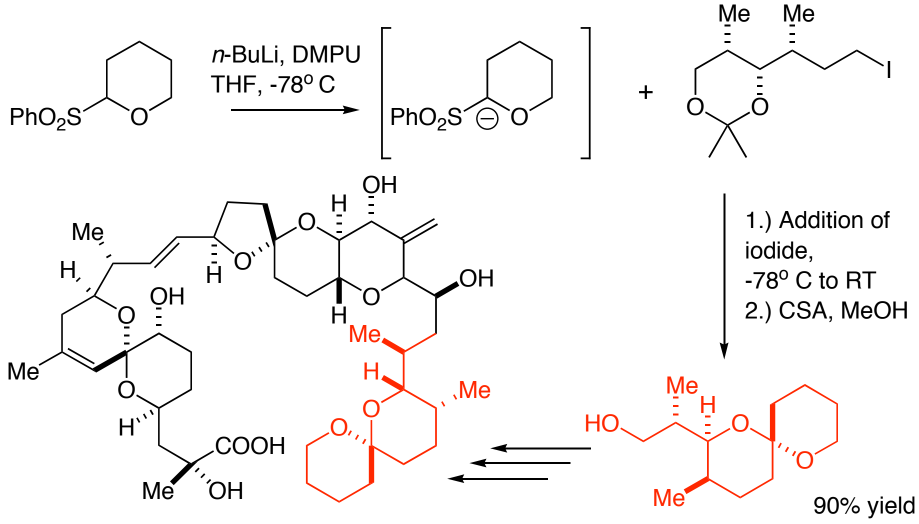


Ley *et al*, *Synlett*, **1992**, 395; Ley *et. al*, *Tetrahedron*, **1992**, *48*, 7899

Total Synthesis of Routiennocin (CP-61,405)

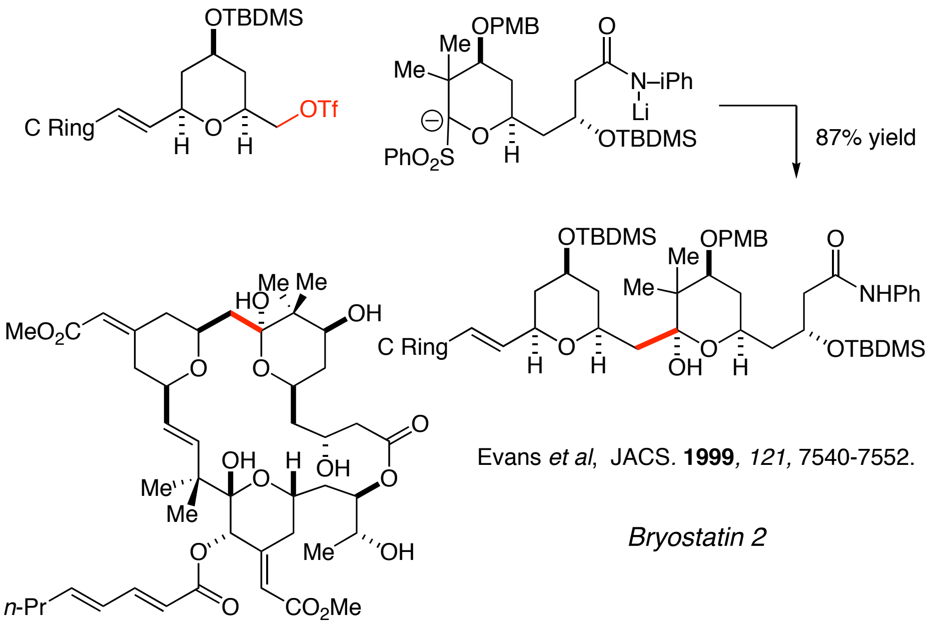


Total synthesis of Okadaic Acid



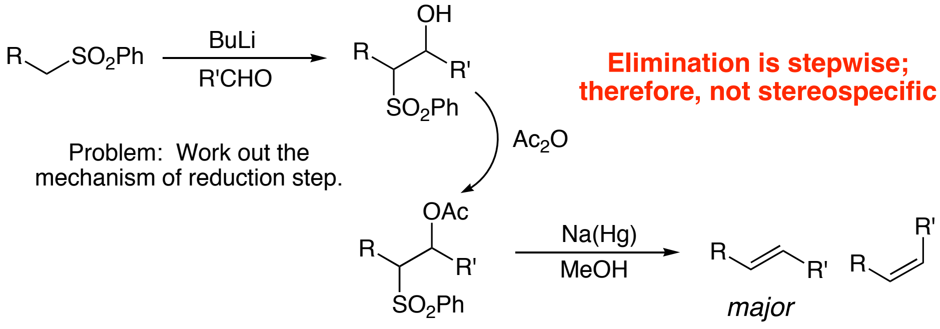
Ley *et al*, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3907.

Total synthesis of Bryostatin 2



Evans *et al*, JACS. **1999**, *121*, 7540-7552.

First Generation Julia Trans Olefin Synthesis:



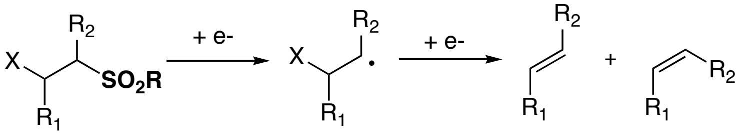
Elimination is stepwise; therefore, not stereospecific

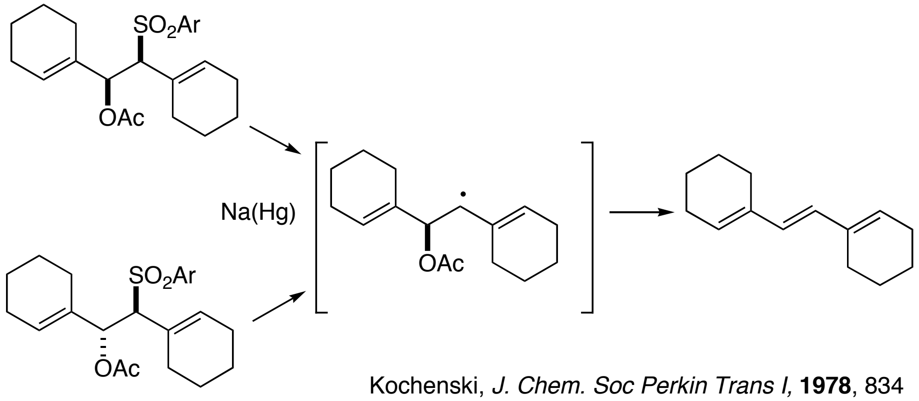
Problem: Work out the mechanism of reduction step.

Good sulfone review: Trost, *Bull Chem. Soc. Japan*, **1988**, *61*, 107-124.

Julia Review,
Blakemore, *J. Chem. Soc. Perkin Trans I.* **2002**, 2563. **(electronic handout)**

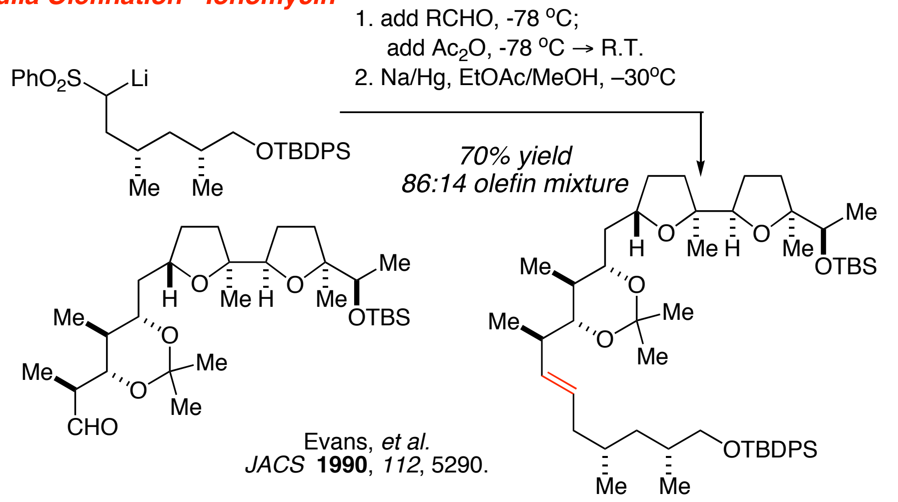
The reduction step is not stereosecific





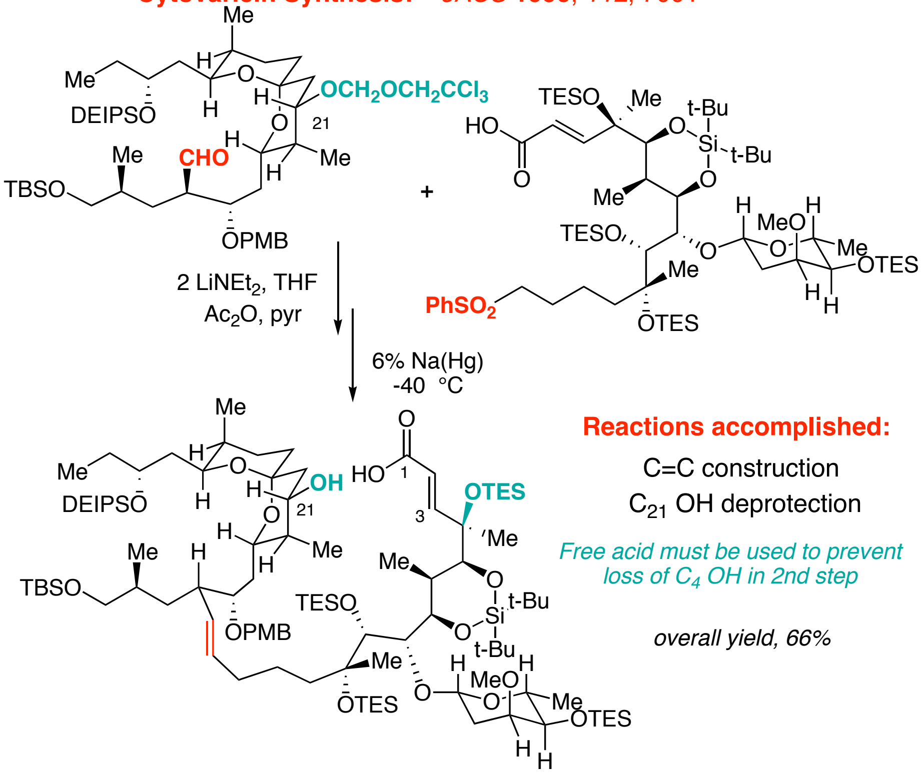
Kochenski, *J. Chem. Soc Perkin Trans I,* **1978**, 834

Julia Olefination - Ionomycin



Evans, *et al.*
JACS **1990**, *112*, 5290.

Cytovaricin Synthesis: *JACS* **1990**, *112*, 7001



Reactions accomplished:

C=C construction

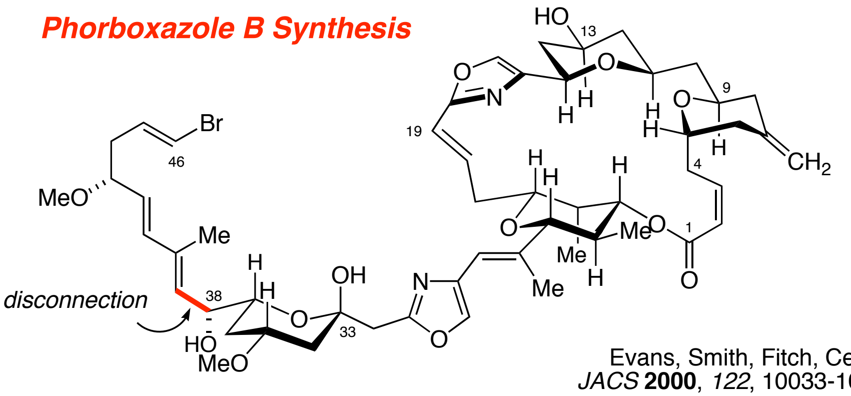
C$_{21}$ OH deprotection

Free acid must be used to prevent loss of C$_4$ OH in 2nd step

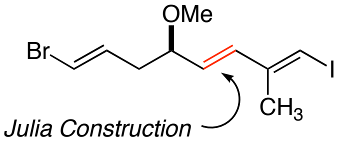
overall yield, 66%

Sulfur-Based Functional Groups-5: Julia Olefin Synthesis-2

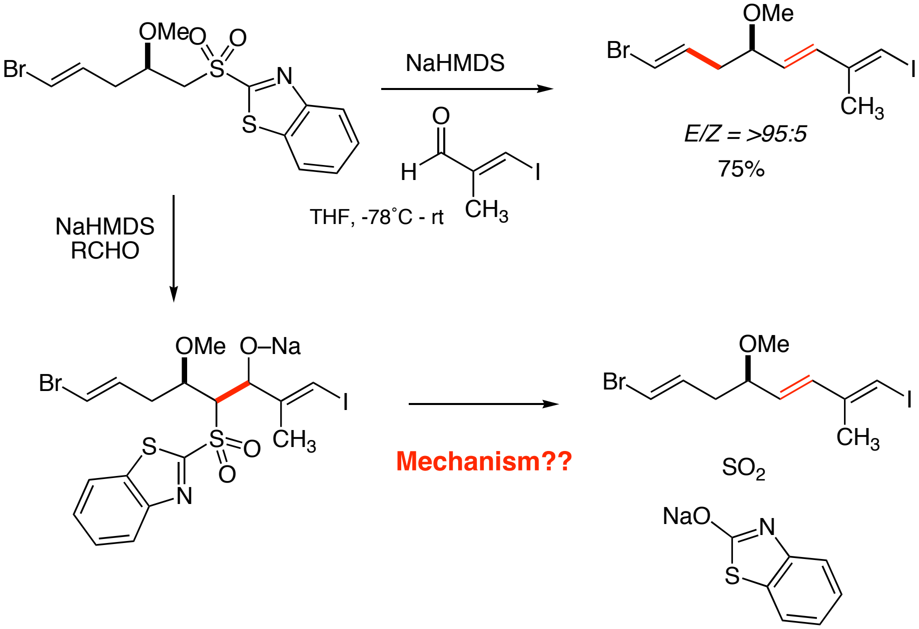
Phorboxazole B Synthesis



Evans, Smith, Fitch, Cee
JACS **2000**, *122*, 10033-10046.

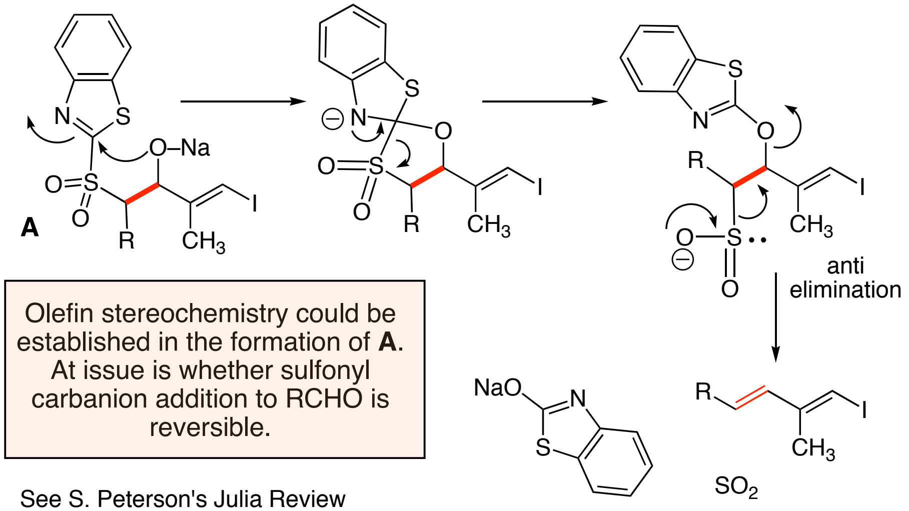


C_{39}–C_{46} Synthon



Mechanism??

The Mechanism:

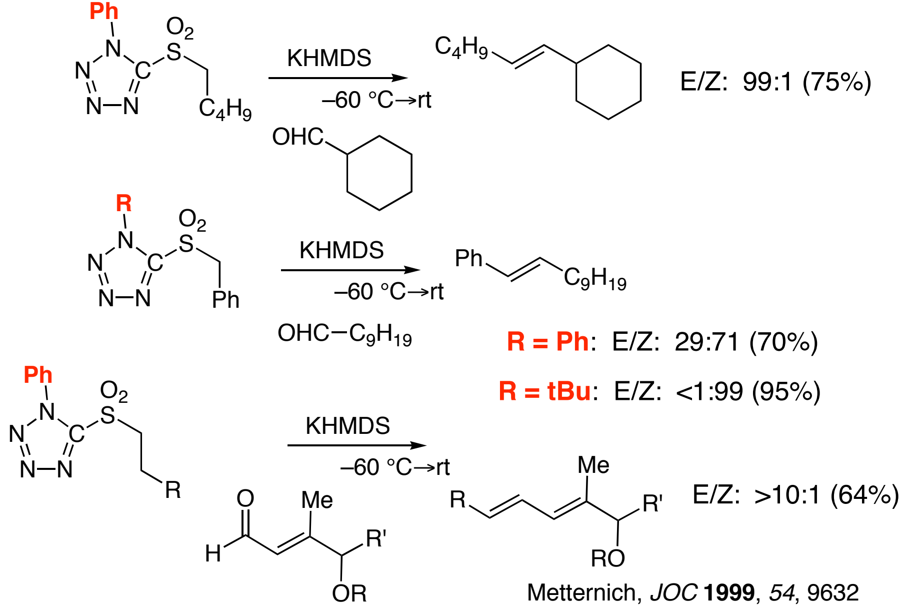


Olefin stereochemistry could be established in the formation of **A**. At issue is whether sulfonyl carbanion addition to RCHO is reversible.

See S. Peterson's Julia Review
(electronic handout)

Recent Modifications of the Julia Process:

Kocienski, *SynLett* **2000**, *3*, 365-366.



E/Z: 99:1 (75%)

R = Ph: E/Z: 29:71 (70%)

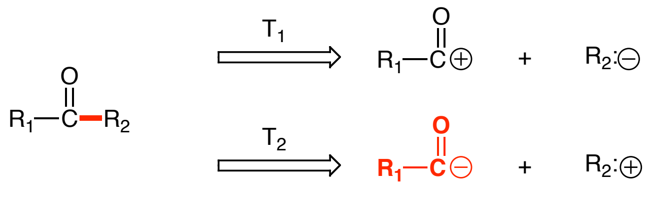
R = tBu: E/Z: <1:99 (95%)

E/Z: >10:1 (64%)

Metternich, *JOC* **1999**, *54*, 9632

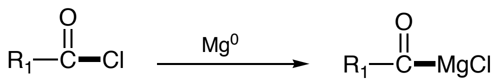
Carbonyl Anions: A useful Reversed Polarity Equivalent

Consider the two possible polar disconnections of the C–R_2 bond of the ketone shown below:



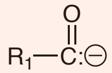
carbonyl anion

Carbonyl anions are not normally accessible via aldehyde deprotonation



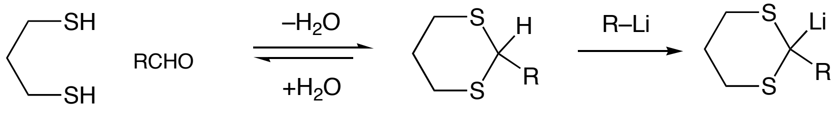
not feasible !! Why??

Operational equivalents to the carbonyl anion are useful in synthesis



1,3-Dithianes as Carbonyl Anion Equivalents

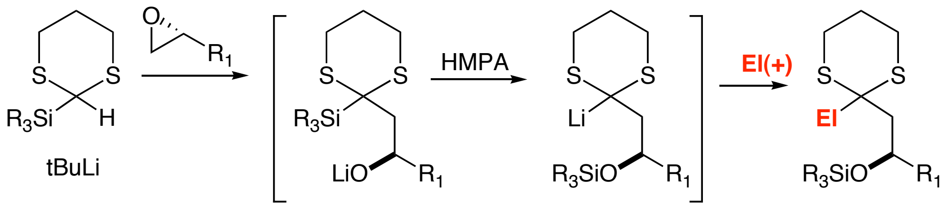
Dithiane Review:A. B. Smith, *Acc. Chem. Res*. 2004, *37*, 365 (Handout)



pKa ~ 39

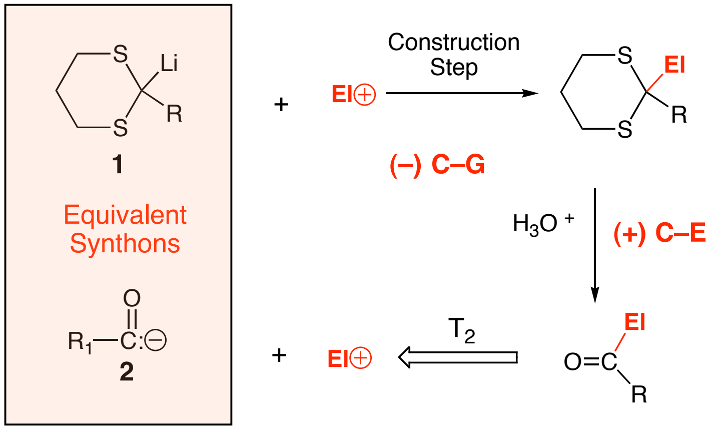
Reactivity Patterns: $(RS)_2$–C(+) $(RS)_2$–C(–)

Latest Innovations: A. B. Smith, *JACS* **2003**, *125*, 14435-14445 (Handout)



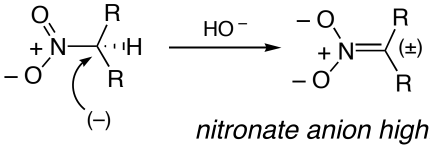
Brook Rearrangement

The overall set of reactions which establishes the equivalency of the hypothetical carbonyl anion **1** and its equivalent synthon **2** is shown below:

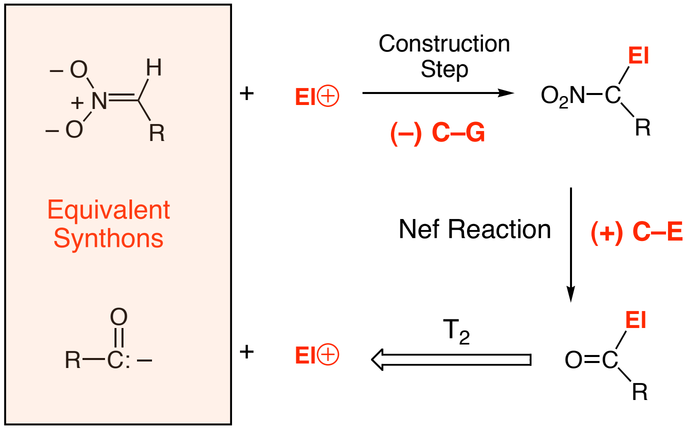


Nitronate Anions are also useful Carbonyl Anions

pKa 18



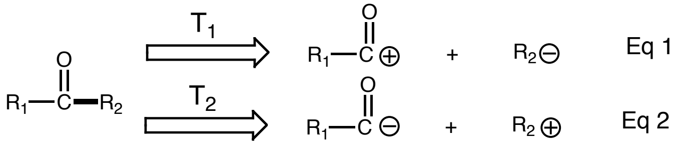
nitronate anion highly stablized



Dithianes anions highly nucleophilic (indiscriminate):
Nitonate anions higly discriminating

Charge Affinity Inversion Operators

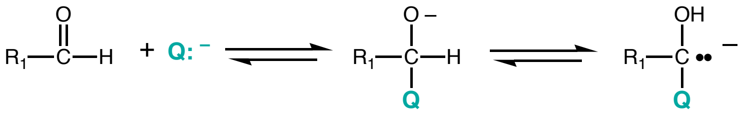
Introduction. As you know, transform T_1 conforms to the polar bias mapped on to the carbon skeleton by =O, while transform T_2 does not. Although T_1 is the more common transform, sometimes, because of the presence other functionality in either R_1 or R_2, the "reversed-polarity" transform is more suitable for the particular synthesis at hand.



Reversed Polarity Synthon

Ideally, one might visualize a catalytic agent (**Q**) which might react reversibly with an aldehyde in conjunction with inverting its charge affinity pattern. Nature has designed such reagents.

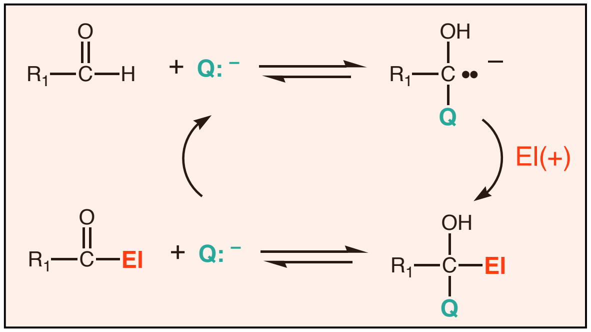
Charge Affinity Inversion Step: The structural constraints on (Q) are that it must be nucleophilic, add reversibly to aldehydes, and stabilize an adjacent carbanionic center.



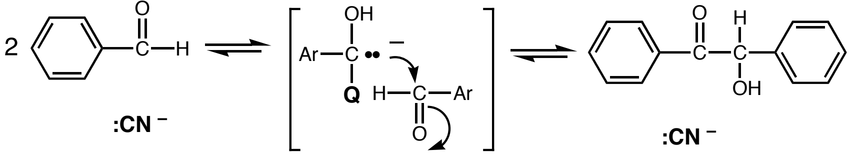
Lets call (Q) a charge affinity inversion operator since in operates on RCHO and reverses the intrinsic polar reactivity of the RCHO carbon from (+) to (–).

Overall Process:

Inversion Operator (**Q**)



Benzoin Condensation:

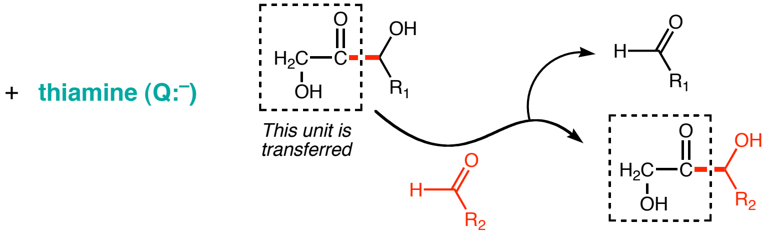


Cyanide ion is the best example of a reagent which functions as an inversion operator. The benzoin reaction is restricted to aromatic aldehydes. Why?

Nature's Inversion Operators

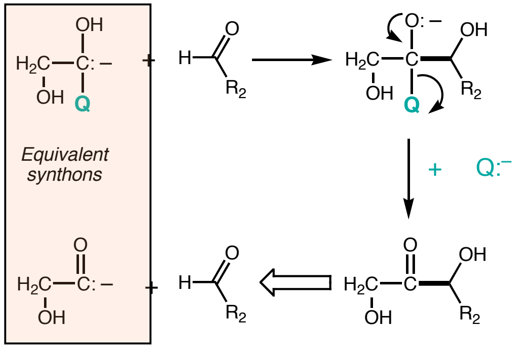
There is a clear need in nature to have both types of polar bond constructions exemplified by Transforms T_1 and T_2 (Eq 1-2). One such reaction is shown below.

This reaction, which is enzyme-catalyzed, requires the cofactor thiamine which functions as the inversion operator in these biological processes.

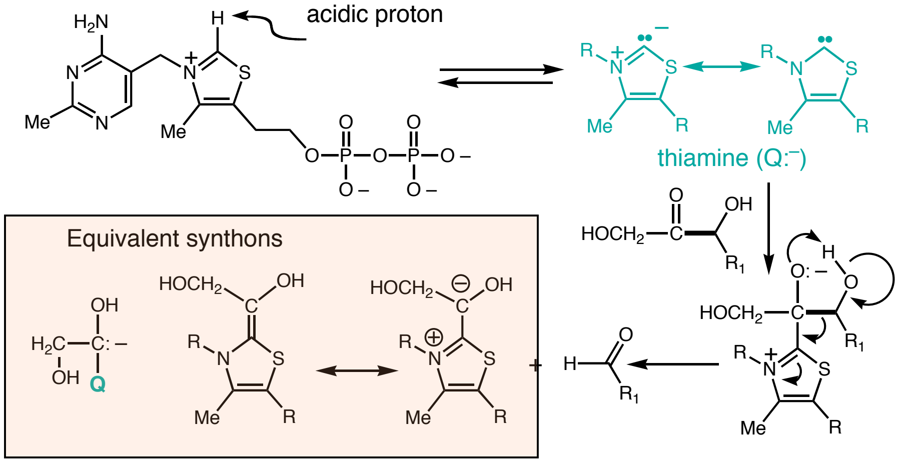


Crucial bond construction:

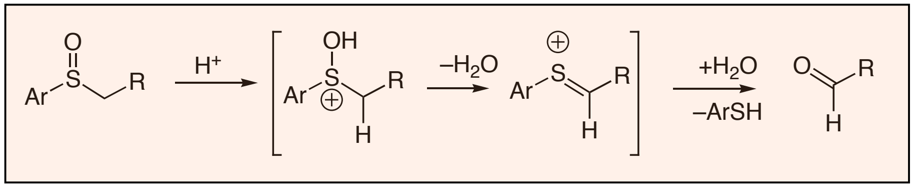
Related transform:



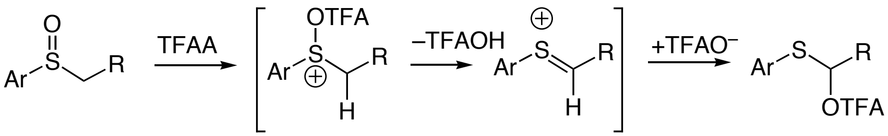
The Thiamine Coenzyme (Virtamin B$_1$) & how it functions



Basic Transformation:



The Pummerer Rearrangement facilitates the transformation of a sulfinyl → aldehyde transformation. The rearrangement may be initiated by either a Bronsted acid or an anhydride such as trifluoroacetic anhydride (TFAA). With the latter reagent, the transformation occurs at room temperature.



Leading References

De Lucchi, Miotti, et al. (1991). "The Pummerer reaction of sulfinyl compounds." *Organic Reactions* **1991**, *40*: 157.

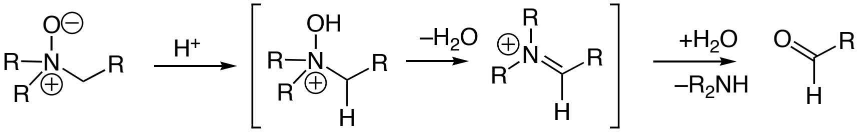
Grierson, and Husson (**1991**). Polonovski- and Pummerer-type Reactions and the Nef Reaction. *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. *6*: 909.

Padwa, A., D. E. Gunn, et al. "Application of the Pummerer reaction toward the synthesis of complex carbocycles and heterocycles." *Synthesis* **1997** 1353-1377.

Carreno, "Applications of sulfoxides to asymmetric synthesis of biologically active compounds." Chem. Reviews **1995** *95*, 1717-1760.

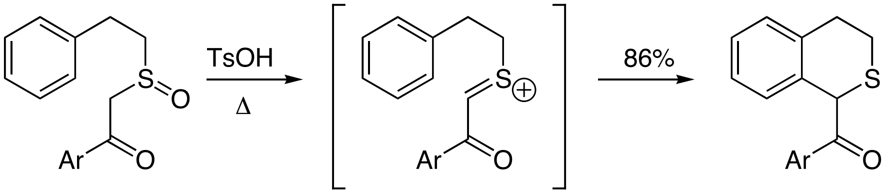
Kita, Y. and N. Shibata (1996). "Asymmetric pummerer-type reactions induced by O-silylated ketene acetals." Synlett(4): 289-296.

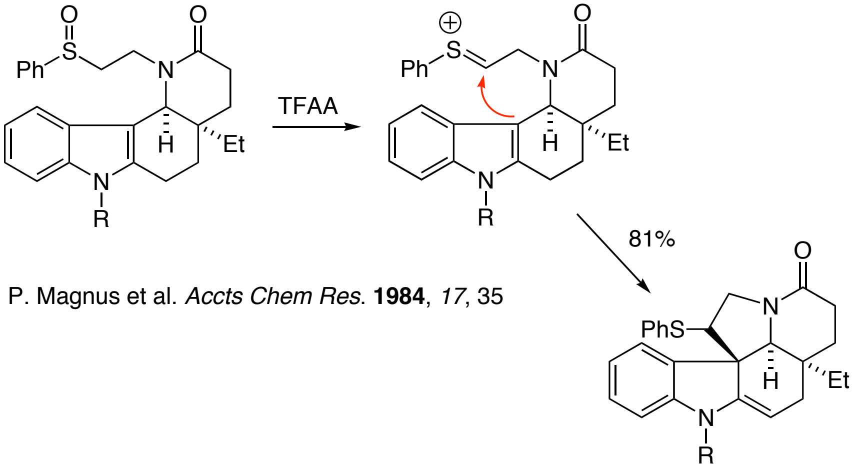
The Related Polonovski Reaction:



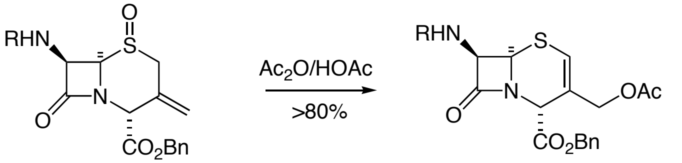
Regioselectivfity: *Depends on the relative kinetic acidy of the α protons*

Transformations Mediated by the Pummer Rearrangement

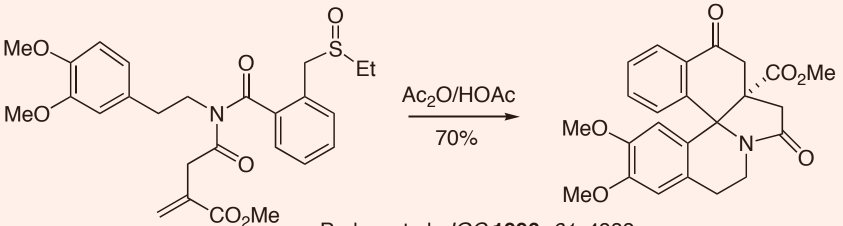




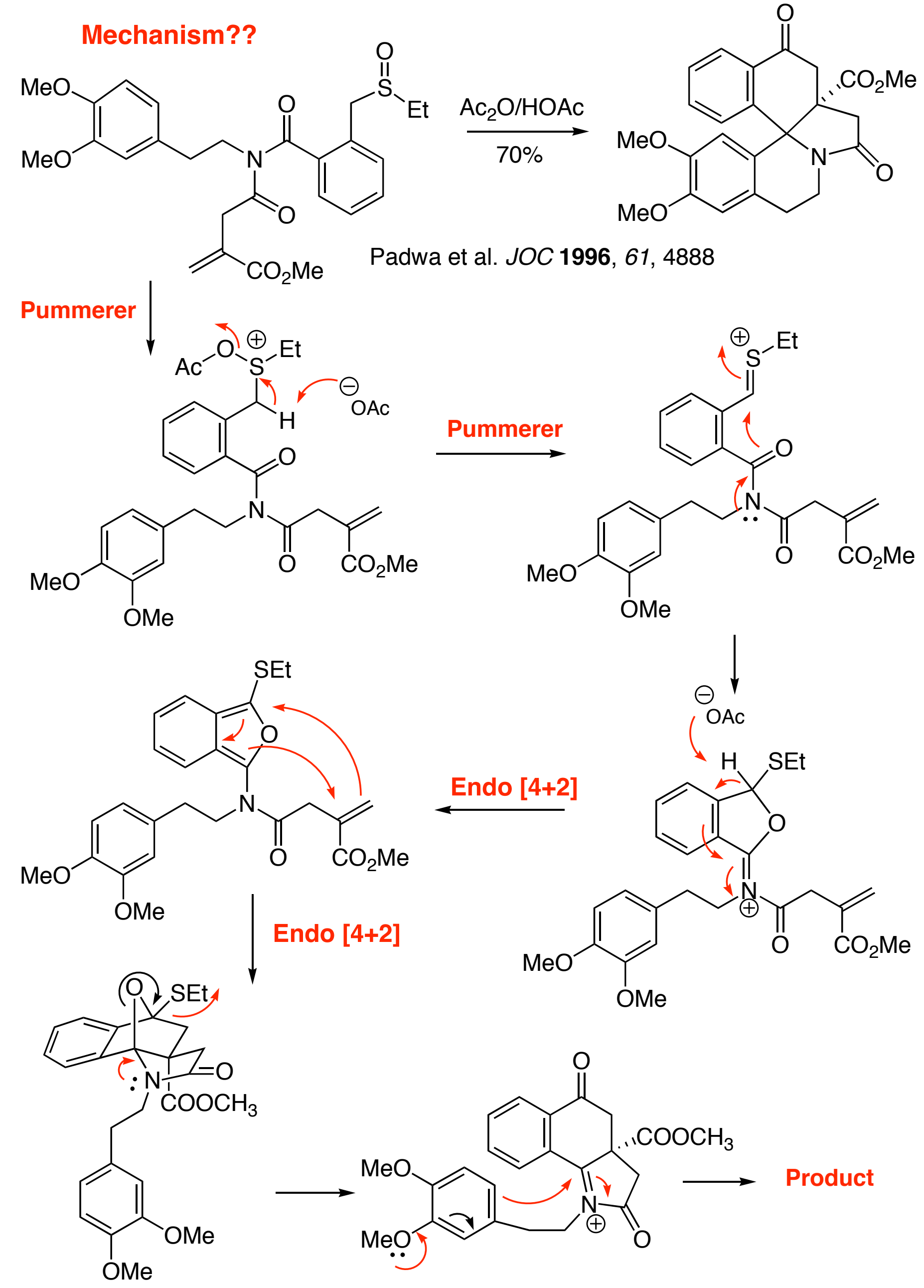
P. Magnus et al. *Accts Chem Res*. **1984**, *17*, 35



The cruel mechanistic problems that you should be prepared for in Chem 206

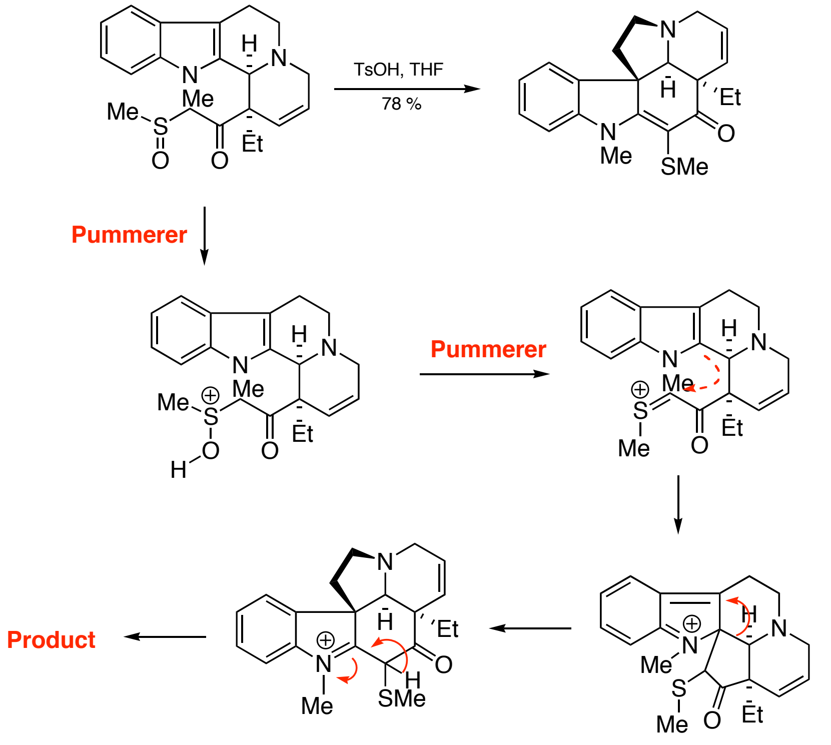


Padwa et al. *JOC* **1996**, *61*, 4888



Padwa et al. *JOC* **1996**, *61*, 4888

Exam 3, 2000: Question 5 (11 points). An interesting rearrangement which also results in the construction of this same ring system (Question 4) has been reported by Langlois & coworkers (*J.Org. Chem.* **1985**, *50*, 961). This rearrangement is illustrated below. Provide a mechanism for this transformation.



http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 33

Introduction to Carbonium Ions

- Carbocation Stabilization
- Carbocation Structures by X-ray Crystallography
- Vinyl & Allyl Carbonium Ions

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Birladeanu, L. (**2000**). "The Story of the Wagner-Meerwein Rearrangement." *J. Chem. Ed.* **2000**, *77*, 858. **(handout)**

Olah, G. A. (**2001**). "100 Years of Carbocations and their Significance in Chemistry." *J. Org. Chem.* **2001**, *66*, 5944-5957. **(handout)**

Walling, C. (**1983**). "An Innocent Bystander Looks at the 2-Norbornyl Cation." *Acc. Chem. Res.* **1983**, *16*, 448. **(handout)**

Laube (**1995**). "X-Ray Crystal Structures of Carbocations Stabilized by Bridging or Hyperconjugation." *Acc. Chem. Res.*.**1995**, *28*,: 399 **(electronic pdf)**

D. A. Evans

Monday
December 11, 2006

Other Relevant Background Reading

March, *Advanced Organic Chemistry*, 4th Ed. Chapter 5, pp165-174.
Lowery & Richardson, M*ech. & Theory in Org, Chem.*, 3rd Ed. pp 383-412.
Arnett, Hoeflich, Schriver in *Reactive Intermediates* **Vol 3**, Wiley, 1985, Chapter 5, p 189.

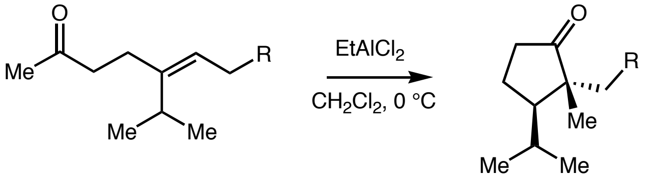
Saunders, M. and H. A. Jimenez-Vazquez (**1991**). "Recent studies of carbocations." Chem. Rev. 91: 375.

Stang, P. J. (**1978**). "Vinyl Triflate Chemistry: Unsaturated Cations and Carbenes." Acc. Chem. Res. 11: 107.

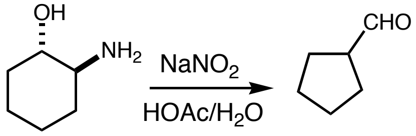
Olah, G. A. and G. Rasul (**1997**). "Chemistry in superacids .26. From Kekule's tetravalent methane to five-, six- and seven-coordinate protonated methanes." Acc. Chem. Res. 30(6): 245-250.

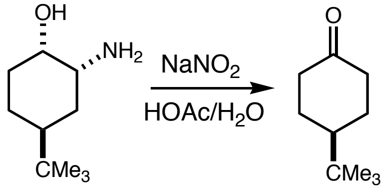
Olah, G. A. (**1995**). "My search for carbocations and their role in chemistry (Nobel lecture)." *Angew. Chem., Int. Ed. Engl.* **34**, 1393-1405

Problem 17: The reaction illustrated below was recently reported by Snider and co-workers (*Org. Lett.* **2001**, *123*, 569-572). Provide a mechanism for this transformation. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.



Carey & Sundberg-A, p 337: Provide mechanisms for the following reactions.



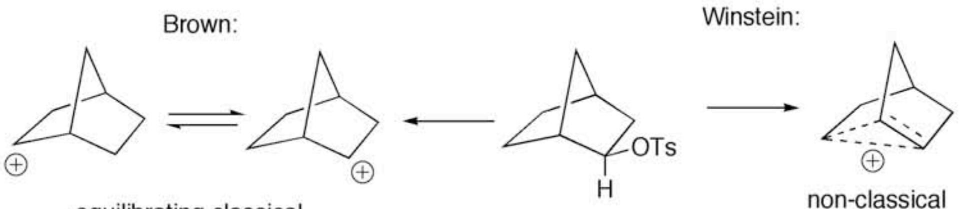


Quotes for the Day

"That man is nothing but a shyster lawyer."

Saul Winstein in reference to H. C. Brown
September, 1969

Winstein, a Canadian by birth, spent most of his professional career at UCLA, where he did research at the forefront of physical organic chemistry. He is best known for probing deeply the mechanisms of organic reactions, among them, allylic rearrangements, replacements and eliminations, using kinetics, stereochemistry, isotopic labelling and other physical methods. He developed concepts such as neighboring group participation, classical and non-classical carbocations, homoallylic and homoaromatic stabilization, tight and solvent-separated ion pairs, anchimeric assistance, and Y-values as a measure of solvent ionizing power. Winstein maintained a prodigious output of work of rigorous quality and perceptiveness, with an emphasis on logic and a search for answers to fundamental questions. He received many honors including, posthumously, the National Medal of Science.



equilibrating classical carbonium ion

non-classical carbonium ion

John D. Roberts, Institute Professor of Chemistry, Emeritus, Caltech

B.A., 1941, University of California (Los Angeles)
Ph.D. 1944, University of California (Los Angeles)

John D. Roberts inspecting an early natural-abundance ^{13}C spectrum taken by Frank J. Weigert with the Varian DFS NMR spectrometer in

John D. Roberts was born in 1918.

He became Prof. at MIT and then Prof. at Caltech where he is still active. His work has been centered on mechanisms of organic reactions.

One of the joys of being a professor
is when an exceptional student
comes along and wants to work
with you.

J.D. Roberts, The Right Place at
the Right Time. p. 63.

John D. Roberts graduated from the University of California at Los Angeles where he had received A. B. (hons) degree in 1941 and the Ph. D. degree in 1944. In 1945-1946 he was a National Research Council Fellow and Instructor at Harvard. Later on, he went to MIT in 1946 as an Instructor. He had introduced the terms "nonclassical" carbocations and "benzyne" into organic chemistry. He had won numerous awards; he is a member of the National Academy of Sciences (1956) and the American Philosophical Society (1974). He received the Welch Award (1990, with W. E. Doering), the National Medal of Science (1990), and the ACS Arthur C. Cope Award (1994). Since 1939 his research has been concerned with the mechanisms of organic reactions and the chemistry of small-ring compounds. His current work involves applications of nuclear magnetic resonance spectroscopy to physical organic chemistry.

Roberts made major research and pedagogic contributions to mechanistic organic chemistry. He pioneered the use of 14C and other isotopic labels to follow molecular rearrangements as, for example, in the complex and subtle solvolysis of cyclopropyl-carbinyl systems. He introduced the terms "nonclassical" carbocations and "benzyne" into organic chemistry, and used isotopic labeling to establish the intermediacy of each. Roberts was early to recognize NMR's potential, and used 1H NMR to study nitrogen inversion, long-range spin-spin coupling and conformational isomerism, and later 13C and 15N NMR to study other reactions, including the active sites of certain enzymes. Roberts' superb short books on "Nuclear Magnetic Resonance" (1959), "Spin-Spin Splitting in High Resolution NMR" (1961) and "Notes on Molecular Orbital Calculations" (1961) did much to popularize and clarify these subjects for organic chemists. His highly successful text "Basic Principles of Organic Chemistry" (1964), written with Marjorie Caserio, introduced spectroscopy early to undergraduates. Roberts received many awards, including the Roger Adams (1967) and Priestley (1987) Medals. An excellent photographer, Roberts graciously supplied several of the photographs for the MSU collection.

The Gathering at JDR's 70th Birthday Celebration

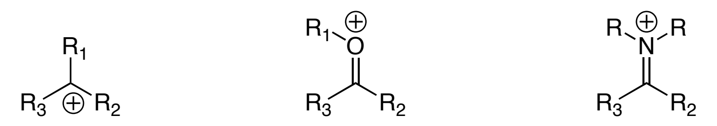
1988

Dervan, Ireland, Evans, Bergman, Grubbs, JDR, Myers, Dougherty, Hammond
Recent organic faculty at CIT, present and departed

Carbocations: Stability

Carbocation Subclasses

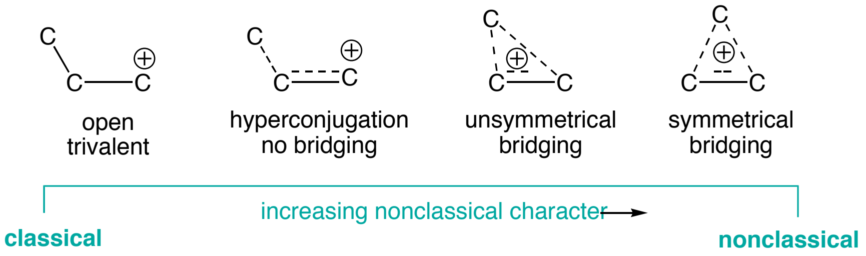
Carbon-substituted **Heteroatom–stabilized**



R–R_3 = alkyl or aryl R–R_3 = alkyl or aryl R–R_3 = alkyl or aryl

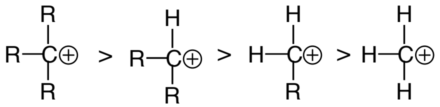
The following discussion will focus on carbocations unsubstitutred with heteroatoms

Classical vs nonclassical carbonium ions



Stability: Stabilization via alkyl substituents (hyperconjugation)

Order of carbocation stability: 3°>2°>1°



Due to increasing number of substituents capable of hyperconjugation

The relative stabilities of various carbocations can be measured in the gas phase by their affinity for hydride ion.

$$R^{\oplus} + H^{\ominus} \longrightarrow R\text{–}H + HI$$

Hydride Affinity = –ΔG°

ΔHI increases → C(+) stability decreases

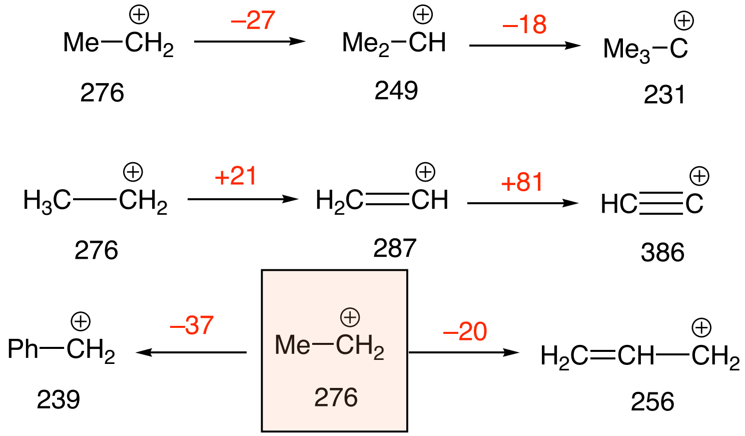
Note: As S-character increases, cation stability decreases due to more electronegative carbon.

J. Beauchamp, *J. Am. Chem. Soc.* **1984**, *106*, 3917.

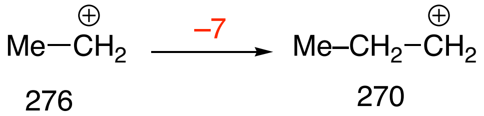
	Hydride ion affinities
CH_3^+	314
$CH_3CH_2^+$	276
$(CH_3)_2CH^+$	249
$(CH_3)_3C^+$	231
$H_2C{=}CH^+$	287
$H\text{—}C{\equiv}C^+$	386
$PhCH_2^+$	239

Carey & Sundberg–**A**, pp 276-

Hydride ion affinities (HI)



The effect of beta substituents: Rationalize



Hydride ion affinities versus Rates of Solvolysis

	$PhCH_2$–Br	CH=CH–CH_2–Br	Me_2CH–Br
rel rate	100	52	0.7
HI	239	256	249
Δ-HI	0	+17	+10

Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

Conclusion:
Gas phase stabilities do not always correlate with rates of solvolysis

Carbocation Generation & Stability

Carbocation Stability: The pK_{R+} value

Definition: $R^+ + H_2O \rightleftharpoons ROH + H^+$

$$K_{R+} = \frac{a_{ROH} \cdot a_{H+}}{a_{R+} \cdot a_{H2O}}$$

a = activity

$$\boxed{pK_{R+} = -\log K_{R+}}$$

Carey & Sundberg, A, p 277

Table: **pK_{R+} values of some selected carbenium salts**

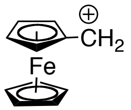
$(4\text{-MeO-}C_6H_4)_3C^{\oplus}$ 0.82

$Ph_3C^{\oplus}$ – 6.63

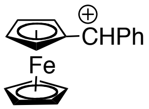
$(3\text{-Cl-}C_6H_4)_3C^{\oplus}$ – 11.0

$Ph_2\overset{\oplus}{C}H$ – 13.3

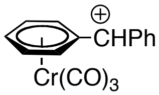
least stable



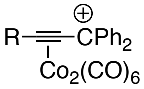
0.40



0.75

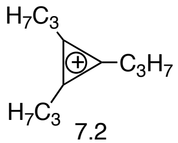


–10.4

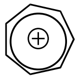


$R{-}{\equiv}{-}\overset{\oplus}{C}Ph_2 \cdot Co_2(CO)_6$

–7.4



7.2



4.77

most stable

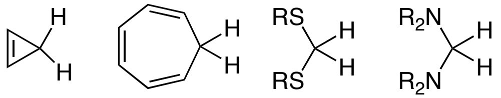
Carey & Sundberg, A, pp 276-

Carbocation Generation

Hydride abstraction from neutral precursors

$$\boxed{R_3C{-}H + \text{Lewis-Acid} \longrightarrow R_3C^{\oplus}}$$

$R_3C{-}H$ =



etc.

Lewis-Acid: $Ph_3\overset{\oplus}{C}\,\overset{\ominus}{B}F_4$, BF_3, PCl_5

Removal of an energy-poor anion from a neutral precursor via Lewis Acids

$$\boxed{R_3C{-}X + \mathbf{LA} \longrightarrow R_3C^{\oplus} + LA{-}X^{\ominus}}$$

LA: Ag , $AlCl_3$, $SnCl_4$, $SbCl_5$, $\mathbf{SbF_5}$, BF_3, $FeCl_3$, $ZnCl_2$, PCl_3, PCl_5, $POCl_3$ ...
X: F, Cl, Br, I, OR

Acidic dehydratization of *secondary* and *tertiary* alcohols

$$\boxed{R_3C{-}OH + H{-}X \xrightarrow{-\,H_2O} R_3C^{\oplus} + X^{\ominus}}$$

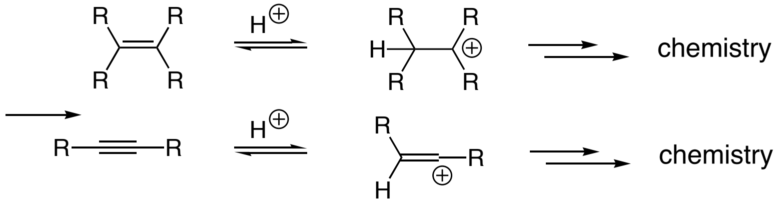
R: Aryl + other charge stabilizing substituents
X: SO_4^{2-}, ClO_4^-, FSO_3^-, $CF_3SO_3^-$

From neutral precursors via heterolytic dissociation (solvolysis) - First step in S_N1 or E1 reactions

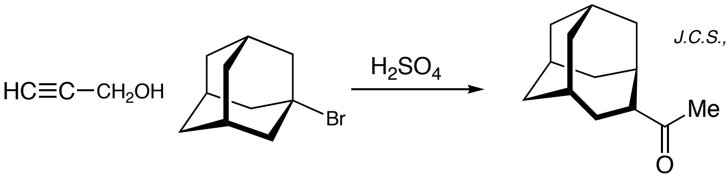
$$\boxed{R_3C{-}X \xrightarrow{\text{solvent}} R_3C^{\oplus} + X^{\ominus}}$$

Ability of X to function as a leaving group:
$-N_2^+ > -OSO_2R' > -OPO(OR')_2 > -I \geq -Br > Cl > OH_2^+$ ...

Addition of electrophiles to π-systems



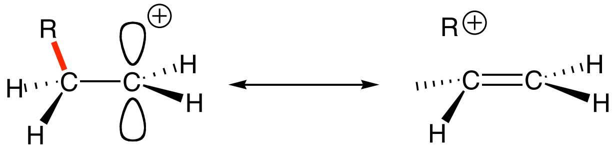
Problem 897: Provide a Mechanism of this transformation



J.C.S.,CC **1971**, 556

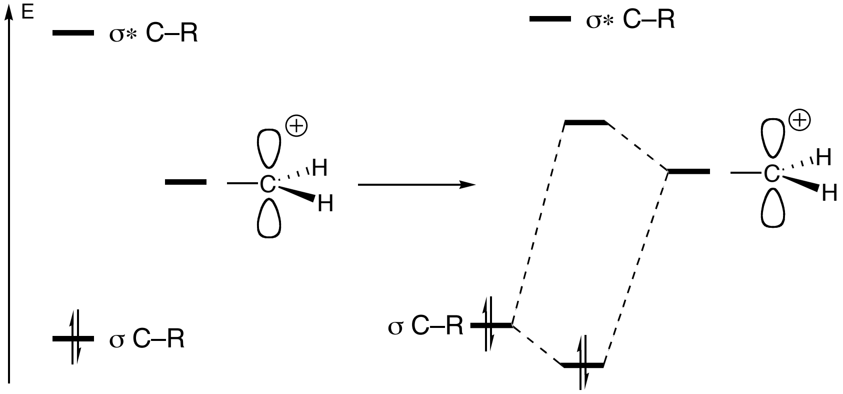
Carbocations: Structure

Carbocation Stabilization Through Hyperconjugation



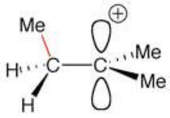
■ FMO Description

Take linear combination of σ C–R (filled) and C p_z-orbital (empty):

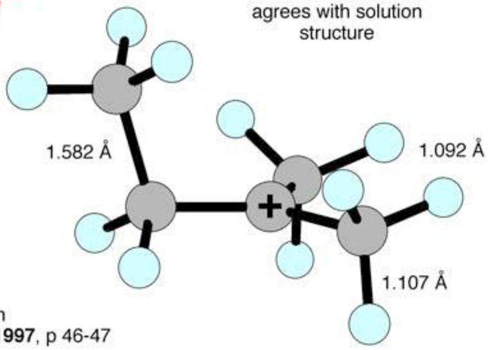


Syn-planar orientation between interacting orbitals

C–H versus C–C Hyperconjugation: The t-Pentyl Cation



Calculated carbocation agrees with solution structure

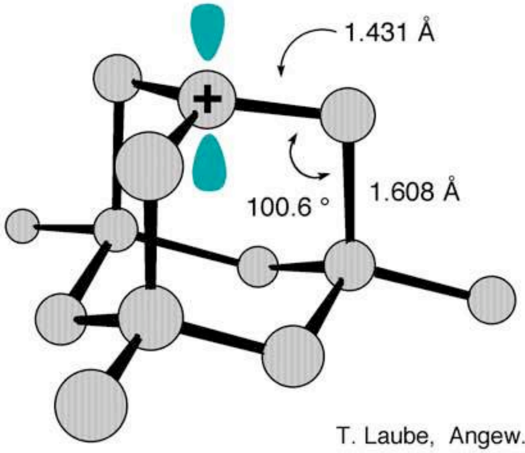


R. P von Schleyer in *Stable Carbocation Chemistry*, **1997**, p 46-47

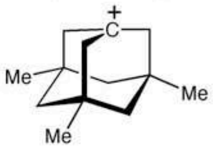
Physical Evidence for Hyperconjugation: The Adamantyl Cation

Bonds participating in the hyperconjugative interaction, e.g C–R, will be lengthened while the C(+)–C bond will be shortened.

First X-ray Structure of an Aliphatic Carbocation

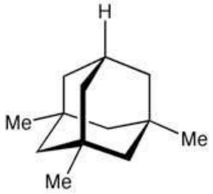


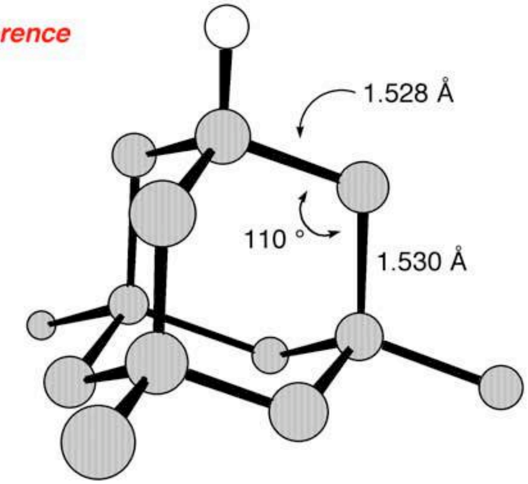
$[F_5Sb–F–SbF_5]^–$



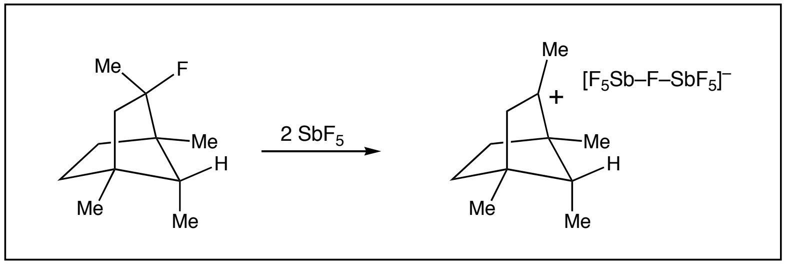
T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

The Adamantane Reference (MM-2)

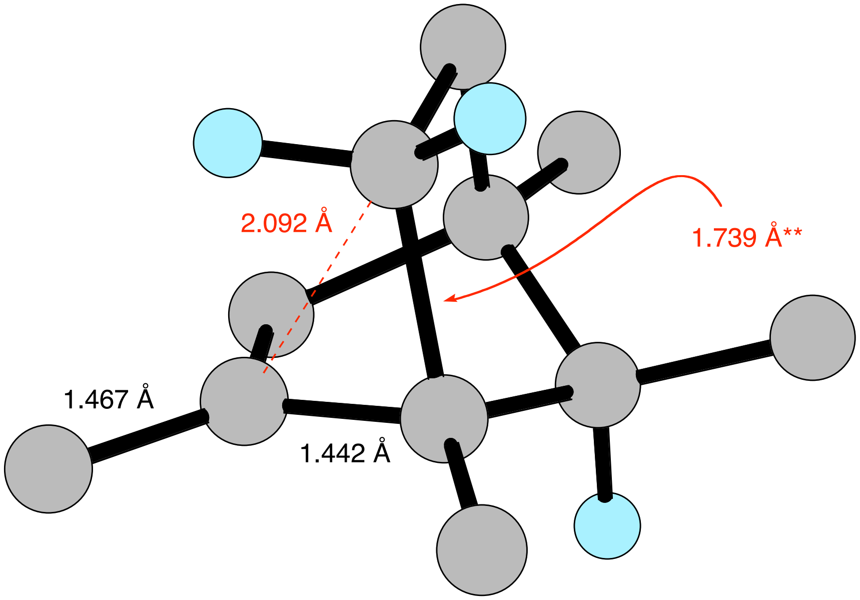




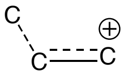
Carbonium Ion X-ray Structures: Bridged Carbocations



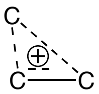
T. Laube, Angew. *Chem. Int. Ed.* **1987**, *26*, 560



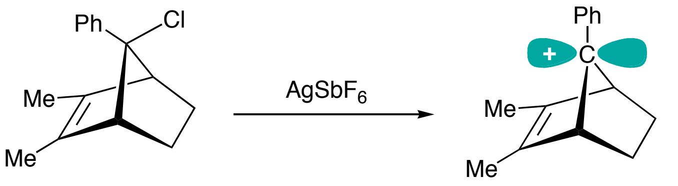
**One of the longest documented C–C bond lengths.



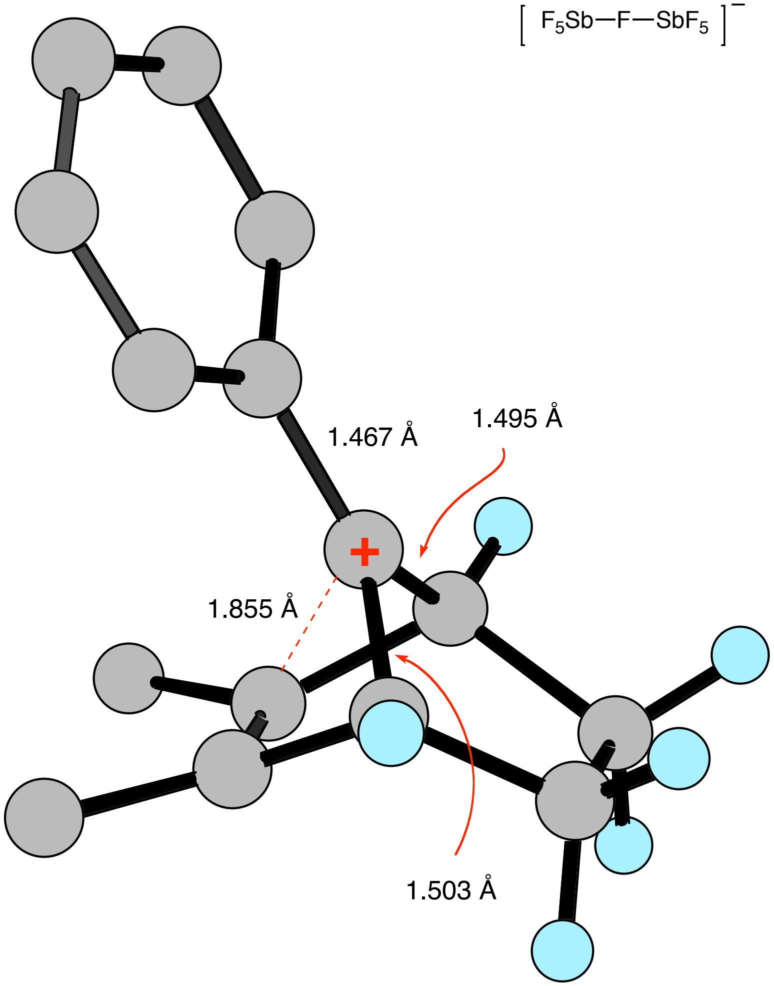
hyperconjugation
no bridging



unsymmetrical
bridging

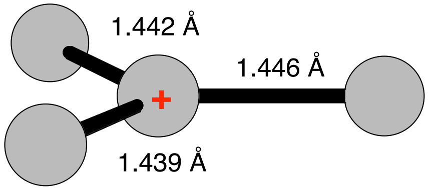


$[F_5Sb—F—SbF_5]^–$

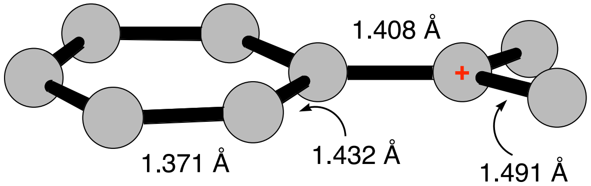


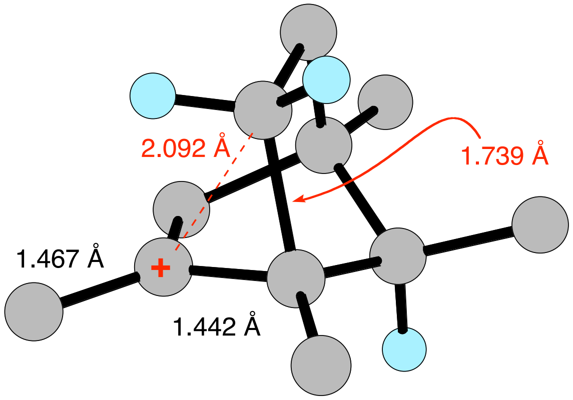
T. Laube, *JACS* **1989**, *111*, 9224

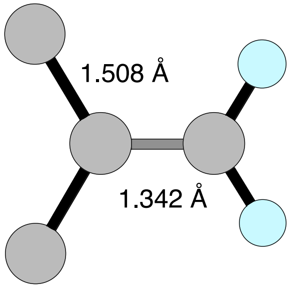
Carbonium Ion X-ray Structures: A Summary

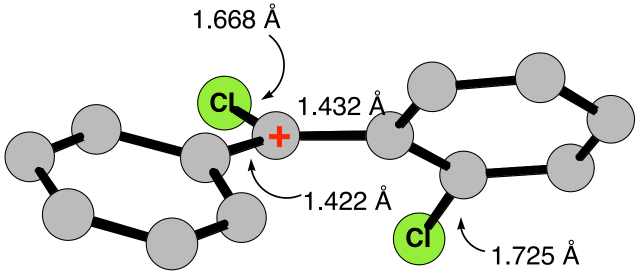


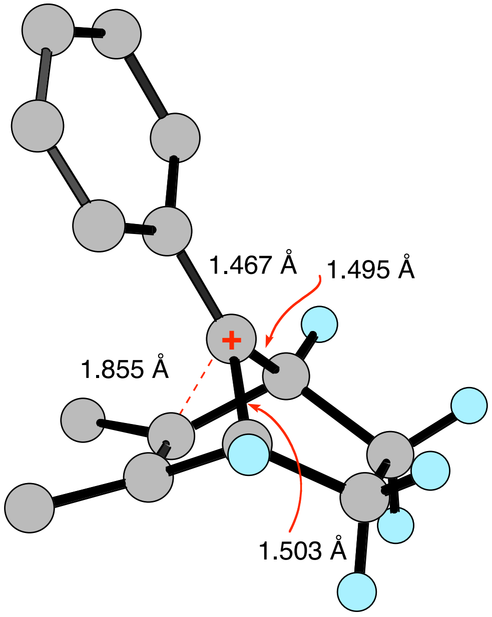
(ref 1.513 Å)Ph–C(Me)=CH2

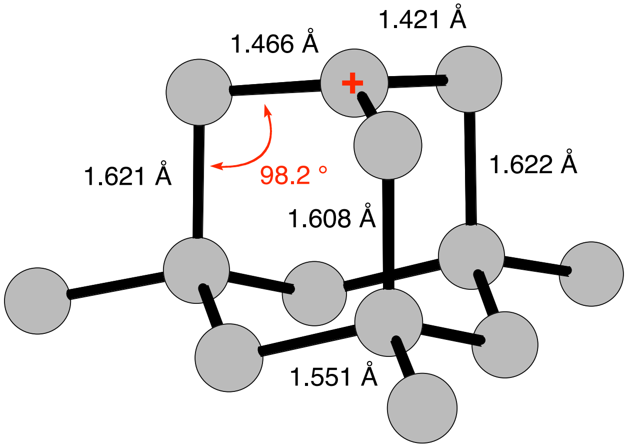




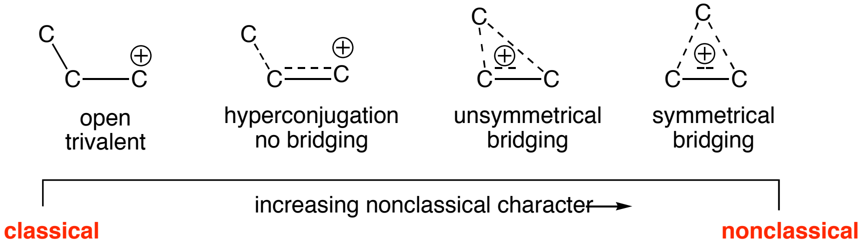








Nomenclature: classical vs nonclassical

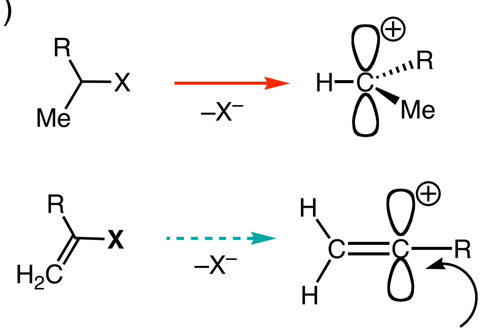


Substitution Reactions

Substitution (S_N1)

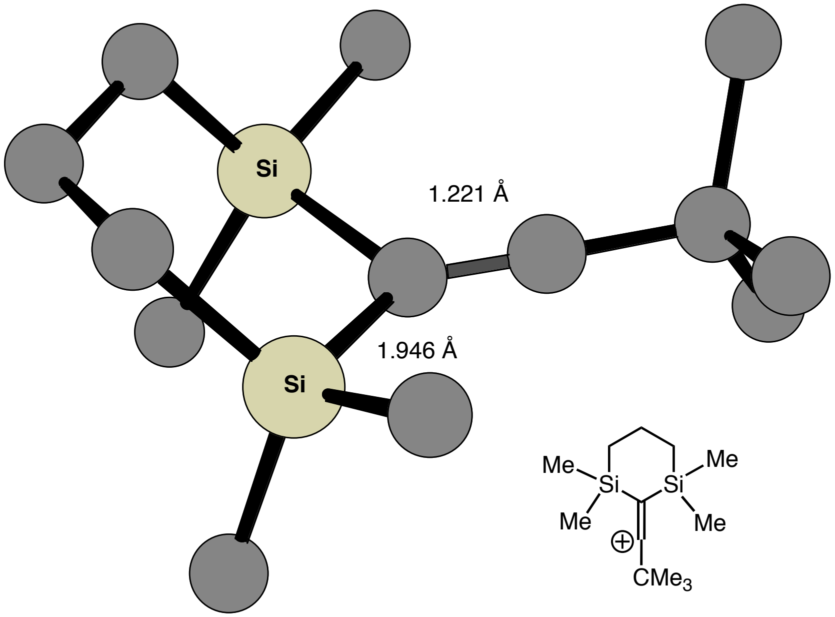
Favorable

Unfavorable



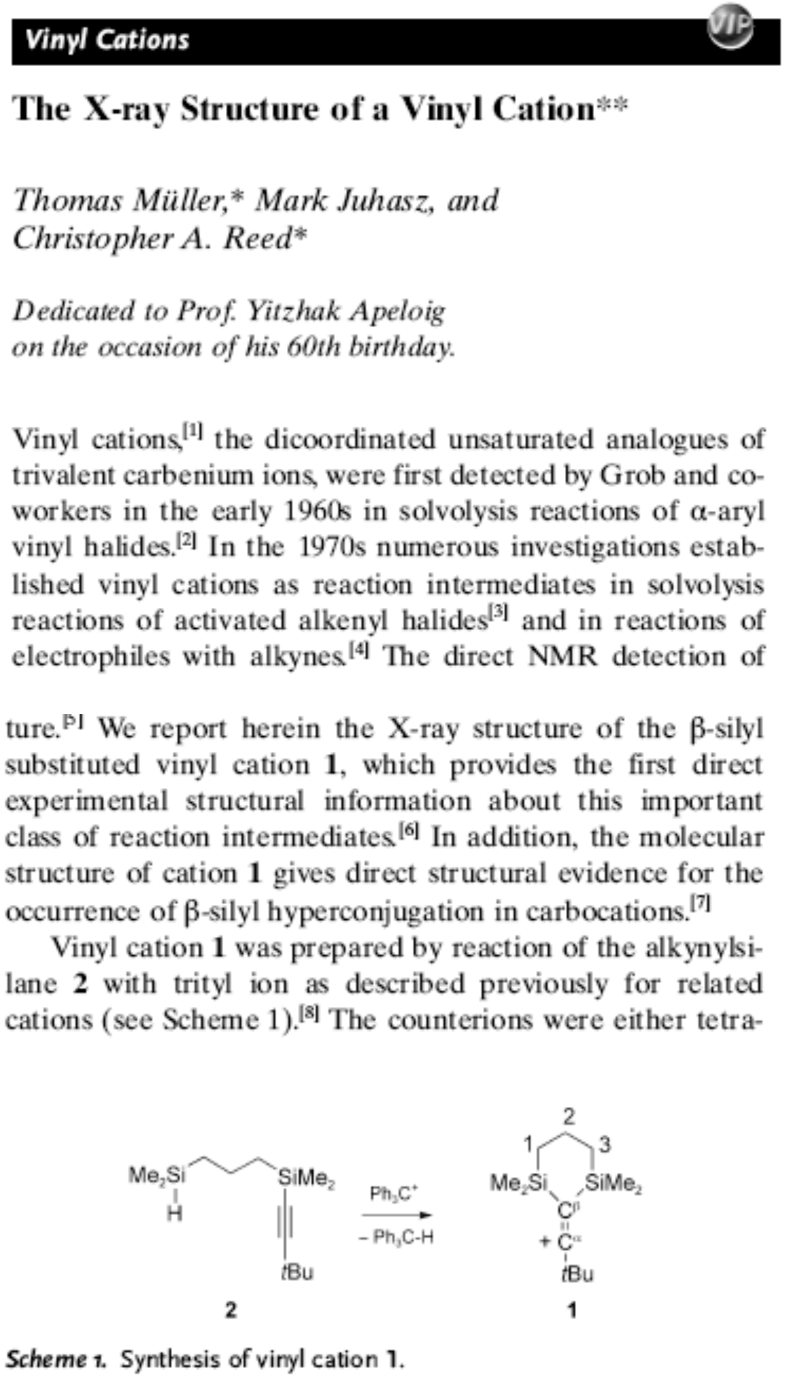
Sp hybridized Carbon
is more electronegative

CSp2 Carbonium Ions do exist!



Normal CC triple bond lengths are ~1.21 Å

Angew. Chem. Int. Ed. 2004, 43, 1543–1546



Vinyl Cations

The X-ray Structure of a Vinyl Cation**

Thomas Müller, Mark Juhasz, and*
*Christopher A. Reed**

Dedicated to Prof. Yitzhak Apeloig
on the occasion of his 60th birthday.

Vinyl cations,[1] the dicoordinated unsaturated analogues of trivalent carbenium ions, were first detected by Grob and coworkers in the early 1960s in solvolysis reactions of α-aryl vinyl halides.[2] In the 1970s numerous investigations established vinyl cations as reaction intermediates in solvolysis reactions of activated alkenyl halides[3] and in reactions of electrophiles with alkynes.[4] The direct NMR detection of

ture.[5] We report herein the X-ray structure of the β-silyl substituted vinyl cation **1**, which provides the first direct experimental structural information about this important class of reaction intermediates.[6] In addition, the molecular structure of cation **1** gives direct structural evidence for the occurrence of β-silyl hyperconjugation in carbocations.[7]

Vinyl cation **1** was prepared by reaction of the alkynylsilane **2** with trityl ion as described previously for related cations (see Scheme 1).[8] The counterions were either tetra-

2

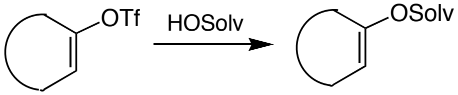
1

Scheme 1. Synthesis of vinyl cation **1**.

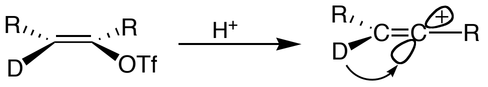
Vinyl & Allyl Carbocations

Vinyl & Phenyl Cations: Highly Unstable

Evidence suggests that vinyl cations are linear.



As ring size decreases, the rate of hydrolysis also diminishes. Implying that the formation of the linear vinyl cation is disfavored due to increasing ring strain.



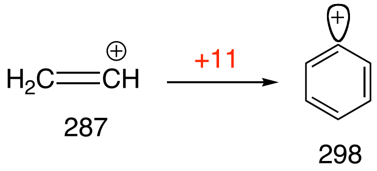
Hyperconjugation

A secondary kinetic isotope effect was measured to be $K_H/K_D = 1.5$ (quite large) indicating strong hyperconjugation and an orientation of the vacant p orbital as shown above.

P. J. Stang *J. Am. Chem Soc.* **1971**, *93*, 1513; P. J. Stang *J.C.S. PT II* **1977,** 1486.

Hydride ion affinities (HI)

$$\underset{276}{H_3C{-}\overset{\oplus}{C}H_2} \xrightarrow{+21} \underset{287}{H_2C{=}\overset{\oplus}{C}H} \xrightarrow{+81} \underset{386}{HC{\equiv}\overset{\oplus}{C}}$$

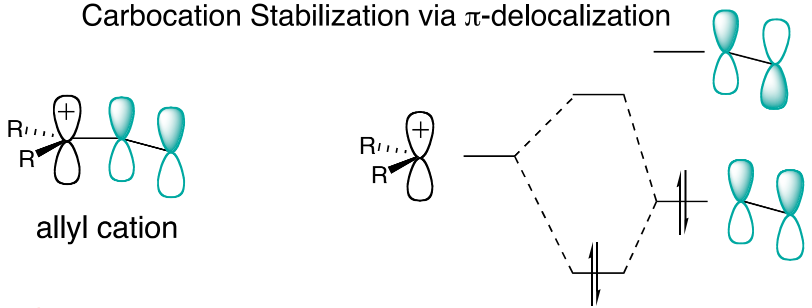


Phenyl Cations

The ring geometry opposes rehybridization (top) so the vacant orbital retains sp^2 character. Additionally, the empty orbital lies in the nodal plane of the ring, effectively prohibiting conjugative stabilization.

Allyl & Benzyl Carbocations

Carbocation Stabilization via π-delocalization



■ Stabilization by Phenyl-groups

The Benzyl cation is approximately as stable as a t-Butylcation.

	ΔH^0_r [kcal/mol]
$(CH_3)_3\overset{\oplus}{C} + PhCH_3 \rightleftharpoons (CH_3)_3CH + Ph\overset{\oplus}{C}H_2$	3.8
$(CH_3)_3\overset{\oplus}{C} + PhCH_2Cl \rightleftharpoons (CH_3)_3CCl + Ph\overset{\oplus}{C}H_2$	– 0.8

Hydride ion affinities (HI) $\underset{239}{Ph{-}\overset{\oplus}{C}H_2} \xrightarrow{-8} \underset{231}{Me_3{-}\overset{\oplus}{C}}$

Hydride ion affinities versus Rates of Solvolysis

	$PhCH_2$–Br	Me_2CH–Br	$CH{=}CH{-}CH_2$–Br
	100	0.7	52
HI	239	249	256
Δ-HI	0	+10	+17

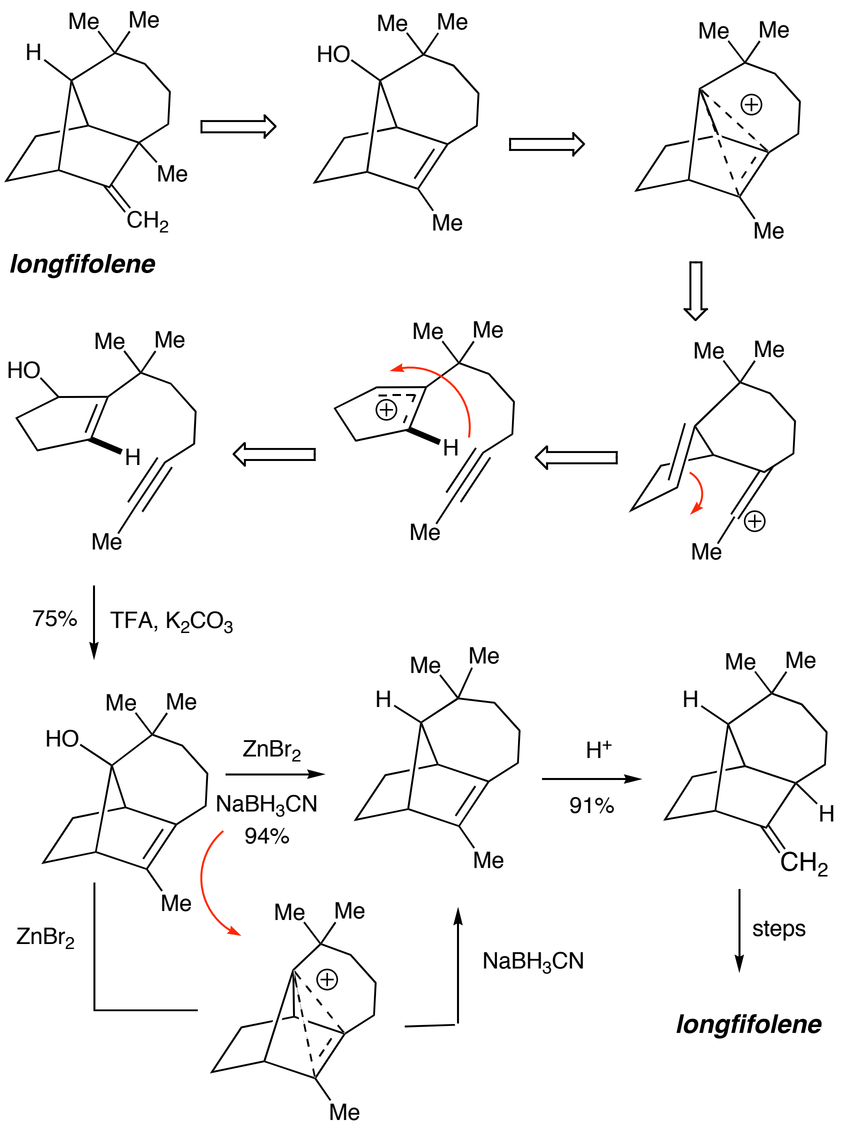
Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

The Johnson Longifolene Synthesis

Volkman, Andrews, Johnson, *JACS* 1975, *97,* 4777

The plan (According to Volkman):



Ho, Nouri, Tantillo, *JOC* 2005, *70*, 5139-5143

The Cationic Cascade Route to Longifolene

W. S. Johnson's total synthesis of the sesquiterpenoid longifolene is a classic example of the power of cationic polycyclizations for constructing complex molecular architectures. Herein we revisit the key polycyclization step of this synthesis using hybrid Hartree-Fock/density functional theory calculations and validate the feasibility of Johnson's proposed mechanism. We also explore perturbations to the 3-center 2 electron bonding array in a key intermediate that result from changing the polycyclic framework in which it is embedded.

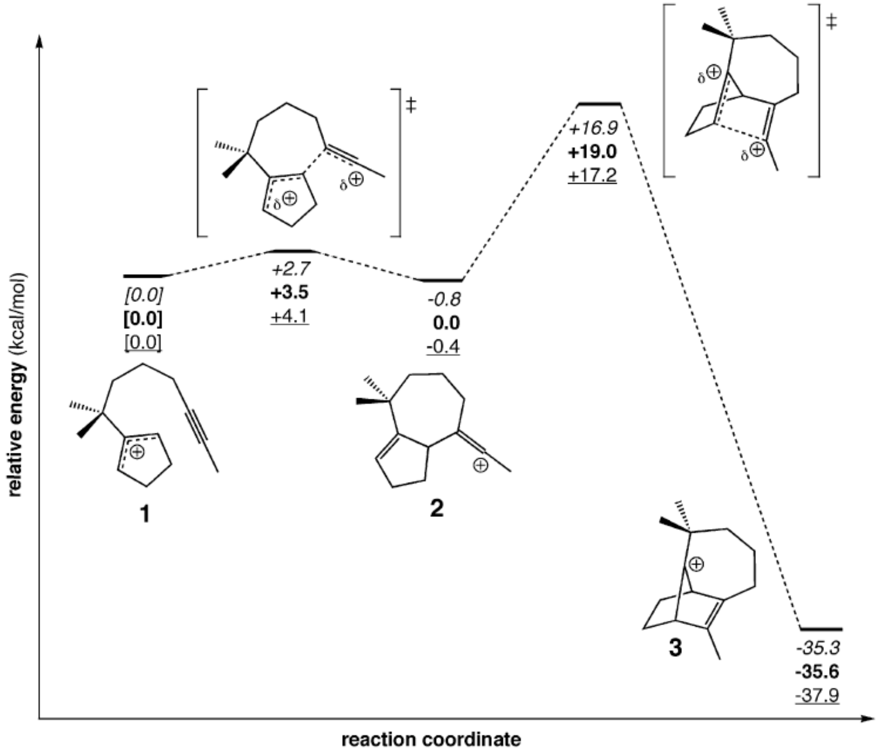
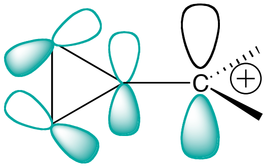


FIGURE 1. Relative energies (kcal/mol) of stationary points for the mechanism shown in Scheme 2 (B3LYP/6-31G(d) zero-point corrected energies in italics, B3LYP/6-31G(d) free energies at 0 °C in bold, and CPCM-B3LYP/6-31G(d) energies in water underlined).

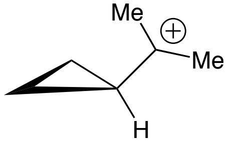
Cyclopropyl-carbinyl & Bridgehead Carbocations

Carbocation Stabilization via Cyclopropylgroups



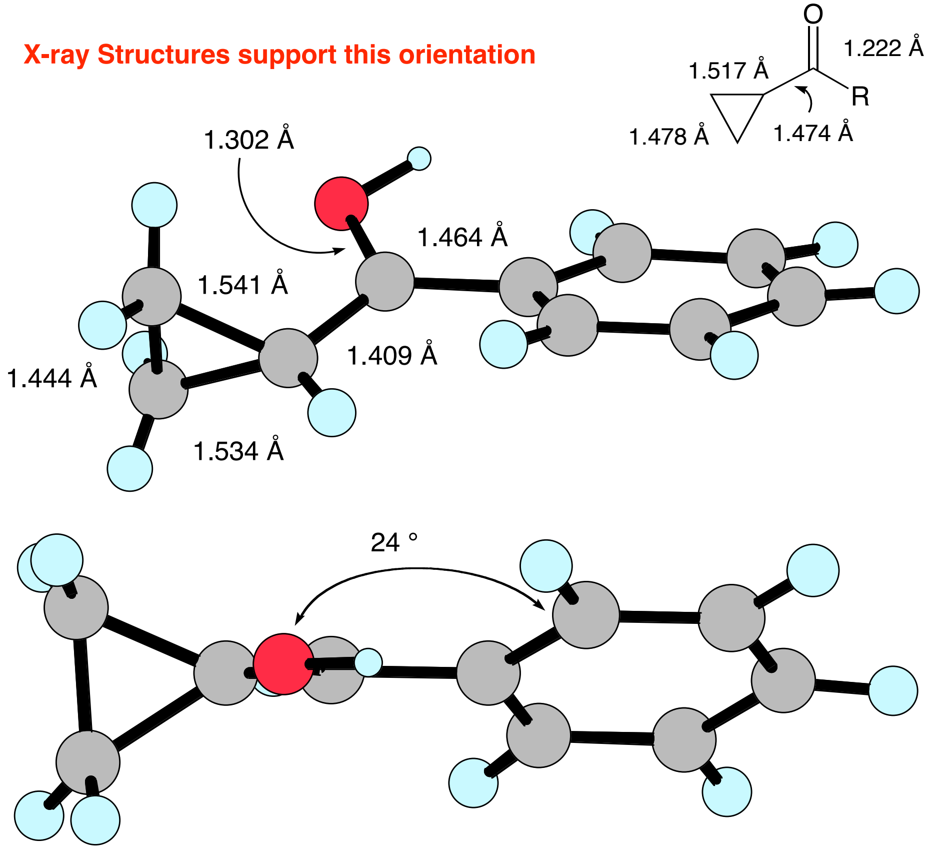
See Lecture 5, slide 5-05 for discussion of Walsh orbitals

A rotational barrier of about 13.7 kcal/mol is observed in following example:



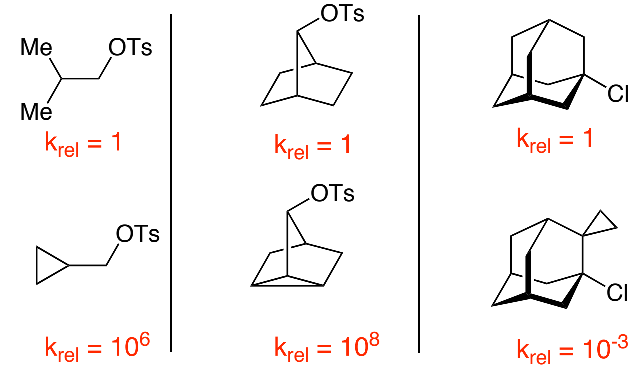
NMR in super acids $\delta(CH_3)$ = 2.6 and 3.2 ppm

X-ray Structures support this orientation



R. F. Childs, *JACS* **1986**, *108*, 1692

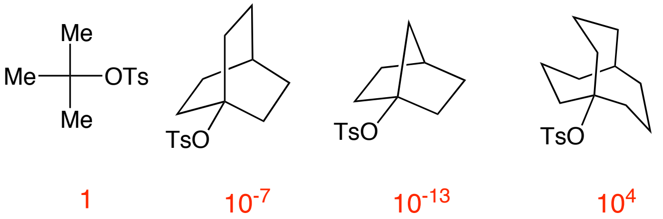
Solvolysis rates represent the extend of that cyclopropyl orbital overlap contributing to the stabiliziation of the carbenium ion which is involved as a reactive intermediate:



Why??

Carey–A, p 286

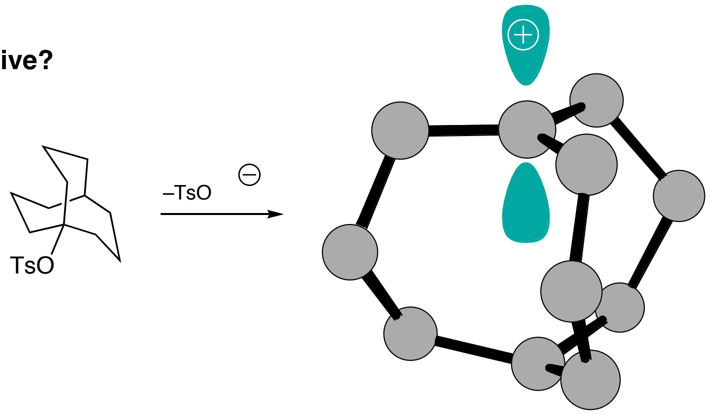
Bridgehead Carbocations



why so reactive?

Bridgehead carbocations are highly disfavored due to a strain increase in achieving planarity. Systems with the greatest strain increase upon passing from ground state to transition state react slowest.

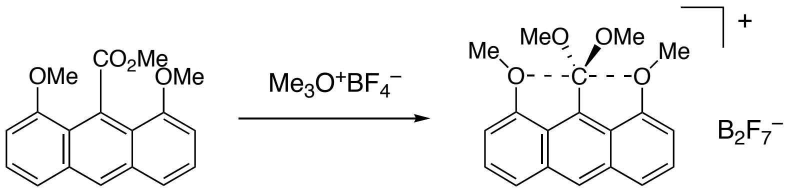
why so reactive?



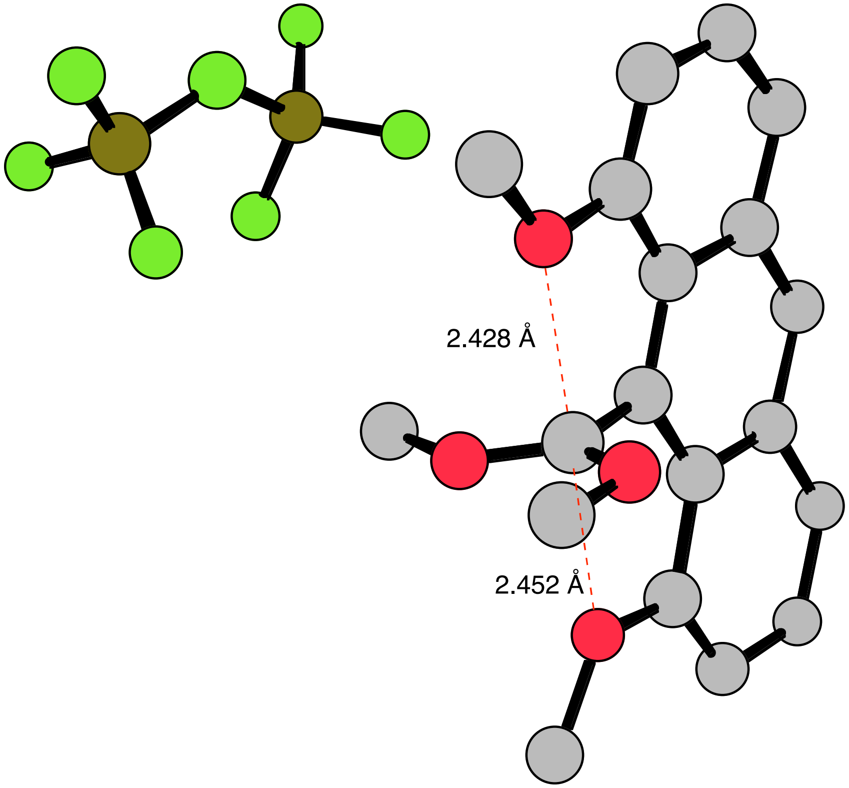
A Stable Hypervalent Carbon Compound ?

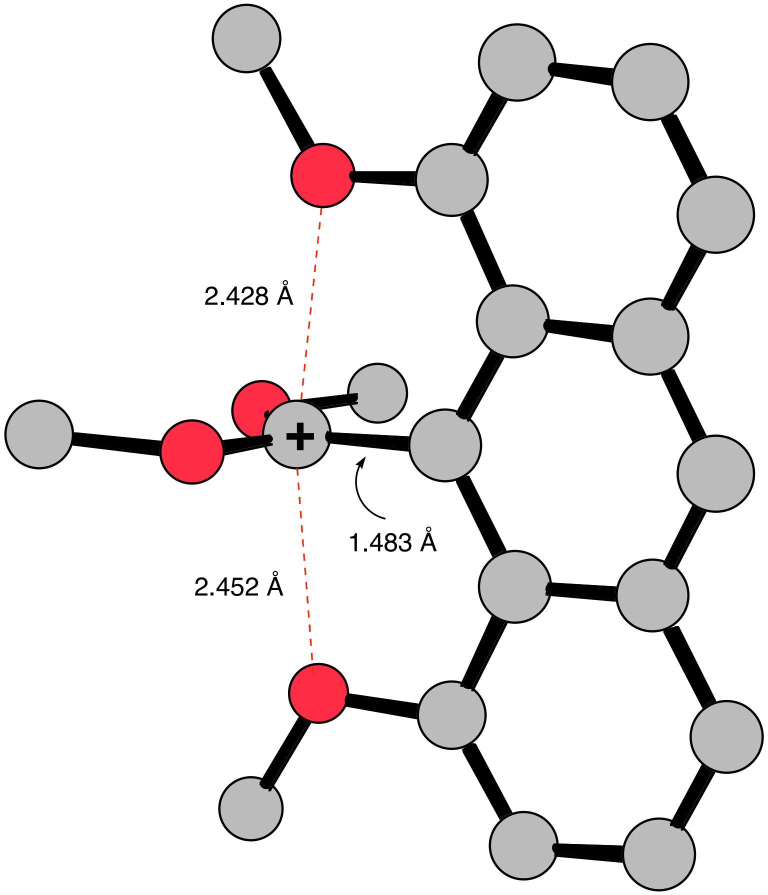
"The Synthesis and Isolation of Stable Hypervalent Carbon Compound (10-C-5) Bearing a 1,8-Dimethoxyanthrecene Ligand"

Akibe, et al. *JACS* **1999**, *121*, 10644-10645



"The relevant C–O distances are longer than a covalent C–O bond (1.43 Å) but shorter than the sum of the van der Waals radii (3.25 Å)."





For a recent monograph on hypervalent Compounds see:
"Chemistry of Hypervalent Compounds", K. Akiba, Wiley-VGH, 1999

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 34

Introduction to Carbonium Ions–2

- Allyl- & Vinylsilanes: The β-Silicon Effect
- Carbonium Ion Rearrangements
- Iminium Ion Rearrangements

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Birladeanu (**2000**). "The Story of the Wagner-Meerwein Rearrangement." *J. Chem. Ed. 77*: 858. **(handout)**

Lambert, (**1999**). "The β effect of silicon and related manifestations of σ conjugation." *Acc. Chem. Res. 32*, 183-190. **(handout)**

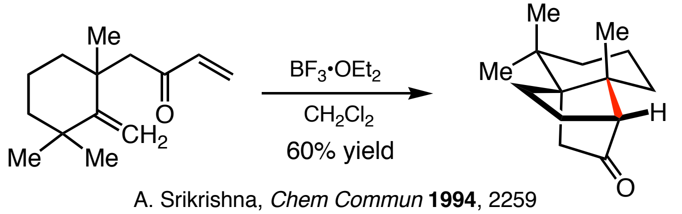
Saunders, M. and H. A. Jimenez-Vazquez (**1991**). "Recent studies of carbocations." *Chem. Rev*. 91: 375.

Problems Website: select key words **"rearrangement"** and pair it with either **"carbonium ion", "oxo-carbenium ion", or "iminium ion"**. This exercise will provide you with a wonderful set of challenging problems that are relevant to this lecture.

D. A. Evans

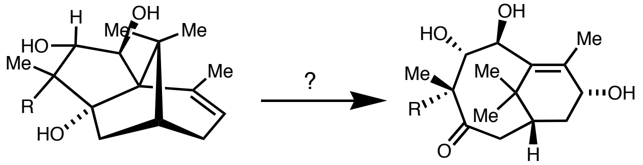
Wednesday
December 13 , 2006

Problem 56: Here is a typical carbonium ion question that you should be able to handle by the end of the course. Write out a mechanism for the following transformation.



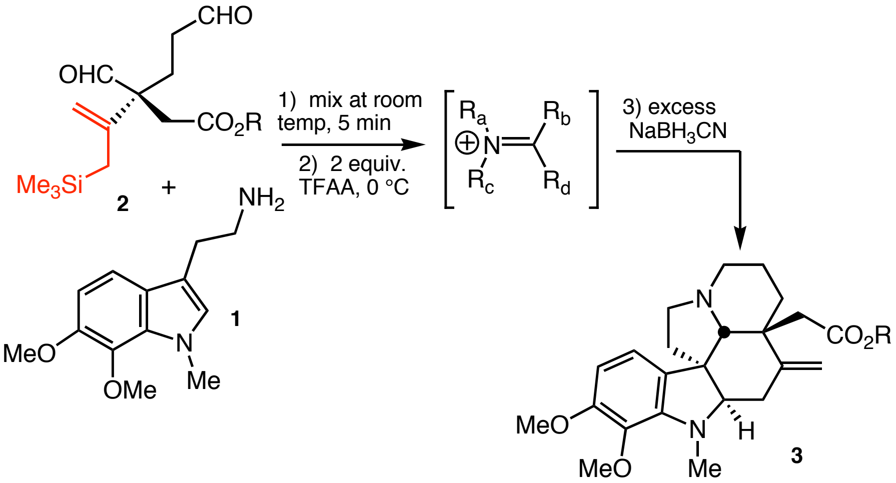
A. Srikrishna, *Chem Commun* **1994**, 2259

Problem 79: In a synthesis of taxusin, the pivotal reaction(s) which generated the bicyclo [5.3.1.] undecane ring system charactertistic of this family of terpenoids are illustrated below. Given the illustrated transformation, what specific reagents would you employ to carry out this process.



Holton & Co-workers, *JACS*, **110**, 6558 (1988).

Problem 185: Final Exam, 1999. During Corey's synthesis of Aspidophytine (*JACS*, **1999**, *121*, 6771), the pivotal intermediate **3** was assembled by the union of **1** and **2** under the specified conditions. Provide a mechanism for this single-pot transformation.

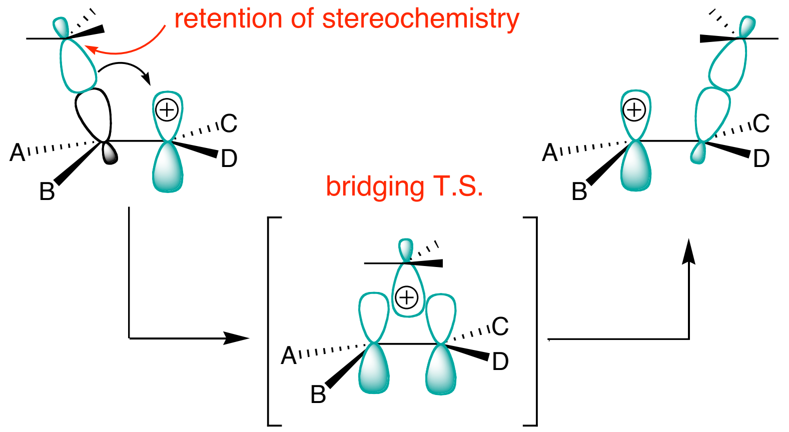


Carbocation [1,2] Sigmatropic Rearrangements

1,2 Sigmatropic shifts are the most commonly encountered cationic rearrangements. When either an **alkyl** substituent or a **hydride** is involved, the term **Wagner-Meerwein shift** is employed to identify this class of rearrangments.

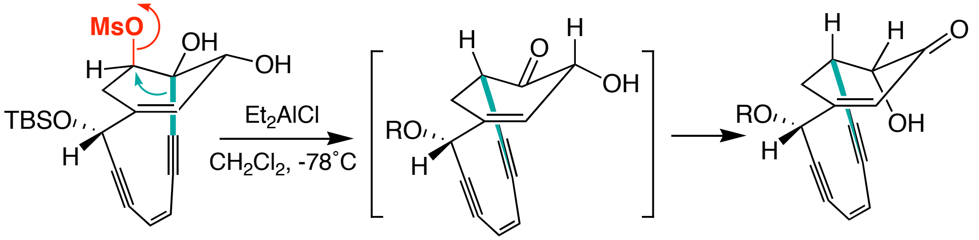
Birladeanu (**2000**). "The Story of the Wagner-Meerwein Rearrangement." J. Chem. Ed. 77: 858. **(handout)**

Stereoelectronic requirement for migration....



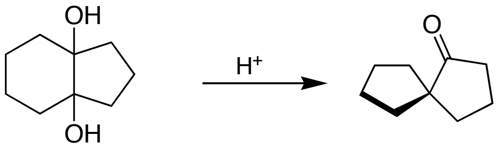
2-electron Huckel transition state

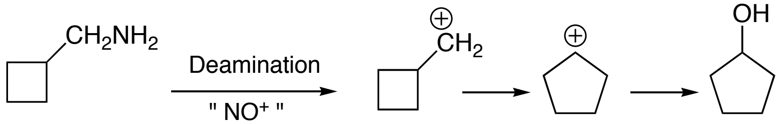
If **migration accompanies ionization**, the migration terminus will be **inverted**. Overlap between the σ C-C (migration origin) and the σ* C-X (migration terminus) will be maximized in an **antiperiplanar** arrangement.



S. L. Schreiber et al *Tetrahedron Lett.* **1989**, *30*, 3765.

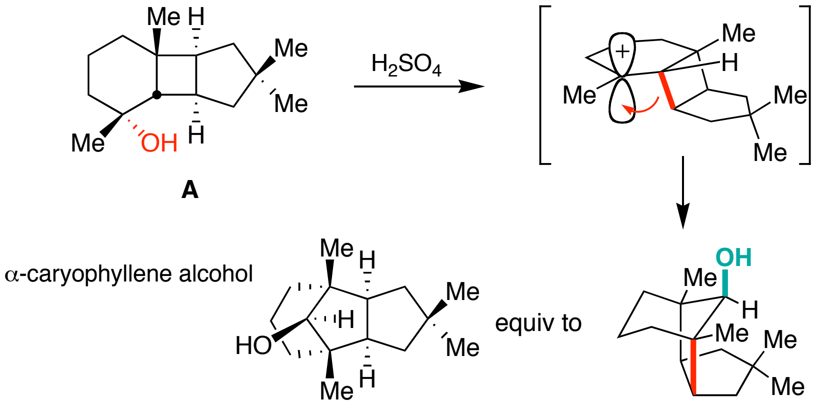
Pinacol rearrangement (vicinal diol): Driving force is the gen. of C=O



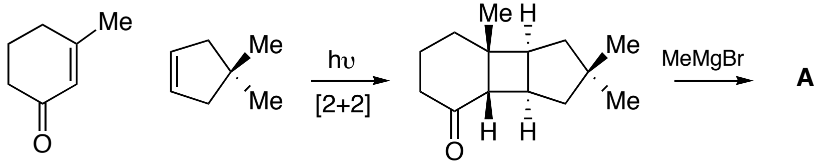


Demjanov-rearrangement (Driving force: relief of ring strain)

Wagner-Meerwein Rearrangements: Application in Total Synthesis



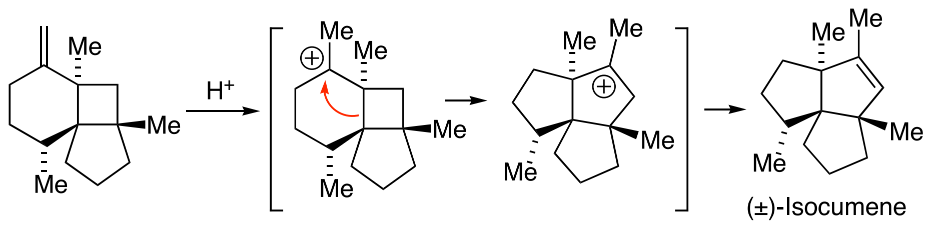
Preparation of A:



E. J. Corey *JACS* **1964**, *86*, 1652 **(electronic handout).**

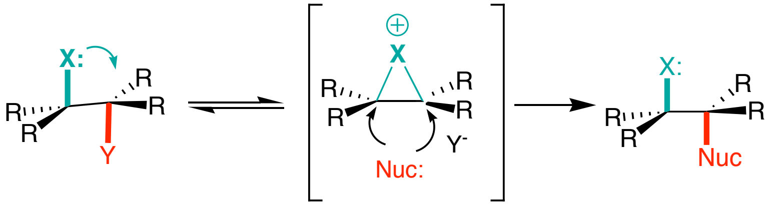
Carbocation Rearrangements-2

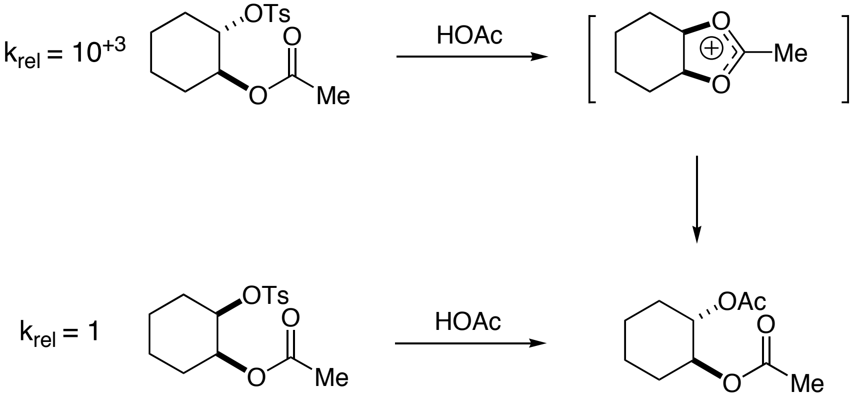
Synthesis of (±)-Isocomene: Pirrung, *JACS* **1979**, 7130; *1981*, 82.

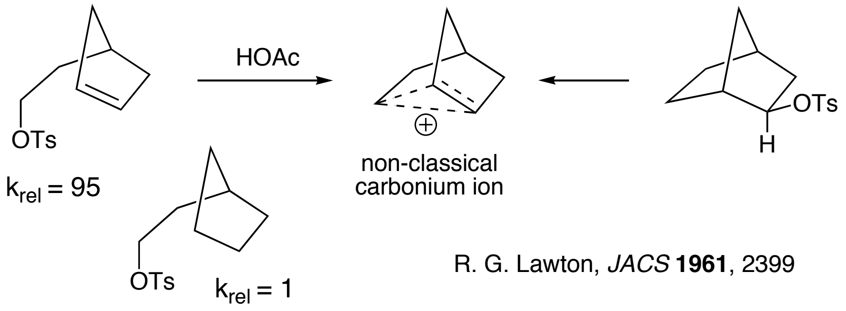


Carbocations: Neighboring Group Participation

Groups with accessable electron density (heteroatoms, arenes) and the correct stereoelectronic orientation (anti-periplanar) can "assist" in the ionization of a leaving group.

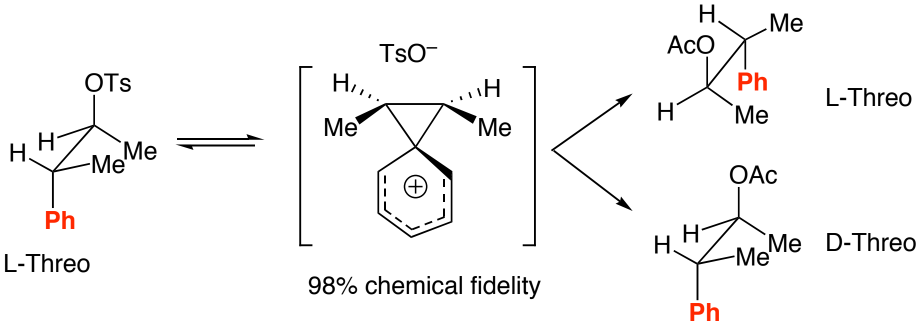


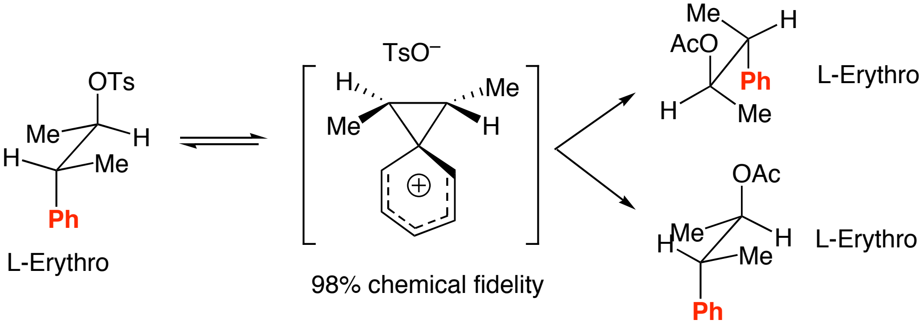




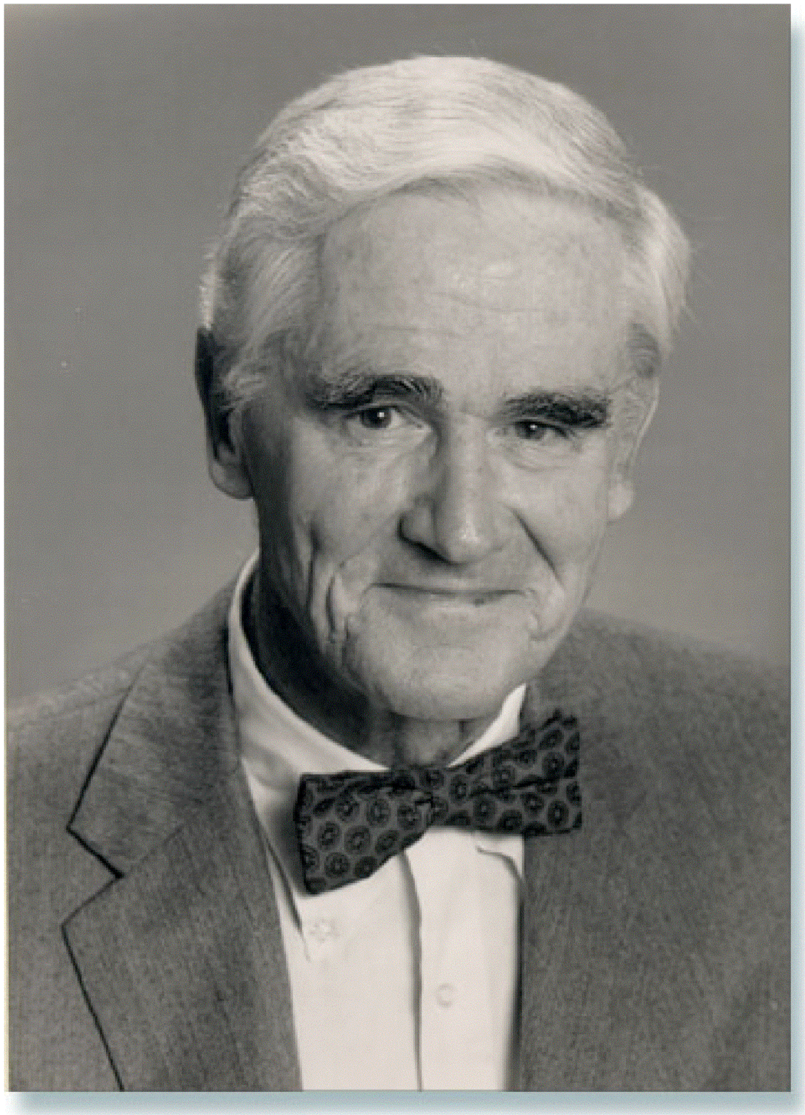
R. G. Lawton, *JACS* **1961**, 2399

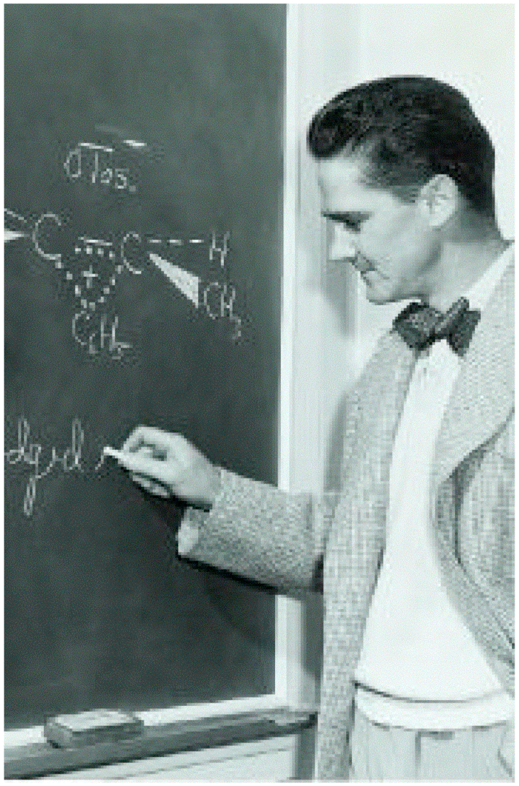
The Cram Phenonium Ion Experiments: Cram, *JACS* **1949**, *71*, 3865



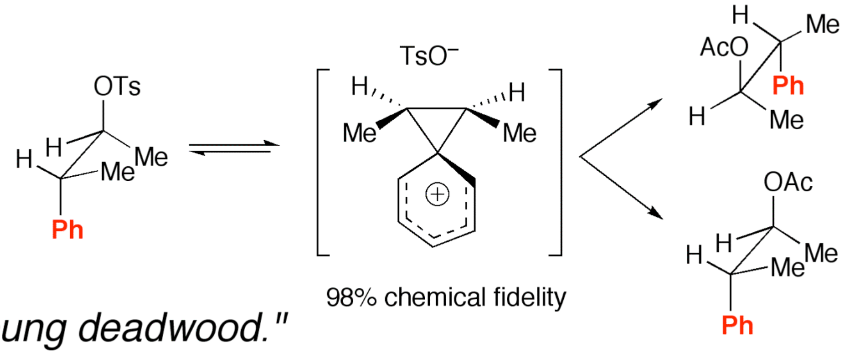


Donald J.Cram (1919–2001)





Phenonium Ion Experiments: Cram, *JACS* **1949**, *71*, 3865



98% chemical fidelity

Cram: *"Just remember Dave, old deadwood is better than young deadwood."*

"A View from the Far Side. Memorable Characters and Interesting Places." Evans, D. A. *Tetrahedron* **1999**, *55*, 8589-8608.

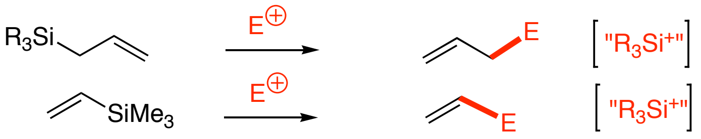
Allyl- & Vinylsilanes: The β-Silicon Effect

References:

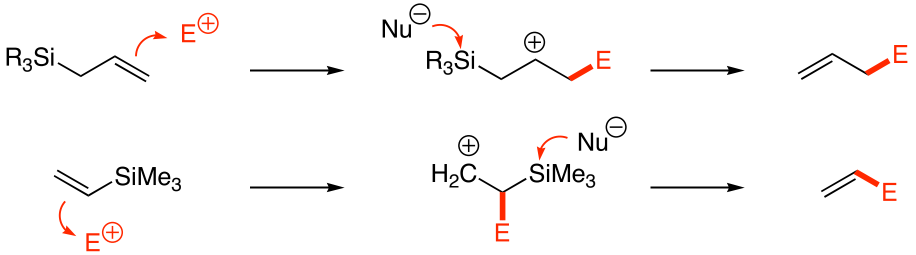
Lambert *Acc. Chem. Res.* **1999**, *32*, 183-190
Lambert, *JACS* **1990**, *112*, 8120; **1996**, *118*, 7867.
Fleming, *Organic Reactions* **1989**, *37*, 54.
Fleming, *Chem. Rev.*, **1997**, 2063.

Allyl– & Vinylsilanes react with electrophiles

(trapped by solution Nu)

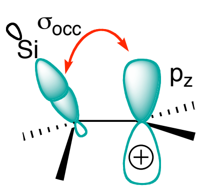


Mechanism - the simple picture: β-Silicon stabilizes carbocation

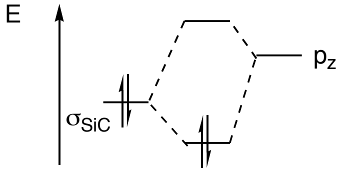


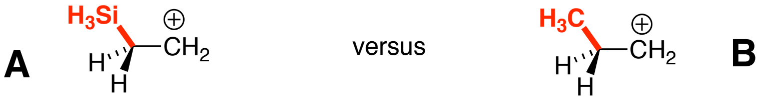
Fleming, *Organic Reactions* **1989**, *37*, 54.

β-Silicon Effect: the origin of regioselectivity



$\sigma_{Si-C} \rightarrow p_z$ empty

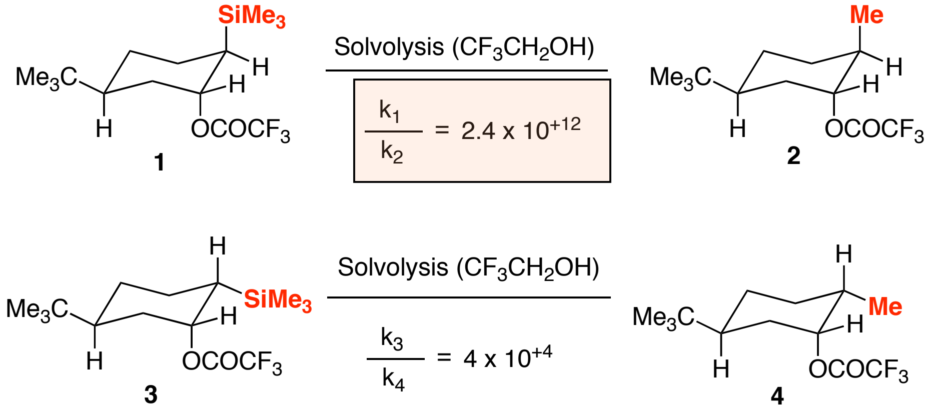




Calculation: A more stable than B by 38 kcal/mol.

Jorgensen *JACS* **1985**, *107*, 1496.

Magnitude of the β-Silicon Effect



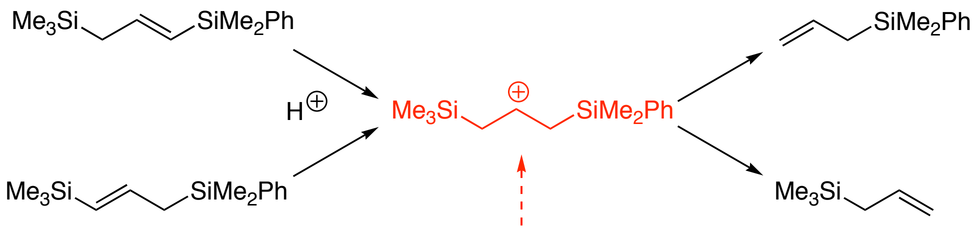
$SiMe_3$
Me_3C
H
H
H
$OCOCF_3$
1
Solvolysis (CF_3CH_2OH)
$\frac{k_1}{k_2} = 2.4 \times 10^{+12}$
Me
Me_3C
H
H
H
$OCOCF_3$
2
H
Me_3C
$SiMe_3$
H
H
$OCOCF_3$
3
Solvolysis (CF_3CH_2OH)
$\frac{k_3}{k_4} = 4 \times 10^{+4}$
H
Me_3C
Me
H
H
$OCOCF_3$
4

In all instances, the solvolysis product is 1-tert-butylcyclohexene

"These figures established the β-effect as one of the kinetically strongest in organic chemistry": J. Lambert

Data provide no distinction between open and bridged intermediates

Proof for a stepwise mechanism provided the following protodesilylation experiment:

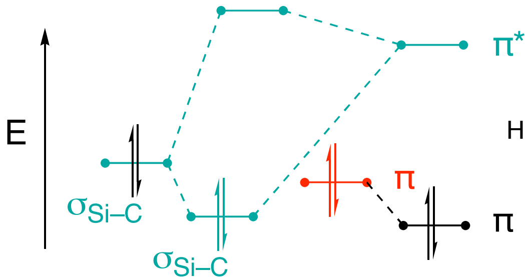


both silanes yield the same product mixture. Hence, the reaction proceeds most likely via a **common intermediate**, a carbeniumion

Allyl- & Vinylsilanes: The β-Silicon Effect-2

Allylsilanes are more nucleophilic than alkenes

⇨ HOMO is higher in energy due to ***negative hyperconjugation***

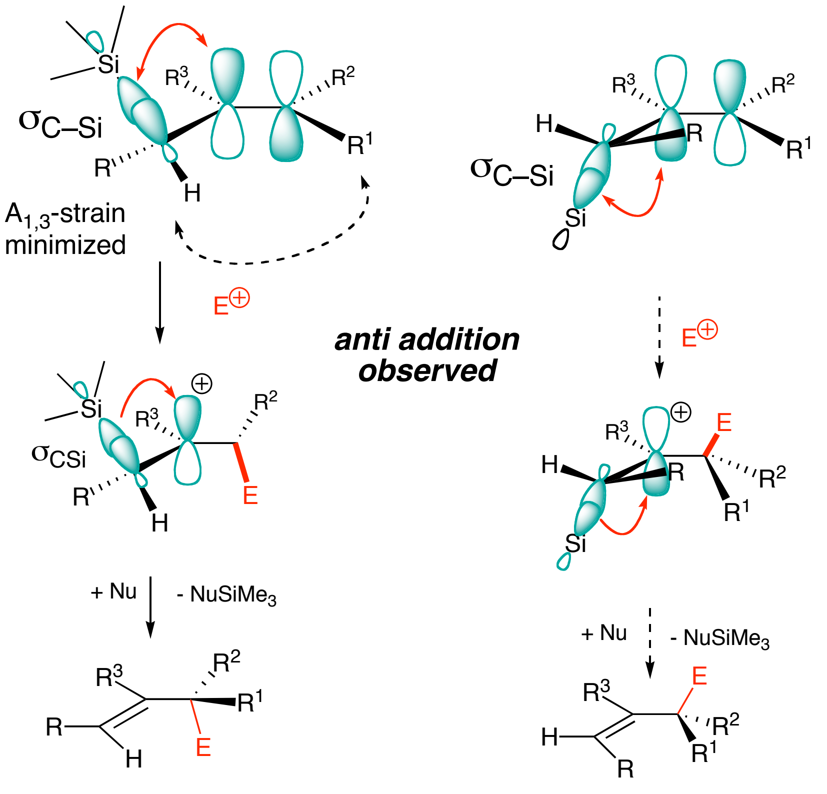


π (π^*) ⟷ σ_{C-Si}

Houk, *JACS* **1982**, *104*, 7162.

Electrophile Addition - Stereoelectronics

anti addition observed



anti addition observed

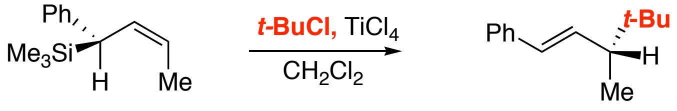
major (trans)

minor (cis)

The stereochemical consequences for the major product are:

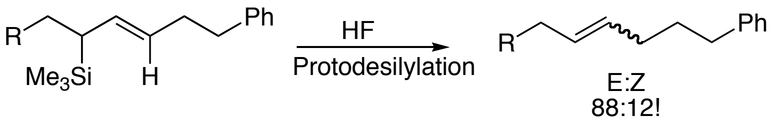
- ❒ trans-alkene:
- ❒ anti-addition of E^+ with respect to SiR_3

Examples:



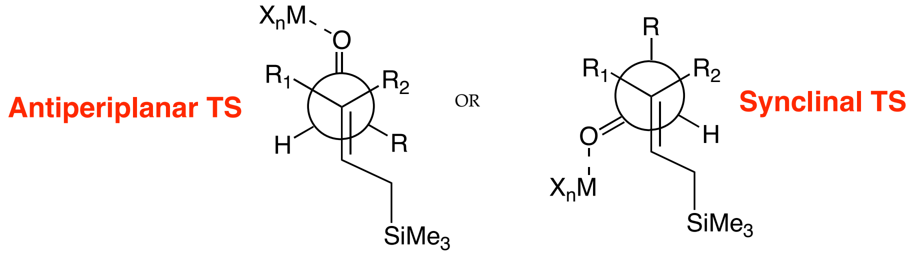
JACS **1982**, *104*, 4962.

But

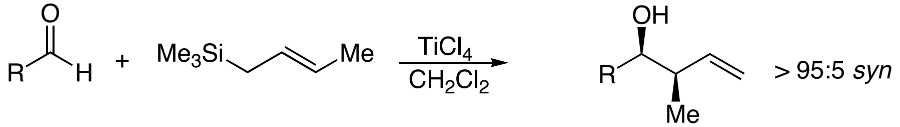


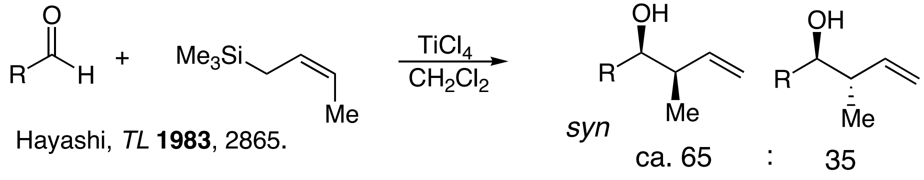
Carbonyl Addition of Allylsilanes: Open Transition States

Me_3Si^- is not sufficiently Lewis acidic to activate C=O through pre-association; however $(RO)_2MeSi^-$ is Lewis acidic enough to activate C=O through pre-association. These allylsilanes add to RCHO througl closed transition states



Calculations by Houk et al. show that the relative energy differences between the antiperiplanar and and synclinal transition states are negligible. Both the antiperiplanar and synclinal models predict a ***syn*** selectivity for the newly formed stereogenic centers.



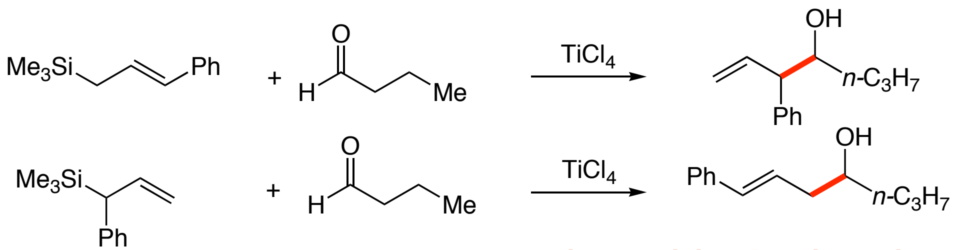


Hayashi, *TL* **1983**, 2865.

Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones, Denmark and Jiping Fu, *Chem. Rev.* **2003,** *103,* 2763-2793 **(handout)**

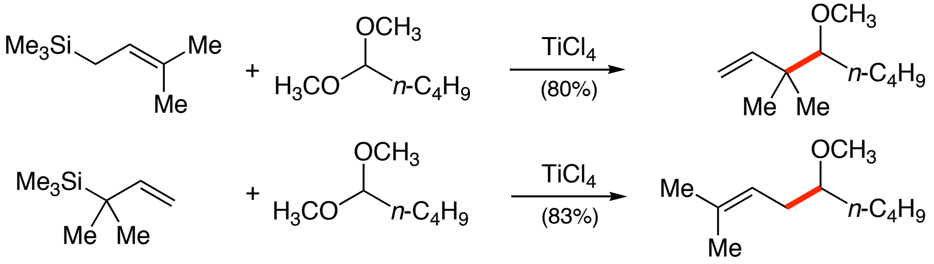
Allylsilanes: Reactions with Electrophiles

Allylsilanes add to aldehydes and acetals under Lewis acid promotion

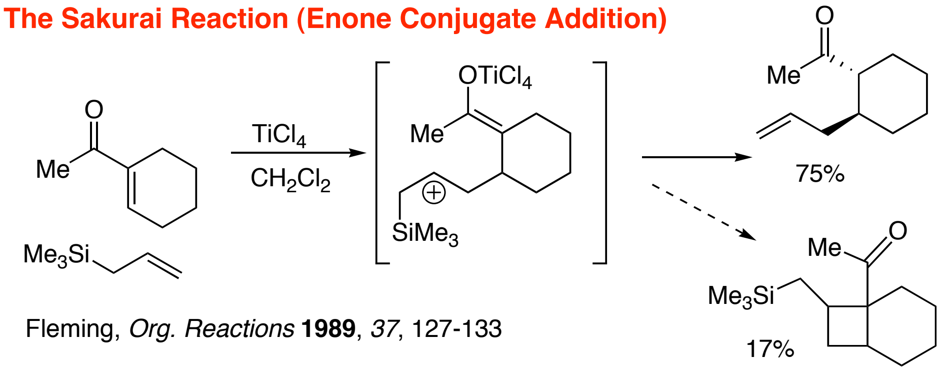


regioselectivity: Allyl inversion

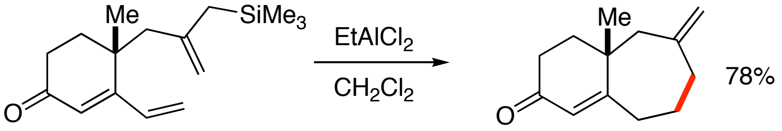
Acetals can be used as well



The Sakurai Reaction (Enone Conjugate Addition)



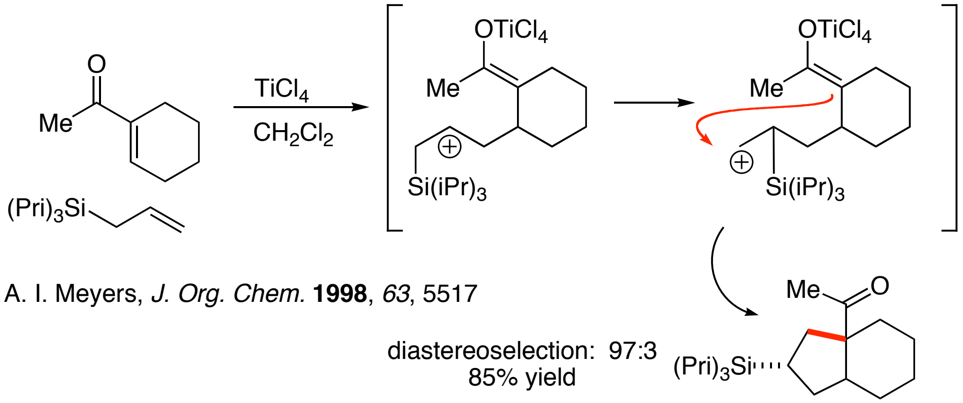
Fleming, *Org. Reactions* **1989**, *37*, 127-133



Majetich, *Tetrahedron* **1987**, *43*, 5621

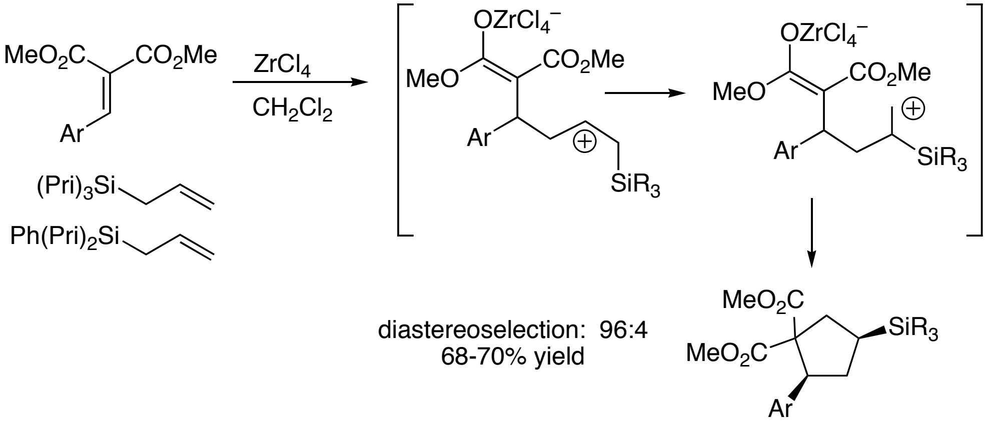
Reactions Proceedilng through Silicon-Migration

Si migration may be promoted by using hindered Si substituents



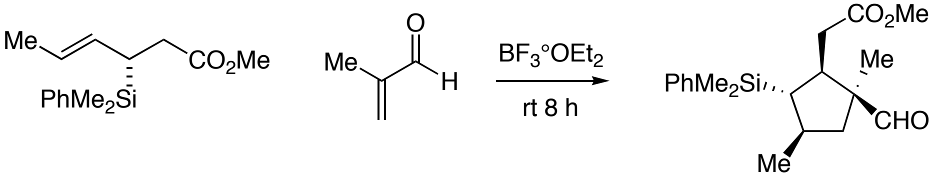
A. I. Meyers, *J. Org. Chem.* **1998**, *63*, 5517

diastereoselection: 97:3
85% yield



diastereoselection: 96:4
68-70% yield

Can you work out the mechanism??



diastereoselection: >30:1
93% yield

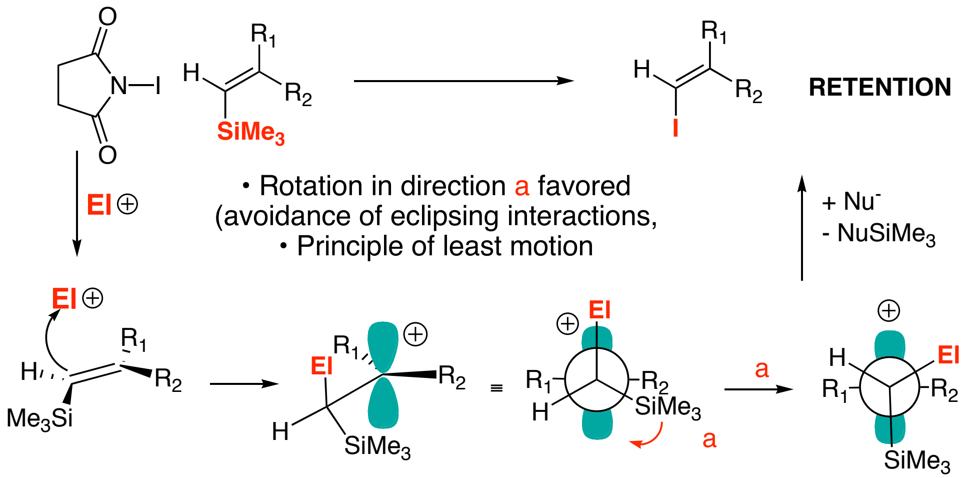
Panek, *J. Org. Chem.* **1993**, *58*, 2345

Vinylsilanes: Reactions with Electrophiles

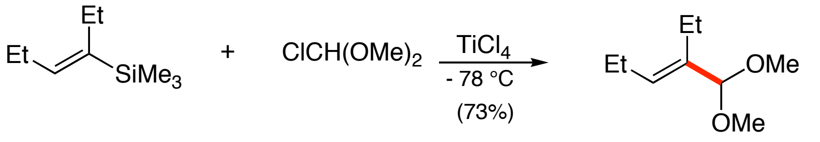
Stereochemistry of Electrophile Addition to Vinylsilanes

Vinyl/Allylsilanes in Organic Synthesis - Selected Examples

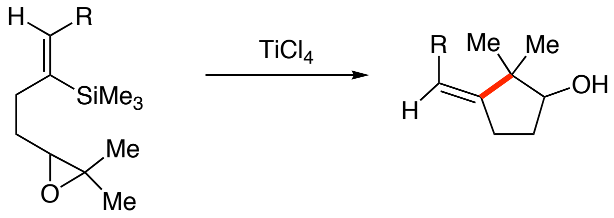
Fleming, *Org. Reactions* **1989**, *37*, 54.



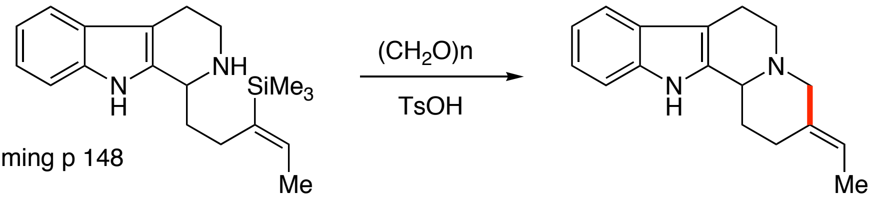
- Rotation in direction a favored (avoidance of eclipsing interactions,
- Principle of least motion



Fleming p 289

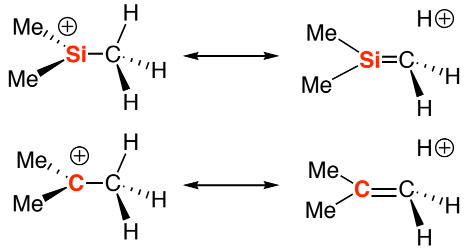


Fleming p 148



Summary Statements

1. Me_3C+ is more stable than Me_3Si+ in spite of the fact that Si is less electronegative than C.

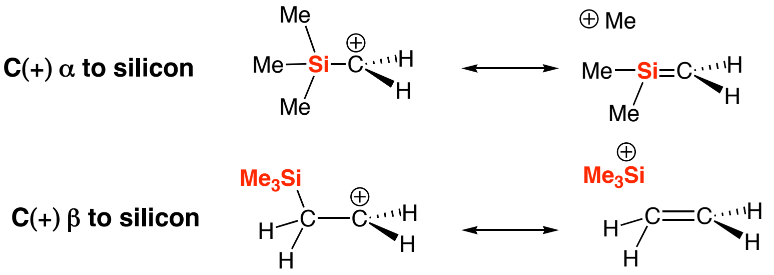


C–Si bond length: 1.87 Å

C–C bond length: 1.54 Å

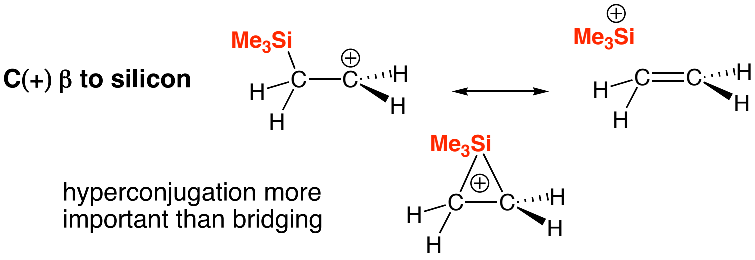
C–Si hyperconjugation is less pronounced than the anaologous C–C hyperconjugation do to the impact of the longer C–Si bond lengths.

2. Carbonium ions α to Si are less stabilized than carbonium ions β to Si.



C–Si hyperconjugation is less pronounced than the anaologous C–C hyperconjugation do to the impact of the longer C–Si bond lengths.

3. According to Lambert, silicon has a propensity to stabilize β carbonium ion via hyperconjugation (vertical stabilization) rather than bridging (nonvertical stabilization.

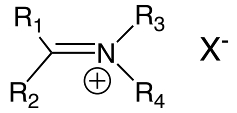


hyperconjugation more important than bridging

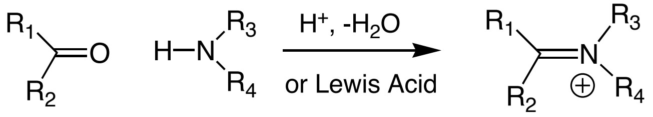
4. Silicon has a lower propensity to undergo Wagner–Meerwein like rearrangements than carbon.

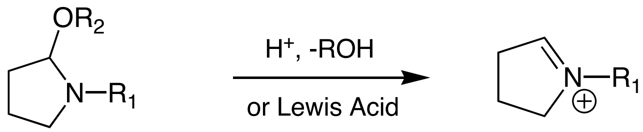
Stabilized Cations: Iminium-Ions 1

Iminium Ions

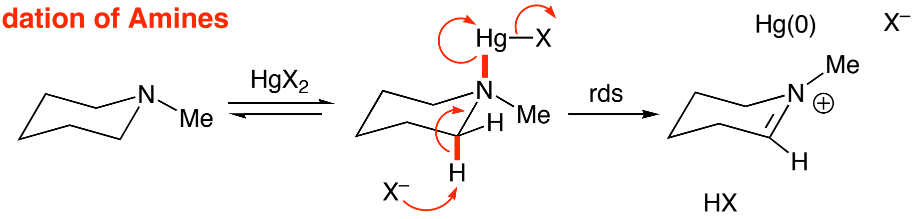


Common Methods of Generation:

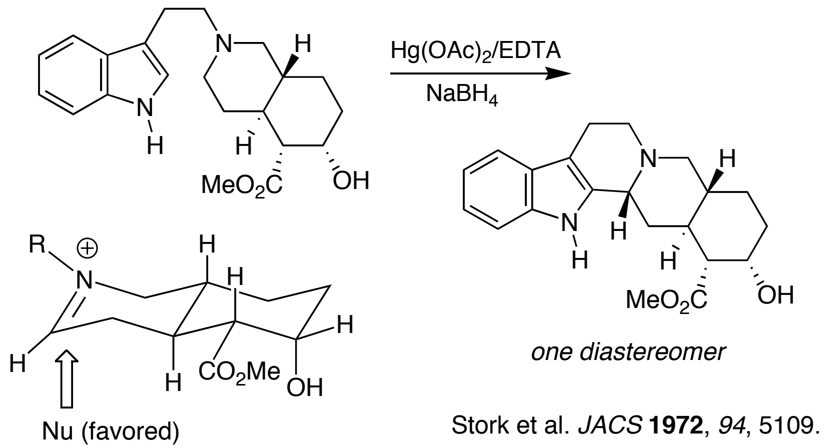




Oxidation of Amines

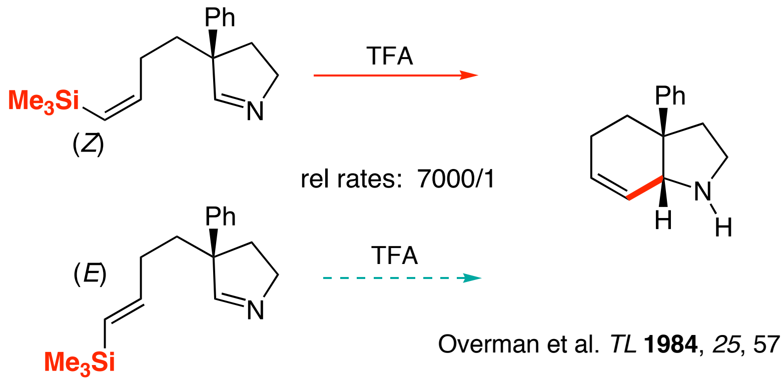


Stereoelectronic Effects on Nu Addition to Iminium Ions

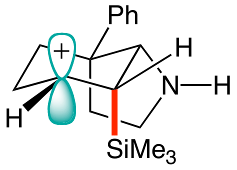


Stork et al. *JACS* **1972**, *94*, 5109.

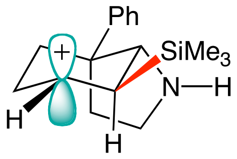
C=N Stereoelectronic Effects: Lecture 20



Overman et al. *TL* **1984**, *25*, 5739.

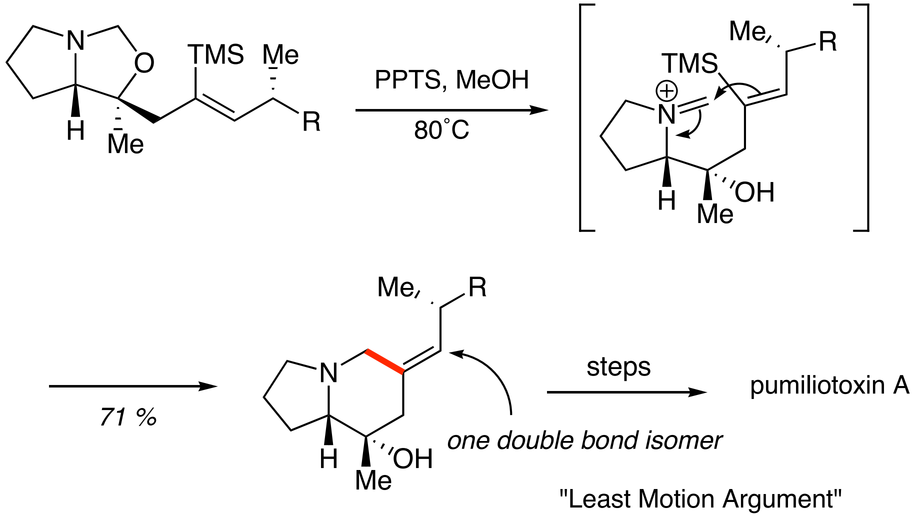


(Z) vinylsilane)



(E) vinylsilane)

Only in the case of the (Z) vinylsilane is the emerging p orbital coplanar with C-Si bond. Full stabilization of the empty orbital cannot occur with the (E) vinylsilane.....hence the rate difference.



Overman et al. *JOC* **1989**, *54*, 2591.

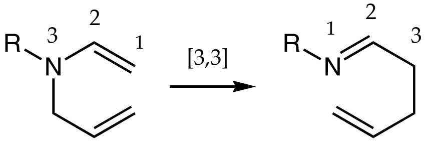
The Aza-Cope Rearrangement

Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

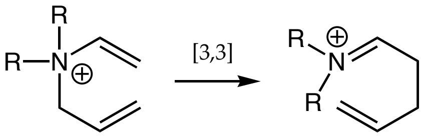
The 3-aza-Cope Rearrangement:

Neutral Variant:



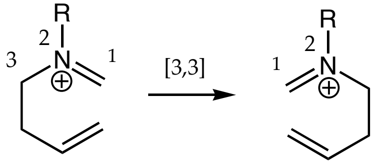
Exothermic as written by ~7-10kcal/mole.

Ammonium Variant:



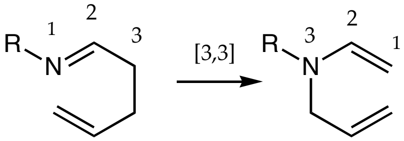
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

2-aza-Cope Rearrangement:



In the simplest case, degenerate. Steric effects, conjugation, or selective trapping of a particular isomer, will drive equilibrium. As with the 3-aza-Cope, the cationic version proceeds under much milder conditions.

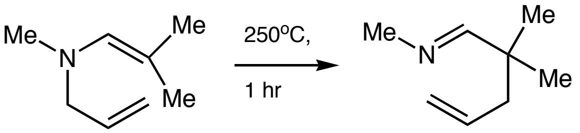
1-aza-Cope Rearrangement:



The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates(i.e., incorporating the imine into a strained ring or by making R an acyl group).

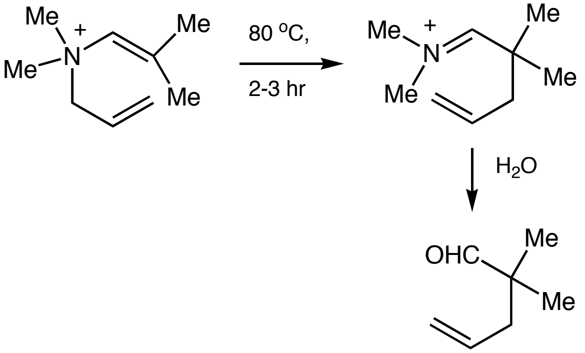
The 3-aza-Cope Rearrangement

First Neutral Case: Hill TL **1967**, 1421.



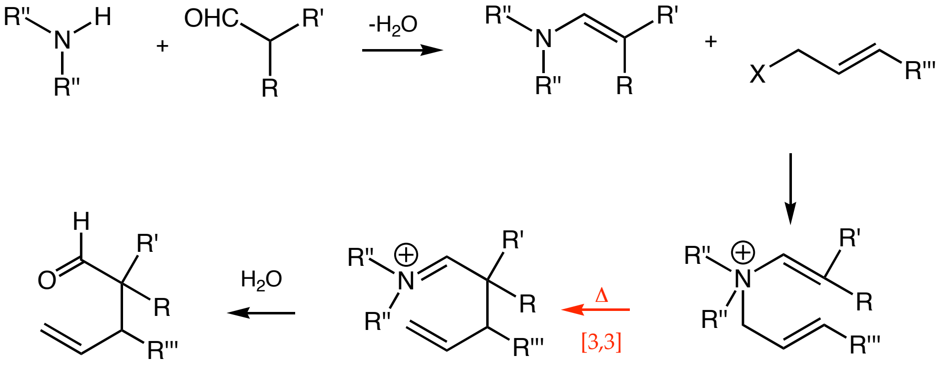
"Practically quantitative", no real yields given.

First Cationic Case: Elkik *Compt. Rend.* **1968**, *267*, 623.



No yields given.

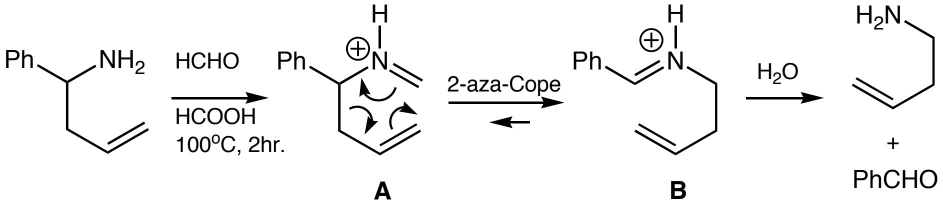
Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, *72*, 169.



The Aza-Cope Rearrangement

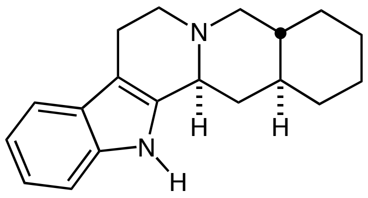
The 2-aza-Cope Rearrangement

First Reported Case: Horowitz JACS 1950, *72*, 1518.

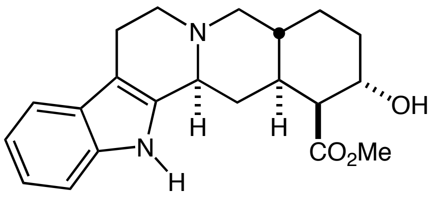


Equilibrium between **A** and **B** driven towards **B** by conjugation of iminium double bond to the aromatic ring in **B**.

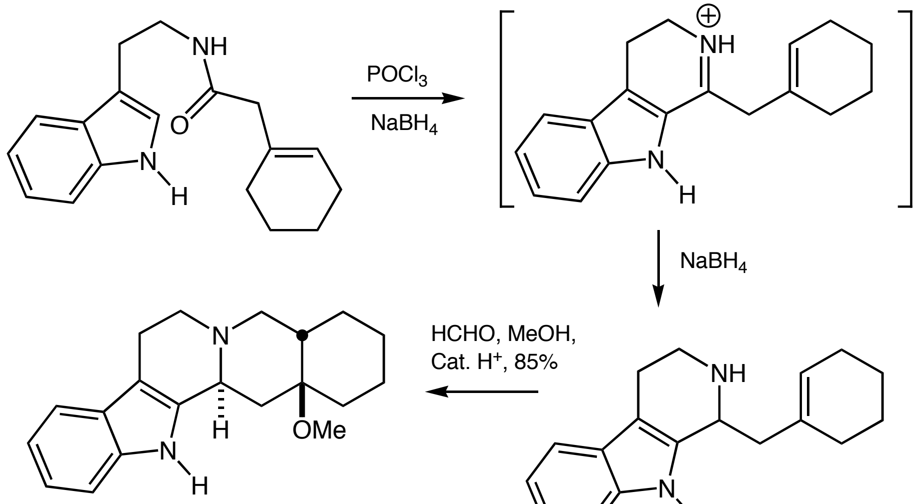
Application to Yohimbine Analog Synthesis: Winterfeldt *Chem. ber.* **1968**, *101*, 2938.



Yohimbane

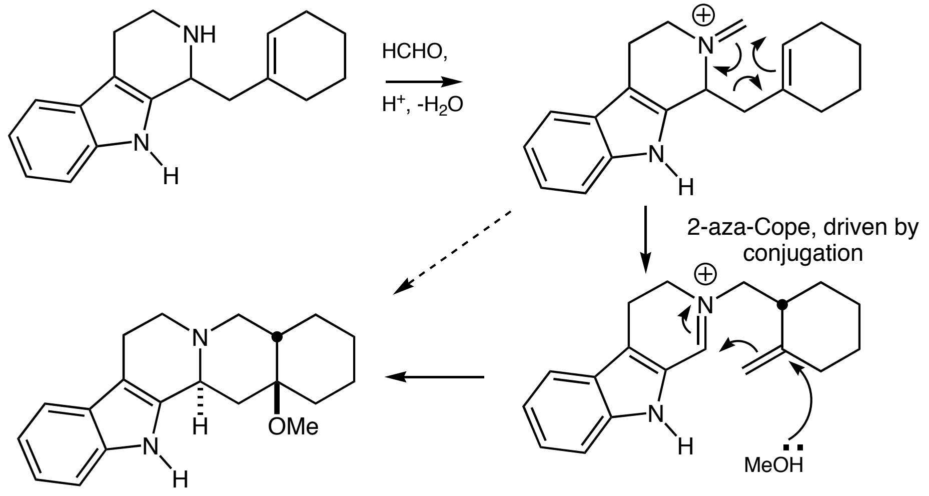


Yohimbine



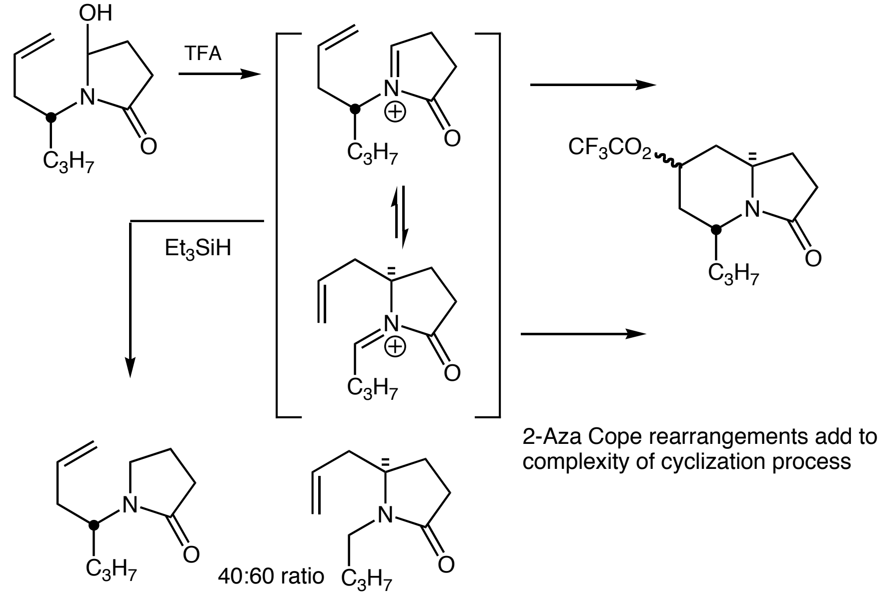
15-Methoxy-isoyohimbane

Mechanism for Yohimbane Analog Formation:



*N-Acyliminium Ion Rearrangements: Hart JOC **1985**, 50, 235.*

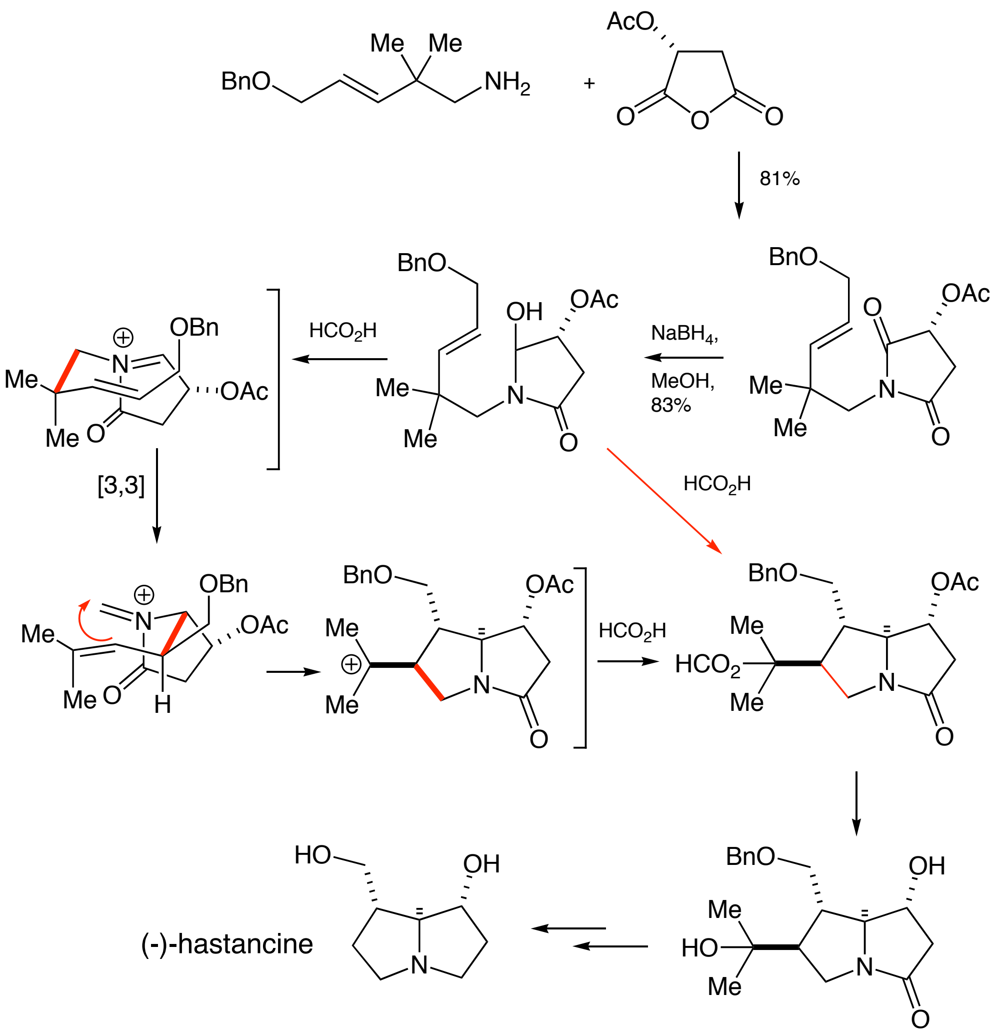
Hart observed an unusual product while trapping the intermediates of N-acyliminium olefin cyclizations.

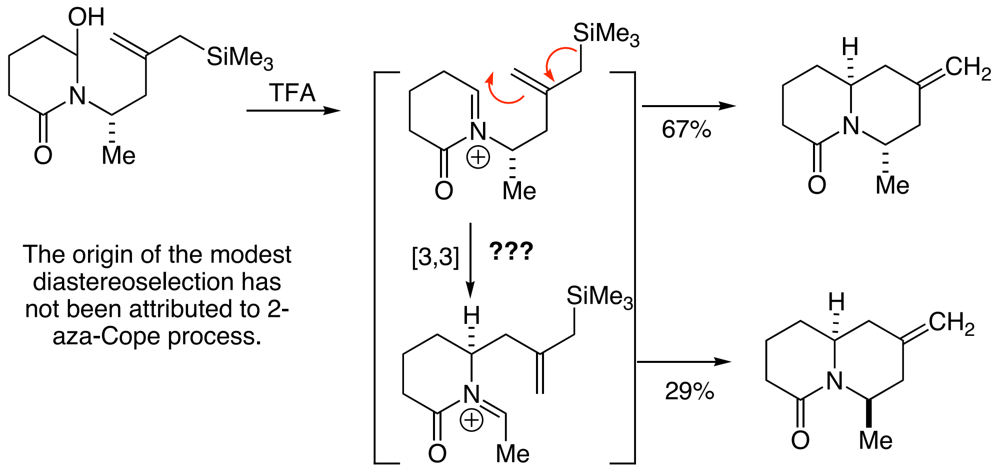


2-Aza Cope rearrangements add to complexity of cyclization process

N-Acyliminium Ion Rearrangements

Synthesis of (-)-hastanecine: Hart JOC ***1985****, 50, 235.*

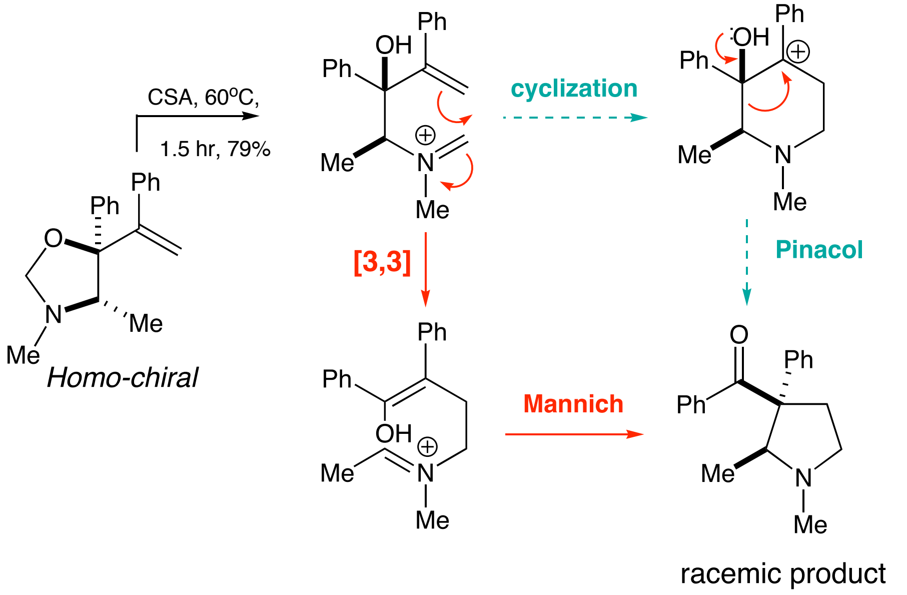




The origin of the modest diastereoselection has not been attributed to 2-aza-Cope process.

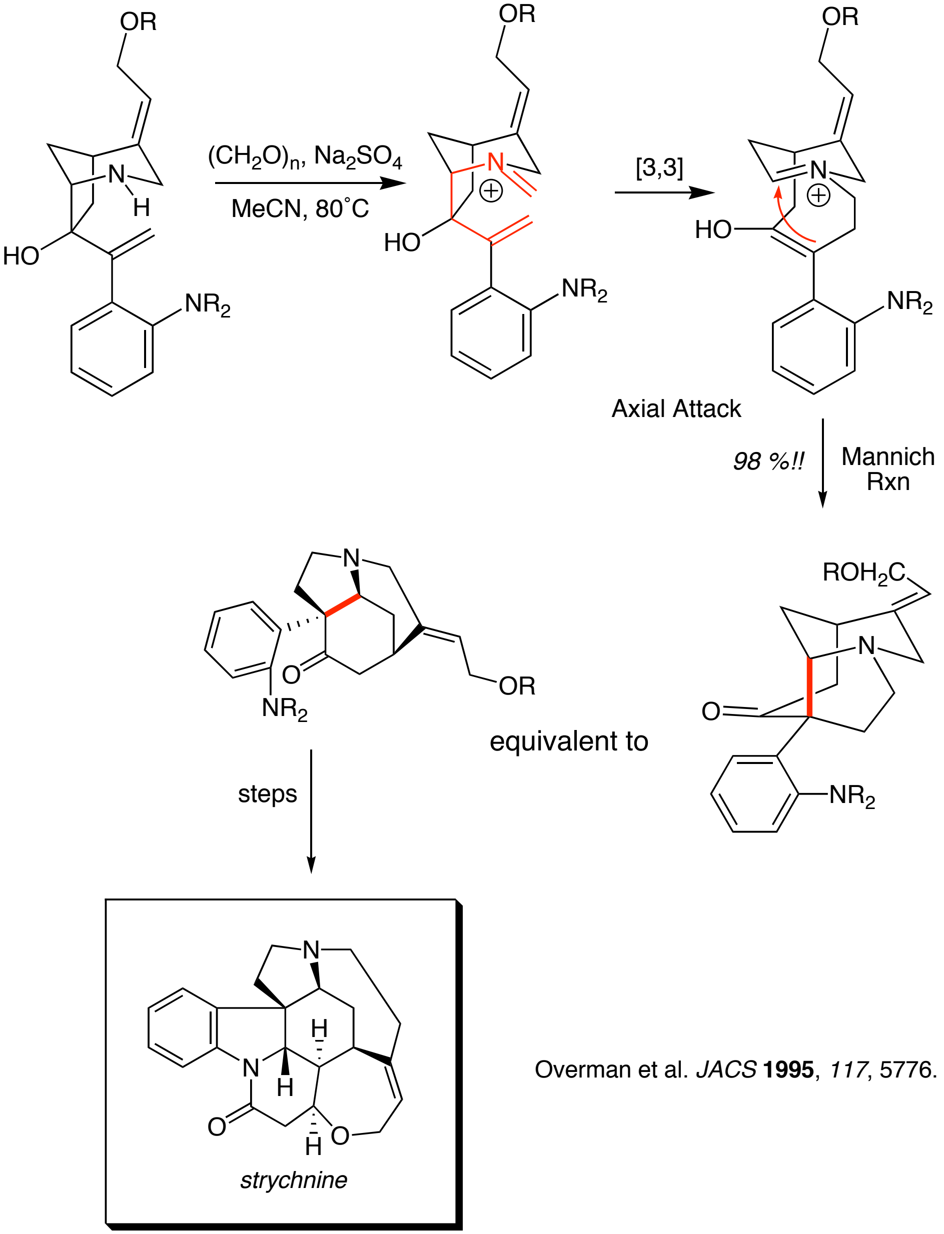
Gelas-Mailhe, *Tet. Lett*, **1992**, *33*, 73

Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??



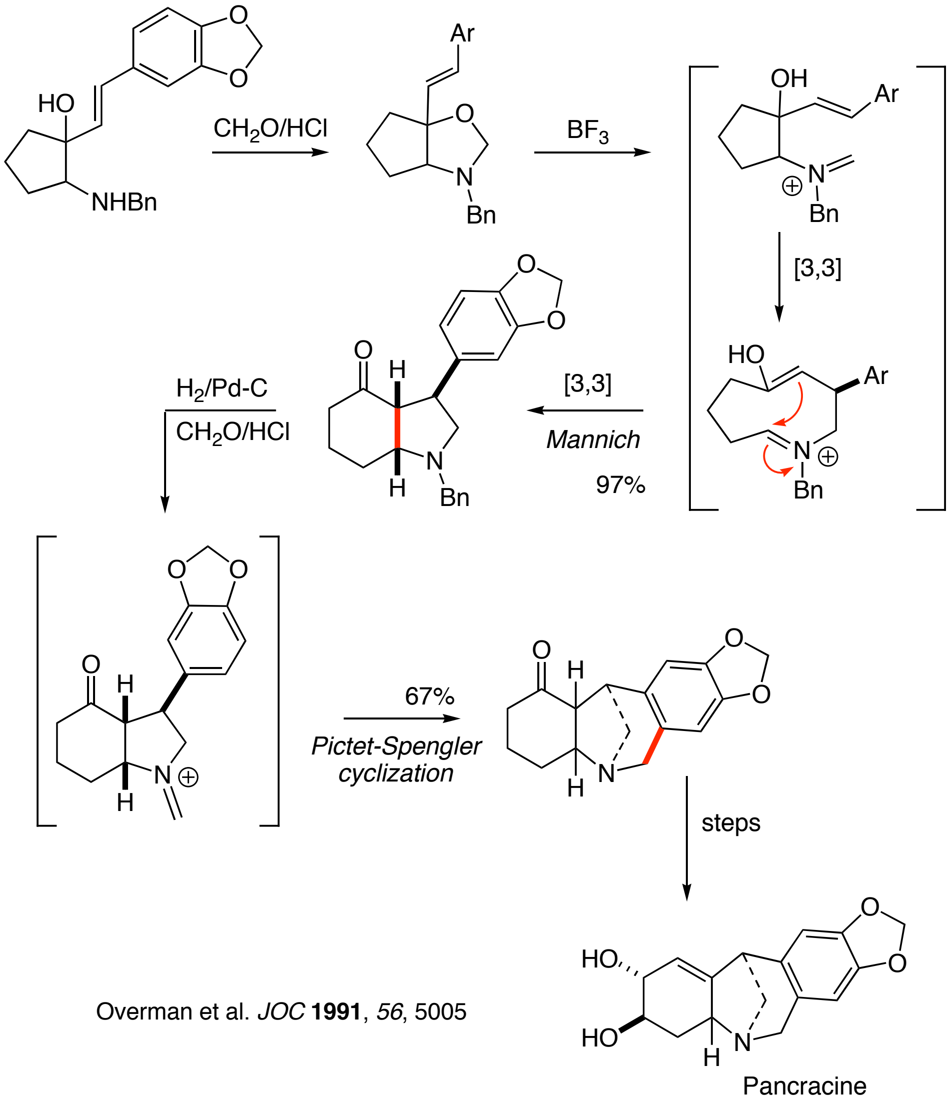
2-aza-Cope rearrangements afford a low-barrier to competing processes

2-Aza-Cope-Mannich sequence:



Overman et al. *JACS* **1995**, *117*, 5776.

Another aza-Cope-Mannich sequence:



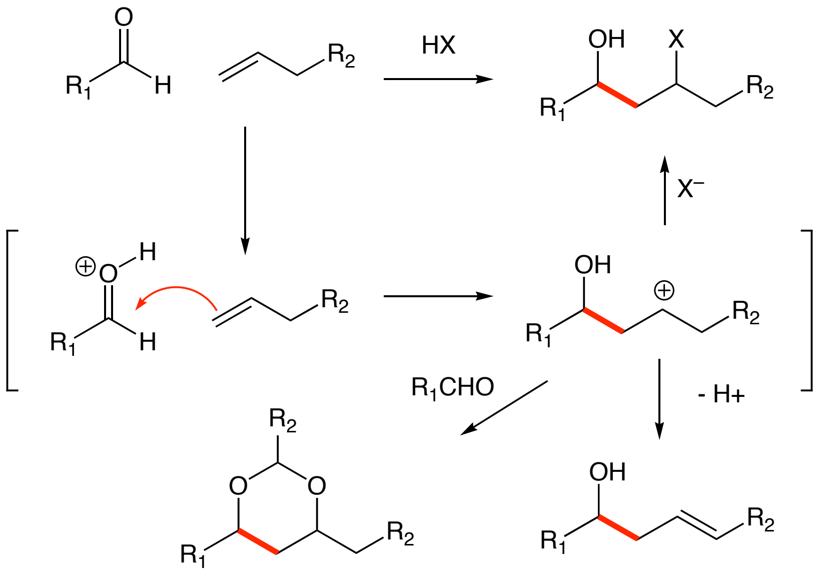
Overman et al. *JOC* **1991**, *56*, 5005

The Prins-Pinacol Reaction

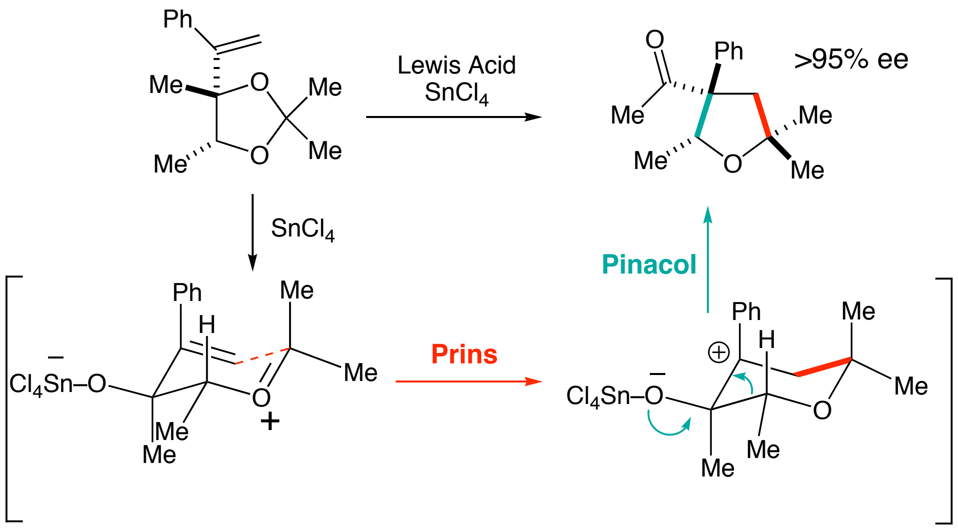
References

Prins reaction: Adams, D.R.; Bhaynagar, S. D. *Synthesis* **1977**, 661
Prins & carbonyl ene reactions: Snider, *Comprehensive Organic Synthesis*, **1991**, *Vol. 2*

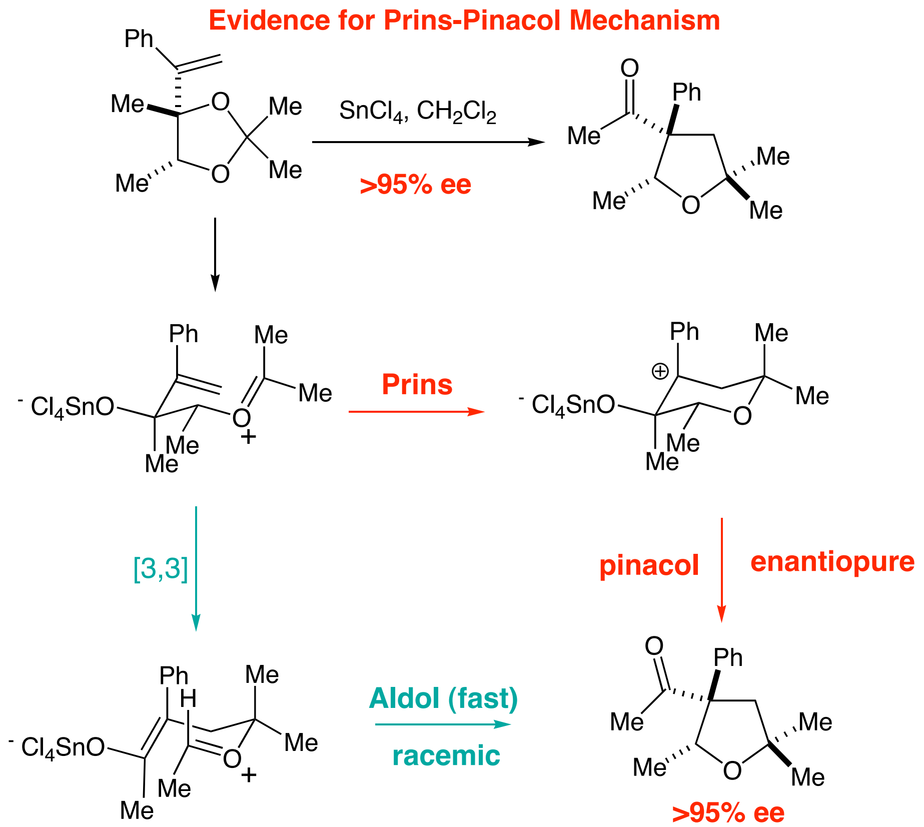
The Prins Process:



The Prins-Pinacol Variant:

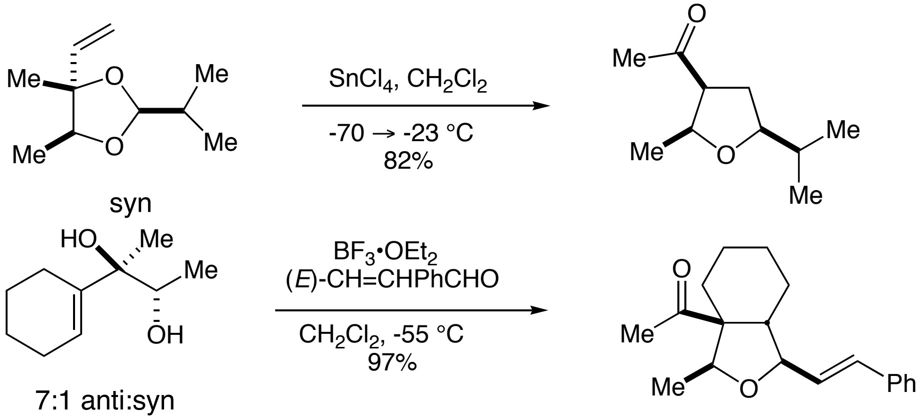


Evidence for Prins-Pinacol Mechanism



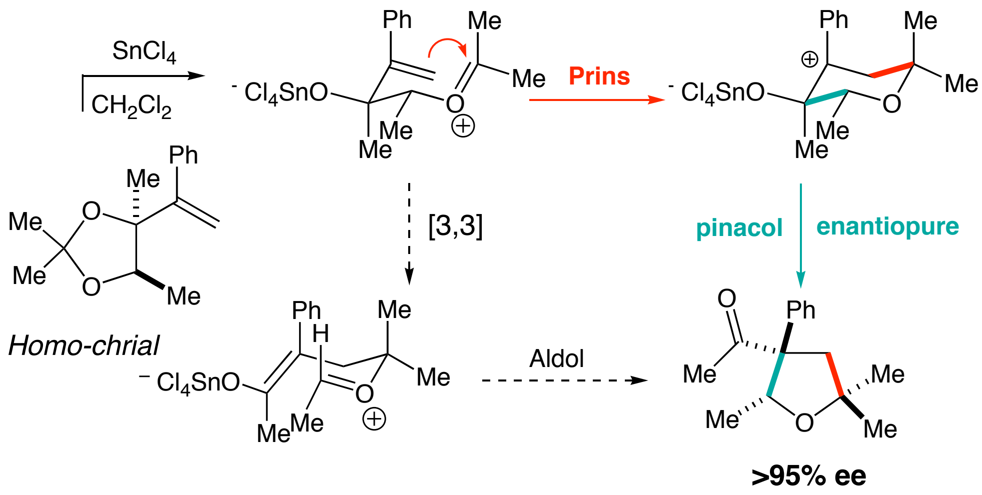
If a [3,3] rearrangement were intervening, the product would be racemic.
Overman, *JACS* **2000**, *122*, 8672
Overman, *Org Lett* **2001**, *3*, 1225

Examples of Stereoselective THF Formation



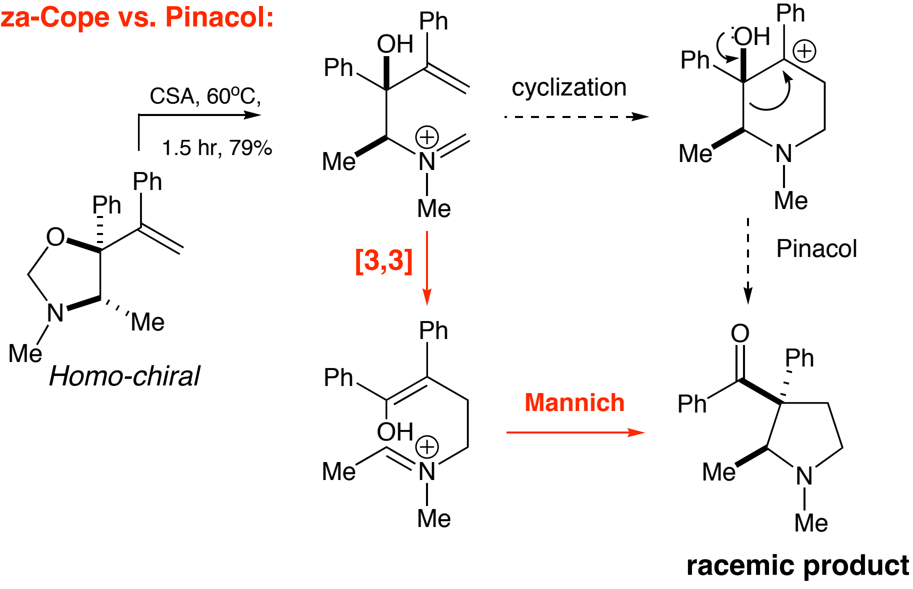
The Prins-Pinacol Reaction

Prins-Pinacol Mechanism



Prins cyclization faster than [3,3] rearrngement

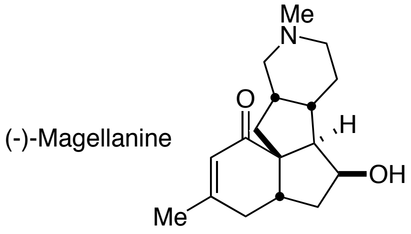
2-aza-Cope vs. Pinacol:



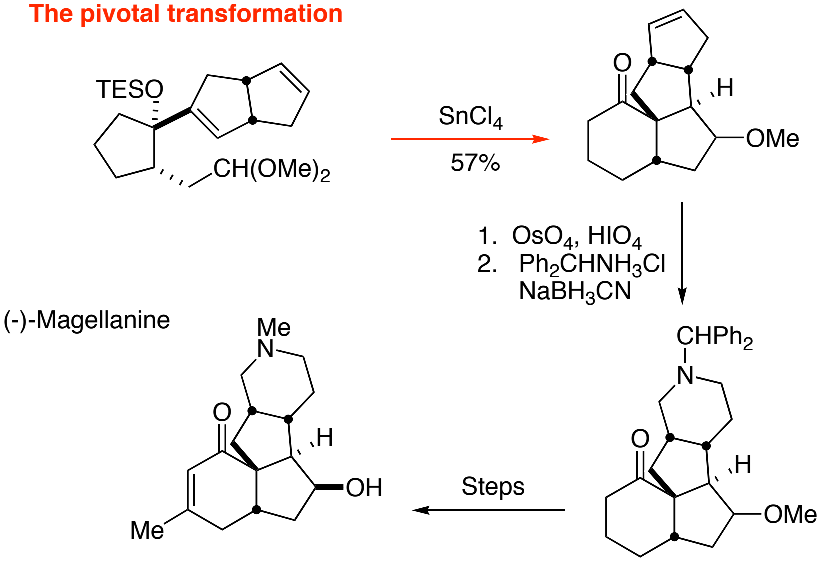
[3,3] rearrngement faster than Mannich cyclization

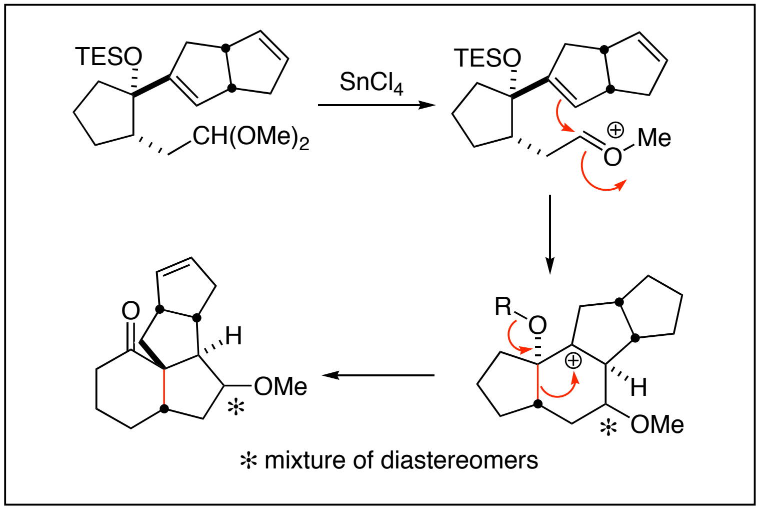
Overman: Magellanine Synthesis

JACS, **1993**, *115*, 2992



The pivotal transformation



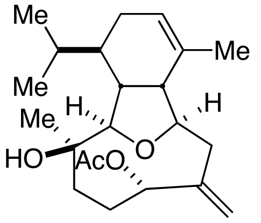


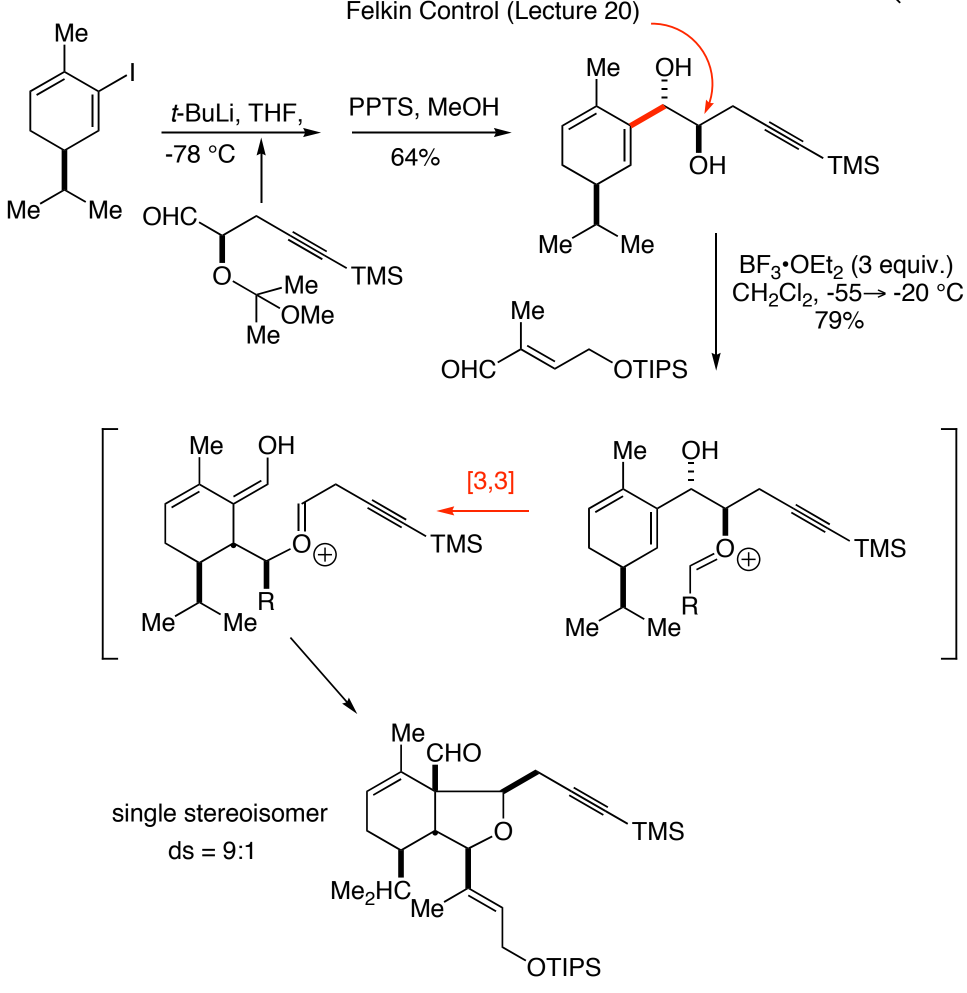
✻ mixture of diastereomers

Overman Synthesis of a Eunicellin Diterpene

Overman & MacMillan JACS, **1995**, *117,* 10391

(-)-7-Deacetoxy-alcyoninacetate



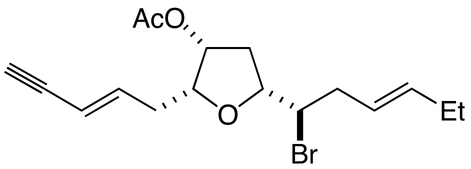


single stereoisomer
ds = 9:1

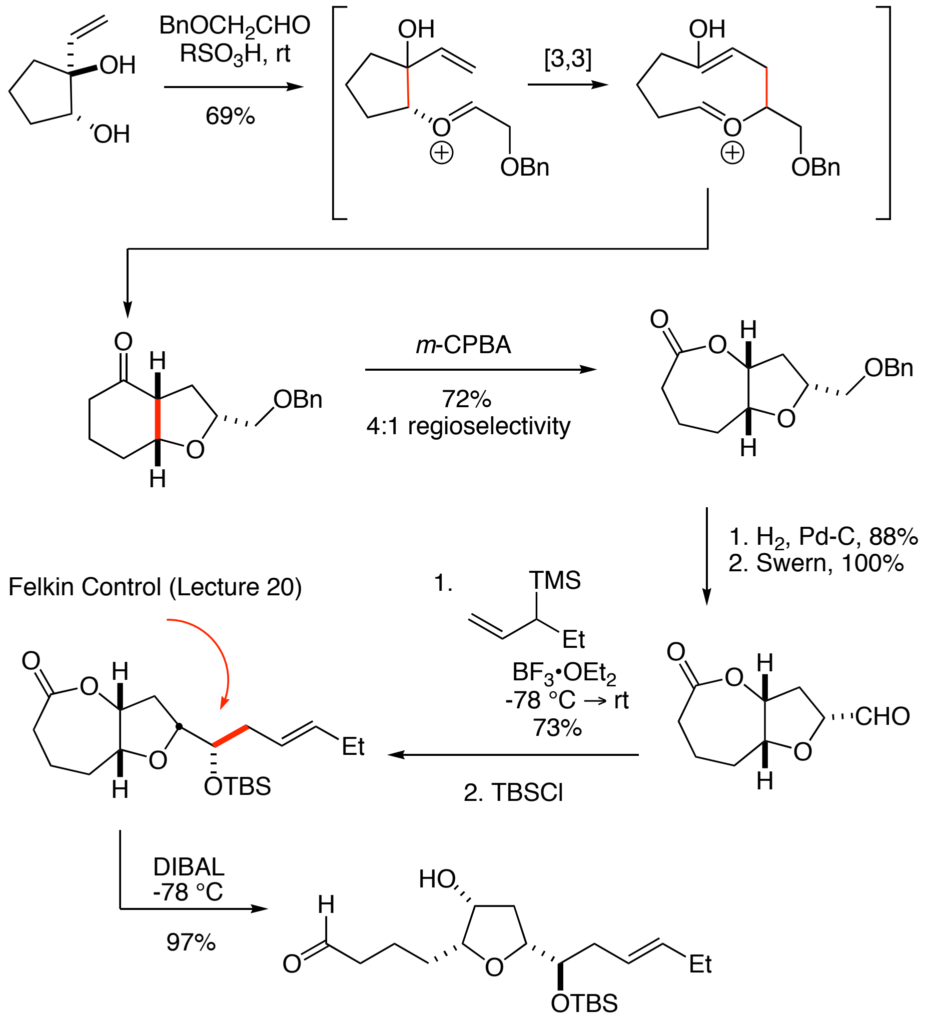
6 steps, 39% yield from (*S*)-carvone

Overman: Synthesis of *trans*-Kumausyne

JACS, **1991**, *113,* 5378



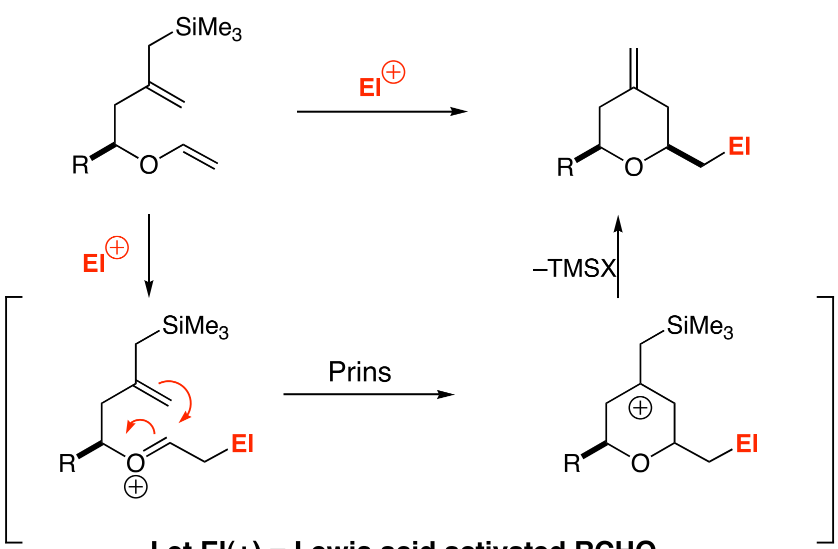
trans-Kumausyne



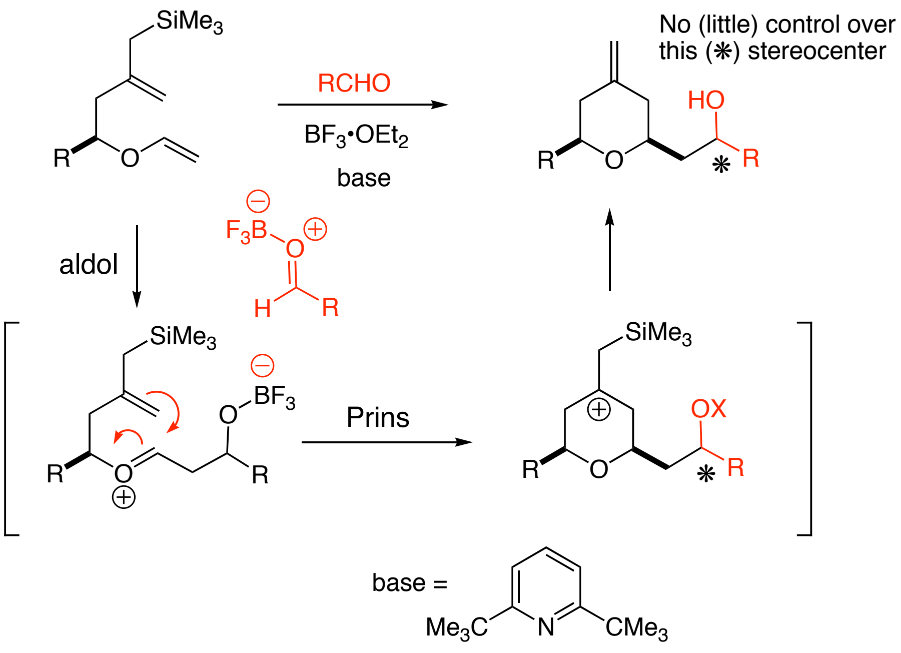
Mukaiyama Aldol–Prins Cascade

Rychnovsky JACS, **2001**, *123,* 8420

The Basic Process

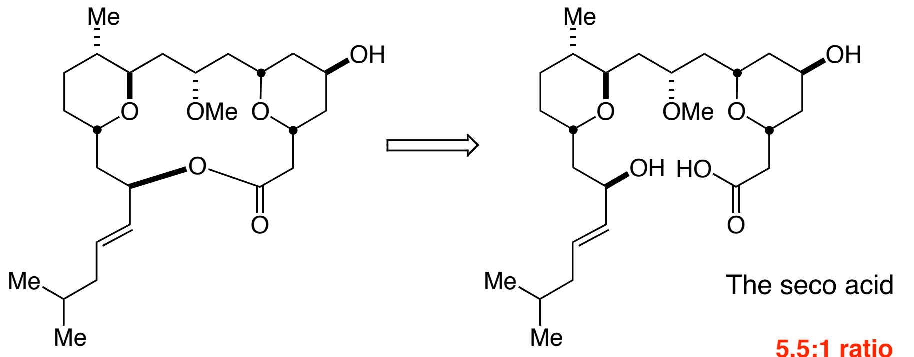


Let El(+) = Lewis acid activated RCHO



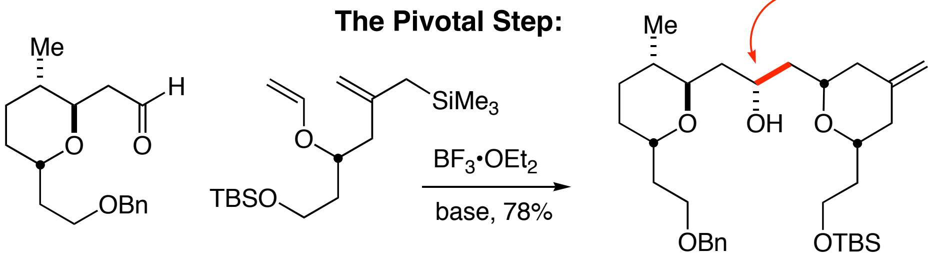
No (little) control over this (✻) stereocenter

Application to Leucasandrolide

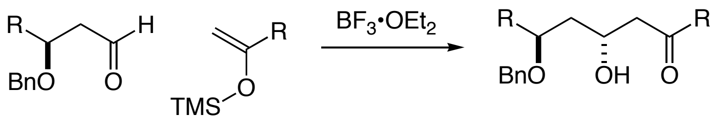


The seco acid

The Pivotal Step:



Control of hydroxyl center: see Lecture 20

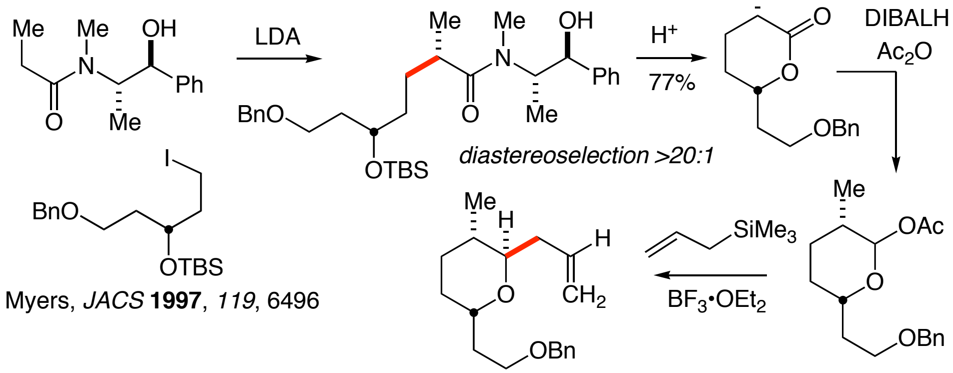


anti selection: ~5–8:1

Evans et al., *JACS* **1996**, *116*, 4322

Aldehyde Synthesis

Chiral enolate alkylation: see Lecture 23



diastereoselection >20:1

Myers, *JACS* **1997**, *119*, 6496

cyclic oxo-carbenium ion addition: see Lecture 19

http://www.courses.fas.harvard.edu/colgsas/1063

Chemistry 206

Advanced Organic Chemistry

Lecture Number 34

Introduction to Carbenes & Carbenoids-1

- Carbene Structure & Electronics
- Methods for Generating Carbenes
- Simmons-Smith Reaction
- Carbene-Olefin Insertions
- Carbene Rearrangements

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 10, "Reactions Involving Highly Reactive Electron-Deficient Intermediates", 595–680.

Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, *29*, 3 **(handout)**

Doyle, Catalytic Methods for Metal Carbene Transformations, *Chem. Rev.* **1986**, *86*, 919-939 **(electronic handout)**

McKervey, Organic Synthesis with α-Diazocarbonyl Compounds, *Chem. Rev.* **1994**, *94*, 1091-1160 **(electronic handout)**

Muller, Catalytic Enantioselective Aziridinations & Asymmetric Nitrene Insertions, *Chem. Rev.* **2003**, *103*, 2905-2919 **(electronic handout)**

Problems Database Keywords: Carbenes & Carbenes + rearrangements

D. A. Evans

Friday
December 15 , 2006

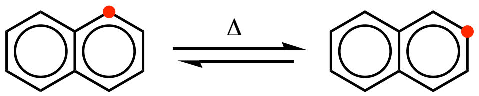
Useful References to the Carbene Literature

Books: Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

Provide a mechanism for the following transformations.

Problem 410: Automerization of Naphthalene (The Cume Question from Hell!)

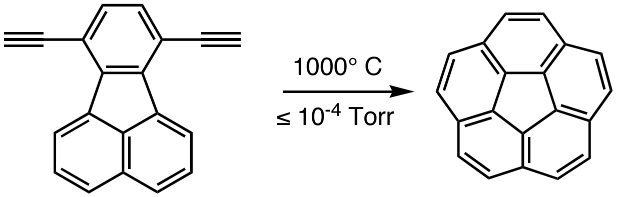
Rationalize



α–^{13}C-labeled $C_{10}H_8$ is isomerized into β–^{13}C-labeled $C_{10}H_8$ at 1035 °C

L. T. Scott, *JACS* **1991**, *113*, 9692.

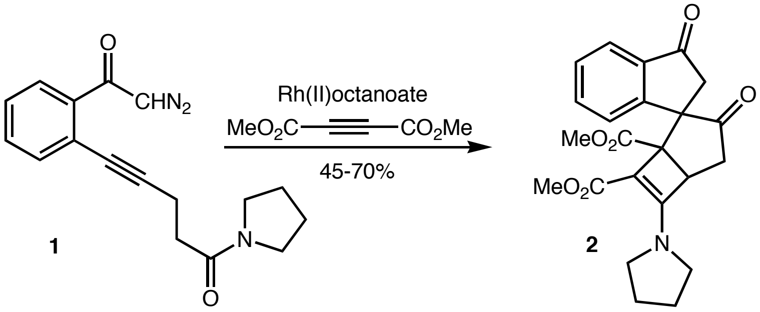
Problem 411: Provide a Mechanism for this Transformation



Corannulene 10%

Scott, L.T., et. al., *JACS* **113** 7082 (1991)

Problem 411: While investigating the reactivity of α-diazoketones, Padwa and co-workers (*Tetrahedron Lett.* **1993**, *49*, 7853) discovered the interesting reaction of diazoketone **1** under the conditions shown below. Provide a detailed mechanism for the formation of spirocycle **2**.

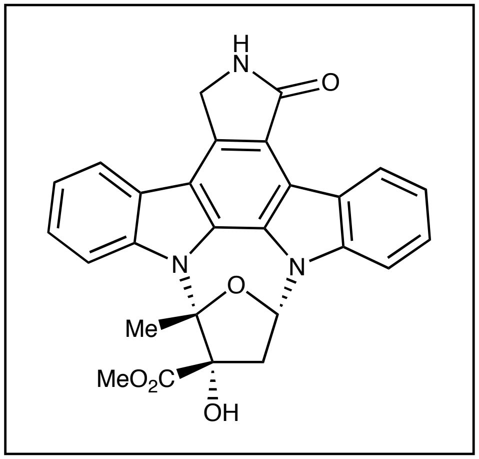


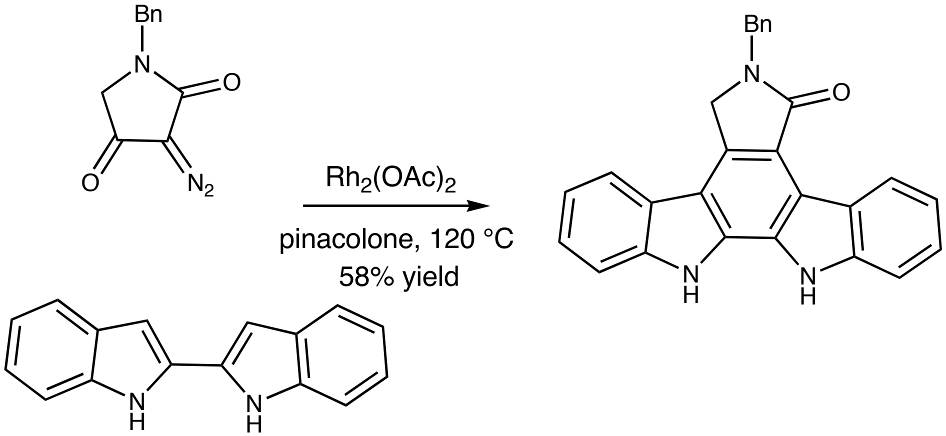
1 **2**

1:1 mixture of diastereomers

Problem 47

Wood recently reported a very clever approach to the synthesis of the indolocarbazole family of natural products (*JACS* **1995**, *117*, 10413). His approach to the indolocarbazole core is the one-pot transformation outlined below.

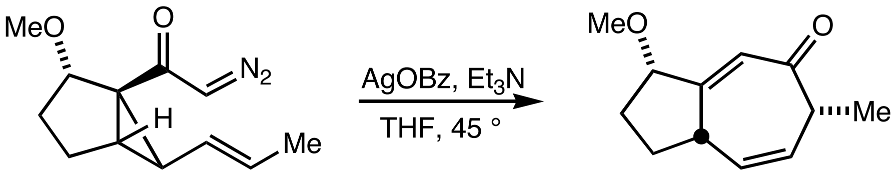




Provide a plausible mechanism for this multi-step transformation in the space below.

Problem 332

Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, *125*, 13624).

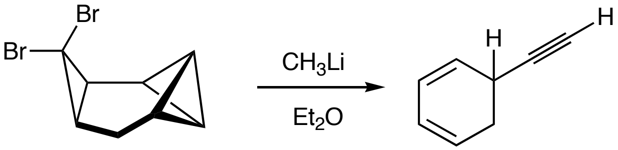


95% yield

Please provide a mechanism for the illustrated transformation. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

Problem 405

Lechner and Christl described this interesting, albeit unintended degradation of **1** upon treatment with methyllithium (*Angew. Chem. Int. Ed.* **1975**, 765). These studies were undertaken en route to tetrahedrane, although the ultimate goal was never realized.



Please provide a mechanism for this transformation.

Carbenes: An Introduction

Suggested Reading:

Doyle, *Chem Rev.* **1988,** *86*, 919.
Kodadek, *Science*, **1992**, *256*, 1544.

Recent Review Article:
Chemistry of Diazocarbonyls: McKervey et al. *Chem Rev*. **1994**, *94*, 1091.

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

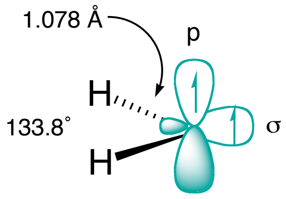
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

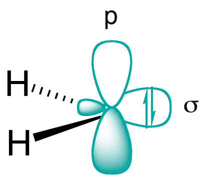
Carbenes: Electronic Structure

■ Carbene Configuration: Triplet vs. Singlet



Triplet (two unpaired e$^-$)

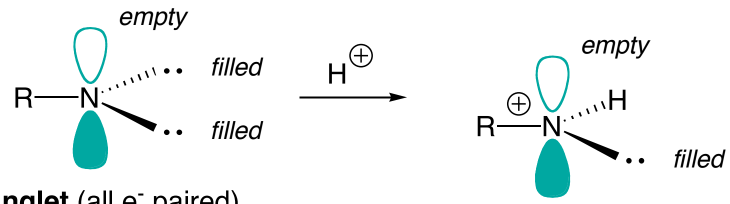
Often has **radica**l-like character



Singlet (all e$^-$ paired)

Often has **electrophilic** or **nucleophilic** character: **A**-type (**Ambiphilic)**

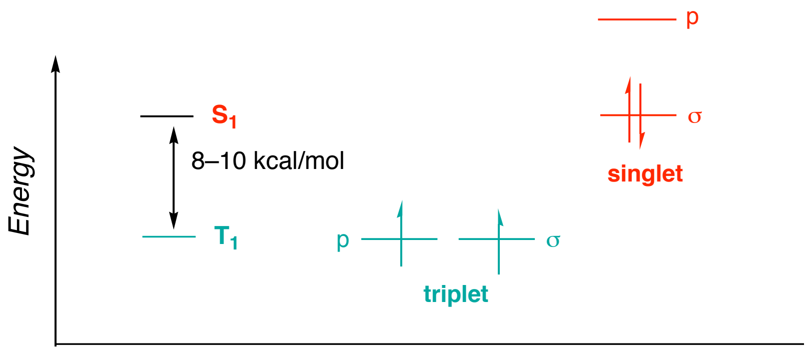
■ Nitrene



Singlet (all e$^-$ paired)

■ Nitrenium ion

■ Carbene Configuration: Triplet vs. Singlet



Due to electron repulsion, there is an energy cost in pairing both electrons in the σ orbital. If a **small energy difference** between the σ and p orbitals exists, the electrons will remain **unpaired (triplet)**. If a **large gap** exists between the σ and p orbitals the electrons will **pair** in the σ orbital (**singlet**).

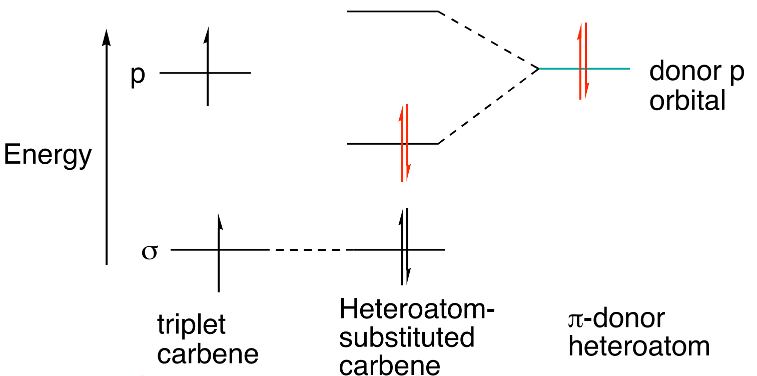
■ the History of the Singlet-Triplet Gap

Year	Method	Author	HCH Angle	Grnd State	S–T Splitting kcal/mol
1932	Qual.	Muliken	90-100°	*singlet*	—
1947	Thermochem	Walsh	180°	*triplet*	*small*
1957	Qual. QM	Gallup	160°	*triplet*	30
1969	Ab initio	Harrison	138°	*triplet*	>33
1971	Kinetics	Hase	—	*triplet*	8–9
1971	SCF	Pople	132°	*triplet*	19
1974	MINDO	Dewar	134°	*triplet*	8.7
1976	Expt	Lineberger	138°	*triplet*	19.5
1976	An Initio	Schaeffer	—	*triplet*	19.7
1978	**Expt**	**Zare**	—	***triplet***	**8.1**
1982	**Expt**	**Haydon**	—	***triplet***	**8.5**

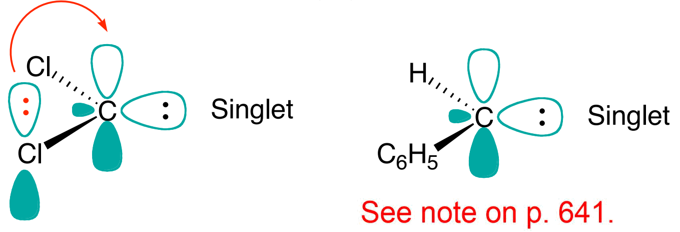
(Wentrup)

Heteroatom-Substituted Carbenes: Singlets

The p orbital of carbenes substituted with **p-donor atoms** (N, O, halogen) is raised high enough in energy to make the pairing of the electrons in the σ orbital energetically favorable. As a result, these carbenes are often in the **singlet** state.



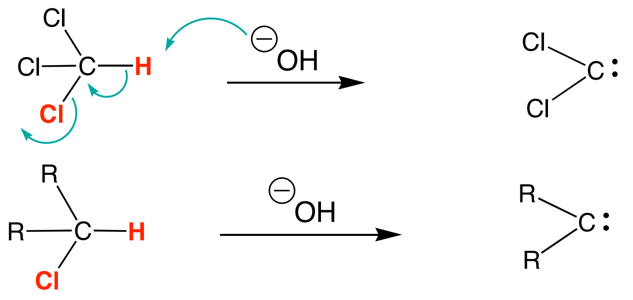
Examples:



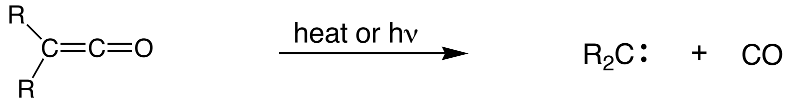
See note on p. 641.

Methods of Synthesis

■ Alkyl Halides:

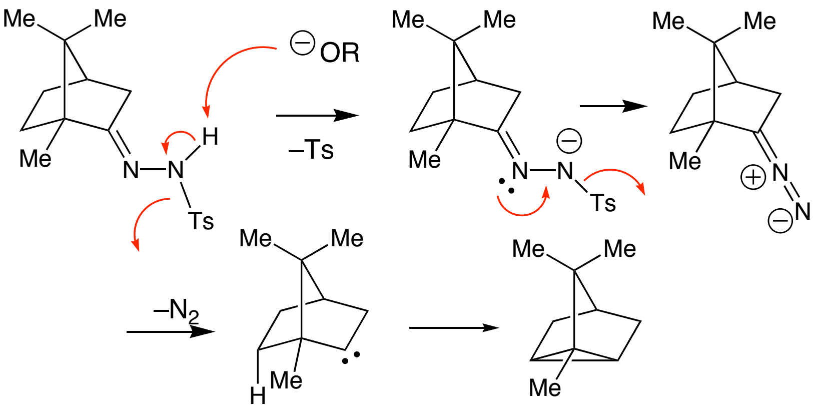


■ ketenes

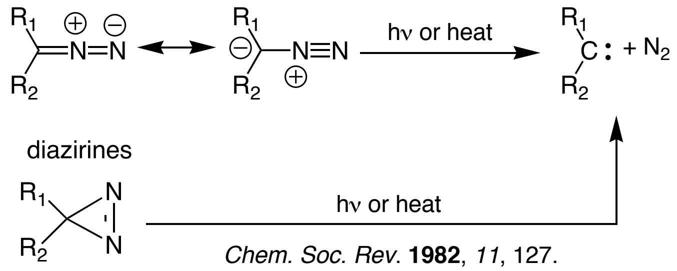


■ Bamford-Stevens Reaction: See Lecture 31 on Hydrazones

Shapiro *Org. Rxns.* **1976**, *23*, 405.

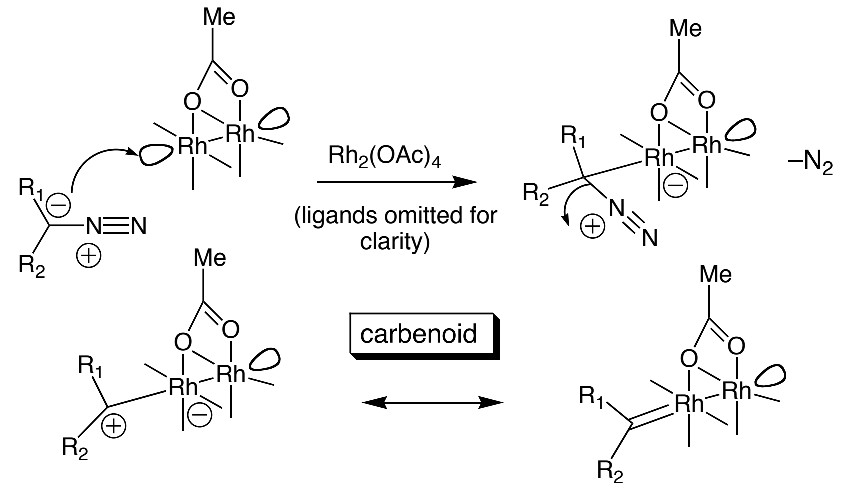


■ diazo compounds



Chem. Soc. Rev. **1982**, *11*, 127.

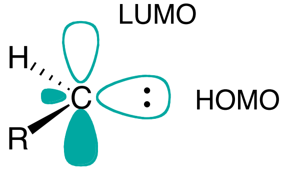
■ metal-catalyzed decomposition Doyle *Chem Rev.* **1986**, *86*, 919 **(handout)**



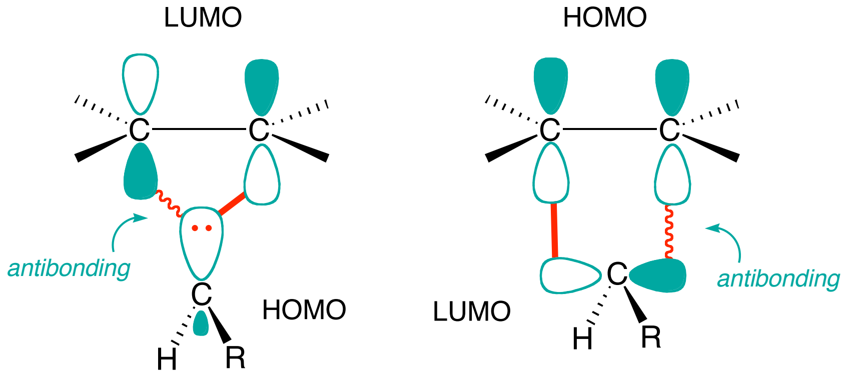
Carbenoids: Cyclopropanation

Carfbene–Olefin Cycloaddition: The FMO Analysis

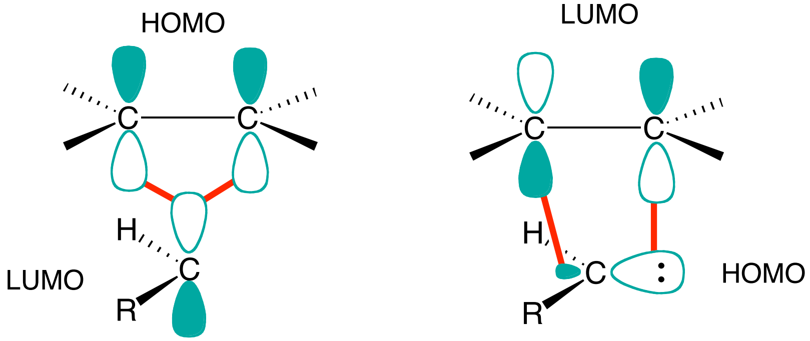
See discussion in Fleming pp 95–96



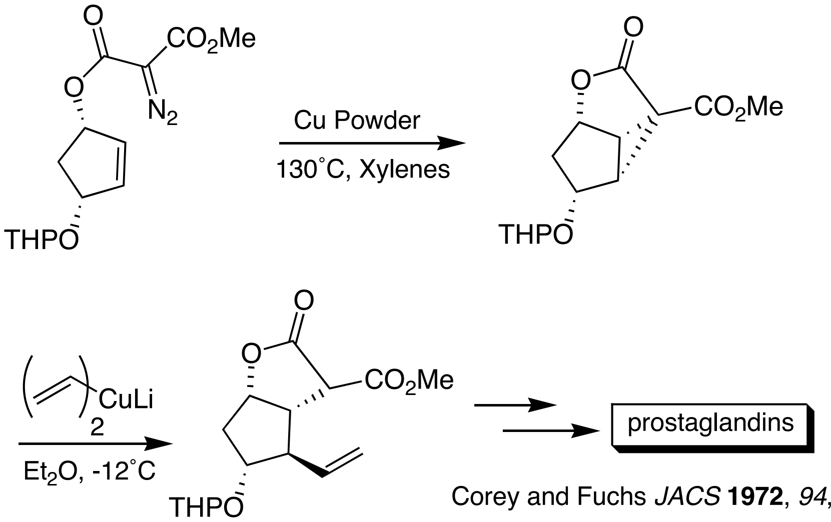
Linear Approach



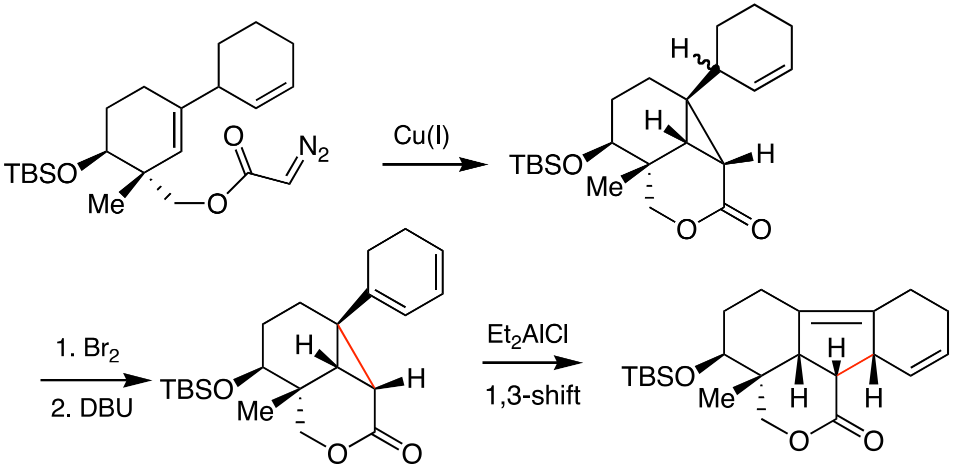
Non-linear Approach



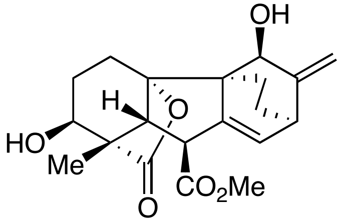
Synthetic Applications



Corey and Fuchs *JACS* **1972**, *94*, 4014.



Corey & Myers *JACS* **1985**, *107*, 5574.



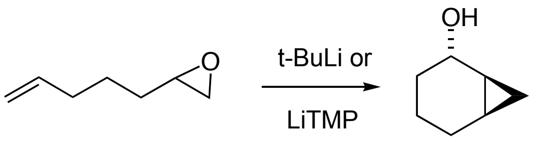
Antheridic Acid

Carbenoids: Cyclopropanation

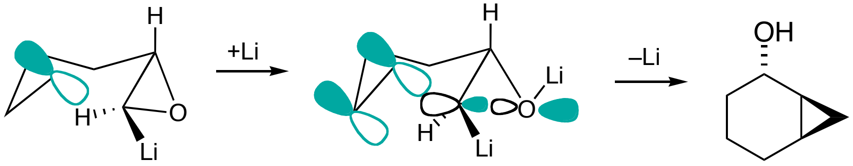
Carbenes from Epoxides

Hodgson and co-workers recently reported the highly diastereoselective cyclopropanation illustrated below (*JACS*, **2004**, *126*, 8664).

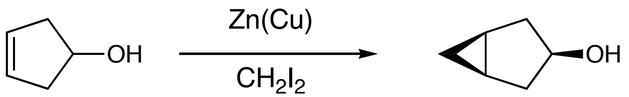
This intramolecular cyclopropanation appears to be general for five- as well as six-membered ring fomation.



65%, "single diastereomer"

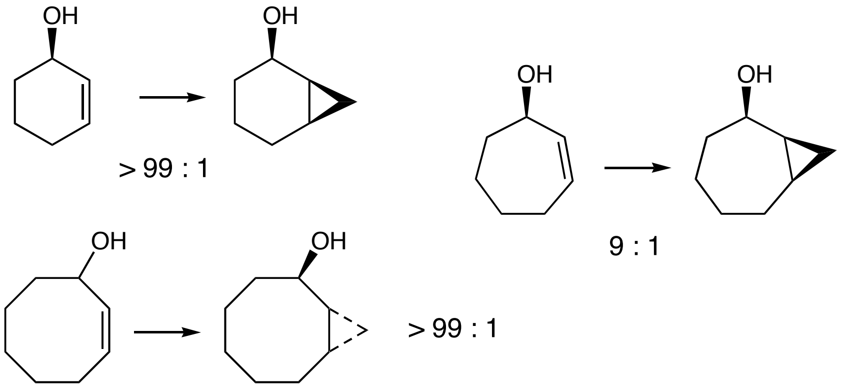


The Simmons-Smith Reaction



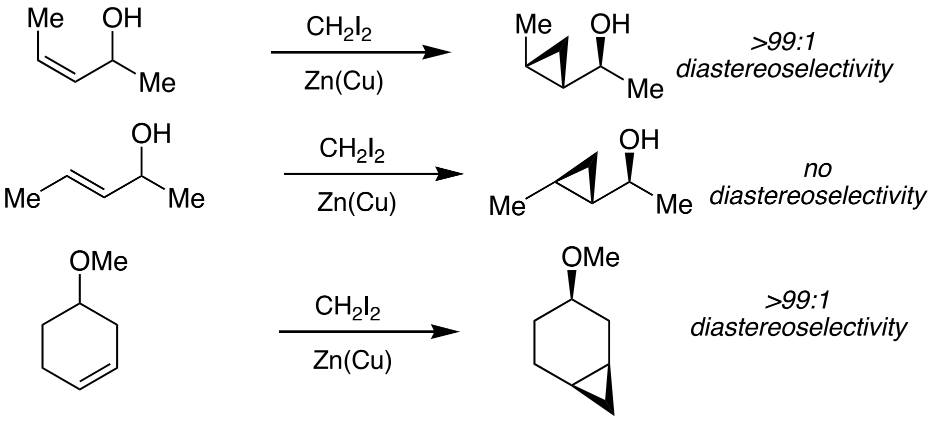
150:1 cis: trans
75% yield

Winstein et al.
JACS, **1961**, *91*,3235



Winstein, S. *JACS* **1969,** *91,* 6892

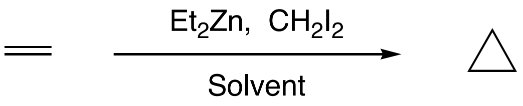
Hydroxyl directivity is a powerful atribute of the S–S Rxn


Me
OH
Me
CH_2I_2
Zn(Cu)
Me
OH
Me
>99:1 diastereoselectivity
OH
Me
Me
CH_2I_2
Zn(Cu)
OH
Me
Me
no diastereoselectivity
OMe
CH_2I_2
Zn(Cu)
OMe
>99:1 diastereoselectivity

For an review of the directed Simmons-Smith, see:
Evans, D. A.; Hoveyda, A.; Fu, G. *Chem. Rev.* **1993**, *93*, 1307.

The Furakawa Simmons-Smith Variant

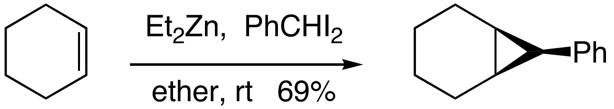
For a recent general review of the Simmons-Smith reaction see:
Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



$$\text{Et–Zn–Et} + \text{I–CH}_2\text{–I} \rightleftharpoons 2\ \text{I–CH}_2\text{–Zn–Et}$$

Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron,* **1968,** *24,* 53

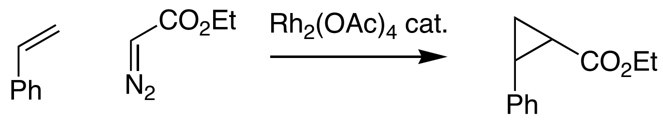
Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron,* **1970,** *26,* 243



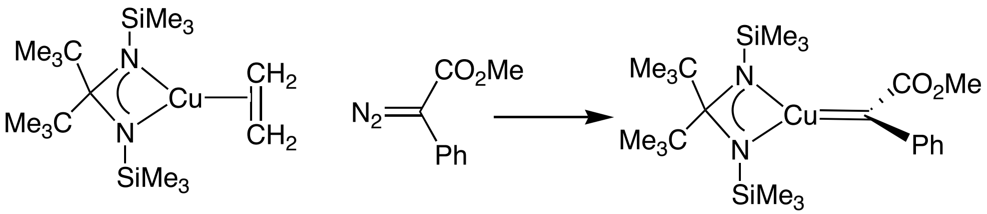
syn : anti
94 : 6

Carbenes: Enantioselective Cyclopropanation

Characterization of metal carbenoid intermediates: not much data!



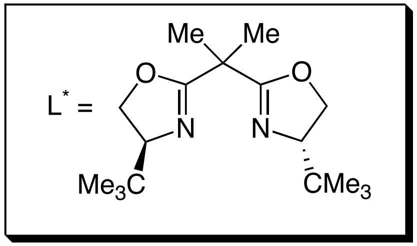
For a detailed mechanistic study which provides supporting evidence for the intermediacy of a Rh carbene, see: Kodakek, *Science*, **1992**, *256*, 1544.

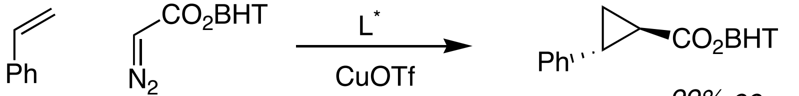


spectroscopically observed

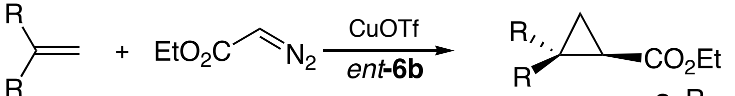
"Copper(I) Carbenes: The Synthesis of Active Intermediates inCu-Catalyzed Cyclopropanation" P. Hoffmann et al, *Angew. Chem. Int. Ed*. **2001**, *40*, 1288-1290

■ Catalytic Asymmetric Variants: Chiral Cu(I) Complexes





99% ee
94:6 trans/cis

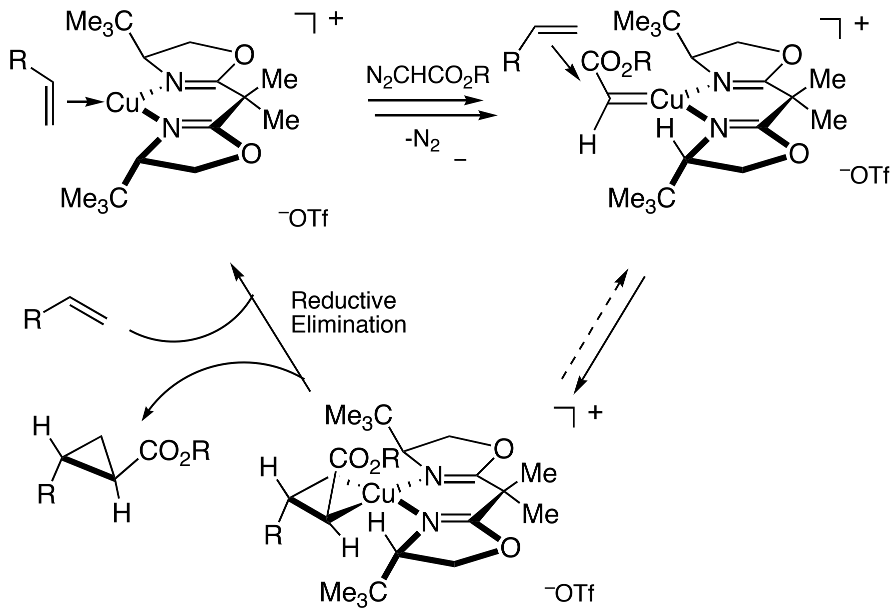


a, R = Ph, >99% ee
b, R = Me, >99% ee

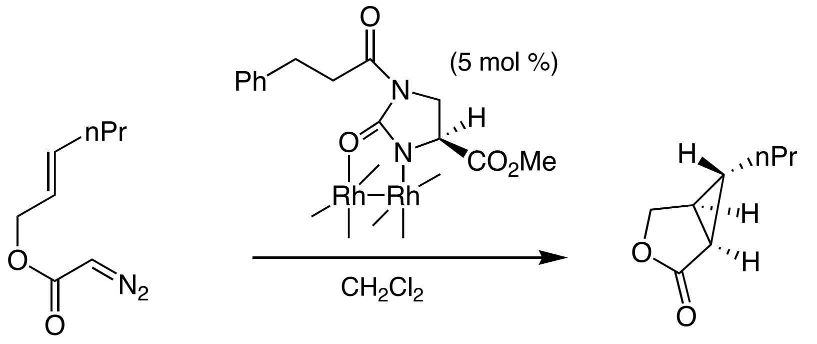
Evans, et al. *J. Am. Chem. Soc.* **1991**, *113*, 726.

■ Mechanism

There is no definitive evidence for metal-catalyzed cyclopropanation and the possibility that metallacyclobutane intermediates are involved cannot be ruled out.



■ Catalytic Asymmetric Variants:Chiral Rh(II) Complexes



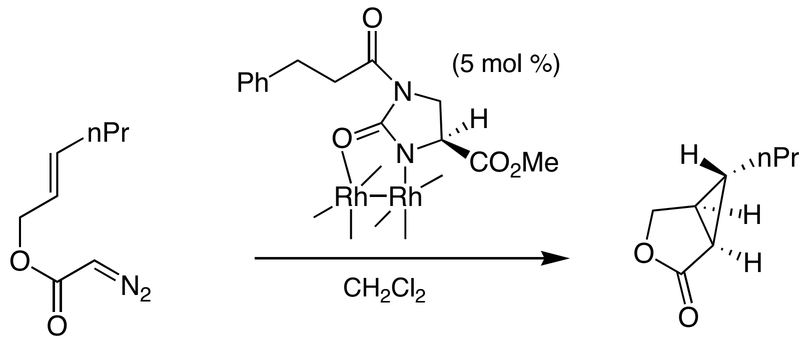
Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.

95% ee

How do these complexes really work??

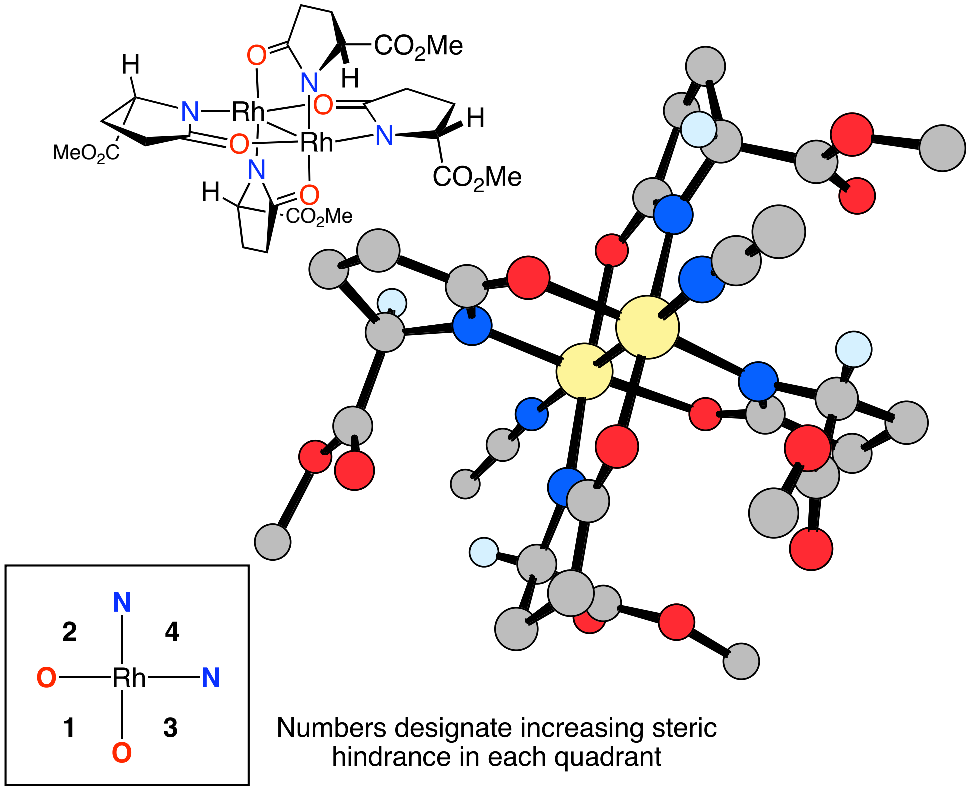
Carbenes: Enantioselective Cyclopropanation

Catalytic Asymmetric Variants: Chiral Rh(II) Complexes



95% ee

Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.



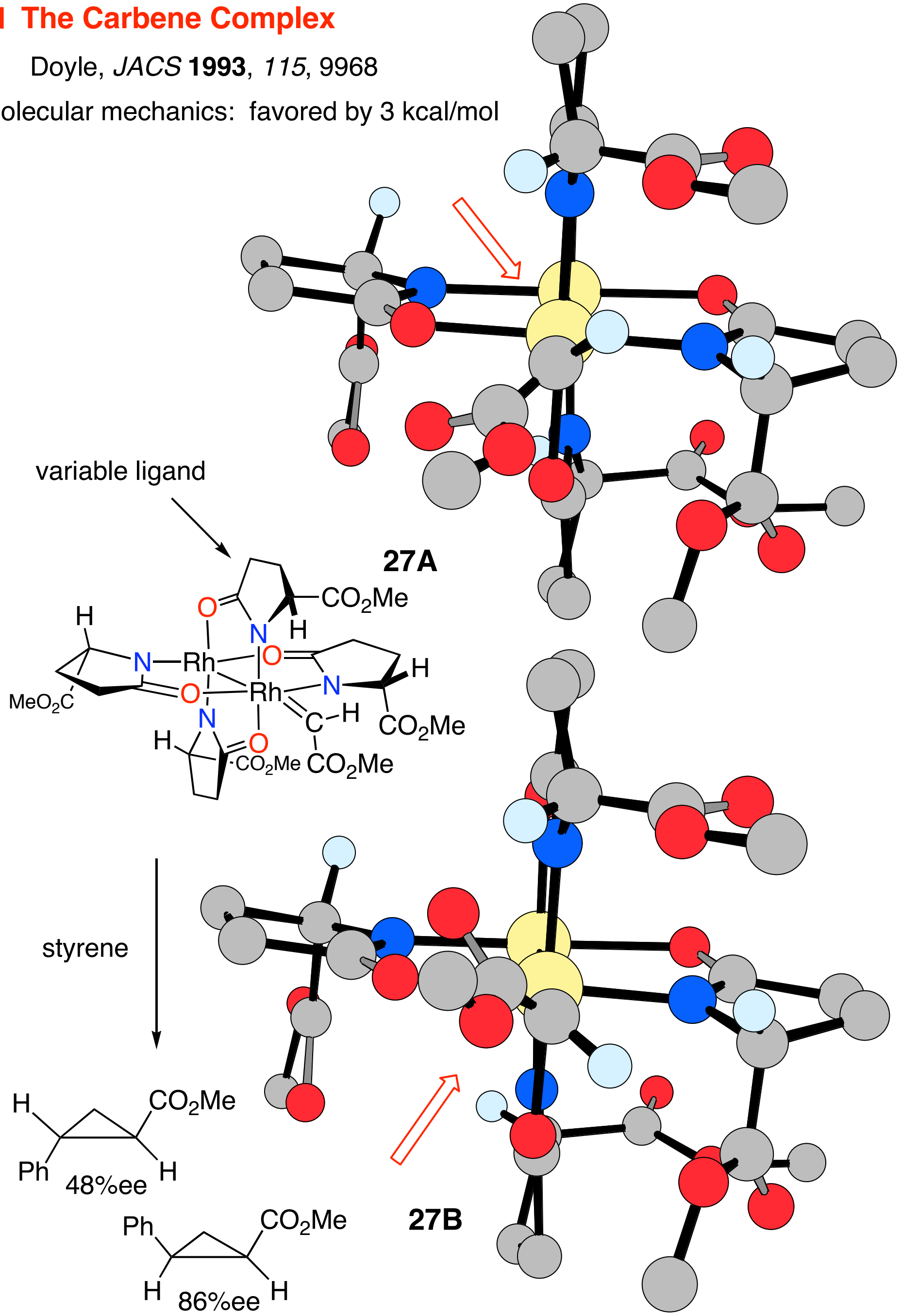
Numbers designate increasing steric hindrance in each quadrant

Doyle, *JACS* **1993**, *115*, 9968

The Carbene Complex

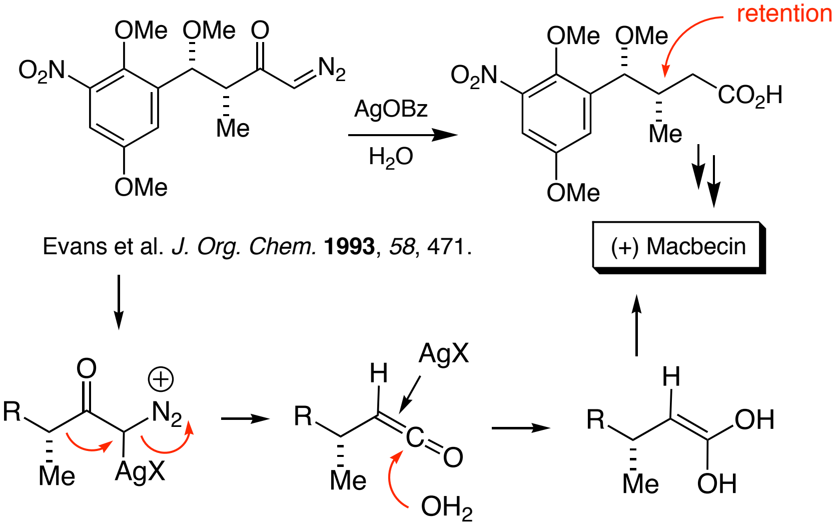
Doyle, *JACS* **1993**, *115*, 9968

Molecular mechanics: favored by 3 kcal/mol



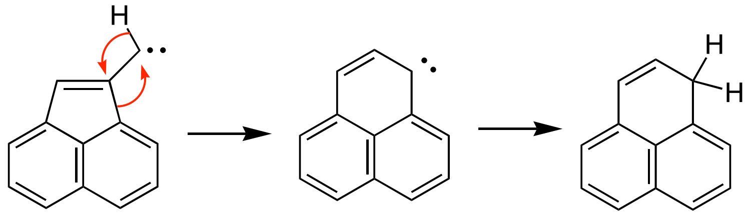
Carbenes: Rearrangements

Wolff Rearrangement



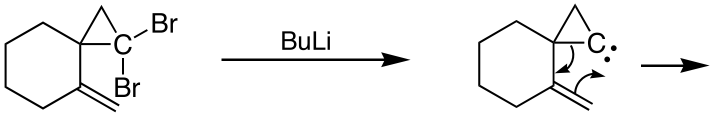
Evans et al. *J. Org. Chem.* **1993**, *58*, 471.

Carbene-Carbene Rearrangements

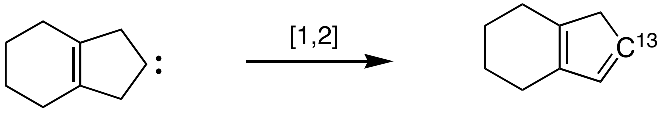


Wu, *Tetrahedron Lett.* **1973**, 3903.

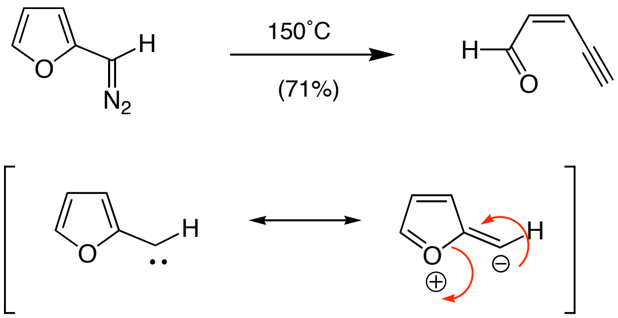
Skattebol Rearrangement



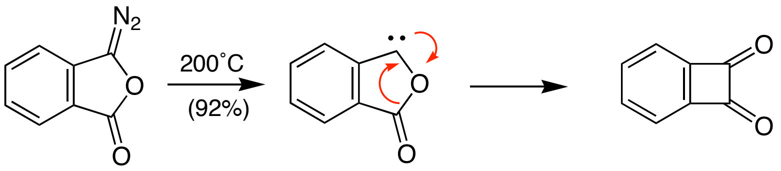
Tetrahedron Lett. **1973**, 2283.



Other Rearrangements



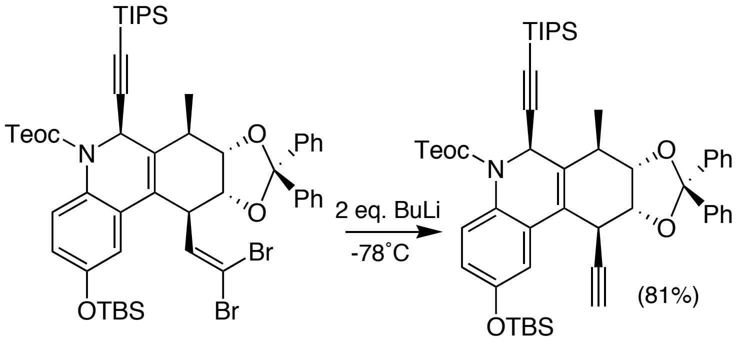
Schecter, *J. Am. Chem. Soc.* **1971**, *93*, 5940.

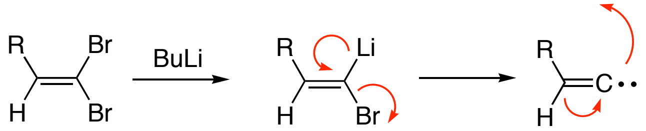


Sammes, *Chem. Comm.* **1975**, 328.

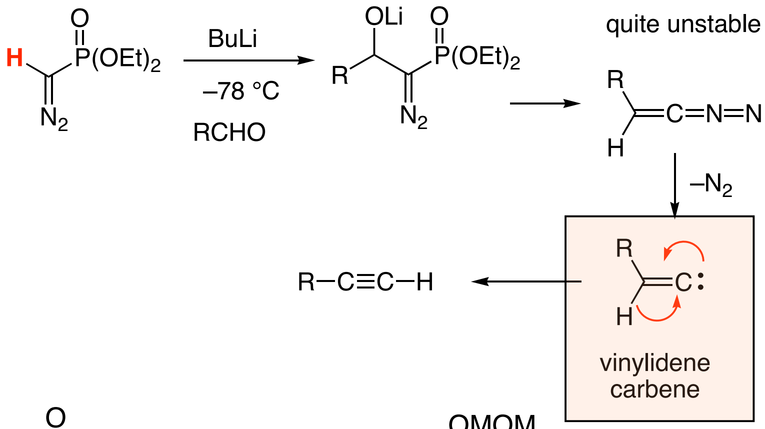
Vinylidenes

Corey-Fuchs: Danishefsky et al.
J. Am. Chem. Soc. **1996**, *118*, 9509.



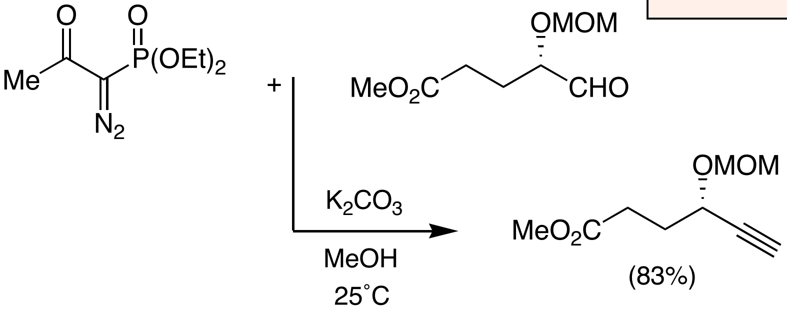


Carbene Rearrangements

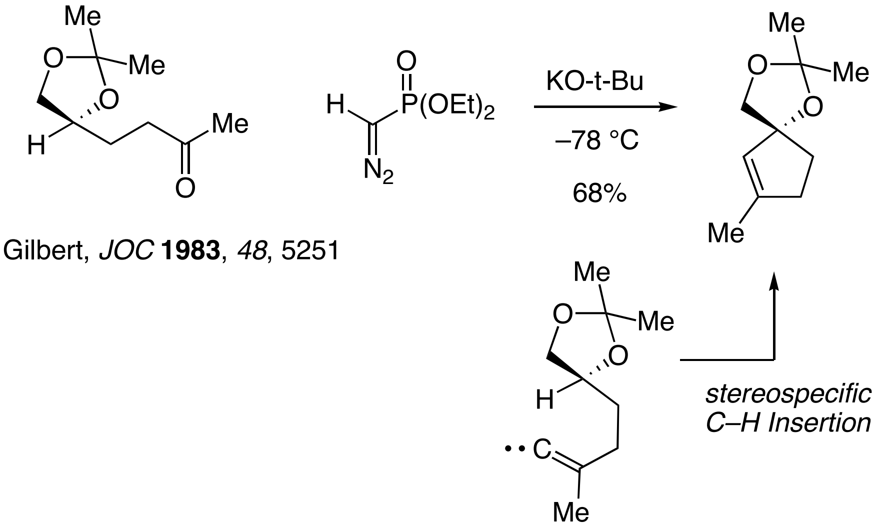


quite unstable

vinylidene carbene

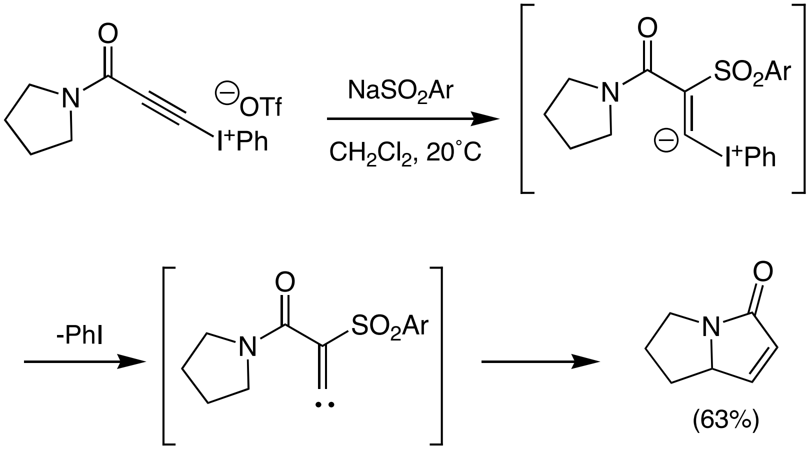


Bestmann, et al. *Synlett* **1996**, 521.



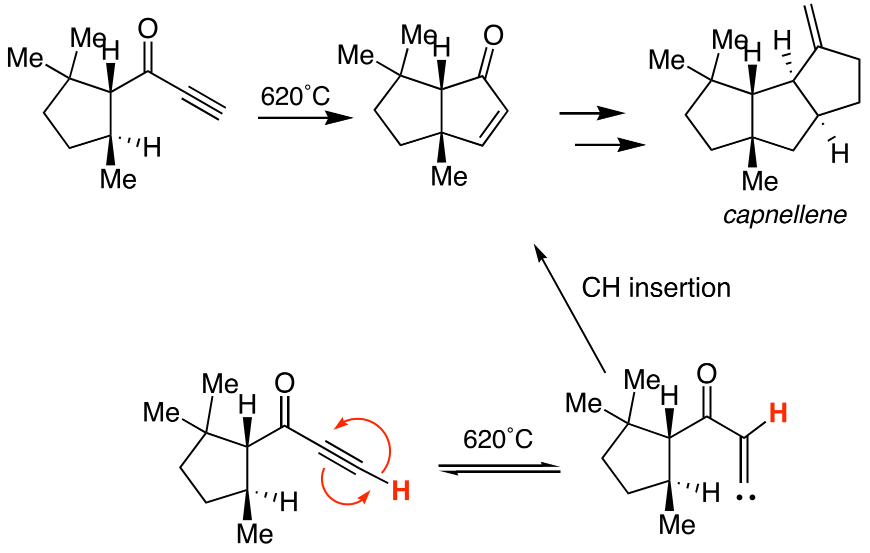
Gilbert, *JOC* **1983**, *48*, 5251

stereospecific C–H Insertion



Stang et al. *J. Am. Chem. Soc.* **1994**, *116*, 93.

carbene intermediates are accessible at high temperatures, more later!



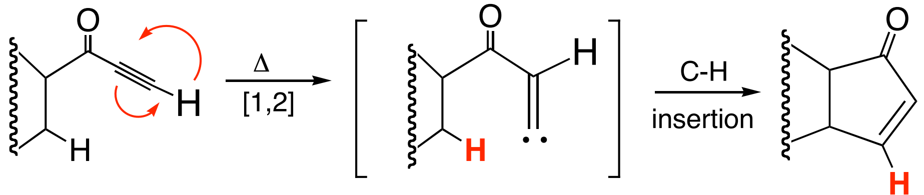
capnellene

CH insertion

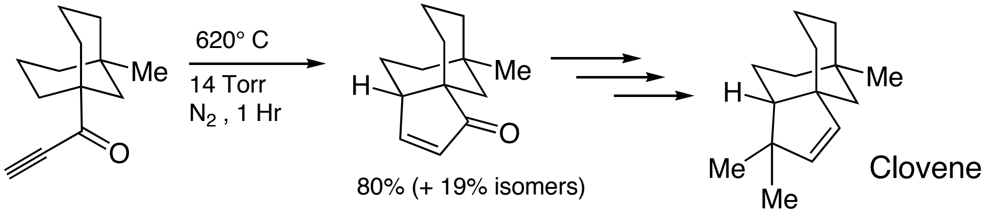
Thermal Generation of Carbene Intermediates

Carbenes are Accessible via Sigmatropic Rearrangement

[1,2] Shifts: Alpha-Alkynone Cyclizations



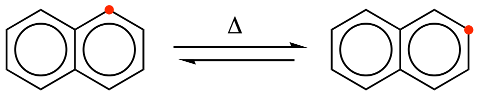
Conditions: 620° C, 12-16 Torr, Quartz filled Quartz Tube



Karpf, M., Dreiding, A.S., *Helv. Chim. Acta.* **67** 1963 (1984)

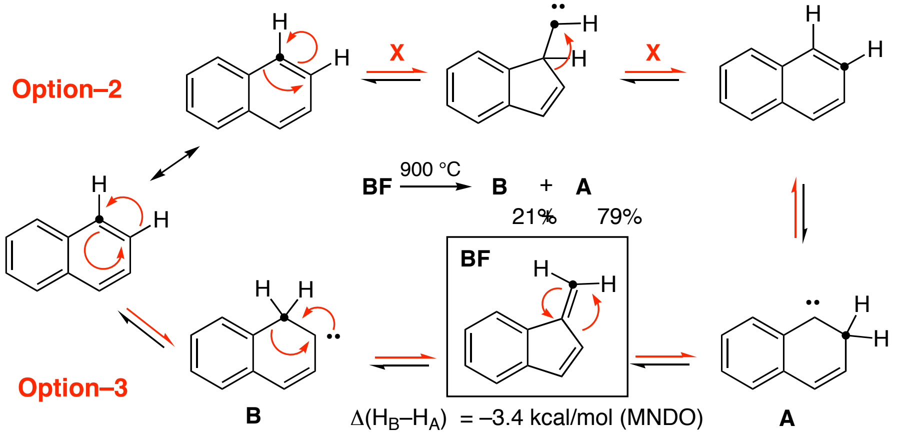
The Automerization of Naphthalene (The Cume Question from Hell!)

Rationalize

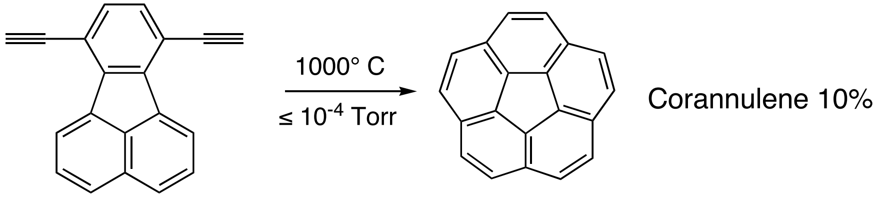


α–^{13}C-labeled $C_{10}H_8$ is isomerized into β–^{13}C-labeled $C_{10}H_8$ at 1035 °C

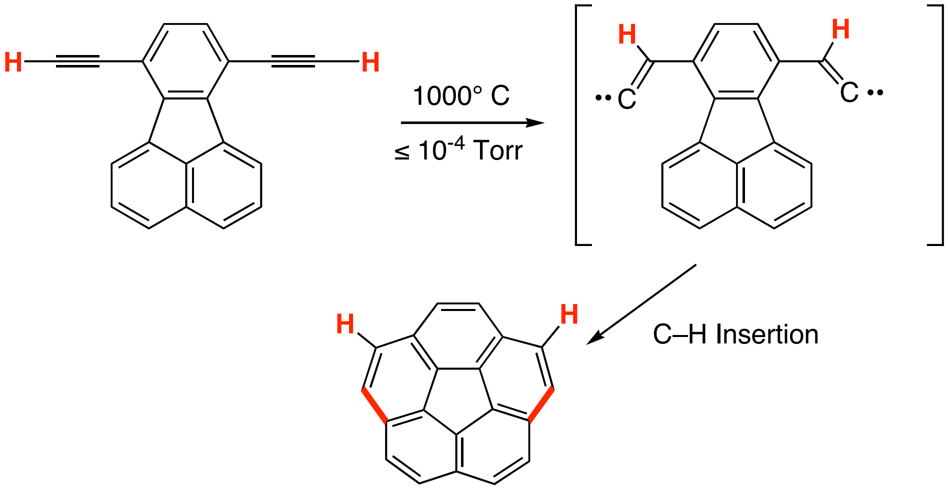
Mechanism-2,3: L. T. Scott, *JACS* **1991**, *113*, 9692.



Provide a Mechanism for this Transformation

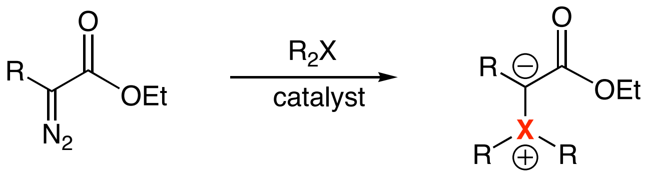


Scott, L.T., et. al., *JACS* **113** 7082 (1991)



Carbene Heteroatom Transformations: Sulfonium & Oxonium Ylids

Ylide Formation

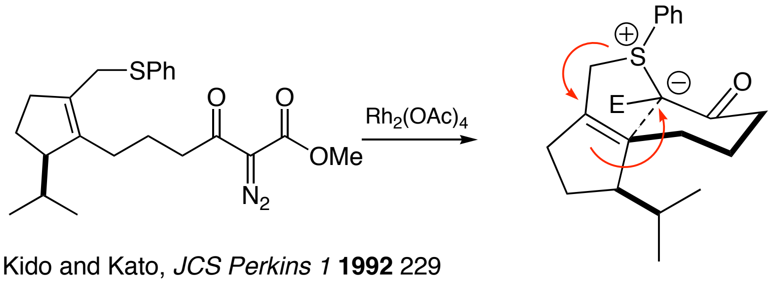


Reviews: Padwa, *Chem. Rev.* **1991** 263
Padwa, *Chem. Rev.* **1996** 223
Barnes, Evening Seminar, March 16, 1993

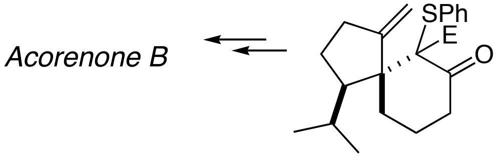
X is generally S, O or N and can be sp^2 or sp^3 hybridized

Ylides often undergo sigmatropic rearrangements or cycloadditions

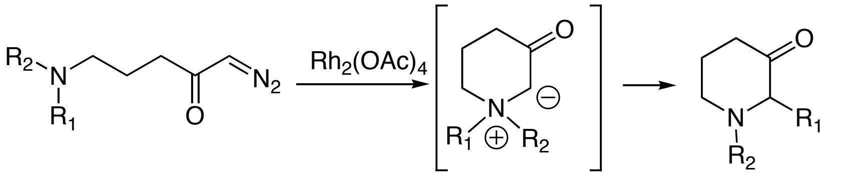
[2,3]-Sigmatropic rearrangement:



Kido and Kato, *JCS Perkins 1* **1992** 229



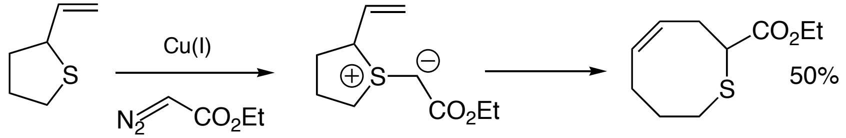
Stevens Rearrangement ([1,2] alkyl shift):

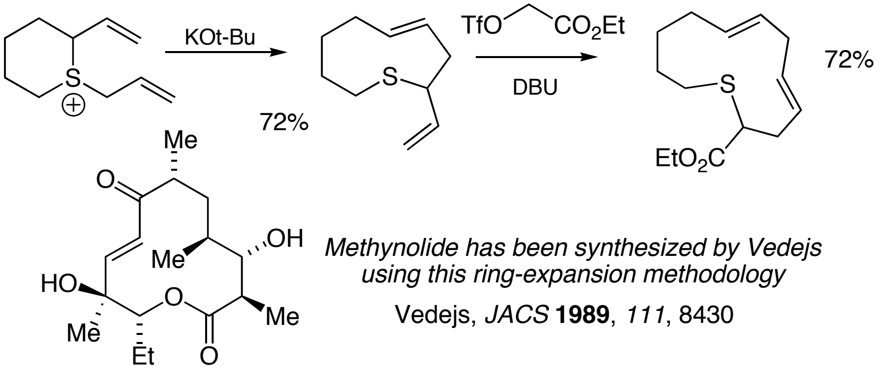


West, *JACS* **1993** 1177

Ring expansion reactions have been investigated

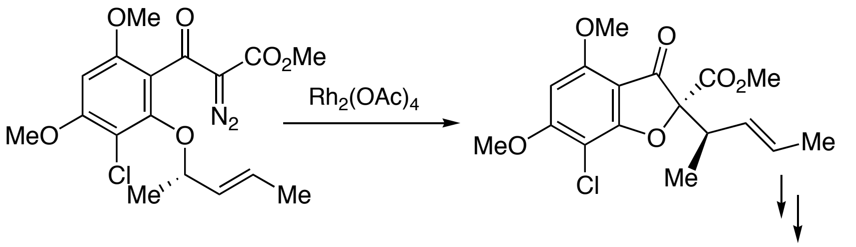
Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358



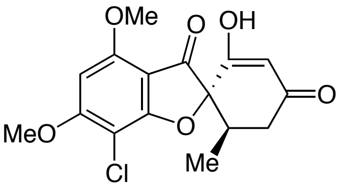


Methynolide has been synthesized by Vedejs using this ring-expansion methodology

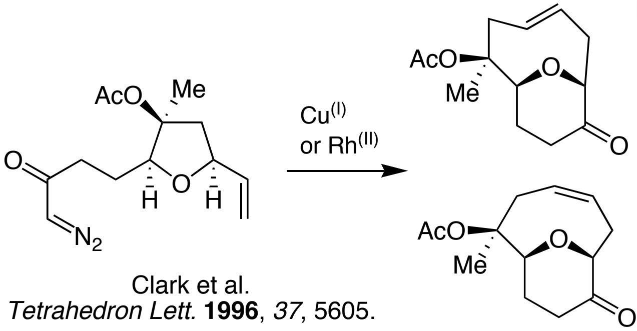
Vedejs, *JACS* **1989**, *111*, 8430



Pirrung et al *JACS*, **1991**, *113*, 8561.



griseofulvin



Clark et al.
Tetrahedron Lett. **1996**, *37*, 5605.

Carbonyl Ylids: Dipolar Cycloaddition

Carbenes: Reaction with Heteroatoms

Suggested Reading

Houk and Wu *J. Org. Chem.* **1991**, *56*, 5657.

Padwa and Hornbuckle *Chem. Rev.* **1991**, *91*, 263.

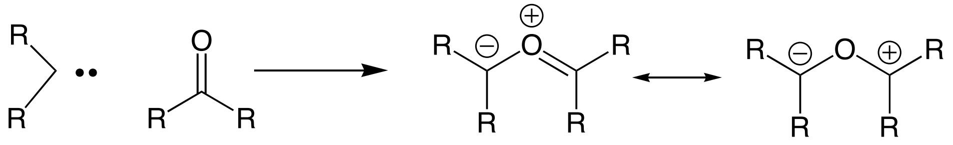
Review Articles

Padwa and Krumpe *Tetrahedron* **1992**, *48*, 5385.

Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563.

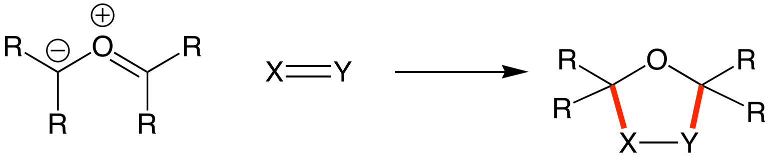
McKervey et al. *Chem. Rev.* **1994**, *94*, 1091.

Ylide Formation by the Interaction of Carbeneoids with Carbonyl Lone Pairs

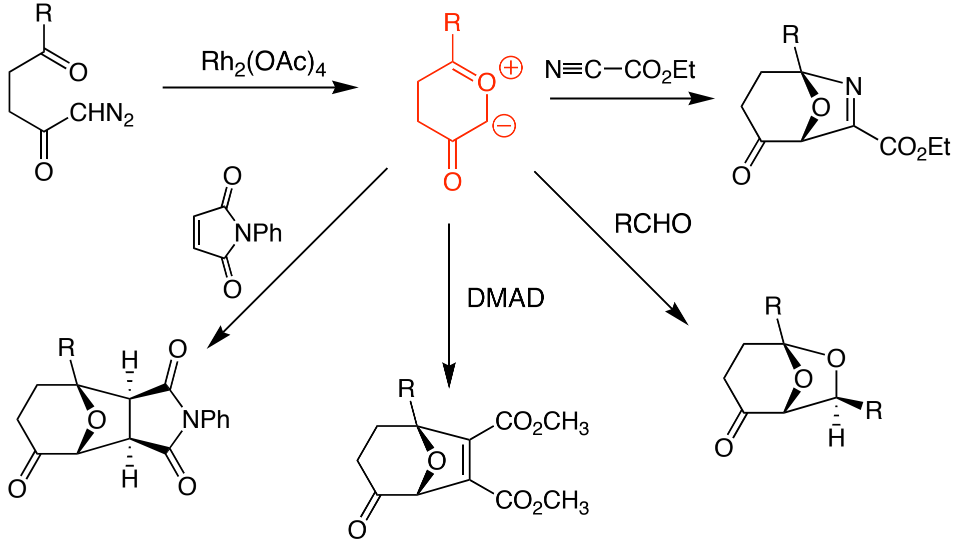


Generally, the carbene precursor of choice is a diazoalkane or, more frequently, an α-diazocarbonyl reagent. These can be decomposed via thermolysis or photolysis. However, the most common method involves catalytic amounts of transition metals, such as copper or rhodium.

Dipolar Cycloaddition (See Lecture 18)

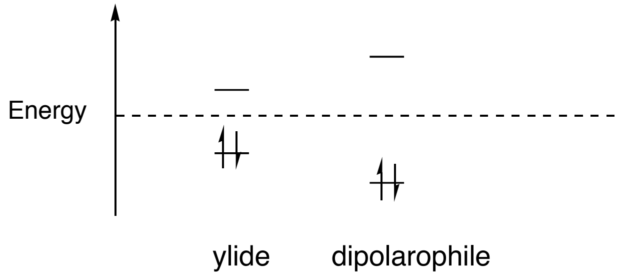


Tandem Intramolecular Cyclization–Intermolecular Cycloaddition (Lecture 18)

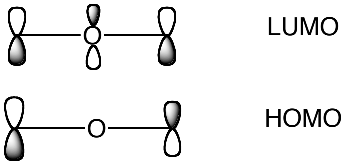


Dipolar-Dipolarophile Cycloadditions: HOMO–LUMO Energies

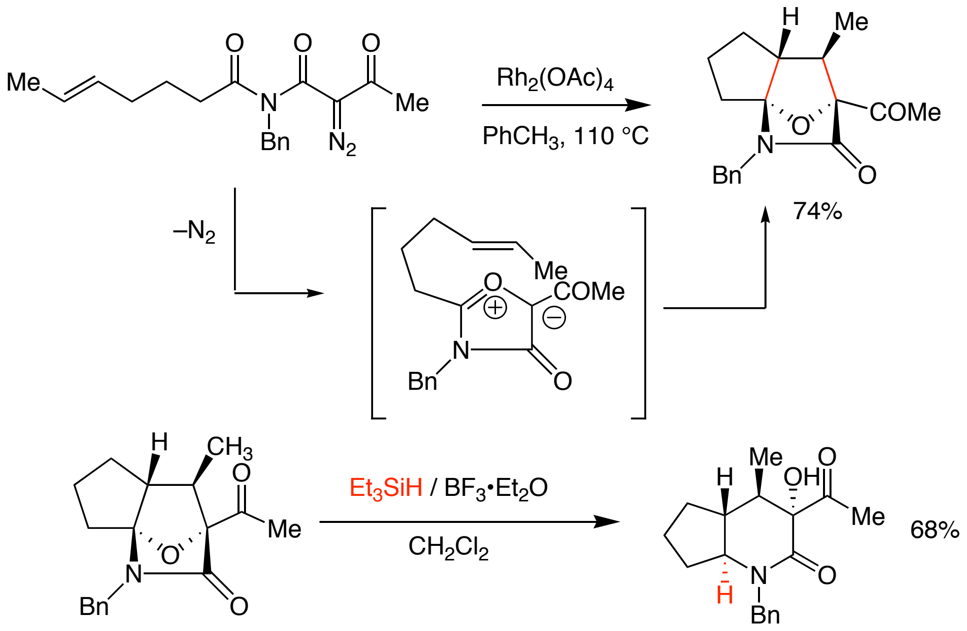
Carbonyl Ylides have very small HOMO-LUMO gaps



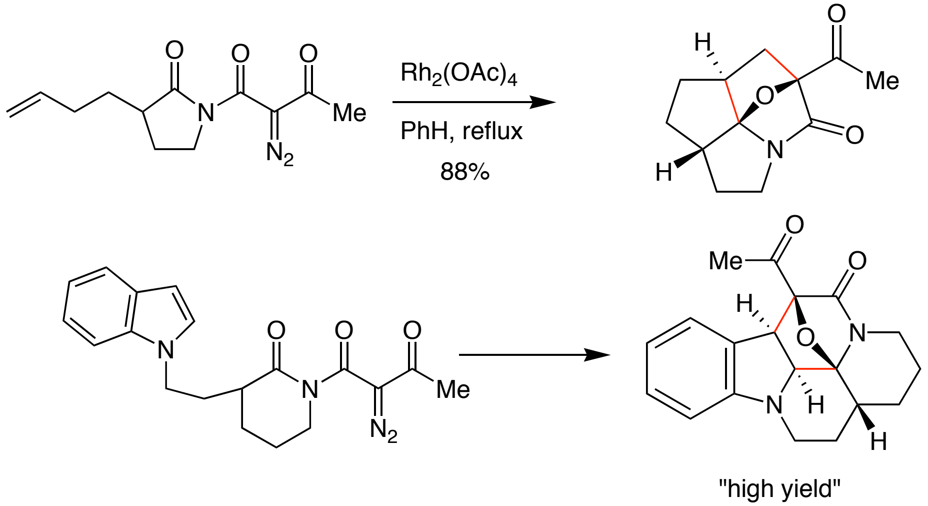
Therefore, either raising the dipolarophile HOMO (electron-donating substituents) or lowering the LUMO (electron-withdrawing) will accelerate the reaction.



Reactions of Diazoimides: [3+2] addition

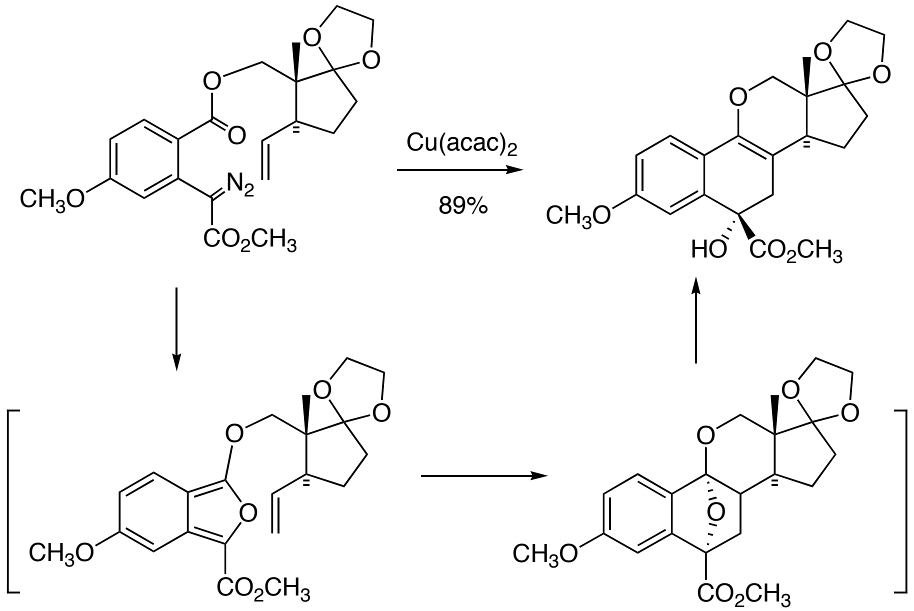


Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677-1680.

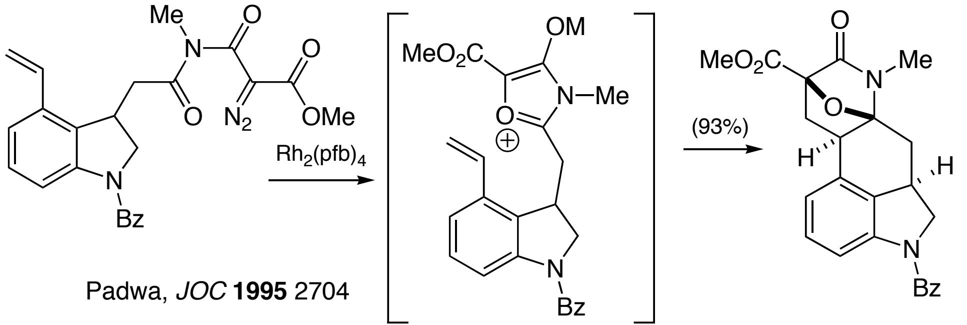


Padwa et. al. *Tetrahedron Lett.* **1992**, *33*, 4731-4734.

Can you propose a rational mechanism for this transformation?



Hildebrandt, *Tetrahedron Lett.* **1988**, *29*, 2045-2046.

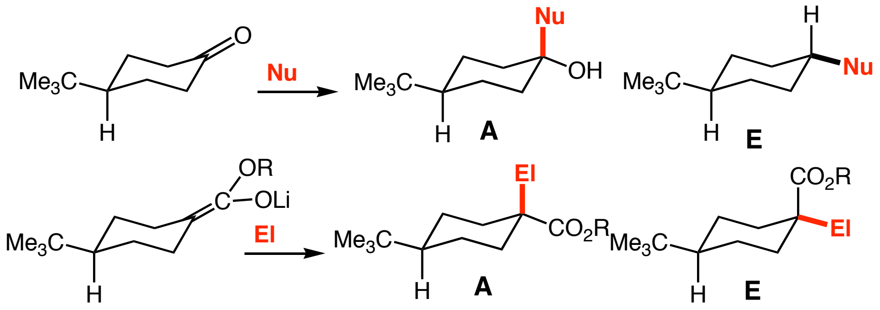


Padwa, *JOC* **1995** 2704

Lysergic Acid Skeleton

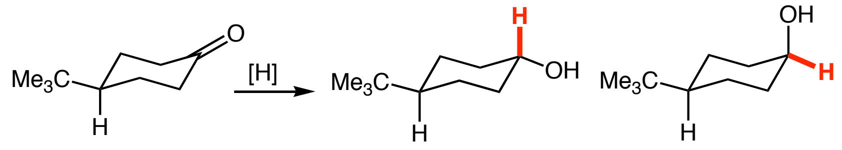
Stereochemical Trends in C=O Addition

Stereoselective Additons: A Measure of Steric Effects

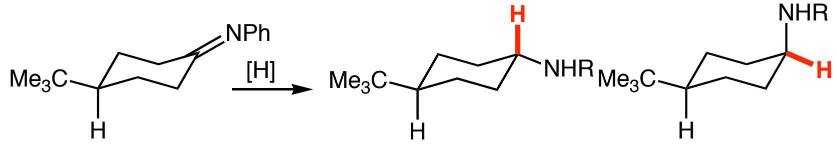


The Trend Increasingly bulky reagents (El or Nu) prefer to attack from the equatorial C=O face to afford **E**.

Stereoselective Reductions; A Good Illustration



Reagent	Ratio	Control Element
$KBH(s\text{-}Bu)_3$	03 : 97	Steric Efects
Li in NH_3	99 : 01	Torsional Efects

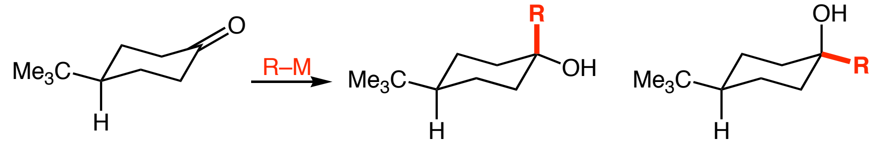


Ganem, *Tet. Let* **1981**, *22*, 3447
Hutchins, *JOC* **1983**, *48*, 3412
private communication

(R)	Reagent	Ratio
R = Bn	$LiBH(s\text{-}Bu)_3$	03 :97
R = Ph	$LiBH(s\text{-}Bu)_3$	01 :99
	Al/Hg/MeOH	~90 :10

Stereoselective Organometallic Addition Reactions:

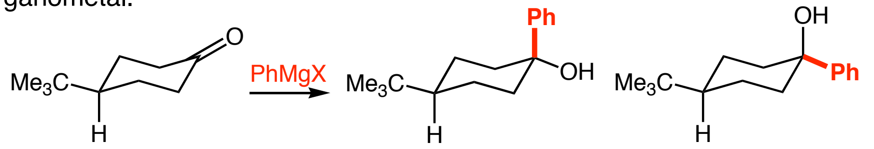
As the cases below indicate, reaction diastereoselection is strongly coupled to the steric requirements of the organometallic reagent

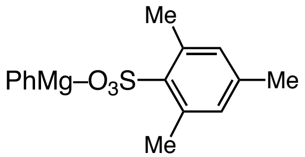


Ashby, *Chem. Rev.* **1975**, *75*, 521

Reagent	Ratio	Control Element
HC≡C-Li	88 : 12	Torsional Efects
Et–MgBr	53 : 47	
Me_2CH–MgBr	18 : 82	
Me_3C–MgBr	0 : 100	Steric Efects

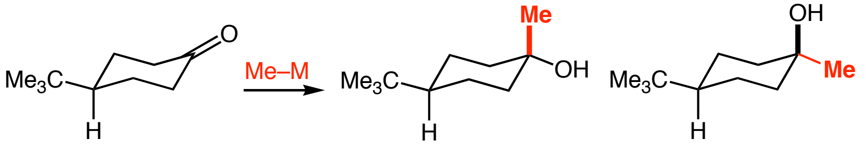
One can enhance C=O face selectivity by modifying the ligands on a given organometal.



PhMg–Br	51%	49%
PhMg–OTf	27%	73%
PhMg–OTs	15%	85%
 PhMg–O_3S–	10%	90%

Reetz, *Angew. chem. Int. Ed.* **1992**, *31*, 343

One can also enhance C=O face selectivity by changing the organometal.



Me–Li	35%	65%
Me–Ti(OiPr)$_3$	6%	94%
Yb(OYf)$_3$ + Me–Li	18%	82%

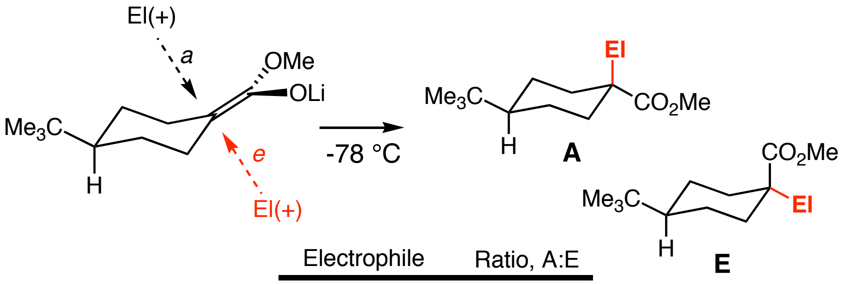
(Yb) Molander, *J. Org. Chem.* **1990**, *55*, 4990

(Ti) Reetz, *Tetrahedron* **1986**, *42*, 2931

(Mn) Reetz, *Tet. Let.* **1992**, *33*, 6963

Stereoselective Enolate Alkylations

Steric Effects In this case, both **E** and **A** paths are stereoelectronically equivalent. Diastereoselectivity is now determined by the differential steric effects encountered in the two TS‡s.

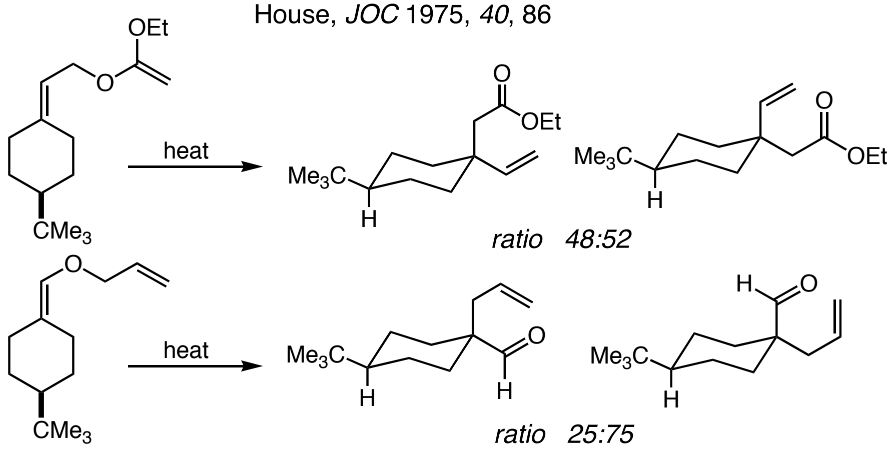


Electrophile	Ratio, A:E
Me-I	16:84
n-Bu-Br	13:87

By inspection, steric effects appear to be the dominant control element in these reactions.

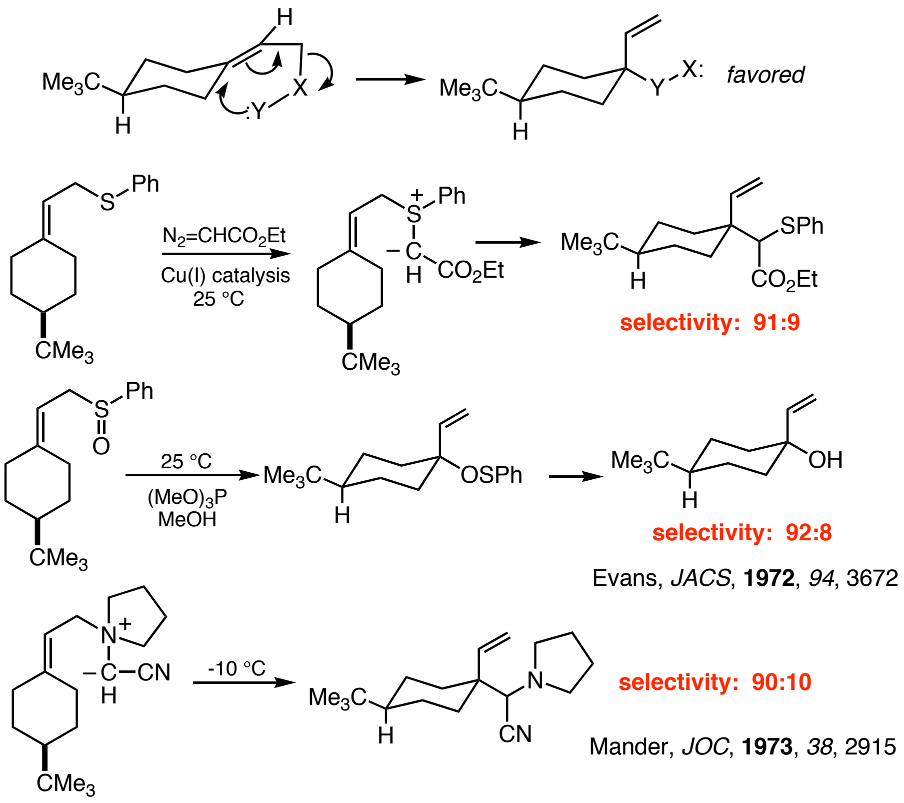
Steric effects in [3,3] Sigmatropic Rearrangements

House, *JOC* 1975, *40*, 86



For exoocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack."

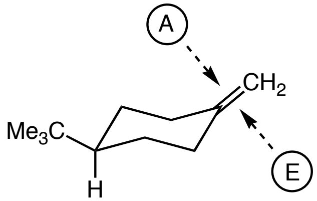
Steric effects in [2,3] Sigmatropic Rearrangements



Evans, *JACS*, **1972**, *94*, 3672

Mander, *JOC*, **1973**, *38*, 2915

Response to steric effects in Hydroboration and Epoxidation



Oxidant	Ratio, A:E	Reference
MCPBA	69:31	*JOC*, **1967**, *32*, 1363
BH_3, H_2O_2	34:66	*JOC*, **1970**, *35*, 2654

Chemistry 206

Advanced Organic Chemistry

Handout–27A

An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships

D. A. Evans

Wednesday ,
November 19, 2003

An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships

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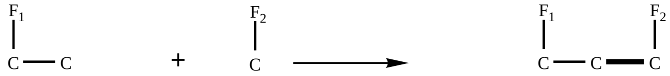
Introduction

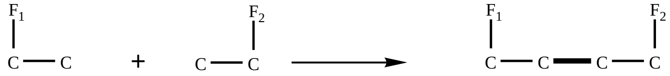
Among the subdisciplines of chemistry the area of organic synthesis is probably the least organized in terms of unifying concepts and general methodology. This conclusion has been made quite obvious by the relative scarcity of critical monographs covering this important topic.[1] The wide structural diversity of organic molecules, the vast abundance of organic reactions, and the restrictions imposed upon these reactions when applied to the synthesis of a complex structure all contribute to the magnitude of the problem of making generalizations in this area.

However difficult the overall task of explicitly defining *a priori* a total synthesis of an organic structure may be, there are certain simplifying features which can be developed to generate logical sets of potential synthetic pathways to a given molecular target . Some of the general guidelines which help to define this task have been outlined.[2] Recently, some of the problems associated with reducing synthetic design to a mathematical basis and the application of machine computation to synthetic analysis have been reported.[3,4]

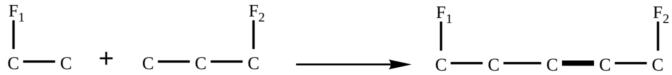
Difunctional Relationships. One aspect of the synthesis of any polyfunctional target structure deals with strategies associated with the construction of arrays of relationships between heteroatom functional groups which may be denoted as F_1, F_2, etc. The general reactions illustrated below simply represent the union of two monofunctional organic fragments where the functional groups F_1, F_2 provide the necessary activation for the coupling process. In these reactions, the oxidation states of the associated carbon fragments are purposely left undefined. In relating the generalized notation below to a real situation, if F_1-C-C were an enolate, Equation 1 might be used to represent a generalized aldol or Mannich reaction while equation 3 might represent a Michael reaction.



$$\overset{F_1}{\mathrm{C}}-\mathrm{C} + \overset{F_2}{\mathrm{C}} \longrightarrow \overset{F_1}{\mathrm{C}}-\mathrm{C}\boldsymbol{-}\overset{F_2}{\mathrm{C}} \quad (1)$$



$$\overset{F_1}{\mathrm{C}}-\mathrm{C} + \mathrm{C}-\overset{F_2}{\mathrm{C}} \longrightarrow \overset{F_1}{\mathrm{C}}-\mathrm{C}\boldsymbol{-}\mathrm{C}-\overset{F_2}{\mathrm{C}} \quad (2)$$



$$\overset{F_1}{\mathrm{C}}-\mathrm{C} + \mathrm{C}-\mathrm{C}-\overset{F_2}{\mathrm{C}} \longrightarrow \overset{F_1}{\mathrm{C}}-\mathrm{C}-\mathrm{C}\boldsymbol{-}\mathrm{C}-\overset{F_2}{\mathrm{C}} \quad (3)$$

Henrickson has provided some useful generalizations on the construction of difunctional relationships which are worth summarizing. For example, he defines the **construction span** as the number of carbons linking F_1 and F_2. In the cases illustrated above, the product of the reaction illustrated in Equation 1 has a construction span of three. The **construction fragments** are then defined as the monofunctional reactants, such as F_1-C-C and F_1-C. *In general, construction spans are limited to six or less.* This is a consequence of the fact that the operational utility of a given functional group diminishes as it is removed from the C-C bond being formed. The problem of site or ambident reactivity in systems possessing extended conjugation is the principal liability in the extension of the construction span. This point is illustrated below for both conjugate addition and enolate alkylation (Scheme I).

---

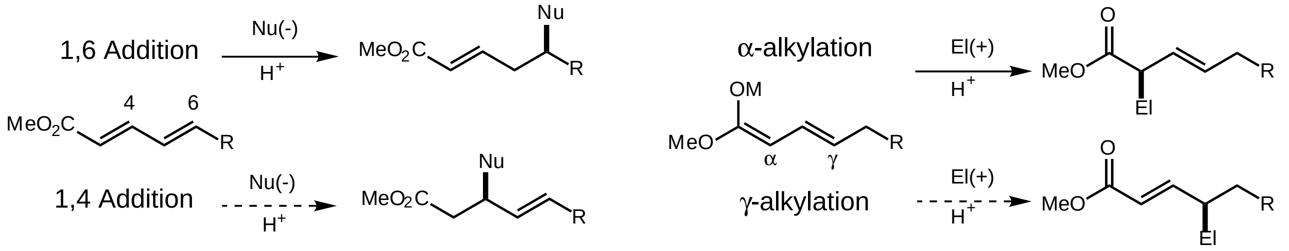
[1] (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley, New York, 1979. (b) Fuhrhop, J.; Penzlin, G. *Organic Synthesis: Concepts, Methods, Startimg Materials*; Verlag Chemie, Weinheim, 1983. (c) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3nd ed.; Cambridge Univ. Press, Cambridge, 1987. (d) *Organic Synthesis, The Disconnection Approach*; Wiley, New York, 1982. (e) Payne, C. A.; Payne, L.B. *How To Do An Organic Synthesis*; Allyn and Bacon., Boston, 1969. (f) Ireland, R. E. *Organic Synthesis*, Prentice-Hall, Inc., Englewood Cliffs, 1969.

[2] (a) Corey, E. J. *Pure Appl. Chem.* **1967**, *14*, 19. (b) Corey, E. J. *Quart. Rev.* **1971**, *25*, 455.

[3] (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 6487. (b) Ugi, I; Gillespie, P. *Angew. Chem. Int. Ed.* **1971**, *10*, 914. (c) Corey, E. J.; Wipke, W. T.; Cramer, III, R. D.; Howe, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 421. (d) Corey, E. J.; Cramer, III, R. D.; Howe, W. J. *ibid.* **1972**, *94*, 440, and earlier references cited therein. (e) Corey, E. J.; Howe, W. J.; Pensak, D. A. *ibid.* **1974**, *96*, 7724. (f) Blair, J.; Gasteiger, J.; Gillespie, C.; Gillespie, P. D.; Ugi, I. *Tetrahedron* **1974**, *30*, 1845. (g) Bersohn, M. *J. Chem. Soc., Perkin I* **1973**, 1239.

[4] (a) Thakkar, A. J. *Fortschritte Chem. Forschung* **1973**, *39*, 3. (b) Dungundji, J.; Ugi, I. *ibid.* **1973**, *39*, 19. (c) Gelernter, H.; Sridharan, N. S.; Hart, A. J.; Yen, S. C.; Fowler, F. W.; Shue, J.-J. *ibid.* **1973**, *41*, 113.

Scheme I The Problem of Ambident Reactivity



The objectives of the present discourse are to present an organizational format which can serve to correlate strategies for the construction simple pairwise functional group relationships. As a result of the overwhelming predisposition of nature to employ **polar** rather than **free radical** processes in the biosynthesis of organic compounds the chosen organizational format reflects this bias in reaction type. The designation of reactions as polar is recognized to be rather arbitrary since known reactions vary widely in their polar character, ranging from essentially nonpolar radical reactions and weakly polar electrocyclic reactions to strongly polar ionic processes. *Of primary concern in this discussion will be those reactions that involve charged species at some point along the reaction coordinate.*

Charge Affinity Patterns.

In order to describe an organizational model for the classification and synthesis of heteroatom-heteroatom (difunctional) relationships in organic molecules, two familiar ideas will be employed. The first is that in a given target molecule the various bonds can be ionically "disconnected" (eq 4, 5). That is, if the A-B bond could be cleaved heterolytically, the indicated set of polar fragments would result.

$$\mathrm{A{-}B} \Longrightarrow \mathrm{A{:}^{-}} \quad \mathrm{B^{+}} \qquad (4)$$

$$\mathrm{A{-}B} \Longrightarrow \mathrm{A{:}^{+}} \quad \mathrm{B{:}^{-}} \qquad (5)$$

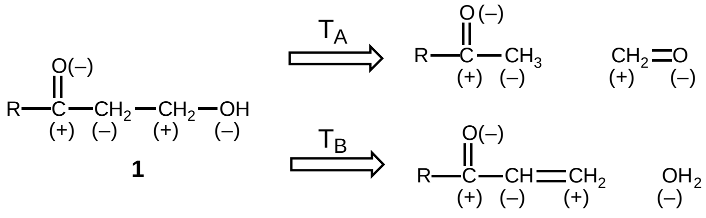
This antithetic process suggests ionic precursors suitable for the construction of the target molecule *via* polar coupling processes. *The second well accepted idea is that functional groups determine site reactivities on a carbon skeleton based upon known reactions.* That is, the oxygen atom in both acetone and anisole dictates the site reactivities that are displayed for each molecule with nucleophilic and electrophilic reagents. Thus, if the molecule A-B contained one or more functional groups proximal to the bond to be disconnected, one pair of ionic precursors, eq 6 or 7, would be strongly favored as plausible precursors. In such a case the favored ionic precursors to A-B could be symbolized with either (+) or (-) in the target molecule, e.g.[5]

$$\overset{(-)}{\mathrm{A}}{-}\overset{(+)}{\mathrm{B}} \Longrightarrow \mathrm{A{:}^{-}} \quad \mathrm{B^{+}} \qquad (6)$$

$$\overset{(+)}{\mathrm{A}}{-}\overset{(-)}{\mathrm{B}} \Longrightarrow \mathrm{A{:}^{+}} \quad \mathrm{B{:}^{-}} \qquad (7)$$

As an example, two possible polar disconnections for ketone **1** are illustrated below. The parity labels in the target structure suggest plausible monofunctional precursors from which the target structure can be assembled by polar processes. It is also evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

cheme II Polar Disconnections and Charge Affinity Pattterns



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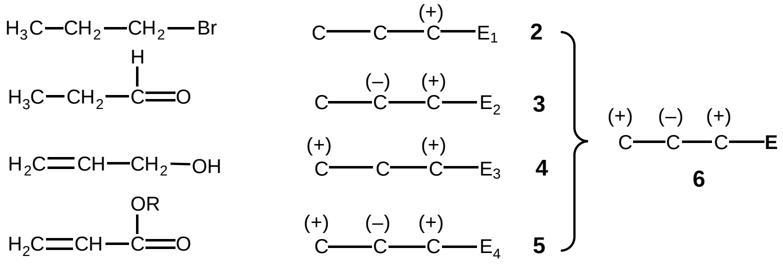
[5] The use of the symbols, (+) and (-), in no way represents formal positive or negative charges and will always be bracketed to denote this distinction. Other forms of notation have been considered such as (0) and (1) to denote a potential site of electrophilicity or nucleophilicity; however, the chosen symbols convey more direct information to the organic chemist.

For any given atom or heteroatom assemblage which is defined as a functional group linked to a carbon skeleton, the parity labels, (+) and (-), may be employed to denote the positional polar site reactivity, or ***charge affinity pattern*** *which the functional group confers upon the carbon framework.* For the simple molecules shown below (Scheme III) containing a homogeneous set of activating functions, E, there are associated charge affinity patterns **2 - 5** of which each is a sub-pattern of the generalized structure **6**. Note that the carbonyl function is defined as =O rather that C=O in this discussion. You might contemplate why this functional group is defined in this fashion.

Scheme III Charge Affinity Patterns of Common Functional Groups

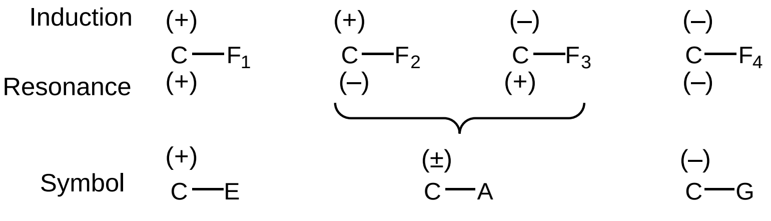


The notion that an organic structure can be viewed as an "ion assemblage" has an interesting history originating with the work of Lapworth and others.[6,7] Although the ion assemblage viewpoint was developed historically to predict site reactivity in both aliphatic and aromatic systems, this description of an organic structure is equally instructive in defining rational sets of synthetic pathways for a given target structure employing heterolytic processes as the primary set of coupling reactions. Indeed, the thought processes associated with the construction of organic molecules operate intuitively to recognize many subunits of a given structure in terms of polar fragments. The present use of parity labels to denote viable polar fragments simply formalizes this intuition.

Classification of Functional Groups (FG).

In order to organize general strategies that have been developed to construct heteroatom-heteroatom relationships from monofunctional precursors it is useful to develop a self-consistent classification scheme for single functional groups (FG) based on the concepts of polar disconnection and conferred site reactivity towards nucleophiles and electrophiles. The proposed scheme recognizes the dominate inductive and resonance components of various substituents and establishes[8] broad categories for activating functions which correlate similar conferred chemical properties to carbon.[9] Four possible functional group categories (F_1-F_4) are shown below. Those FGs which are *more electronegative than carbon* provide inductive activation defining the electrophilic potential at the point of attachment denoted as (+). In a complementary fashion, FGs which are *less electronegative than carbon* provide inductive activation creating nucleophilic potential at the point of attachment denoted as (–). Since FG activation through induction and resonance are independent variables which contribute to the overall FG reactivity pattern, four possible classes of functional groups can be defined (Scheme IV). This discussion is reminiscent of the classification of FGs according to their impact on electrophilic aromatic substitution.[10]

Scheme IV Classification of Functional Groups



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6) (a) Lapworth, A. *Mem. Proc. Manchester Lit. Phil. Soc.* **1920**, *64*, 1. (b) Lapworth, A. *J. Chem. Soc.* **1922**, *121*, 416. (c) Lapworth, A. *Chem. Ind.* **1924**, *43*, 1294. (d) Lapworth, A. *ibid.* **1925**, *44*, 397. For an excellent review of Arthur Lapworth's contributions to chemistry see: Saltzman, M. *J. Chem. Ed.* **1972**, *49*, 750-753.

7) (a) Vorländer, D. *Chem. Ber.* **1919**, *52B*, 263. (b) Stieglitz, J. *J. Am. Chem. Soc.* **1922**, *44*, 1293.

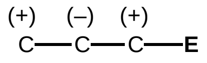
8) See reference 3c for an alternate classification scheme for functional groups.

9) For an analysis of the relative importance of field and resonance components of substitutent effects see: Swain, C. G.; Lupton, Jr., E. C. *J. Am. Chem. Soc.* **1968**, *90*, 4328.

10) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 507-512.

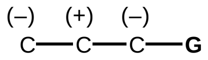
E & G-Functions. From the preceding discussion, one might opt for the creation of four classes of functional groups; however, for the sake of simplicity, three FG class designations will be chosen. To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G,[11] having the charge affinity patterns denoted in **6** and **7** respectively. Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated potential site reactivity patterns towards both electrophilic and nucleophilic reagents. *Any functional groups whose reactivity pattern conforms to the ideal pattern or to a sub-pattern of these hypothetical functions will be thus classified as an E- or G-function respectively.* For example, the halogen and oxygen-based functional groups in four molecules illustrated in Scheme III may be classified as E-functions since their respective charge affinity patterns conform to a subset of the charge affinity pattern of the hypothetical E-function.

ypothetical E-function



6

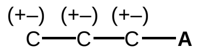
ypothetical G-function



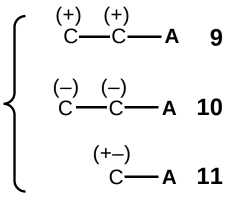
7

A-Functions. A third hypothetical function, A, (A for amphoteric!) can be defined which has an unbiased charge affinity pattern as in **8**. Such an idealized functional group activates all sites to both nucleophilic and electrophilic reactions and, as such, include those functions classified as either E or G. The importance of introducing this third class designation is that it includes those functional groups having non-alternate charge affinity patterns as in **9**, **10** and **11**.

ypothetical A-function

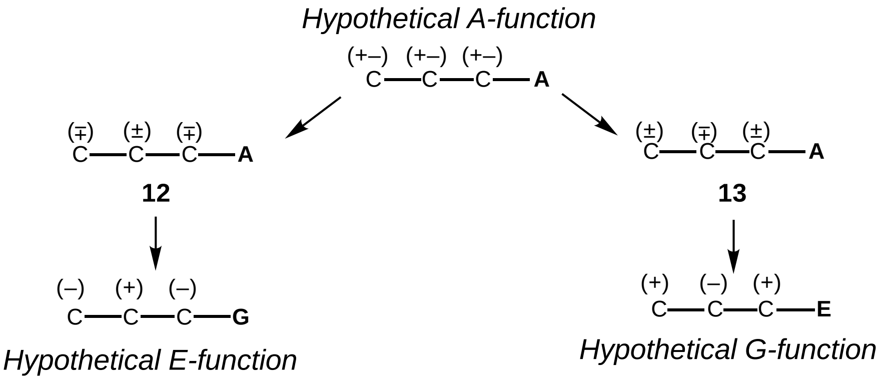


8



The differentiation of polar reactivity patterns can be described in an alternative manner. Starting with an ideal A-function, one could imagine a process in which the reactivity pattern is gradually polarized towards E- or G-behavior (Scheme V). Since site reactivity is not an on-off property but varies continuously over a wide range, one could further subdivide A-class functions into those functions with a bias towards E-class or G-class properties. Such a bias could be denoted by the dominant subordinate charge affinity notation in **12** and **13**; however, for the concepts to be presented in this discourse, such A-function subclasses are nonessential. It should be emphasized that the purpose of the E- and G-classification is not to rigidly pigeon-hole functional groups based on site reactivity, but only to separate those which are strongly polarized toward E or G behavior. The decision has been made to avoid the pursuit of an overly detailed FG classification scheme since such attempts will dangerously oversimplify problems since an essentially contiguous function cannot be segmented in to discrete parts.

Scheme V Alternate vs Nonalternate Reactivity Patterns



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[11] The symbol E was selected to denote *electrophilic* at the point of attachment to the carbon skeleton Unfortunately, the symbol N cannot be used to represent those FGs which are *nucleophilic* at the point of attachment since this is also the symbol for nitrogen. To avoid this conflict, the symbol G was chosen for this FG class designation.

FG Classification Rules. In the proposed classification scheme the following rules are followed in the assignment of class designations to functional groups.

- Activating functions are to be considered as heteroatoms appended to or included within the carbon skeleton.
- Activating functions are inspected and classified according to their observed polar site reactivities.
- Since both proton removals and addition processes are frequently an integral component in functional group activation, the function, its conjugate acid or base, and its possible proton tautomers are considered together in determining its class designation.
- The oxidation state of the FG is de-emphasized since this is a subordinate strategic consideration.

E-Functions. For example, carbonyls and carbonyl derivatives will be represented as =X where X may be either oxygen or substituted nitrogen. Well recognized exceptions to the polar class designations illustrated in Scheme I may be found in the chemistry of CO and HCN. In these instances the carbon bearing the heteroatom exhibits well-defined nucleophilic properties. Accordingly these two functional groups will be classified as A-functions by inspection (*vide infra*).

Table I. Common E-Functions: Symbol $\overset{(+)}{\mathrm{C}}-\mathrm{E}$

$-\mathrm{OR}$ $=\mathrm{O}$

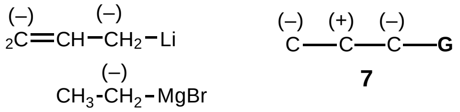
$-\mathrm{NR_2}$ $=\mathrm{NR}$

$-\mathrm{X}$, X = halogen

exception: $\equiv\mathrm{O}$
exception: $\equiv\mathrm{N}$

Also consider all combinations of of above FGs; e.g =O + OR

G-Functions. Typical G-class functions are the Group I-IV metals whose reactivity pattern, falls into a subset of **7**.



$\overset{(-)}{_2\mathrm{C}}{=}\mathrm{CH}{-}\overset{(-)}{\mathrm{CH_2}}{-}\mathrm{Li}$ $\qquad \overset{(-)}{\mathrm{C}}{-}\overset{(+)}{\mathrm{C}}{-}\overset{(-)}{\mathrm{C}}{-}\mathbf{G}$

$\mathrm{CH_3}{-}\overset{(-)}{\mathrm{CH_2}}{-}\mathrm{MgBr}$ $\qquad$ **7**

A-Functions. A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se). Typical A-functions, classified by inspection, are provided in Table II.

Table II. Common A-Functions: Symbol $\overset{(\pm)}{\mathrm{C}}-\mathrm{A}$

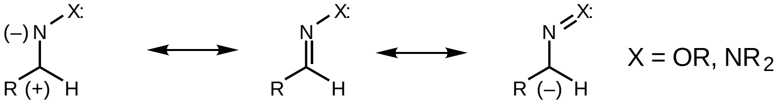
$-\mathrm{NO_2}$ $=\mathrm{NOR}$ $=\mathrm{NNR_2}$ $=\underset{+}{\mathrm{N}}\mathrm{(O)R}$ $=\mathrm{N_2}$ $\equiv\mathrm{N}$

$-\mathrm{SR}$ $-\mathrm{S(O)R}$ $-\mathrm{SO_2R}$ $-\underset{+}{\mathrm{S}}\mathrm{R_2}$

$-\mathrm{PR_2}$ $-\mathrm{P(O)R_2}$ $-\underset{+}{\mathrm{P}}\mathrm{R_3}$

Functional groups possessing the following general structure, =N-X where X is a hetroatom bearing a nonbonding electron pair, have an expanded set of resonance options which create either an electrophilic or nucleophilic potential at the point of attachment. Remarkably, the dual electronic properties of oximes were first discussed by Lapworth[12] in 1924 before the modern concepts of valence bond resonance was developed.

- These FG's are capable of conferring both (+) and (–) at the point of attachment.



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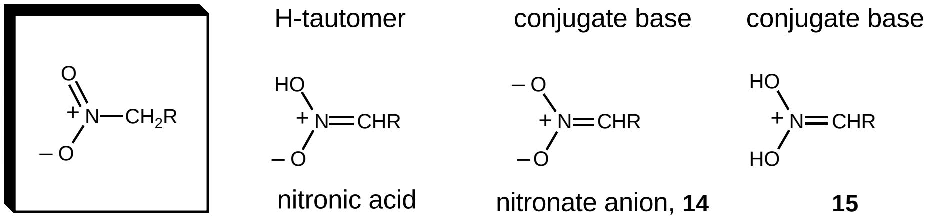
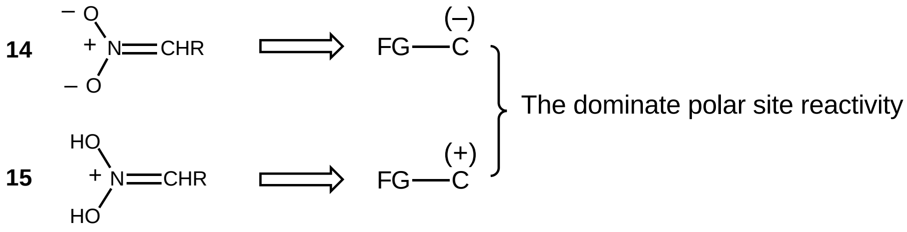
12) Lapworth, A. *Chemistry and Industry* **1924**, *43*, 1294-1295.

A Case Study: The Nitro Group. As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base **14** and **15**.

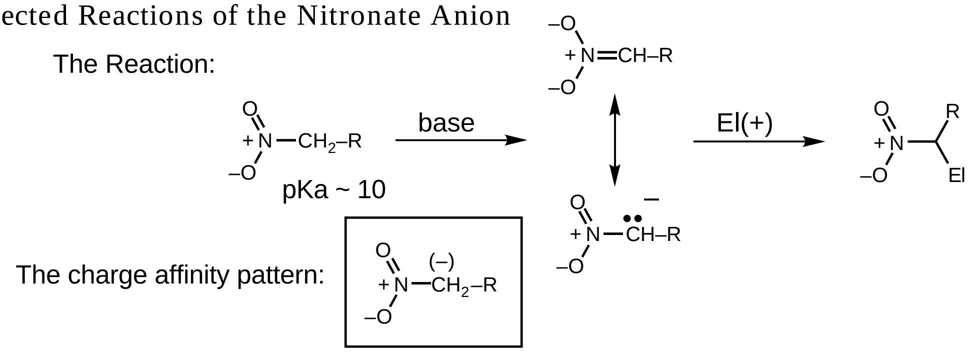


From the collection of transformations of the nitro group one finds that the dominate mode of reactivity of the nitronate anion **14** is that of a G-function while the protonated nitronic acid **15** mirrors the reactivity of an E-function.



The typical behavior of nitronate anions **14** is summarized in the representative transformations provided in Scheme VI. These moderately nucleophilic species, although they are not readily alkylated, readily undergo aldol and conjugate addition reactions.

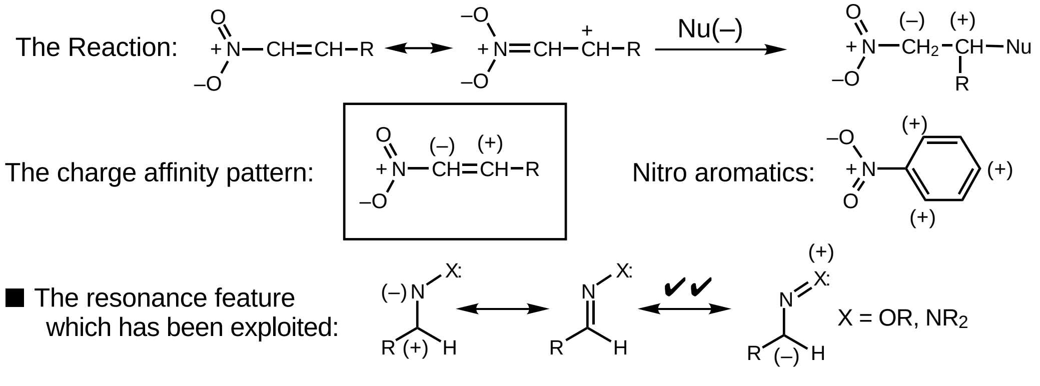
cheme VI Selected Reactions of the Nitronate Anion



■ This reactivity pattern may be extended via conjugation:

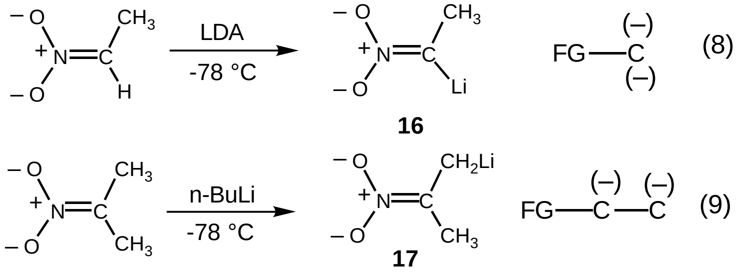
It is no surprise that the charge affinity pattern of this FG may be extended by conjugation, and α,β-unsaturated nitro compounds readily participate in conjugate addition reactions (Scheme VII).

Scheme VII Selected Reactions of the Nitronate Anion


The Reaction:
Nu(–)
The charge affinity pattern:
Nitro aromatics:
■ The resonance feature which has been exploited:
X = OR, NR2

The non-alternate behavior of the nitro functional group is dramatically illustrated in the transformations provided in Scheme VIII. In both instances the derived anions **16** and **17** are highly nucleophilic.[13] The non-alternate charge affinity patterns of these nucleophiles is provided.

Scheme VIII Deprotonated Nitronate Anions



16

17

The nitro group also exhibits the potential of undergoing direct displacement under specific conditions, a general transformation characteristic of E-functions. A recent review by Tamura provides numerous literature precedents for this general class of reactions.[14] while table III provides some of the cited reactions. Although the NO_2 group cannot be considered as a general leaving group, there are a number of conditions under which this moiety can be exploited, particularly when it is either allylic or tertiary.

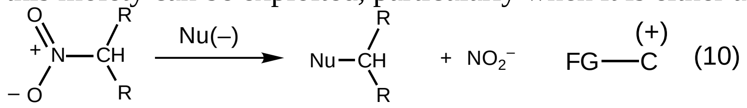
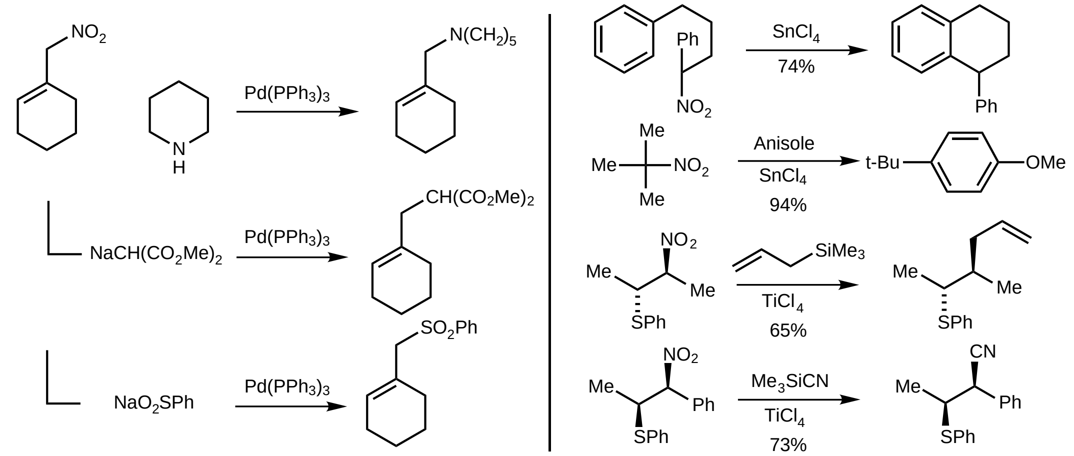


Table III. Representative Substitution Reactions of the Nitro Group (eq 10).



A particularly useful transformation of the nitro group is the Nef Reaction, a process which transforms NO_2 into =O (Scheme IX). A recent comprehensive review of this transformation provides a detailed discussion of this process.[15] In addition to the Pinnick review, Seebach has also written a comprehensive review of the diverse chemistry of the nitro functional group.[16]

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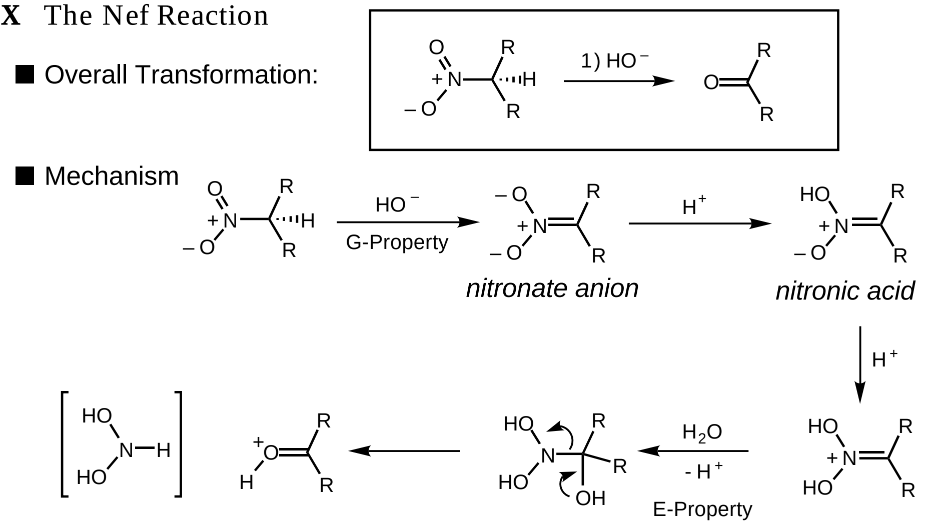
[13] (a) Henning, R.; Lehr, F.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2213-2217; (b) Seebach, D.; Henning, R.; Lehr, F.; Gonnermann J. *Tetrahedron Lett.* **1977**, 1161-1164.

[14] Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434.

[15] Pinnick, H. W.; *Org. Reactions* **1990**, *38*, 655-792.

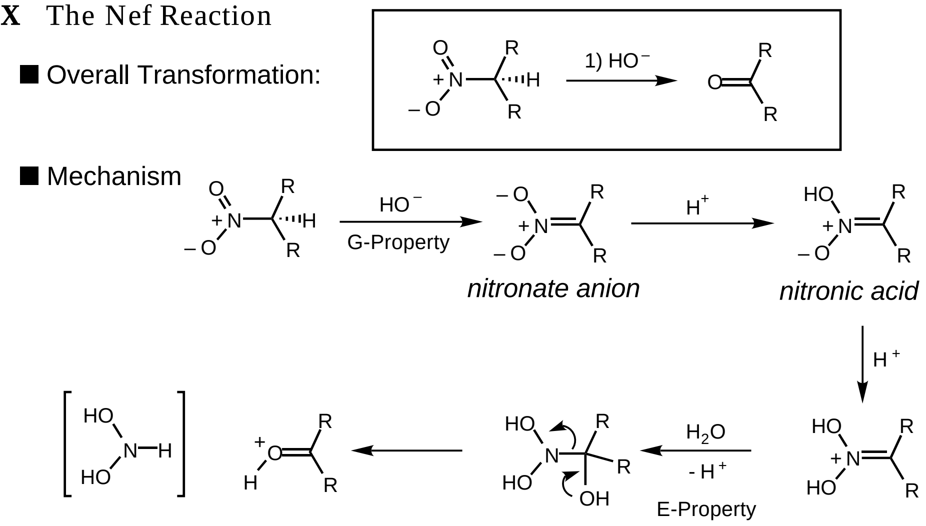
[16] Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T.; *Chimia* **1979**, *33*, 1-18.

Scheme IX The Nef Reaction



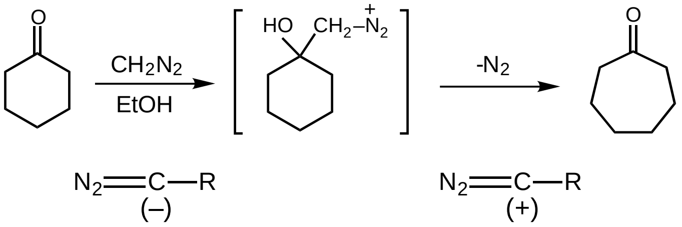
The Diazo Functional Group. This functional group provides one of the best illustrations of an A-function. As illustrated in Scheme X, both (–) and (+) polar site reactivity is observed in is reactions with carboxylic acids.

Scheme IX The Nef Reaction



The same overall reactivity pattern is expressed by the diazo functional group in the Tiffeneau-Demjanov ring expansion reaction[17] wherein diazomethane functions as the nucleophilic agent in the first step and the functional group is lost as a leaving group in the subsequent step (Scheme XI).

Scheme XI The Tiffeneau-Demyanov Ring Expansion



Restriction: Starting ketone must be more reactive than product ketone

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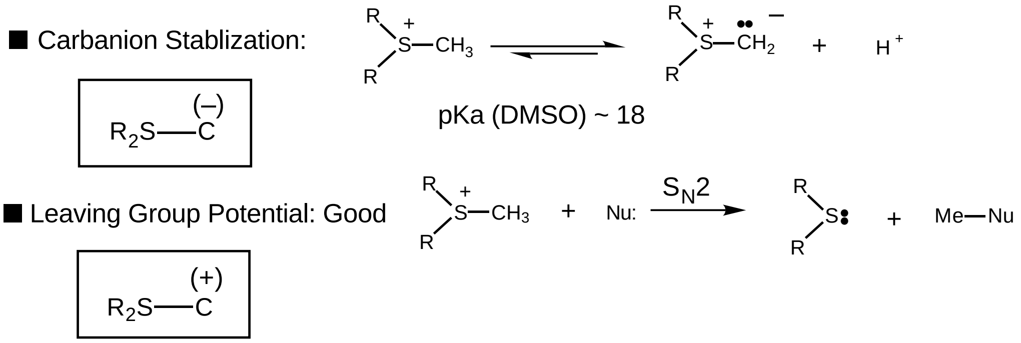
[17] For a monograph on ring expansion reactions see: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991.

Sulfur-Based Functional Groups

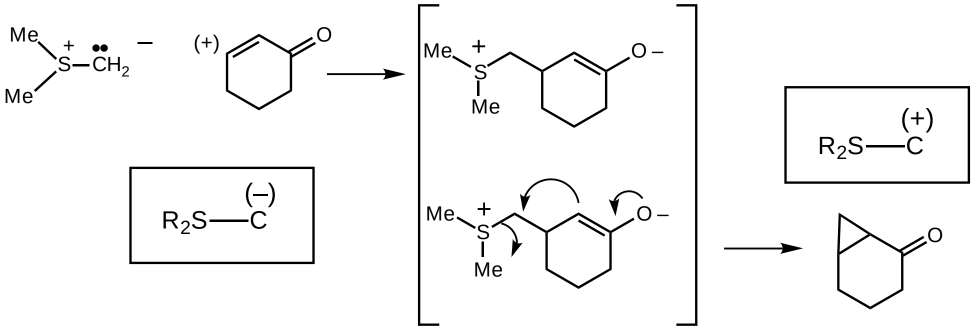
Sulfonium Salts. The dual electronic behavior of sulfur functions may be illustrated in the reactions of sulfur ylids which are excellent examples of A-functions. As illustrated in Scheme XII, sulfonium salts are effective in carbanion stabilization, a characteristic of G-functions, and sulfonium salts are effective leaving groups, a characteristic of E-functions.

Scheme XII. Sulfonium Salts: Modes of Reactivity



The non-alternate reactivity pattern of trimethylsulfonium ylids is revealed in the cyclopropanation of unsaturated ketones as illustrated in the case below (Scheme XIII).[18]

Scheme XIII. Reactions of Sulfonium Ylids: Conjugate Addition

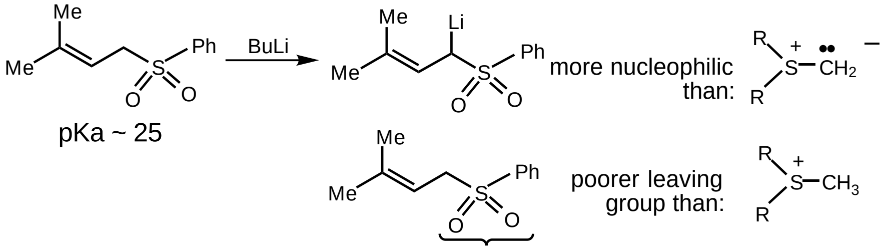


■ Nonalternate reactivity pattern revealed in consecutive reactions

Sulfones. Other types of sulfur-derived functional groups exhibit reactivity profiles similar to that exhibited by sulfonium salts. A number of excellent applications of the arylsulfonyl functional group illustrate this point. Two applications utilizing the sulfone functional groups are presented below.

The phenylsufonyl moiety strongly stabilizes carbanions and may be equated with the –CN FG in its potential for hydrocarbon acidification.[19] In addition, this FG is a respectable leaving group in selected situations. In comparisons with sulfonium ions (Scheme XV), arylsulfonyl-stabilized carbanions are more nucleophilic than sulfonium ylids (G-property), while ArSO$_2$- is a poorer leaving group than Me$_2$S- (E-Property).

Scheme XV. Sulfones: Modes of Reactivity



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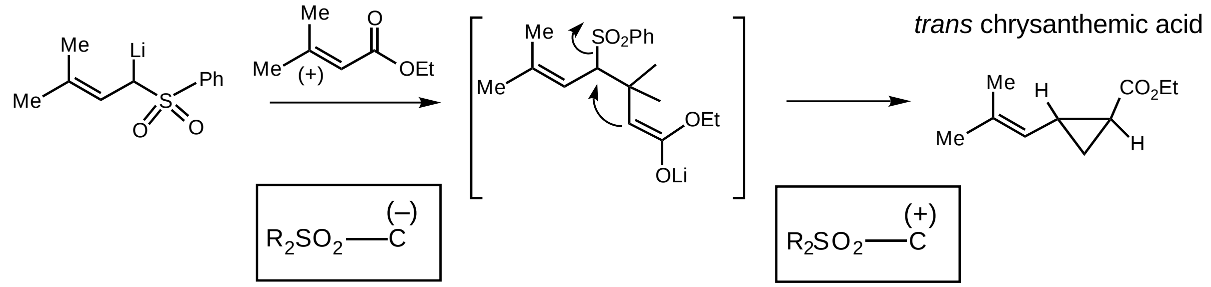
[18] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1352-1364.

[19] For an excellent compilation of pKa data for organic functional groups in DMSO see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

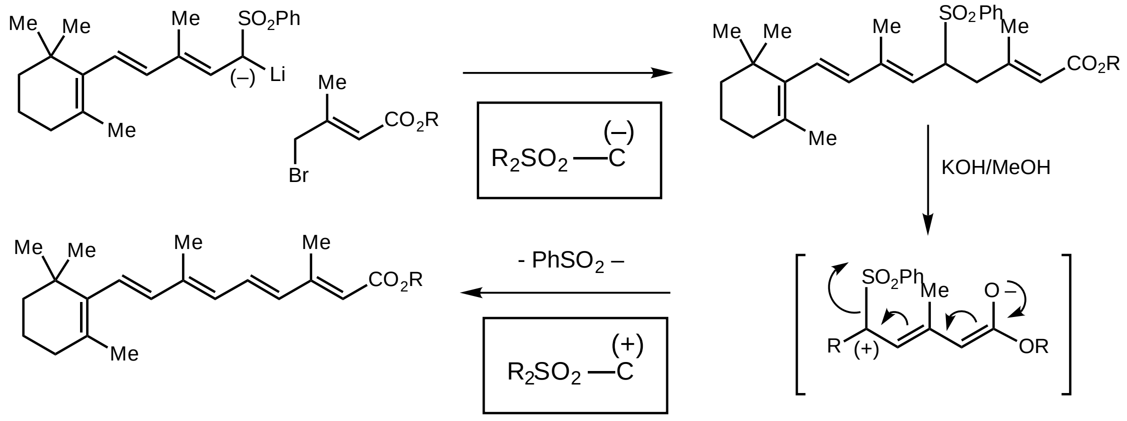
Julia's use of phenylsulfonyl carbanions in the synthesis of *trans*-chrysanthemic acid provides the justification for defining this functional group as an A-function (Scheme XVI).[20]

Scheme XVI. The Julia Chrysanthemic Acid Synthesis



The dual electronic properties of the sulfone functional group are illustrated in the Julia synthesis of vitamin A (Scheme XVII).[21] In this application, the E-property of the FG is exploited in the base-induced elimination reaction to generate the fully conjugated polyene.

Scheme XVII. The Julia Vitamin A Synthesis



Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130

For additional reading on the utility of the utility of sulfones in organic synthesis a monograph on this subject has recently appeared.[22] Several other reviews providing extensive literature coverage are worth reading.[23]

Organoboranes. The boron atom exhibits many of the common reactions normally attributed to metals, and when bound to carbon, serves as an excellent source of nucleophilic carbon.[24] The transformations provided in (Table IV) represent but a few cases which demonstrate the G-properties of this activating function.[25,26,27,28,29,30,31]

---

[20] (a) Julia, M.; Guy-Rouault, *Bull. Soc. Chim. Fr.* **1967**, 1141. (b) Campbell, R. V. M.; Crombie, L.; Findley, D. A. R.; King, R. W.; Pattenden, G.; Whiting, J. *J. Chem. Soc., Perkin Trans. I* **1975**, 897.

[21] Arnould, D.; Chabardes, P. Farge, G.; Julia, M. *Bull. Soc. Chim. Fr.* **1985**, 130.

[22] Simpkins, N. S. *Sulfones in Organic Synthesis*, Pergamon Press, New York 1993.

[23] (a) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107-124. (b) Magnus, P. D. *Tetrahedron*, **1977**, *33*, 2019-2045.

[24] (a) Brown, H. C. *Boranes in Organic Chemistry*, Cornell University Press, New York 1973. (b) Cragg, G. M. L. *Organoboranes in Organic Synthesis*, Marcel Dekker, New York, 1973

[25] (a) Kow, R.; Rathke, M. *J. Am. Chem. Soc.* **1973**, *95*, 2715. (b) Zweifel, G.; Fisher, R. P.; Horng, A. *Synthesis* **1973**, *37*. (c) Matteson, D. S. *ibid.* **1975**, 147.

[26] Negishi, E.; Abramovitch, A.; Merrill, R. E. *J. Chem. Soc., Chem. Commun.* **1975**, 138.

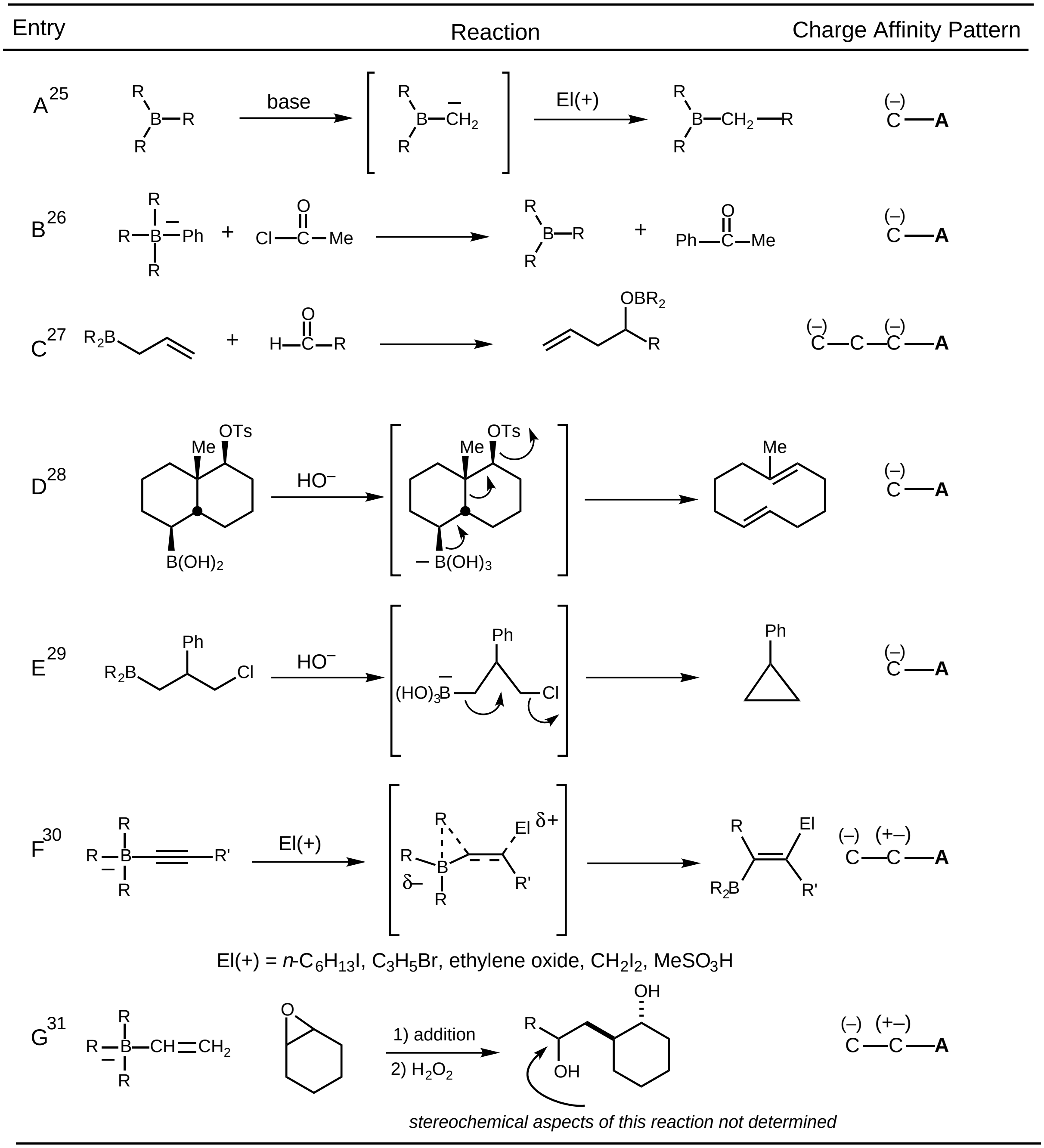
[27] For a recent citation on allylboron-based nucleophiles see: Wang, Z.; meng, X. J.; Kablaka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677-5680 and references cited therein.

[28] Marshall, J. A. *Synthesis* **1971**, 229.

[29] (a) Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *2149*, 2149. (b) Hawthorne, M. F.; Dupont, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 5830.

[30] (a) Pelter, A.; Subrahmanyan, C.; Laub, R. J.; Gould, K. J.; Harrison, C. R. *Tetrahedron Lett.* **1975**, 1633. (b) Pelter, A.; Harrison, C. R.; Kirkpatrick, D. *ibid.* **1973**, 4491. (c) Pelter, A.; Harrison, C. R. *J. Chem. Soc., Chem. Comm.* **1974**, 828. (d) Naruse, M.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1974**, *30*, 3037.

Table IV. Reactivity Patterns for Organoboranes



El(+) = n-$C_6H_{13}I$, C_3H_5Br, ethylene oxide, CH_2I_2, $MeSO_3H$

stereochemical aspects of this reaction not determined

The potential for non-alternate charge affinity patterns for boron have been revealed in the reactions of acetylenic and vinylic boron ate complexes (Table IV, entries F, G).[30,31] *These compounds exhibit high nucleophilicity towards a variety of electrophiles β to the boron atom.* The origin of such β-nucleophilicity could be a consequence of σ–π conjugation[32] (e.g., **19**) not observed with the heavier metallic elements which are attacked by electrophiles α to the metal where the alternate mode of conjugation **18** is possible.[33] In principle, both types of conjugative stabilization are possible with a range of organometaloids; however, in practice this is not the case. It would be expected that the effects of

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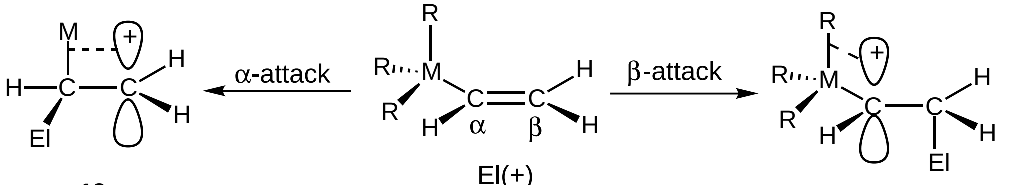
31) (a) Utimoto, K.; Uchida, K.; Nozaki, H. *Tetrahedron* **1973**, *30*, 4527. (b) Utimoto, K.; Uchida, K.; Nozaki, H. *Chem Lett.* **1974**, 1493.

32) (a) Harmon, G. D.; Traylor, T. G. *Tetrahedron Lett.* **1975**, 939, and reference cited therein. (b) for example of σ–π delocalization of type **25** involving R_3B— see Hanstein W.; Traylor, T. G. *ibid.* **1967**, 4451; (c) for the reaction of vinylsilanes electrophiles see Miller, R. B.; Reichenbach, T. *ibid.* **1974**, 543, and references cited therein.

33) Kitching, W. in "Organometallic Reactions," Vol. 3, E. I. Becker and M. Tsutsui, Ed., Wiley-Interscience, New York 1972, pp. 319-398.

σ–π conjugation, such as that illustrated in **24**, would be more important in those systems having shorter C-M bonds, a situation which may be unique to boron. It is noteworthy that the other group III and IV organometallic compounds, R_3M—$CH{=}CH_2$ (M = Al, Si, Ge, Sn) react with electrophilic reagents α to the metal. These elements all exhibit polar reactivity patterns common to G-class functions.



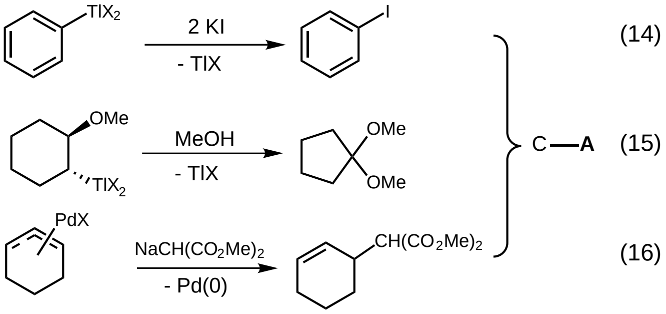
18 **19** (11)

Metals. In deriving a class designation for metals, M, bound to carbon, two reaction types are considered. Metals undergoing *exclusive* substitution at the metal-carbon bond by electrophiles, El^+, are classified as G-functions (eq 12), while metals which are involved in redox processes (eq 13) are classified as A-functions since such organometallic compounds also exhibit G-type behavior.

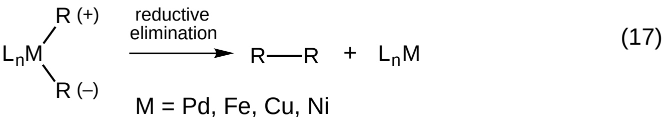
$$\overset{(-)}{R}—\overset{(+)}{M} \;+\; El(+) \;\rightleftharpoons\; R—El \;+\; M(+) \qquad (12)$$

$$\overset{(+)}{R}—\overset{(-)}{M} \;+\; Nu(-) \;\rightleftharpoons\; R—Nu \;+\; M(-) \qquad (13)$$

The organic chemistry of Tl(III),[34] and Pd(II)[35] (eq 14-16) illustrate the role of metals as leaving groups (reductive elimination). Oxidative addition reactions of metal carbonyl anions and alkyl halides provide examples of the reverse process.[36] In general, transition metal-mediated cross-coupling reactions provide a useful illustration of the A-classification of redox metals (eq 17).[37] The assignment of charge affinity labels to R_1 and R_2 in this case is arbitrary.



Employing polar processes as the basis set of synthetic reactions, existing functional groups may be organized according to their known chemical properties. Any number of positions may be taken relative to the classification of atom reactivity. The goal of this section has been to define a general classification scheme which may be used to organize the multitude of different strategies which have been developed to construct pairwise functional group relationships in organic molecules.



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[34] Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338.

[35] Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393.

[36] Ellis, J. E. *J. Organomet. Chem.* **1975**, *86*, 1.

[37] (a) Neuman, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (b) Normant, J. F. *Synthesis* **1972**, 63. (c) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. (d) Tamaki, A.; Magennis, S. A.; Kochi, J. K. *ibid.* **1973**, *95*, 6487.

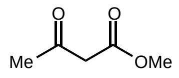
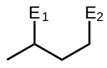
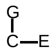
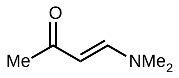
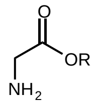
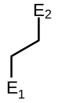
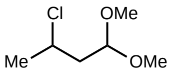
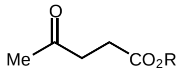
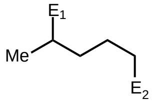
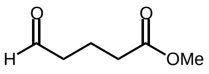
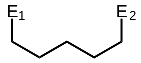
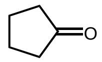
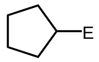
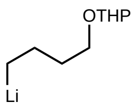
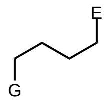
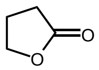
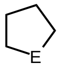
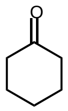
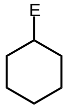
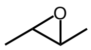
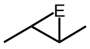
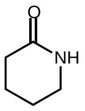
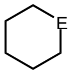
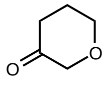
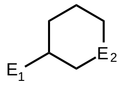
Classification of Difunctional Relationships.

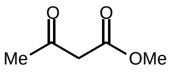
One of the basic assumptions employed in synthetic design involves the *maximum utilization of existing functionality at all intermediate points in the construction of a polyfunctional molecule*. Such guidelines aid in minimizing the number of side reactions and protection-deprotection steps during the assemblage operation. In the synthesis of even simple difunctional organic molecules, the relative positioning of the two activating functions on the carbon framework strongly influences the reaction types that will usually be employed to establish the difunctional relationship. Using the general notation developed in the previous section for activating functions, two distinct classes of difunctional relationships which may be defined between ideal E- and G-functions which may be defined are illustrated in Table V.

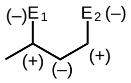
Paths. *Difunctional relationships between heteroatoms having "matched" charge affinity patterns will be defined as* ***consonant*** *while unmatched relationships will be labeled* ***dissonant****.*

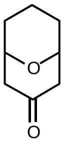
It should be pointed out that the charge affinity notation is unnecessary to define the appropriate relation; other parity labels could serve equally well. For example, the number of bonds between E- and G-functions could be used to define the appropriate relationship. Employing E-functions for the purpose of illustration, the two carbonyl groups in **20a** have a matched charge affinity pattern along the potential construction path. Since they are separated by three atoms they can be defined as 1,3-consonant (1,3-C). The symbol notation **20b** transmits information relative to the E—E' positioning along the construction path and since the E-symbol represents a homogeneous class of electronically equivalent functional groups, a common symbol is employed. In those cases where it is necessary to recognize oxidation states of carbon to derive a symbolic structural notation, one may easily do so.

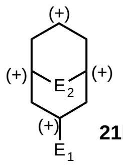
Table V. Consonant & Dissonant Difunctional Pairwise Functional Group Relationships

Consonant Relationships	Symbol	Notation	Dissonant Relationships	Symbol	Notation
		1,3–C	$\mathrm{Li{-}CH_2{-}Cl}$		1,1–D
					1,2–D
					1,4–D
		1,5–C			D-cycles
		1,4–C			
		C-cycles			
					1,2–D, 1,4–D


20a


20b

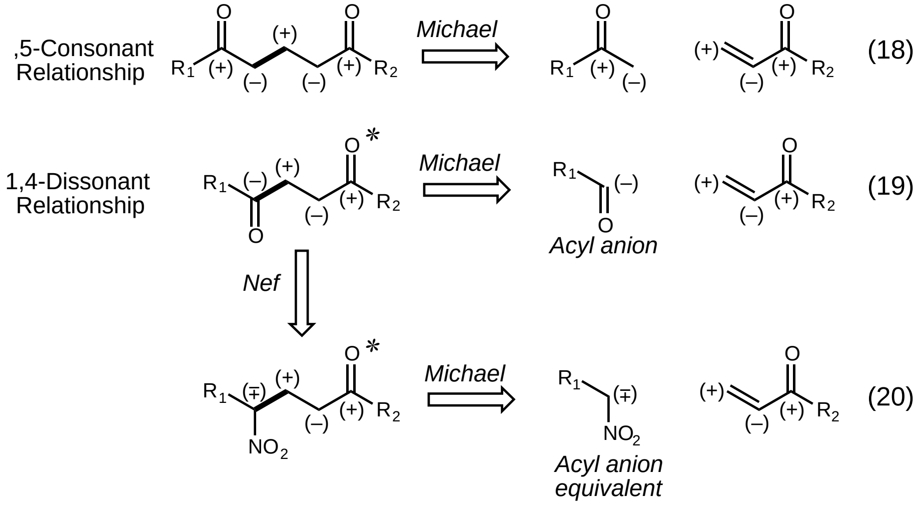

21a


21b

(-) symbol deleted for convenience

Cycles. *In cyclic structures, a heteroatom attached to or contained within the cycle creates a relationship with itself. For non-arbitrary mathematical considerations it is convenient to define an even-membered ring with or without a single functional group as consonant and corresponding odd-membered rings as dissonant.* For the bicyclic ketone **21a**, both of the oxygen heteroatoms, denoted as E_1 and E_2, establish consonant relationships with each other via all bond paths and individually by virtue of their position either attached to or contained within an even-membered ring.

Consonant and Dissonant Bond Paths. In contrast to the uniformity with which consonant relationships may be established through common classes of polar processes, the synthetic methods and functional groups required for the construction of the bonds define a D-relationship are quite varied and involve either more steps, more functional groups or more reactive intermediates than reactions leading to C-paths. This statement will be reinforced in a series of case studies (*vide infra*); however a single case is presented to reinforce this assertion. Consider the Michael transform executed on the 1,5- and 1,4-diketones shown below (eq 18, 19). In the first instance, the transform may be executed using only the functional groups illustrated; however, this is not possible with the dissonant dicarbonyl relationship since one of the resulting polar fragments will be electronically mismatched with its associated FG. In the illustrated disconnection (eq 19), the electronically mismatched fragment is the carbonyl anion.

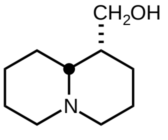


One possible solution to the construction of this dissonant relationship is through FG manipulation. In the present instance the application of the Nef transform (vide supra) provides the opportunity to match the charge affinity patterns so that the Michael transform may be properly executed. The use of A-functions in this fashion is just one of a number of strategies which may be employed to construct dissonant difunctional relationships.

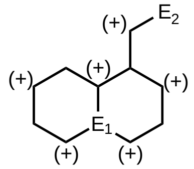
In conclusion, dissonant pairwise relationships, either identified in simple acyclic molecules or within complex cyclic structures, generally pose a greater synthetic challenge and represent seams of lower flexibility within the carbon framework. At this point, it may be instructive to the reader to contemplate a synthesis strategy based on how and when D-relationships are incorporated into target structures. This point will be addressed later in the discussion.

Synthesis of Consonant Difunctional Relationships.

Every complex polyfunctional molecule may be analyzed structurally in terms of its individual consonant or dissonant construction paths or cycles. For example, in the alkaloid lupinine (**22**) all possible construction paths interconnecting E_1 and E_2 are consonant. On the other hand, mesembrine (**23**)[38] contains the potential dissonant paths and cycles illustrated in heavy lines. *Consonant paths within the polyatomic framework define seams in the structure that may be constructed using aldol and related condensation processes.*



22 ***(lupinine)***



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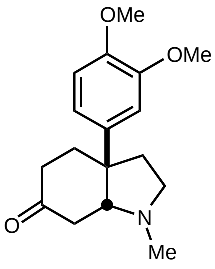
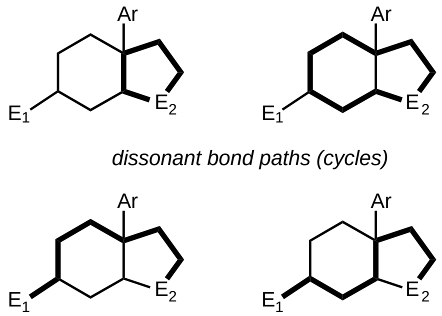
[38] (a) Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441. (b) Keely, S. L.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584. (c) Stevens, R. V.; Wentland, M. P. *ibid.* **1968**, *90*, 5580; (d) Shamma, M.; Rodrigues, H. R. *Tetrahedron* **1968**, *24*, 6583.

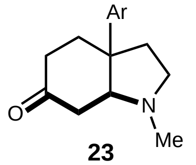
■ Regarding the number of different possibilities available for the synthesis of a consonant difunctional relationship interconnected by **n** bonds, there exists a set of **n** different connective operations that may be employed to establish any bond along the construction path from monofunctional or consonant polyfunctional precursors.[39]



23 ***(lupinine)***



dissonant bond paths (cycles)

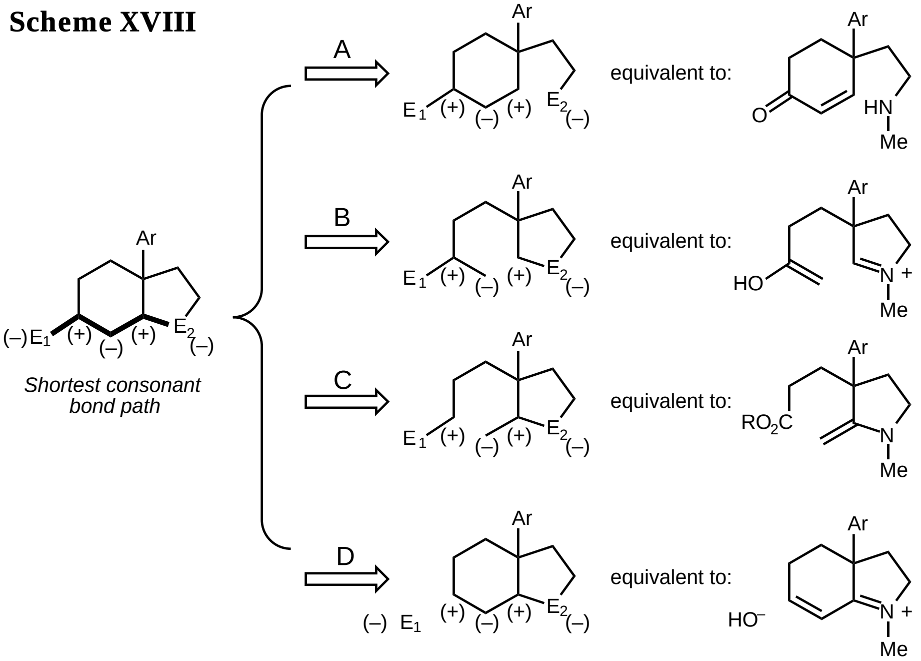


23

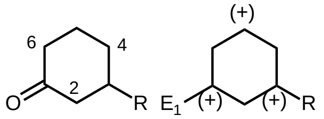
Shortest consonant bond path

In the analysis of potential routes to structures like lupinine, identify the shortest consonant bond path and then proceed to carry out all polar disconnections along that bond path (Scheme XVIII). Since there four bonds interconnecting =O and N (E_1 and E_2), there will be four associated transforms which one may execute using the illustrated functional groups. In each set of precursors the intrinsic polar reactivity patterns of the heteroatoms are accommodated in the coupling process. The resulting adducts containing the requisite nitrogen-oxygen relationship may then be ranked in order of desirability by considering criteria such as chemical feasibility of the coupling step, ease of subsequent transformation to the target structure, and availability of precursor fragments. In the present example, transforms A and B might be more highly ranked that transform C while transform D might be discarded since it does not lead to structural simplification.

Scheme XVIII



In those cases when a given consonant or dissonant relationship is separated by a significant number of bonds, it is strategically worthwhile to consider the option of incorporating additional functions to aid in the construction of the desired target molecule. The relative placement of such a functional group is of prime importance in dictating the subsequent polar disconnections that are perceived in generating a plausible synthetic tree. This point is illustrated when considering plausible precursors to ketone **24** (Scheme XIX). In this structure, the =O FG establishes a 1,5-relationship with itself on the six-membered ring. Through the addition of an appropriate second



24

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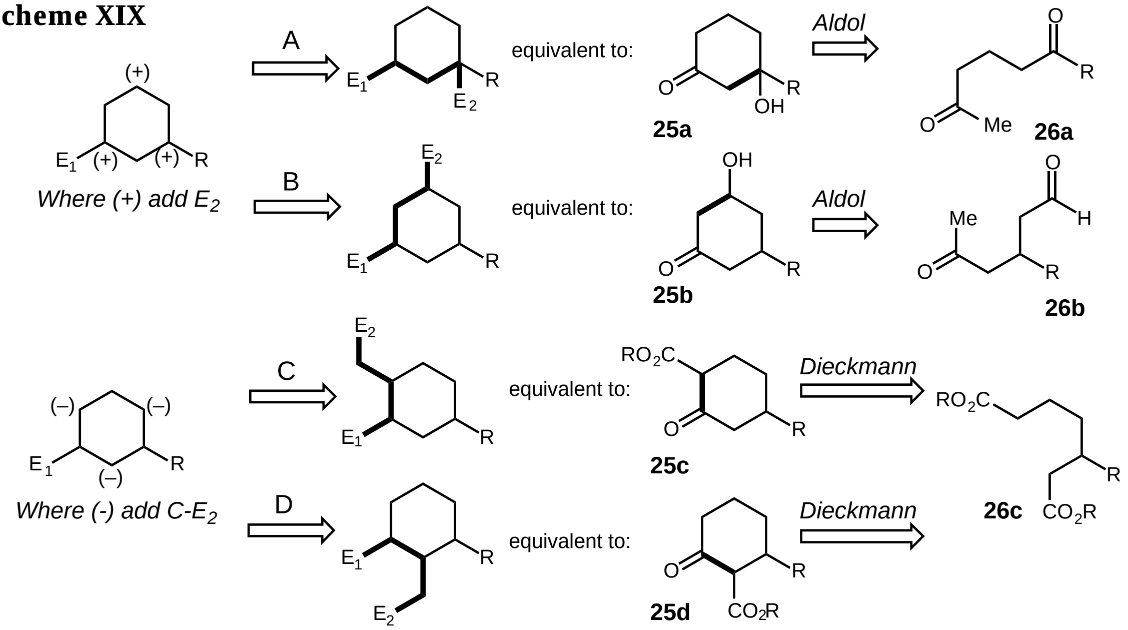
[39] The presence of a quaternary or bridgehead center along the construction path limits bond construction to those adjacent to the center.

activating function to the target molecule **24**, an expanded set of potential disconnections is created. In the placement of the second FG, the charge affinity pattern of the resident FG should be used. *For example, consider the installation of a second FG, E_2, at the (+) sites on the ring to set up aldol or Claisen transforms. In a complementary fashion the addition of C-E_2 fragments to the (–) sites will open up the execution of the two possible Dieckmann transforms.*[40] The preceding analysis leads to the three precursors **26a-26c**. Each of which contains a 1,5-consonant difunctional relationship between the carbonyl functions. These subgoals now become the focus of the next level of analysis wherein the preceding logic is again applied. It should be emphasized that the precursors illustrated in Scheme XIX are not inclusive but represent one set which leads to the generation of a synthetic tree based upon aldol and related reactions. *The point to be emphasized is that in the first stage of the analysis where functionality is being added to the target structure, consonant, rather than dissonant relationships should be created.*

Scheme XIX



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[40] To be completely rigorous with regard to this analysis, the addition of C-E_2 to the 4-position should also be considered; however, the E_1-E_2 construction span from such a precursor is sufficiently large as to render this precursor less attractive than the other precursors **25a-25d**.

Chemistry 206
First Hour Examination

D. A. Evans
October 14, 2005

Name (please print): ____________________
last first initial

Signature: ____________________

Teaching Fellow: ____________________

Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (15)	______
No. 7 (15)	
Total (100)	

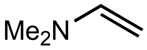
You have two hours to complete the exam
10:05 am to 12:05 pm

Please record your answers **with a pen** in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

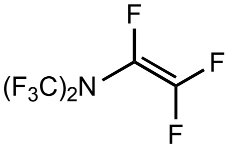
Question 1. (10 points). Oberhammer recently studied the gas phase structures of *N,N*-Dimethylvinylamine (**1**) and perfluorodimethylvinylamine (**2**) (*JACS*, **2001**, *123*, 2865).

Part A. (5 points). Please provide a clear three-dimensional representation of the lowest energy conformer of *N,N*-Dimethylvinylamine (**1**). Label all relevant stereoelectronic interactions.



1

Part B. (5 points). The perfluorinated example **2** adopts an entirely different conformation than *N,N*-Dimethylvinylamine (**1**). Please provide a clear three-dimensional representation of the lowest energy conformer of **2**. Label all relevant stereoelectronic interactions.

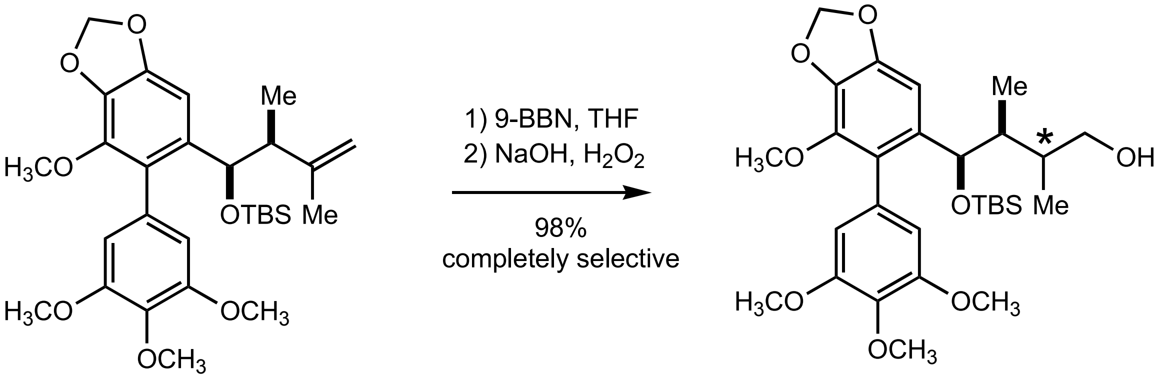


2

Question 2. (15 points). One of the most recent examples of selective hydroboration is given below (Coleman, *OL,* **2004**, *6, 4025*).

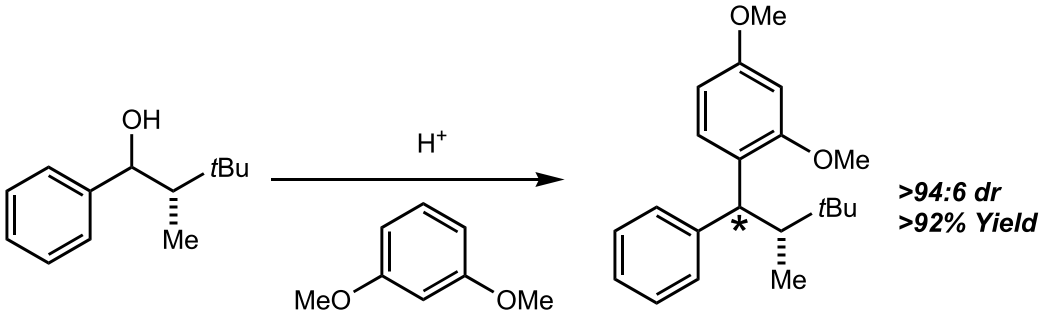
Part A. (10 points). Please predict the stereochemical outcome of this reaction and provide a clear three-dimensional representation of the transition state leading to the observed sense of stereochemical induction.

Part B. (5 points). Please provide a mechanism for the subsequent hydrogen peroxide mediated oxidation of the initially formed alkyl borane. Be sure to identify any important stereoelectronic requirements.



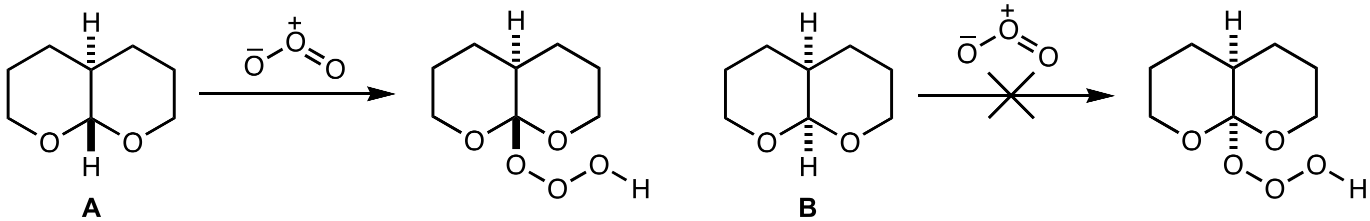
Question 3. (15 points). Bach recently showed that stereocenters adjacent to a benzylic hydroxy group can dictate the facial preference for the subsequent acid promoted Friedel-Crafts reaction (*JACS,* **2005**, *127*, 9348).

Please provide a mechanism for this reaction that predicts the major product that accounts for the high level of stereoinduction that is observed. Be sure to indicate all relevant stereoelectronic and steric interactions. Please note that the starting material is a mixture of diastereomers.



Question 4. (15 points). The oxidation of acetals by electrophilic ozone is known to be sensitive to structure. Two striking examples of different reactivity are detailed in the questions below.

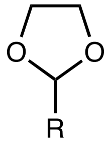
Part A. (7.5 points). Using clear three-dimensional drawings provide a rationale for the observation that rigid glycoside **A** readily undergoes oxidation but glycoside **B** does not. Be sure to indicate all relevant stereoelectronic interactions.



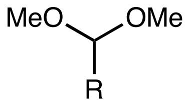
A **B**

Deslongchamps, *Can. J. Chem.* **1974**, 3651-3664.

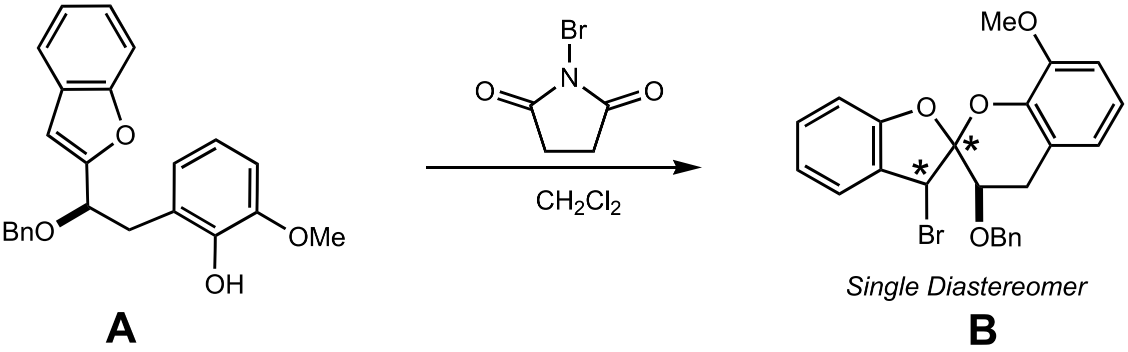
Part B. (7.5 points). Ozone oxidation of cyclic acetals is faster than oxidation of the corresponding acyclic acetals (Taillefer, *Can. J. Chem.* **1979**, 3041-3046). Using clear three-dimensional drawings please provide an explanation for this observation.



faster than

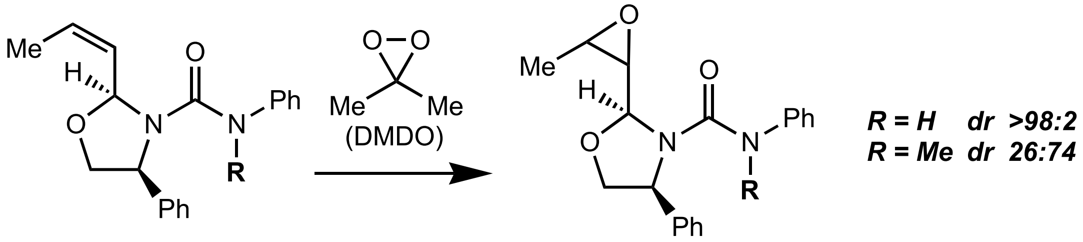


Question 5. (15 points). Danishefsky and coworkers reported that the *N*-bromosuccinimide-induced spiroketalization of benzofuran **A** affords the spiroketal **B** as a single diastereomer (*ACIEE,* **2001**,*40*, 4709).



Using clear three-dimensional drawings provide a mechanism for this reaction and predict the stereochemistry of the product **B**. Be sure to indicate any important steric or stereoelectronic effects.

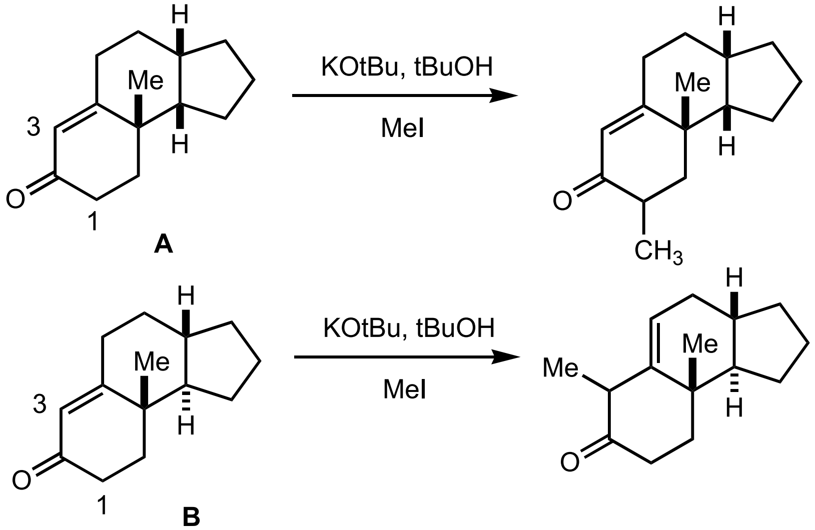
Question 6. (15 points). Adam and coworkers recenty studied the dimethyldioxirane (DMDO) mediated epoxidation of oxazolidine-substituted alkenes and noted that the selectivity of the epoxidation is dependent upon the nature of the R substituent of the urea (*Org. Lett.* **2001**,*3*, 79).



Part A. (5 points). In the space provided please provide a general mechanism for the epoxidation of an alkene with DMDO. Clearly identify and label all the important orbital interactions.

Part B. (10 points). In the space provided predict the major stereoisomer formed for both cases shown above, *i.e.* when R= H and when R= methyl.

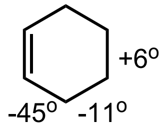
Question 7. (15 points). Enolization of **A** under equilibrating conditions followed by treatment with methyl iodide leads to the preferential introduction of the alkyl group at C1, whereas exposure of **B** to these conditions affords alkylation at C3. Using your knowledge of conformational transmission, assess the relative stability of the two enolates that are generated and thus provide a rational explanation for the divergent regiochemical outcomes.



A

B

Recall:



(A*IEE,* 1**965,** *6(3),* 181)

Chemistry 206
First Hour Examination

D. A. Evans
October 15, 2004

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (15)	_______
No. 2 (10)	_______
No. 3a (10)	_______
No. 3b (10)	_______
No. 4 (15)	_______
No. 5 (15)	_______
No. 6 (15)	_______
No. 7 (10)	_______
Total (100)	

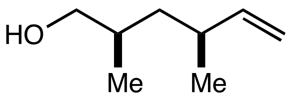
The exam will begin at 1:05 PM and end at 3:00.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

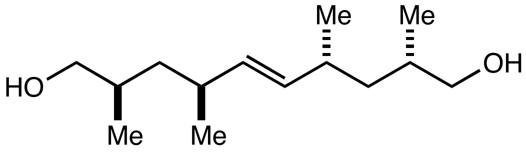
Question 1. (15 points). The structural unit of β-turns is present in many proteins and bioactive peptides and has important implications for both structure and function. As such, the synthesis of β-turn mimics has been an intensive area of research. While most solutions to creating such turns have relied on covalent linkages, Hoffmann and coworkers have developed an approach based on acyclic conformational preferences (*Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1745-1747).

Part A. (5 points). Please provide a clear 3-dimensional representation of the lowest energy conformer of **1**.

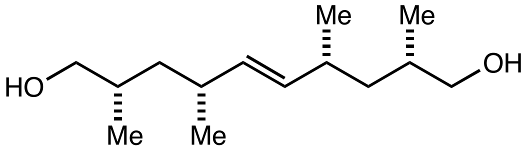


1

Part B. (10 points). Based on your analysis of **1** please draw the low energy conformations of **2** and **3**, and comment on which structure you think could be used as a β-turn mimic. ***Note:*** A β-turn is a structural feature that creates a U-turn in a peptide, bringing the termini into proximity.



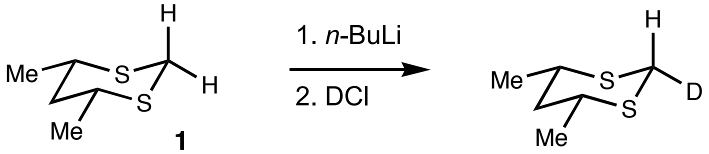
2



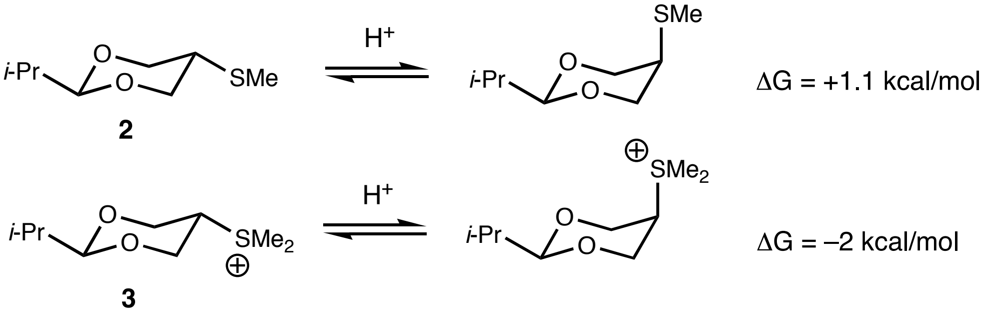
3

Question 2. (10 points). Many factors influence the reactivity and conformational bias of cyclic systems including steric, electronic, and stereoelectronic effects. For each of the following cases involving a six-membered heterocycle, provide a rationalization for the observed selectivity, including clear 3-dimensional representations where relevant.

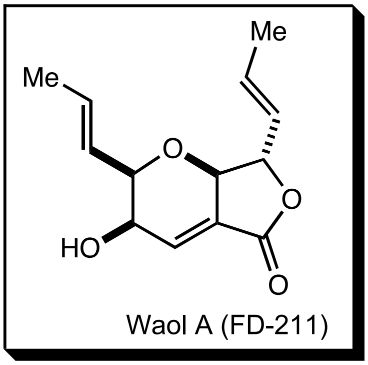
Part A. Eliel and co-workers disclosed that the successive deprotonation of conformationally **1** and trapping with an electrophile occurs with high selectivity at the equatorial position (*J. Am. Chem. Soc.* **1974**, *96*, 1807.)



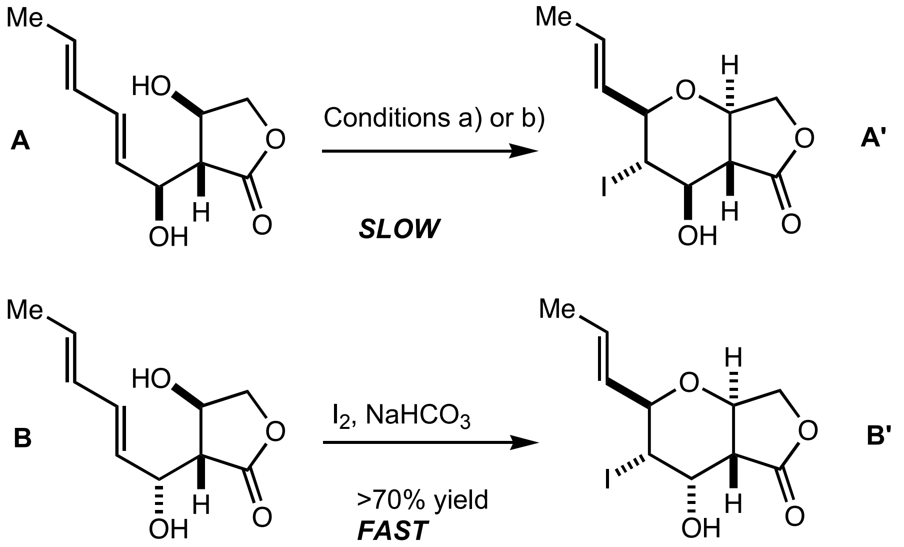
Part B. Eliel has also reported that the acid-catalyzed equilibrium of dioxane **2** favors the equatorial isomer, while the related equilibration of dioxane **3** prefers the axial isomer (*J. Am. Chem. Soc.* **1974**,*96*, 1939). Please provide a rationalization of these observations that is based on stereoelectronic arguments.



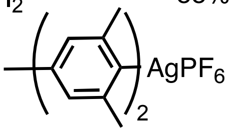
Question 3. Part A. (10 points). During the synthesis of the anti-tumor agent Waol A, Snider (*Org. Lett*. **2003**; 5(4); 451-454) and coworkers prepared the diastereomeric aldol adducts **A** and **B**. These substrates underwent iodoetherification at vastly different rates. In fact, to achieve sufficient conversion a more reactive iodonium reagent (bis(sym-collididne) $AgPF_6$) was necessary. *Please provide a mechanism for the reactions (**A** to **A'** and **B** to **B'**) that accounts for the observed selectivity and difference in rate. 3-dimensional representations are required.*



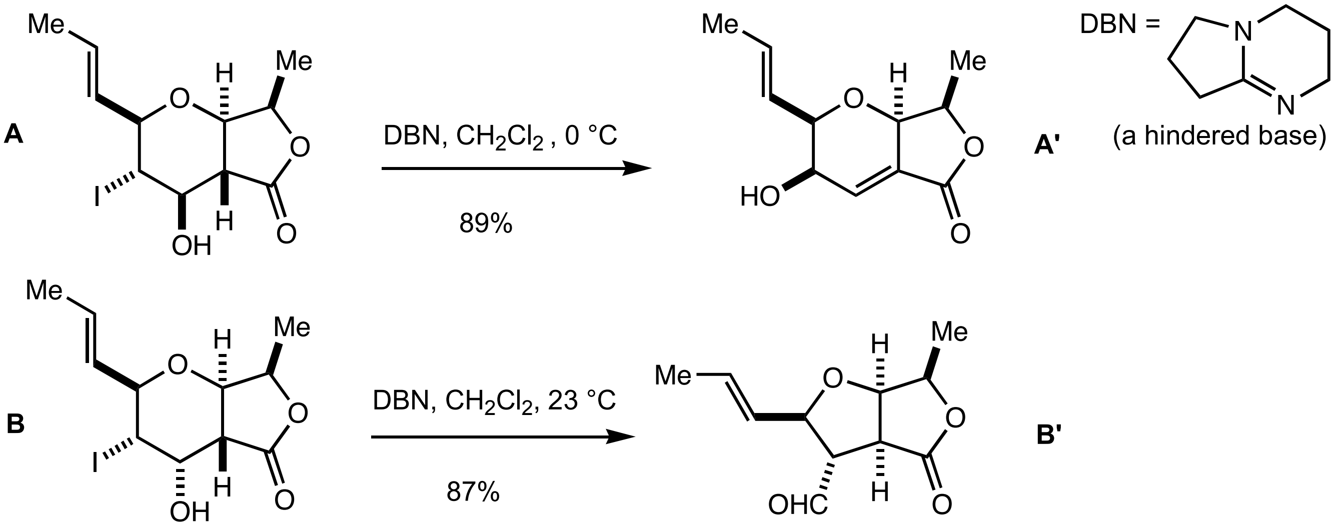
Waol A (FD-211)



Conditions:
a) I_2, $NaHCO_3$ = 5% conv
b) I_2 = 88% yield

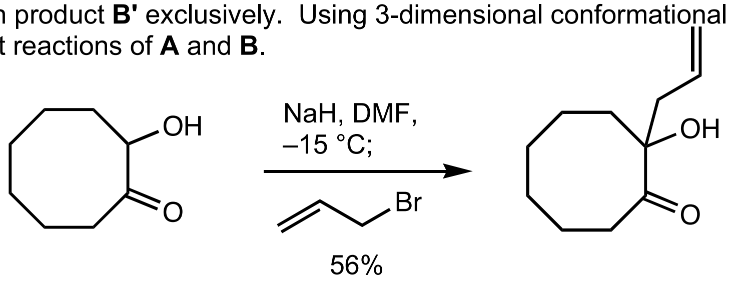


Question 3. Part B. (10 points). Products from the iodoetherification (**A** and **B**), when exposed to base (DBN), undergo different rearrangements. Please provide mechanisms that account for the divergent reaction pathways.



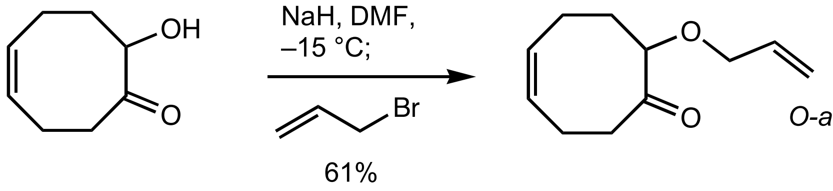
Question 4. (15 points). Paquette and co-workers have recently disclosed interesting regioselective alkylations illustrated below (*Org. Lett.* **2003**, 463.). Deprotonation of 2-hydroxycyclooctanone **A** followed by exposure to allyl bromide gave solely the C-alkylation product **A'**. In constrast, the unsaturated cyclooctanone **B** afforded the O-alkylation product **B'** exclusively. Using 3-dimensional conformational representations, please rationalize the divergent reactions of **A** and **B**.

A



A'
C-alkylation

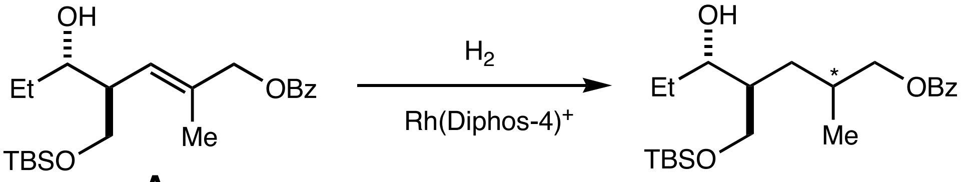
B



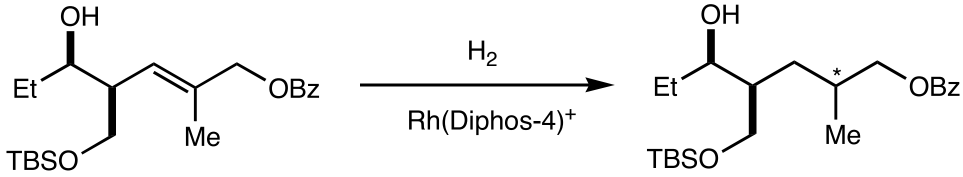
B'
O-alkylation

Question 5. (15 points). The directed reduction of homoallylic alcohols provides a powerful method for the stereoselective construction of acyclic molecules. In particular, cationic rhodium complexes have proven to be highly effective for the relay of stereochemical information by 1,3-asymmetric induction (Evans, *TL*, **1985**, 6005-6008).

Part A. (10 points). For both **A** and **B** predict the major diastereomer expected for indicated transformation. Be sure to indicate all relevent interactions.



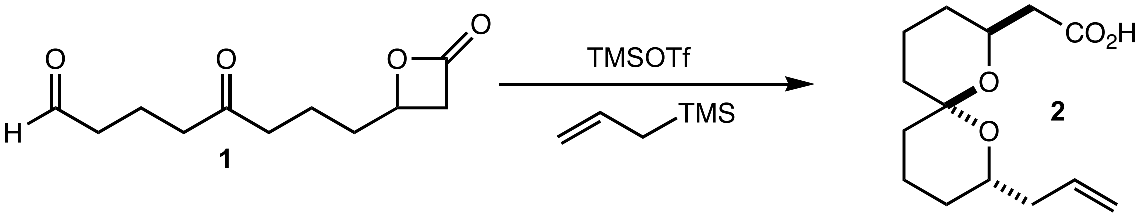
A



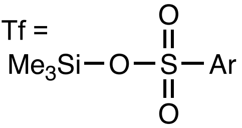
B

Part B. (5 points). Based on your transition states for the above reactions, which substrate would you expect to be more diastereoselective?

Question 6. (10 points). A unique spiroketalization was reported by the Mead group (*Syn. Lett.*, **1996**, 1065). A single diasteromer **2** was obtained when compound **1** was treated with a Lewis acid (TMSOTf) in the presence of allyltrimethylsilane. The observed long-range asymmetric induction immediately signals that the "most obvious" mechanism is probably not operative. Please answer the posed questions with this commentary in mind.



TMSOTf =



$$\mathrm{Me_3Si{-}O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{-}Ar}$$

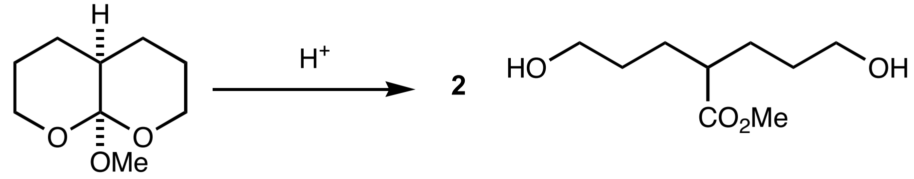
Part A. Draw the most stable conformer of **2**.

Part B. Provide a concise reaction mechanism that rationalizes the observed selectivity. Please use 3-dimensional drawings to illustrate the stereochemical aspects of your answer.

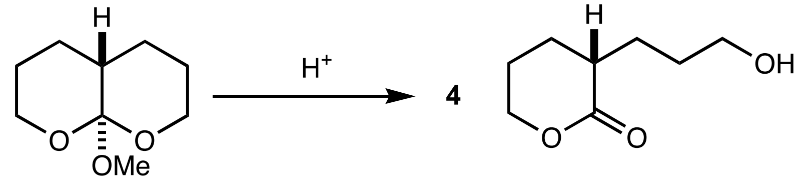
Question 7. (10 points). The hydrolysis of cyclic orthoesters appears to be dominated by stereoelectronic factors. A striking example of the divergent behaviour of orthoesters **1** and **3** is shown below. (Deslongchamp, *Can. J. Chem.* **1984**, 2493-2500).

Using clear three-dimensional drawings please provide an explantion for why **1** undergoes hydrolysis to give hydroxy ester **2**, and why **3** provides lactone **4**.

1



3



Chemistry 206
First Hour Examination

D. A. Evans
October 10, 2003

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

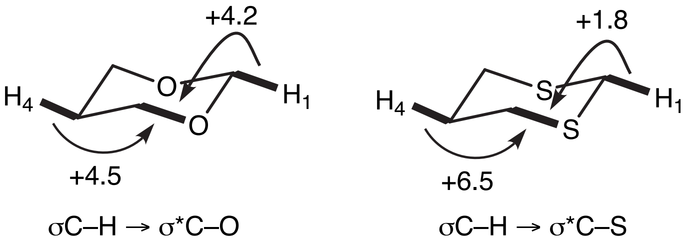
Question (pts)	Score
No. 1 (10)	________
No. 2 (15)	________
No. 3 (15)	________
No. 4 (15)	________
No. 5 (15)	________
No. 6 (15)	________
No. 7 (15)	
Total (100)	

The exam will begin at 9:05 AM and end at 11:00.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

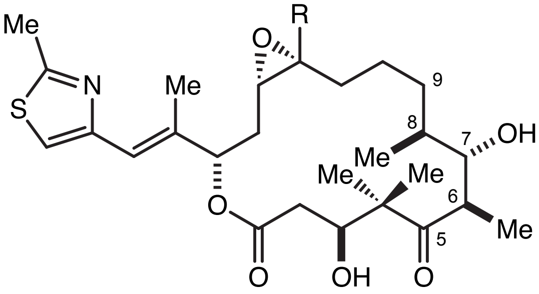
Question 1. (10 points). Natural bond order (NBO) analysis is a powerful computational tool that allows one to quantitatively estimate the energy of hyperconjugative effects (Alabugin & Zeiden, *JACS* **2001**, *124*, 3175). The stabilizing interactions for the H_1 and H_4 equatorial hydrogens for 1,3-dioxane and 1,3-dithiane are provided below. It is interesting that the two indicated hyperconjugative interactions in dioxane are approximately the same (4.5 vs 4.2) but that the same interactions in dithiane are quite different (6.5 vs 1.8). In fact, the authors refer to C–S bonds as "one directional" acceptor orbitals.



numbers refer to interaction energies in kcal/mol at the B3LYP/6-31+G*** level

There is one quite reasonable qualitative argument that can rationalize the "one directional" character of σ*C–S. Please provide your argument in the space provided below.

Question 2. (15 points). Epothilone is a potent macrolide natural product shown to bind tubulin in a similar fashion to the anticancer agent Taxol. In order to understand, and possibly enhance, the biological activity of epothilone, a detailed study of the conformation of the macrolactone has been recently reported (Taylor, *JOC*, **1999**, 7224-7228). The findings suggest that epothilone exists as a mixture of two conformations in solution, only one of which is medicinally relevant. Interestingly, the two conformations vary only in the C5-C9 carbon region of the structure.

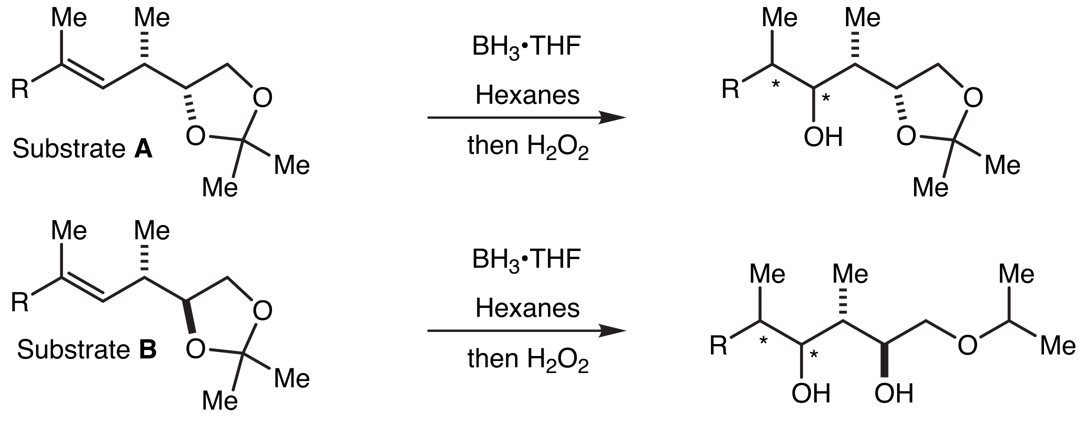


R = H, epothilone A
R = Me, epothilone B

Part A (5 points): Draw the most favorable 2,4-dimethylpentane conformer in a three dimensional drawing.

Part B (10 points): Extrapolate your answer from Part A and draw the two lowest energy conformations of the C5-C9 section of epothilone. *(Do not draw the whole molecule)*

Question 3. (15 points). The indicated olefins were subjected to hydroboration/oxidation as shown (*Synlett,* **1993**, 696).

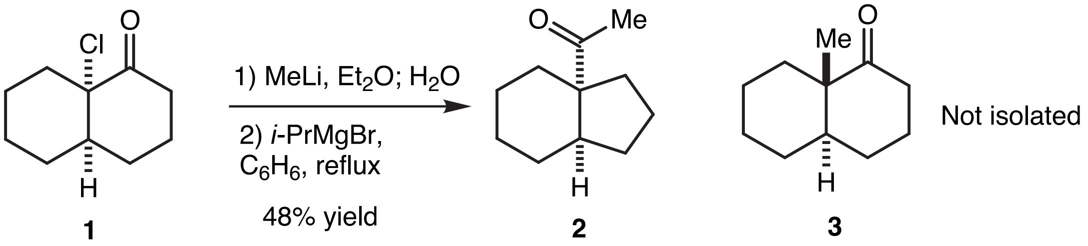

Substrate **A**

Substrate **B**

Part A. (8 points). Please predict the major stereoisomer obtained from these reactions and illustrate your predictions with clear 3D drawings.

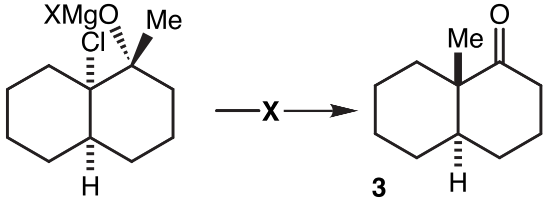
Part B. (7 points). Please also explain the fact that **B** suffers reductive ring opening while **A** does not..

Question 4 (15 points). Sisti and Citale (*J. Org. Chem.* **1972**, *37*, 4090) have reported that cis chlorodecalone (**1**) was treated with methyllithium and a mixture of stereoisomeric alcohols was isolated. When this mixture of alcohols was converted to the derived magnesium alkoxides and heated in benzene, the ring contracted product (**2**) was isolated in 48% overall yield. It is interesting that none of the trans methyldecalone (**3**) was observed.

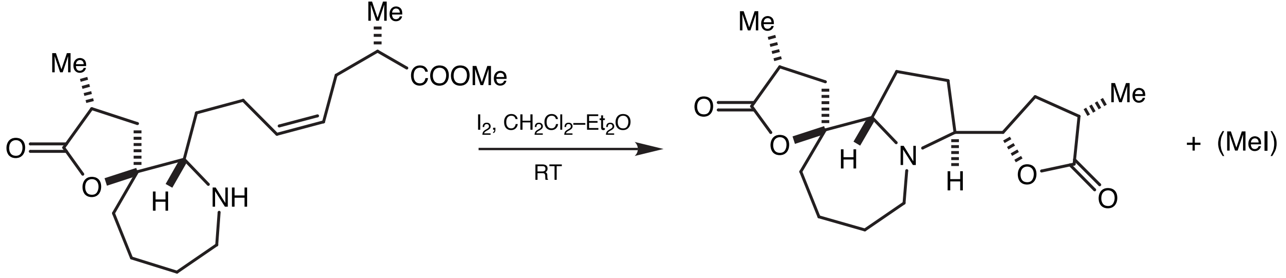


Part A (10 points). Rationalize the formation of **2** from both diastereomeric alcohols derived from **1**. Please use carefully rendered three dimensional drawings to illustrate your answer.

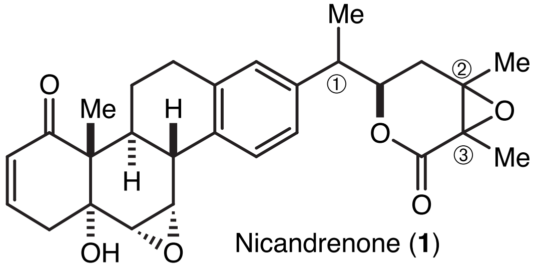
Part B (5 points). Explain why the indicated alkoxide does not lead to the formation of **3**.



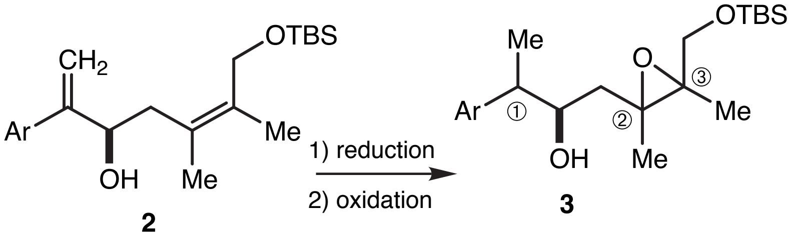
Question 5. (15 points). The iodine-induced transformation shown below is a key step in the Williams synthesis of croomine (*JACS* **1989**, *111*, 1923). Given the stereochemical outcome of the illustrated transformation, propose a detailed mechanism for this reaction sequence. Williams has recently provided another closely reaction of the same design (*Org. Lett* **2003**, *5*, 3361).



Question 6. (15 points). The Corey laboratory recently reported the first synthesis of several members of the Nicandrenone family of natural products that are produced from plants that have insectidal and antifeedent properties (*JACS* **2000**, *122*, 9044). In the terminal stages of the synthesis, the synthesis employs **two consecutive hydroxyl-directed transformations** to transform **2** into **3** and subsequently into the stereochemically elaborated lactone-containing sidechain. The first reaction is a reduction and the second is an oxidation.



Nicandrenone (**1**)

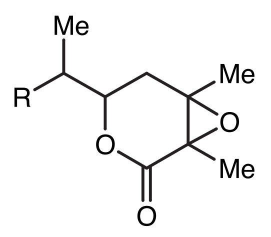


2 **3**

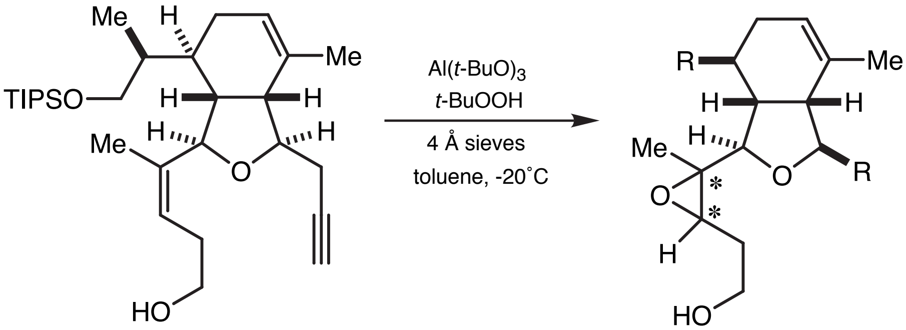
Part A (6 points). Illustrate, with conformational drawings, the reaction that leads to the generation of stereocenter ①. Predict the stereochemical relationship of this methyl-bearing stereocenter relative to the hydroxyl group. *Use part structures lacking the tetracyclic nucleus in your answer*. Please also precisely define the reagents that you will employ in this step.

Part B (6 points). Illustrate, with conformational drawings, the reaction that leads to the generation of the epoxide (centers ② and ③) Predict the stereochemical relationship of the epoxide relative to the hydroxyl group. Please also precisely define the reagents that you will employ in this step.

Part C (3 points). Finally, provide the full stereo structure of the illustrated terminal portion of this molecule. Pencil in the relevant stereochemical relationsips on the structure provided in the box



Question 7 (15 points). Overman and co-workers recently reported the indicated selective epoxidation in conjunction with a synthesis of briarellins A and E, a new family of diterpenes (*JACS* **2003,** *125*, 6650)**.** It should be noted that the Al(t-BuO)$_3$/(t)-BuOOH reagent system is both highly diastereoselective and site selective. It is also relevant to the mechanism of the reaction that the ring-trisubstituted olefin lacking an allylic oxygen substituent would normally be more prone to epoxidation with a peracid than the acyclic trisubstituted olefin.



Part A (7 points). Provide a general mechanism illustrating how the Al(t-BuO)$_3$/(t)-BuOOH reagent epoxidizes olefins. Three-dimensional drawings are recommended.

Part B (8 points). Provide a general mechanism illustrating how the above epoxidation proceeds and provide the stereochemistry (*) of the product epoxide along with a stereochemical analysis of the noted face selectivity.

Chemistry 206
First Hour Examination

D. A. Evans

October 13, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (10)	______
No. 7 (10)	______
No. 8 (10)	
Total (100)	

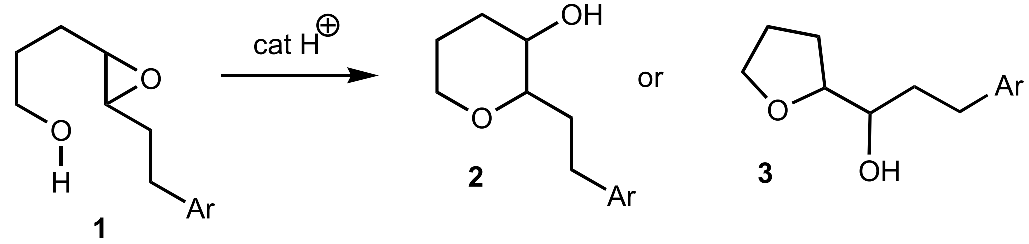
You have two hours to complete the exam
10:05 am to 12:05 pm

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate.
This examination has nine pages.

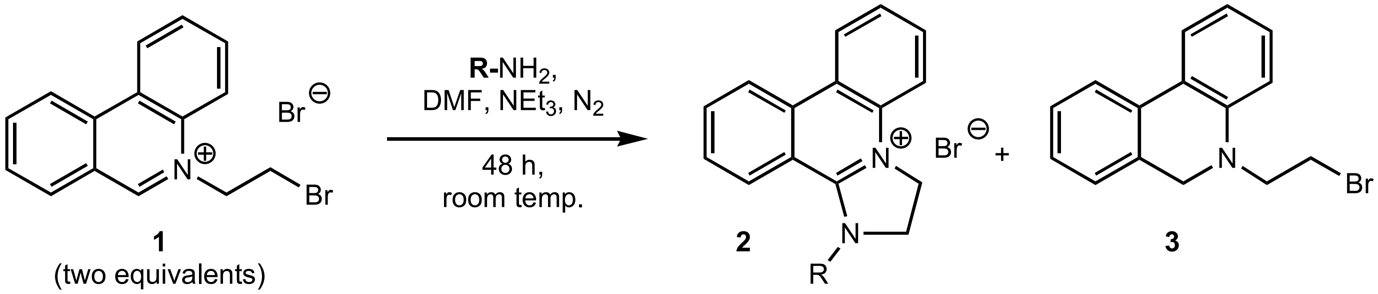
"Any man who, upon looking down at his bare feet, doesn't laugh, has either no sense of symmetry or no sense of humor."
Descartes

Question 1. (10 points). The acid catalyzed cyclization of trans epoxide **1** yields a single kinetic product *JACS* **1993**, *115*, 8453.



Predict the kinetic product of this reaction and its stereostructure (relative stereochemistry). Assume carbonium ions are not involved in this transformation. Provide an explanation that accounts for the selectivity of this process.

Question 2. (15 points). The following reaction was found serendipitously by Cronin while attempting to functionalize the side chain of starting material **1** (JOC **2004**, *69*, 5934, see also Tetrahedron **2005**, *61*, 8410).



1
(two equivalents)

2

3

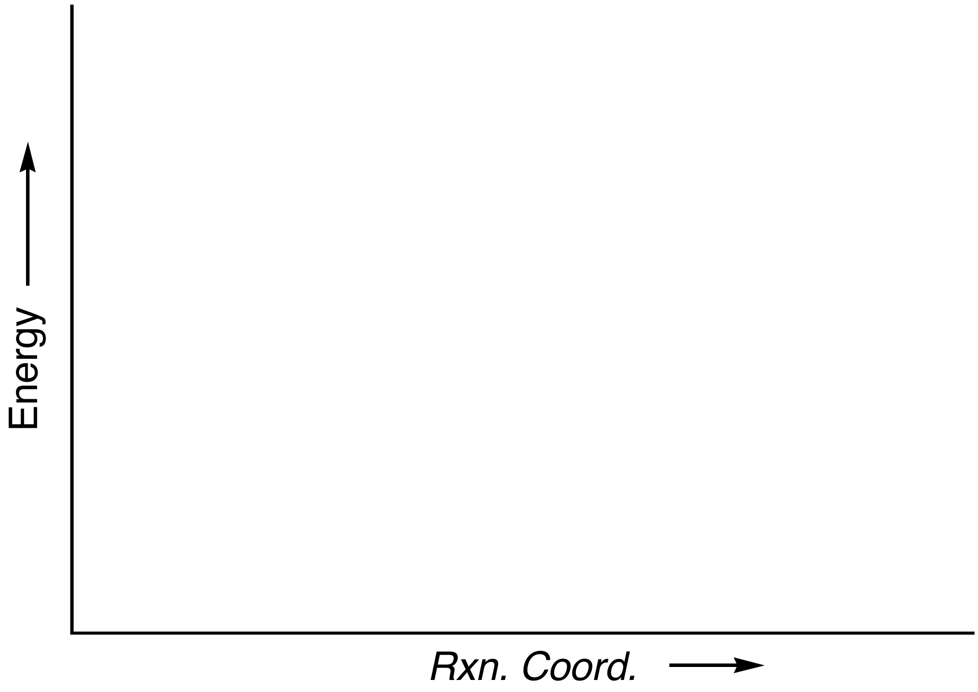
98% R = -CH_2CH_2OH

Provide a plausible mechanism for the indicated transformation. Your answer should include an explanation for the formation of **3** and a rationalization for the driving force for its formation.

Question 3. (15 points). Assume that you have a rapidly equilibrating mixture of two conformers **A** and **B** from which two products, $\mathbf{P_A}$ and $P_\mathbf{B}$ are produced (eq 1).

$$\mathbf{P_A} \xleftarrow[\text{slow}]{k_1} \mathbf{A} \underset{\text{fast}}{\underset{k_B}{\overset{k_A}{\rightleftharpoons}}} \mathbf{B} \xrightarrow[\text{slow}]{k_2} \mathbf{P_B} \qquad (1)$$

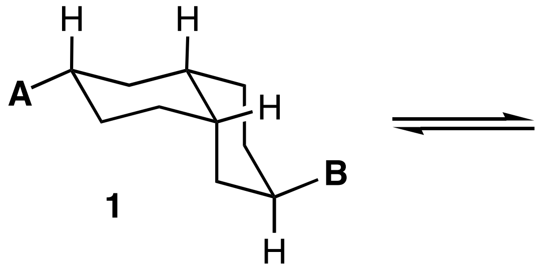
Part A. (10 points). Draw an energy diagram that reflects the situation where the equilibrium population of conformers is the same as the product ratio.



Part B. (5 points). Provide a concise statement of this circumstance in terms of free energy relationships.

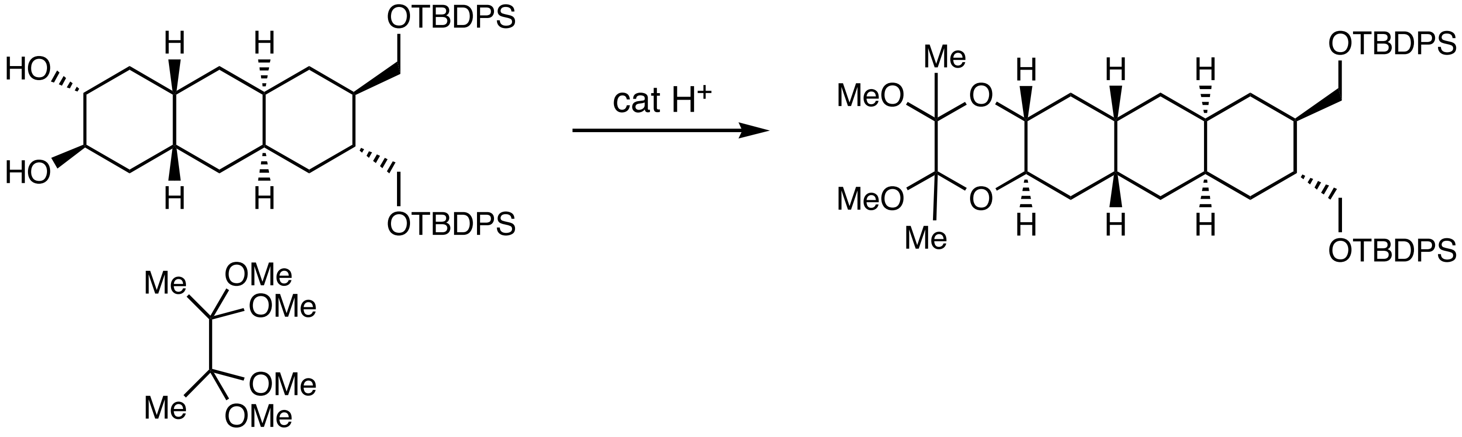
Question 4 (15 points). As you know trans decalins are conformationally rigid, while cis decalins can undergo a chair-chair conformational change.

Part A (5 points). Draw the the other chair-chair conformation of **1 i**n the space provided. Please Include the H-atoms on the stereogenic centers as well.



1

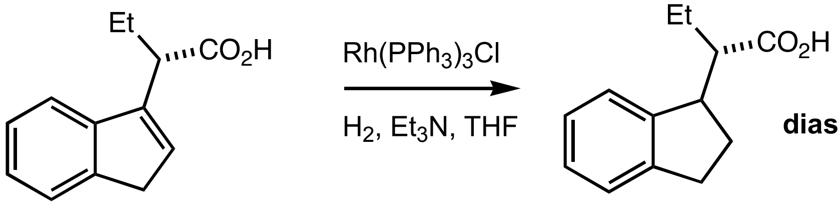
Part B (10 points). Provide 3D representations of the lowest-energy conformations of both the starting material and product in the following reaction. Be sure to indicate clearly all stereochemical relationships. Include the H-atoms on the stereogenic centers as well.



Your Answer:

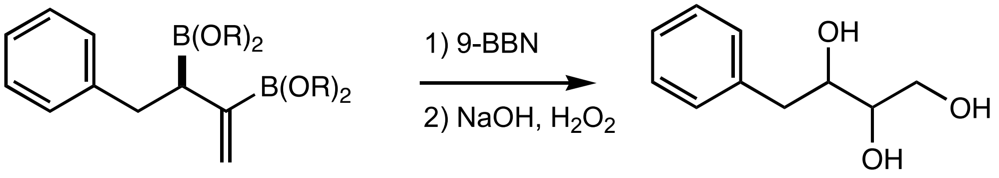
Question 5 (15 points). Please predict the stereochemical outcome of the following reactions by *indicating the stereochemistry of the product*. Please use clear 3D drawings of the relevant conformations to explain your prediction.

Part A (7 points).



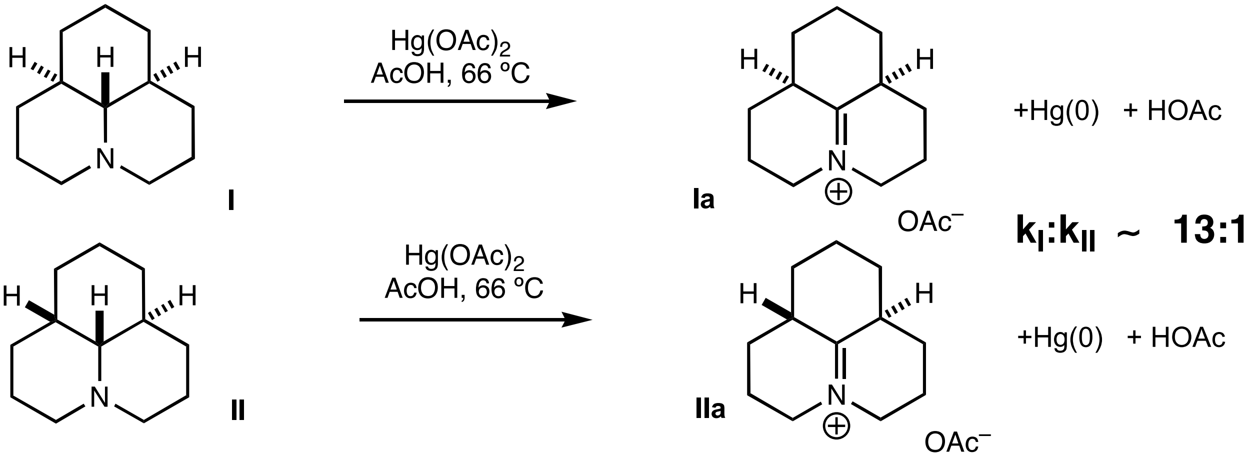
diastereoselection
>99:1

Part B (8 points).



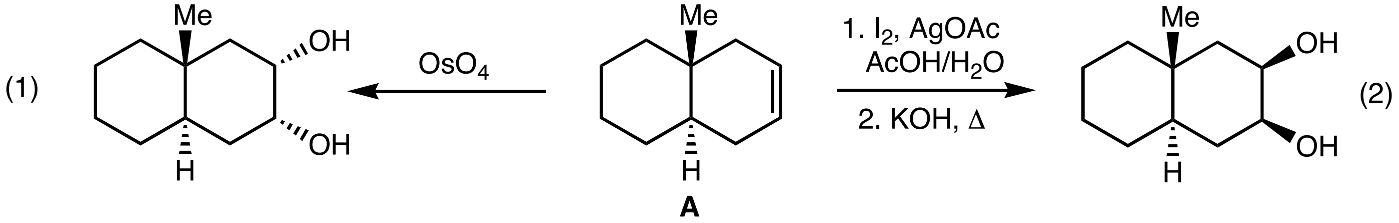
diastereoselection
10:1

Question 6. (10 points). Mercury(II) acetate is a mild oxidant that oxidizes tertiary amines **I** and **II** to the corresponding iminium cations **Ia** and **IIa** (Bohlmann, et al. *Chem. Ber.* **1958**, *91*, 2167). Interestingly, the rates for these oxidations are dramatically different with the oxidation of **I** being almost 13 times faster.



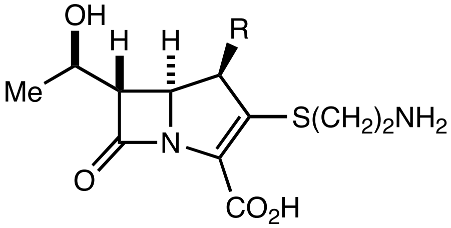
Using clear 3D drawings please provide the mechanism for this oxidation and explain the difference of reactivity using the FMO theory.

Question 7. (10 points). If an olefin such as **A** experiences a facial bias, one may count on steric effects to direct the course of a OsO_4 dihydroxylation to the *less hindered olefin diastereoface* (eq 1). Strategically, it is limportant to be able access the other stereochemical option: dihydroxylation from the *more hindered olefin diastereoface*. This stereochemical option may be implemented through the reaction summarized in equation 2. This reaction has been referred to as the Prevost-Winstein-Woodward dihydroxylation.

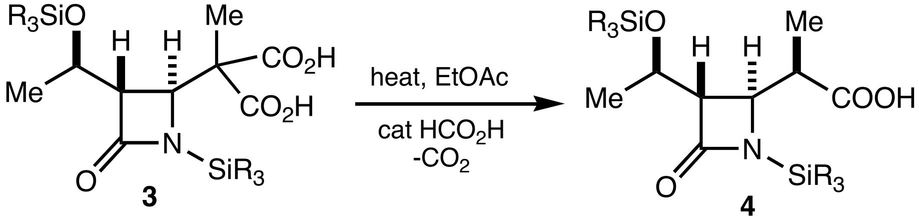


Provide a mechanism for the reaction illustrated in eq 2 in the space below. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

Question 8. (10 points). Thienamycin (**1**) is a potent antibiotic that has served as the template for the production of analogues with improved therapeutic properties. Several thienamycin derivatives currently marketed contain the indicated methyl substituent at the 1-position, a substitution that improves the chemical and metabolic stability of the antibiotic. In conjunction with the synthesis of **2**, the stereochemically interesting decarboxylation, **3**→**4**, has been reported (*Tetrahedron Lett*. **1994**, *35*, 2275).

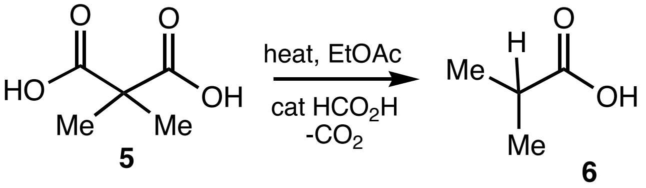


Thienamycin (**1**), R = H
1-β-methyl thienamycin (**2**), R = Me



diastereoselection: 94:6

Part A (5 points). In the space below, draw out each of the intermediates that might be anticipated in the transformation of **5** to **6**, simplified analogs of **3** and **4**.



Part B (5 points). In the space below, provide a rationalization for the sense of asymmetric induction that was observed in the transformation of **3** to **4**. Carefully rendered 3D drawings that clearly illustrate and support your argument should be included.

Chemistry 206
Second Hour Examination

D. A. Evans

November 20, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

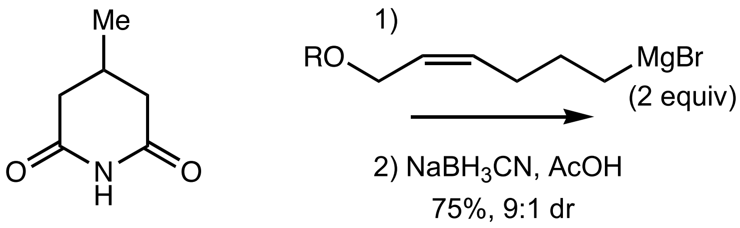
Question (pts)	Score
No. 1 (15)	
No. 2 (10)	
No. 3 (10)	
No. 4 (15)	
No. 5 (10)	
No. 6 (15)	
No. 7 (10)	
No. 8 (15)	
Total (100)	

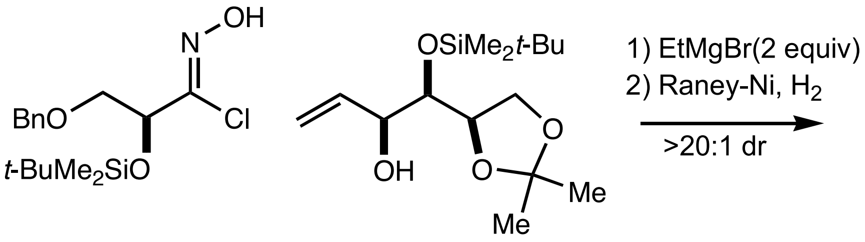
You have two hours to complete the exam
10:05 am to 12:05 pm

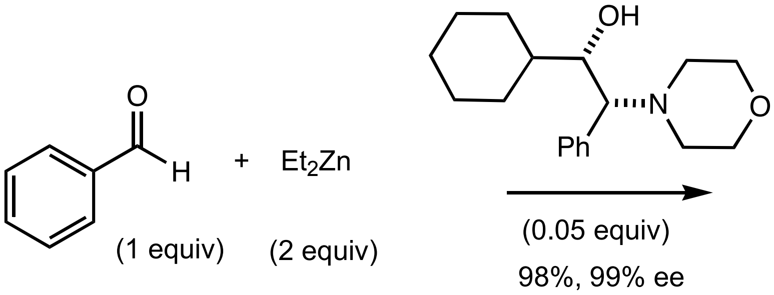
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate. This examination has nine pages.

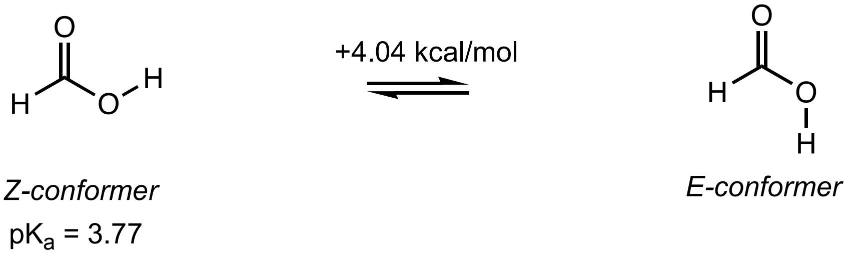
Question 1. (15 points). Predict the products for the transformations below. Also, provide mechanisms with the appropriate 3D models that explain your answer.



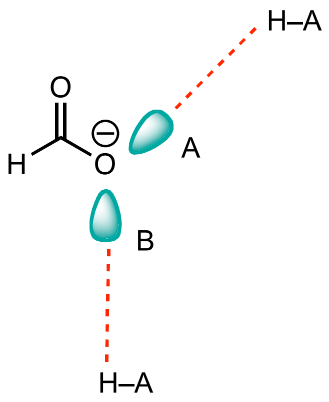




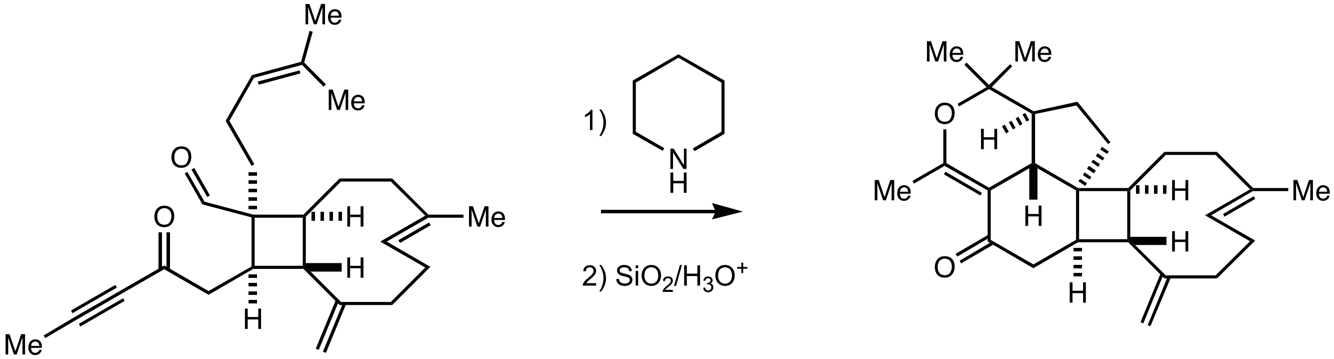
Question 2. Part A (7 points). A carboxylic acid can exist in two conformations *E* and *Z* that are different by the dihedral angle around the C–O bond. Recent theoretical calculations demonstrated that the *Z* isomer of formic acid is more stable by 4.04 kcal/mol (Ratajczyk *et al. Tetrahedron* **2004**, *60*, 179-185). Assuming that the pK_a of the *Z* isomer of formic acid is equal to 3.77 calculate the pK_a of the *E* isomer of formic acid. Assume that $\Delta G = 1.4 \cdot pK$ kcal/mol.



Part B (3 points). Based on your calculations propose which lone pair of the carboxylate anion shown below is going to be more basic. Is the FMO theory consistent with your answers?

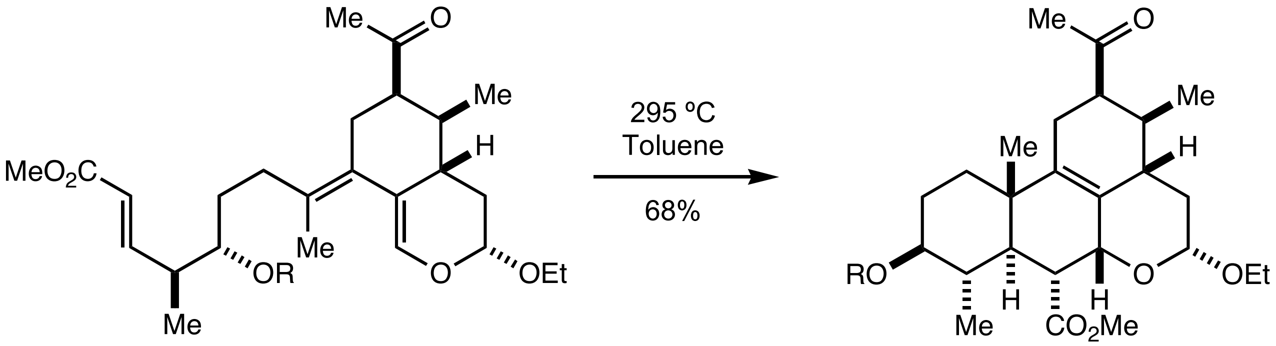


Question 3. (10 points). Recently, the sequence of reactions outlined below was used by Corey et al. (*JACS* **2006**, *128*, 14050) in their route to antheliolide A. Provide a mechanism for this reaction and explain the stereochemistry of the product.

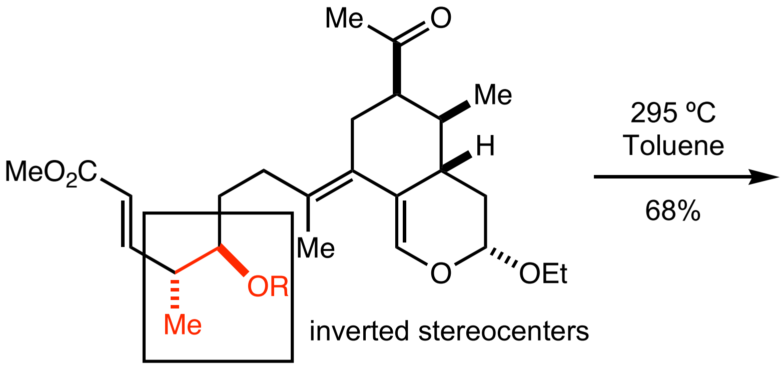


Antheliolide A

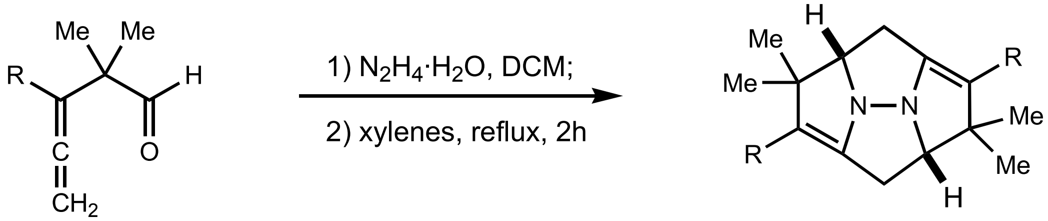
Question 4. Part A. (5 points). The following cycloaddition reaction was recently explored by Spino and Perreault (*Org. Lett.* ***2006***, *8*, 4385.) Provide a reasonable transition state that explains the stereochemistry of the product.



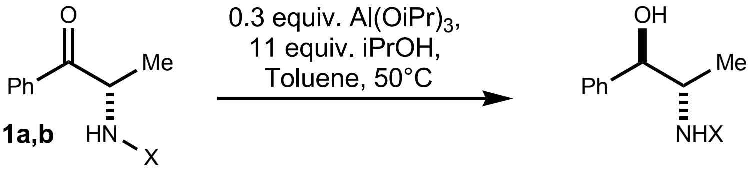
Part B. (10 points). Based on your solution above predict the stereochemical outcome of the cycloaddition carried out on the diastereomeric compound shown below. Use clear 3D drawing to explain your answer.



Question 5. (10 points). Provide a mechanism for the following reaction sequence recently published by the group of Potacek (*Eur. J. Org. Chem.* **2005**, 2548):



Question 6. (15 points). The Merck Research Laboratories have recently reported the following preparation of ephedrine analogues (*JOC* **2006**, *71*, 840):

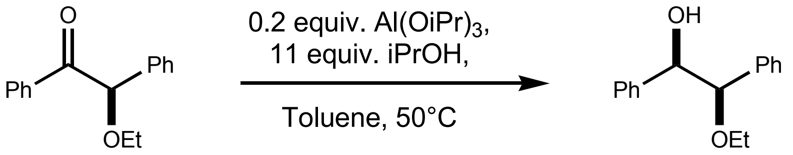


1a,b

1a: X = BnO(C=O)-: dr > **99:1**
1b: X = *p*-MePhSO$_2$-: dr = 82:18

Part A (10 points): Explain the reactions of **1a-b** using clear 3D-drawings. Discuss the role of the nitrogen substituents. Note that **no racemization** was observed during the reaction!

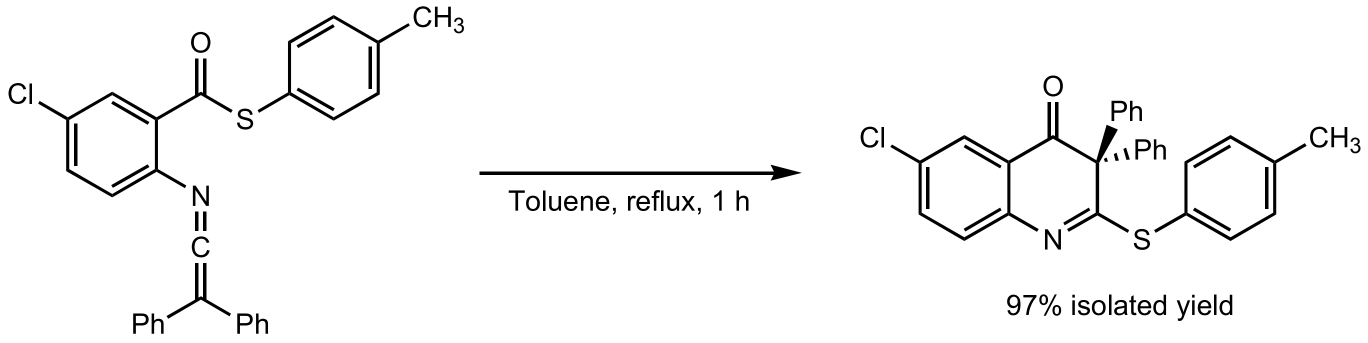
Part B (5 points): After subjecting ether **2** to the same conditions, the *syn*-product was obtained with high selectivity. Provide a 3D transition state drawing that explains this selectivity.



2

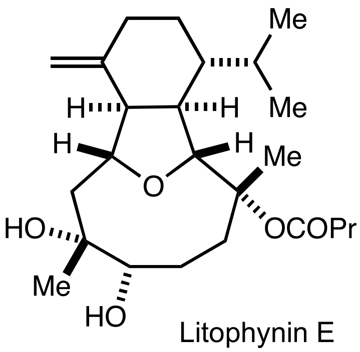
dr = 95.5:4.5

Question 7. (10 points). The quinolinone synthesis depicted below was recently reported by Alajarín and coworkers (*J. Org. Chem.* **2006**, *71*, 8126-8139). Please provide a mechanism for this transformation.



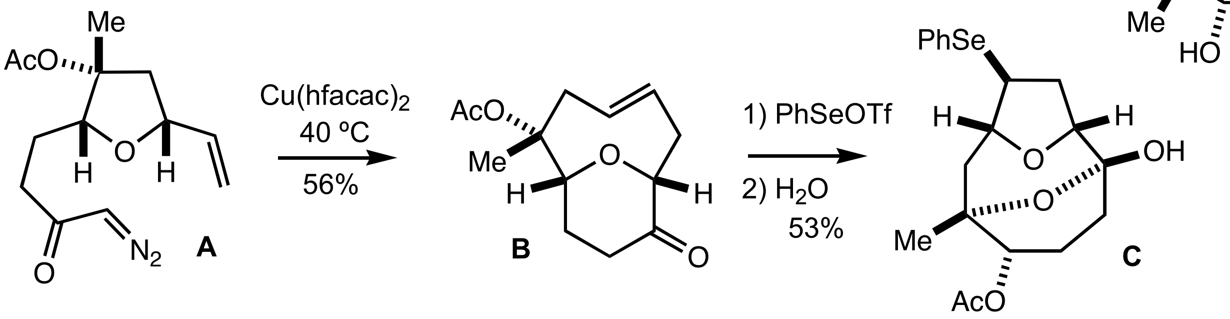
97% isolated yield

Question 8. (15 points). In a recent report of the synthetic studies towards cladiellins (Clark *et al. Synlett* **2006**, *14*, 2191) the depicted below transformations were used to construct the macrocycle of litophynin E.



Litophynin E

Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism of these transformations.



Chemistry 206
Third Hour Examination

D. A. Evans

December 18, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

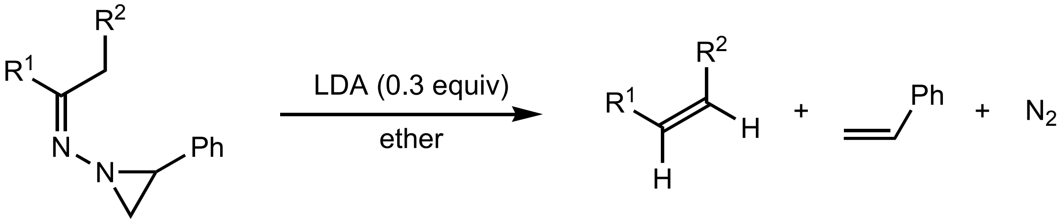
Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (10)	______
No. 4 (10)	______
No. 5 (10)	______
No. 6 (20)	______
No. 7 (10)	______
No. 8 (15)	______
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

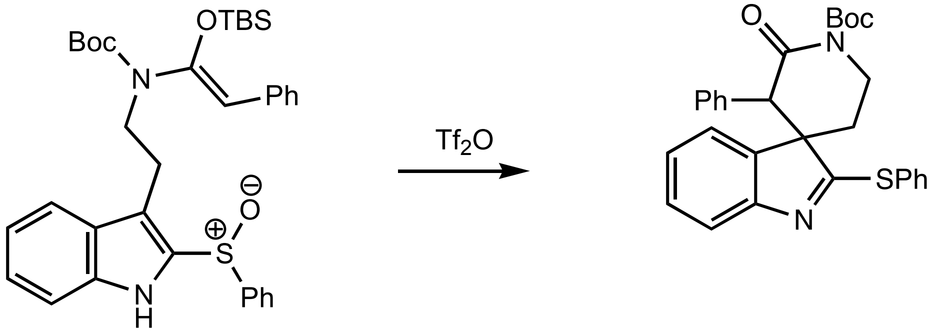
Be certain to address stereochemical and stereoelectronic issues where appropriate.
This examination has nine pages.

Question 1. (10 points). In 1996, Maruoka and Yamamoto published the illustrated reaction of ketone phenylaziridinylhydrazones with catalytic amounts of lithium amides (*J. Am. Chem. Soc.* **1996**, *118*, 2289-2290).

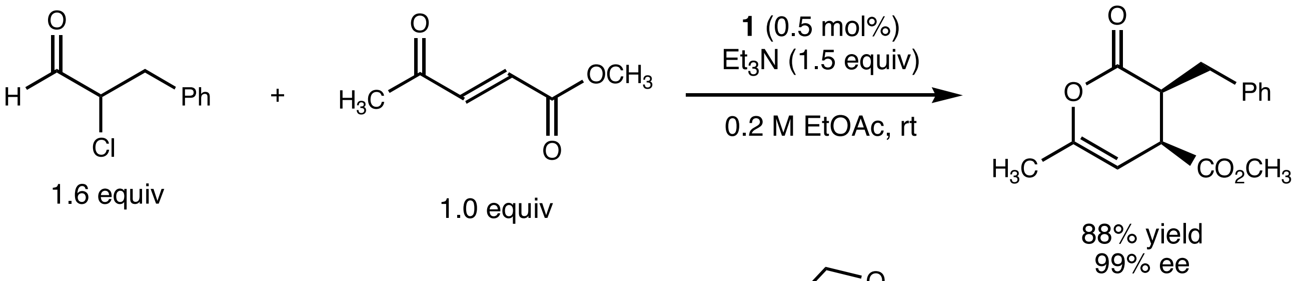


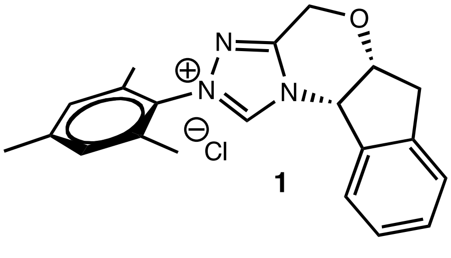
Provide a plausible mechanism that accounts for the observed *cis* selectivity and explain why 0.3 equivalents of LDA is enough to accomplish this transformation.

Question 2. (15 points). In 2004, Feldman and coworkers published a construction of 3,3-spirosubstituted oxindoles. (*Org. Lett*. **2004**, *6*, 1869-1871). Provide the reaction mechanism and predict the relative stereochemistry of the product. Explain the origins of diastereoselectivity using clear 3D drawings.



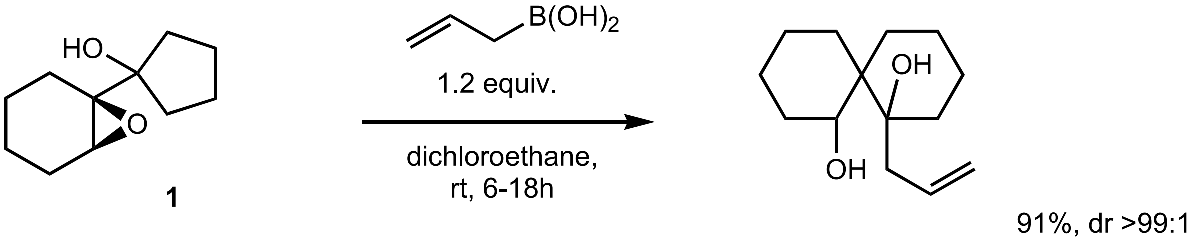
Question 3. (10 points). The transformation depicted below was recently reported by Bode and coworkers (*J. Am. Chem. Soc.* **2006**, *128*, 15088-15089.). Provide a mechanism for this transformation that accounts for the observed **relative** stereochemistry. **The absolute stereochemistry of the product does not need to be justified.**





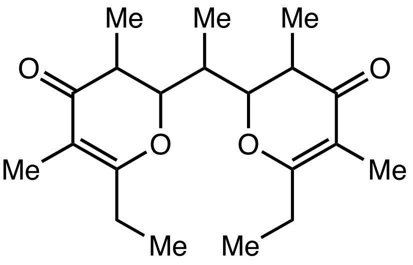
1

Question 4. (10 points). Tu *et al.* reported the following useful construction that could be used for a diastereoselective generation of the illustrated bicyclic structures with quaternary stereocenters. (*ACIEE* **2004**, *43*, 1702).

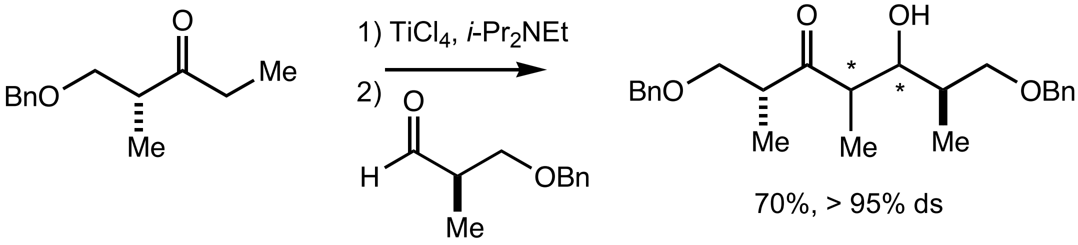


Please predict the absolute stereochemistry of the product and provide a mechanism that would support your predictions.

Question 5. (10 Points). The aldol addition reaction illustrated below was used to construct the core of the natural product (–)-membrenone-C (Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3*, 123-126). Provide the absolute stereochemistry of the product and show the transition state of this reaction with clear 3D drawings.

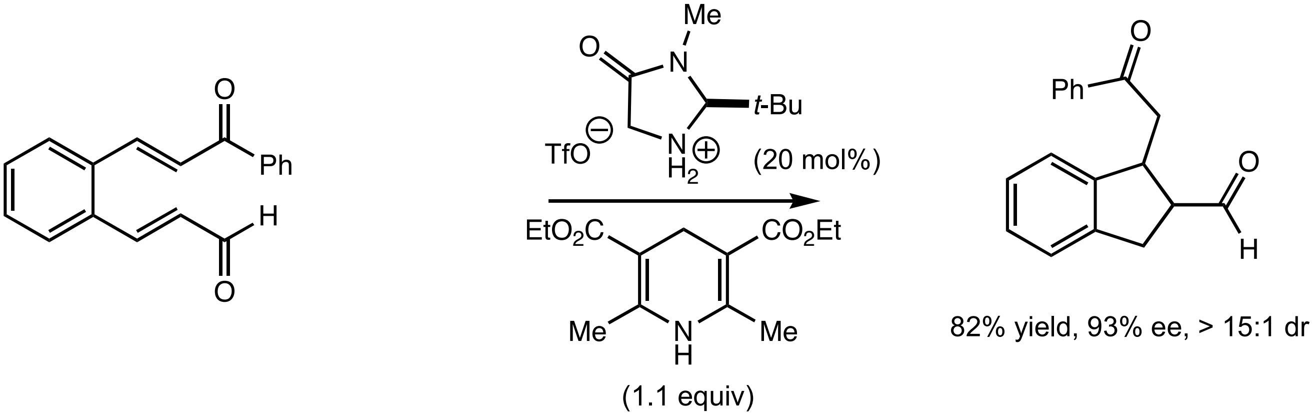


membrenone-C

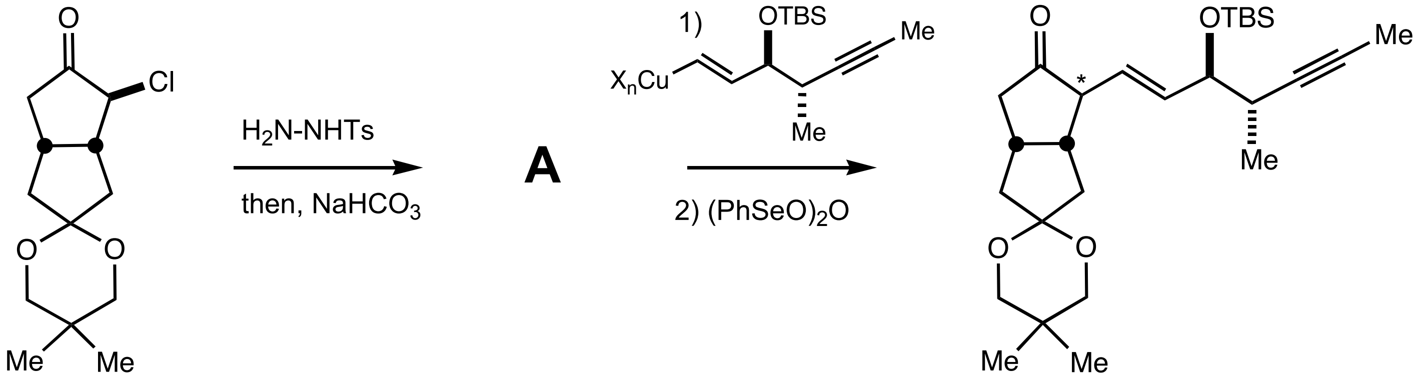


70%, > 95% ds

Question 6. (20 Points). The following tandem process was recently reported by the List group (*J. Am. Chem. Soc.* **2005**, *127*, 15036-15037). Please provide the mechanism for this transformation, predict the stereochemistry of the product and explain your predictions with clear 3D drawings.

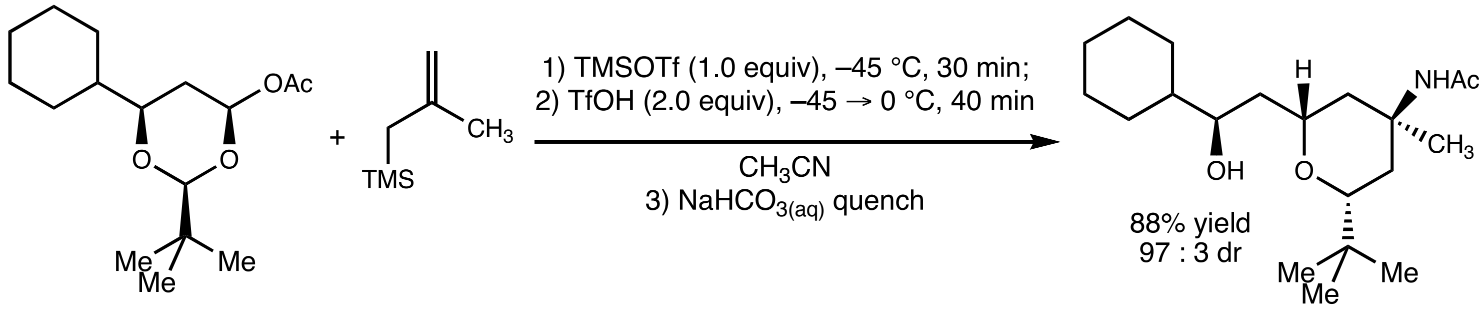


Question 7. (10 points). The following sequence has recently been developed during the synthesis of Prostacyclin (Gais *et al. JACS* **2005**, *ASAP*).



Please provide the structure of compound **A**, absolute stereochemistry of the product and mechanism for the transformation above. *You do not need to provide the mechanism for the* $(PhSeO)_2O$ *step.*

Question 8. (15 points). The transformation depicted below was recently reported by Rovis and coworkers (Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, ASAP). Provide a mechanism for this transformation that accounts for the observed diastereoselectivity.



Chemistry 206
Second Hour Examination

D. A. Evans

November 20, 2006

Name (please print): ____________________
last first initial

Signature: ____________________

Teaching Fellow: ____________________

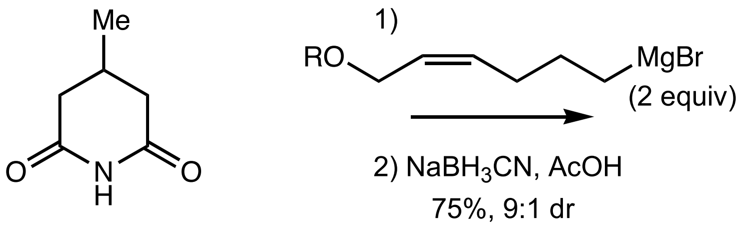
Question (pts)	Score
No. 1 (15)	______
No. 2 (10)	______
No. 3 (10)	______
No. 4 (15)	______
No. 5 (10)	______
No. 6 (15)	______
No. 7 (10)	______
No. 8 (15)	
Total (100)	

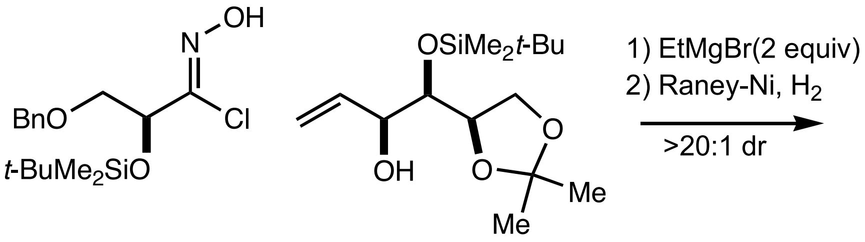
You have two hours to complete the exam
10:05 am to 12:05 pm

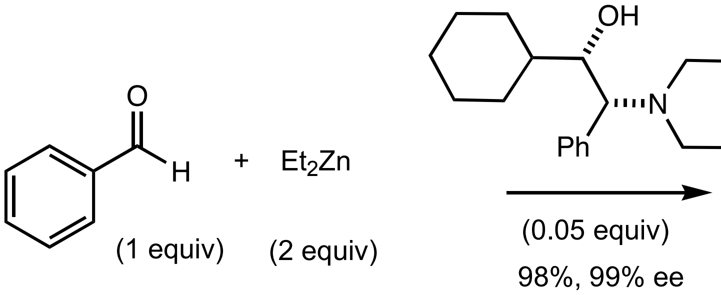
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate.
This examination has nine pages.

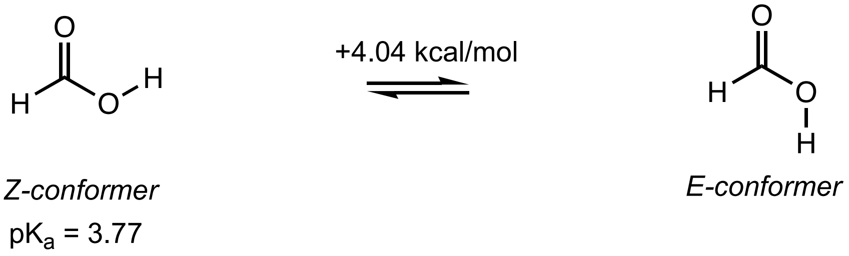
Question 1. (15 points). Predict the products for the transformations below. Also, provide mechanisms with the appropriate 3D models that explain your answer.



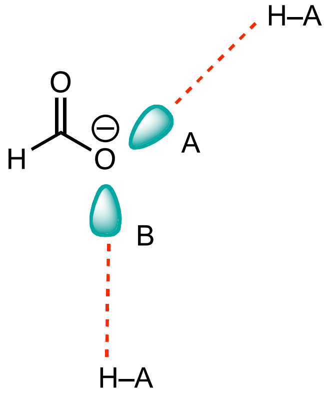




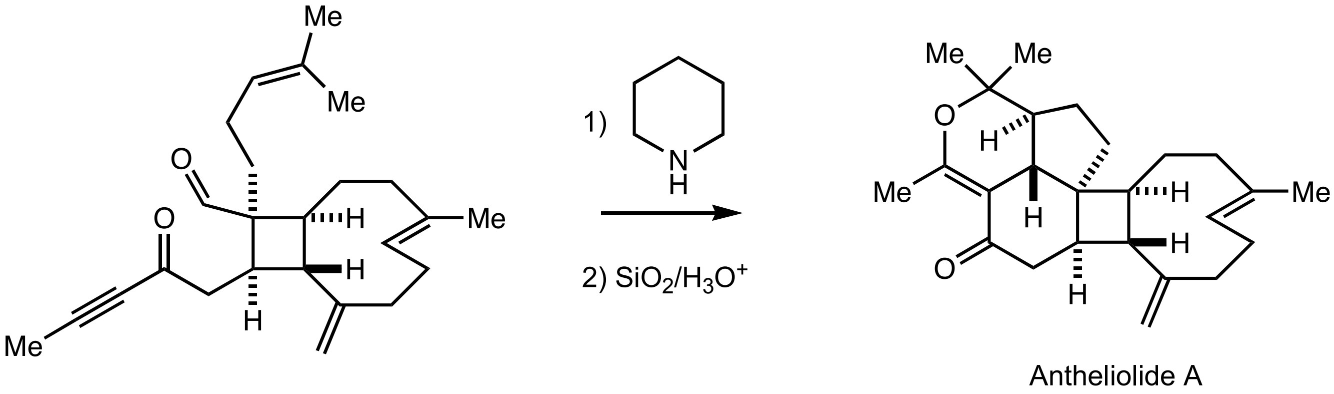
Question 2. Part A (7 points). A carboxylic acid can exist in two conformations *E* and *Z* that are different by the dihedral angle around the C–O bond. Recent theoretical calculations demonstrated that the *Z* isomer of formic acid is more stable by 4.04 kcal/mol (Ratajczyk *et al. Tetrahedron* **2004**, *60*, 179-185). Assuming that the pK_a of the *Z* isomer of formic acid is equal to 3.77 calculate the pK_a of the *E* isomer of formic acid. Assume that $\Delta G = 1.4 \cdot pK$ kcal/mol.



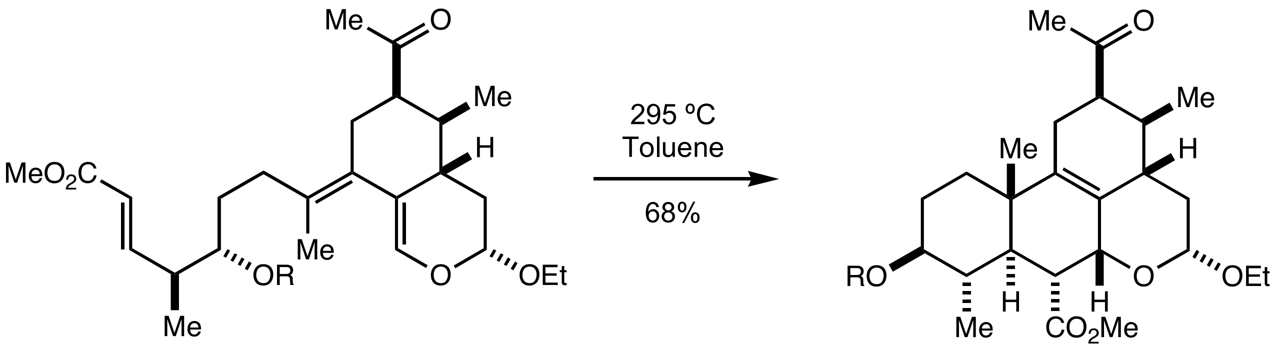
Part B (3 points). Based on your calculations propose which lone pair of the carboxylate anion shown below is going to be more basic. Is the FMO theory consistent with your answers?



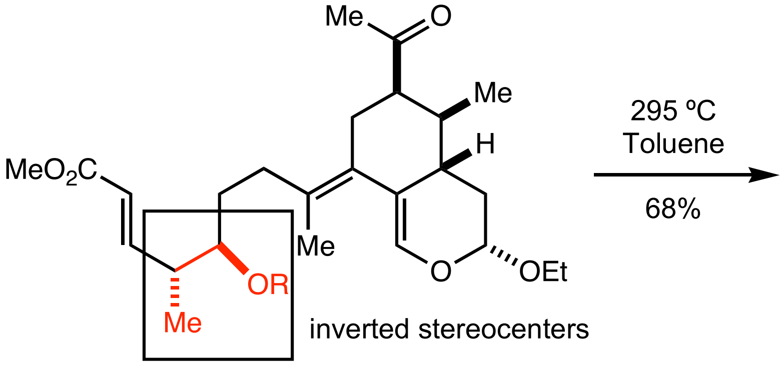
Question 3. (10 points). Recently, the sequence of reactions outlined below was used by Corey et al. (*JACS* **2006**, *128*, 14050) in their route to antheliolide A. Provide a mechanism for this reaction and explain the stereochemistry of the product.



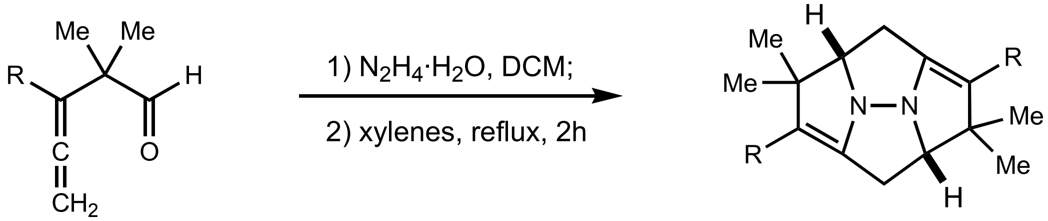
Question 4. Part A. (5 points). The following cycloaddition reaction was recently explored by Spino and Perreault (*Org. Lett.* ***2006***, *8*, 4385.) Provide a reasonable transition state that explains the stereochemistry of the product.



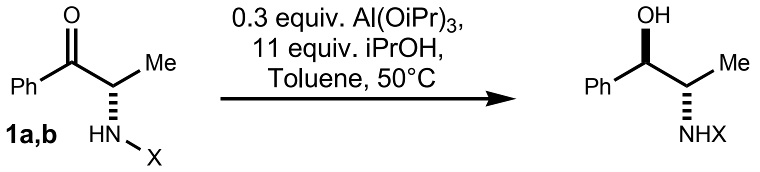
Part B. (10 points). Based on your solution above predict the stereochemical outcome of the cycloaddition carried out on the diastereomeric compound shown below. Use clear 3D drawing to explain your answer.



Question 5. (10 points). Provide a mechanism for the following reaction sequence recently published by the group of Potacek (*Eur. J. Org. Chem.* **2005**, 2548):



Question 6. (15 points). The Merck Research Laboratories have recently reported the following preparation of ephedrine analogues (*JOC* **2006**, *71*, 840):

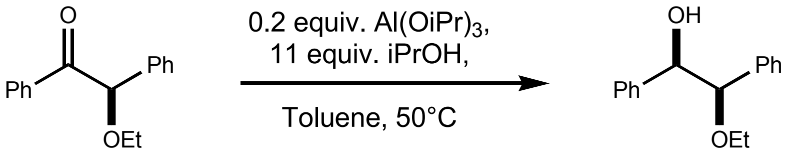


1a,b

1a: X = BnO(C=O)-: dr > **99:1**
1b: X = *p*-MePhSO$_2$-: dr = 82:18

Part A (10 points): Explain the reactions of **1a-b** using clear 3D-drawings. Discuss the role of the nitrogen substituents. Note that **no racemization** was observed during the reaction!

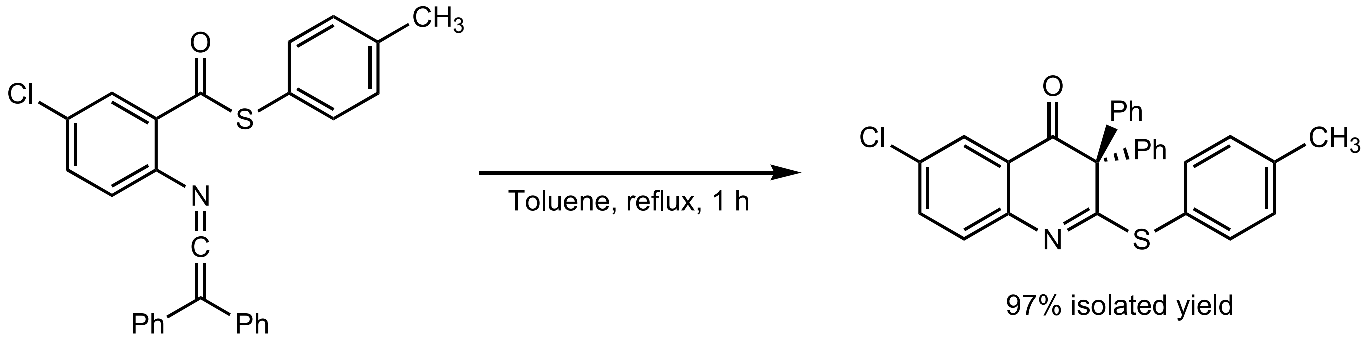
Part B (5 points): After subjecting ether **2** to the same conditions, the *syn*-product was obtained with high selectivity. Provide a 3D transition state drawing that explains this selectivity.

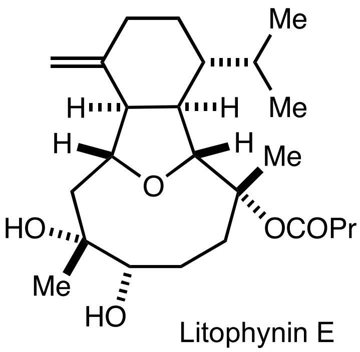


2

dr = 95.5:4.5

Question 7. (10 points). The quinolinone synthesis depicted below was recently reported by Alajarín and coworkers (*J. Org. Chem.* **2006**, *71*, 8126-8139). Please provide a mechanism for this transformation.

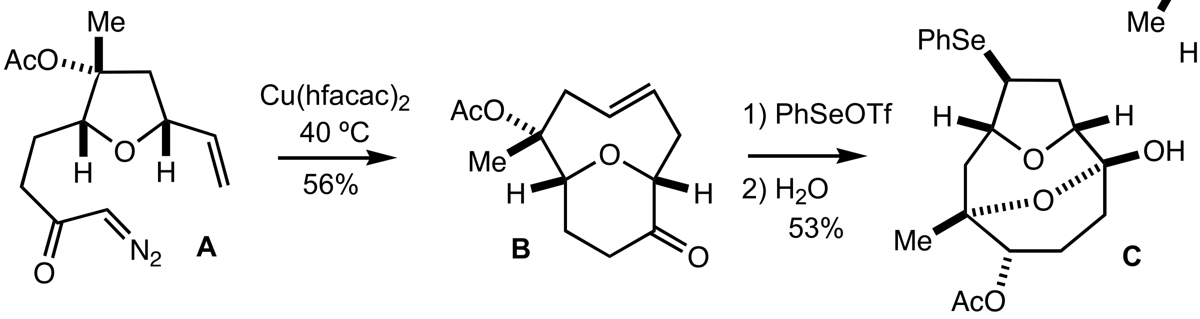




Litophynin E

Question 8. (15 points). In a recent report of the synthetic studies towards cladiellins (Clark *et al. Synlett* **2006**, *14*, 2191) the depicted below transformations were used to construct the macrocycle of litophynin E.

Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism of these transformations.



Chemistry 206
Final Examination

D. A. Evans
January 18, 2007

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

This examination contains **17** questions (17 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

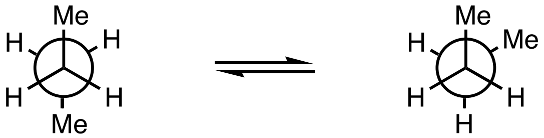
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**15**)	_______	No. 9 (**15**)	_______
No. 2 (**15**)	_______	No. 10 (**15**)	_______
No. 3 (**20**)	_______	No. 11 (**15**)	_______
No. 4 (**20**)	_______	No. 12 (**20**)	_______
No. 5 (**20**)	_______	No. 13 (**20**)	_______
No. 6 (**20**)	_______	No. 14 (**20**)	_______
No. 7 (**20**)	_______	No. 15 (**20**)	_______
No. 8 (**15**)	_______	No. 16 (**15**)	_______
Subtotal (**145**)		No. 17 (**15**)	
		Subtotal (**155**)	

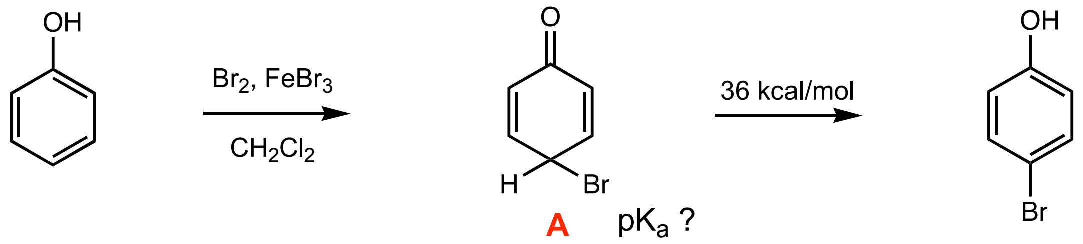
exam average

Total (300)

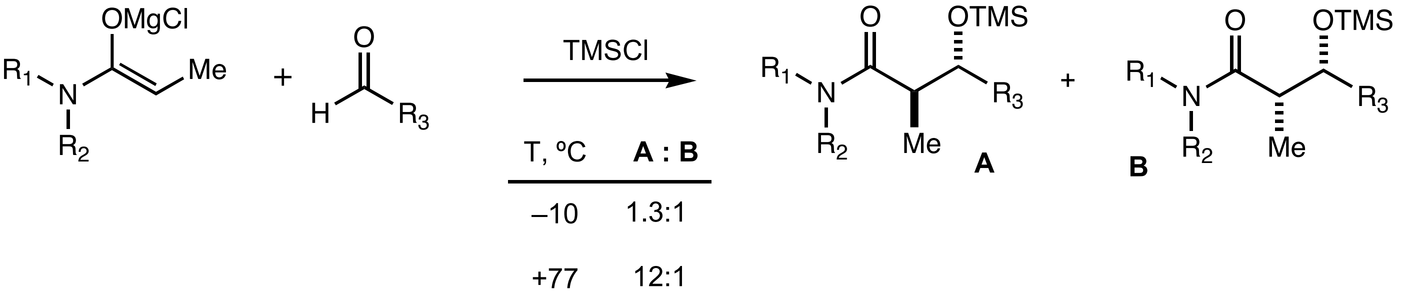
Question 1 (15 points). Estimate the relative percentage of *anti* and *gauche* *n*-butane conformers in the equilibrium shown below.



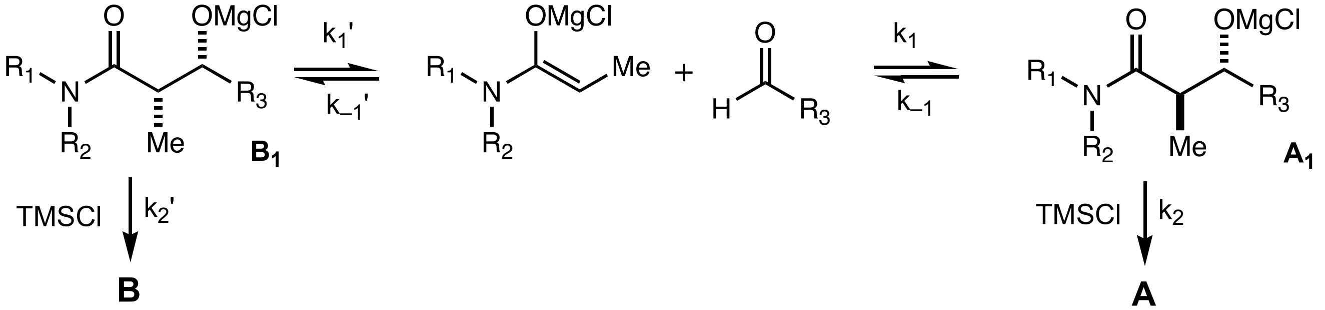
Question 2. (15 points). The ferric bromide promoted bromination of phenol proceeds through σ-complex **A**. Estimate the pKa of **A** assuming that the phenol resonance energy is 36 kcal/mol.



Question 3. (20 points). Consider an aldol addition reaction of the type illustrated below. It was found that the ratio of the diastereomeric products **A:B** increases with temperature. Assume that TMSCl is present at the beginning of the reaction and that RCHO is a better enolate electrophile than is TMSCl.

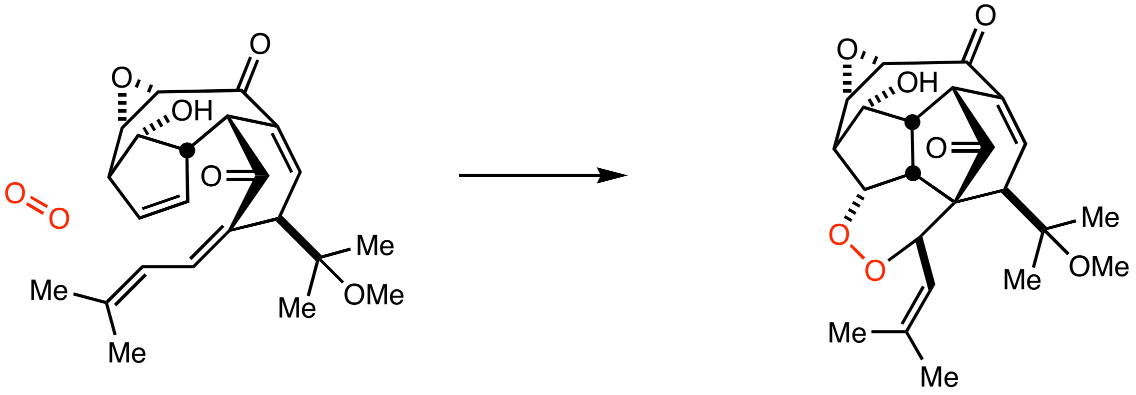


T, °C	**A : B**
–10	1.3:1
+77	12:1

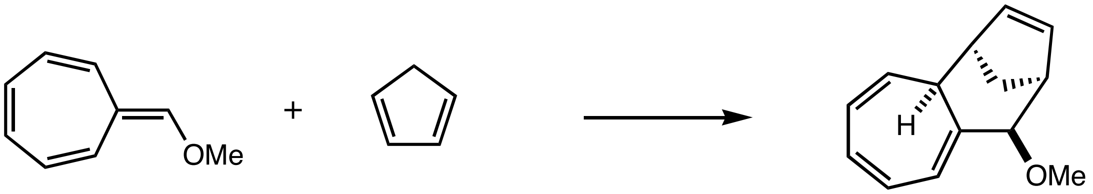


Using the mechanism provided draw the corresponding energy diagrams for –10 and +77 °C that would describe this situation. Comment on how rate constants should change with temperature in order for the illustrated effect to take place.

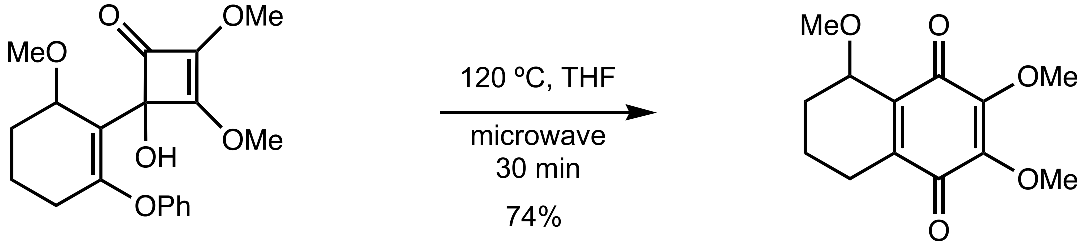
Question 4. Part A (10 points). Using Dewar-Zimmerman analysis predict whether this [2+2+2] cycloaddition with the participation of *singlet oxygen* is a thermally allowed pericyclic process.



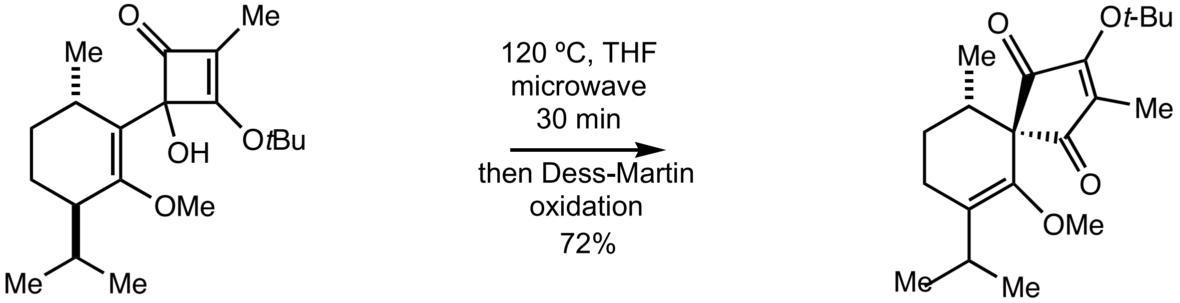
Part B (10 points). Using FMO analysis predict whether a cycloaddition illustrated below is a thermally allowed process.



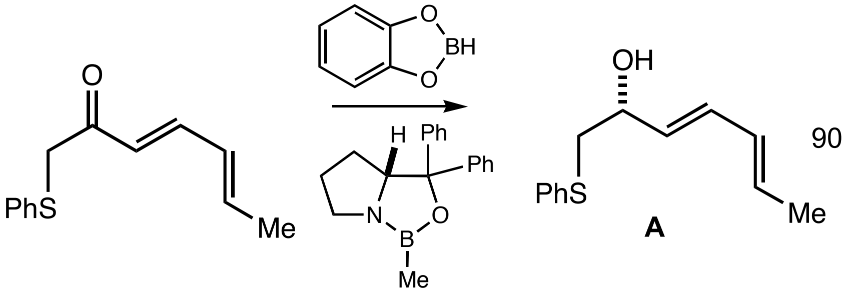
Question 5. Part A. (10 points). During a systematic study of thermally induced cyclobutenone rearrangements Harrowven discovered the illustrated transformation *(Angew. Chem. Int. Ed.* **2007**, *46*, 425-428) . Provide a detailed mechanism that accounts for the formation of the product.



Part B (10 points). As illustrated below, it was also discovered that the substrate structure plays an important role in the rearrangement outcome. Provide the mechanism of this transformation and explain the diastereoselectivity of this reaction. *You do not need to provide the mechanism of Dess-Martin oxidation.*

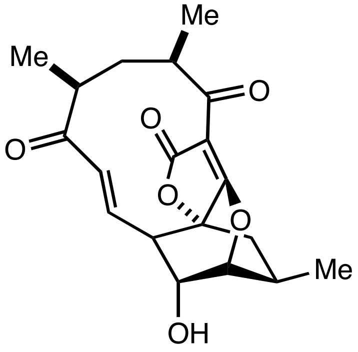


Question 6. (20 points). The following reaction sequence was used by the Nicolau group in their total synthesis of abyssomicin C (*JACS* **2007**, *129,* 429-440).



A

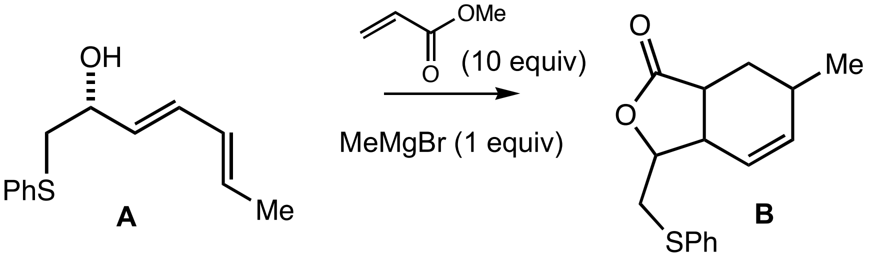
90% ee



Abyssomicin C

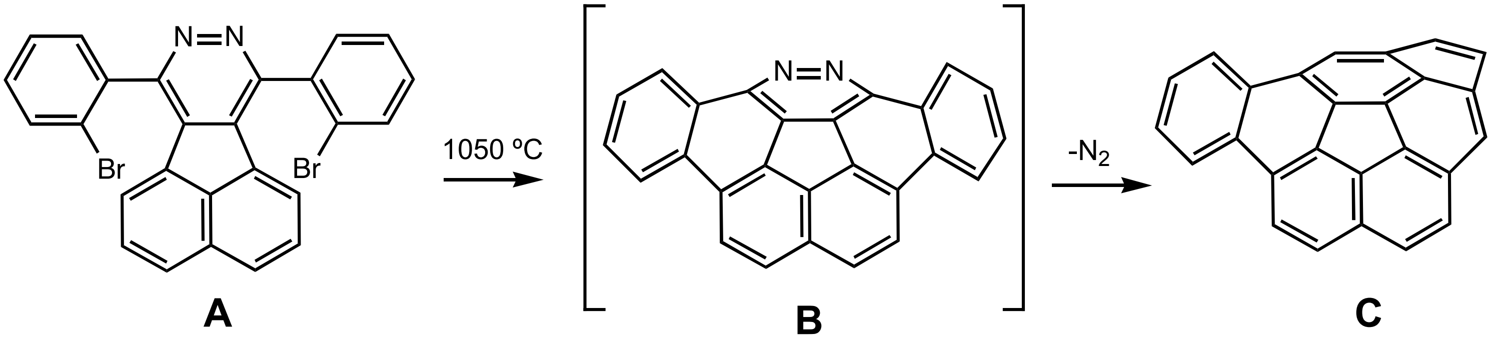
Part A (10 points). Rationalize the stereochemical course of this reduction via the well-accepted transition structure.

Part B (10 points). In the reaction below, product **B** is formed as a predominant diastereomer. Predict the absolute stereochemical relationships in **B** and explain your answer using clear drawings.



A **B**

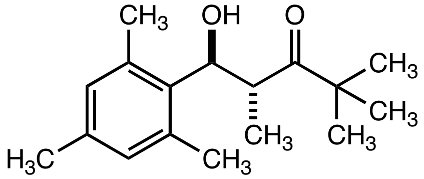
Question 7 (20 points). In their recent attempt to prepare compound **B** by the flash vacuum pyrolysis of dibromide **A**, Scott and Bodwell discovered the formation of the hydrocarbon **C** (*Org. Lett.* **2006**, *8*, 5195-5198). It was postulated that **C** is obtained by decomposition of **B** under the indicated reaction conditions.



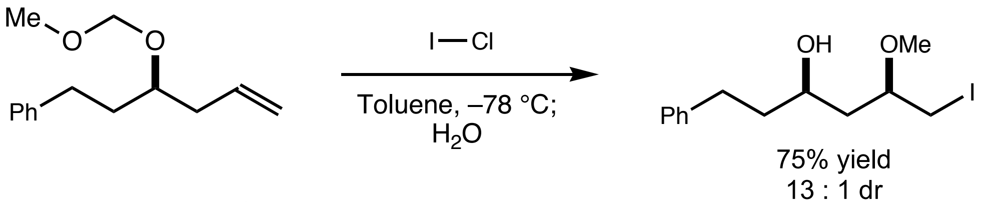
Part A. (10 points). Propose a reasonable mechanism for the transformation of **A** to **B**.

Part B. (10 points). Propose a reasonable mechanism for the transformation of **B** to **C**.

Question 8. (15 points). Draw what you would predict to be the most stable conformation of the product depicted below (*J. Org. Chem.* **2006**, *71*, 8835-8841).

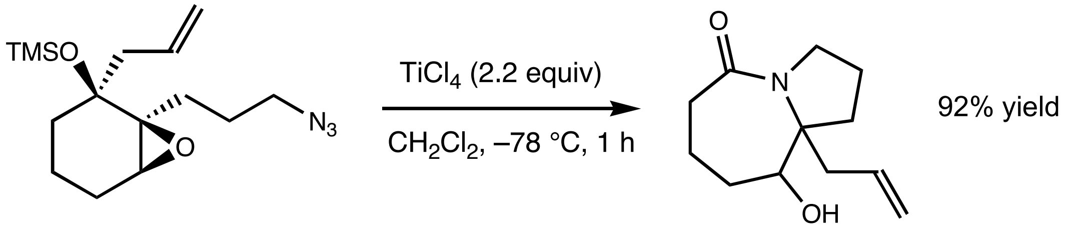


Question 9 (15 points). The highly diastereoselective iodoetherification depicted below was recently published by Taylor and coworkers (*Org. Lett.* **2006**, *8*, 5393-5395).



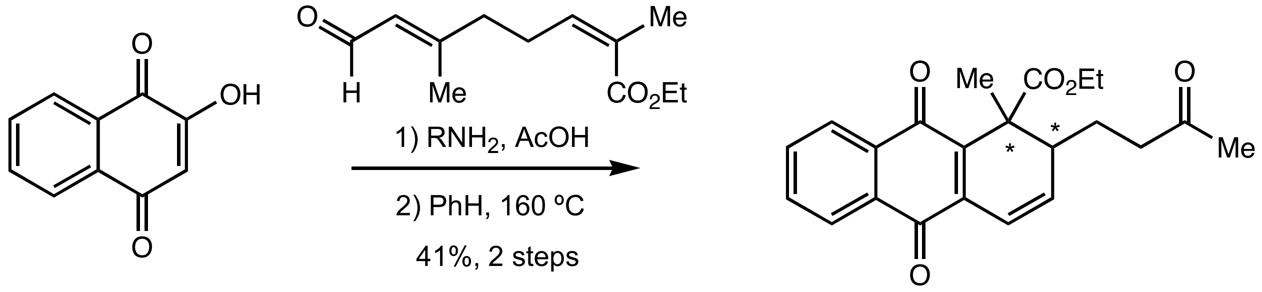
Provide a mechanism that accounts for the observed diastereoselectivity.

Question 10. (15 points). The transformation depicted below allows rapid access to azabicyclic ring systems (*Org. Lett.* **2006**, *8*, 5271-5273).



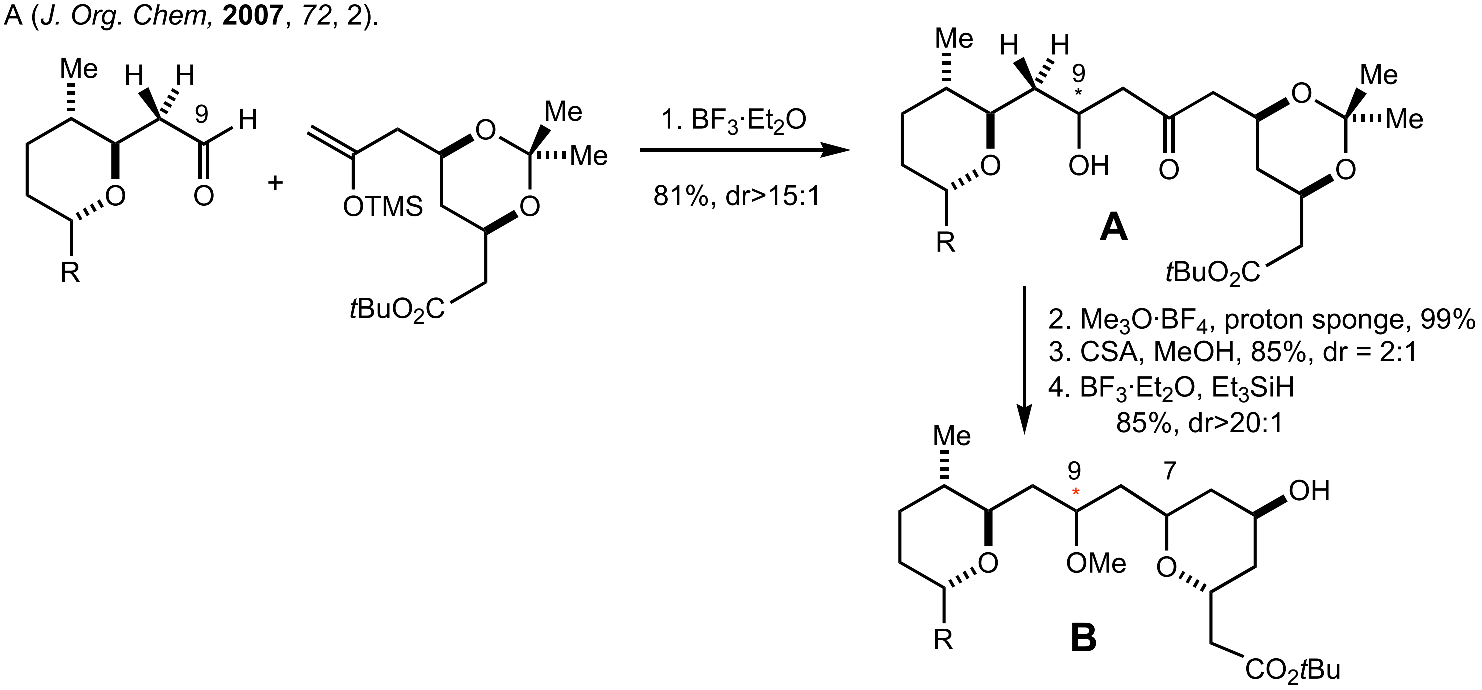
Provide a mechanism for this transformation and predict the stereochemistry of the product.

Question 11. (15 points). The following reaction cascade was recently employed by Trauner and coworkers (*JACS* **2005**, *127*, 6276).



Please provide a mechanism for this transformation and predict the relative stereochemistry of the product.

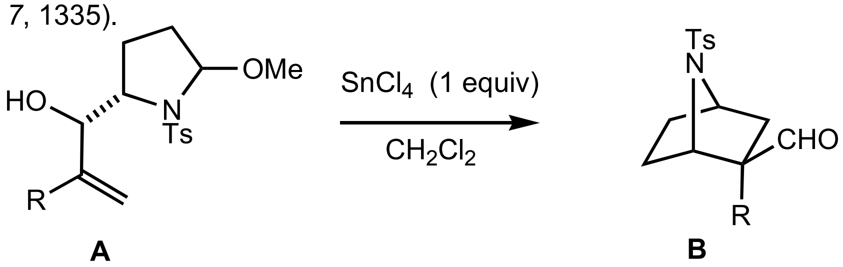
Question 12 (20 points). Below you see a short reaction sequence from Panek's recent synthesis of leucascandrolide A (*J. Org. Chem,* **2007**, *72*, 2).



Part A (10 points): Please predict the stereochemistry of the product **A** and draw a clear 3D transition state picture to support your predictions.

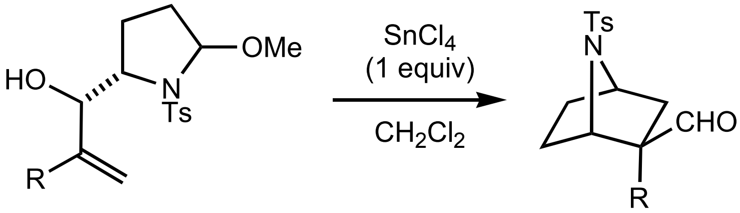
Part B (10 points). Draw the absolute configuration of the product **B** and rationalize the stereochemistry at the C7 stereocenter using clear 3D drawings.

Question 13 (20 Points). The illustrated rearrangement was recently investigated by Armstrong and Shanahan (*Org. Lett.* **2005**, *7*, 1335).



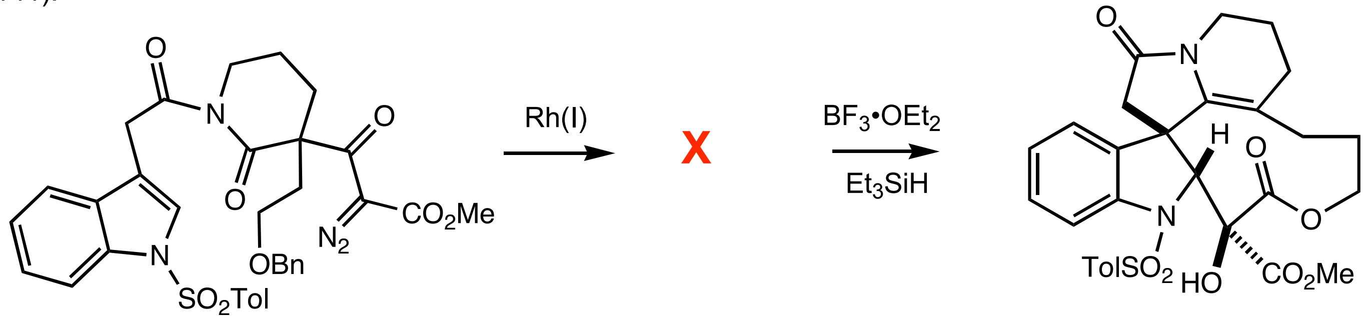
Part A (10 points). Provide two possible mechanisms for the formation of **B** from **A.**

Part B (10 points). Given the following evidence, analyze which pathway is the more plausible of the two paths presented in **Part A** .



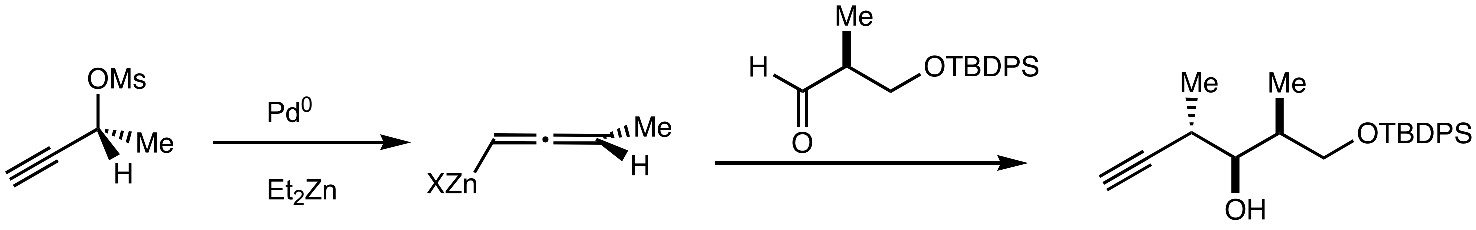
R	time	temp	yield
Ph	8 min	0 ºC	96%
Me	8 min	0 ºC	81%
H	14.5 h	20 ºC	32%
$PhSO_2$	–	–	NR

Question 14. (20 points). The following reaction cascade was resently reported by Padwa et al. (*Org. Lett.* **2006**, *8*, 5141).



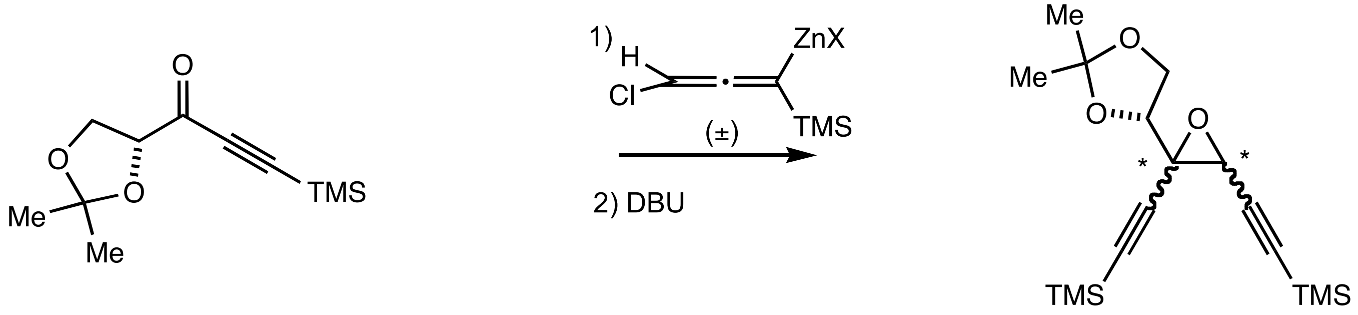
Provide the mechanism for this cascade and identify intermediate **X**.

Question 15 (20 points). Marshall and coworkers have reported the following diastereoselective addition of chiral allenylzinc reagents to aldehydes (*J. Org. Chem.* **1999**, *64*, 5201-5204).



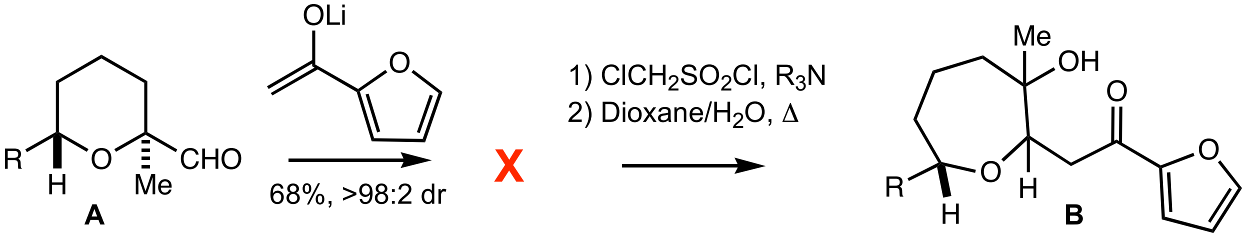
Part A (10 points). Propose a mechanism (i.e. transition state structure) for the addition of the allenylzinc that accounts for the observed stereochemistry and classify the products as Felkin or Anti-Felkin. *You do not need to show the mechanism for the formation of the allenylzinc species.*

Part B (10 points). The illustrated racemic allenylzinc reagent was recently used in the synthesis of the chiral epoxydiyne (Baker *et. al*, *Org. Lett.* **2007**, *9*, 45-48). Provide a plausible mechanism for this transformation and predict the relative stereochemistry of the resultant epoxide.



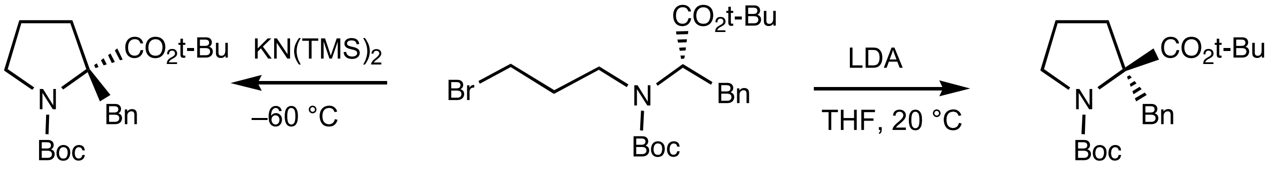
45%, >95:5 dr

Question 16. (15 points). An interesting approach to oxepanes has been developed by Nelson *et al. (Org. Lett.* **2006**, *8*, 4231) in their studies directed toward the synthesis of brevetoxin B. Thus, oxepane **B** is constructed by a three-step procedure starting from aldehyde **A**.



Identify intermediate **X,** provide the mechanism of these transformations and predict the stereochemistry of **B.**

Question 17. (15 points). Kawabata has recently reported the rather remarkable enolate alkylation of the indicated (S)-phenylalanine derivative **1** *(JACS* **2006**, *128,* 15394-19395). The reaction is strongly counter ion dependent with the potassium enolate reacting with nearly complete retention while the lithium enolate alkylates with inversion.



P-(*S*), Retention (98% ee) **1** (99% ee) **P-(*R*)**,Inversion (91% ee)

Part A. (10 points). Provide a rationalization for the transformation of **1** to **P-(*S*).**

Part B. (5 points). Provide a rationalization for the transformation of 1 to **P-(*R*).**

Chemistry 206
Final Examination

D. A. Evans
January 23, 2000

Name (please print):____________________________
last first initial

Signature:____________________________

Teaching Fellow:____________________________

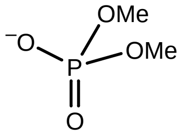
This examination contains **19** questions for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**10**)	_______	No. 11 (**20**)	_______
No. 2 (**10**)	_______	No. 12 (**15**)	_______
No. 3 (**10**)	_______	No. 13 (**15**)	_______
No. 4 (**15**)	_______	No. 14 (**20**)	_______
No. 5 (**10**)	_______	No. 15 (**20**)	_______
No. 6 (**10**)	_______	No. 16 (**20**)	_______
No. 7 (**15**)	_______	No. 17 (**15**)	_______
No. 8 (**20**)	_______	No. 18 (**20**)	_______
No. 9 (**15**)	_______	No. 19 (**20**)	_______
No. 10 (**20**)			
Subtotal (**135**)		Subtotal (**165**)	

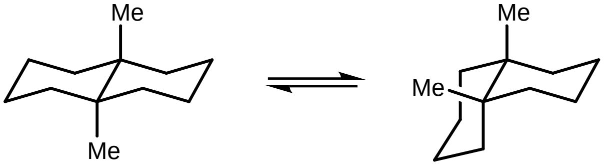
Total (300)

Question 1 (10 points). As mentioned in class, the conformation of the sugar-phosphate backbone in DNA is found to exist in one principal conformation. Consider dimethyl phosphate anion, $[(MeO)_2PO_2]^-$, as a model for DNA. Draw a detailed 3D structure of the preferred conformation of $[(MeO)_2PO_2]^-$. Indicate the specific interactions responsible for your predicted geometry.



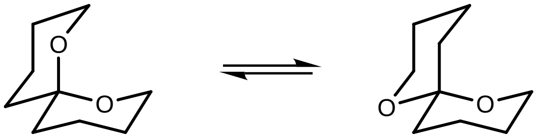
Question 2 (10 points). For each of the questions below, provide the requested information. When you are requested to estimate the relative energies of two conformers (**Parts A-B**), indicate: (1) the A-value(s) or A-value estimate(s) that you have employed; (2) the logic used to make the Δ G° estimate. If you follow this procedure, we may assign partial credit to those answers that are not completely correct.

Part A (5 points). Estimate the energy difference between these two decalin isomers.



Δ skew interactions	Δ G° (kcal/mol) estimate

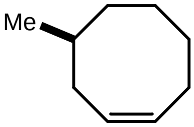
Part B (5 points). Estimate the energy difference between these two dioxaspirane isomers.



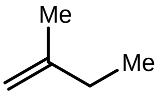
Δ G° (kcal/mol) estimate ____________

Question 3 (10 points).

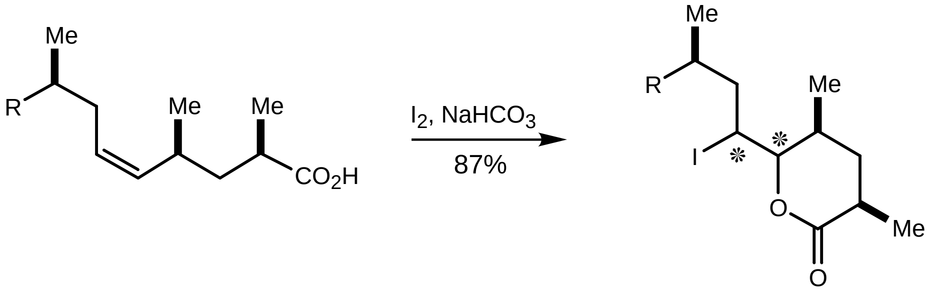
Part A (5 points). Draw the preferred conformation of this cyclooctene derivative.



Part B (5 points). Draw the lowest-energy conformation of 2-methyl-1-butene.

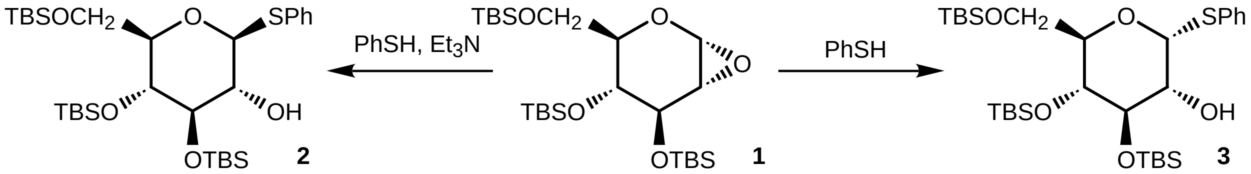


Question 4 (15 points). The Still synthesis of monensin (*JACS* **1980**, *102*, 218) features the diastereoselective iodo-lactonization shown below.



Provide a concise mechanism for this reaction in the space below. Be sure to identify all intermediates. In your answer, predict the stereochemical outcome of this transformation and identify the relevant stereochemical control element(s) operating in this reaction.

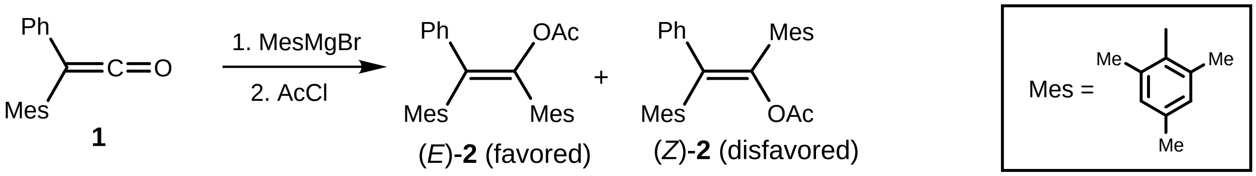
Question 5 (10 points). The illustrated glycal epoxide **1** reacts with thiophenol to afford in high selectivity either **2** or **3** depending on the reaction conditions (Jackson, *Chem. Commun.* **1997**, 1855).



Provide a concise mechanism for each transformation in the space below. Clear three dimensional representations should be employed in your answer.

Question 6 (10 points). Draw the two chair conformations of **3** below. Based on an analysis of the vicinal ring ^{1}H-NMR coupling constants it is evident that the –SPh substituent is oriented in the equatorial position in the favored conformation of **3**. Explain why your conformation illustrated below possessing the equatorial substituent is more stable than the other illustrated conformer.

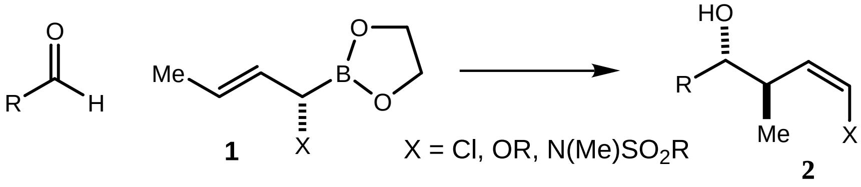
Question 7 (15 points). Rappoport has recently reported the transformation illustrated below (*JACS* **1996**, *118*, 12580). The kinetic stereochemical outcome of this reaction is superficially unanticipated in that the Grignard reagent adds to ketene **1** from the "more hindered" carbonyl π-face. This value judgement evolves from the assumption that the *mesityl substituent is more sterically demanding than the phenyl substituent*.



(*E*)/(Z) = 3:1 (kinetic ratio)

Provide a rationalization for this "contrasteric" ketene addition.

Question 8 (20 points). A recent paper by Hoffmann (*Eur. J. Org. Chem.* **2001**, 323) highlights important advances made by this laboratory over the years in enantioselective aldehyde allylboration. A typical reaction developed by Hoffmann is illustrated below. In this case the enantiopure allylboronate **1** is transformed into the *anti* adduct **2** with high selectivities. The absolute stereochemical relationships of **1** and **2** are as illustrated.

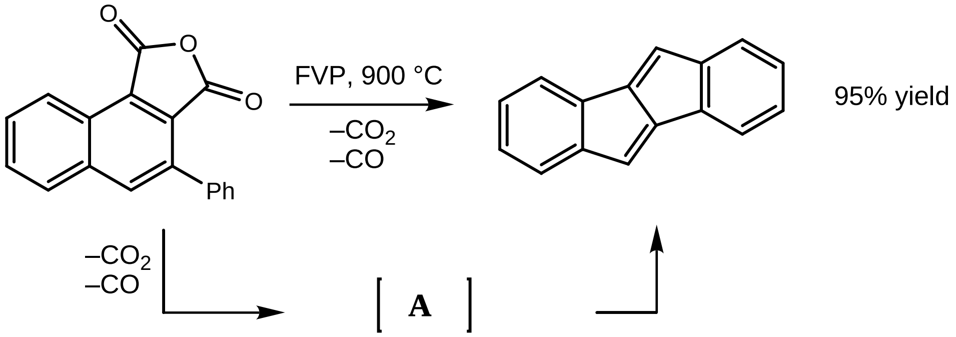


Anti/syn diastereoselection
> 15:1
enantioselection
> 95%

Part A (15 points). Draw the obligatory transition state for this transformation below. A carefully rendered three dimensional illustration is requested.

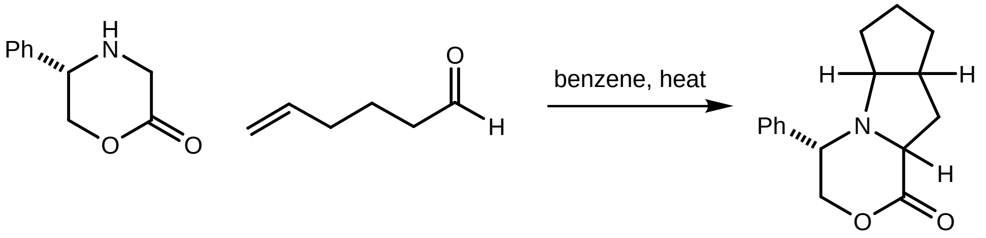
Part B (5 points). Identify those hyperconjugative effects, if any, that might be involved in transition state stabilization.

Question 9 (15 points). Anderson has reported the transformation illustrated below (*Aust J. Chem.* **1990**, *43*, 1137) which is implemented by flash vacuum pyrolysis (FVP) at the indicated temperature. As indicated, this reaction proceeds through intermediate **A**.



Provide a concise mechanism for this reaction in the space below and identify intermediate **A** in your answer.

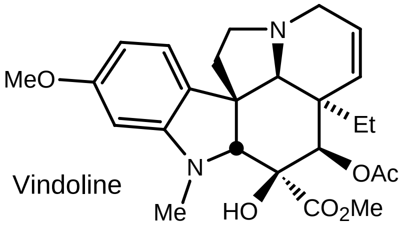
Question 10 (20 points). A recent paper by Harwood and Park highlights the rapidity which whch one may assemble complex architecture in a single chemical operation (*Tetrahedron Lett.* **1999**, *40*, 2907 and earlier cited references). The transformation in question is illustrated below. You are asked to address two aspects of this transformation.

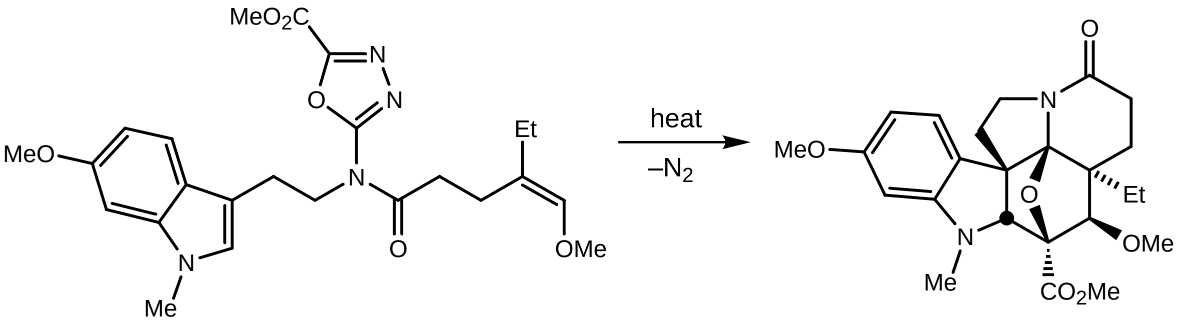


Part A. (10 points). Provide a concise mechanism for the indicated transformation. For now, ignore the stereochemical aspects of the reaction.

Part B. (10 points). Predict the stereochemical outcome of the reaction at the three new stereocenters, and provide a three-dimensional drawing of the transition state wherein these centers are produced.

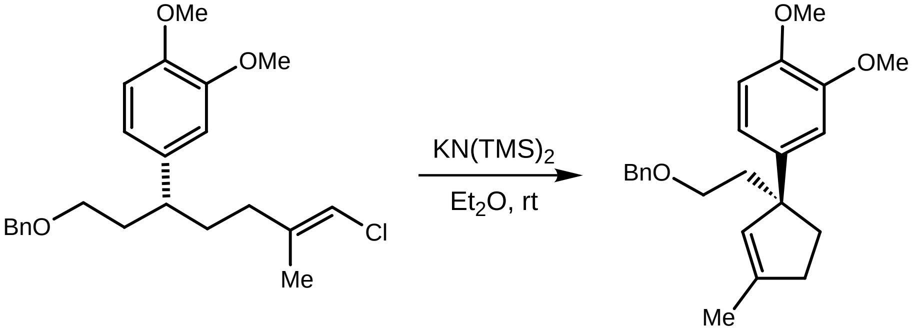
Question 11 (20 points). The indole alkaloid vindoline is an important subunit of the alkaloid vinblastine, an anticancer agent isolated from periwinkle. Boger has reported the transformation illustrated below (*C & E News* **2001**, 27) which has been designed to rapidly assemble the vindoline skeleton.





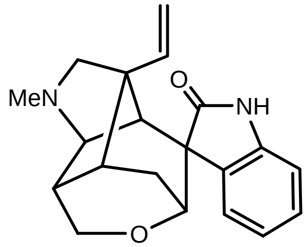
Provide a concise mechanism for this reaction in the space below. Be sure to rationalize the observed stereochemistry using clear three-dimensional drawings.

Question 12 (15 points). Taber has recently reported the transformation illustrated below (*J. Org. Chem.* **2001**, *66*, 143). The enantiopure starting material was transformed into the cyclopentene product with complete retention of stereochemical integrity.

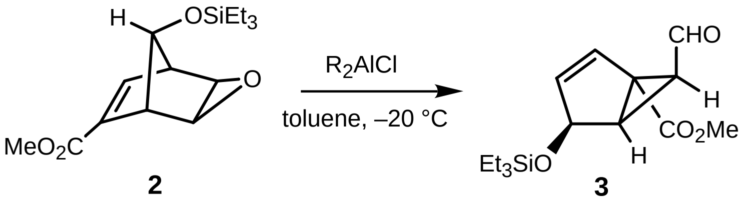


Provide a concise mechanism for this reaction in the space below.

Question 13 (15 points). Fukuyama has recently reported an elegant synthesis of gelsamine (**1**) (*Angew. Chem. Int. Ed.* **2000**, *39*, 4073). During the course of the synthesis, the rearrangement of **2** → **3** was reported (eq 1).



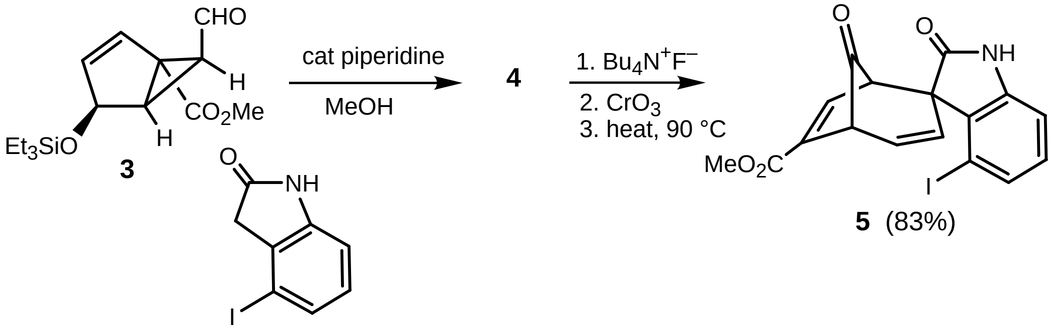
*gelsamine (**1**)*



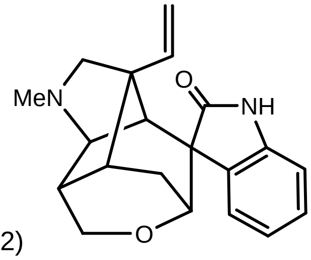
2 **3** (1)

Provide a concise mechanism for this reaction in the space below.

Question 14 (20 points). In Fukuyama's gelsamine synthesis (*Angew. Chem. Int. Ed.* **2000**, *39*, 4073), the rearrangement product **3** was subjected to an aldol condensation with 4-iodooxindole to afford **4**. which, upon deprotection, oxidation, and heating afforded intermediate **5** in an 83% overall yield. Be sure to identify **4** in your answer, and assign all stereochemistry.



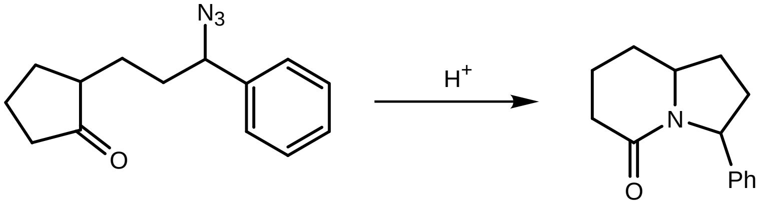
(2)



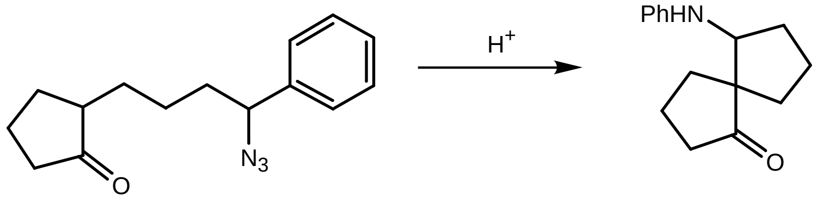
*gelsamine (**1**)*

Provide the stereostructure of **4** and a concise mechanism for this reaction sequence in the space below.

Question 15 (20 points). Aube has recently reported the transformations illustrated below (*J. Org. Chem.* **2001**, ASAP). In this study he has documented that the observed product is dependent on the tether length between the azide and carbonyl functional groups.



(eq 1)



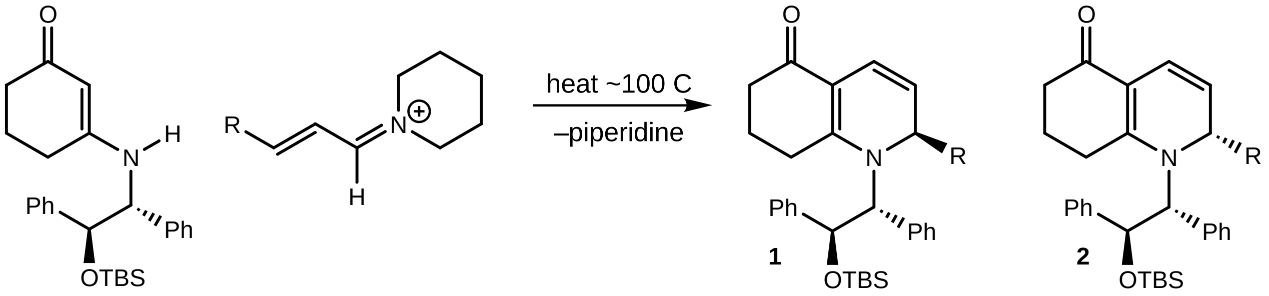
(eq 2)

Part A (8 points). Provide a mechanism for the transformation illustrated in Eq 1.

Part B (8 points). Provide a mechanism for the transformation illustrated in Eq 2.

Part C (4 points). Briefly rationalize the difference in reactivity.

Question 16 (20 points). Hsung and co-workers have recently reported the diastereoselective reaction shown below (*Org. Lett.* **2000**, *2*, 1161). While there is mechanistic ambiguity associated with this process, the authors have suggested that a pericyclic process is involved in the stereochemistry-determining step, an assumption that is consistent with the sense of asymmetric induction observed in the reaction.



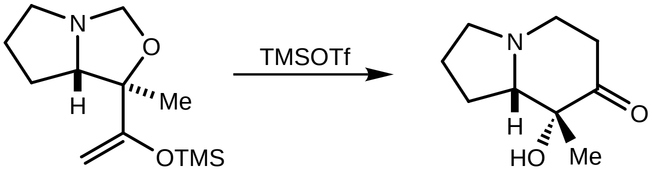
1 **2**

diastereoselection **1: 2** >10:1

Provide a concise mechanism for this reaction in the space below. Please rationalize the observed sense of asymmetric induction.

Question 17 (15 points). During the course of the synthesis of pumilotoxin (*J. Org. Chem.* **1992**, *57*, 1179) the indicated transformation was carried out with the expectation that the bicyclic ketone **2** would be enantiopure since the starting amine **1** was enantiomerically pure. Surprisingly, product **2** was obtained as a racemate.

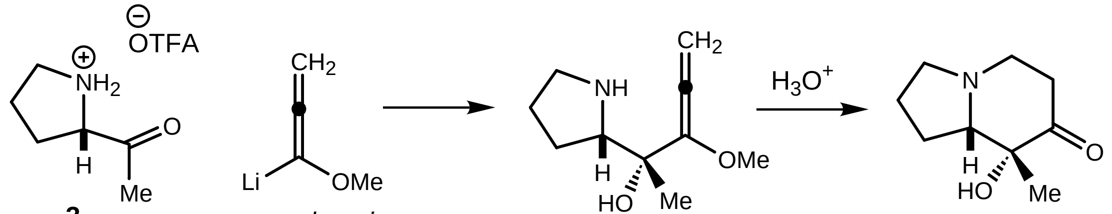
1 *(enantiopure)*



2 *(racemic)*

Provide a mechanism for this transformation that accounts for the illustrated stereochemical outcome.

Question 18 (20 points). The revised synthesis of enantiomerically pure **2** is illustrated below (*J. Org. Chem.* **1992**, *57*, 1179). Addition of **3** to several equivalents of the illustrated allenyllithium reagent afforded carbonyl adduct **4** as a single diastereomer. This intermediate was then transformed into enantiopure **2** under acidic conditions.



3

several equiv

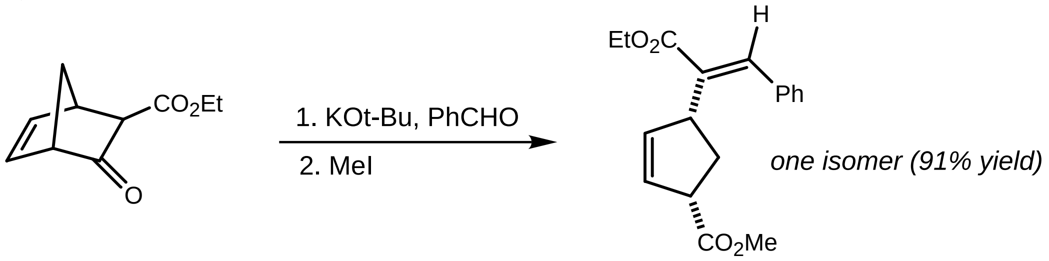
4 *(diastereoselection >97:3)*

2 *(enantiopure)*

Part A. Provide an explanation for the high level of stereocontrol that is observed in the carbonyl addition step. A three dimensional drawing of the carbonyl addition transition state is requested in conjunction with this answer.

Part B. Provide a mechanism for the transformation of **4** to **2**.

Question 19 (20 points). Rainer and Xiu (*Org. Lett.*, **1999**, 27) recently reported the remarkable fragmentation reaction illustrated below.



Part A: Provide a mechanism for this step-wise transformation. (i.e. push arrows)

Part B: Provide an explanation for the observed olefin stereochemistry.

Chemistry 206
Final Examination

D. A. Evans
January 23, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

This examination contains **16** questions (16 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

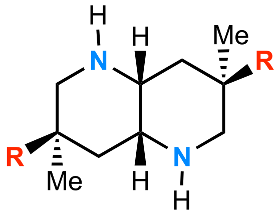
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	Score	Question (pts)	Score
No. 1 (**20**)	_______	No. 9 (**20**)	_______
No. 2 (**20**)	_______	No. 10 (**20**)	_______
No. 3 (**15**)	_______	No. 11 (**20**)	_______
No. 4 (**20**)	_______	No. 12 (**20**)	_______
No. 5 (**20**)	_______	No. 13 (**20**)	_______
No. 6 (**15**)	_______	No. 14 (**20**)	_______
No. 7 (**15**)	_______	No. 15 (**20**)	_______
No. 8 (**20**)	_______	No. 16 (**15**)	_______
Subtotal (**145**)		Subtotal (**155**)	

☐
exam average

☐
Total (300)

Question 1. (20 points). While investigating new diamine ligand scaffolds for asymmetric catalysis, Kozlowski and Xu (*J. Org. Chem.* **2002**, *67,* 3072) constructed a variety of 1,5-diaza-*cis*-decalins. They found that by altering substitution patterns on the parent scaffold, they could stabilize one conformer over the other. For example, when two addional methyl substituents were introduced onto the following dimethyl substituted 1,5-diaza-*cis*-decalin, the preferred ground-state conformer was altered.



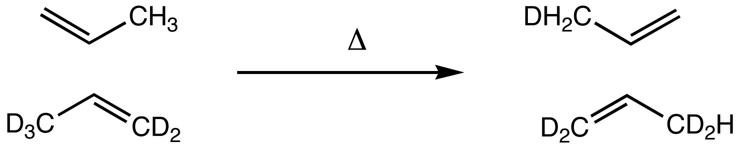
R	Ratio (Conformer A:Conformer B)
H	80:20
Me	10:90

Part A (8 points). Please provide a clear 3-dimensional representation of both conformers when R = H. Identify the more stable conformer and the chief destabilizing interactions in the less stable conformer.

Part B (8 points). Identify the new destabilizing interactions that occur on the more stable conformer from **Part A** when two additional methyl groups are introduced. Provide a clear 3-dimensional drawing of the most stable conformer in the geminal dimethylated case.

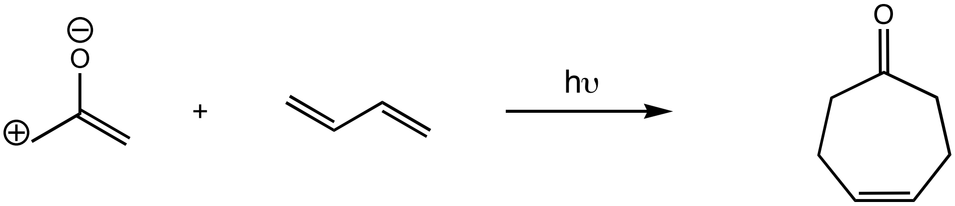
Part C.(4 points) Based on your analysis, which of the two systems (R = H or R = Me) should serve as a better metal chelating agent (ligand) for possible asymmetric catalysis?

Question 2. Part A (10 points). For the process indicated below please use either the Dewar Zimmerman or FMO analysis to predict whether isotope scrambling is allowed under thermal conditions.

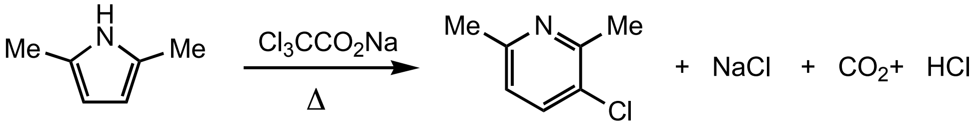


Your Answer:

Part B. (10 points). Using FMO analysis, please predict whether the following cycloaddition is allowed under photochemical conditions.

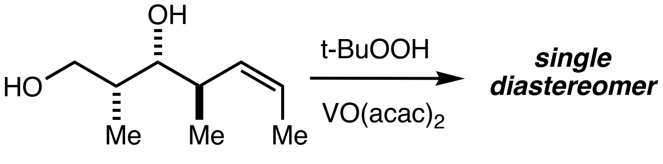


Question 3. (15 points). The following reaction was reported for the synthesis of substituted pyridines as shown below. Provide a reasonable mechanism for the transformation. Identify and describe any pericyclic processes that might be involved(Thomas L. Gilchrist, *Heterocyclic Chemistry.* 3rd Ed. Longman Press: England, **1997**).

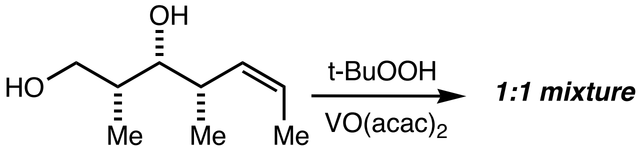


Your Answer:

Question 4. (20 points). Sharpless expoxidation of diol **A** gives rise to a single product, while epoxidation of diol **B** affords a 1:1 mixture (*Eur. J. Org. Chem.* **1999**, 2929-2936).



A



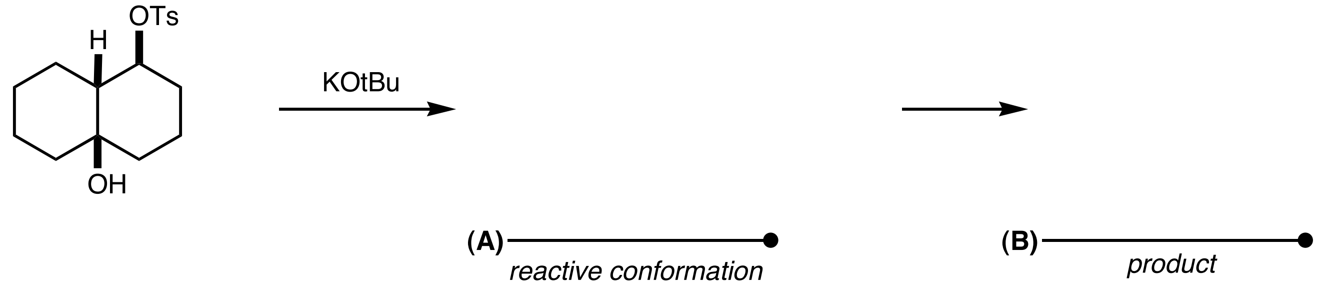
B

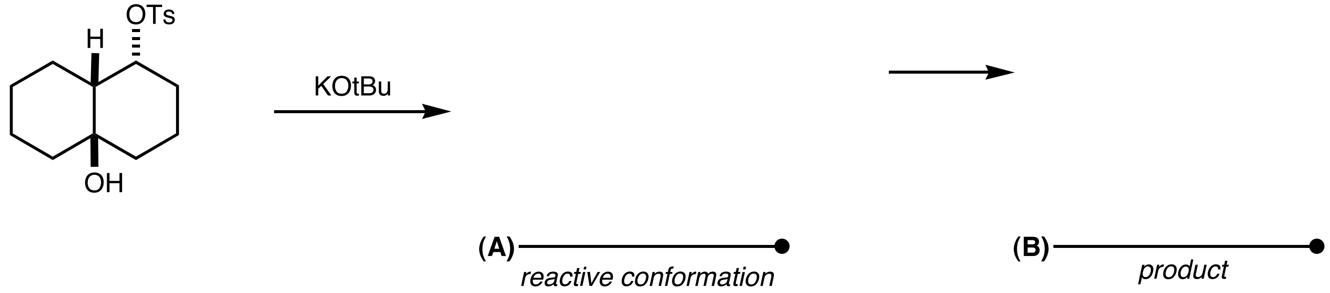
Part A. (10 points). Please provide a clear 3-dimensional representation of the lowest energy conformer of both **A** and **B**. Be sure to indicate why these conformers are favored.

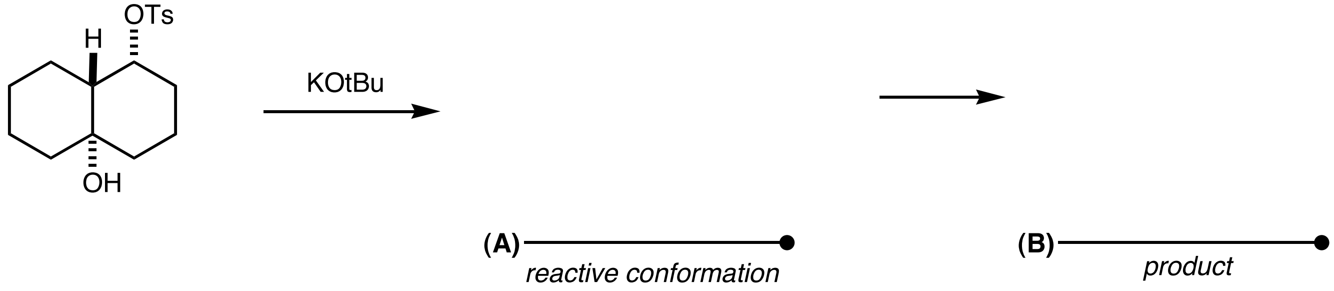
Part B. (10 points). Please predict the product formed by the epoxidation of **A**, and provide a clear rationale as to why **B** displays no diastereoselectivity. Indicate all relevant destabilizing interactions.

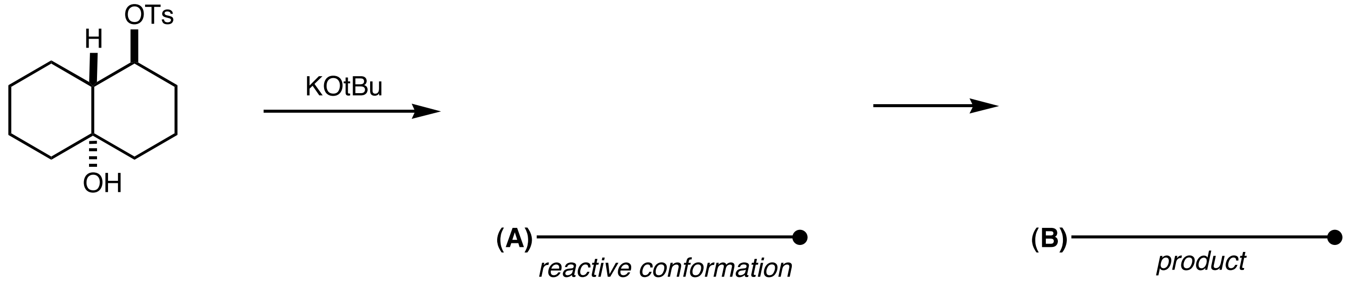
Question 5. (20 points). The following alkoxide-induced reactions have been systematically studied by Wharton et al. (*J. Org. Chem.* **1965,** *30*, 3254 and prior citations). The illustrated substrates will undergo fragmentation to an olefinic ketone if the appropriate stereoelectronic constraints are met. If these constraints cannot be met, E2 elimination to the derived bicyclic olefinic alcohol will take place.

Predict the principal product observed in each instance (**B**) and draw the reactive conformation (**A**) that meets the stereoelectronic conditions for the reaction. Put your answers in the space provided.

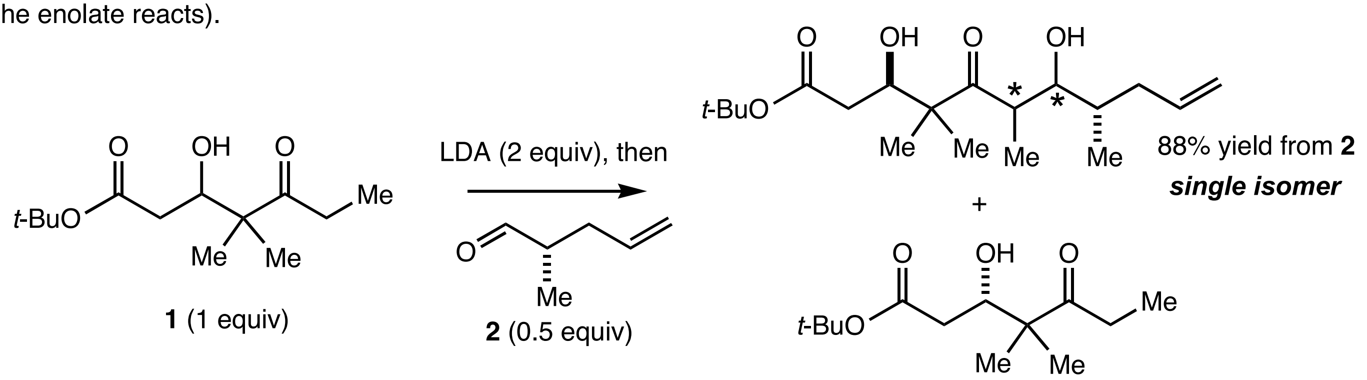








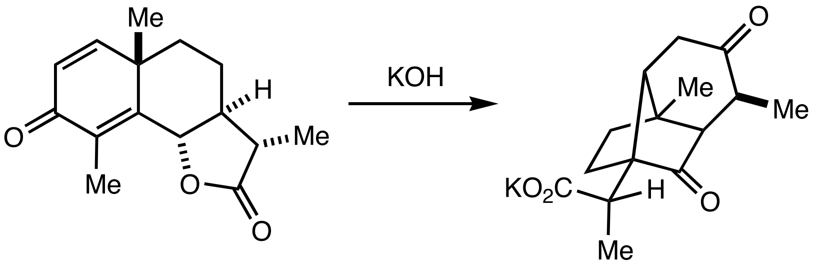
Question 6. (15 points). During the preparation of epothilone analogs, the following aldol reaction was investigated by Danishefsky and Zhang (Zhang, *PHD Dissertation*, **2003**). It was noted that if only 0.5 equivalents of the enantiopure aldehyde **2** was used then effective kinetic resolution of the racemic ketone **1** was achieved (*ie* only one enantiomer of the enolate reacts).



Using clear three dimensional representations please provide a rationale for the observed resolution and predict the relative stereochemistry of the aldol adduct (***HINT***: The enolate is likely to be chelated with the beta-alkoxy substituent).

Your Answer:

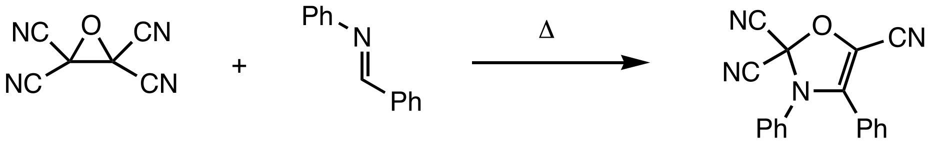
Question 7. (15 points). Woodward and coworkers reported the following base-promoted conversion of α-santonin into potassium santanoate as part of a classic natural product structural determination *(JACS* **1948,** *70*, 4216). In the space below please provide a concise mechanism for this intriguing rearrangement.
Hint: Work on the analysis of this transformation bi-directionally.



Your Answer:

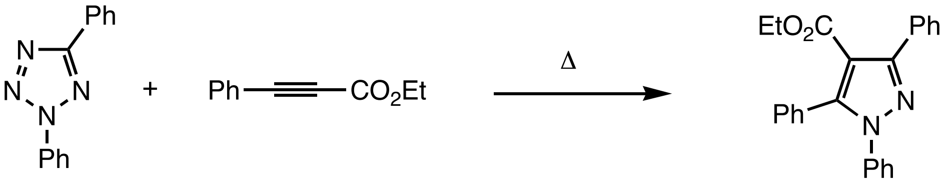
Question 8. (20 points). Many interesting and useful methods have been developed for the synthesis of heterocyclic molecules.

Part A. (10 points). The following reaction for the synthesis of oxazoles was developed by Linn and coworkers (*JOC* **1969**, 2146). Please provide a detailed mechanism for this reaction.



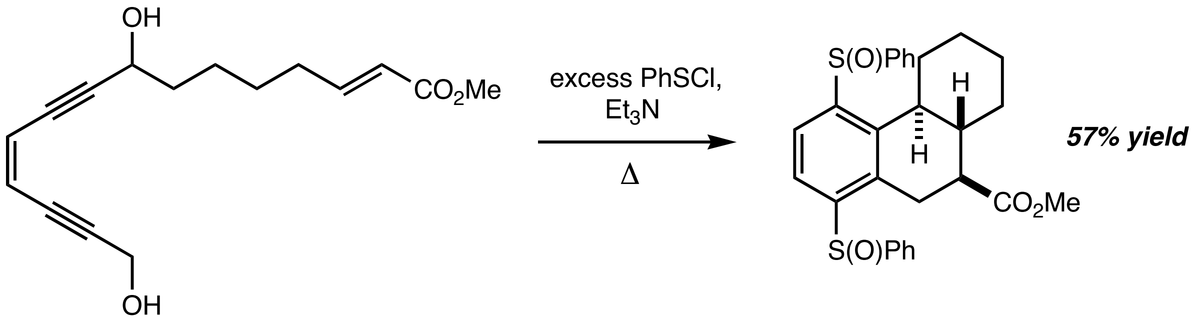
Your Answer:

Part B. (10 points). Huisgen reported the use of tetrazoles as versatile precursors for the synthesis of substituted pyrazoles (*Tetrahedron* **1962**, *17*, 3). Please provide a detailed mechanism for this transformation.



Your Answer:

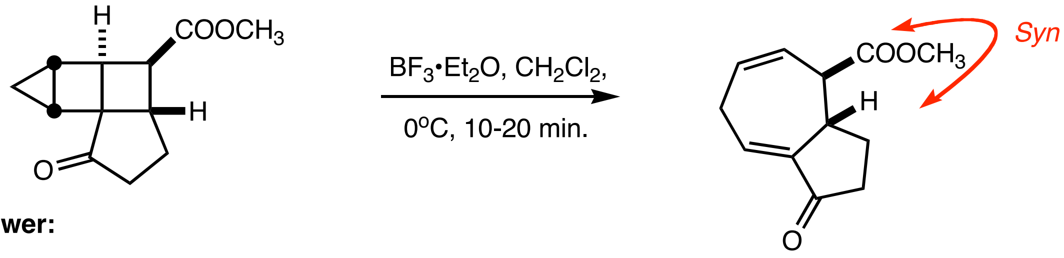
Question 9. (20 points). The following cascade reaction to convert a linear precursor into a complex tricyclic structure was very recently reported (*Org. Lett.* **2006**, *8*, 95). In the space below please provide a detailed mechanism for this reaction. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.



Your Answer:

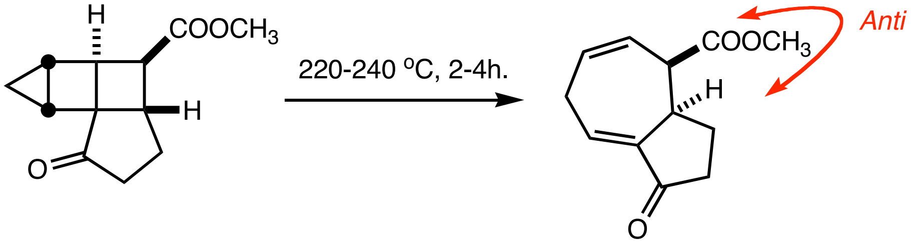
Question 10. (20 points). Snapper and co-workers have recently identified a mild, Lewis acid-mediated fragmentation of cyclobutane-containing adducts as a rapid entry into bicyclo[5.3.0]decane ring systems (*Org. Lett.* **2005**, *7*, 5785). They also noted that the stereochemical outcome of the acid-mediated fragmentations in such systems is complementary to the observed thermal ring expansions.

Part 1. (10 points). Please provide a plausible mechanism for the following Lewis acid-mediated transformation.



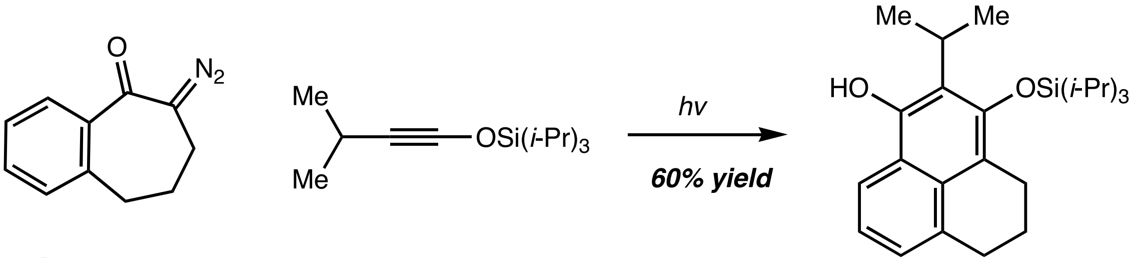
Your Answer:

Part 2. (10 points). Propose a mechanism that rationalizes the complementry stereochemical outcome of the following thermal rearrangement.



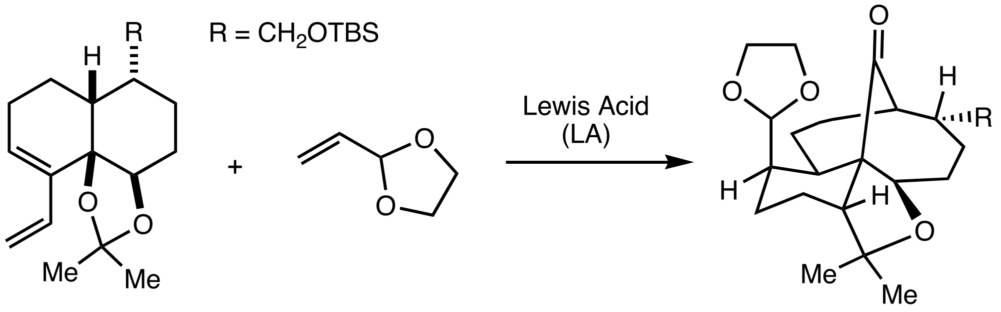
Your Answer:

Question 11. (20 points). As part of a study directed towards the synthesis of the natural product Hyellazole, Danheiser and coworkers developed a clever route to the synthesis of complex fused polycyclic structures (*JACS* **1990**, *112*, 3093). Please provide a mechanism for the following rearrangement. Be sure to label all relevant pericyclic rarrangements.

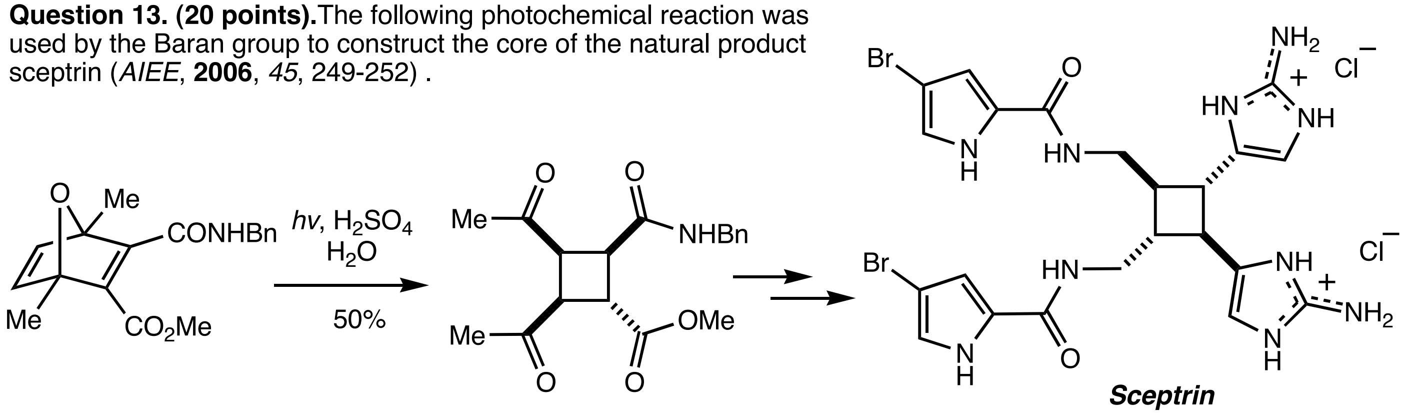


Your Answer:

Question 12. (20 points). Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones (*Org. Lett.* **2005**, *7*, 5921). Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.



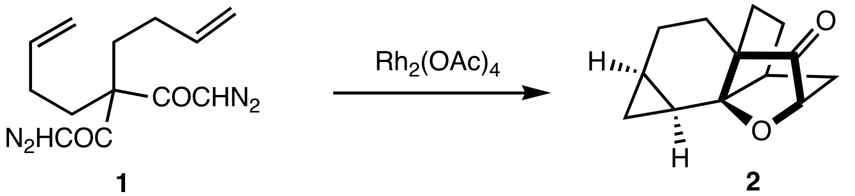
Question 13. (20 points). The following photochemical reaction was used by the Baran group to construct the core of the natural product sceptrin (*AIEE*, **2006**, *45*, 249-252) .



Sceptrin

In the space below please provide a reasonable mechanism for this powerful, multistep transformation.

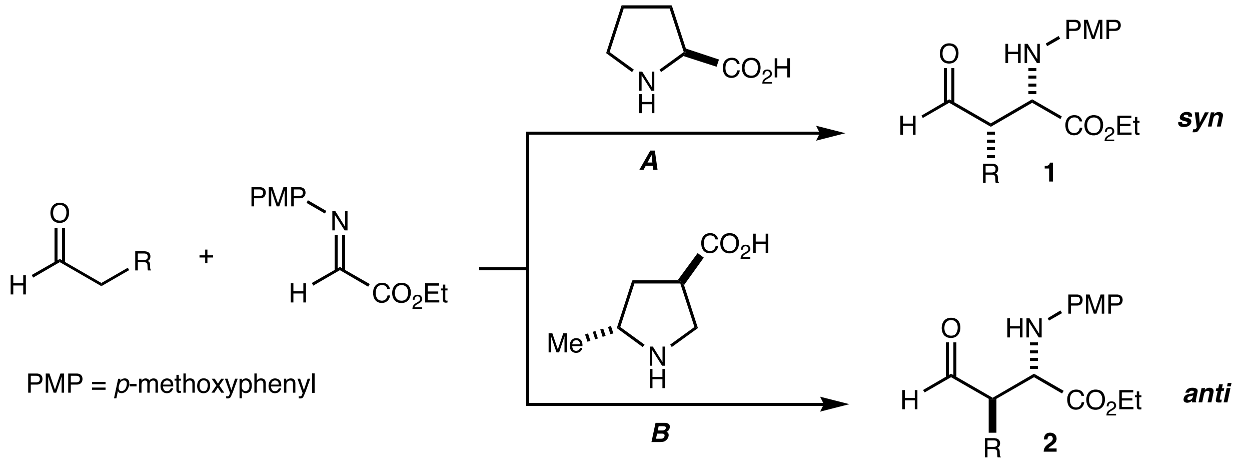
Question 14. (20 points). Bien and coworkers have reported the illustrated rhodium-catalyzed transformation of bis(diazo-ketone) **1** into the functionalized polycyclic product **2** (*Org. Lett.* **2005**, *7*, 5921). Please provide a mechanism for the following rearrangement that accounts for the observed relative stereochemistry. Be sure to label all relevant pericyclic processes.



1 **2**

Your Answer:

Question 15. (20 points). The Mannich reaction catalyzed by proline (**A**) typically provides the **syn** adduct **1** with high levels of syn diastereocontrol. However, Barbas and coworkers have recently reported that catalyst **B** affords the corresponding **anti** adduct **2** with high selectivity (*JACS* **2006,** *128,* **ASAP**).



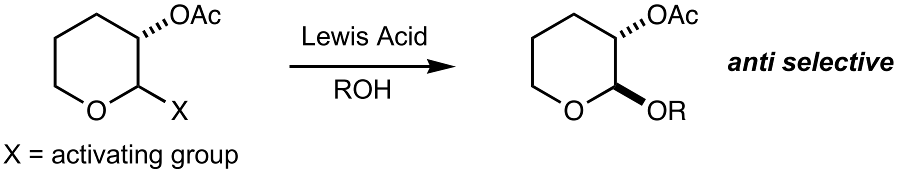
PMP = *p*-methoxyphenyl

Part A. (10 points). Please provide a clear depiction of the transition state leading to the formation of the observed syn adduct **1** when using **A**. Your answer should discuss the issues associated with the initially formed enamine intermediate, and identify all important control elements that determine enantio- and diastereoselectivity.

Part B. (10 points). In contrast to above, please provide a clear depiction of the transition state leading to the formation of the observed anti product **2** when using **B**. Your answer should discuss the issues associated with the initially formed enamine intermediate and identify important control elements that determine enantio- and diastereoselectivity.

Question 16. (15 points). Stereoselective formation of the glycosidic linkage is the principal challenge in the synthesis of biologically important oligosaccharides. Anchimeric assistance (neighboring group participation) can be a powerful tool for the selective construction of glycosidic bonds.

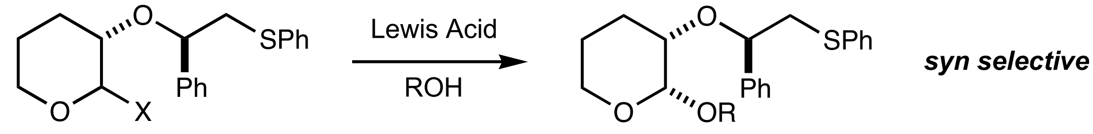
Part A. (5 points). For the following α-selective glycosylation please provide a clear mechanism, using three-dimensional representations, that accounts for the observed stereochemical outcome. Indicate all relevant orbital interactions.



X = activating group

Your Answer:

Part B. (10 points). Boons and coworkers (*JACS*, **2005**, *127*, 12090) have recently reported a highly selective synthesis of the corresponding syn di-substituted system by employing a participating phenyl-2-(phenylsulfanyl)ethyl moiety, as indicated below. Using clear three-dimensional drawings provide a rational mechanism for this interesting reaction. Be sure to indicate all favorable and unfavorable interactions, both steric and electronic. NOTE: This reaction is under ***kinetic*** *control.*



X = activating group

Your Answer:

Chemistry 206
Final Examination

D. A. Evans
January 24, 2005

Name (please print):______________________
last first initial

Signature:______________________

Teaching Fellow:______________________

This examination contains **15** questions (15 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**
No. 1 (**15**)	_______
No. 2 (**20**)	_______
No. 3 (**20**)	_______
No. 4 (**20**)	_______
No. 5 (**25**)	_______
No. 6 (**20**)	_______
No. 7 (**15**)	_______
No. 8 (**15**)	_______
Subtotal (**150**)	

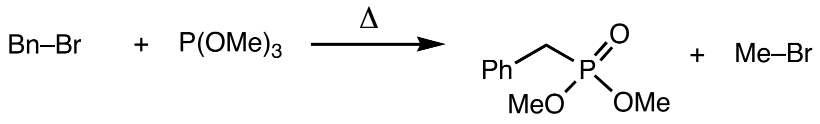
Question (pts)	**Score**
No. 9 (**25**)	_______
No. 10 (**20**)	_______
No. 11 (**20**)	_______
No. 12 (**25**)	_______
No. 13 (**20**)	_______
No. 14 (**20**)	_______
No. 15 (**20**)	_______
Subtotal (**150**)	

exam average

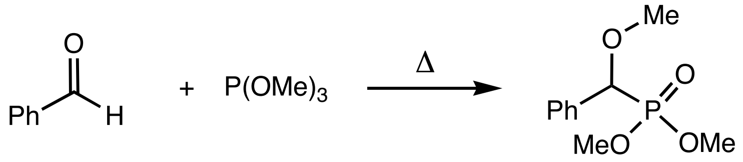
Total (300)

Question 1. (15 points). Equation (1) is a typical example of an Arbuzov rearrangement while Equation (2) is an Arbuzov variant carried out with an aldehyde.

(1)

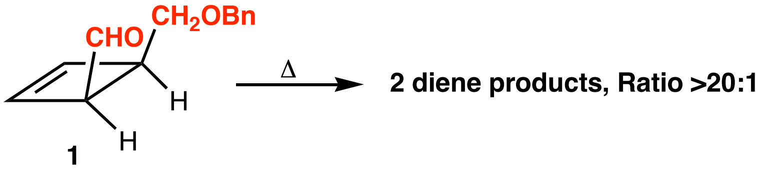


(2)



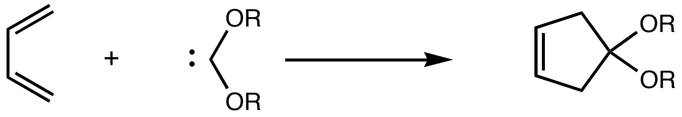
Please comment on the mechanism of the transformation in equation (2).

Question 2. (20 points). The ring opening of cyclobutene **1** is highly selective affording the isomeric dienes in a ratio >20:1. Please predict the structure of the major product and rationalize the stereochemical course of the transformation. It is suggested that your explanation employ orbital representations.



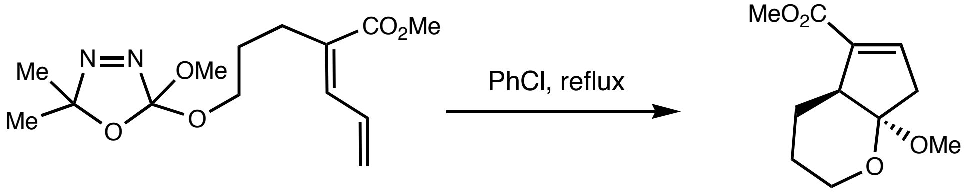
1

Question 3. (20 points). A [4+1] cycloaddition between a diene and a carbene has recently been reported by Spino and co-workers (*JACS*, **2004**, *126*, 9926).

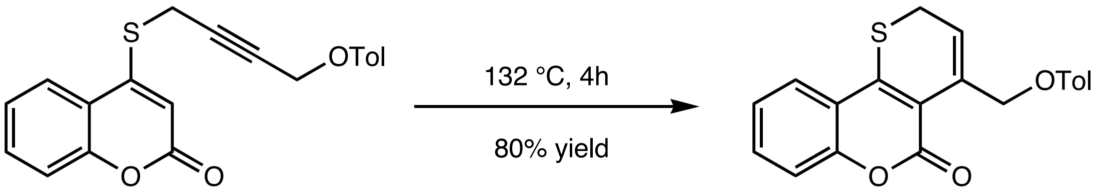


Part A. (10 points). Using a Dewar-Zimmerman or an FMO analysis, determine if this reaction is thermally allowed. Be sure to consider both the approach and the geometry of the carbene carefully.

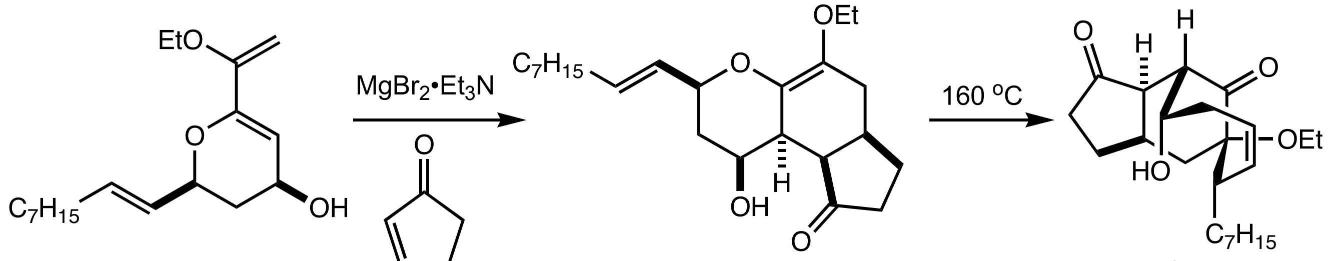
Part B. (10 points). Provide a mechanism for the following reaction reported by Spino.



Question 4. (20 points). Please provide a mechanism for the following transformation (*Org. Lett.*, **2002**, 4, 2629.), being sure to classify any pericyclic processes that intervene.

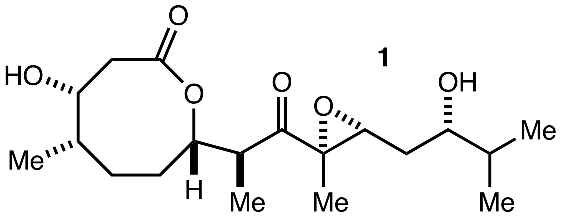


Question 5. (25 points). The rapid assembly of the bicyclo[5.3.1]undecane core of penostatin F was recently reported by Barriault and coworkers (*Org. Lett.* **2004**, *6*, 1317). In this remarkable transformation dihydropyran **1** is converted to the highly complex tricycle **3** in only two operations. Please provide a detailed mechanism for this reaction sequence. Be sure to indicate all pericyclic reactions.



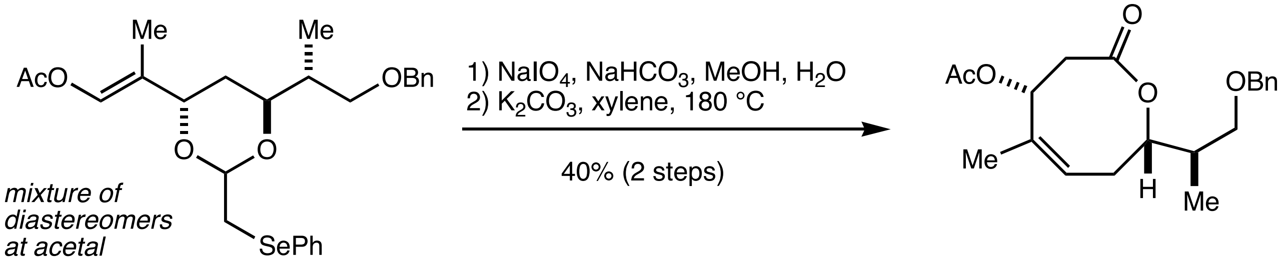
1 **2** **3**

Question 6. (20 points). In 1991, Fenical and Clardy reported the isolation of eight-membered lactones, which were termed octalactins. The parent member, octalactin A (**1**), was recently synthesized by Holmes and co-workers (*JACS*, **2004**, *126*, 2194.).



1

Part A. (15 points). Please provide a mechanism for the two-step sequence below that provides the eight-membered ring. Use 3-D illustrations in your explaination. *($NaIO_4$ is only an oxidant)*

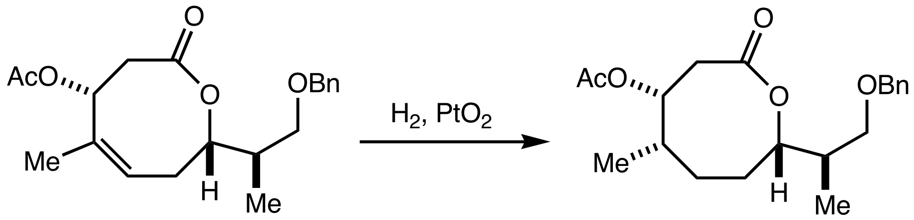


mixture of diastereomers at acetal

1) $NaIO_4$, $NaHCO_3$, MeOH, H_2O
2) K_2CO_3, xylene, 180 °C

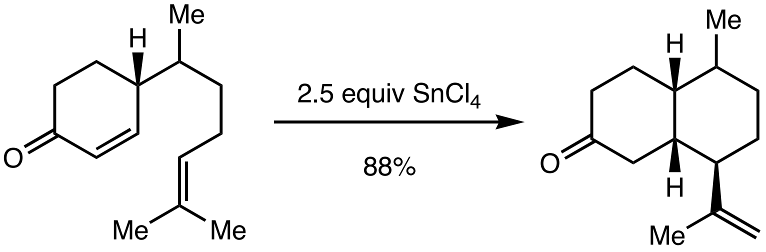
40% (2 steps)

Part B. (5 points). Please provide a rationale for the selective hydrogenation illustrated below.

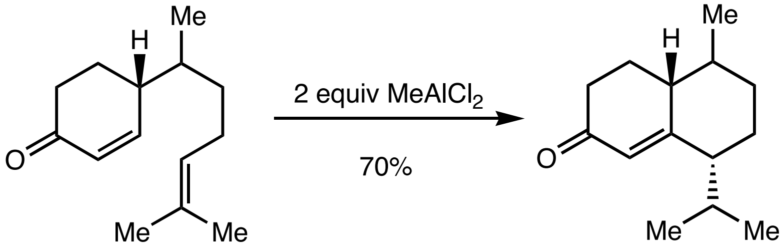


Question 7. (15 points). A recent report has investigated the cationic cyclization of olefins under Lewis acidic conditions (*ACIE*, **2005**, *44*, 99.). The examples below (**A-B**) are of increasing difficulty. The following question (8) will build on the foundation of this question. Please provide a mechanism for each part illustrated. Your answer can focus on the 2-D mechanistic analysis (3-D figures are not required).

Part A (5 points):

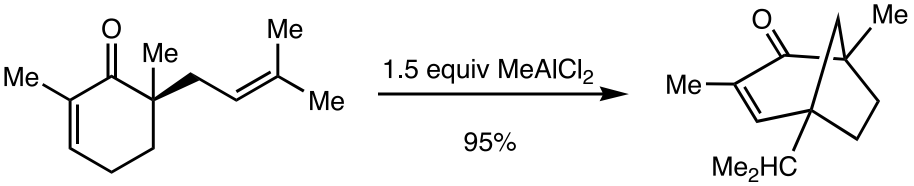


Part B (10 points):



Question 8. (15 points). This question builds on the foundation of the previous question . Please provide a mechanism for the case illustated (ACIE, **2005**, 44, 99).

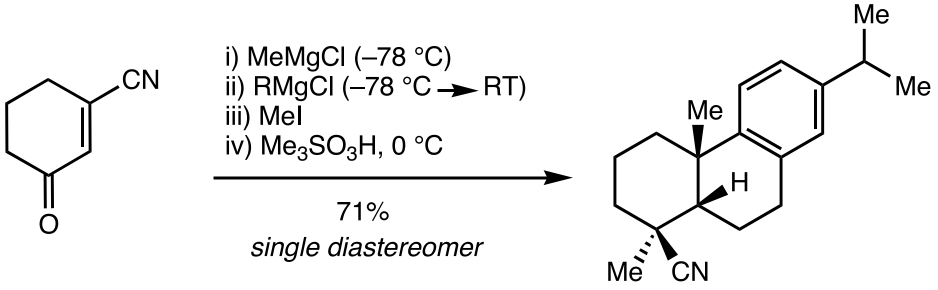
For this question please provide 3-dimensional representations.



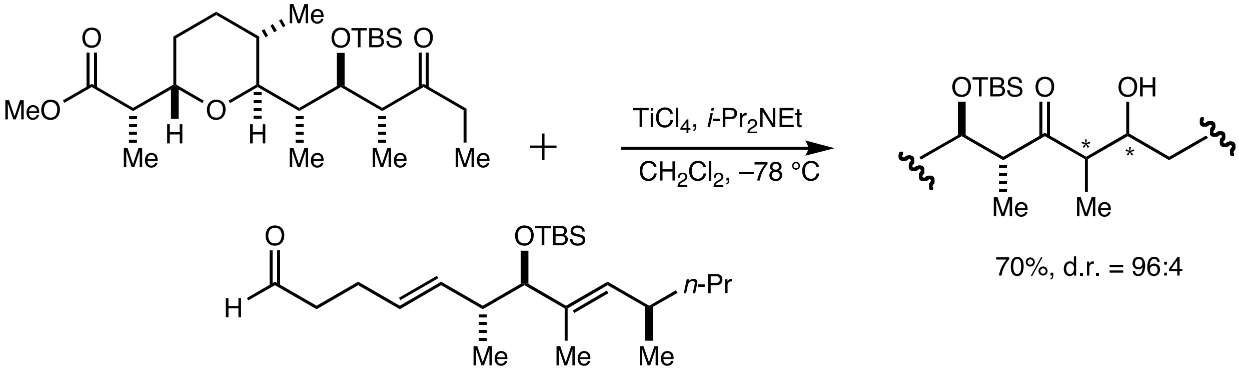
Question 9. (25 points). The following multi-component, one-pot reaction was recently reported by Fleming (*Angew. Chem. Int. Ed.* **2004**, *43*, 1126.). This is an impressive reaction for two specific reasons: 1) only a single diastereomer is observed; 2) the reaction appears to be general for an array of Grignard reagents and electrophiles.

Please provide a mechanism for the reaction that clearly explains the stereoselectivity for each step.

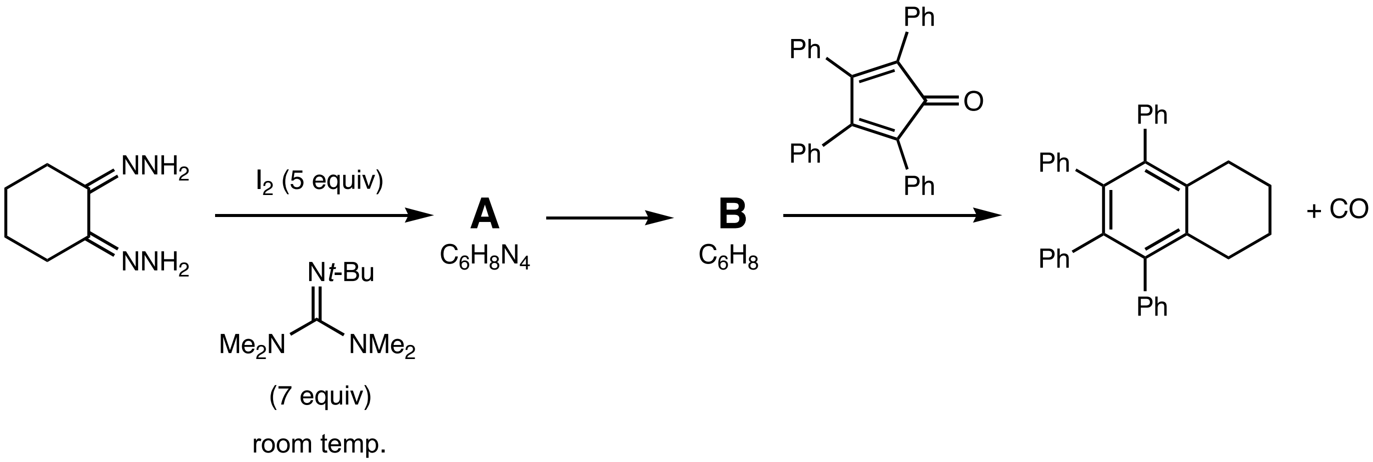
Please use 3-D representations. I recommend working on this problem bi-directionally from both product and starting material until you see the connecting transformations.



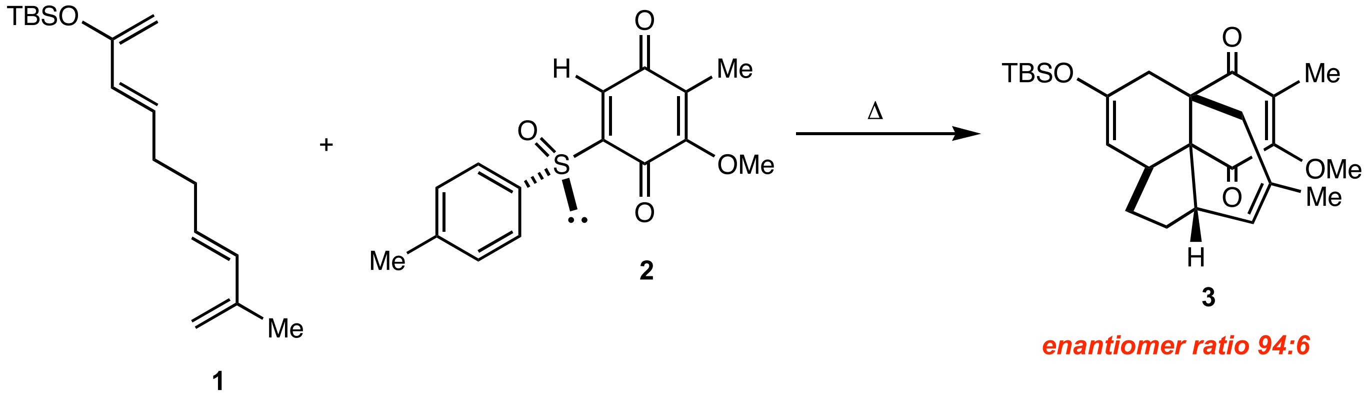
Question 10. (20 points). In a recent total synthesis of Zincophorin methyl ester (*Org. Lett.* **2003**, 4037), the following titanium-mediated aldol reaction was used to efficiently couple two large fragments. Predict the stereochemistry of the product and provide a stereochemical model to support your prediction.



Question 11. (20 points). During research into the chemistry of hydrazone derivatives, Barton and coworkers observed the interesting transformation shown below *(Tetrahedron,* **1988**, *44*, 147). Please provide a plausible mechanism for this reaction and identify intermediates **A** and **B**. (*NB: A and B are not isolable)*

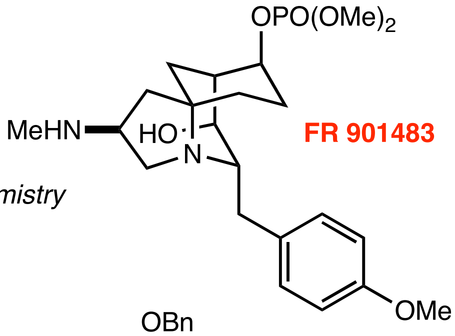


Question 12. (25 points). Flynn and coworkers have reported the rapid construction of **3** from bisdiene **1** and chiral sulfoxide **2** (*Org. Biomol. Chem.* **2003**, *1*, 1842-1844).
Please provide a mechanism that accounts for the observed regiochemical and stereochemical outcome of this interesting transformation. Perspective drawings should be employed where relevant.



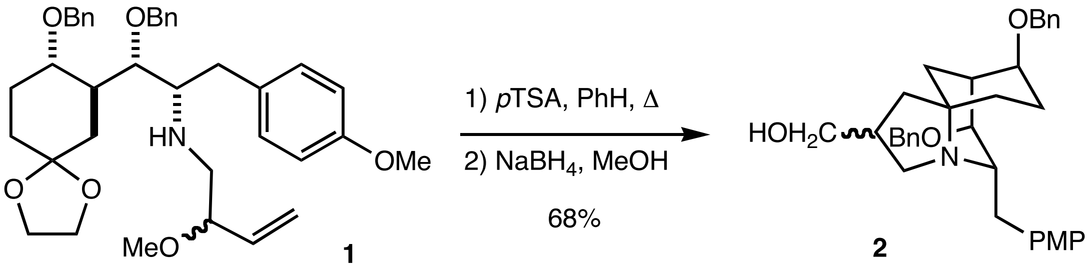
enantiomer ratio 94:6

Question 13. (20 points). FR 901483 is an immunosuppressant developed by Fujisawa Pharmaceutical Company. Recently, a formal total syntheses of FR 901483 was disclosed that utilizes the transformation illustrated below (Brummond and Hong, *JOC,* **2004**, *ASA*P).



FR 901483

Provide a mechanism for the conversion of ***1*** *into* ***2*** *that explains the stereochemistry of the product. Utilize 3-D illustrations where necessary.*



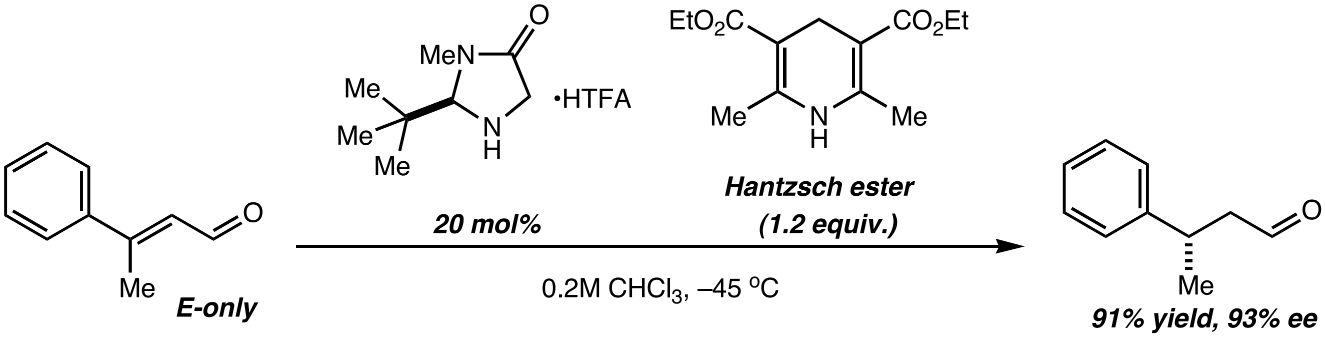
1

2

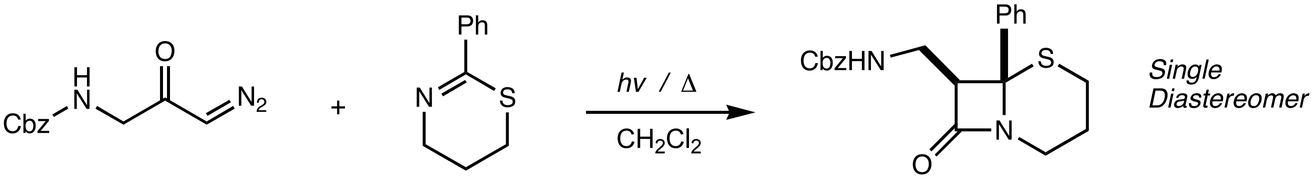
pTSA = tol-SO$_3$H

Question 14. (20 points). MacMillan and coworkers have recently reported the following enantioselective organo catalytic reduction of α,β-unsaturated aldehydes using a chiral iminium catalyst and the Hantzsch ester as the stoichiometric hydride source (*JACS,* **2005**, *127*, 32-33.).

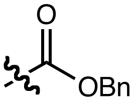
Please provide a detailed reaction mechanism for this reduction and rationalize the observed sense of absolute stereochemical induction.



Question 15. (20 points). α-Diazoketones are known to decompose to carbenes under photochemical excitation. It has recently been shown that in the presence of imines, the photo-decomposition of diazoketones provides β-lactams with good diastereocontrol (*JOC*, **2005**, *70*, 334-337).



Provide a mechanism for the above transformation. Your answer should include an explanation for the diastereoselectivity of this process.

Cbz = 

Chemistry 206
Final Examination

D. A. Evans
January 23, 2004

Name (please print):______________________
last first initial

Signature:______________________

Teaching Fellow:______________________

This examination contains **22** questions for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

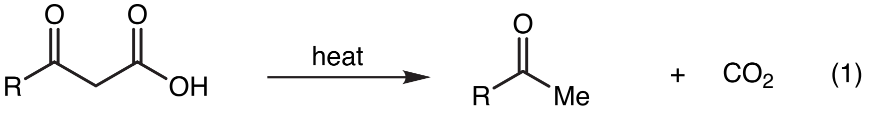
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**15**)	_______	No. 12 (**10**)	_______
No. 2 (**10**)	_______	No. 13 (**10**)	_______
No. 3 (**20**)	_______	No. 14 (**10**)	_______
No. 4 (**20**)	_______	No. 15 (**10**)	_______
No. 5 (**15**)	_______	No. 16 (**10**)	_______
No. 6 (**20**)	_______	No. 17 (**15**)	_______
No. 7 (**15**)	_______	No. 18 (**15**)	_______
No. 8 (**15**)	_______	No. 19 (**10**)	_______
No. 9 (**10**)	_______	No. 20 (**15**)	_______
No. 10 (**10**)	_______	No. 21 (**15**)	_______
No. 11 (**15**)	_______	No. 22 (**15**)	_______
Subtotal (**165**)		Subtotal (**135**)	

exam average

Total (300)

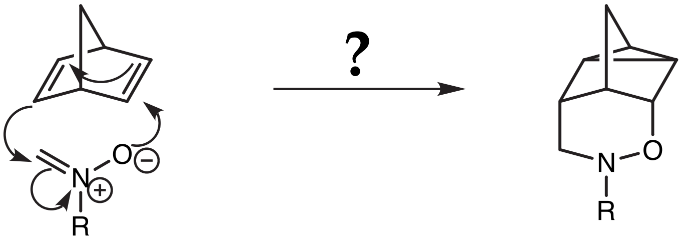
Question 1. (15 points). It is well-established that β-keto acids undergo thermal decarboxylation (Eq 1).



Part A. (5 points). Draw a mechanism for this transformation

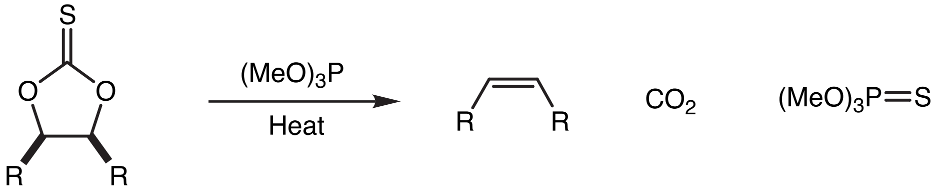
Part B. (10 points). Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.

Question 2. (10 points). Is the following cycloaddition allowed thermally? Please justify your answer with an FMO **or** Dewar-Zimmerman analysis.



Question 3. (20 points). In the Corey-Winter olefin synthesis, diol-derived thionocarbonates such as **1** are transformed *stereospecifically* to olefins when heated in the presence of phosphites (Eq 1) (*JACS* **1963**, *85*, 2677).

1

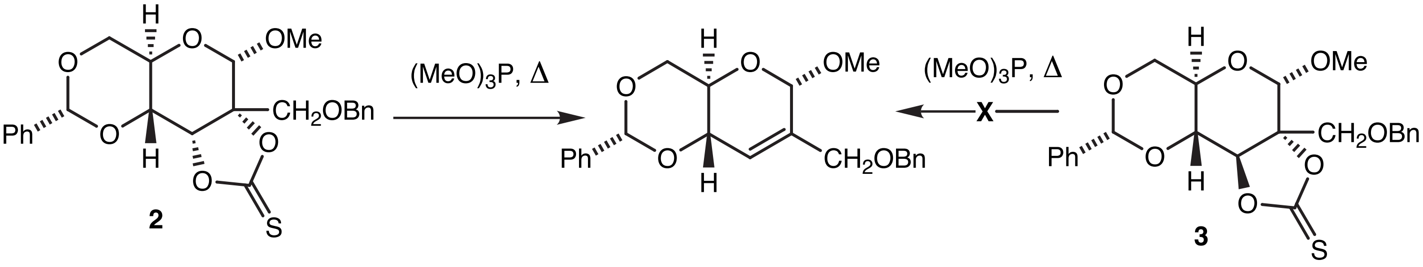


(1)

Part A. (5 points). Draw a mechanism for this transformation that accounts for the reaction specificity.

Part B. (10 points). Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.

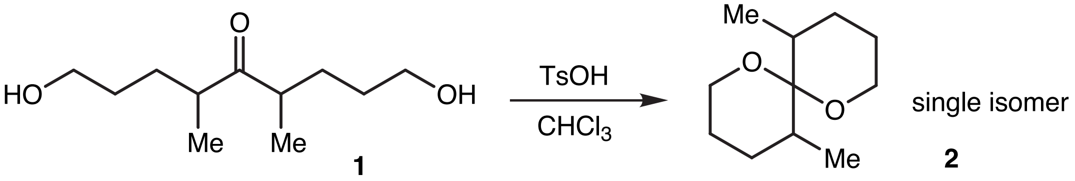
Part C. (5 points). Explain why thionocarbonate **2** undergoes the illustrated reaction smoothly while **3** does not. A good answer will include clear 3-D drawings of all relevant structures. (*Can. J. Chem.* **1994**, *72*, 69)



2

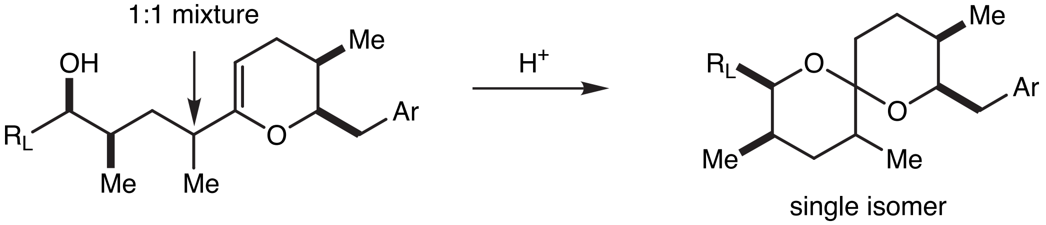
3

Question 4. (20 points). A 1:1 mixture of meso and *d/l* isomers of the hydroxyketone **1** is converted to a single stereoisomer (racemic, of course) of spiroketal **2**.

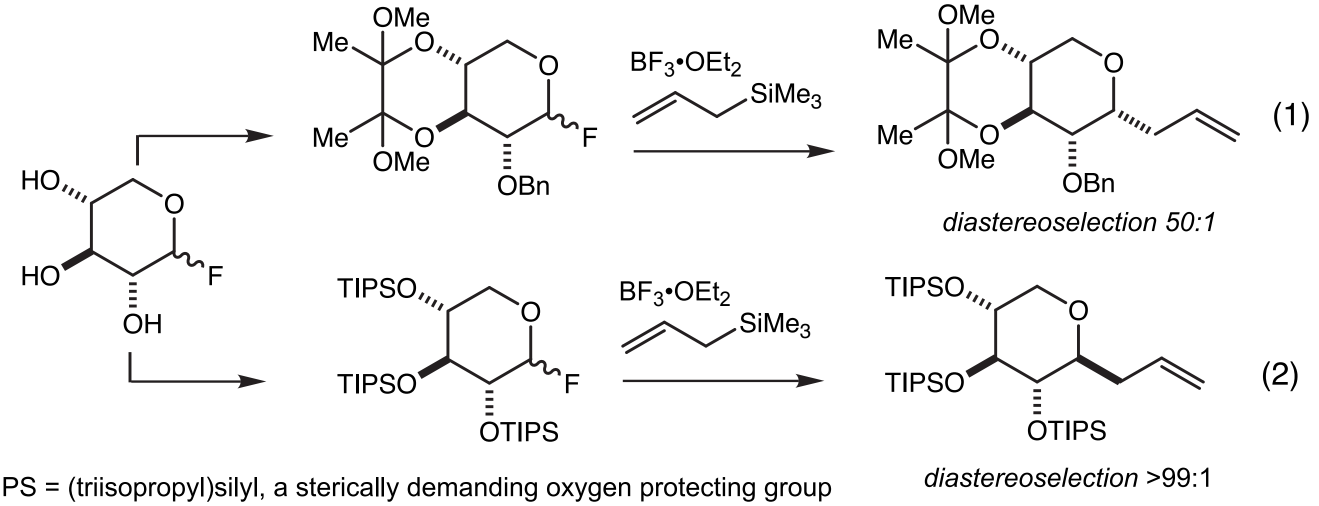


Part A. (10 points). Please provide a 3-D drawing of spiroketal **2** clearly indicating its relative stereochemical configuration. Indicate specific factors responsible for the preferential formation of this isomer. Please also provide a mechanism for the equilibration of both stereoisomers of **1** to spiroketal **2**.

Part B. (10 points). In the Evans' synthesis of calcimycin (*JACS* **1979**, *101*, 6789) a 1:1 mixture of methyl stereoisomers was converted to a single spiroketal diastereomer. Please provide a clear 3-D drawing of the resultant spiroketal. Please also provide a mechanism for the equlibration of both stereoisomers to a single isomer



Question 5. (15 points). The stereochemical course of C-glycosidation may be controlled by the judicius choice of protecting groups (*Angew. Chem. Int. Ed.* **2003**, 1021-3).

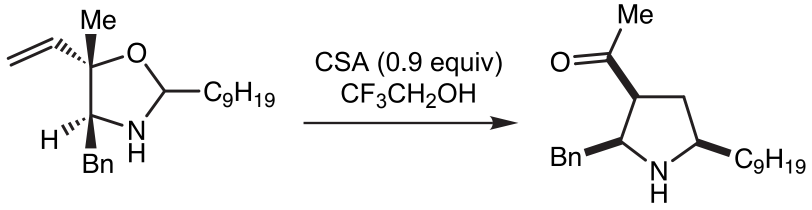


TIPS = (triisopropyl)silyl, a sterically demanding oxygen protecting group

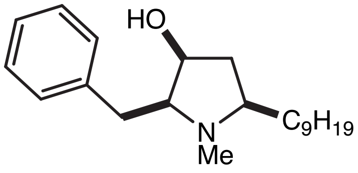
Part A. (7 points). Using conformational drawings, rationalize the stereochemical outcome of of the allylation illustrated in Eq 1.

Part B. (8 points). Using conformational drawings, rationalize the stereochemical outcome of of the allylation illustrated in Eq 2.

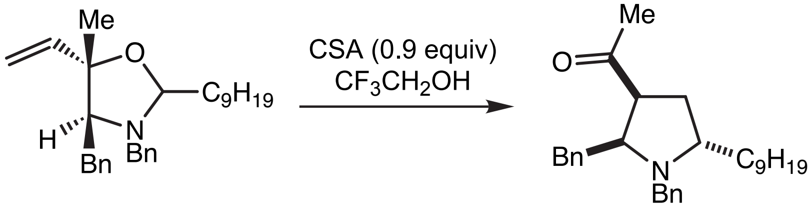
Question 6. (20 points). An elegant enantiodivergent synthesis of the potent anti-fungal reagent Preussin was reported by Overman (*JACS* **1994,** 11241.).



(1)



(+)-Preussin
natural configuration

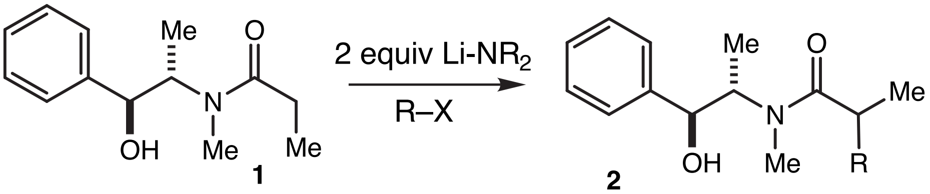


(2)

Part A. (10 points). Provide a mechanism for the transformation illustrated in Eq 1. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

Part B. (10 points). Provide a mechanism for the transformation illustrated in Eq 2. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

Question 7. (15 points). The pseudoephedrine-derived propionamide **1,** upon successive enolization with LiN(I-Pr)$_2$ (LDA) and alkylation with alkyl halide R–X, affords **2** with high diastereoselection (Myers, *JACS* **1997**, *119*, 6496).



Part A. (5 points). Enolization of **1** with LDA affords a single enolate geomerty. Provide an analysis of this enolization event and draw the enolate thus produced.

Part B. (5 points). Provide a 3-dimensional drawing of the transition state for this reaction in **Box-1.** *Hint: In answering this question, you do not need to assume that chelation is involved. Rather, a suitable transition state model may be derived purely from the consideration of non-bonding interactions.*

Box-1

5 points

Part C. (5 points). Provide the absolute stereochemistry of the alkylation product **2** of this reaction in **Box-2**.

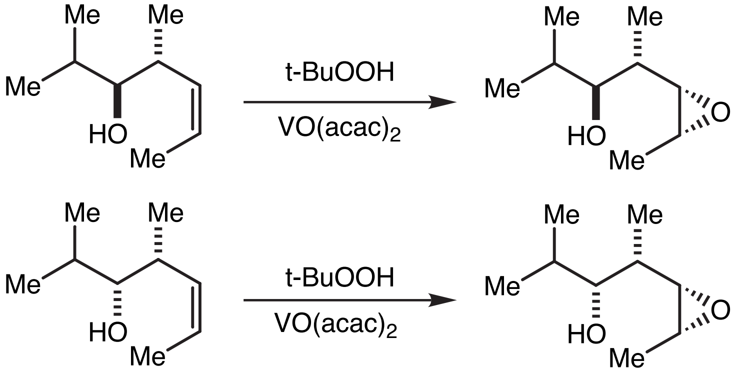
Box-2

5 points

Question 8. (15 points). Mihelich has carried out an elegant study on the vanadium (V) hydroxyl-directed epoxidation of homoallylic alcohols (*JACS* **1981**, *103*, 7690). Two examples taken from this study are illustrated below (Eq 1, 2).

Anti isomer: (1)

Syn isomer: (2)



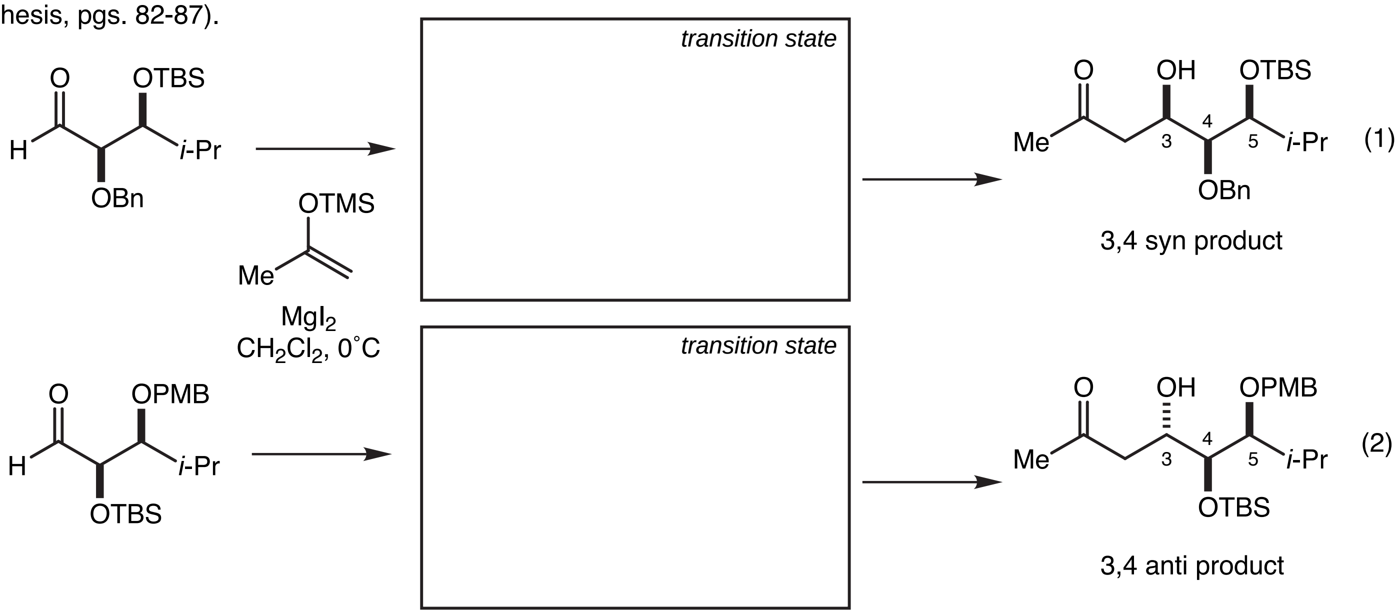
dr = 400:1 (1)

dr = 2:1 (2)

Part A. (7 points). Illustrate the low-energy conformation of alcohol **1** that apparently leads to the observed epoxidation product.

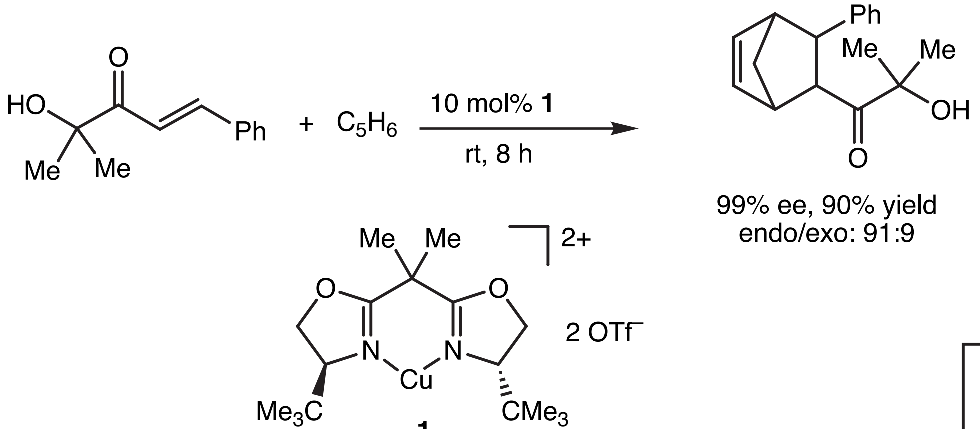
Part B. (8 points). The syn alcohol **2** is poorly diastereoselective in the directed epoxidation. Illustrate the connformations of **2** that should exhibit hydroxyl directivity and identify the principal destabilizing interation.

Question 9. (10 points). The two illustrated MgI_2–promoted Mukaiyama aldol reactions occur with high diastereoselectivity (Eq 1, 2). In contrast, only poor selectivity is observed in both reactions when MgI_2 is replaced with $BF_3•OEt_2$. Provide a transition state model that explains the formation of the 3,4 syn product in (Eq 1) and the 3,4 anti product in (Eq 2). Assume that the Bn and PMB protecting groups are chemically equivalent. (Victor Cee, Ph.D. Thesis, pgs. 82-87).



When the chelating protecting group is in the alpha position (Eq1), a five member chelate is formed and incoming nucleophile attacks from pi face opposite to the R group (TS-1). In contrast, a six-membered chelate is formed when the chelating protecting group is in the beta position and the nucleophile approaches from the face away from both the OP and R groups. The observation that $BF_3•OEt_2$ gives poor selectivity implies that the reaction is not simply under Felkin control, as one may predict for Eq 2.

Question 10. (10 points). The C_2-symmetric cationic Cu(II) complex **1** is a chiral Lewis acid catalyst that exhibits good chelating potential. Palomo has reported the utilization of **1** in the catalyzed Diels-Alder reaction is illustrated below (*JACS*, **2003**, *125*, 3943).



1

99% ee, 90% yield
endo/exo: 91:9

Box-1

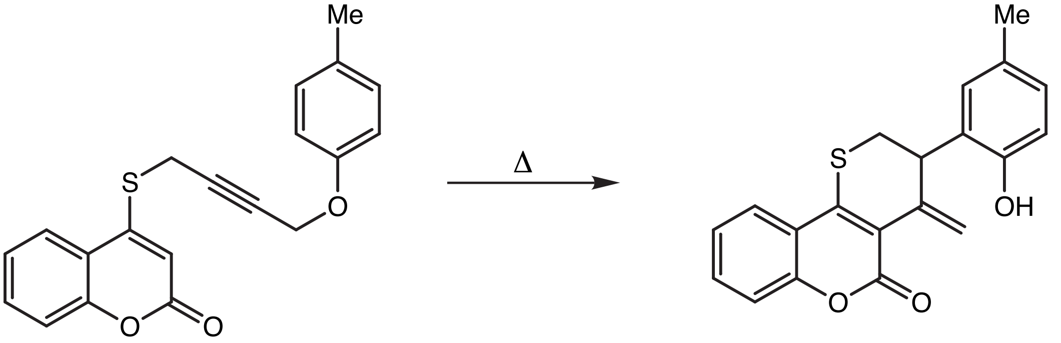
(5 points)

Box-2

(5 points)

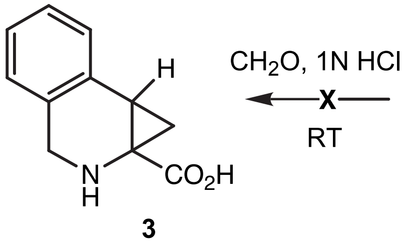
Provide the absolute stereochemistry of the product of this reaction in **Box-1**.
Provide a 3-dimensional drawing of the transition state for this reaction in **Box-2**.
Hint: Cu(II) complexes strongly prefer square-planar geometries

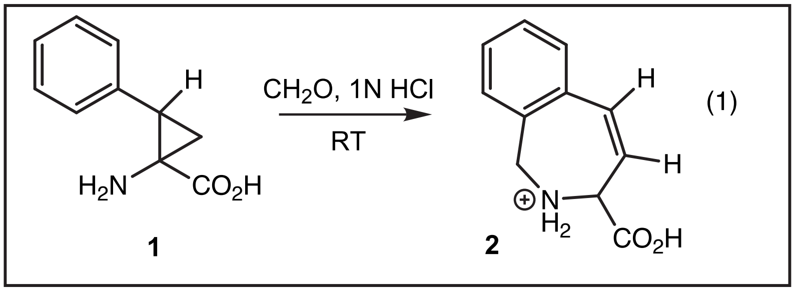
Question 11. (15 points). A recent paper by Majumdar and co-workers reported the transformation illustrated below (*Organic Lett* **2002**, *4*, 2629). Please provide a mechanism for this process. Feel free to use trace quantities of HX when needed.



Question 12. (10 points). A recent paper by Martens (*JOC*. **2001**, *66*, 2884) reported the reaction shown below (Eq 1). Please provide a mechanism for the conversion of **1** to **2**. It is noteworthy that the Pictet-Spengler of 1 does not give **3**.

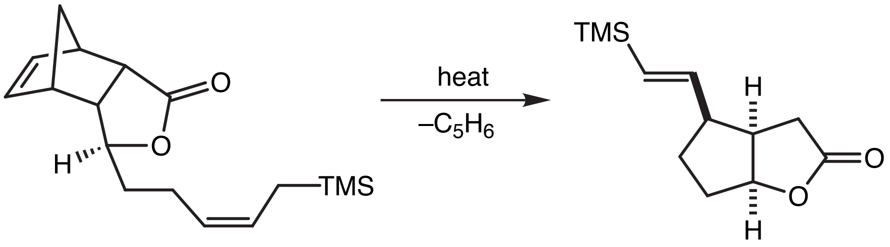
(2)



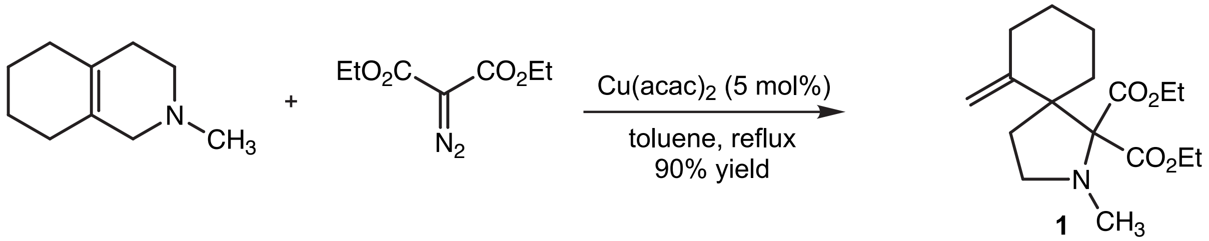


(1)

Question 13. (10 points). Inomata has reported the interesting thermal process in the context of methyl jasmonate (*Organic Lett.* **2004**, ASAP). Provide a mechanism for this overall transformation. Be sure to account for the stereochemical details of this process with the judicous use of 3-dimensional drawings.

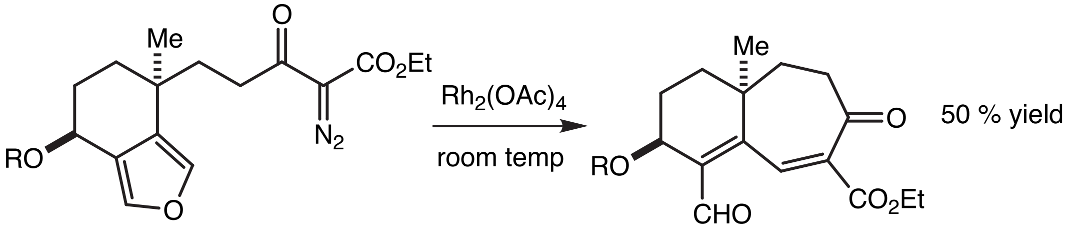


Question 14. (10 points). A recent paper by Workman and co-workers (*Org. Lett*. **2003**, *5*, 4775) describe an efficient reaction for the formation of spiro-heterocycle **1**. Propose a mechanism for the formation of **1**.



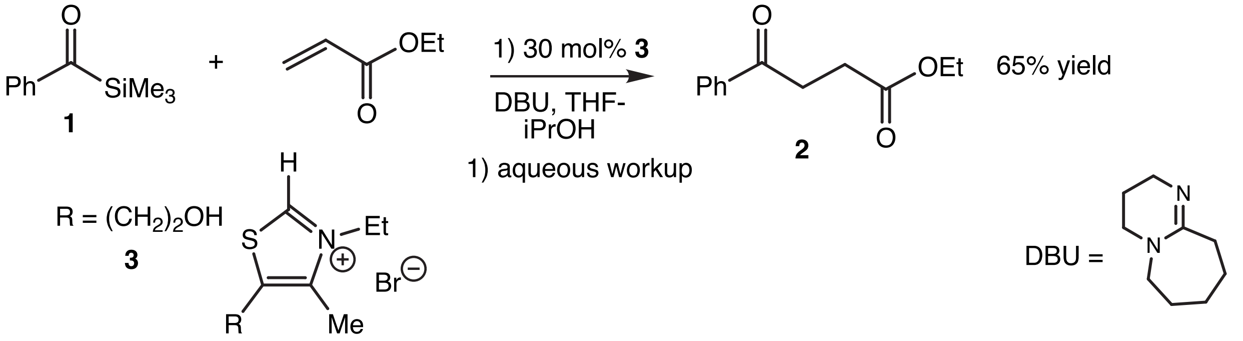
1

Question 15. (10 points). The following transformation was recently reported by Trauner and co-workers (*Organic Lett.* **2003**, *5*, 4113) as a pivotal reaction in the synthesis of specific members of the guanacastepene diterpenes. These natural products have attracted interest as potent antiobiotics against *Staphylococcus aureus*.

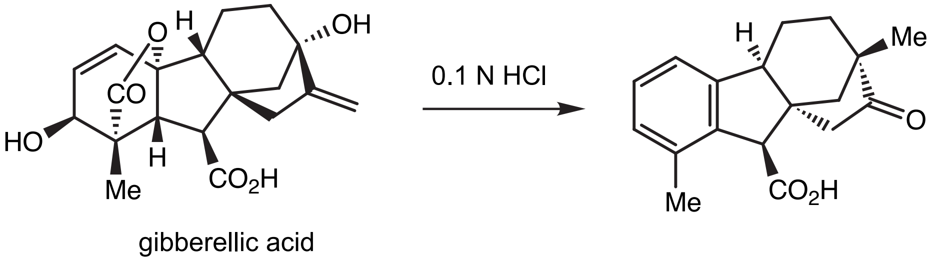


Provide a mechanism for the transformation illustrated above.

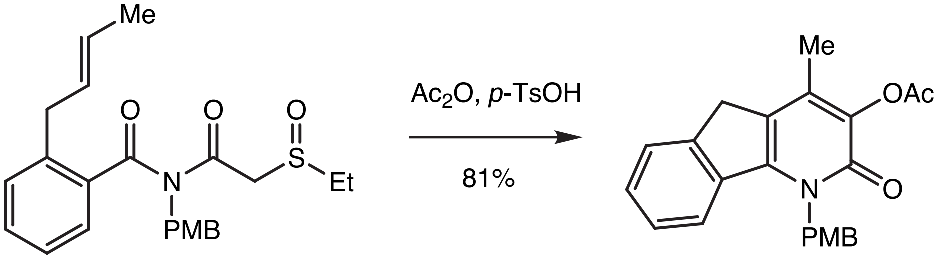
Question 16. (10 points). The first example of a "Silyl-Stetter reaction" will appear in the literature shortly (Scheidt, *JACS*, **2004**, 125, in press). Provide a mechanism for this transformation.



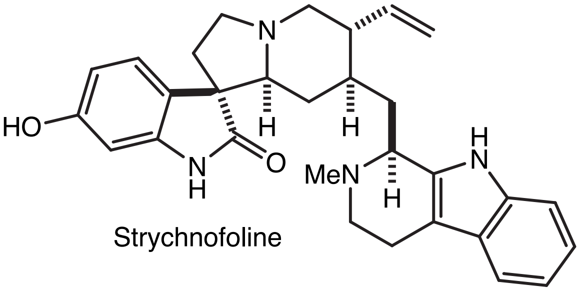
Question 17. (15 points). Gibberellic acid is a notoriously sensitive natural product. Rearrangement occurs readily in both acidic and basic conditions. Provide a mechanism for the illustrated rearrangement under dilute HCl.



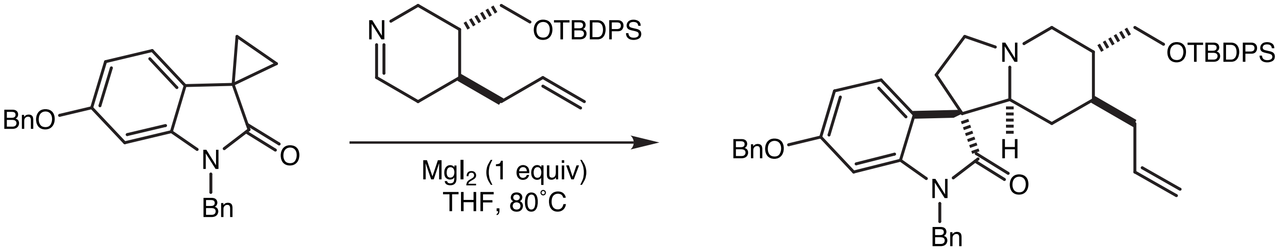
Question 18. (15 points). Padwa and co-workers recently reported this reaction cascade as an example of an efficient approach to the construction of a polycyclic piperidine ring system *(J. Org. Chem*. **2000**, *65*, 2368). Provide a mechanism for this complex transformation.



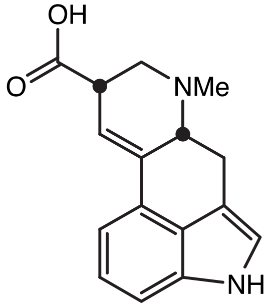
Question 19. (10 points). In conjunction with the total synthesis of *rac*-Strychnofoline (*JACS*, **2002**, *124*, 14826), Carreira utilizes the following MgI_2 catalyzed reaction to form the fused nitrogen heterocycle in one step. Provide a plausible mechanism for this transformation that accounts for the observation that *$Mg(OTf)_2$ does not catalyze this reaction.*



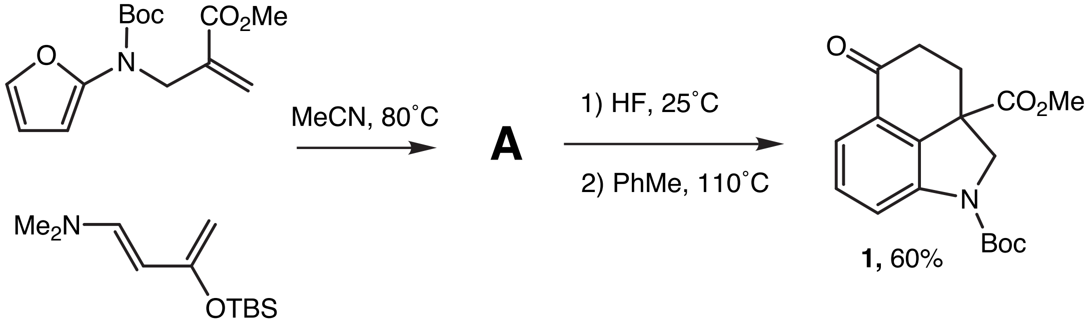
Strychnofoline



Question 20. (15 points). Lysergic acid (**1**) and its numerous derivatives possess broad pharmalogical activity, arguably the broadest spectrum of activities found in any class of natural products. This has driven the pharmaceutical industry to agressively evaluate structural analogues of the lysergic acid skeleton. The reaction sequence illustrated below provides easy access to the tricyclic ketone **1**, a useful intermediate for further analogue studies (*Org. Lett.* **2002**, *4*, 4135).



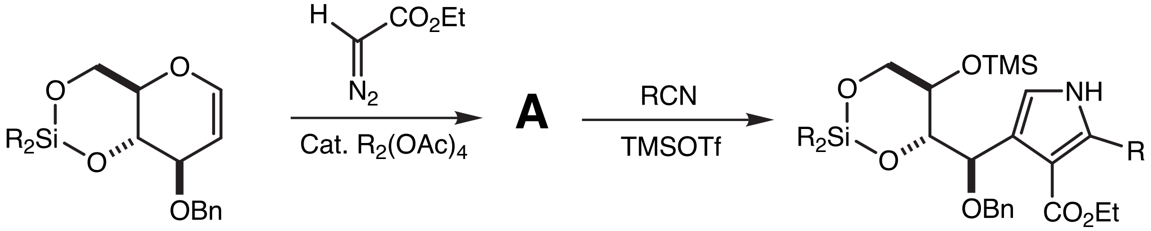
lysergic acid



1, 60%

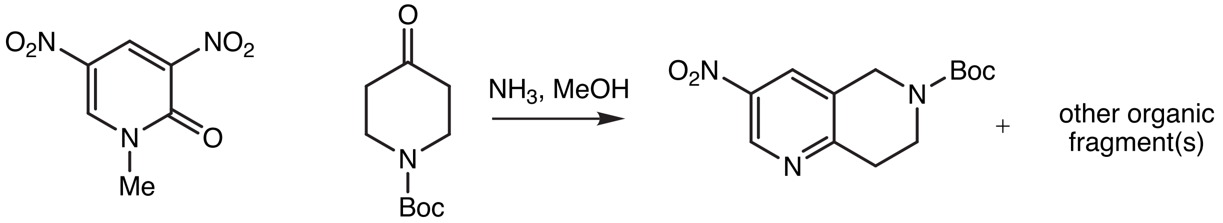
Provide a mechanism for the overall process and clearly identify intermediate **A**.

Question 21. (15 points). Pagendorf and Yu have recently reported a new "diversity-oriented" synthesis of pyrroles (*Org. Lett.* **2003**, *5*, 5099). The two-step process illustrated below will accomodate a range of "R" substituents.



Provide a mechanism for the overall process and clearly identify intermediate **A**.

Question 22. (15 points). This is a classic problem in multistep electron pushing. The following pyridine synthesis has been reported by Tohda (*Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820-2827). Provide a plausible mechanism for this complex transformation. *Hint: To begin to solve a problem of this type, orient the two reacting components in such a fashion that they mirror their orientation in the observed product.*



Provide a mechanism for the overall process in the space below.

Chemistry 206
Second Hour Examination

D. A. Evans
November 14, 2003

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

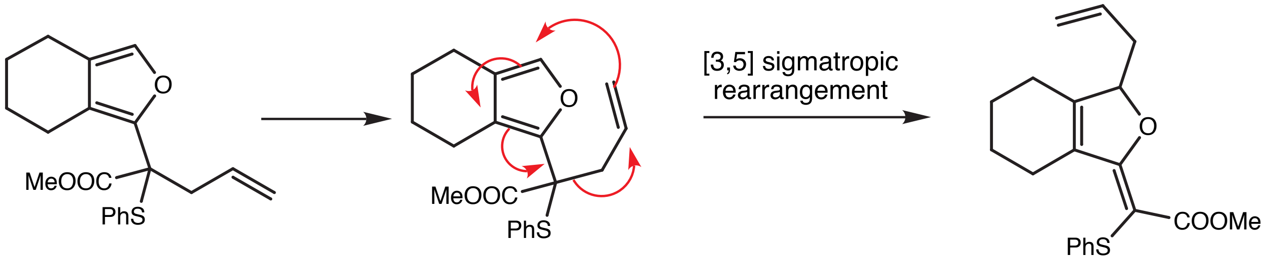
Question (pts)	Score
No. 1 (15)	______
No. 2 (10)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (15)	______
No. 7 (15)	
Total (100)	

The exam will begin at 9:05 AM and end at 11:00.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

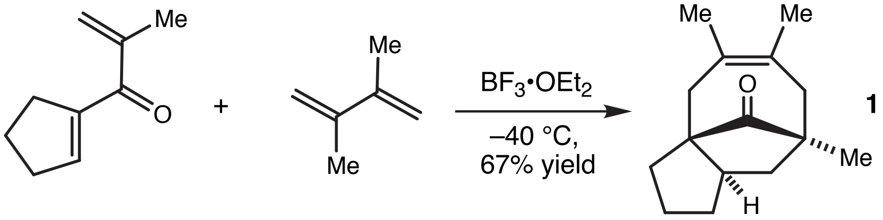
Question 1. (15 points). The furan shown below rearranges on standing at room temperature to the isomeric form shown (*Org. Lett.* **2003**, *5*, 2619). The mechanism proposed in the article for this isomerism is a [3,5] sigmatropic rearrangement.



Part A (7 points). Please provide a Dewar-Zimmerman **and** an FMO analysis that illustrates why this is **not** a plausible mechanism.

Part B (8 points). Please provide a mechanism for this rearrangement that is more consistent with the rules of orbital symmetry. You do not need to provide a justification for the step(s) of your mechanism.

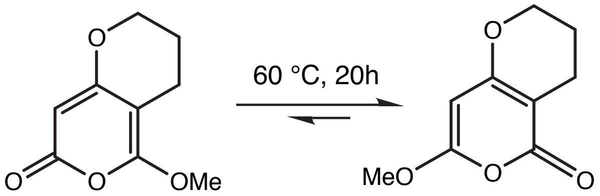
Question 2. (10 points). The illustrated transformation reported this year by West and co-workers (*Org. Lett*. **2003**, *5*, 2747-2750) rapidly facilitates the construction of the complex tricyclic ketone **1** in 67% yield.



Please provide a concise mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.

Question 3. (15 points). In 1989, Cha reported a study on the thermal isomerization of alkoxypyrones (*Tet. Lett.* **1989**, *30*, 3509-3512). One of the cases studies was the rearrangement of **1**→**2**.

1



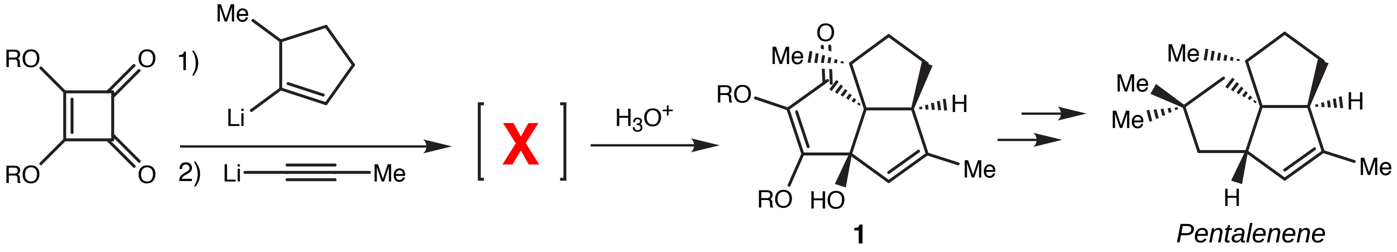
2

2:1 > 20:1

Part A. (10 points). Provide a mechanism for this rearrangement in the space below.

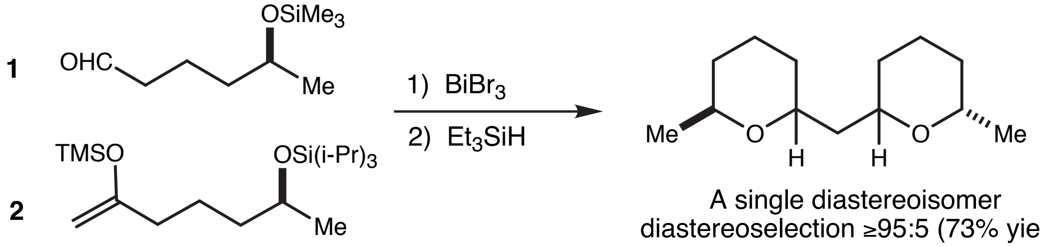
Part B. (5 points). At equilibrium, **2** is strongly favored over **1** (**2:1** > 20:1). Please rationalize product stability on the basis of the anomeric effect as was done by the authors.

Question 4. (15 points). A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett*. **2002**, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core **1** is illustrated below.



Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core **1**. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate **X**.

Question 5. (15 points). P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans (*JACS* **2003**, *125*, 11456-11457). One of their cases is illustrated in Eq 1. In this transformation $BiBr_3$ is employed as a mild Lewis acid.

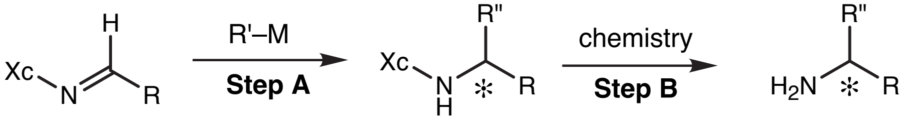


(1)

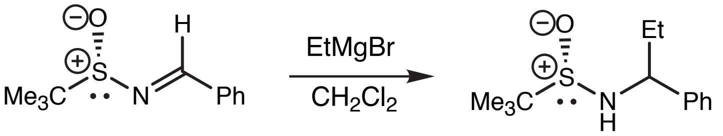
A single diastereoisomer
diastereoselection ≥95:5 (73% yield)

Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

Question 6. (15 points). Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of the chirality transfer process.

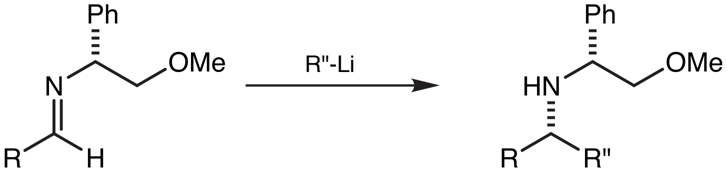


Part A. (9 points). Provide a mechanism for the following transformation reported by Ellman and co-workers. (*Tet*, **1999**, 8883). Include a clear transition state representation that predicts the major product diastereomer. Clearly illustrate the absolute stereochemistry of the product.



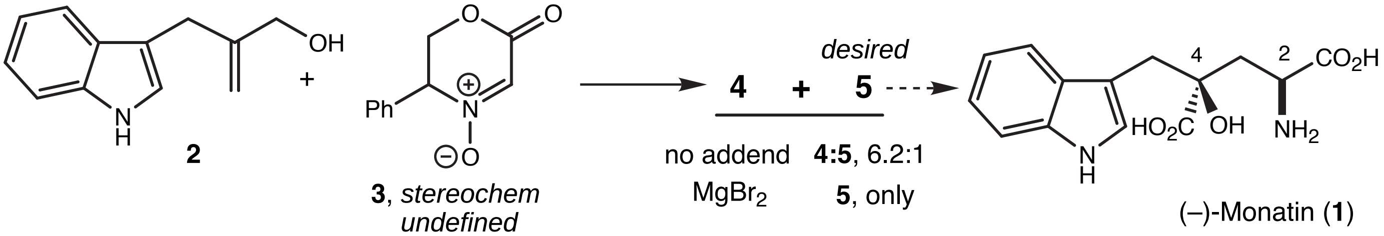
diastereomer ratio 92:8

Part A. (6 points). The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the stereostructure of the product, rationalize the stereochemical outcome.



diastereomer ratio >97:3

Question 7. (15 points). In 1992, (–)-monatin (**1**) was isolated from the bark and roots of *Schlerochiton ilicifolius*. This natural product was found to be a powerful sweetening agent (>1000X sucrose). Recently a stereoselective, nitrone-based synthesis of this natural product was reported by Tamura and co-workers (*Chem. Commun*. **2003**, 2678).



2

3, *stereochem undefined*

no addend **4:5**, 6.2:1

$MgBr_2$ **5**, only

(–)-Monatin (**1**)

Part A. (8 points). In the initial study, the reaction of **2** and **3** afforded at 6.2:1 mixture of diastereomeric cycloadducts **4** and **5** respectively where the minor cycloadduct **5** was the desired product. Provide 3-dimensional absolute stereochemical representations of **4** and **5** below. Do not concern yourself at this point with a rationalle for this selectivity. In this exercise, you must work backwards to the two cycloadducts and then deduce the required absolute stereochemistry for **3**.

Part B. (7 points). When the reaction of **2** and **3** was carried out in the presence of 1.5 equiv of $MgBr_2$, the exclusive formation of the desired cycloadduct **5** was observed in 97% yield. Provide a 3-dimensional representation of the transition state leading to **5** that illustrates the role of $MgBr_2$.

Chemistry 206
Final Examination

D. A. Evans
November, 2006

Name (please print):________________________
last first initial

Signature:________________________

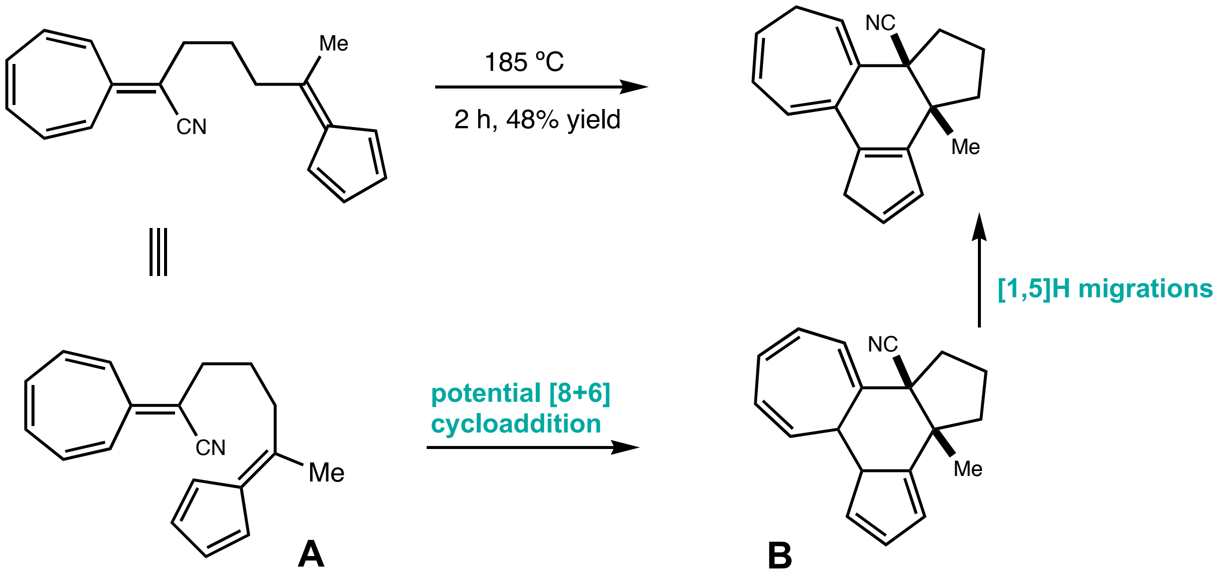
Teaching Fellow:________________________

This examination contains **15** questions (15 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

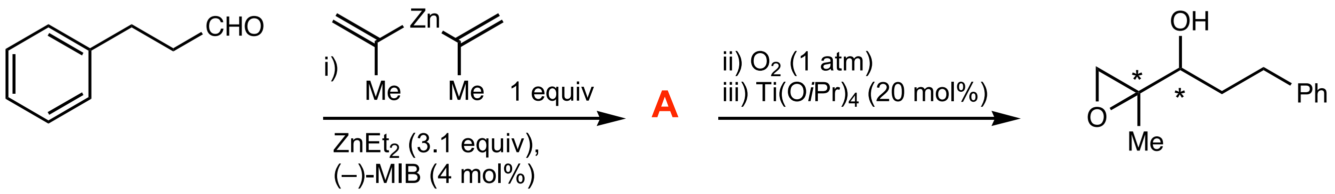
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**
No. 1 (**10**)	______
No. 2 (**15**)	______
No. 3 (**15**)	______
No. 4 (**15**)	______
No. 5 (**10**)	______
No. 6 (**15**)	______
No. 7 (**10**)	______
No. 8 (**10**)	______
Subtotal (**100**)	

Question 1. (10 points). The following reaction was reported (*Tet. Lett.*, **1986**, *27*, 4881.) The Authors propose a [8+6] cycloaddition for the conversion of **A** to **B**. Please analyze this proposed cycloaddition and determine using FMO or Dewar-Zimmerman analysis whether the ring-closing step is concerted or stepwise under the reaction conditions.

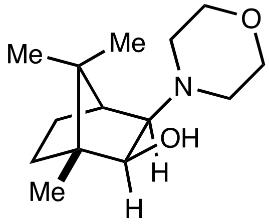


Question 2. (15 points). A one-pot procedure for the enantioselective addition / diastereoselective epoxidation was recently developed in the laboratories of Patrick Walsh (*JACS*, **2004**, *126*, 13608.). This methodology can directly prepare up to 3 contiguous stereocenters. Please provide a mechanism for this transformation and predict the stereochemistry of the product. Your anwser should use 3-D representations and highlight intermediate **A**. *(Hint: oxygen is known to insert into organozinc species, forming zinc peroxides and titanium can transmetallate with zinc. The organometallic aspects of this question may be de-emphasized in your answer.)*



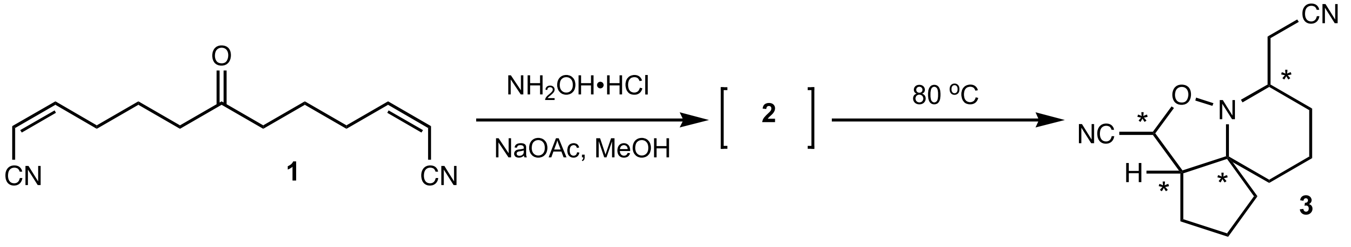
90% yield
85% ee

(–)-MIB

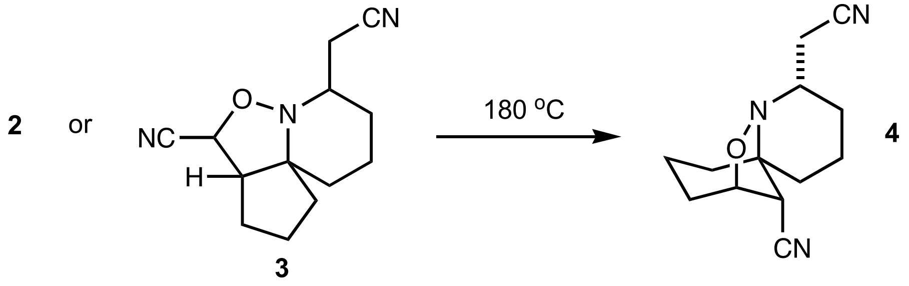


Question 3. (15 points). Stockman and co-workers have reported a rapid and elegant route to the core of the histrionicotoxins (*J. Org. Chem.* **2004**, *69*, 1598-1602). A key step in their synthesis was the conversion of symmetrical ketone **1** to tricyclic compound **3**.

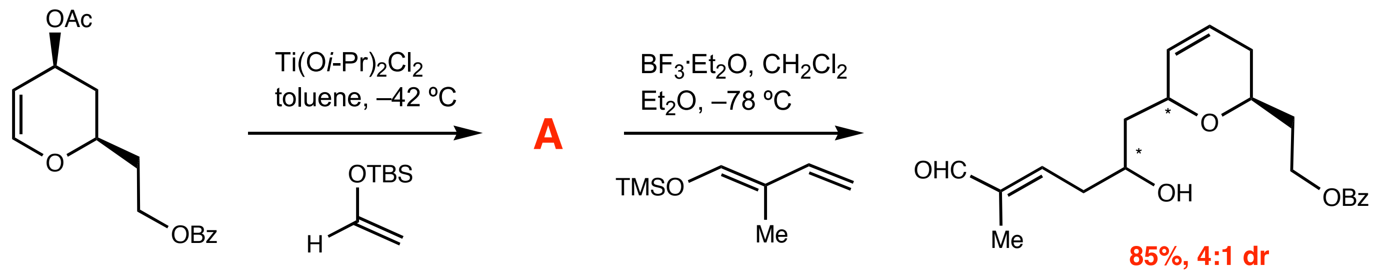
Part A. Using clear three-dimensional drawings, please provide a mechanism for the conversion of **1** to **3**. Be sure to identify intermediate **2** and indicate the relative stereochemisty of **3**.



Part B Heating of either **2** or **3** at 180 °C gave rise to the tricyclic compound **4**. Please provide a mechanism for the conversion of **3** into **4**.



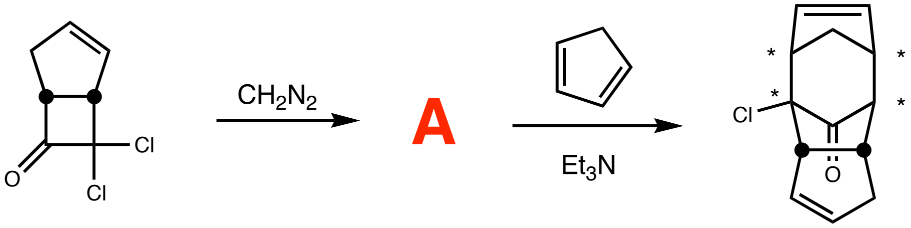
Question 4. (15 points). The Paterson group used the following reaction sequence in a synthesis of swinholide A (*Tetrahedron*, **1995**, *51*, 9413):



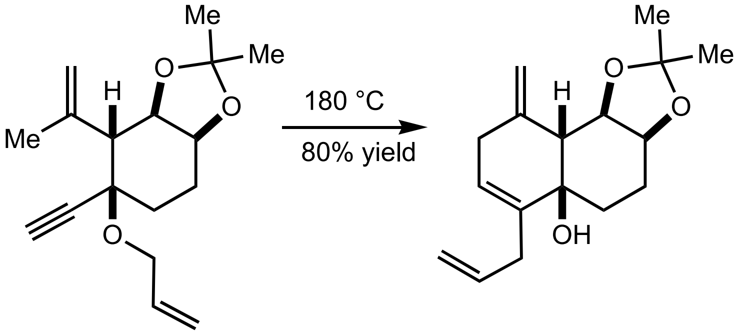
Part A. Provide the structure of intermediate **A** and the mechanism for its formation. Predict and account for the stereochemistry of **A** in your mechanism. Include 3-D drawings when relevant.

Part B. Provide a mechanism for the formation of the final product from intermediate **A**. Predict and account for the stereochemistry of the product in your mechanism. Include 3-D drawings when relevant.

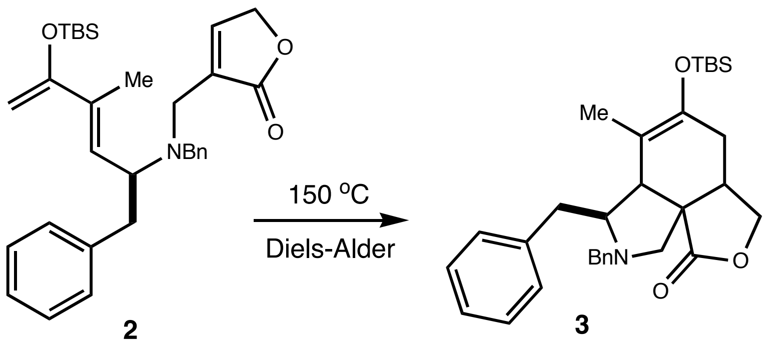
Question 5. (10 points). Harmata and co-workers reported the following interesting transformation (*Org. Lett.* **2001**, *3*, 2533.) Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product.



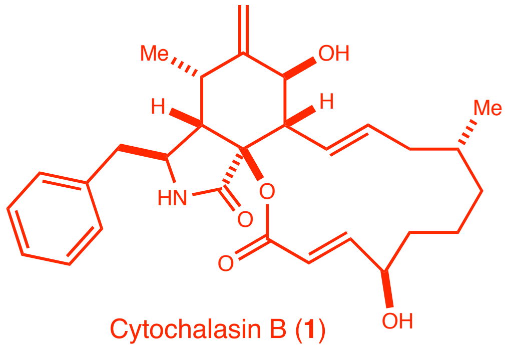
Question 6. (15 points). In a recent paper by Morency and Barriault (*Tet. Lett.* **2004**, *45*, 6105), the following transformation was reported. The series of thermally induced rearrangements afforded the cis decalin product as a single diastereoisomer in 80% yield. This transformation was reported as a model study for eventual application to the synthesis of vinigrol (**1**). Provide a plausible mechanism for this transformation and explain the selectivity



Question 7. (10 points). The intramolecular Diels-Alder reaction of **2** was recently employed in a total synthesis of the structurally complex natural product cyctochalasin B (**1**). (Haidle and Myers, *PNAS*, **2004**, *101*, 12048-12053)



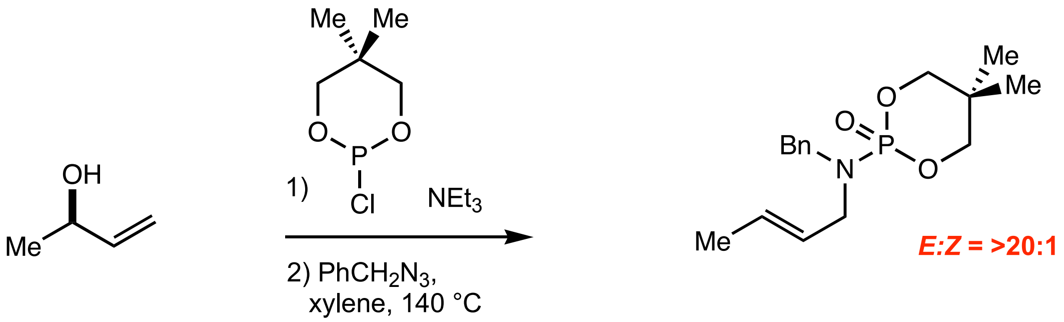
2 → **3**



Cytochalasin B (**1**)

Please predict the major product **3** of this cycloaddition and provide clear three-dimensional drawings to illustrate your answer. Be sure to identify relevant control elements.

Question 8. (10 points). Mapp and co-workers disclosed a unique synthesis of allylic amines (*JACS*. **2004**, *126*, 5364.). Please provide a mechanism for the process that accounts for the observed the olefin selectivity.



Chemistry 206
Second Hour Examination

D. A. Evans
November 21, 2005

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (15)	
No. 2 (15)	
No. 3 (10)	
No. 4 (15)	
No. 5 (15)	
No. 6 (15)	
No. 7 (15)	
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

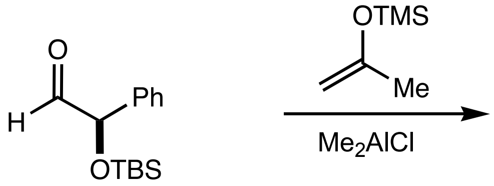
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

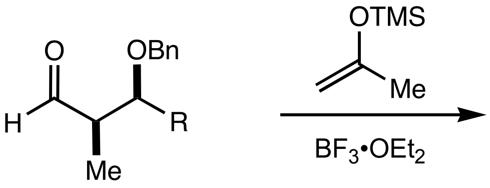
TALKIN' TURKEY...
©Fewings fewings.ca
ARE YOU SERIOUS? THEY HAVE FRIENDS AND FAMILY OVER FOR A GET TOGETHER AND THEY DO WHAT??

Question 1. (15 points). Predict the stereochemical outcome for each of the illustrated reactions. Draw the major diastereomer in the box provided.

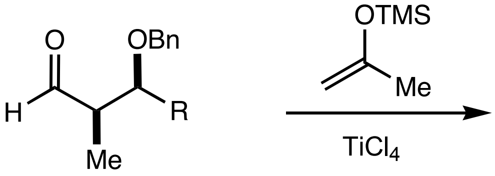
Part A: (3 points)



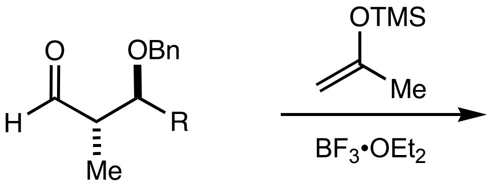
Part B: (3 points)



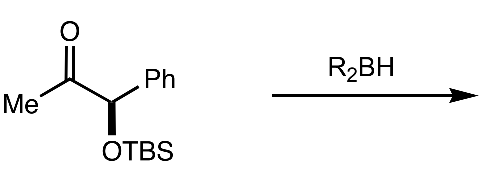
Part C: (3 points)



Part D: (3 points)

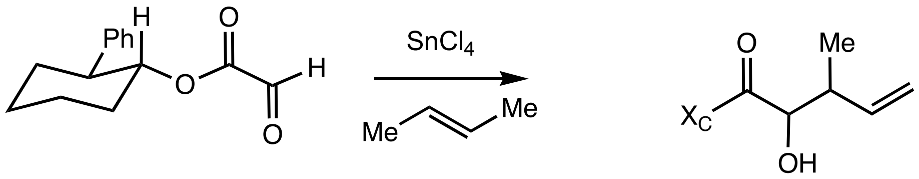


Part E: (3 points)



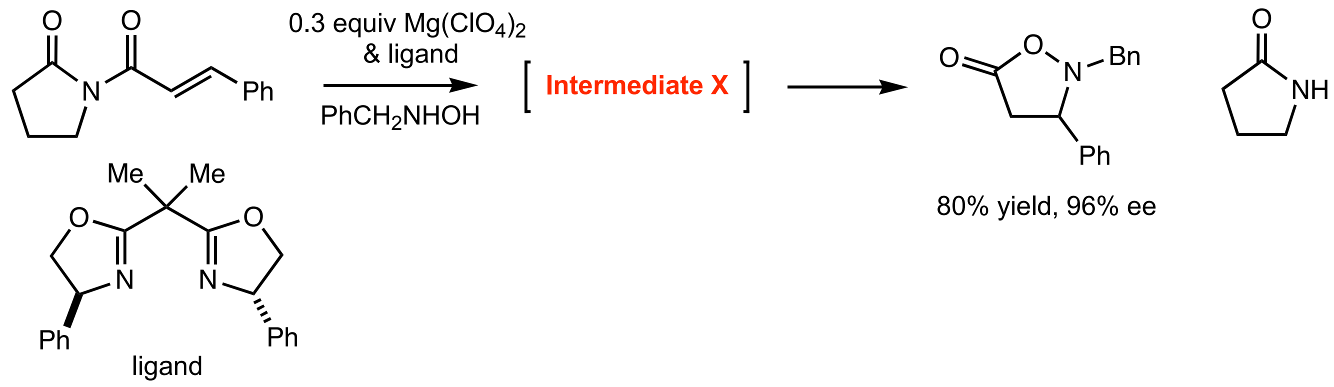
Question 2. (15 points). The following processes result in the transfer of chirality from either chiral auxiliary or catalyst to product. In each instance predict the absolute stereochemistry of the product and draw thetransition state that best rationalizes the sense of asymmetric induction.

Part A. (7 points). The literature reference: Whitesell, et al. *Tetrahedron* **1986,** *42,* 2993-3001.
1: Predict the stereochemistry of the product; **2**: Draw the relevant transition structure.



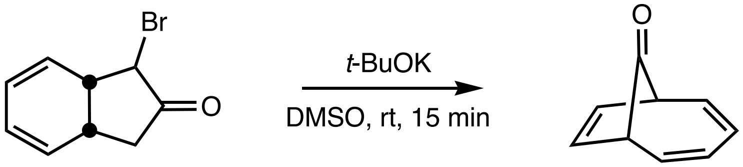
Your Answer

Part B. (8 points). The literature reference: Sibi et al. *Org Lett.* **2000,** *2,*3393-3396.
1: Predict the stereochemistry of the product; **2**: Draw the relevant transition structure for the stereodifferentiating step.

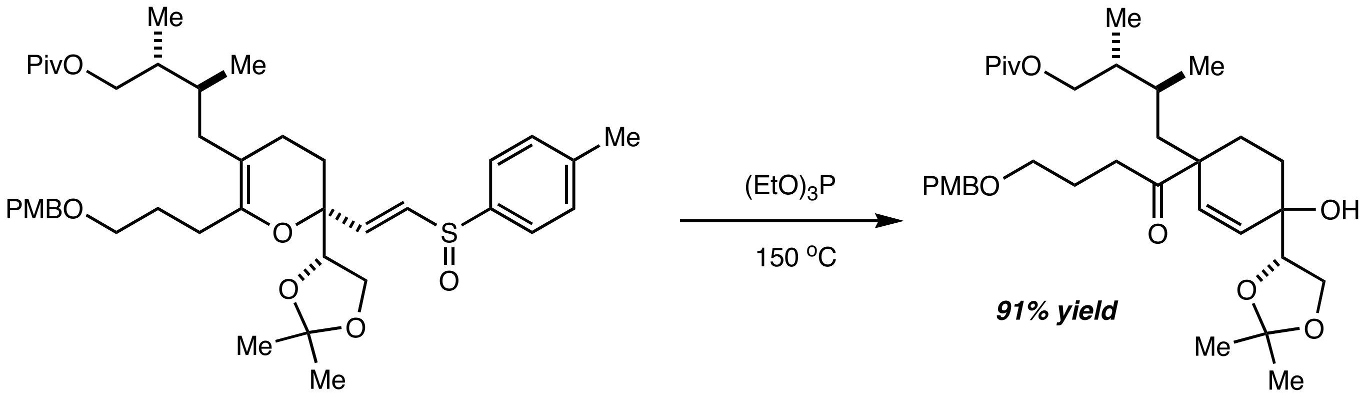


80% yield, 96% ee

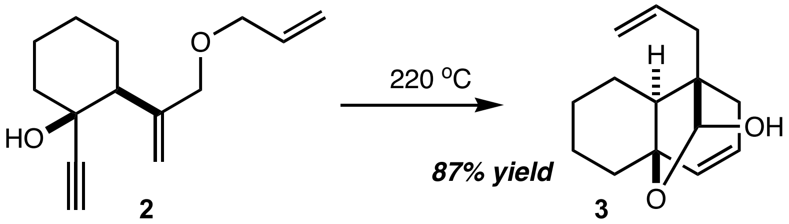
Question 3. (10 points). The following rearrangement was excecuted by Paquette and coworkers (*JACS*, **1973**, *95*, 2230). In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.

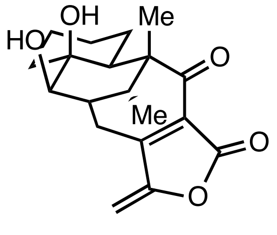


Question 4. (15 points). As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*Org. Lett.* **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the relative stereochemical outcome.



Question 5. (15 points). As part of a strategy directed towards the synthesis of tetradecamycin **(1),** Warrington and Barriault carried out the thermally induced rearrangement of **2** to synthesize the *trans-de*calin system **3** (*Org. Lett*. **2005**, *7*, 4589). Using clear three-dimensional drawings please provide a plausible mechanism for this transformation that is in accordance with the observed stereochemical outcome.



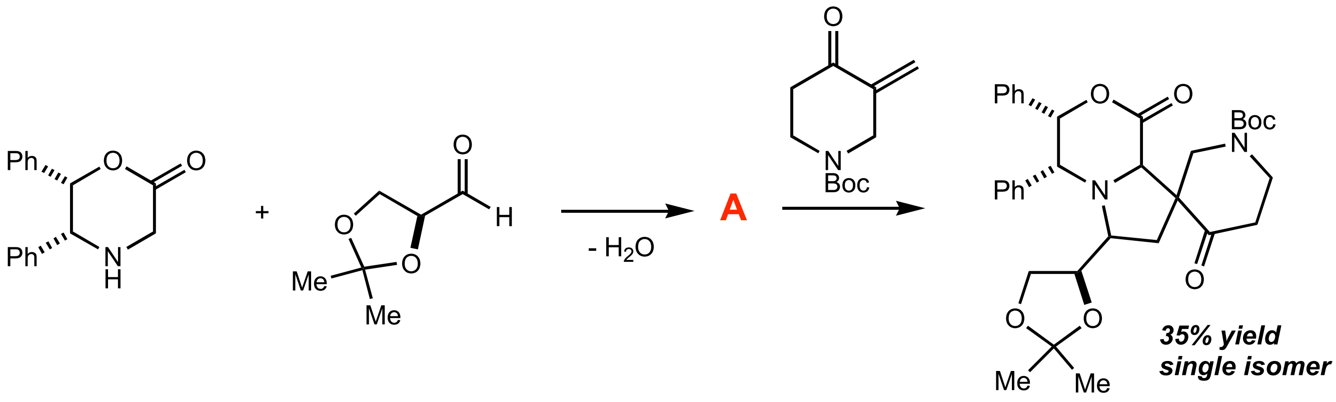


tetradecamycin (**1**)

Question 6. (15 points). As part of a synthetic effort towards the construction of Nakadomarin A, Williams and Ahrendt reported the following highly selective three-component reaction (*Org. Lett.* **2004**, *6*, 4539).

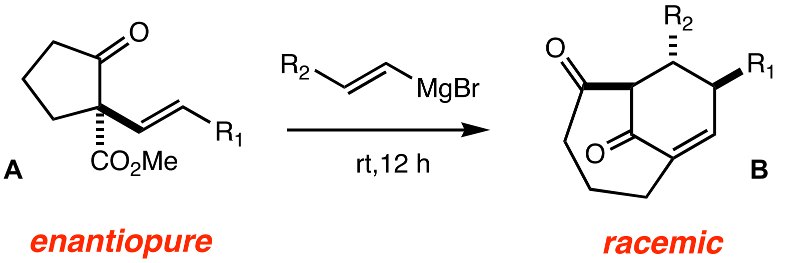
Part A. (X points). Please identify intermediate **A**, and clearly draw its low energy conformation.

Part B. (X points). Using clear three-dimensional drawings please provide a mechanism for the transformation of **A** into the product and predict the relative stereochemical outcome.



35% yield
single isomer

Question 7. (15 points). The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture.*



Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.

Chemistry 206
Second Hour Examination

D. A. Evans
November 14, 2003

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

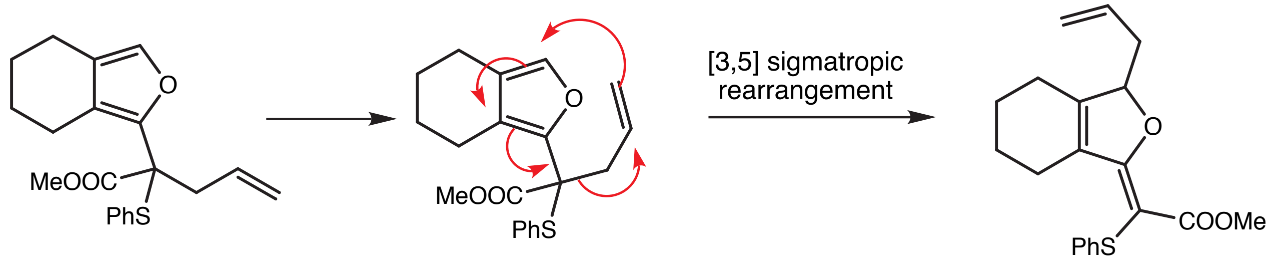
Question (pts)	Score
No. 1 (15)	______
No. 2 (10)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (15)	______
No. 7 (15)	
Total (100)	

The exam will begin at 9:05 AM and end at 11:00.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

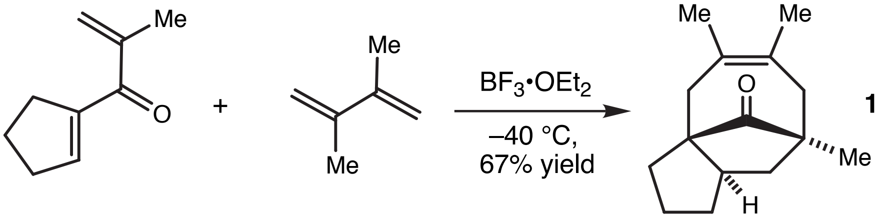
Question 1. (15 points). The furan shown below rearranges on standing at room temperature to the isomeric form shown (*Org. Lett.* **2003**, *5*, 2619). The mechanism proposed in the article for this isomerism is a [3,5] sigmatropic rearrangement.



Part A (7 points). Please provide a Dewar-Zimmerman **and** an FMO analysis that illustrates why this is **not** a plausible mechanism.

Part B (8 points). Please provide a mechanism for this rearrangement that is more consistent with the rules of orbital symmetry. You do not need to provide a justification for the step(s) of your mechanism.

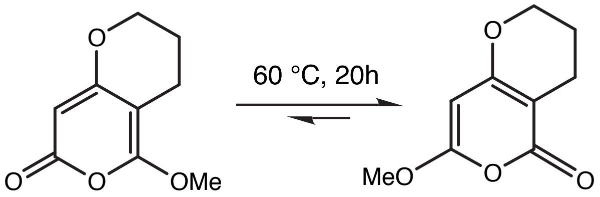
Question 2. (10 points). The illustrated transformation reported this year by West and co-workers (*Org. Lett*. **2003**, *5*, 2747-2750) rapidly facilitates the construction of the complex tricyclic ketone **1** in 67% yield.



Please provide a concise mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.

Question 3. (15 points). In 1989, Cha reported a study on the thermal isomerization of alkoxypyrones (*Tet. Lett.* **1989**, *30*, 3509-3512). One of the cases studies was the rearrangement of **1**→**2**.

1



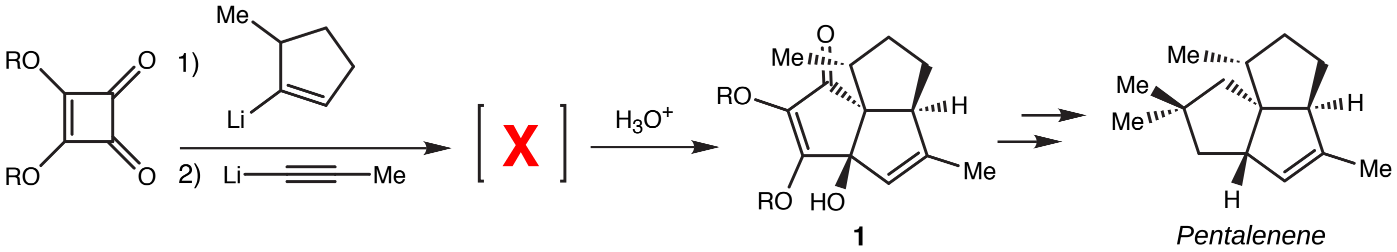
2

2:1 > 20:1

Part A. (10 points). Provide a mechanism for this rearrangement in the space below.

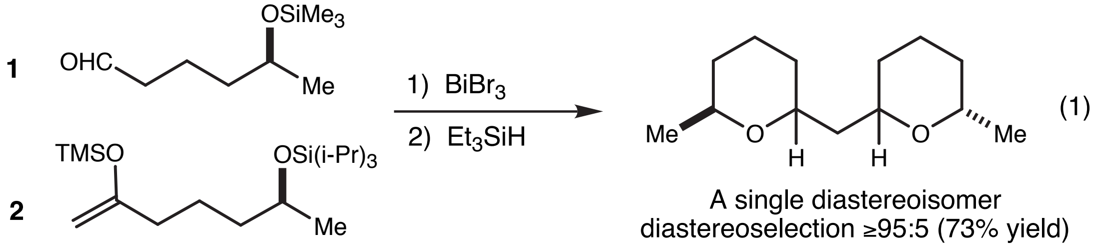
Part B. (5 points). At equilibrium, **2** is strongly favored over **1** (**2:1** > 20:1). Please rationalize product stability on the basis of the anomeric effect as was done by the authors.

Question 4. (15 points). A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett*. **2002**, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core **1** is illustrated below.



Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core **1**. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate **X**.

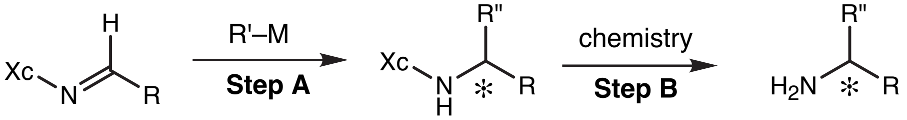
Question 5. (15 points). P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans (*JACS* **2003**, *125*, 11456-11457). One of their cases is illustrated in Eq 1. In this transformation $BiBr_3$ is employed as a mild Lewis acid.



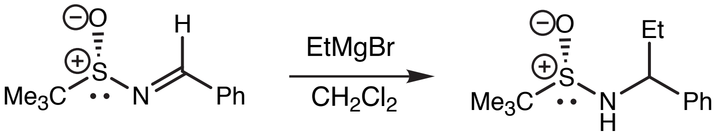
A single diastereoisomer
diastereoselection ≥95:5 (73% yield)

Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

Question 6. (15 points). Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of the chirality transfer process.

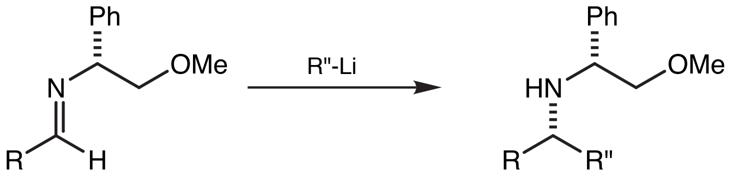


Part A. (9 points). Provide a mechanism for the following transformation reported by Ellman and co-workers. (*Tet*, **1999**, 8883). Include a clear transition state representation that predicts the major product diastereomer. Clearly illustrate the absolute stereochemistry of the product.



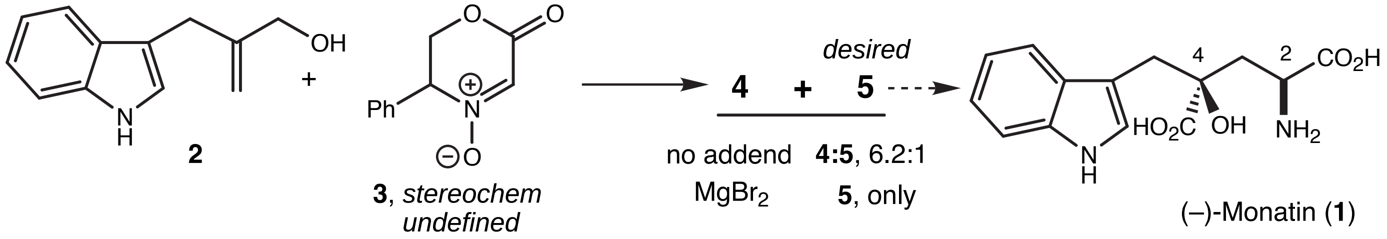
diastereomer ratio 92:8

Part A. (6 points). The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the stereostructure of the product, rationalize the stereochemical outcome.



diastereomer ratio >97:3

Question 7. (15 points). In 1992, (–)-monatin (**1**) was isolated from the bark and roots of *Schlerochiton ilicifolius*. This natural product was found to be a powerful sweetening agent (>1000X sucrose). Recently a stereoselective, nitrone-based synthesis of this natural product was reported by Tamura and co-workers (*Chem. Commun*. **2003**, 2678).



2

3, *stereochem undefined*

(–)-Monatin (**1**)

Part A. (8 points). In the initial study, the reaction of **2** and **3** afforded at 6.2:1 mixture of diastereomeric cycloadducts **4** and **5** respectively where the minor cycloadduct **5** was the desired product. Provide 3-dimensional absolute stereochemical representations of **4** and **5** below. Do not concern yourself at this point with a rationalle for this selectivity. In this exercise, you must work backwards to the two cycloadducts and then deduce the required absolute stereochemistry for **3**.

Part B. (7 points). When the reaction of **2** and **3** was carried out in the presence of 1.5 equiv of $MgBr_2$, the exclusive formation of the desired cycloadduct **5** was observed in 97% yield. Provide a 3-dimensional representation of the transition state leading to **5** that illustrates the role of $MgBr_2$.

Chemistry 206
Final Examination

D. A. Evans
November, 2006

Name (please print):______________________________
last first initial

Signature:______________________________

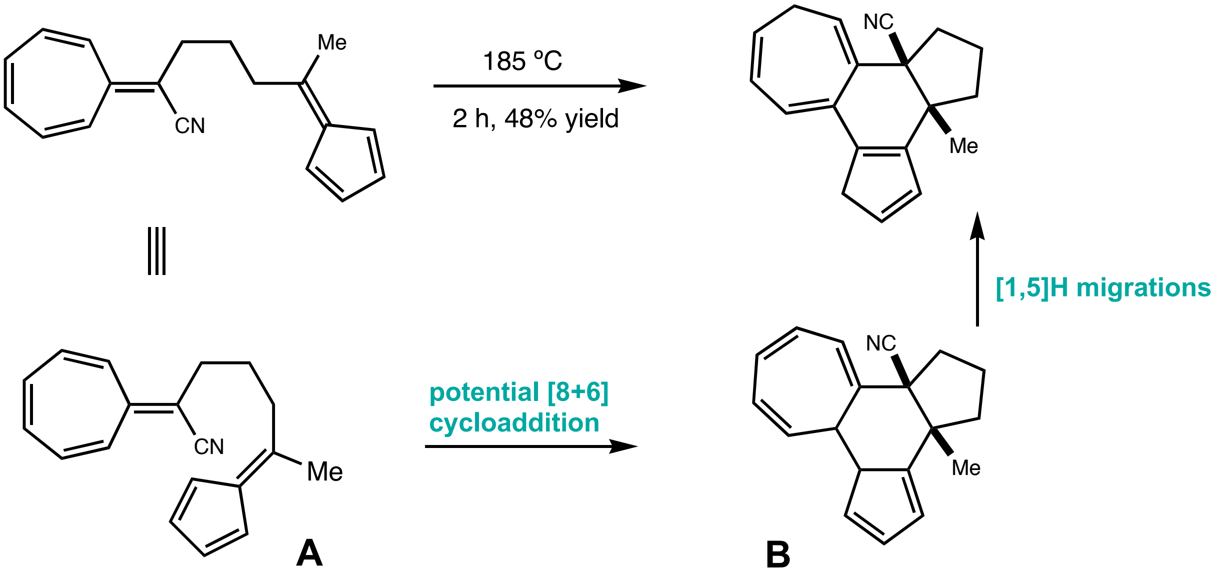
Teaching Fellow:______________________________

This examination contains **15** questions (15 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

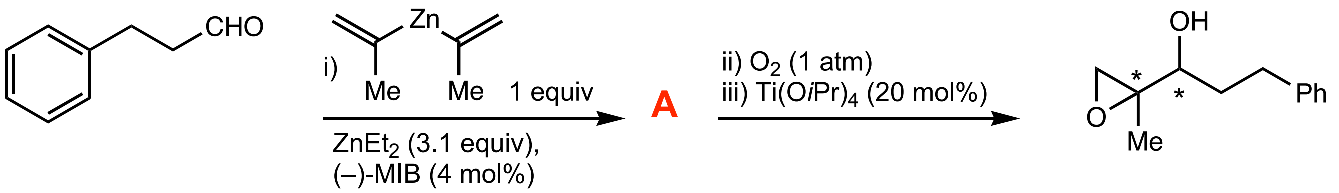
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**
No. 1 (**10**)	______
No. 2 (**15**)	______
No. 3 (**15**)	______
No. 4 (**15**)	______
No. 5 (**10**)	______
No. 6 (**15**)	______
No. 7 (**10**)	______
No. 8 (**10**)	______
Subtotal (**100**)	

Question 1. (10 points). The following reaction was reported (*Tet. Lett.*, **1986**, *27*, 4881.) The Authors propose a [8+6] cycloaddition for the conversion of **A** to **B**. Please analyze this proposed cycloaddition and determine using FMO or Dewar-Zimmerman analysis whether the ring-closing step is concerted or stepwise under the reaction conditions.

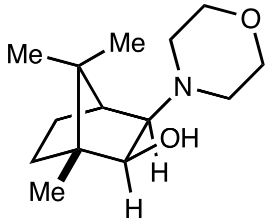


Question 2. (15 points). A one-pot procedure for the enantioselective addition / diastereoselective epoxidation was recently developed in the laboratories of Patrick Walsh (*JACS*, **2004**, *126*, 13608.). This methodology can directly prepare up to 3 contiguous stereocenters. Please provide a mechanism for this transformation and predict the stereochemistry of the product. Your anwser should use 3-D representations and highlight intermediate **A**. *(Hint: oxygen is known to insert into organozinc species, forming zinc peroxides and titanium can transmetallate with zinc. The organometallic aspects of this question may be de-emphasized in your answer.)*



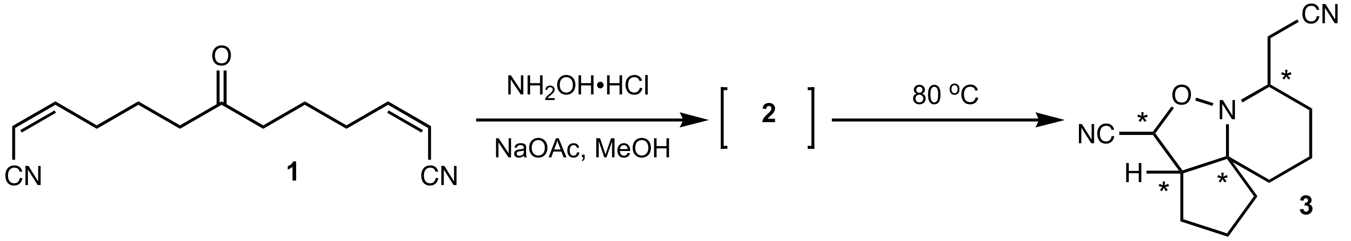
90% yield
85% ee

(–)-MIB

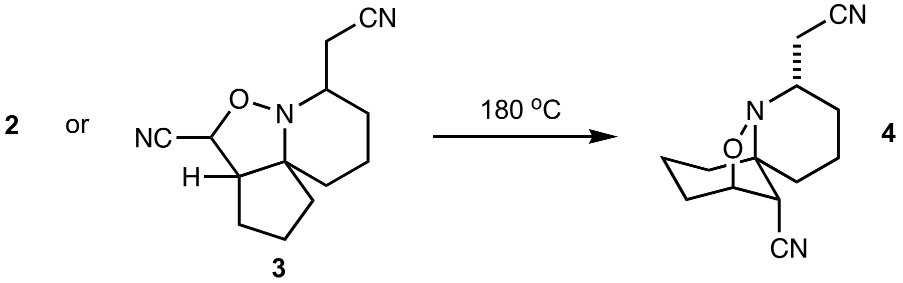


Question 3. (15 points). Stockman and co-workers have reported a rapid and elegant route to the core of the histrionicotoxins (*J. Org. Chem.* **2004**, *69*, 1598-1602). A key step in their synthesis was the conversion of symmetrical ketone **1** to tricyclic compound **3**.

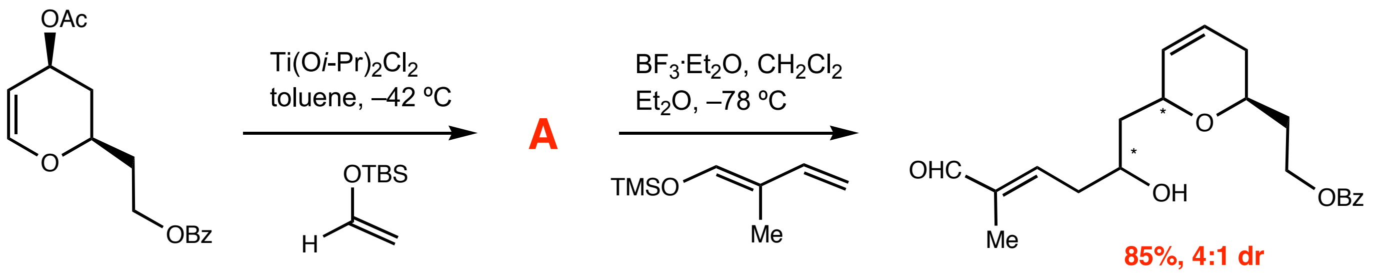
Part A. Using clear three-dimensional drawings, please provide a mechanism for the conversion of **1** to **3**. Be sure to identify intermediate **2** and indicate the relative stereochemisty of **3**.



Part B Heating of either **2** or **3** at 180 °C gave rise to the tricyclic compound **4**. Please provide a mechanism for the conversion of **3** into **4**.



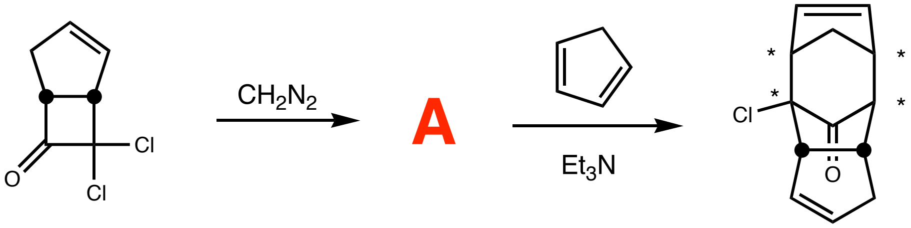
Question 4. (15 points). The Paterson group used the following reaction sequence in a synthesis of swinholide A (*Tetrahedron*, **1995**, *51*, 9413):



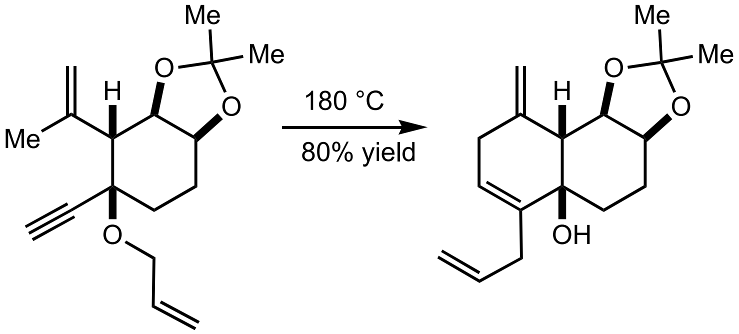
Part A. Provide the structure of intermediate **A** and the mechanism for its formation. Predict and account for the stereochemistry of **A** in your mechanism. Include 3-D drawings when relevant.

Part B. Provide a mechanism for the formation of the final product from intermediate **A**. Predict and account for the stereochemistry of the product in your mechanism. Include 3-D drawings when relevant.

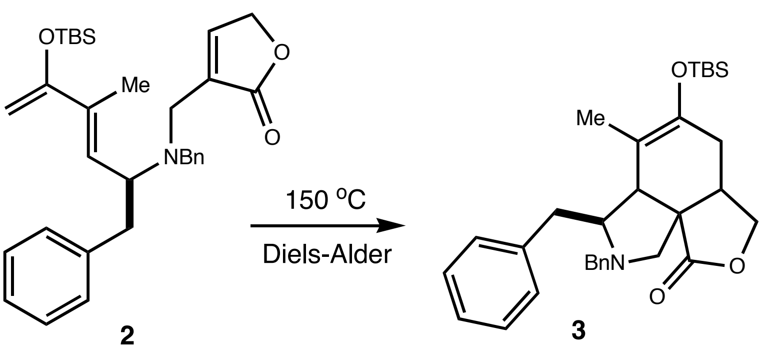
Question 5. (10 points). Harmata and co-workers reported the following interesting transformation (*Org. Lett.* **2001**, *3*, 2533.) Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product.



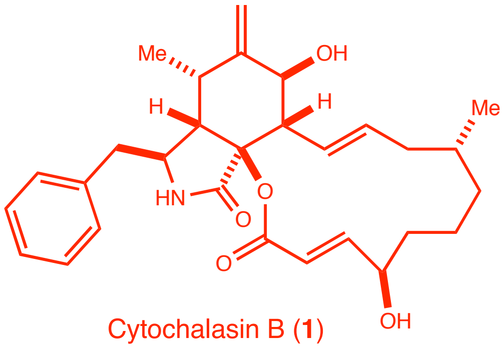
Question 6. (15 points). In a recent paper by Morency and Barriault (*Tet. Lett.* **2004**, *45*, 6105), the following transformation was reported. The series of thermally induced rearrangements afforded the cis decalin product as a single diastereoisomer in 80% yield. This transformation was reported as a model study for eventual application to the synthesis of vinigrol (**1**). Provide a plausible mechanism for this transformation and explain the selectivity



Question 7. (10 points). The intramolecular Diels-Alder reaction of **2** was recently employed in a total synthesis of the structurally complex natural product cyctochalasin B (**1**). (Haidle and Myers, *PNAS*, **2004**, *101*, 12048-12053)



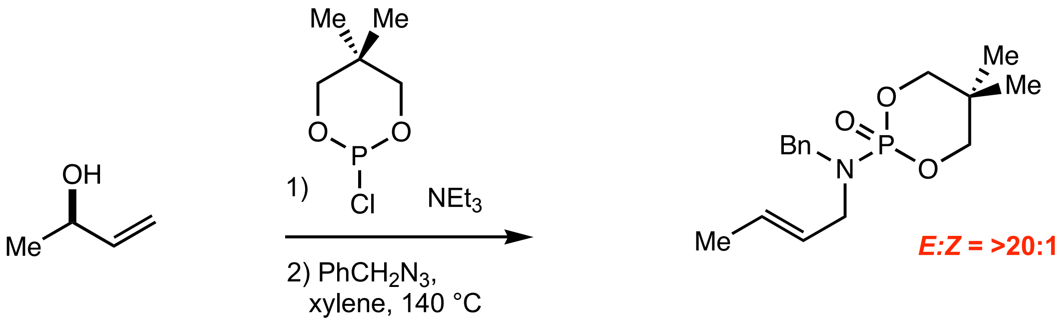
2 **3**



Cytochalasin B (**1**)

Please predict the major product **3** of this cycloaddition and provide clear three-dimensional drawings to illustrate your answer. Be sure to identify relevant control elements.

Question 8. (10 points). Mapp and co-workers disclosed a unique synthesis of allylic amines (*JACS*. **2004**, *126*, 5364.). Please provide a mechanism for the process that accounts for the observed the olefin selectivity.



Chemistry 206
Second Hour Examination

D. A. Evans
November 21, 2005

Name (please print): ____________________
last first initial

Signature: ____________________

Teaching Fellow: ____________________

Question (pts)	Score
No. 1 (15)	______
No. 2 (15)	______
No. 3 (10)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (15)	______
No. 7 (15)	
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

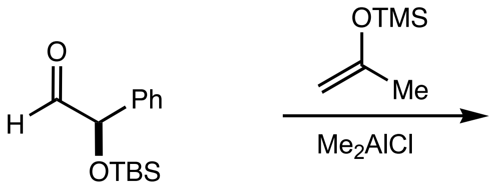
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

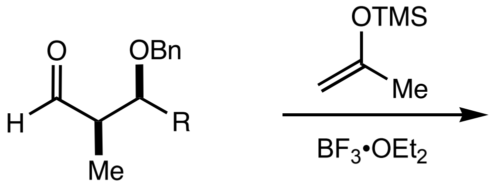
TALKIN' TURKEY...
©Fewings fewings.ca
ARE YOU SERIOUS? THEY HAVE FRIENDS AND FAMILY OVER FOR A GET TOGETHER AND THEY DO WHAT??

Question 1. (15 points). Predict the stereochemical outcome for each of the illustrated reactions. Draw the major diastereomer in the box provided.

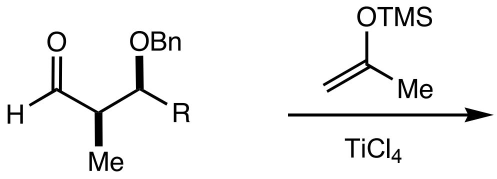
Part A: (3 points)



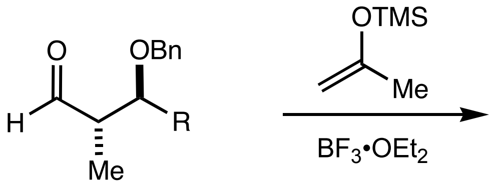
Part B: (3 points)



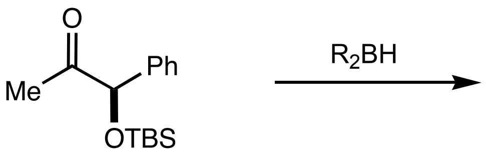
Part C: (3 points)



Part D: (3 points)

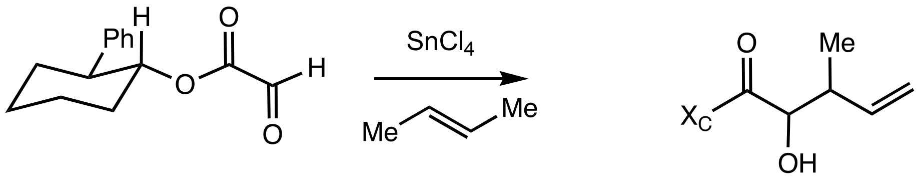


Part E: (3 points)



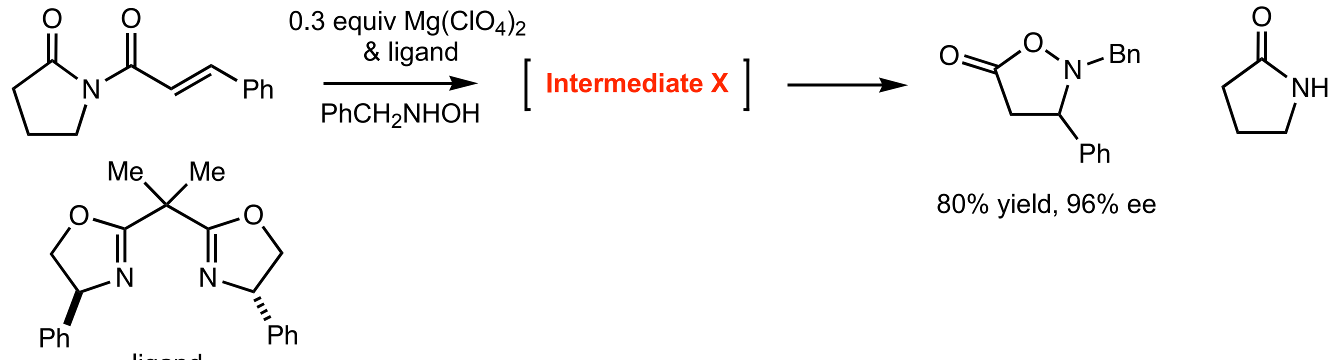
Question 2. (15 points). The following processes result in the transfer of chirality from either chiral auxiliary or catalyst to product. In each instance predict the absolute stereochemistry of the product and draw thetransition state that best rationalizes the sense of asymmetric induction.

Part A. (7 points). The literature reference: Whitesell, et al. *Tetrahedron* **1986,** *42,* 2993-3001.
1: Predict the stereochemistry of the product; **2**: Draw the relevant transition structure.



Your Answer

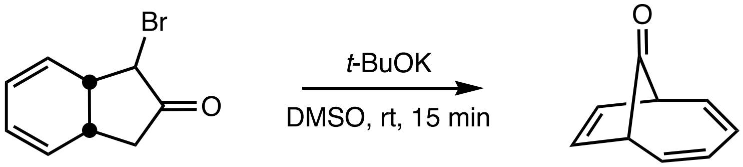
Part B. (8 points). The literature reference: Sibi et al. *Org Lett.* **2000,** *2,*3393-3396.
1: Predict the stereochemistry of the product; **2**: Draw the relevant transition structure for the stereodifferentiating step.



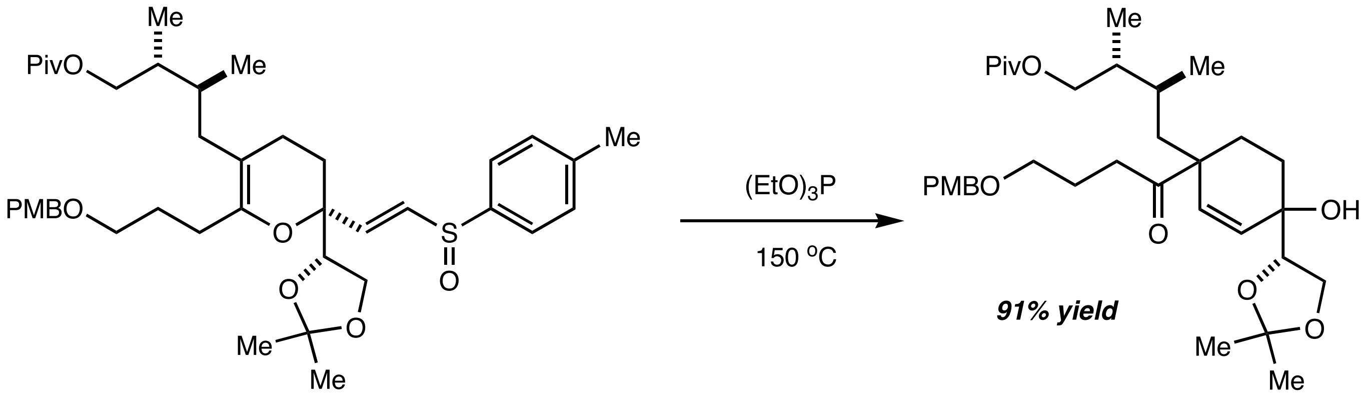
80% yield, 96% ee

ligand

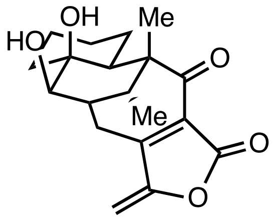
Question 3. (10 points). The following rearrangement was excecuted by Paquette and coworkers (*JACS*, **1973**, *95*, 2230). In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.



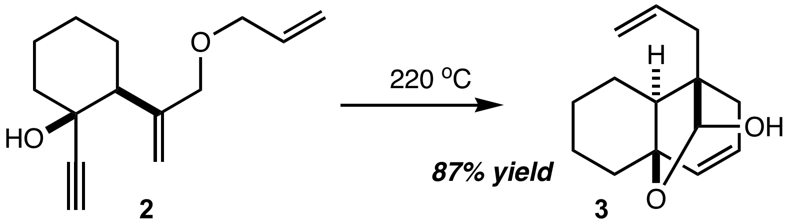
Question 4. (15 points). As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*Org. Lett.* **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the relative stereochemical outcome.



Question 5. (15 points). As part of a strategy directed towards the synthesis of tetradecamycin **(1),** Warrington and Barriault carried out the thermally induced rearrangement of **2** to synthesize the *trans-de*calin system **3** (*Org. Lett*. **2005**, *7*, 4589). Using clear three-dimensional drawings please provide a plausible mechanism for this transformation that is in accordance with the observed stereochemical outcome.



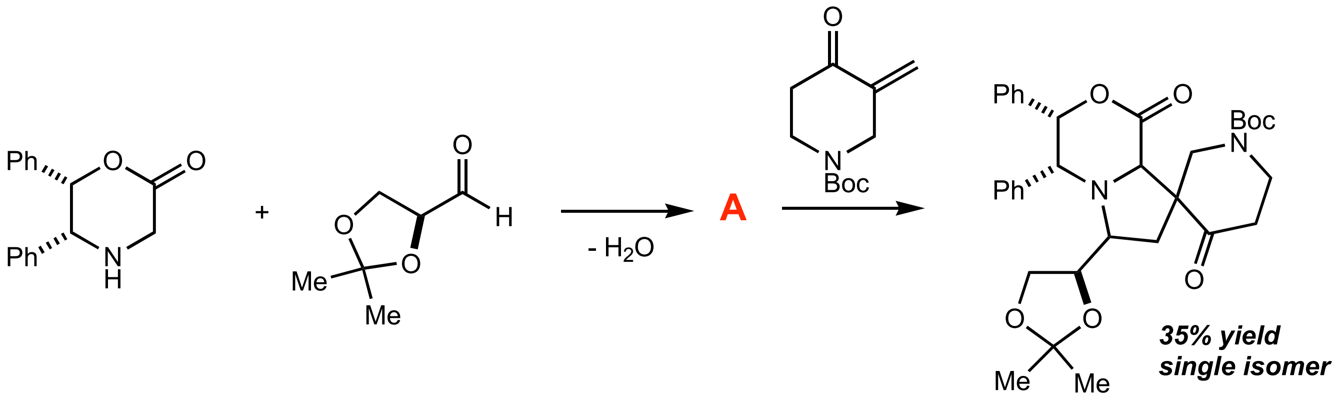
tetradecamycin (**1**)



Question 6. (15 points). As part of a synthetic effort towards the construction of Nakadomarin A, Williams and Ahrendt reported the following highly selective three-component reaction (*Org. Lett.* **2004**, *6*, 4539).

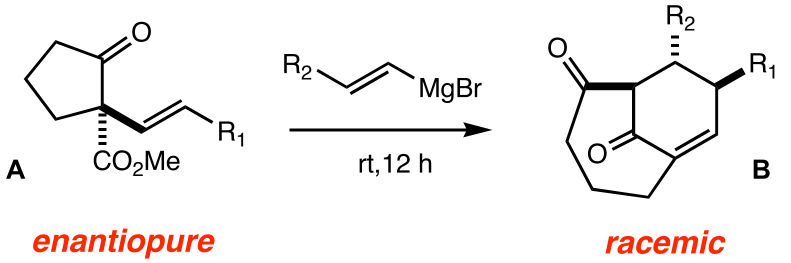
Part A. (X points). Please identify intermediate **A**, and clearly draw its low energy conformation.

Part B. (X points). Using clear three-dimensional drawings please provide a mechanism for the transformation of **A** into the product and predict the relative stereochemical outcome.



35% yield single isomer

Question 7. (15 points). The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture.*



Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.

Chemistry 206
First Hour Examination

Answer Key

D. A. Evans
October 13, 2006

Name (please print): ______________________________
last first initial

Signature: ______________________________

Teaching Fellow: ______________________________

Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (10)	______
No. 7 (10)	______
No. 8 (10)	
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

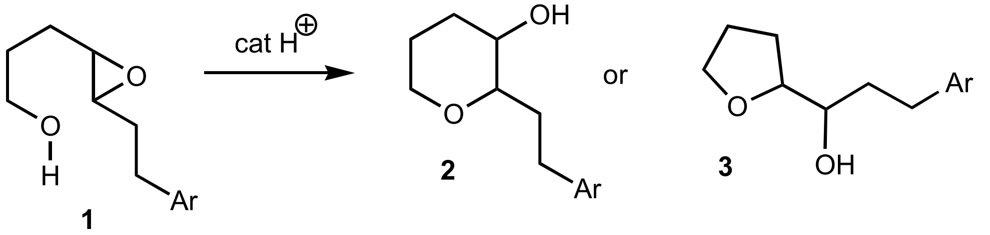
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate. This examination has nine pages.

Examination Average
73.6

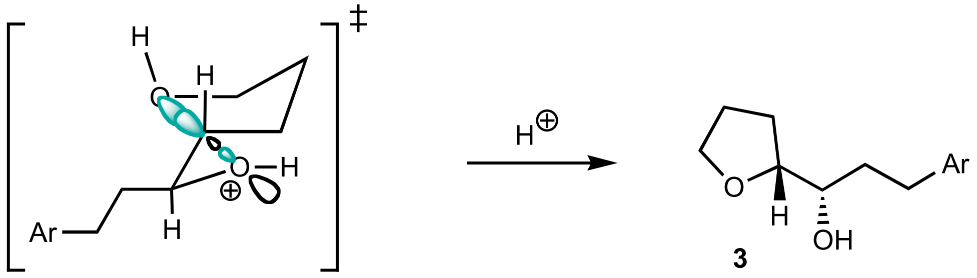
Answer Key

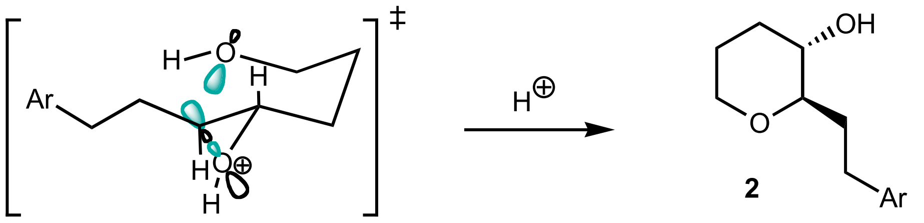
Question 1. (10 points). The acid catalyzed cyclization of trans epoxide **1** yields a single kinetic product *JACS* **1993**, *115*, 8453.



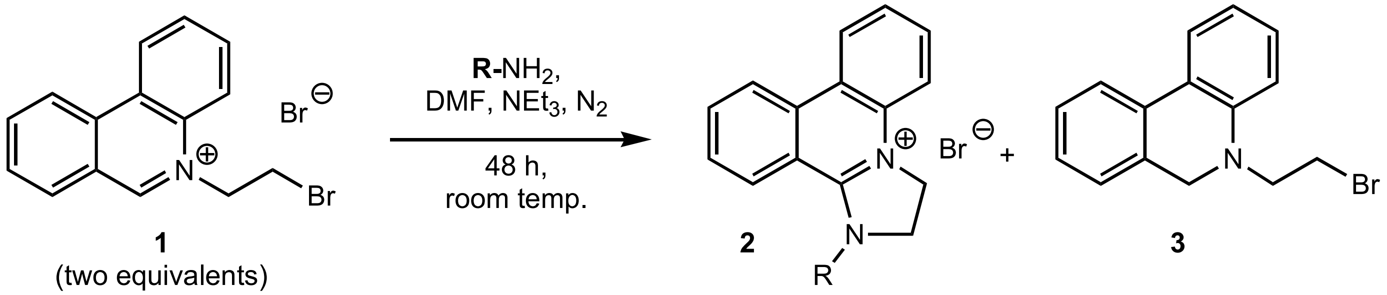
Predict the kinetic product of this reaction and its stereostructure (relative stereochemistry). Assume carbonium ions are not involved in this transformation. Provide an explanation that accounts for the selectivity of this process.

Due to the epoxide geometry and the hybridization of its atoms, the stereoelectronic requirement in the transition state leading to **2** is very similar to the one found in a 5-endo-trig cyclization. Conversely, excellent overlap between the oxygen lone pair and the epoxide $\sigma^*_{C\text{–}O}$ occurs in the five-membered ring transition state leading to **3**.





Question 2. (15 points). The following reaction was found serendipitously by Cronin while attempting to functionalize the side chain of starting material **1** (JOC **2004**, *69*, 5934, see also Tetrahedron **2005**, *61*, 8410).



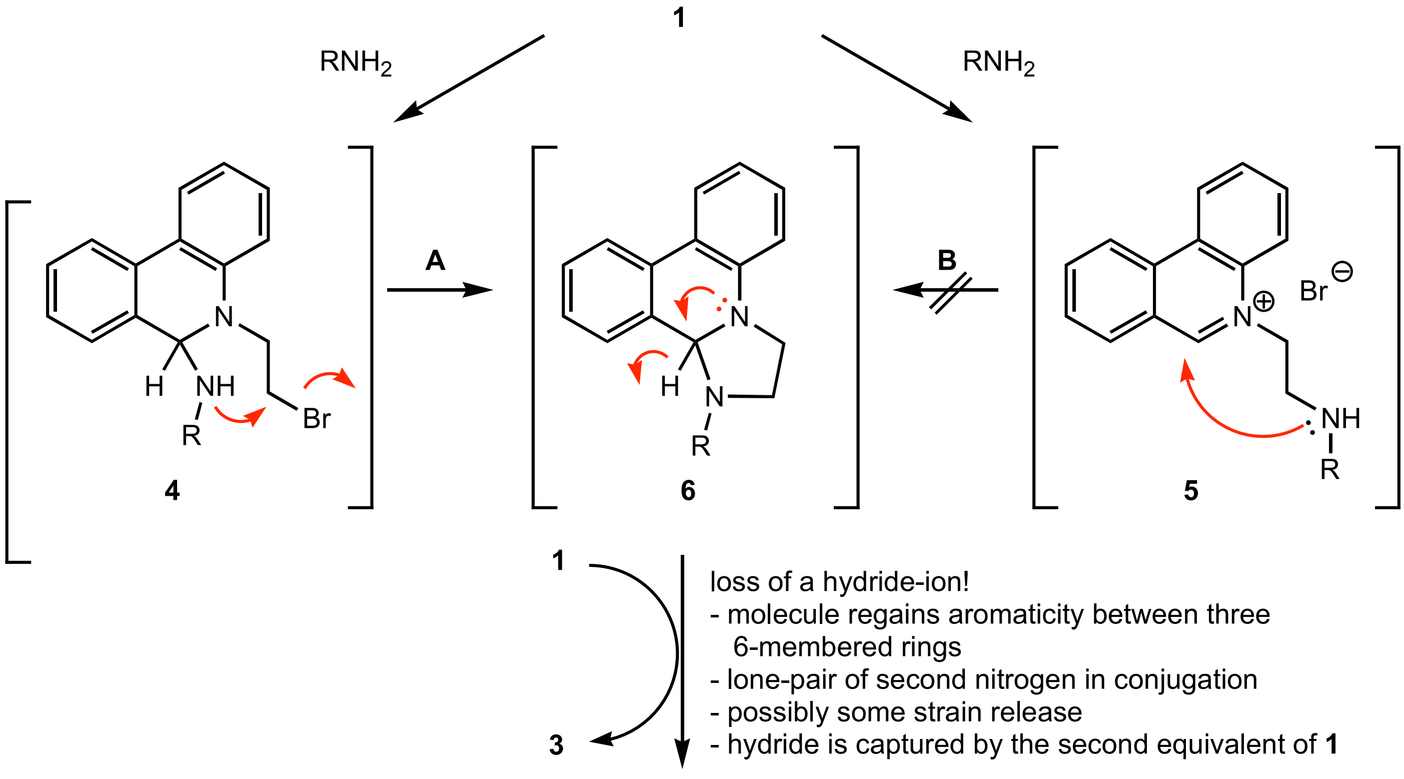
1
(two equivalents)

2

3

98% R = $-CH_2CH_2OH$

Provide a plausible mechanism for the indicated transformation. Your answer should include an explanation for the formation of **3** and a rationalization for the driving force for its formation.



loss of a hydride-ion!
- molecule regains aromaticity between three 6-membered rings
- lone-pair of second nitrogen in conjugation
- possibly some strain release
- hydride is captured by the second equivalent of **1**

2

A: 5-*exo-tet*
B: 5-*endo-trig*

According to the Baldwin rules, **A** should be favored, **B** should be disfavored.

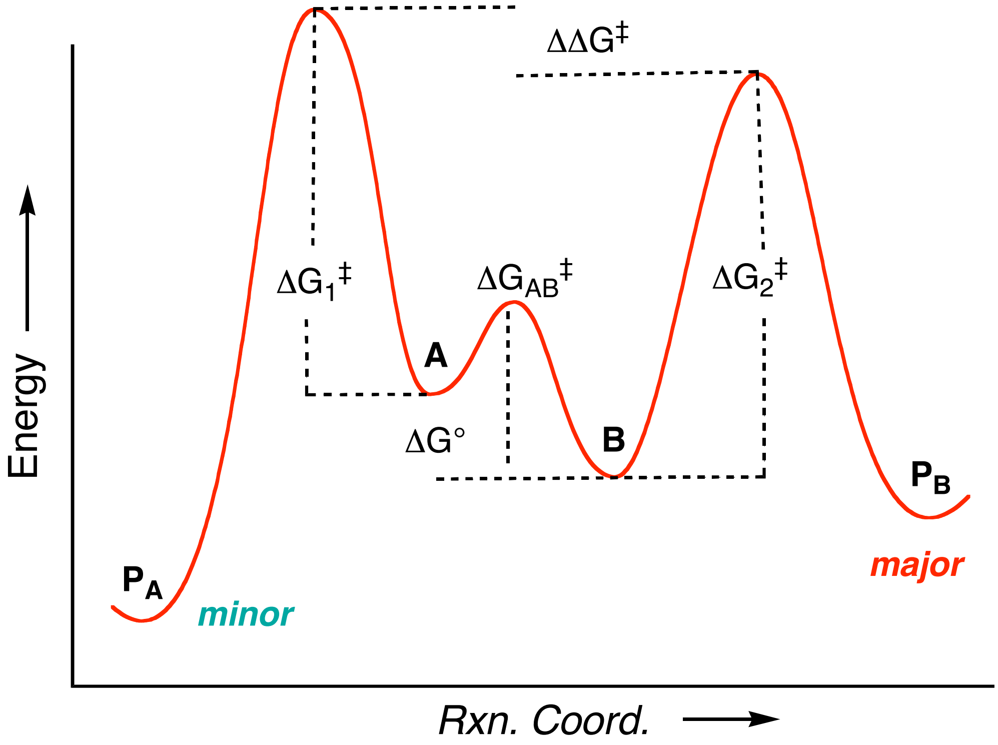
Experimental evidence in favor for **A**:
The protonated intermediate **4** could be characterized in a reaction that had a bulky group R.

Experimental evidence against **B**:
Independently synthesized **5** did not form any product when stored for 1 week.
In a biphasic mixture of $CDCl_3$ and water with NEt_3 added, the reversible addition of water was observed.
Unfortunately, the authors did not subject isolated **5** to the *identical* reaction conditions, which would be a better proof...

Question 3. (15 points). Assume that you have a rapidly equilibrating mixture of two conformers **A** and **B** from which two products, $\mathbf{P_A}$ and P_B are produced (eq 1).

$$\mathbf{P_A} \xleftarrow[\text{slow}]{k_1} \mathbf{A} \underset{\text{fast}}{\underset{k_B}{\overset{k_A}{\rightleftharpoons}}} \mathbf{B} \xrightarrow[\text{slow}]{k_2} \mathbf{P_B} \qquad (1)$$

Part A. (10 points). Draw an energy diagram that reflects the situation where the equilibrium population of conformers is the same as the product ratio.

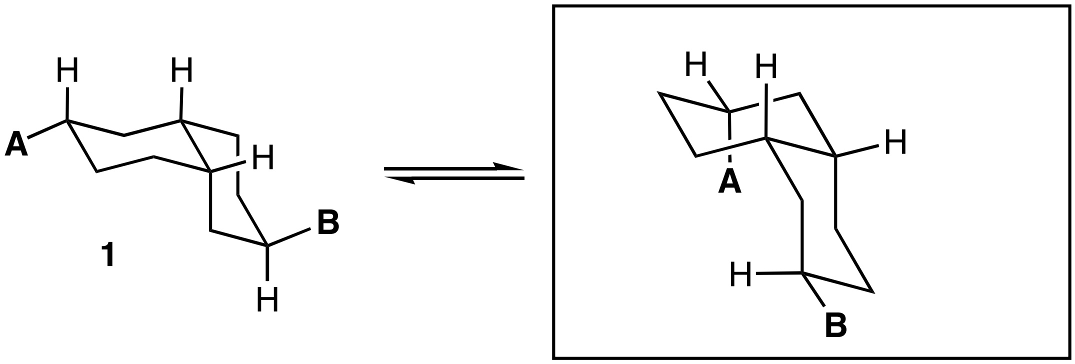


Part B. (5 points). Provide a concise statement of this circumstance in terms of free energy relationships.

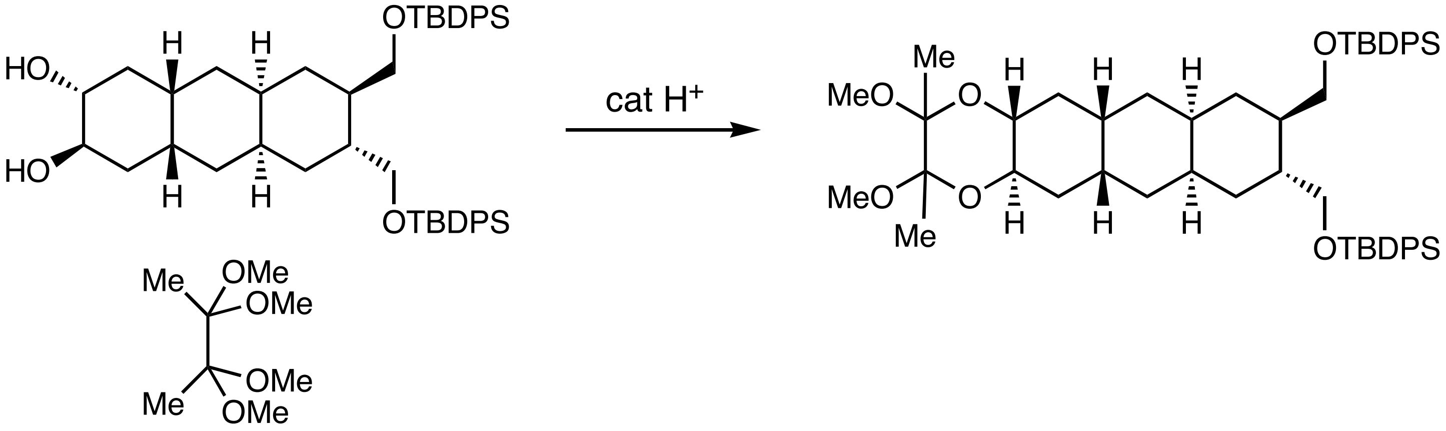
Under this constraint, $\Delta G_1^{\ddagger}$ must equal $\Delta G_2^{\ddagger}$. Accordingly, $\Delta\Delta G^{\ddagger}$ will equal $\Delta G°$.

Question 4 (15 points). As you know trans decalins are conformationally rigid, while cis decalins can undergo a chair-chair conformational change.

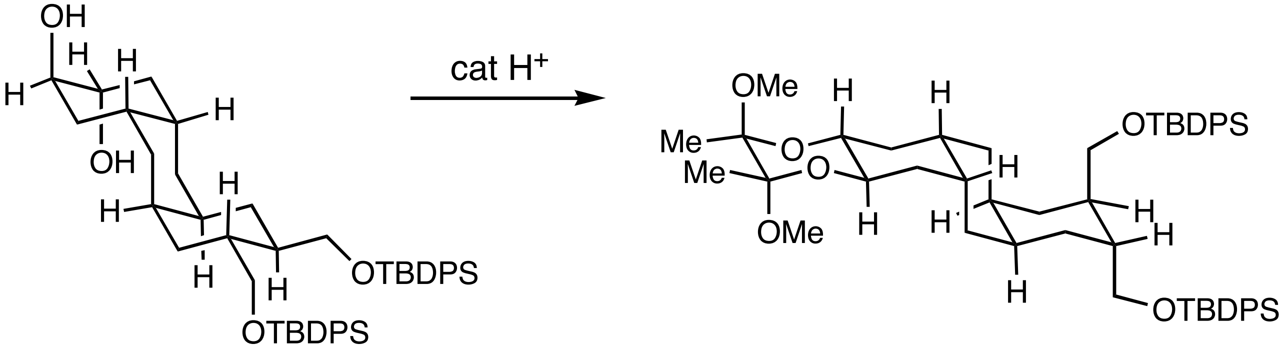
Part A (5 points). Draw the the other chair-chair conformation of **1 i**n the space provided. Please Include the H-atoms on the stereogenic centers as well.



Part B (10 points). Provide 3D representations of the lowest-energy conformations of both the starting material and product in the following reaction. Be sure to indicate clearly all stereochemical relationships. Include the H-atoms on the stereogenic centers as well.

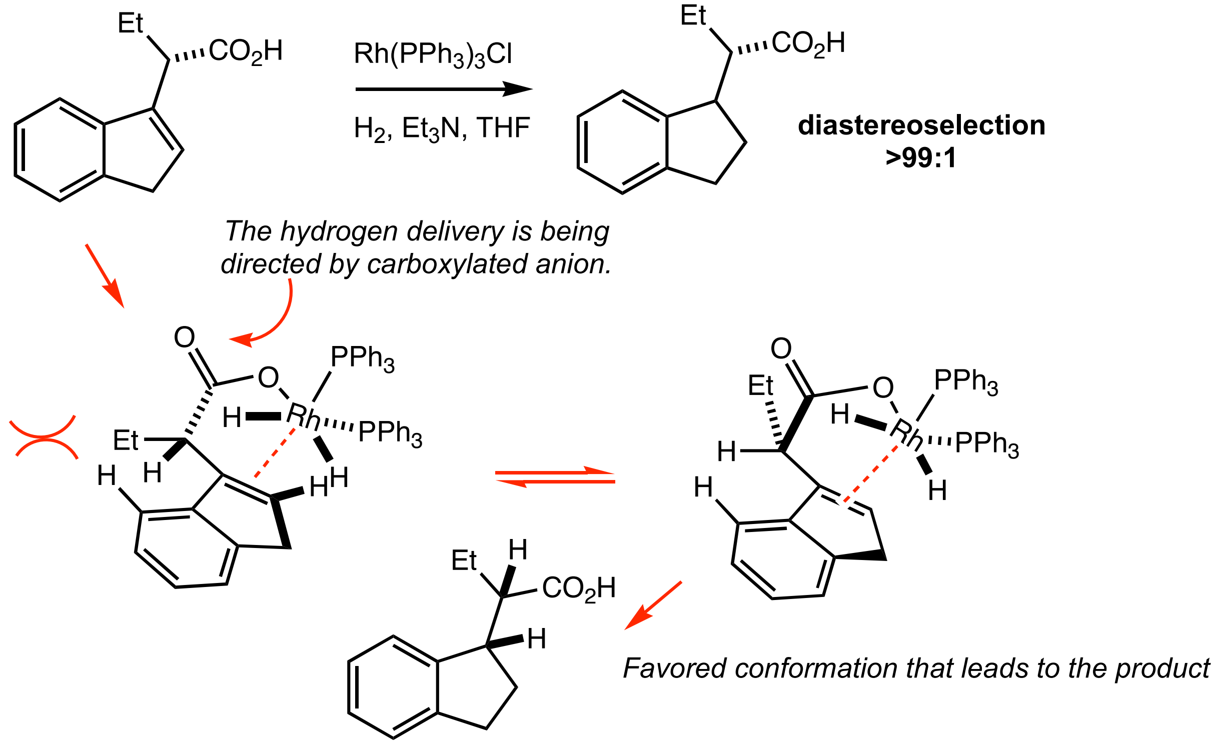


Your Answer:



Question 5 (15 points). Please predict the stereochemical outcome of the following reactions by *indicating the stereochemistry of the product*. Please use clear 3D drawings of the relevant conformations to explain your prediction.

Part A (7 points).



diastereoselection >99:1

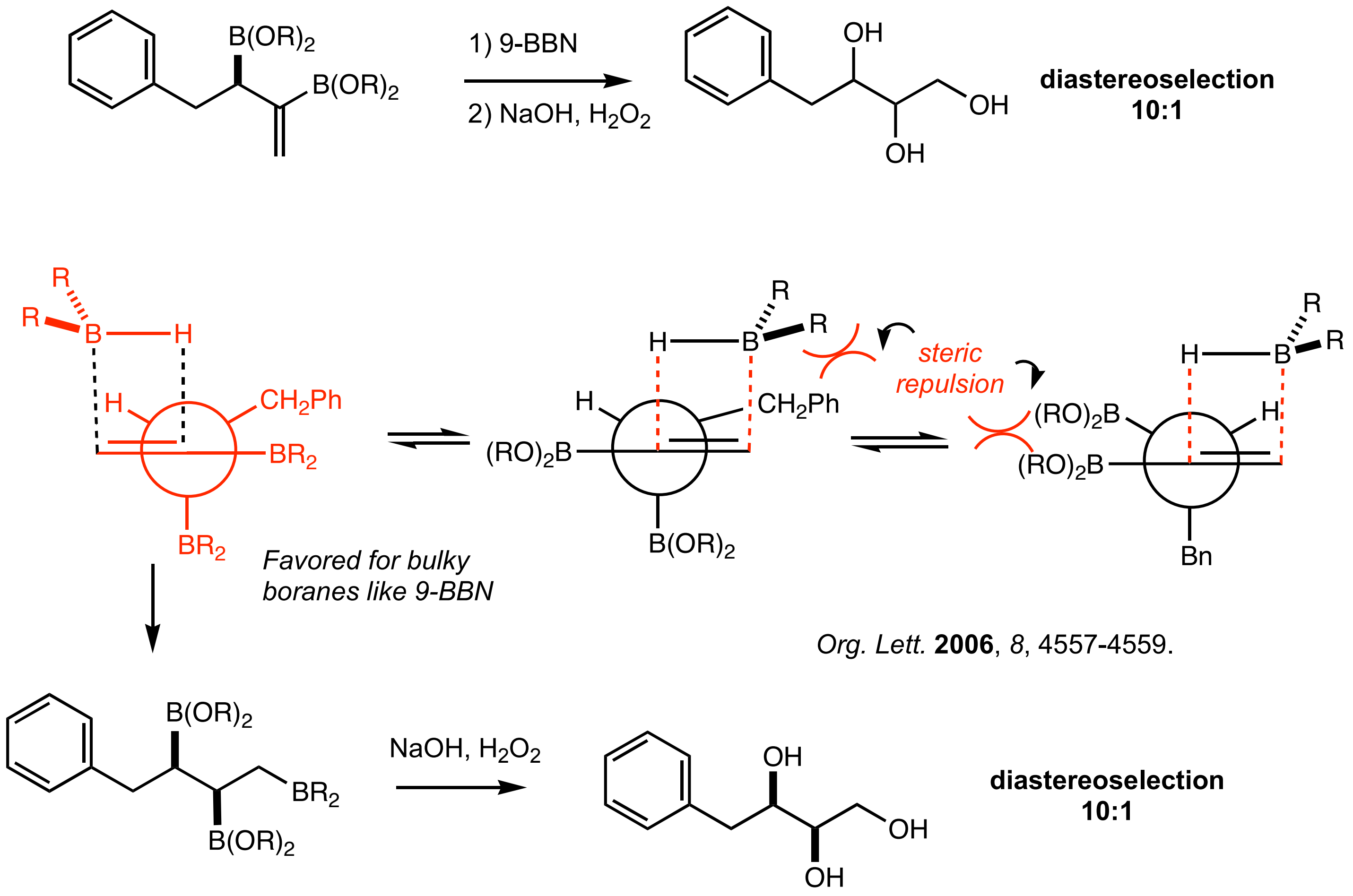
The hydrogen delivery is being directed by carboxylated anion.

Allylic strain makes this conformation unstable

Favored conformation that leads to the product

Part B (8 points).

Org. Lett. **2003**, *5*, 1587-1589.



diastereoselection 10:1

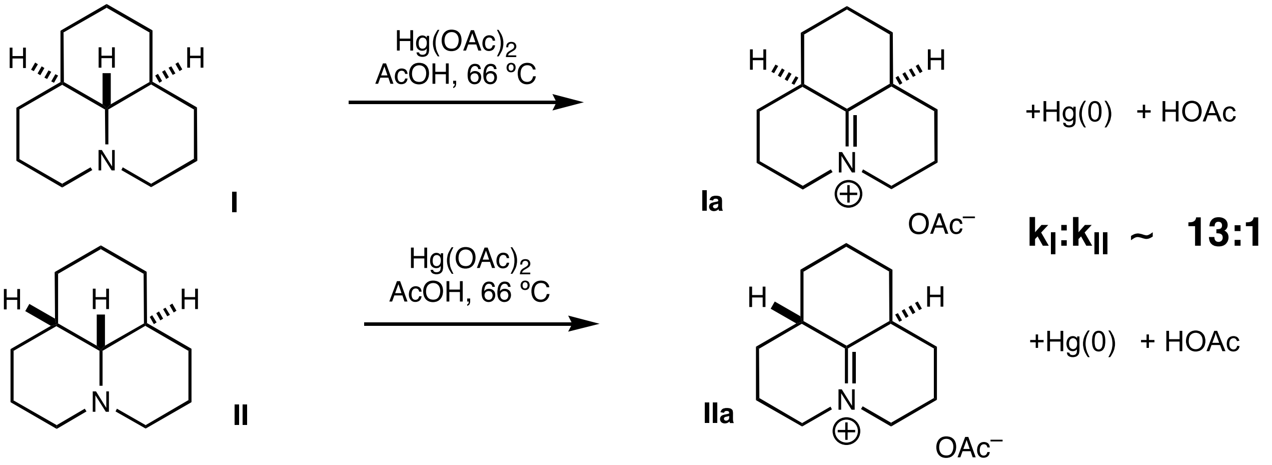
steric repulsion

Favored for bulky boranes like 9-BBN

Org. Lett. **2006**, *8*, 4557-4559.

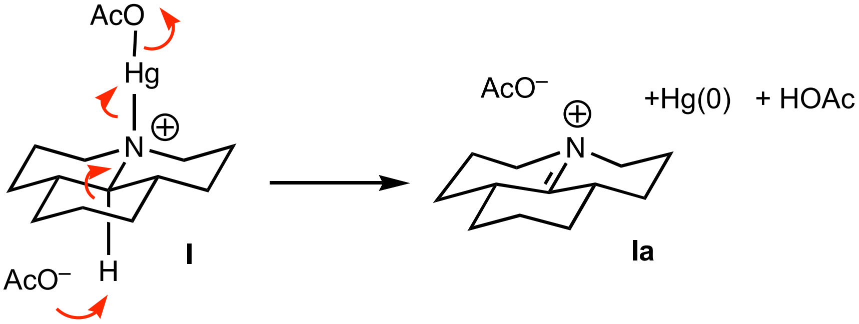
diastereoselection 10:1

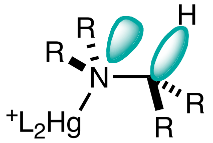
Question 6. (10 points). Mercury(II) acetate is a mild oxidant that oxidizes tertiary amines **I** and **II** to the corresponding iminium cations **Ia** and **IIa** (Bohlmann, et al. *Chem. Ber.* **1958**, *91*, 2167). Interestingly, the rates for these oxidations are dramatically different with the oxidation of **I** being almost 13 times faster.



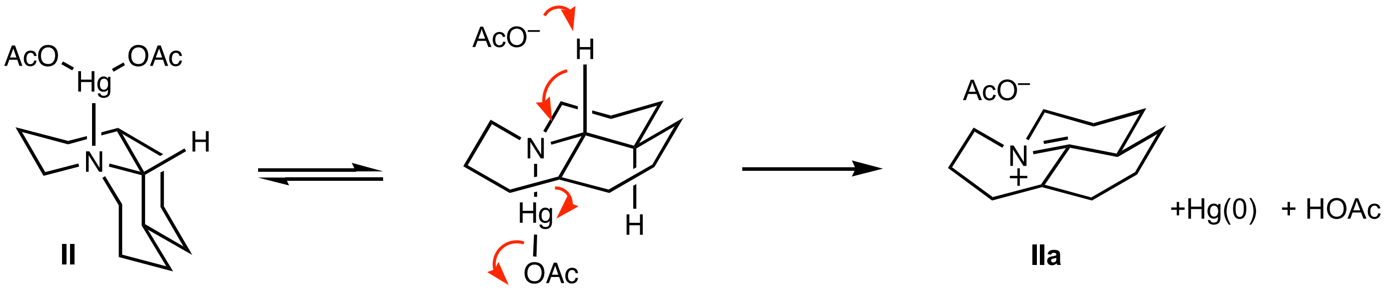
Using clear 3D drawings please provide the mechanism for this oxidation and explain the difference of reactivity using the FMO theory.

Hg(II) complexes amine. The following β-hydride elimination results in production of the Hg(0) species and formation of the iminium cation

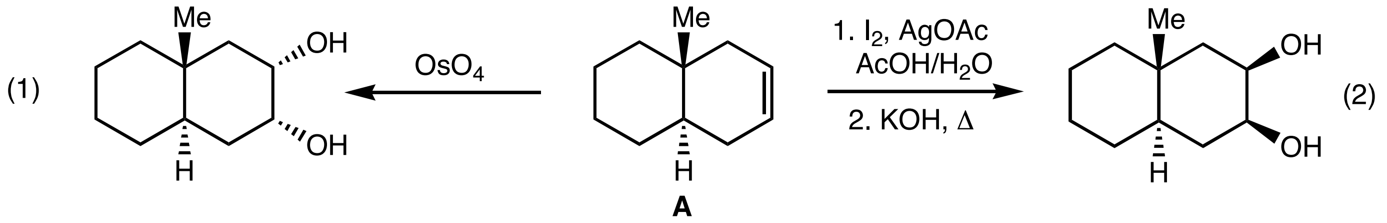




σ(C-H) → σ(N-Hg) interaction weakens the C-H bond for elimination. Thus, in case of **I**, where this overlap is optimal, the elimination is fast. In case of **II**, the most stable conformation has the nitrogen lone pair syn to the eliminated hydrogen so that the conformation change is required to obtain the required σ(C-H) → σ*(N-Hg) overlap.*

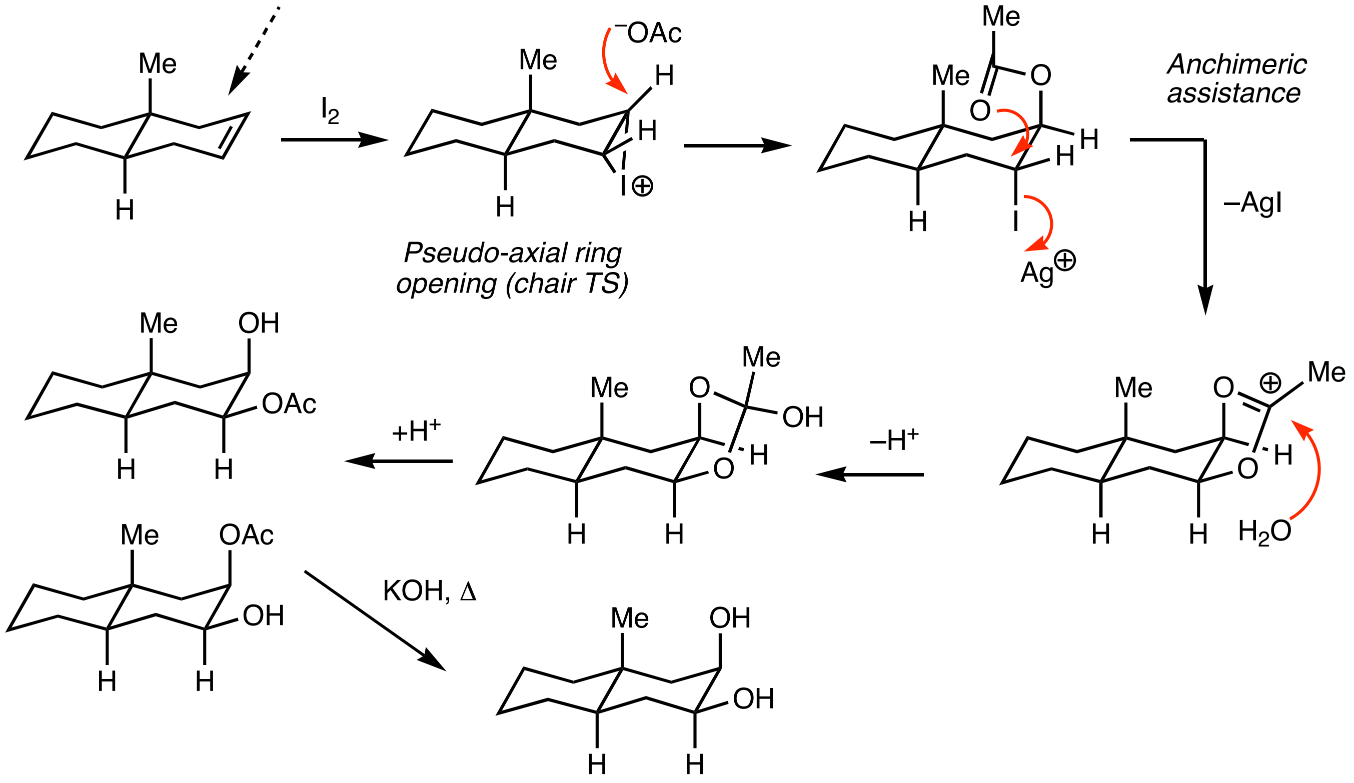


Question 7. (10 points). If an olefin such as **A** experiences a facial bias, one may count on steric effects to direct the course of a OsO_4 dihydroxylation to the *less hindered olefin diastereoface* (eq 1). Strategically, it is limportant to be able access the other stereochemical option: dihydroxylation from the *more hindered olefin diastereoface*. This stereochemical option may be implemented through the reaction summarized in equation 2. This reaction has been referred to as the Prevost-Winstein-Woodward dihydroxylation.

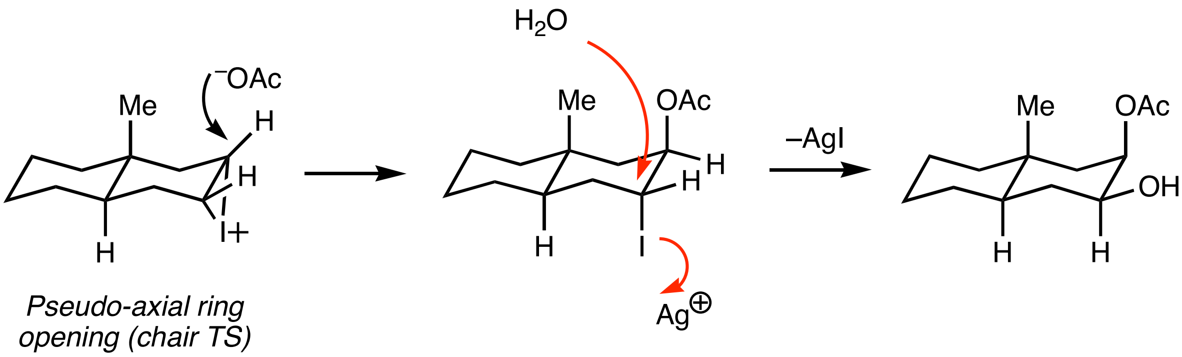


Provide a mechanism for the reaction illustrated in eq 2 in the space below. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

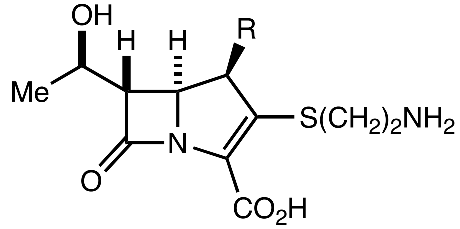
Top face shielded by axial methyl



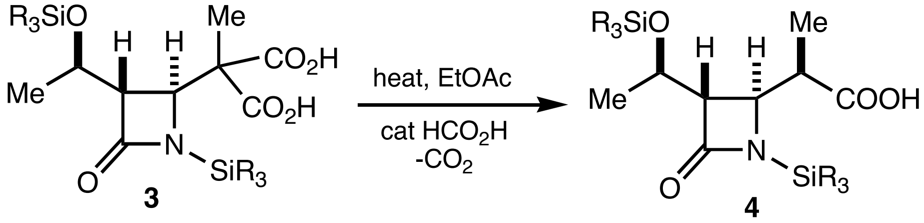
Since you might not be aware of anchimeric assistance by OAc to the ionization process, full credit will also be given for the answer provided below:



Question 8. (10 points). Thienamycin (**1**) is a potent antibiotic that has served as the template for the production of analogues with improved therapeutic properties. Several thienamycin derivatives currently marketed contain the indicated methyl substituent at the 1-position, a substitution that improves the chemical and metabolic stability of the antibiotic. In conjunction with the synthesis of **2**, the stereochemically interesting decarboxylation, **3**→**4**, has been reported (*Tetrahedron Lett*. **1994**, *35*, 2275).

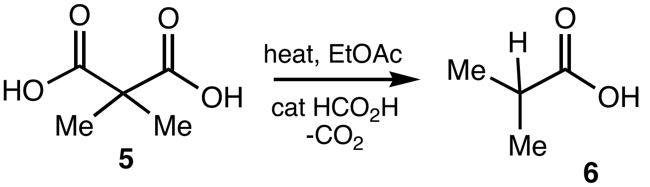


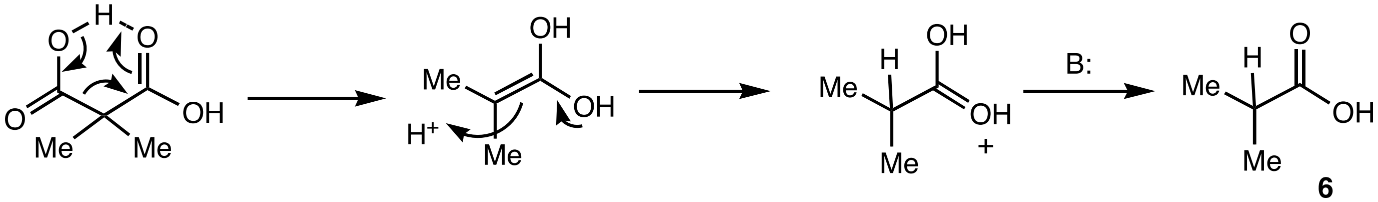
Thienamycin (**1**), R = H
1-β-methyl thienamycin (**2**), R = Me



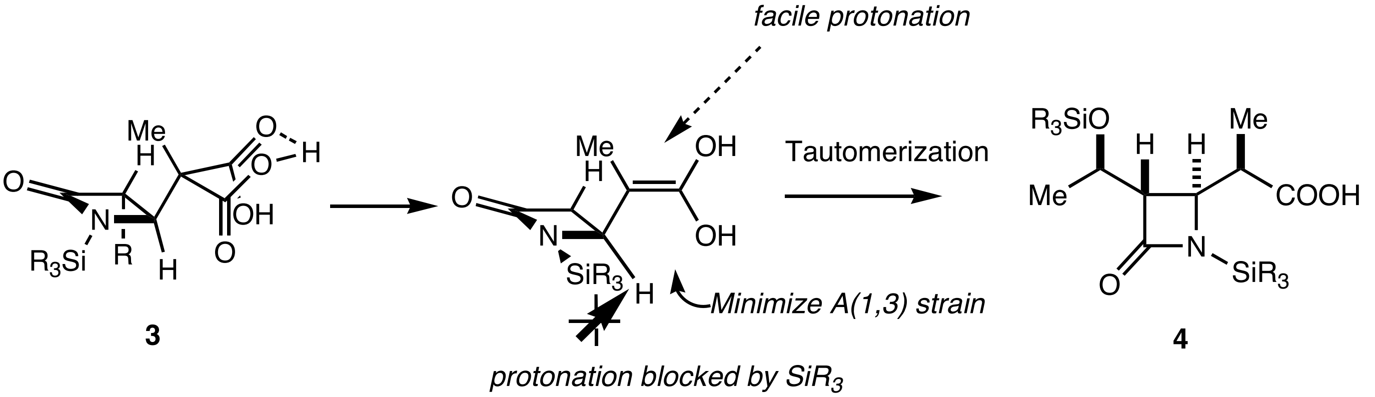
diastereoselection: 94:6

Part A (5 points). In the space below, draw out each of the intermediates that might be anticipated in the transformation of **5** to **6**, simplified analogs of **3** and **4**.





Part B (5 points). In the space below, provide a rationalization for the sense of asymmetric induction that was observed in the transformation of **3** to **4**. Carefully rendered 3D drawings that clearly illustrate and support your argument should be included.



One would expect facile protonation from either enol diastereoface, yielding an unselective process. This is indeed the case.

Chemistry 206
First Hour Examination

D. A. Evans
October 14, 2005

Name (please print): ***ANSWER KEY***
last first initial

Signature: ____________________

Teaching Fellow: ____________________

Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (15)	______
No. 7 (15)	
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

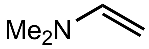
Please record your answers **with a pen** in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

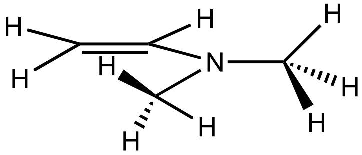
Exam average: 60.4
High grade: 89
Low grade: 13

Question 1. (10 points). Oberhammer recently studied the gas phase structures of *N,N*-Dimethylvinylamine (**1**) and perfluorodimethylvinylamine (**2**) (*JACS*, **2001**, *123*, 2865).

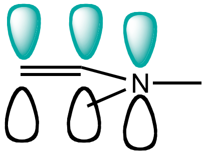
Part A. (5 points). Please provide a clear three-dimensional representation of the lowest energy conformer of *N,N*-Dimethylvinylamine (**1**). Label all relevant stereoelectronic interactions.



1

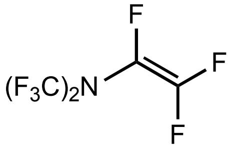


All carbons and the nitrogen lie in the same plane. The methyl groups are oriented to minimize the C-H interactions with the vinyl protons.

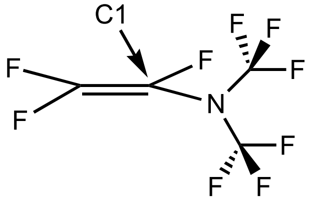


The main interaction that dictates the planarity of the molecule is the delocalization of the nitrogen lone pair into the C=C anti bonding π bond. This is a 3 center 4 electron bond.

Part B. (5 points). The perfluorinated example **2** adopts an entirely different conformation than *N,N*-Dimethylvinylamine (**1**). Please provide a clear three-dimensional representation of the lowest energy conformer of **2**. Label all relevant stereoelectronic interactions.

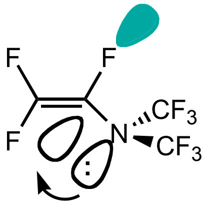


2



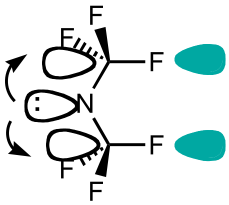
The compound is not planar. The N(CF_3)$_2$ group is perpendicular to the vinyl group. Nitrogen lone pair delocalization into the C1-Fσ^* orbital stablizes the conformation. This hyperconjugation provides greater stablization than when the nitrogen lone pair is delocalized into the C=C anti bonding π bond.

The C-F bond is a better acceptor than the C=C bond



$N\eta \longrightarrow \sigma^*_{CF}$

The CF$_3$ groups are oriented to maximize the Nnp - σ^*CF interaction.



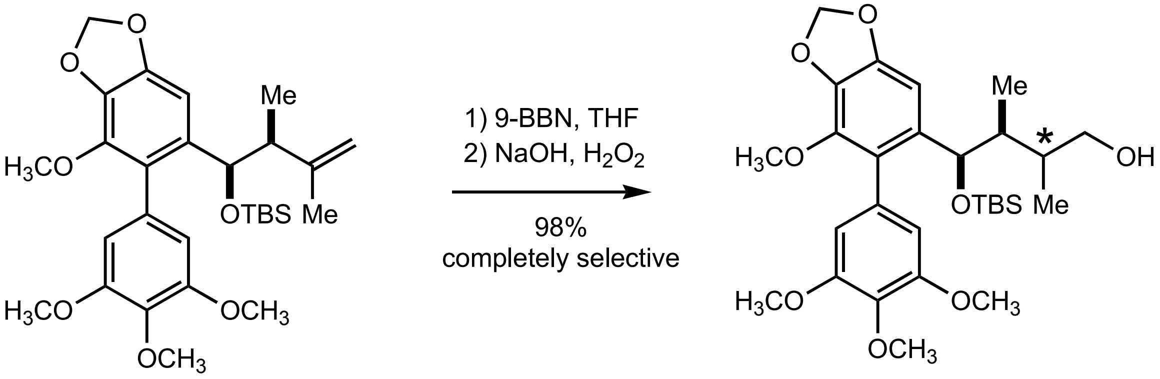
Two separate interactions

$N\eta \longrightarrow \sigma^*_{CF}$

Question 2. (15 points). One of the most recent examples of selective hydroboration is given below (Coleman, *OL,* **2004**, *6, 4025*).

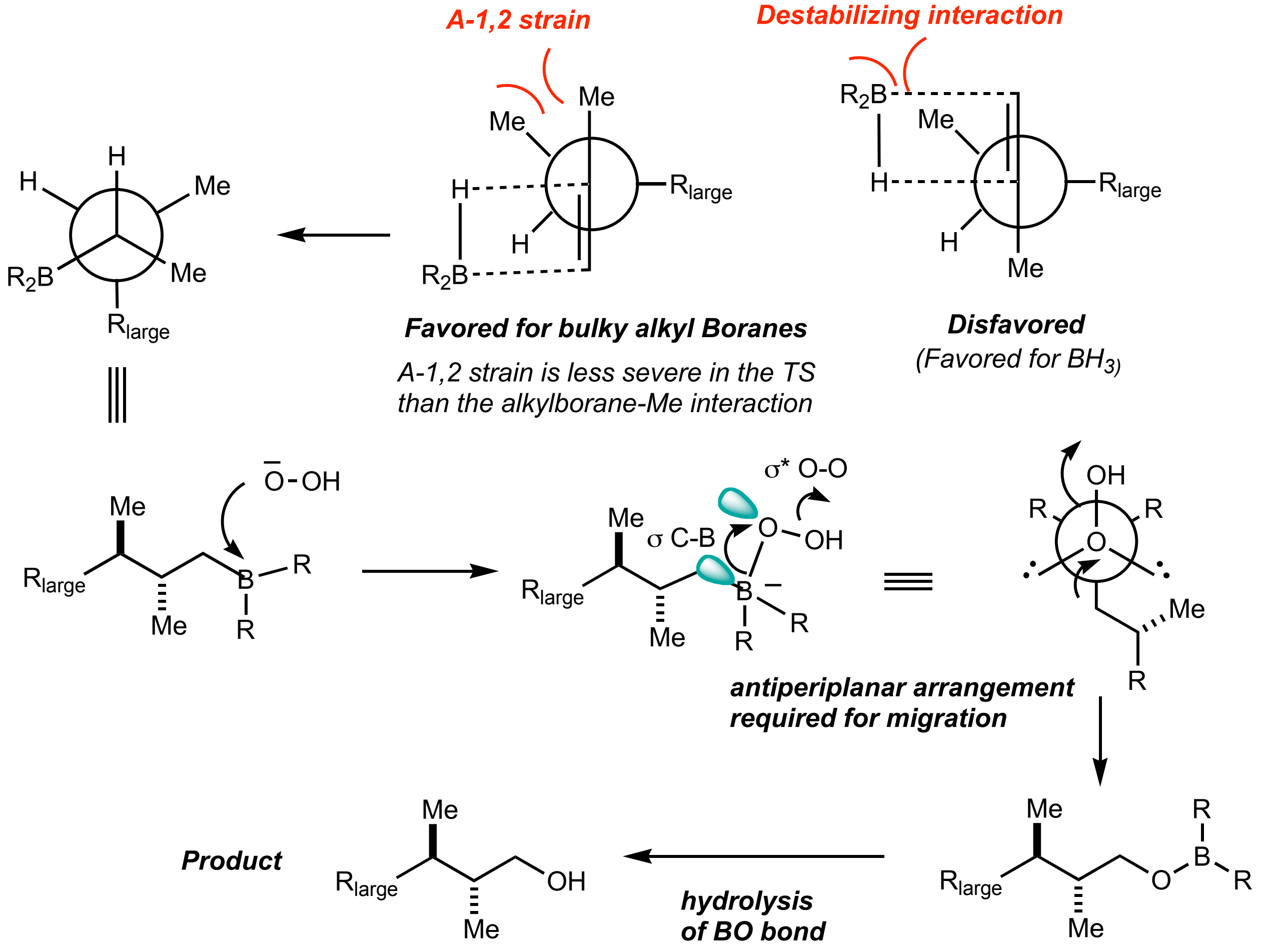
Part A. (10 points). Please predict the stereochemical outcome of this reaction and provide a clear three-dimensional representation of the transition state leading to the observed sense of stereochemical induction.

Part B. (5 points). Please provide a mechanism for the subsequent hydrogen peroxide mediated oxidation of the initially formed alkyl borane. Be sure to identify any important stereoelectronic requirements.



1) 9-BBN, THF
2) NaOH, H_2O_2

98%
completely selective



A-1,2 strain

Destabilizing interaction

Favored for bulky alkyl Boranes

A-1,2 strain is less severe in the TS than the alkylborane-Me interaction

Disfavored
(Favored for BH_3)

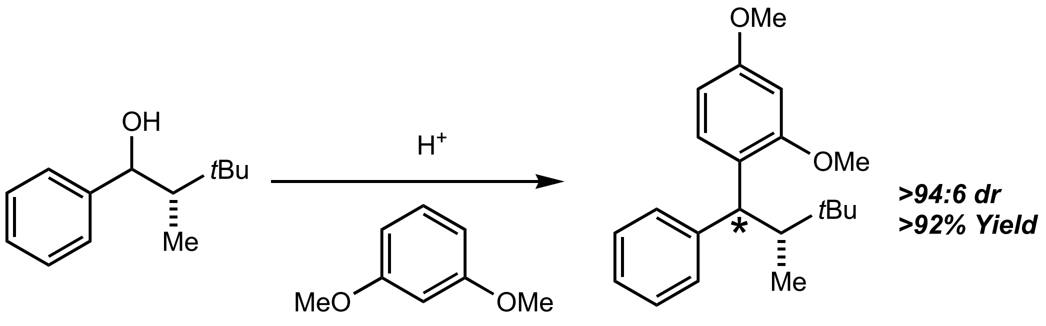
antiperiplanar arrangement required for migration

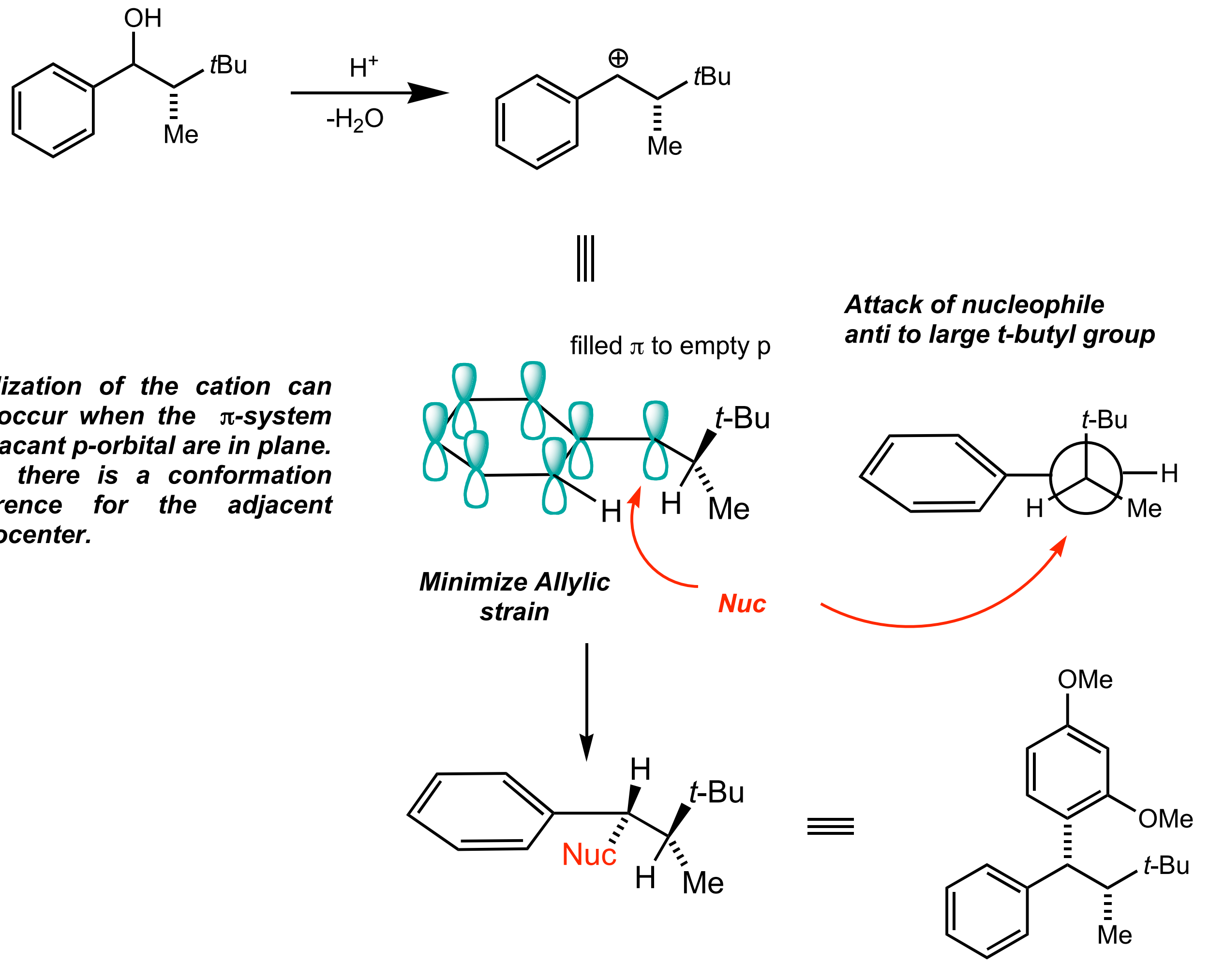
Product

hydrolysis of BO bond

Question 3. (15 points). Bach recently showed that stereocenters adjacent to a benzylic hydroxy group can dictate the facial preference for the subsequent acid promoted Friedel-Crafts reaction (*JACS,* **2005**, *127*, 9348).

Please provide a mechanism for this reaction that predicts the major product that accounts for the high level of stereoinduction that is observed. Be sure to indicate all relevant stereoelectronic and steric interactions. Please note that the starting material is a mixture of diastereomers.



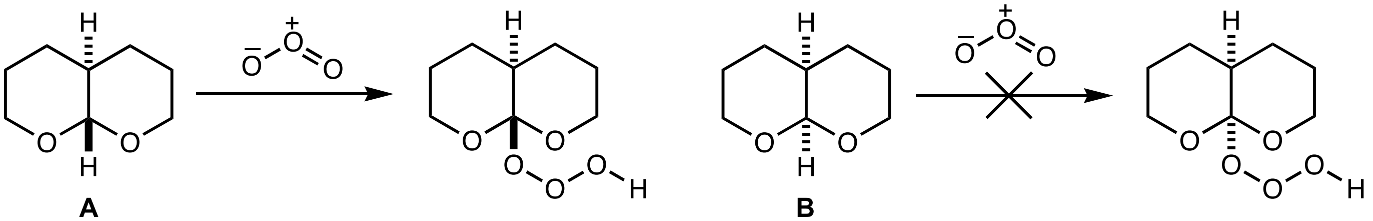


Stabilization of the cation can only occur when the π-system and vacant p-orbital are in plane. Thus, there is a conformation preference for the adjacent stereocenter.

1,2-syn adduct formed

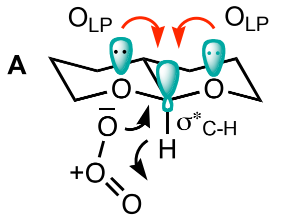
Question 4. (15 points). The oxidation of acetals by electrophilic ozone is known to be sensitive to structure. Two striking examples of different reactivity are detailed in the questions below.

Part A. (7.5 points). Using clear three-dimensional drawings provide a rationale for the observation that rigid glycoside **A** readily undergoes oxidation but glycoside **B** does not. Be sure to indicate all relevant stereoelectronic interactions.



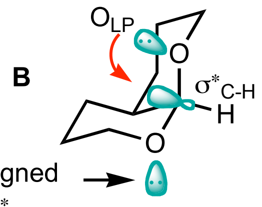
Deslongchamps, *Can. J. Chem.* **1974**, 3651-3664.

Oxidation of the only occurs when ***2*** oxygen lone pairs are aligned antiperiplanar to the CH-bond. The O_{LP} ⟷ $\sigma^*_{C\text{-}H}$ interaction weakens the CH-bond and raises the HOMO energy level thereby bringing it closer to the LUMO of ozone.



2 O_{LP} ⟷ $\sigma^*_{C\text{-}H}$

reacts with ozone

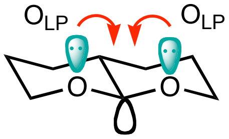


1 O_{LP} ⟷ $\sigma^*_{C\text{-}H}$

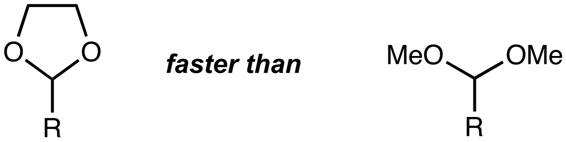
will not react with ozone

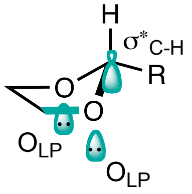
not aligned with $\sigma^*_{C\text{-}H}$ →

Mechanism may also be radical based, in which case the forming radial is stabilized by oxygen lone pairs.

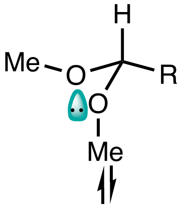


Part B. (7.5 points). Ozone oxidation of cyclic acetals is faster than oxidation of the corresponding acyclic acetals (Taillefer, *Can. J. Chem.* **1979**, 3041-3046). Using clear three-dimensional drawings please provide an explanation for this observation.

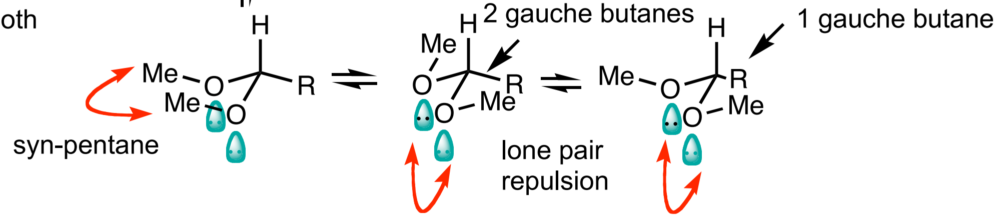




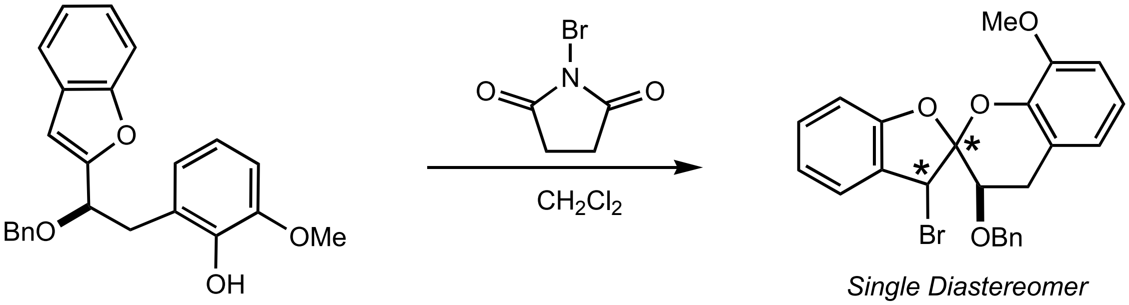
Most stable conformation has both oxygen lone pairs aligned in an antiperiplanar orientation.



The most stable confomer has only one oxygen lone pair aligned (minimized steric and lone pair interactions). In order to acess a reactive conformer structural rearrangement must occur, this lowers the effective concentration of reactive species and hence the slower rate of oxidation.



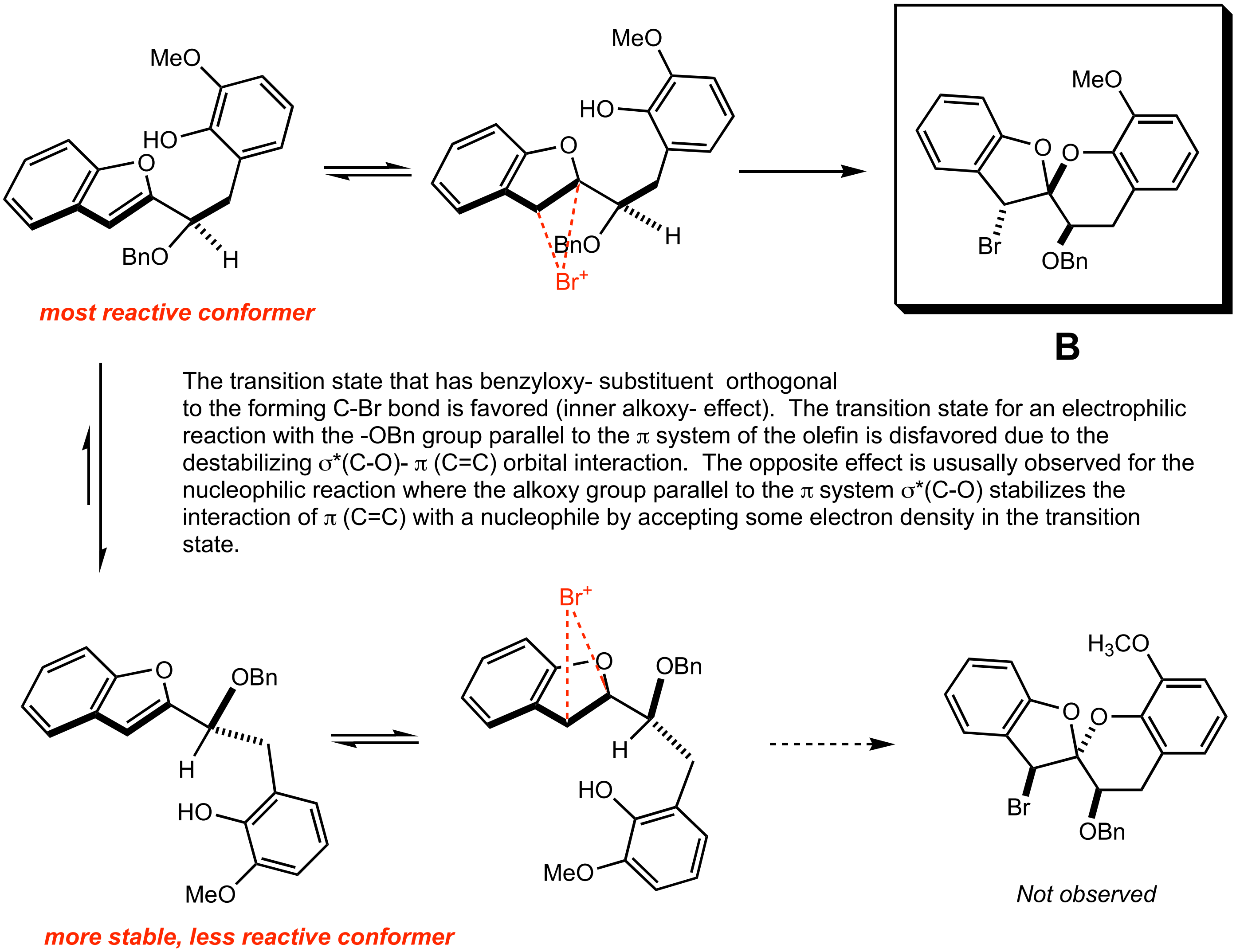
Question 5. (15 points). Danishefsky and coworkers reported that the *N*-bromosuccinimide-induced spiroketalization of benzofuran **A** affords the spiroketal **B** as a single diastereomer (*ACIEE,* **2001**,*40*, 4709).



Single Diastereomer

A **B**

Using clear three-dimensional drawings provide a mechanism for this reaction and predict the stereochemistry of the product **B**. Be sure to indicate any important steric or stereoelectronic effects.



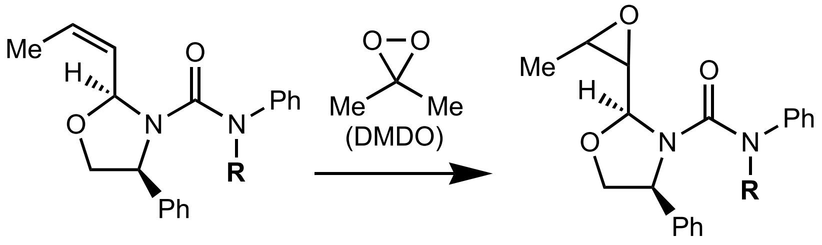
most reactive conformer

The transition state that has benzyloxy- substituent orthogonal to the forming C-Br bond is favored (inner alkoxy- effect). The transition state for an electrophilic reaction with the -OBn group parallel to the π system of the olefin is disfavored due to the destabilizing σ*(C-O)- π (C=C) orbital interaction. The opposite effect is ususally observed for the nucleophilic reaction where the alkoxy group parallel to the π system σ*(C-O) stabilizes the interaction of π (C=C) with a nucleophile by accepting some electron density in the transition state.

Not observed

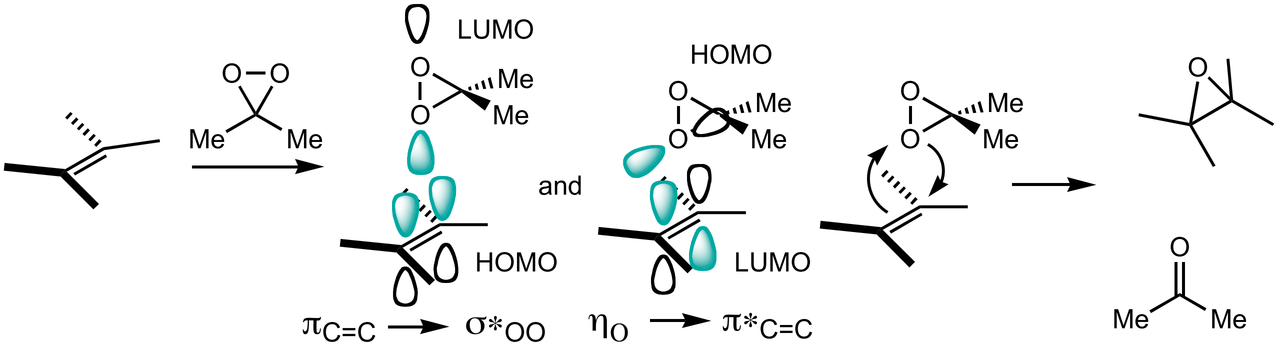
more stable, less reactive conformer

Question 6. (15 points). Adam and coworkers recenty studied the dimethyldioxirane (DMDO) mediated epoxidation of oxazolidine-substituted alkenes and noted that the selectivity of the epoxidation is dependent upon the nature of the R substituent of the urea (*Org. Lett.* **2001**,*3*, 79).



R = H dr >98:2
R = Me dr 26:74

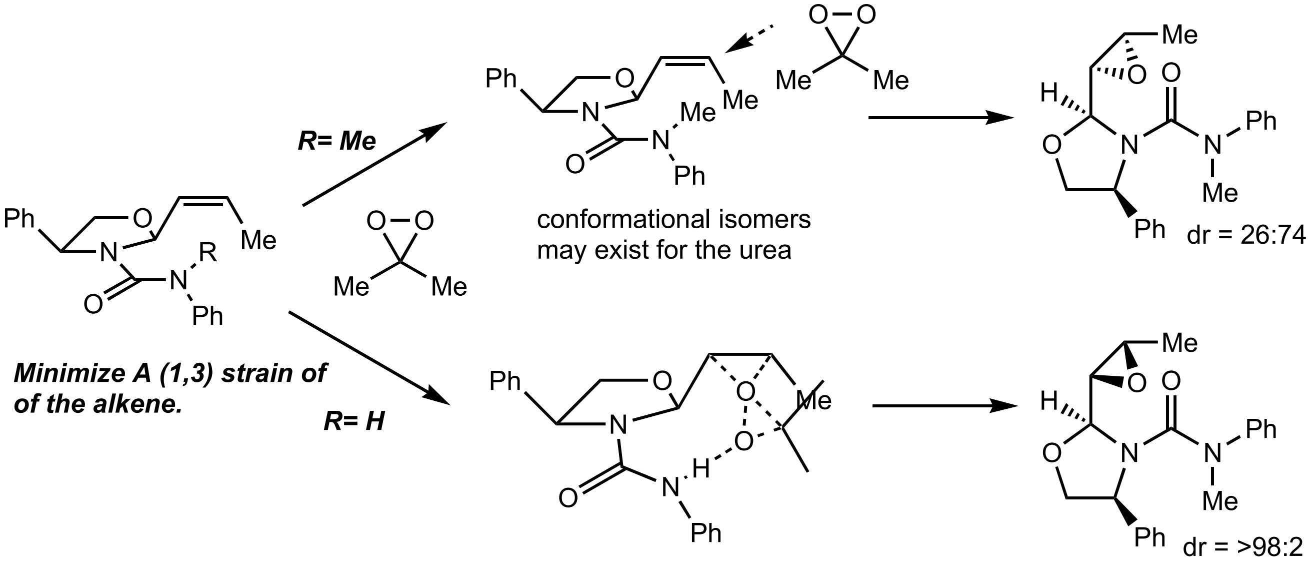
Part A. (5 points). In the space provided please provide a general mechanism for the epoxidation of an alkene with DMDO. Clearly identify and label all the important orbital interactions.


O–O
Me
Me
LUMO
O
O
Me
Me
HOMO
and
HOMO
O
O
Me
Me
LUMO
O
O
Me
Me
O
O
Me
Me
$\pi_{C=C} \longrightarrow \sigma^*_{OO}$
$\eta_O \longrightarrow \pi^*_{C=C}$

The spiro transition state is favored with concurrent orbital overlap shown above.

Part B. (10 points). In the space provided predict the major stereoisomer formed for both cases shown above, *i.e.* when R= H and when R= methyl.

When R= Me the imide effectively shields one side of the olefin from epoxidation

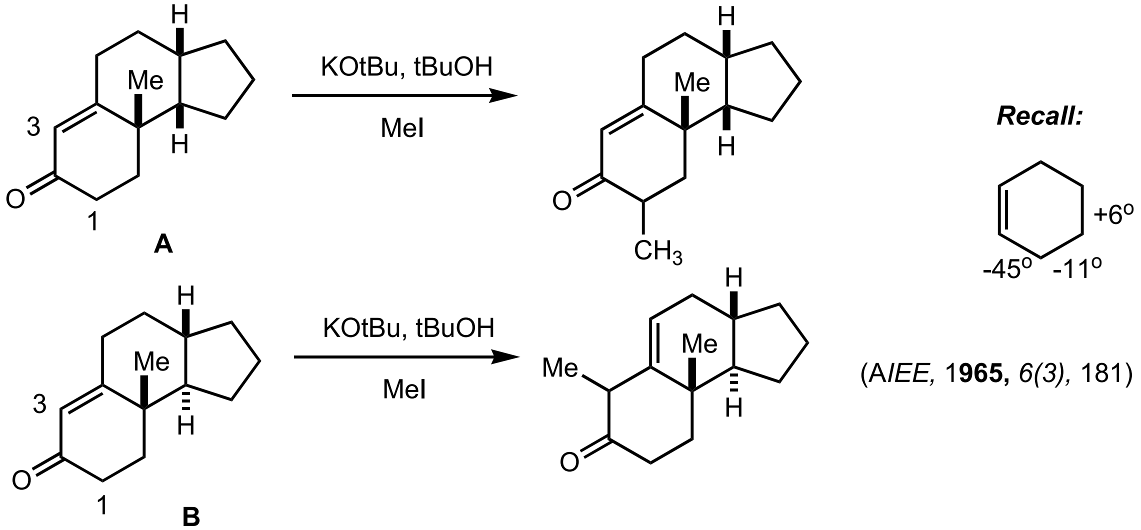


conformational isomers may exist for the urea

Minimize A (1,3) strain of of the alkene.

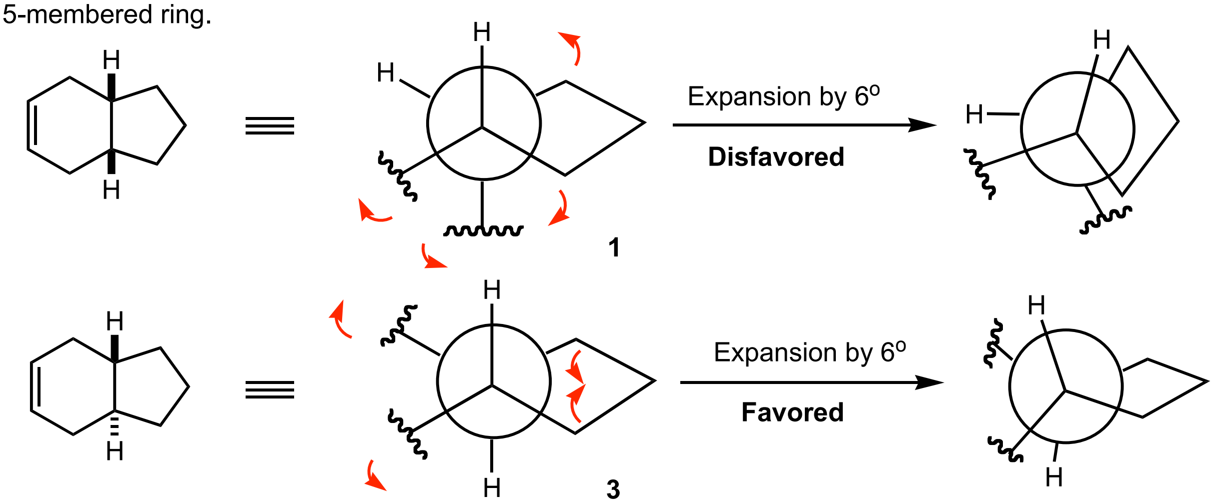
When R= H the imide directs the epoxidation by a hydrogen bond with DMDO

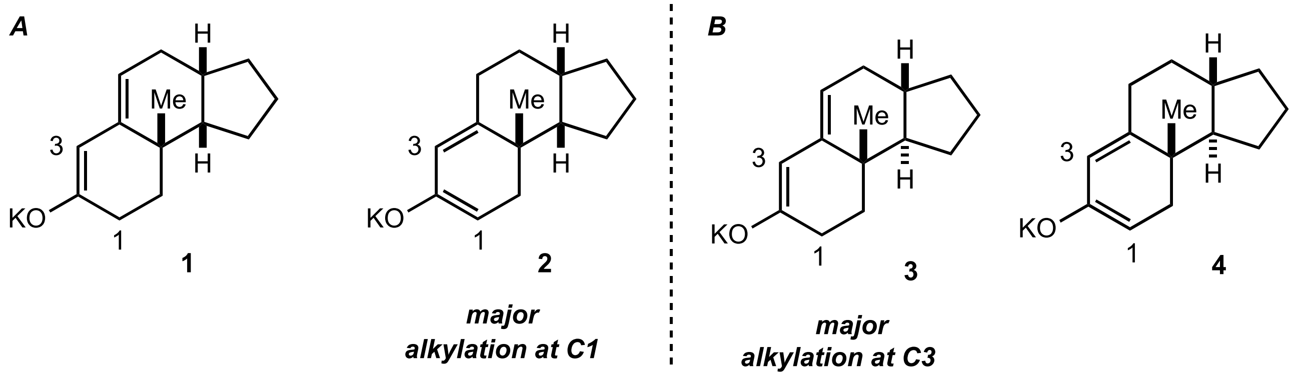
Question 7. (15 points). Enolization of **A** under equilibrating conditions followed by treatment with methyl iodide leads to the preferential introduction of the alkyl group at C1, whereas exposure of **B** to these conditions affords alkylation at C3. Using your knowledge of conformational transmission, assess the relative stability of the two enolates that are generated and thus provide a rational explanation for the divergent regiochemical outcomes.



(A*IEE,* 1**965,** *6(3),* 181)

Alkylation at C3 requires generation of the extended enolate, and therefore introduction of an olefin into the ring adjacent to the cyclopentane. This will cause the internal dihedral angle to expand by 6°. Consequently, for the cis-fused system **A** an increase of the dihedral angle in the cyclopentane will occur; this is disfavored due to increased torsional strain and puckering. The opposite is observed for **B**; an increase in the cyclohexane dihedral angle causes a decrease in the cyclopentane angle. This situation is favored due to relief of torsoinal strain withiin the 5-membered ring.





Chemistry 206
First Hour Examination

D. A. Evans
October 15, 2004

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (15)	_______
No. 2 (10)	_______
No. 3a (10)	_______
No. 3b (10)	_______
No. 4 (15)	_______
No. 5 (15)	_______
No. 6 (15)	_______
No. 7 (10)	_______
Total (100)	

The exam will begin at 1:05 PM and end at 3:00.

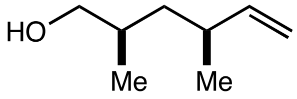
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

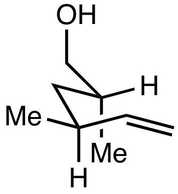
Answer Key

Question 1. (15 points). The structural unit of β-turns is present in many proteins and bioactive peptides and has important implications for both structure and function. As such, the synthesis of β-turn mimics has been an intensive area of research. While most solutions to creating such turns have relied on covalent linkages, Hoffmann and coworkers have developed an approach based on acyclic conformational preferences (*Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1745-1747).

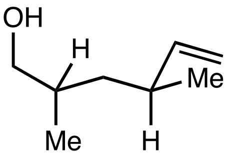
Part A. (5 points). Please provide a clear 3-dimensional representation of the lowest energy conformer of **1**.



1



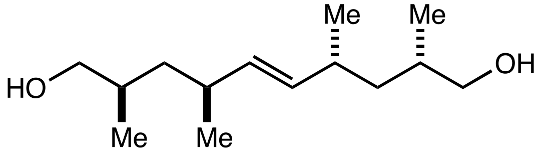
or



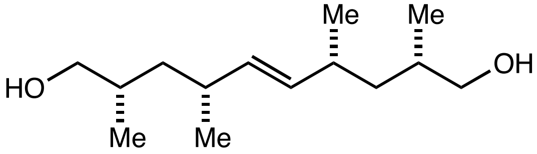
Minimized syn-pentanes

Vinyl group less hindered than Me groop.

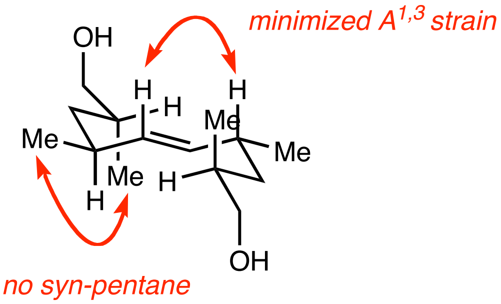
Part B. (10 points). Based on your analysis of **1** please draw the low energy conformations of **2** and **3**, and comment on which structure you think could be used as a β-turn mimic. ***Note:*** A β-turn is a structural feature that creates a U-turn in a peptide, bringing the termini into proximity.

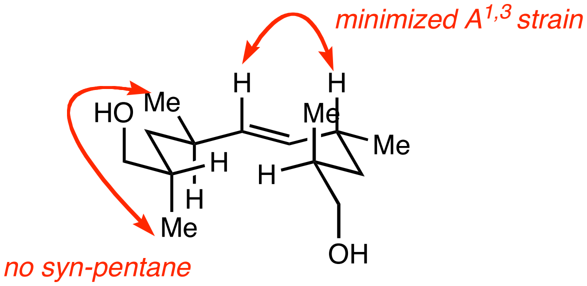


2

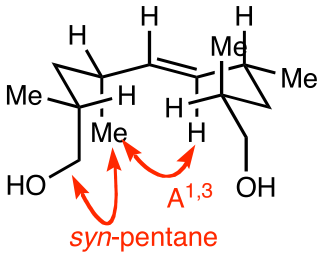


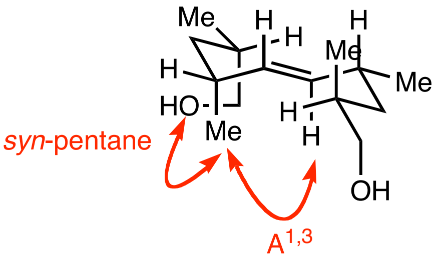
3





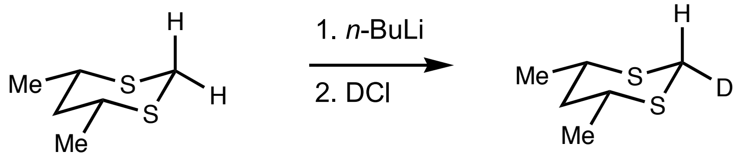
The alternative conformations suffer from unavoidable *syn*-pentane interactions and $A^{1,3}$ strain. Structure **2** prefers the termini "trans", while structure **3** prefers termini "cis". On this basis **3** could be incorporated into a β-turn mimic.



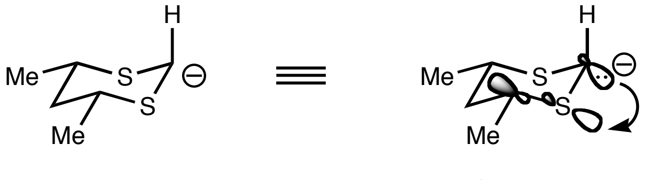


Question 2. (10 points). Many factors influence the reactivity and conformational bias of cyclic systems including steric, electronic, and stereoelectronic effects. For each of the following cases involving a six-membered heterocycle, provide a rationalization for the observed selectivity, including clear 3-dimensional representations where relevant.

Part A. Eliel and co-workers disclosed that the successive deprotonation of conformationally **1** and trapping with an electrophile occurs with high selectivity at the equatorial position (*J. Am. Chem. Soc.* **1974**, *96*, 1807.)

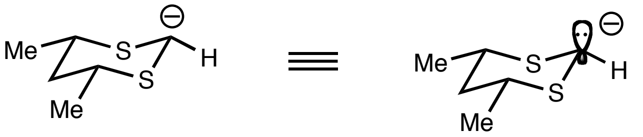


1



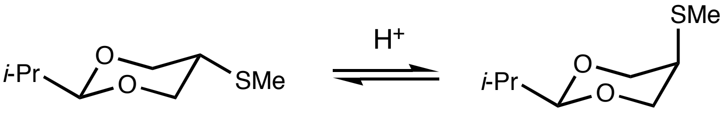
C sp^3lp ➤ S-C σ^*

the equatorial anion is stabilized by two hyperconjative interactions with the adjacent S-C antibonding orbitals



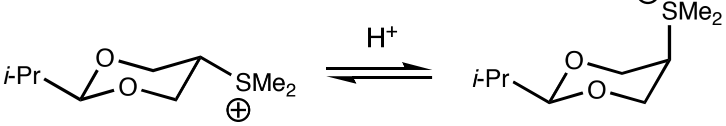
no such stbilizing interactions are available for the axial anion, making it much less stable and therefore less likely to form

Part B. Eliel has also reported that the acid-catalyzed equilibrium of dioxane **2** favors the equatorial isomer, while the related equilibration of dioxane **3** prefers the axial isomer (*J. Am. Chem. Soc.* **1974**,*96*, 1939). Please provide a rationalization of these observations that is based on stereoelectronic arguments.



2

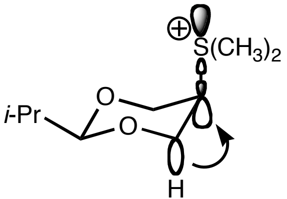
ΔG = +1.1 kcal/mol



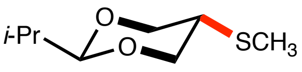
3

ΔG = –2 kcal/mol

For steric reasons, the equatorial isomer is preferred for the compound **2**. But the result with compound **3** is not immediately rationalized using purely a steric *or* stereoelectronic argument. The dimethyl group should be *more* sterically hindered than the sulfide, and at first glance there are no significant hyperconjugative interactions that would stabilize this compound over the previous. There are two possibilities:



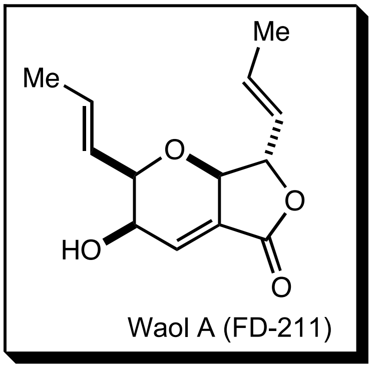
C-S$^{\oplus}$ σ^* is a better acceptor than C-S σ^*
C-H σ is a better donor than C-O σ



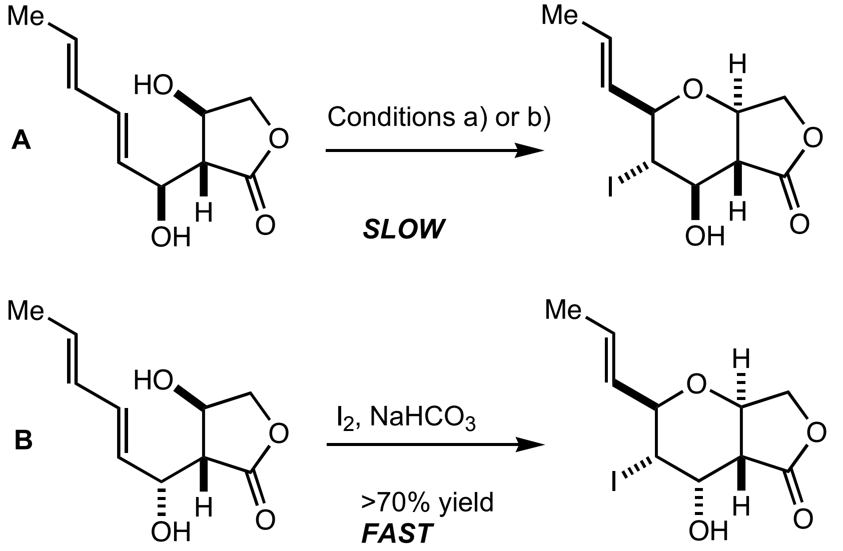
C-O σ^* is a better acceptor than C-S σ^*
C-S σ is a better donor than C-H σ

The illustrated hyperconjugative interactions provide some stabilization.
In the case of SCH_3, there is an interaction between C-S and C-O σ^*
that stabilizes the equatorial isomer

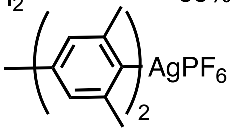
Question 3. Part A. (10 points). During the synthesis of the anti-tumor agent Waol A, Snider (*Org. Lett.* **2003**; 5(4); 451-454) and coworkers prepared the diastereomeric aldol adducts **A** and **B**. These substrates underwent iodoetherification at vastly different rates. In fact, to achieve sufficient conversion a more reactive iodonium reagent (bis(sym-collididne) $AgPF_6$) was necessary. *Please provide a mechanism for the reactions (**A** to **A'** and **B** to **B'**) that accounts for the observed selectivity and difference in rate. 3-dimensional representations are required.*



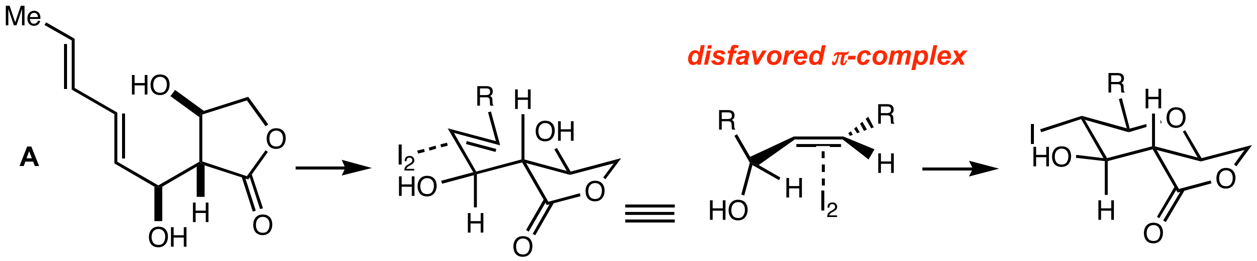
Waol A (FD-211)



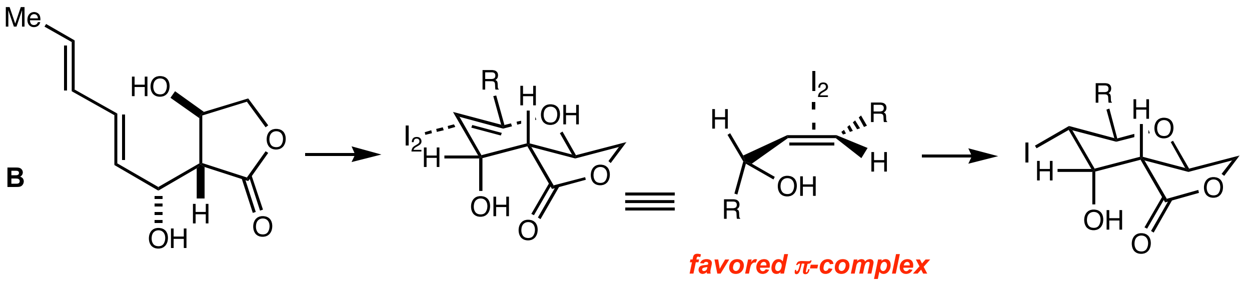
Conditions:
a) I_2, $NaHCO_3$ = 5% conv
b) I_2 = 88% yield



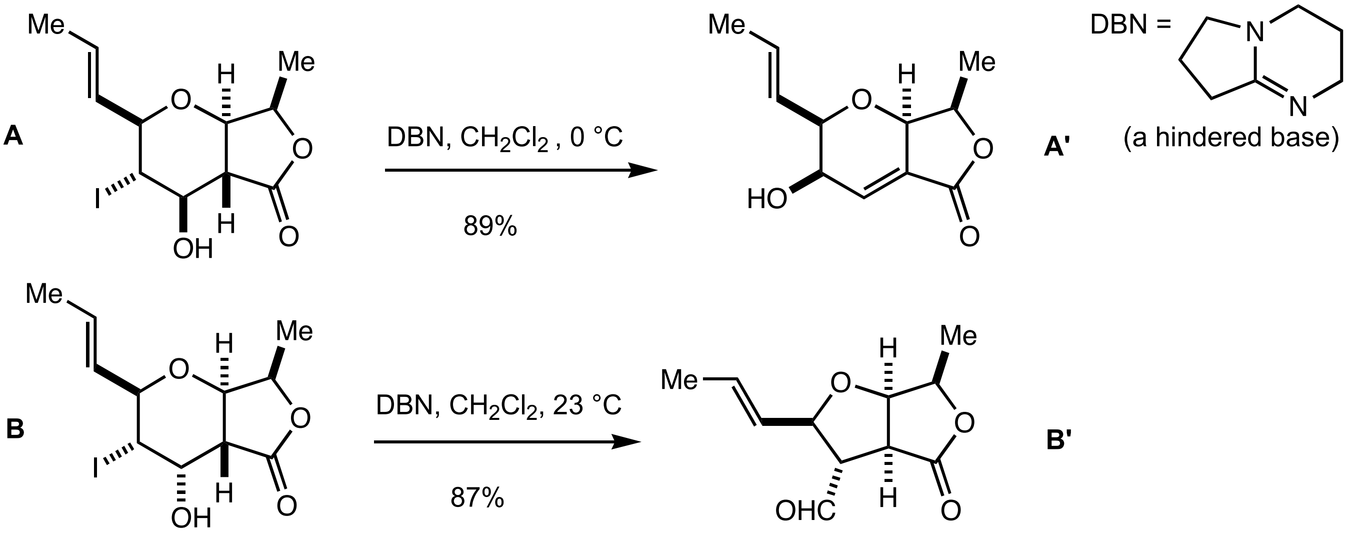
Your Answer --



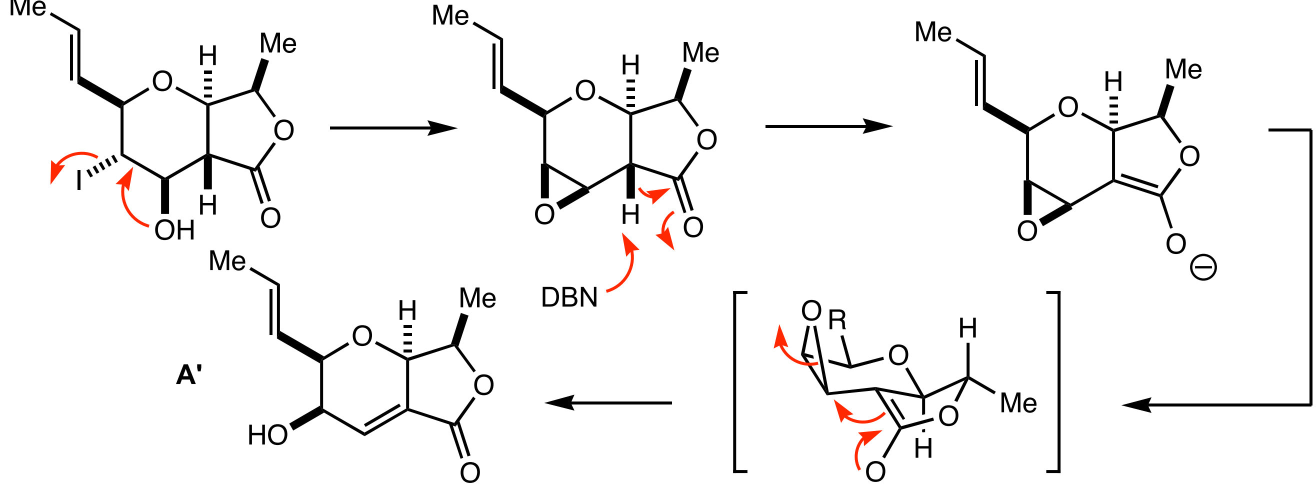
The inside alkoxy effect is operational in the given examples. In **A**, the allylic alcohol can interact with the π system, and withdraw electron density; the olefin in **A** in less reactive (less nucleophilic) in the illustrated conformation. Conversely, **B** orients the hydroxy group in the sigma framework. In this orientation, σ* C-O does not act to withdraw electron density.

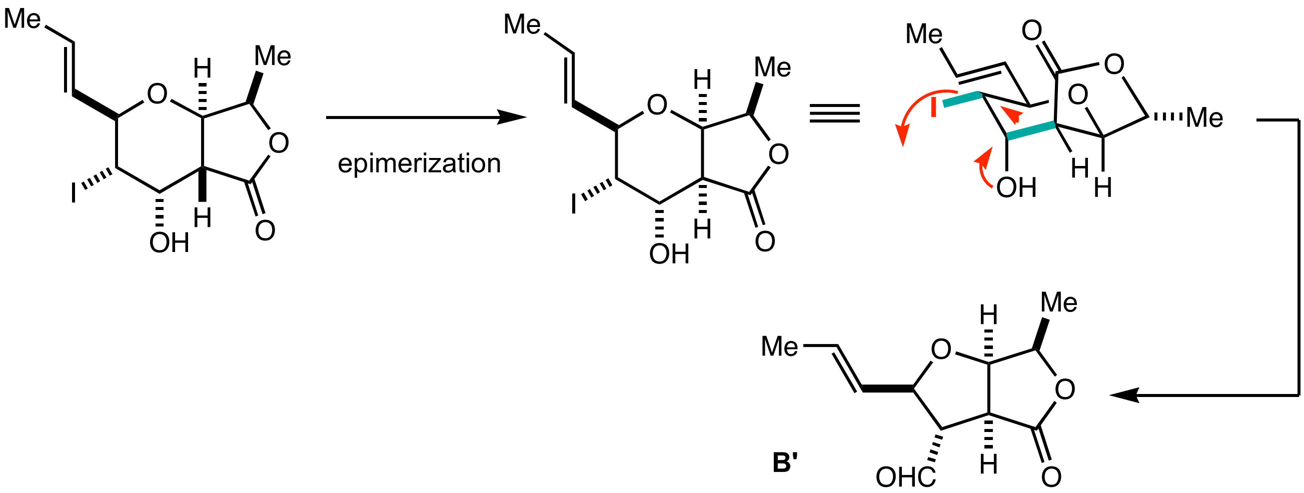


Question 3. Part B. (10 points). Products from the iodoetherification (**A** and **B**), when exposed to base (DBN), undergo different rearrangements. Please provide mechanisms that account for the divergent reaction pathways.



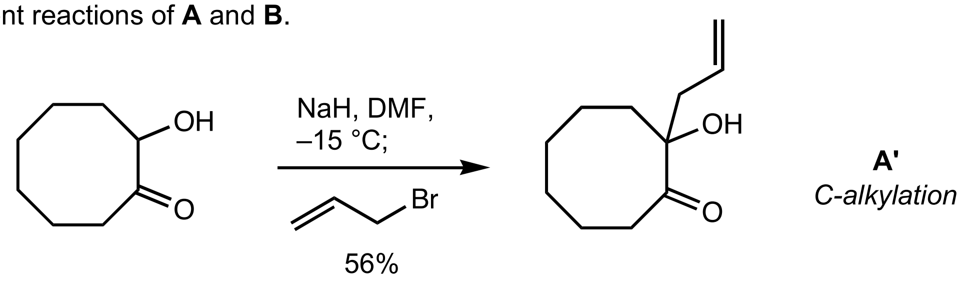
Snider, *JOC*, **2004**, 5517.
Snider, *Org. Lett.* **2003**, 451-454



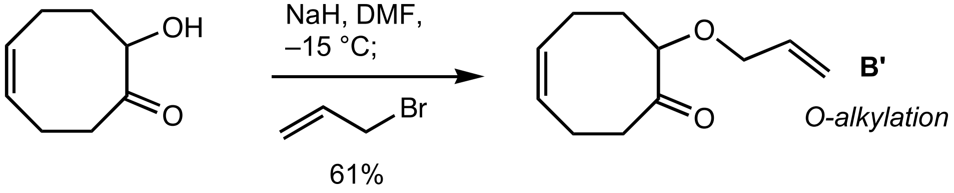


Question 4. (15 points). Paquette and co-workers have recently disclosed interesting regioselective alkylations illustrated below (*Org. Lett.* **2003**, 463.). Deprotonation of 2-hydroxycyclooctanone **A** followed by exposure to allyl bromide gave solely the C-alkylation product **A'**. In constrast, the unsaturated cyclooctanone **B** afforded the O-alkylation product **B'** exclusively. Using 3-dimensional conformational representations, please rationalize the divergent reactions of **A** and **B**.

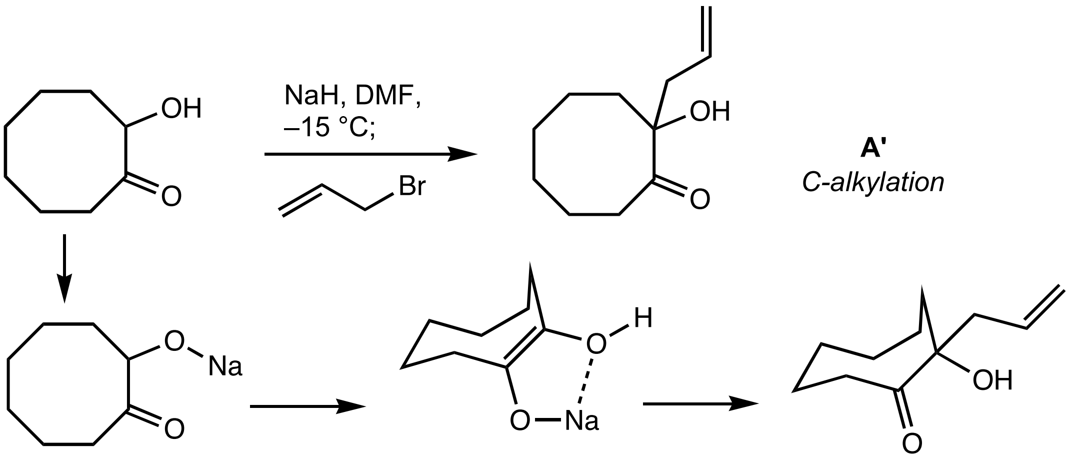
A



B



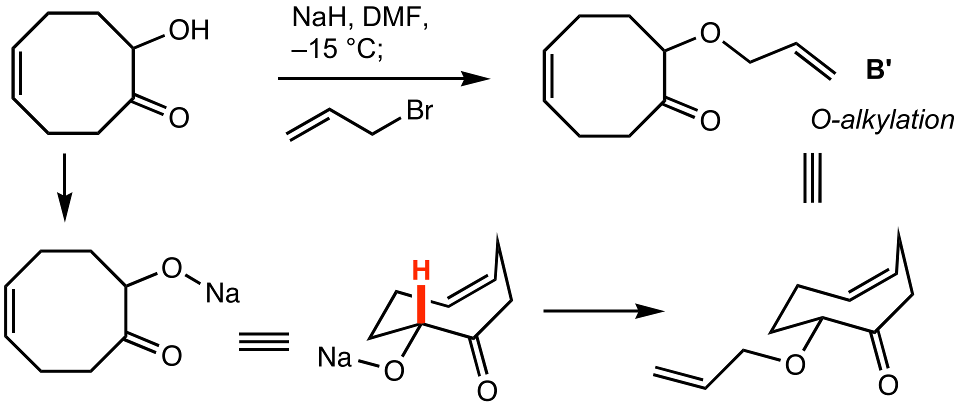
A



kinetic deprotonation of hydroxly

In order to alleviate tranannular strain, enolization occurs which leads to C-alkylation products

B

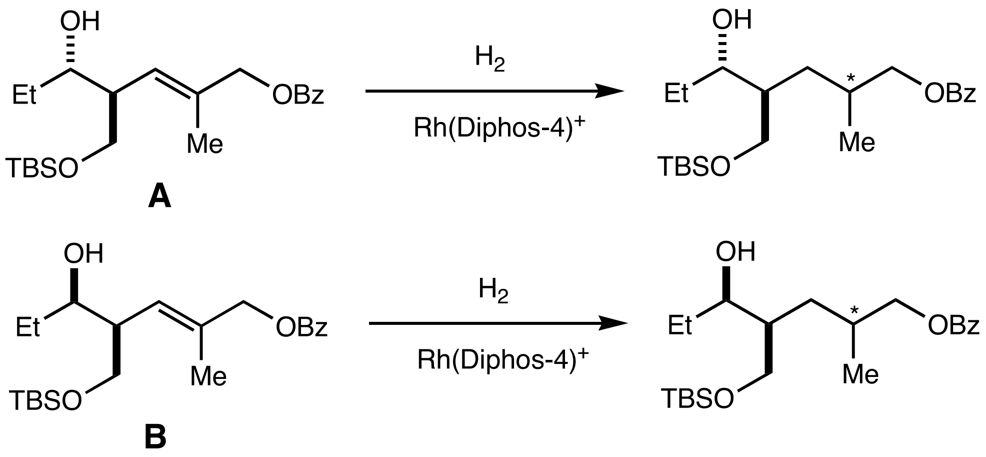


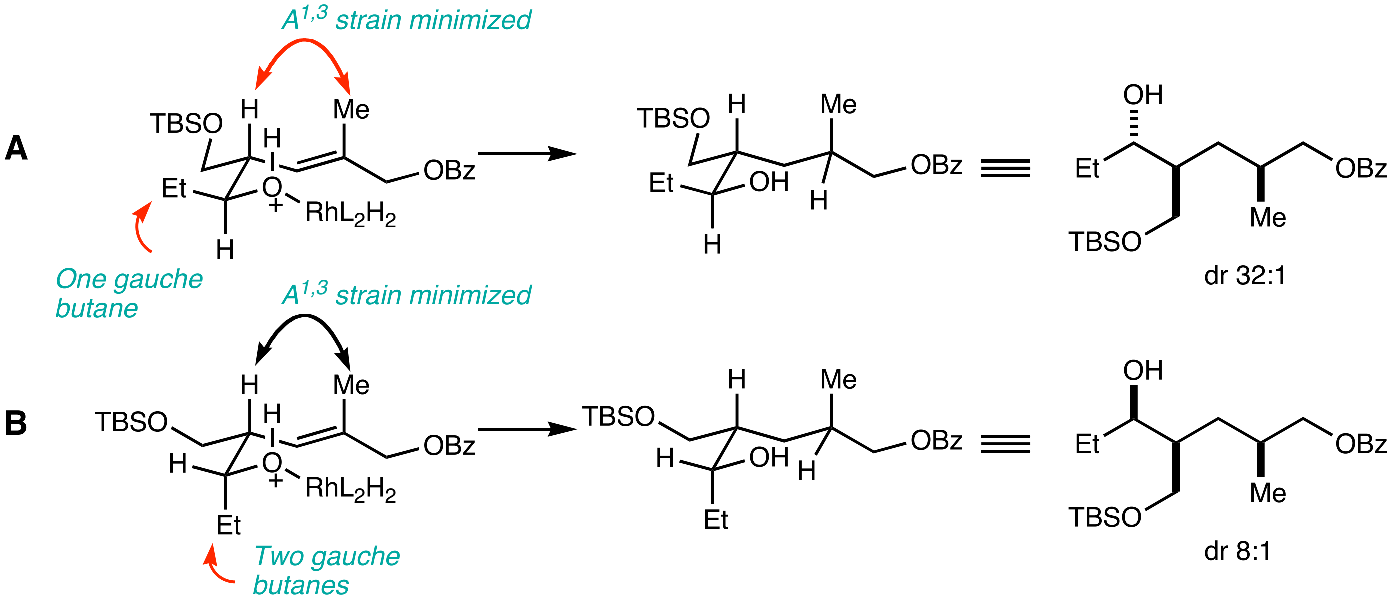
kinetic deprotonation of hydroxly

In **B**, enolization is precluded by the 5-6 olefin. The proton is not aligned for deprotonation in the low-energy conformation illustrated. The O-alkylation dominates

Question 5. (15 points). The directed reduction of homoallylic alcohols provides a powerful method for the stereoselective construction of acyclic molecules. In particular, cationic rhodium complexes have proven to be highly effective for the relay of stereochemical information by 1,3-asymmetric induction (Evans, *TL*, **1985**, 6005-6008).

Part A. (10 points). For both **A** and **B** predict the major diastereomer expected for indicated transformation. Be sure to indicate all relevent interactions.





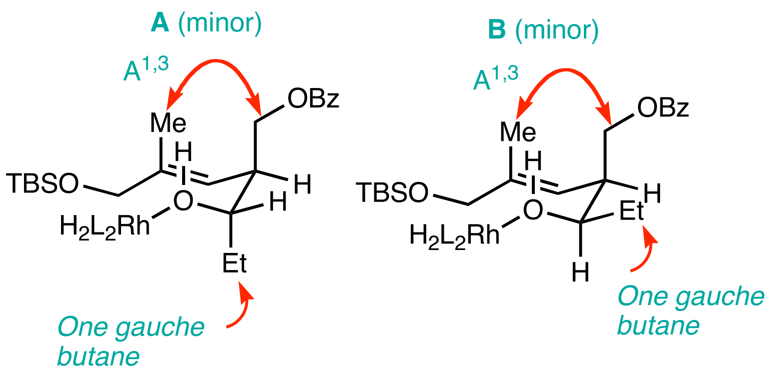
$A^{1,3}$ strain minimized

One gauche butane

$A^{1,3}$ strain minimized

Two gauche butanes

Part B. (5 points). Based on your transition states for the above reactions, which substrate would you expect to be more diastereoselective?



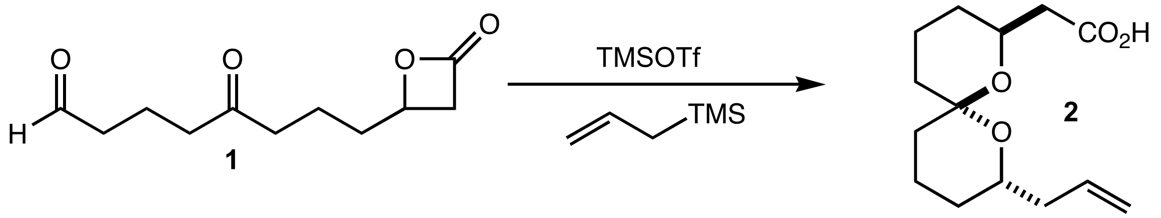
One gauche butane

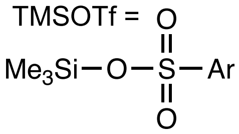
One gauche butane

The two minor diastereomeric TS are about equal in energy. However, for the major TS's, substrate **B** has one more gauche butane interaction than for TS **A**. **A** should be more selective than **B**, which is obsereved experimentally.

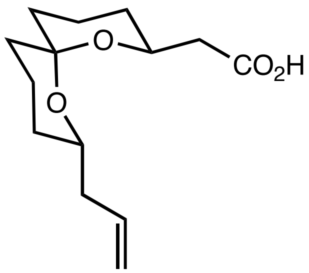
A quick calculation shows the energy difference between 32:1 and 8:1 is about 0.85 kcal/mol, which is approximately equal to one gauche butane interaction.

Question 6. (10 points). A unique spiroketalization was reported by the Mead group (*Syn. Lett.*, **1996**, 1065). A single diasteromer **2** was obtained when compound **1** was treated with a Lewis acid (TMSOTf) in the presence of allyltrimethylsilane. The observed long-range asymmetric induction immediately signals that the "most obvious" mechanism is probably not operative. Please answer the posed questions with this commentary in mind.

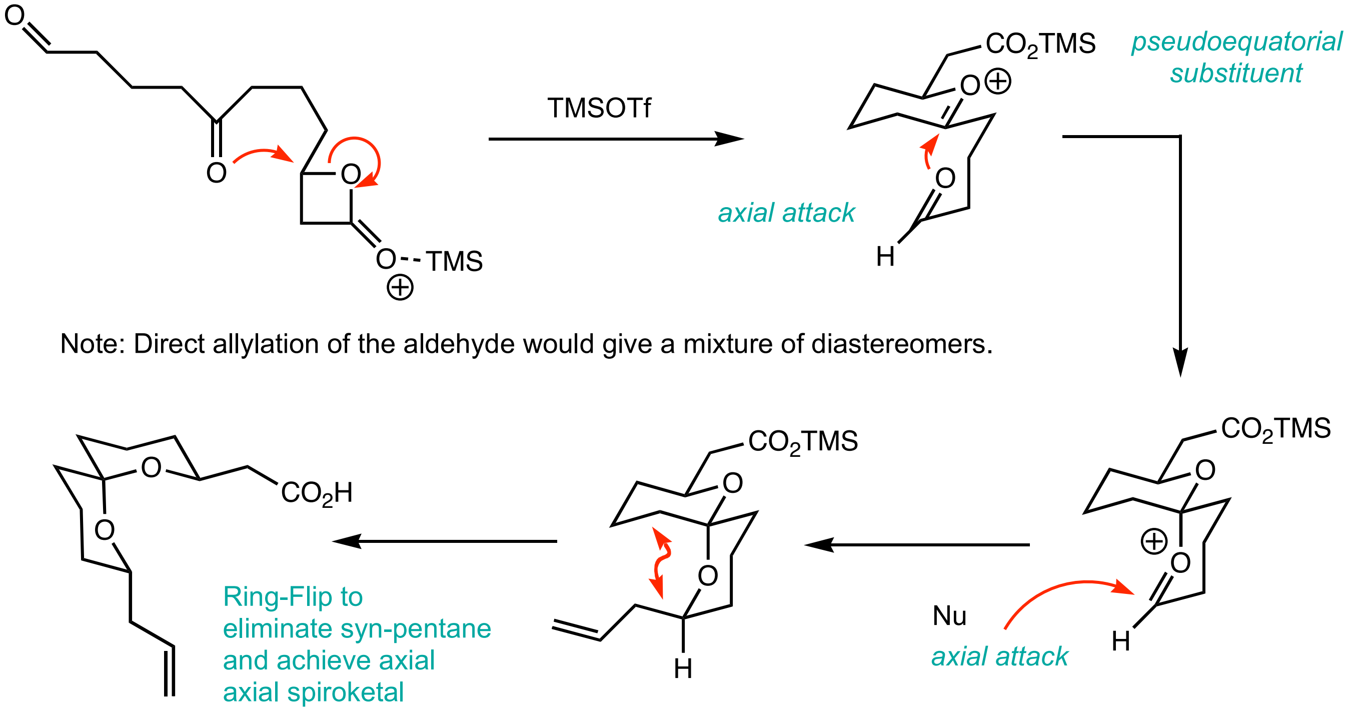



$$\text{TMSOTf} = \mathrm{Me_3Si{-}O{-}S(=O)_2{-}Ar}$$

Part A. Draw the most stable conformer of **2**.



Part B. Provide a concise reaction mechanism that rationalizes the observed selectivity. Please use 3-dimensional drawings to illustrate the stereochemical aspects of your answer.

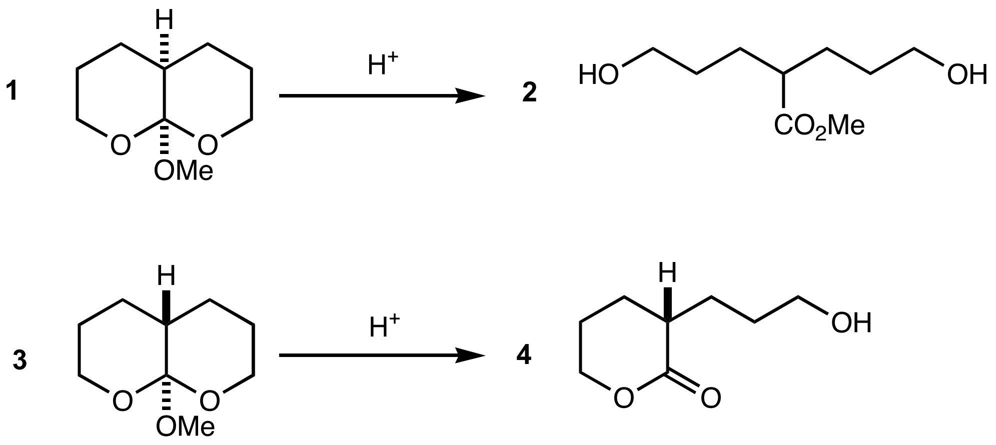

O
O
O
O--TMS
⊕
TMSOTf
CO_2TMS
O⊕
O
H
pseudoequatorial substituent
axial attack
CO_2TMS
O
⊕
O
H
Nu
axial attack
CO_2TMS
O
O
H
CO_2H
O
O
Ring-Flip to eliminate syn-pentane and achieve axial axial spiroketal

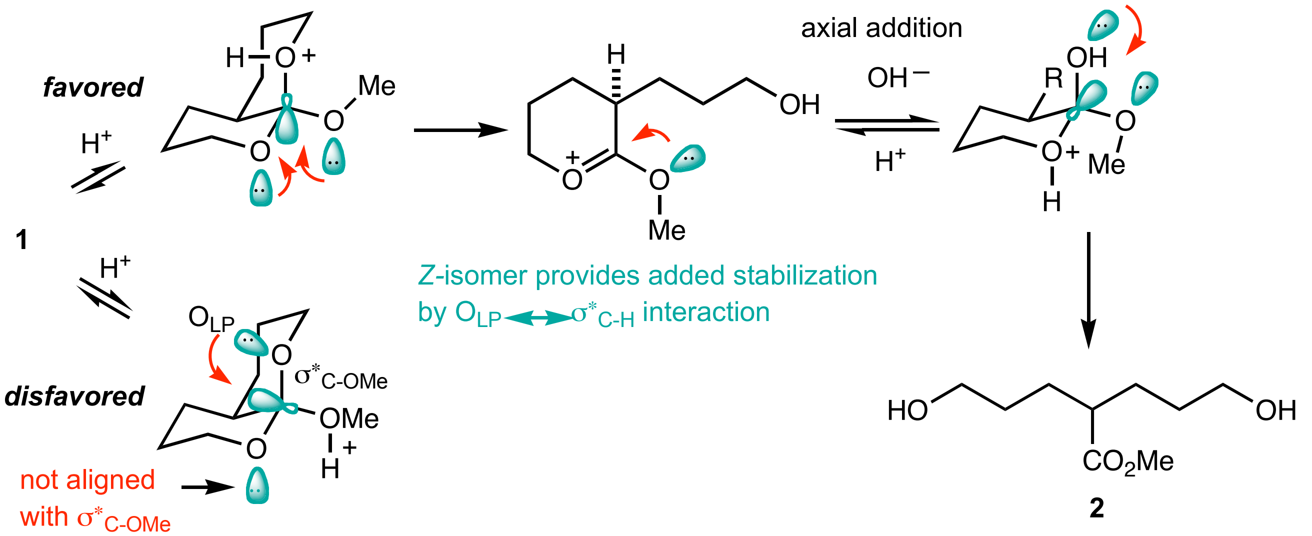
Note: Direct allylation of the aldehyde would give a mixture of diastereomers.

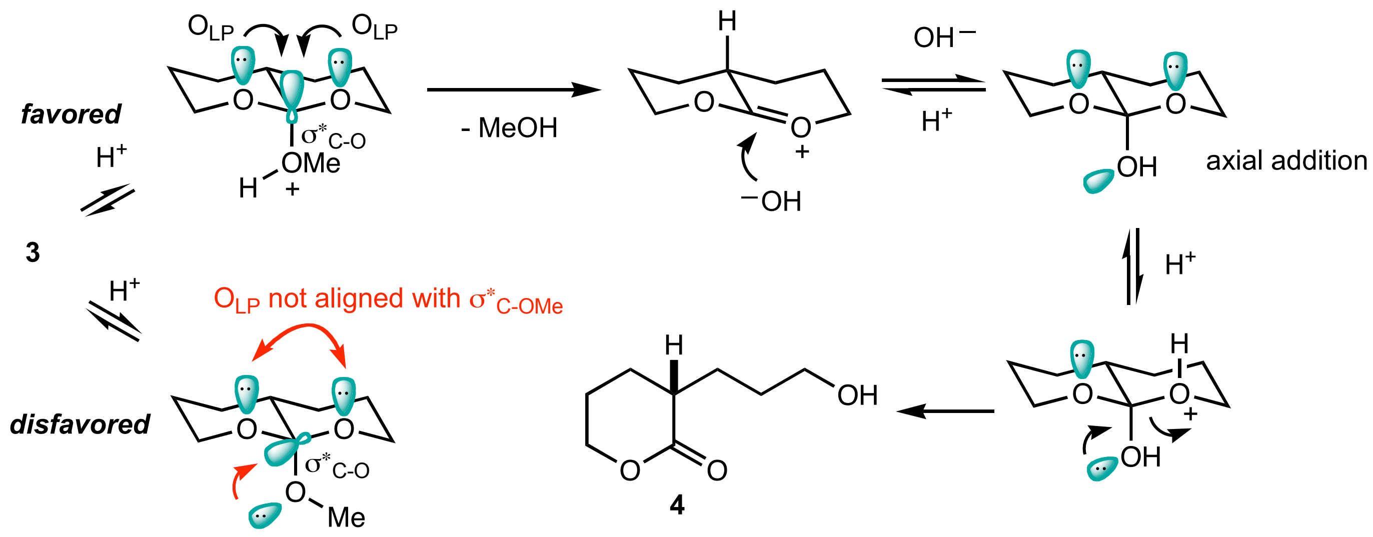
Mead, K. T., *Syn. Lett.*, **1996**, 1065.

Question 7. (10 points). The hydrolysis of cyclic orthoesters appears to be dominated by stereoelectronic factors. A striking example of the divergent behaviour of orthoesters **1** and **3** is shown below. (Deslongchamp, *Can. J. Chem.* **1984**, 2493-2500).

Using clear three-dimensional drawings please provide an explantion for why **1** undergoes hydrolysis to give hydroxy ester **2**, and why **3** provides lactone **4**.







Chemistry 206
First Hour Examination

D. A. Evans
October 10, 2003

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (10)	
No. 2 (15)	
No. 3 (15)	
No. 4 (15)	
No. 5 (15)	
No. 6 (15)	
No. 7 (15)	
Total (100)	

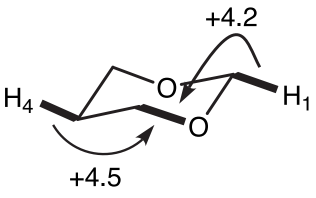
The exam will begin at 9:05 AM and end at 11:00.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

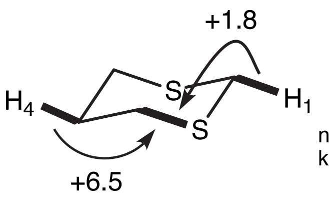
Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

Answer Key

Question 1. (10 points). Natural bond order (NBO) analysis is a powerful computational tool that allows one to quantitatively estimate the energy of hyperconjugative effects (Alabugin & Zeiden, *JACS* **2001**, *124*, 3175). The stabilizing interactions for the H_1 and H_4 equatorial hydrogens for 1,3-dioxane and 1,3-dithiane are provided below. It is interesting that the two indicated hyperconjugative interactions in dioxane are approximately the same (4.5 vs 4.2) but that the same interactions in dithiane are quite different (6.5 vs 1.8). In fact, the authors refer to C–S bonds as "one directional" acceptor orbitals.



σC–H → σ*C–O

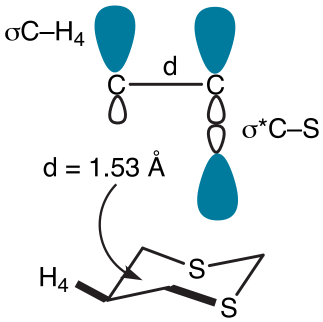


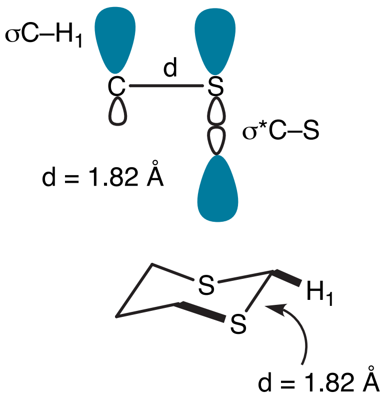
σC–H → σ*C–S

numbers refer to interaction energies in kcal/mol at the B3LYP/6-31+G*** level

There is one quite reasonable qualitative argument that can rationalize the "one directional" character of σ*C–S. Please provide your argument in the space provided below.

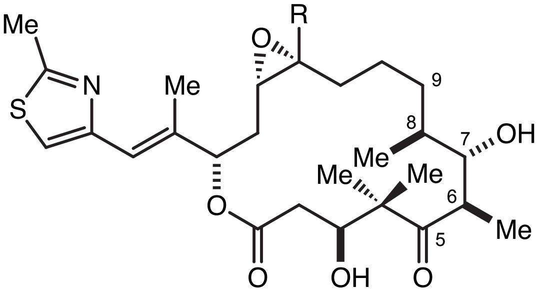
The hyperconjugative interactions to which we refer are pi-bonding in nature. Accordingly, the strength of the pi-bonding interaction is quite sensitive to the distance (d) between the interacting orbitals. In the dithiane, the C–H_4 → σ*C–S conjugative interaction must span a C–C bond affording a good pi-bonding interaction (+6.5). On the other hand, the C–H_1→ σ*C–S conjugative interaction must span a longer C–S bond. This results in a diminshed pi-bonding interaction (+1.8).





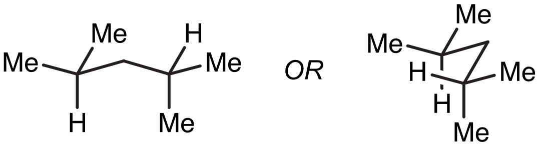
These effects to not surface in the 1,3-dioxane structure due to the fact that C–C and C–O bonds are both short relative to sulfur.

Question 2. (15 points). Epothilone is a potent macrolide natural product shown to bind tubulin in a similar fashion to the anticancer agent Taxol. In order to understand, and possibly enhance, the biological activity of epothilone, a detailed study of the conformation of the macrolactone has been recently reported (Taylor, *JOC*, **1999**, 7224-7228). The findings suggest that epothilone exists as a mixture of two conformations in solution, only one of which is medicinally relevant. Interestingly, the two conformations vary only in the C5-C9 carbon region of the structure.



R = H, epothilone A
R = Me, epothilone B

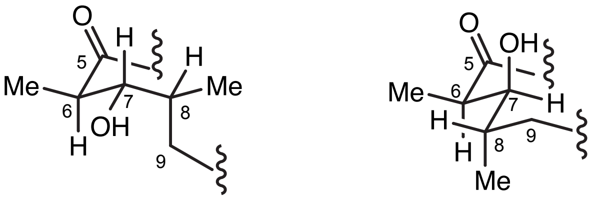
Part A (5 points): Draw the most favorable 2,4-dimethylpentane conformer in a three dimensional drawing.



These are equivalent

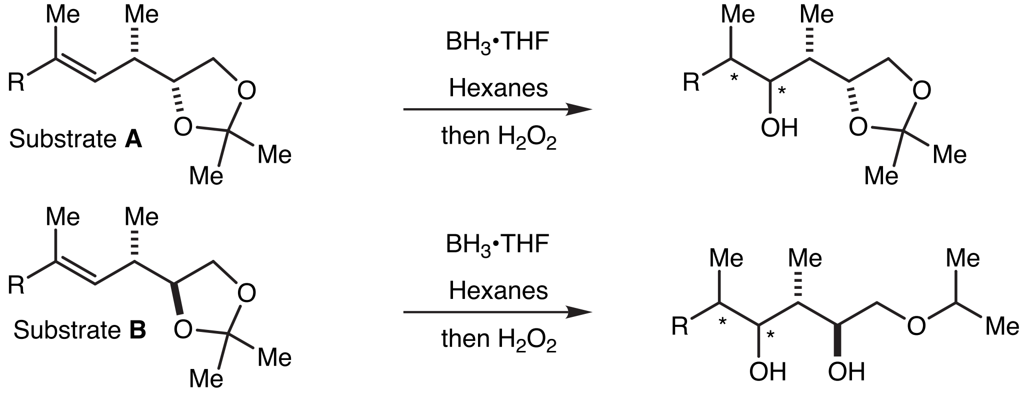
Drawings should minimize syn-pentane interactions

Part B (10 points): Extrapolate your answer from Part A and draw the two lowest energy conformations of the C5-C9 section of epothilone. *(Do not draw the whole molecule)*

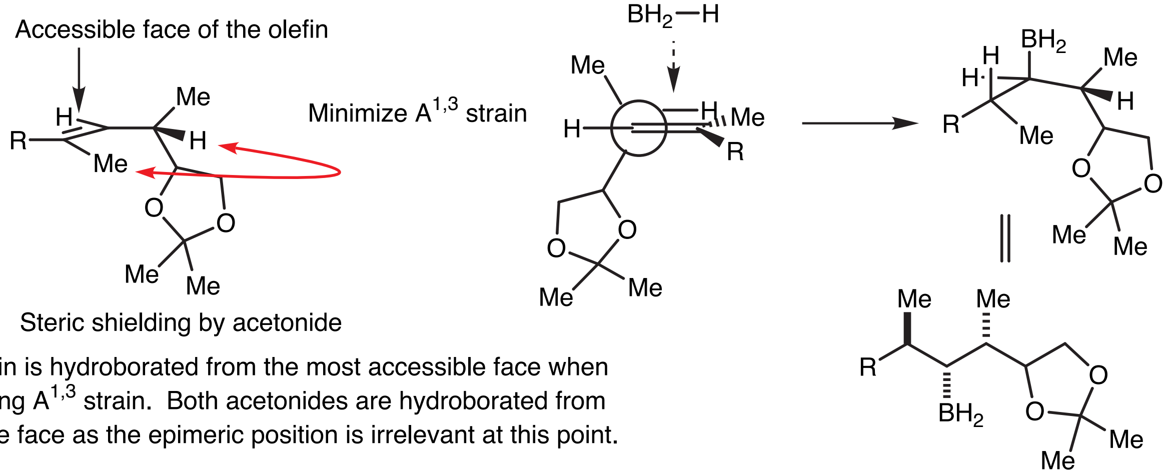


The analysis is the same as **Part A**; syn-pentane interactions avoided. Since dimethyl pentane is symmetric, there is only one minimized structure. When the termini are differentiated, there will be two comparable low energy conformers.

Question 3. (15 points). The indicated olefins were subjected to hydroboration/oxidation as shown (*Synlett,* **1993**, 696).



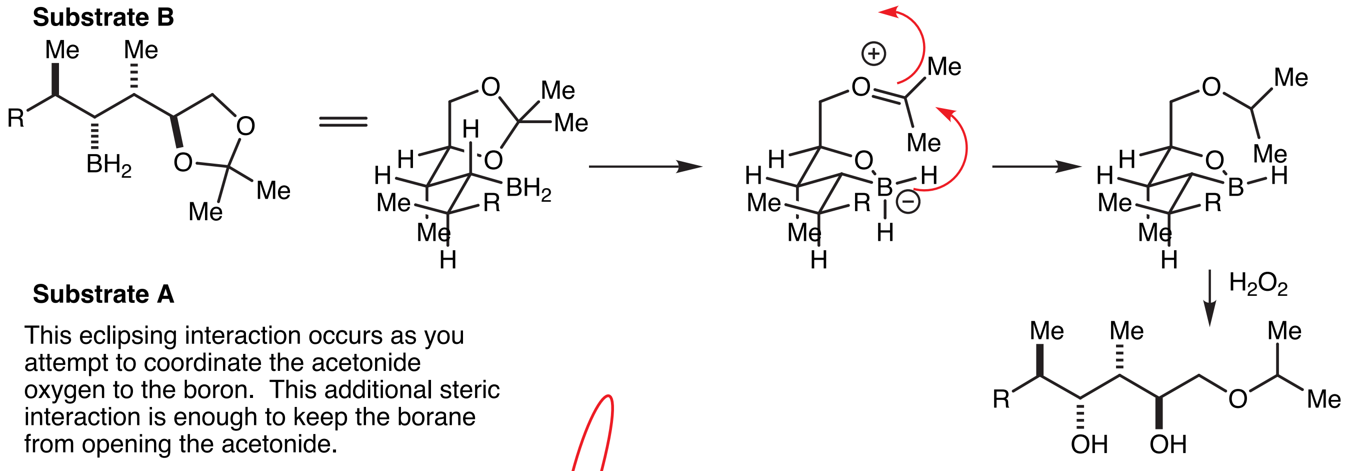
Part A. (8 points). Please predict the major stereoisomer obtained from these reactions and illustrate your predictions with clear 3D drawings.


Accessible face of the olefin
Minimize $A^{1,3}$ strain
Steric shielding by acetonide
BH_2—H
BH_2
R
Me
H
O

The olefin is hydroborated from the most accessible face when minimizing $A^{1,3}$ strain. Both acetonides are hydroborated from the same face as the epimeric position is irrelevant at this point.

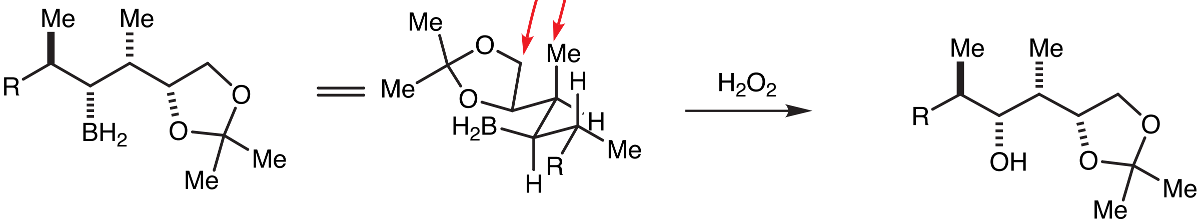
Part B. (7 points). Please also explain the fact that **B** suffers reductive ring opening while **A** does not..

Substrate B

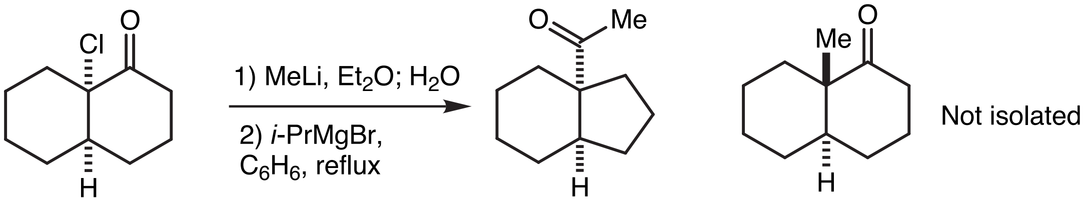


Substrate A

This eclipsing interaction occurs as you attempt to coordinate the acetonide oxygen to the boron. This additional steric interaction is enough to keep the borane from opening the acetonide.

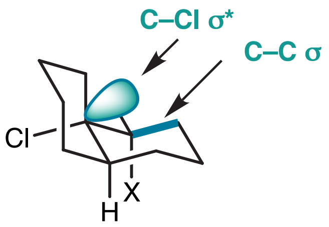


Question 4 (15 points). Sisti and Citale (*J. Org. Chem.* **1972**, *37*, 4090) have reported that cis chlorodecalone (**1**) was treated with methyllithium and a mixture of stereoisomeric alcohols was isolated. When this mixture of alcohols was converted to the derived magnesium alkoxides and heated in benzene, the ring contracted product (**2**) was isolated in 48% overall yield. It is interesting that none of the trans methyldecalone (**3**) was observed.

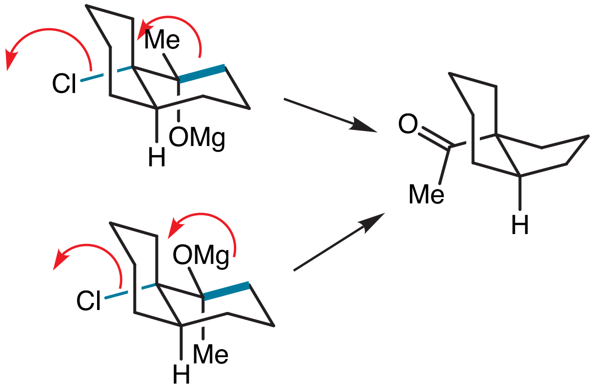


1 **2** **3**

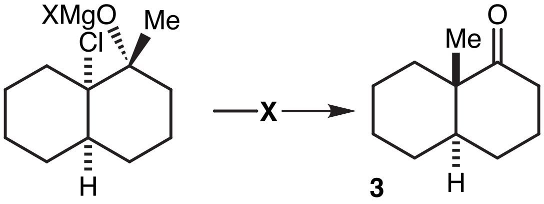
Part A (10 points). Rationalize the formation of **2** from both diastereomeric alcohols derived from **1**. Please use carefully rendered three dimensional drawings to illustrate your answer.



the relevant migrating C–C bond aligns in an antiperiplanar arrangement with the antibonding C–Cl orbital in both instances

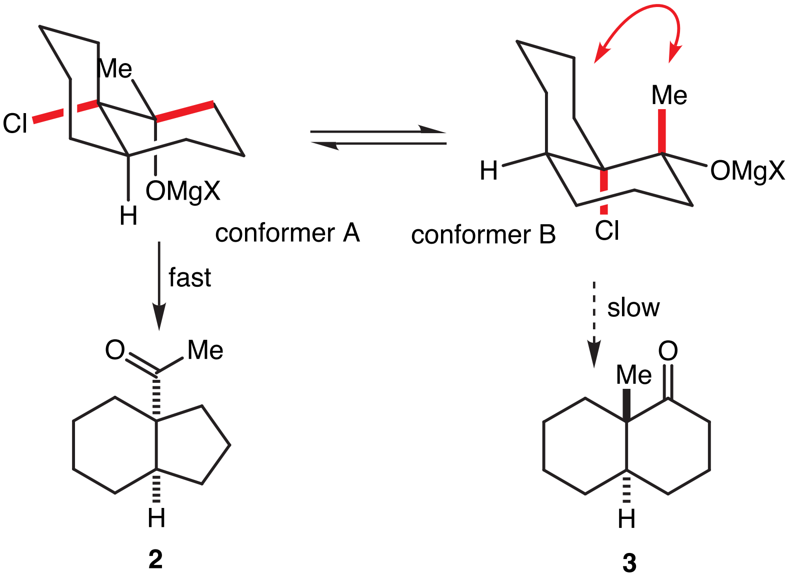


Part B (5 points). Explain why the indicated alkoxide does not lead to the formation of **3**.

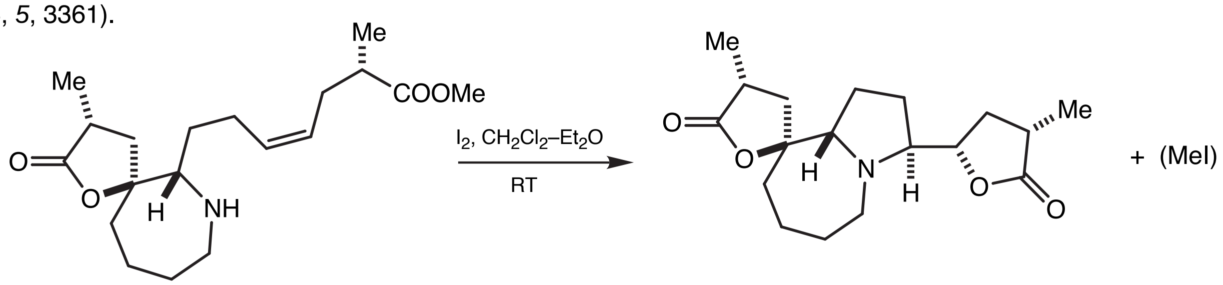


This alkoxide, in principle, could rearrange to give either reaction product. This point is illustrated in the appended scheme.

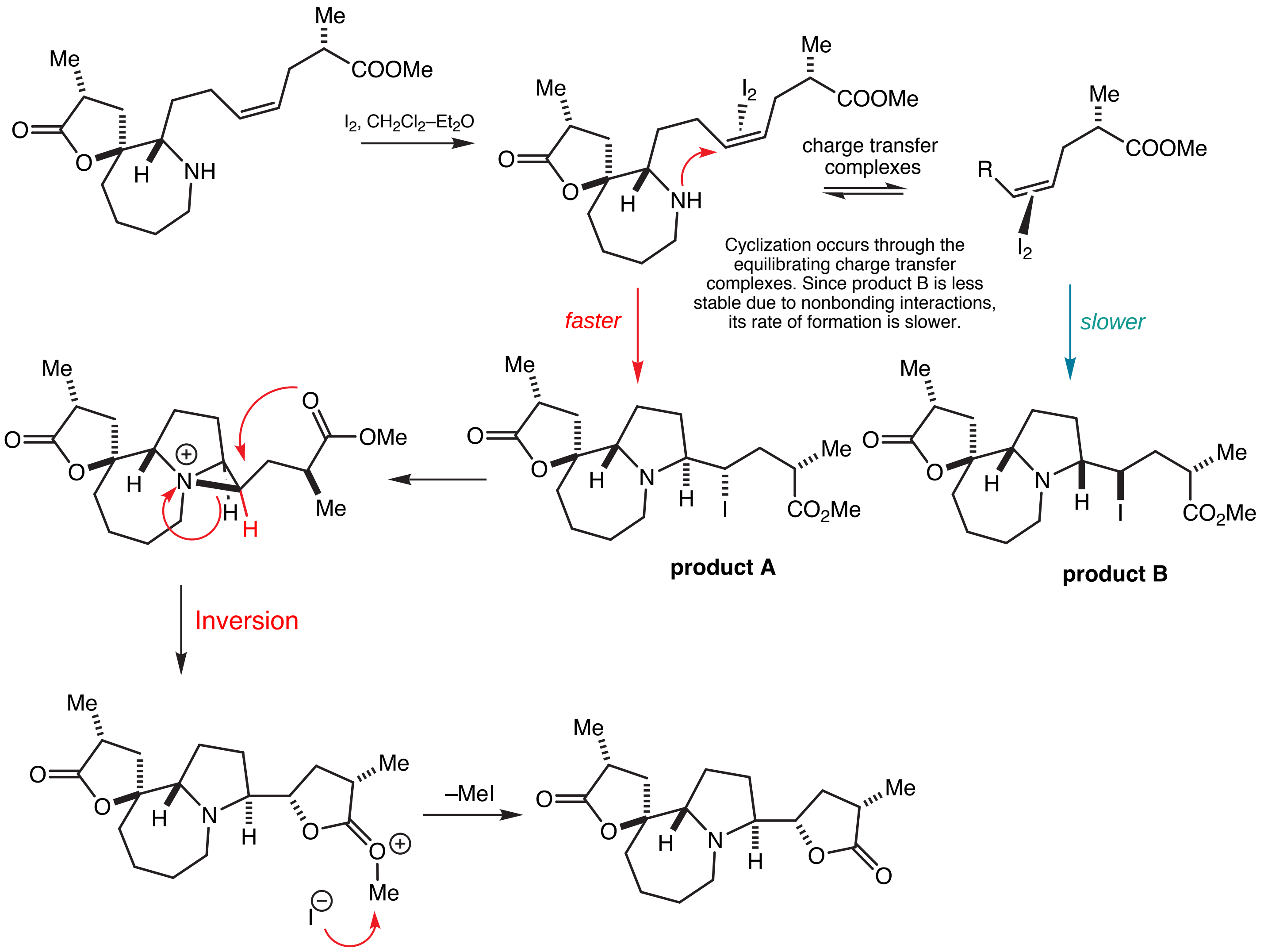
However, conformer B is strongly destabilized by the indicated double gauche pentane interaction. This destabilization is reflected in an increased activation energy for the rearrangement to **3**. The rearrangement via conformer A to product **2** does not suffer such destabilization.



Question 5. (15 points). The iodine-induced transformation shown below is a key step in the Williams synthesis of croomine (*JACS* **1989**, *111*, 1923). Given the stereochemical outcome of the illustrated transformation, propose a detailed mechanism for this reaction sequence. Williams has recently provided another closely reaction of the same design (*Org. Lett* **2003**, *5*, 3361).

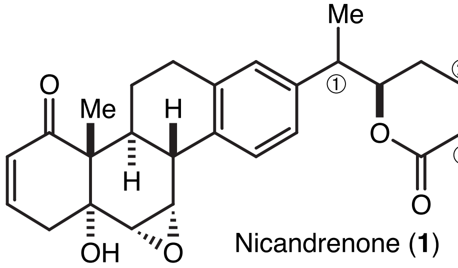


Answer

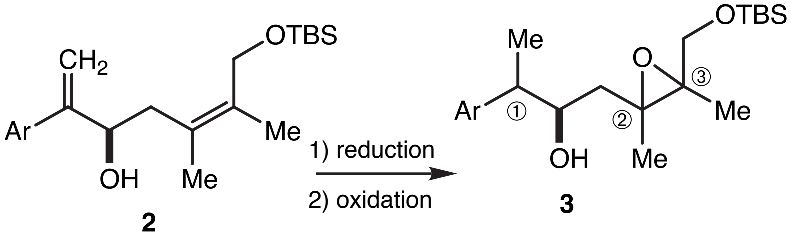


Cyclization occurs through the equilibrating charge transfer complexes. Since product B is less stable due to nonbonding interactions, its rate of formation is slower.

Question 6. (15 points). The Corey laboratory recently reported the first synthesis of several members of the Nicandrenone family of natural products that are produced from plants that have insectidal and antifeedent properties (*JACS* **2000**, *122*, 9044). In the terminal stages of the synthesis, the synthesis employs **two consecutive hydroxyl-directed transformations** to transform **2** into **3** and subsequently into the stereochemically elaborated lactone-containing sidechain. The first reaction is a reduction and the second is an oxidation.

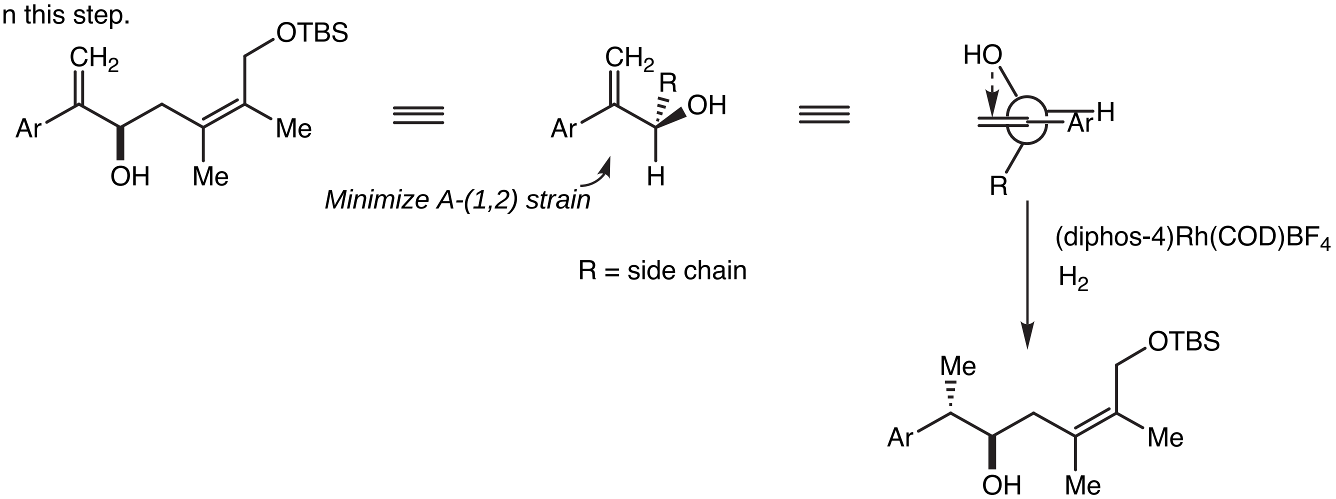


Nicandrenone (**1**)

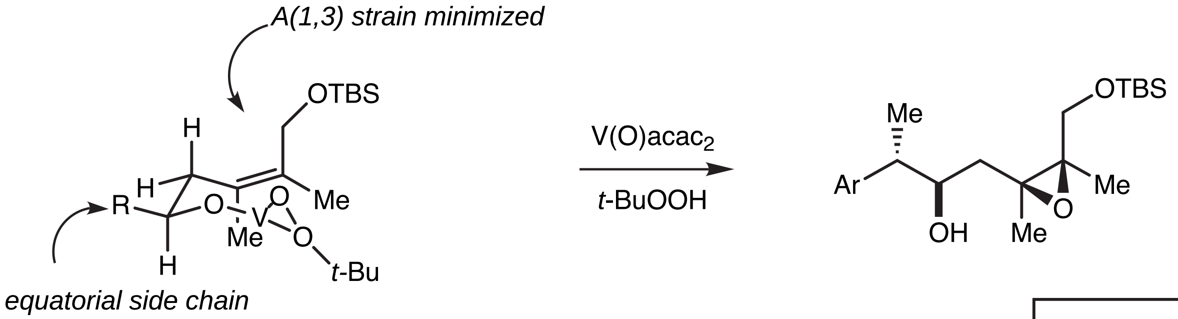


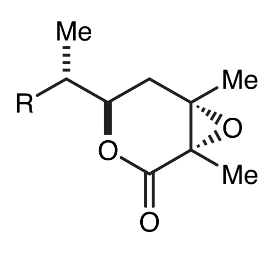
2 **3**

Part A (6 points). Illustrate, with conformational drawings, the reaction that leads to the generation of stereocenter ①. Predict the stereochemical relationship of this methyl-bearing stereocenter relative to the hydroxyl group. *Use part structures lacking the tetracyclic nucleus in your answer*. Please also precisely define the reagents that you will employ in this step.



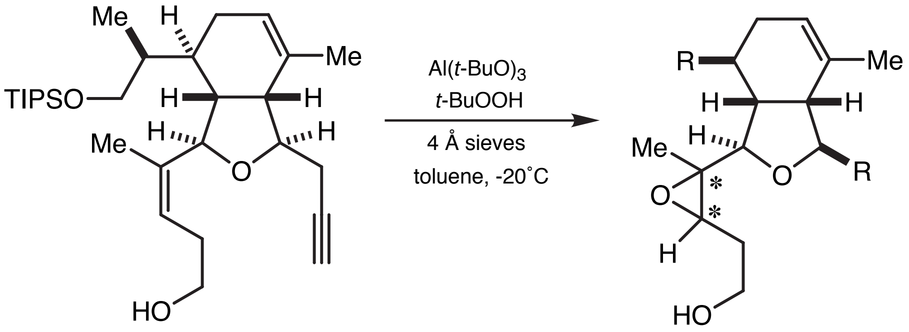
Part B (6 points). Illustrate, with conformational drawings, the reaction that leads to the generation of the epoxide (centers ② and ③) Predict the stereochemical relationship of the epoxide relative to the hydroxyl group. Please also precisely define the reagents that you will employ in this step.



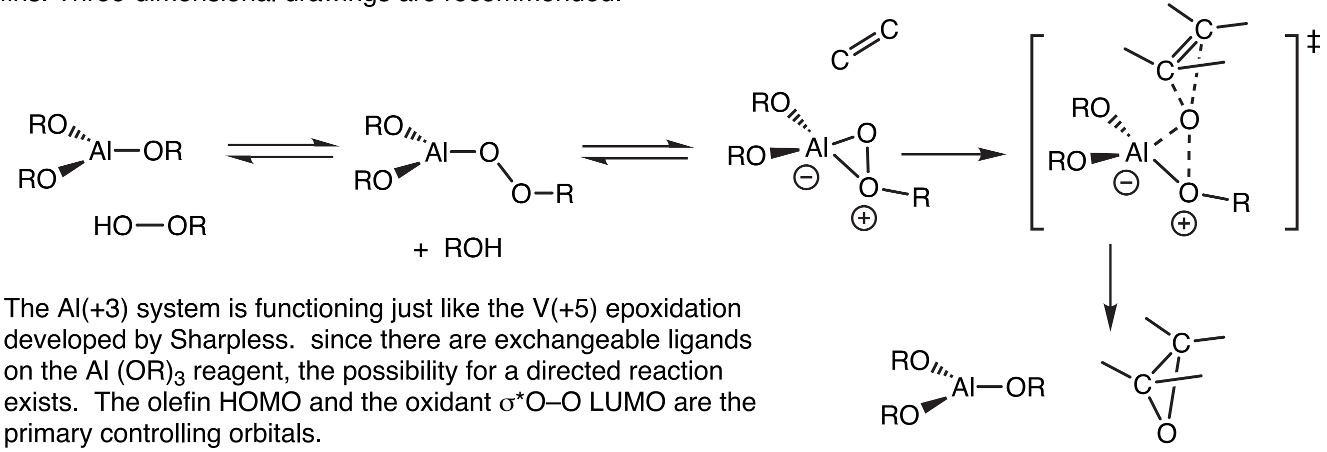


Part C (3 points). Finally, provide the full stereo structure of the illustrated terminal portion of this molecule. Pencil in the relevant stereochemical relationsips on the structure provided in the box

Question 7 (15 points). Overman and co-workers recently reported the indicated selective epoxidation in conjunction with a synthesis of briarellins A and E, a new family of diterpenes (*JACS* **2003,** *125*, 6650)**.** It should be noted that the Al(t-BuO)$_3$/(t)-BuOOH reagent system is both highly diastereoselective and site selective. It is also relevant to the mechanism of the reaction that the ring-trisubstituted olefin lacking an allylic oxygen substituent would normally be more prone to epoxidation with a peracid than the acyclic trisubstituted olefin.

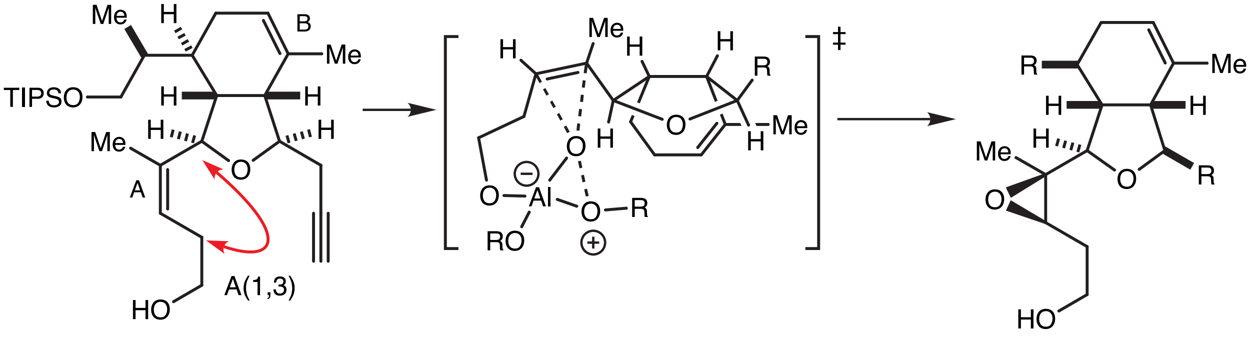


Part A (7 points). Provide a general mechanism illustrating how the Al(t-BuO)$_3$/(t)-BuOOH reagent epoxidizes olefins. Three-dimensional drawings are recommended.



The Al(+3) system is functioning just like the V(+5) epoxidation developed by Sharpless. since there are exchangeable ligands on the Al (OR)$_3$ reagent, the possibility for a directed reaction exists. The olefin HOMO and the oxidant σ^*O–O LUMO are the primary controlling orbitals.

Part B (8 points). Provide a general mechanism illustrating how the above epoxidation proceeds and provide the stereochemistry (∗) of the product epoxide along with a stereochemical analysis of the noted face selectivity.



The fact that C=C B is not oxidized suggtests that the reaction is directed by the OH group. A(1,3) interactions provide a strong conformational bias for the (Z)-olefin A the two olefin diastereofaces are strongly differentiated by the fused cycloxexene steric interactions promoting epoxidation from the illustrated diastereoface.

Chemistry 206
Second Hour Examination

D. A. Evans

November 20, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (15)	
No. 2 (10)	
No. 3 (10)	
No. 4 (15)	
No. 5 (10)	
No. 6 (15)	
No. 7 (10)	
No. 8 (15)	
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

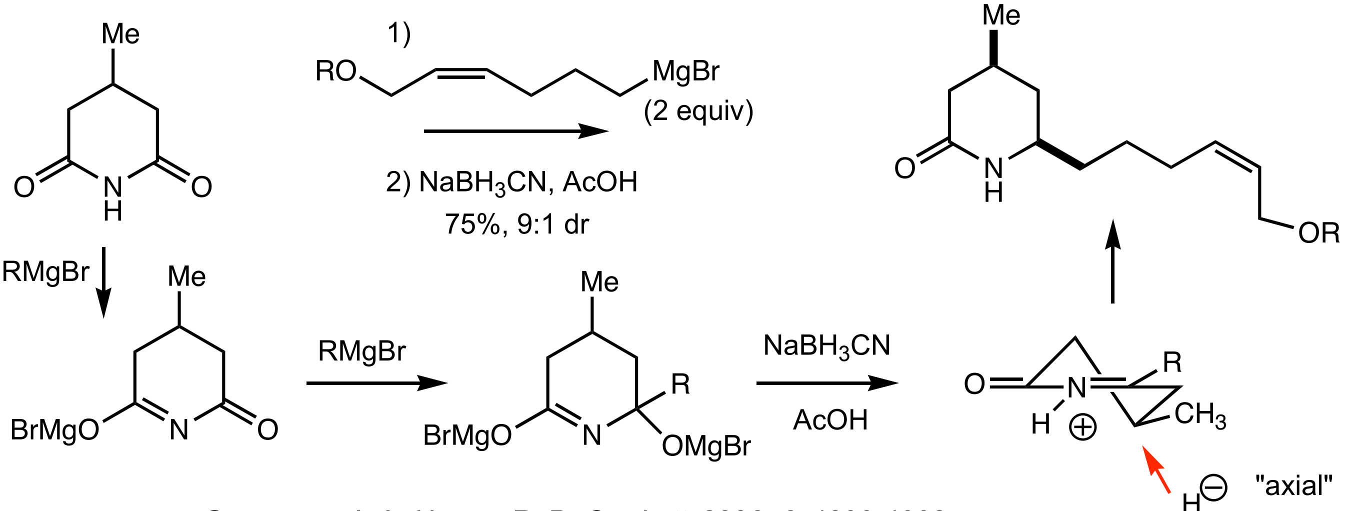
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate. This examination has nine pages.

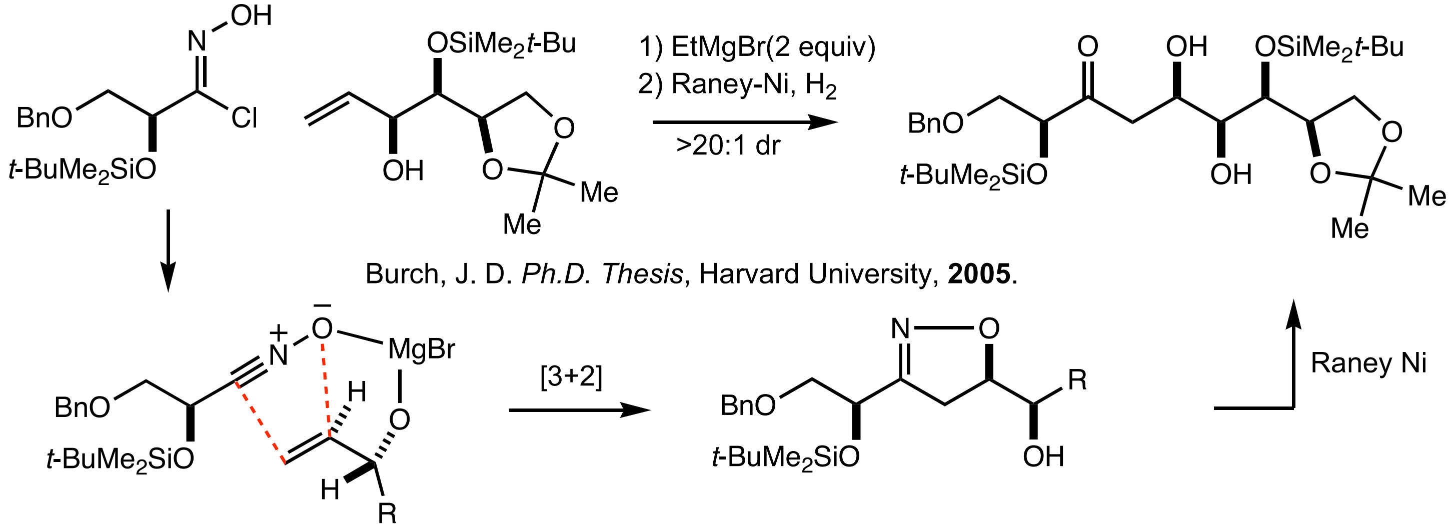
Evam Average: 62
High Grade: 98

Answer Key

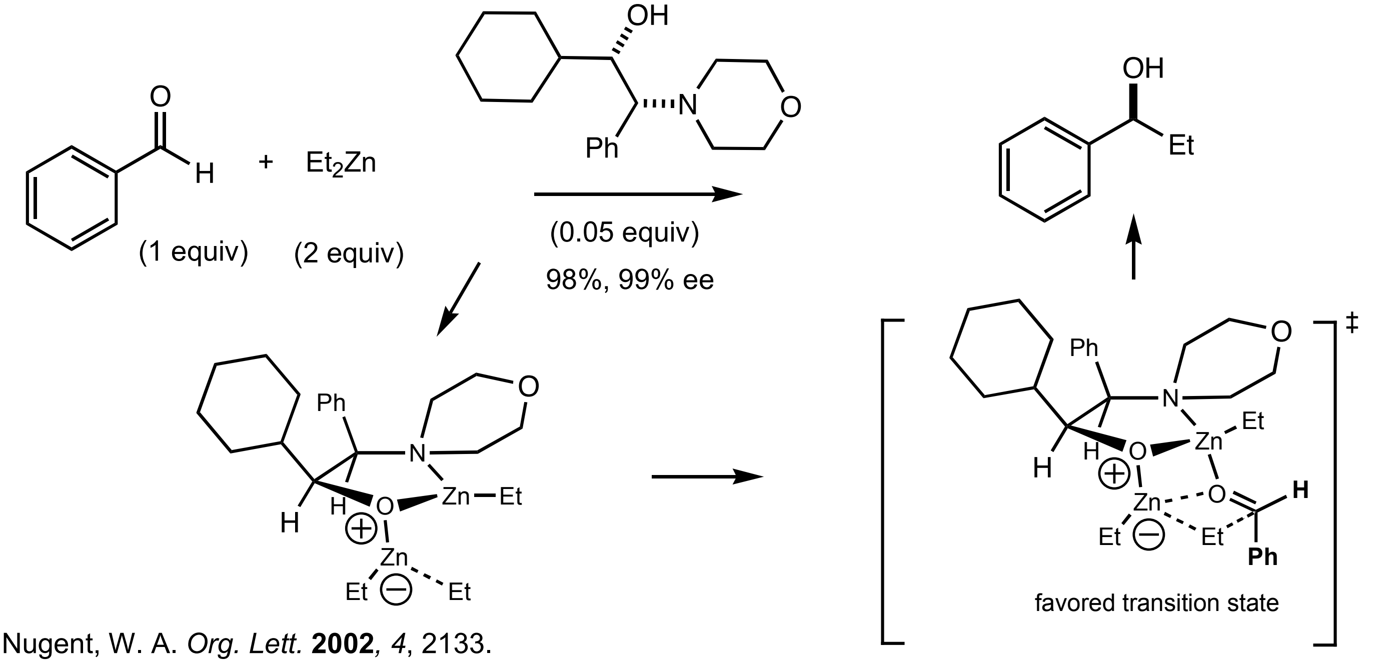
Question 1. (15 points). Predict the products for the transformations below. Also, provide mechanisms with the appropriate 3D models that explain your answer.



Gerasyuto, A. I.; Hsung, R. P. *Org.Lett.* **2006**, *8*, 4899-4902.

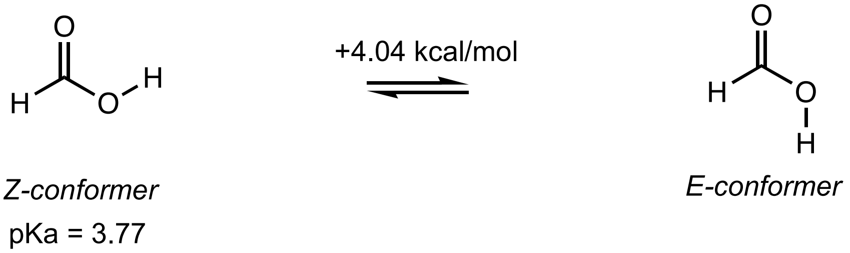


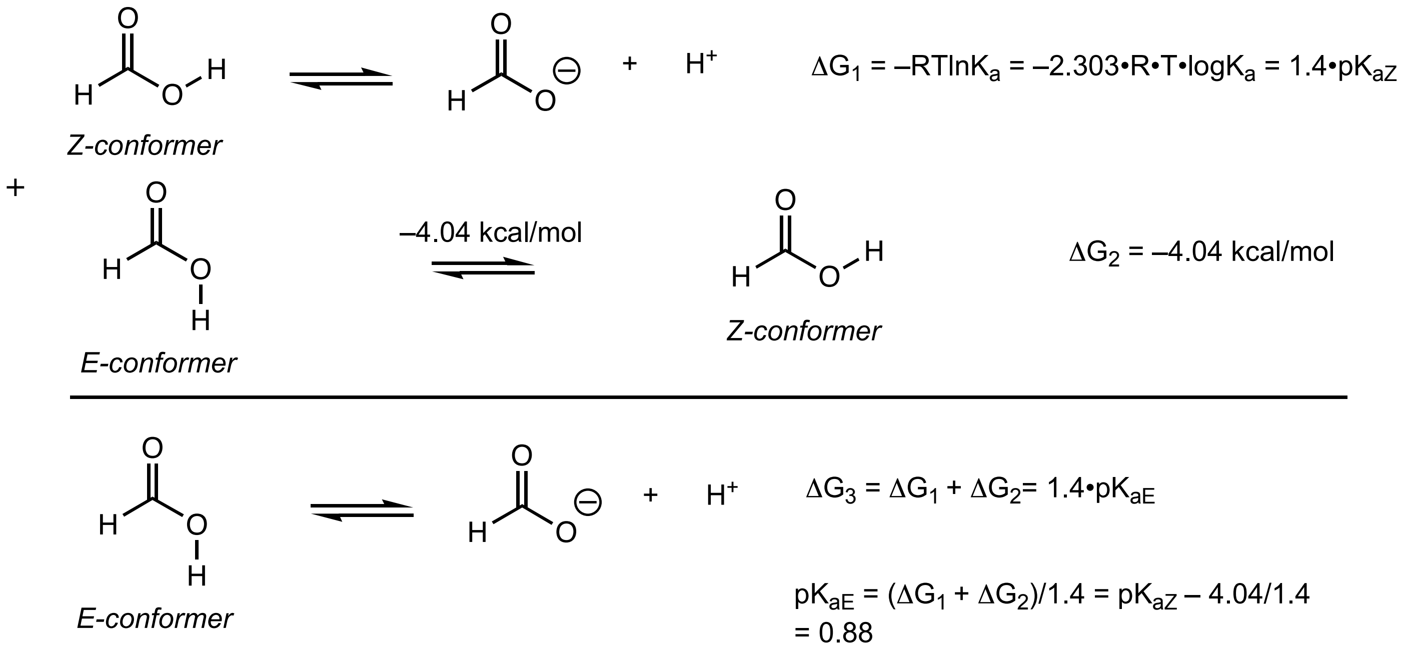
Burch, J. D. *Ph.D. Thesis*, Harvard University, **2005**.



Nugent, W. A. *Org. Lett.* **2002**, *4*, 2133.

Question 2. Part A (7 points). A carboxylic acid can exist in two conformations *E* and *Z* that are different by the dihedral angle around the C–O bond. Recent theoretical calculations demonstrated that the *Z* isomer of formic acid is more stable by 4.04 kcal/mol (Ratajczyk *et al. Tetrahedron* **2004**, *60*, 179-185). Assuming that the pK_a of the *Z* isomer of formic acid is equal to 3.77 calculate the pK_a of the *E* isomer of formic acid. Assume that $\Delta G = 1.4 \cdot pK_a$ kcal/mol.





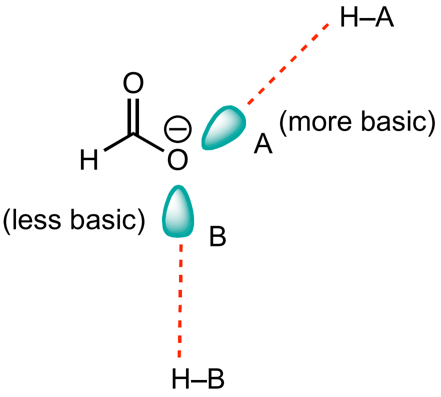
$\Delta G_1 = -RT\ln K_a = -2.303 \cdot R \cdot T \cdot \log K_a = 1.4 \cdot pK_{aZ}$

$\Delta G_2 = -4.04$ kcal/mol

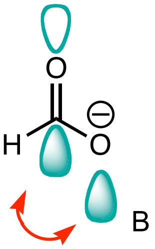
$\Delta G_3 = \Delta G_1 + \Delta G_2 = 1.4 \cdot pK_{aE}$

$pK_{aE} = (\Delta G_1 + \Delta G_2)/1.4 = pK_{aZ} - 4.04/1.4$
$= 0.88$

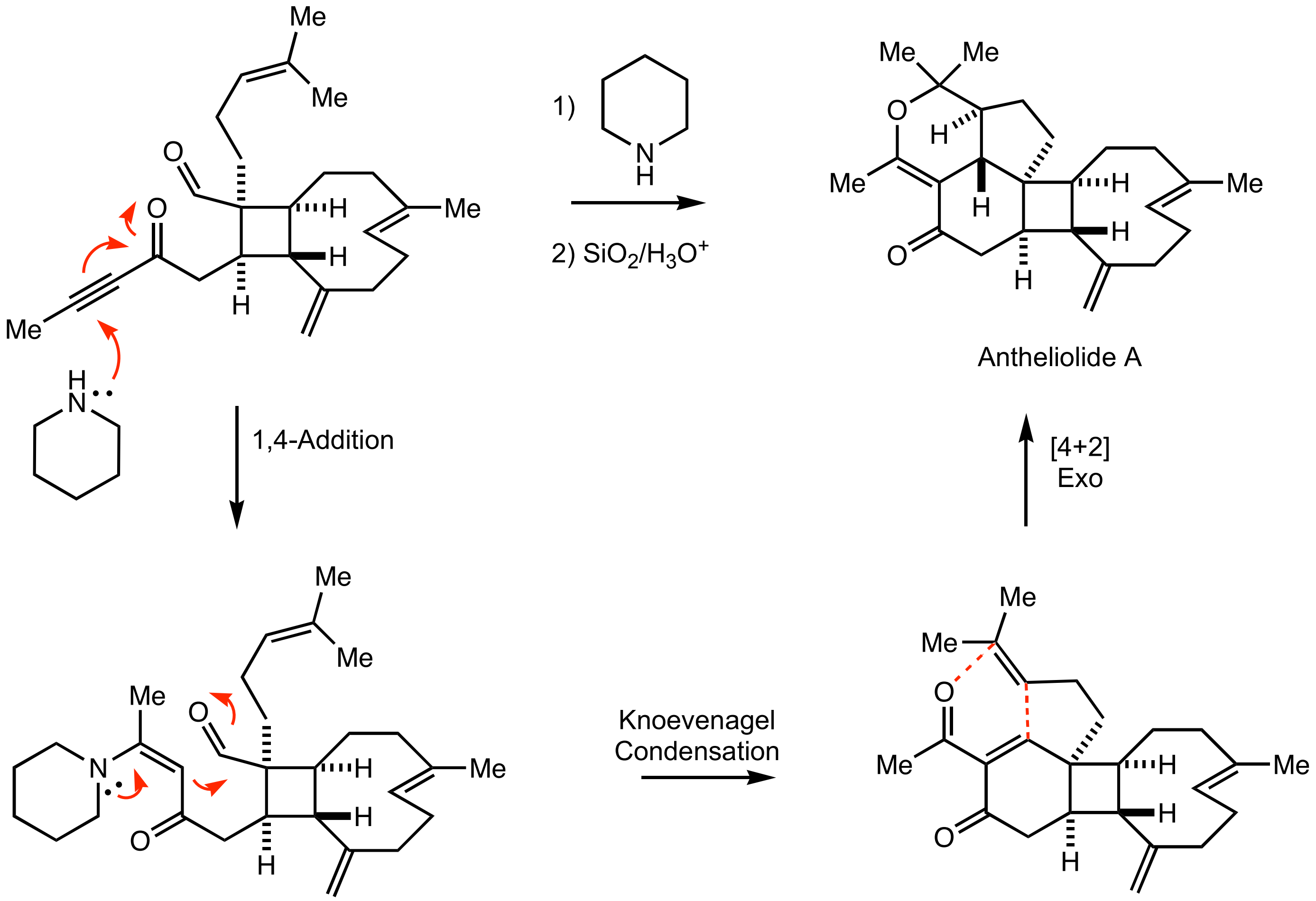
Part B (3 points). Based on your calculations propose which lone pair of the carboxylate anion shown below is going to be more basic. Is the FMO theory consistent with your answers?



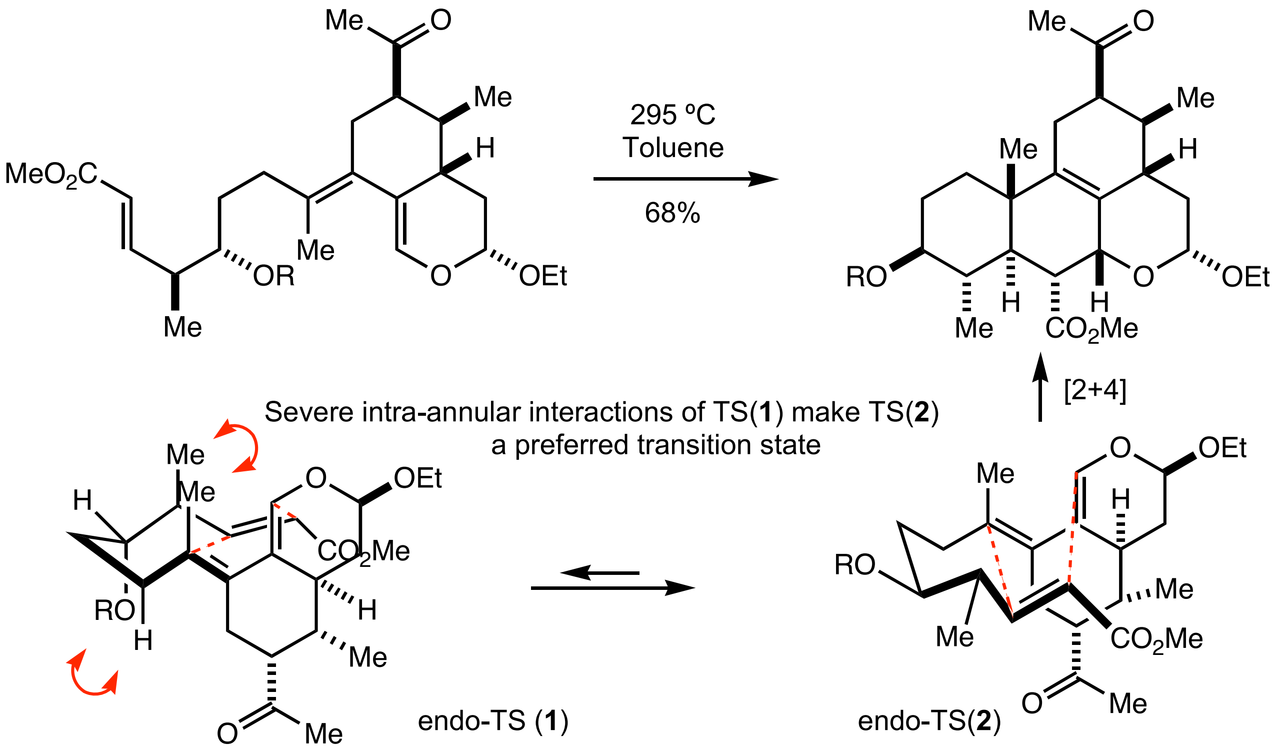
Our calculations are consistent with the FMO theory. Lone pair B can interact with σ*(C=O) while lone pair A can overlap with σ*(C–H). The former is a better acceptor that withdraws the electron density from the lone pair B and makes it less basic.



Question 3. (10 points). Recently, the sequence of reactions outlined below was used by Corey et al. (*JACS* **2006**, *128*, 14050) in their route to antheliolide A. Provide a mechanism for this reaction and explain the stereochemistry of the product.

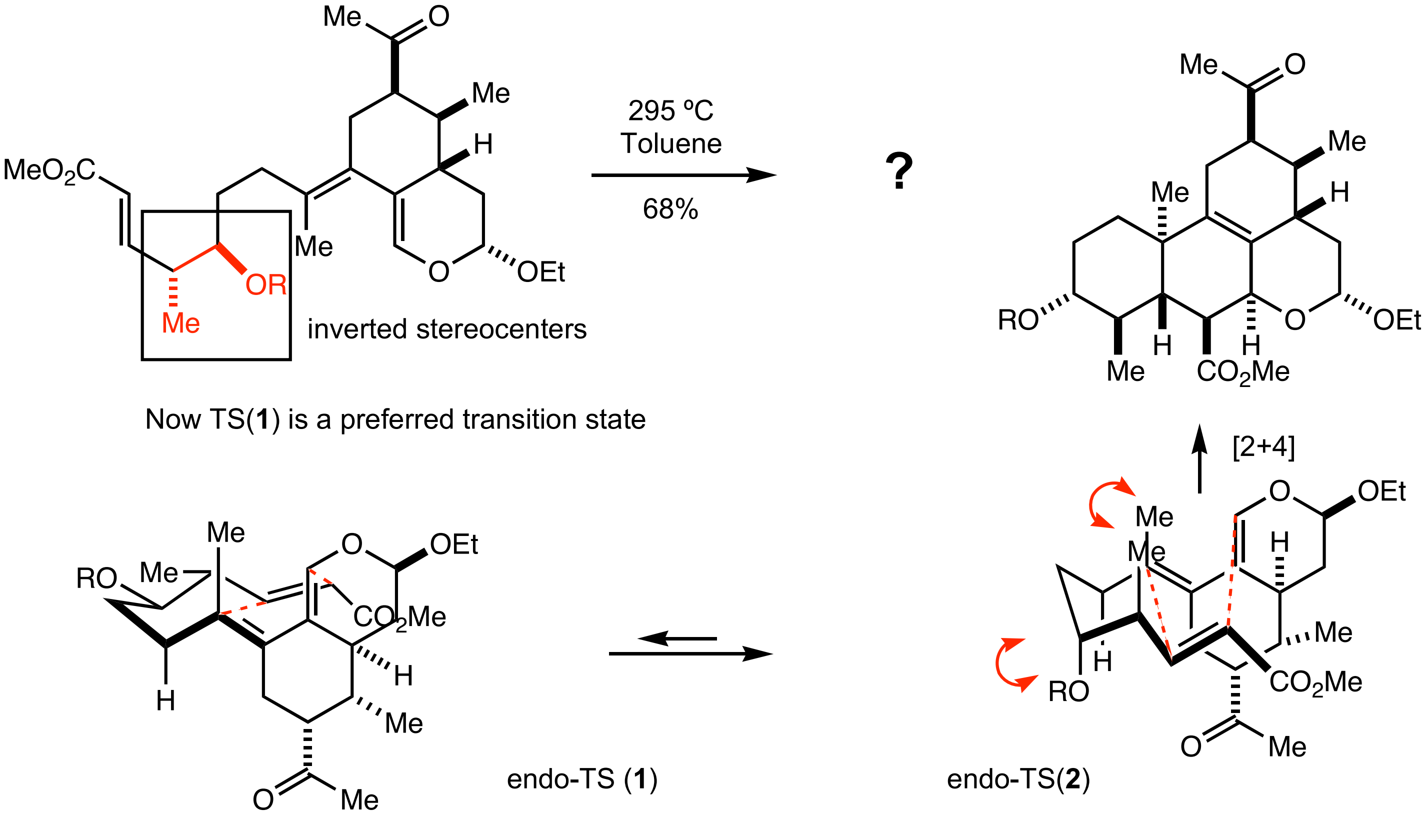


Question 4. Part A. (5 points). The following cycloaddition reaction was recently explored by Spino and Perreault (*Org. Lett.* ***2006***, *8*, 4385.) Provide a reasonable transition state that explains the stereochemistry of the product.



Severe intra-annular interactions of TS(**1**) make TS(**2**) a preferred transition state

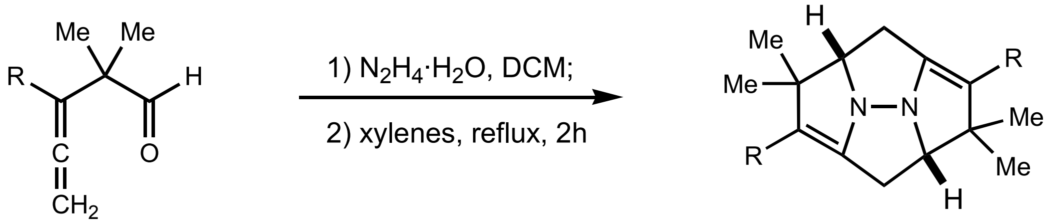
Part B. (10 points). Based on your solution above predict the stereochemical outcome of the cycloaddition carried out on the diastereomeric compound shown below. Use clear 3D drawing to explain your answer.

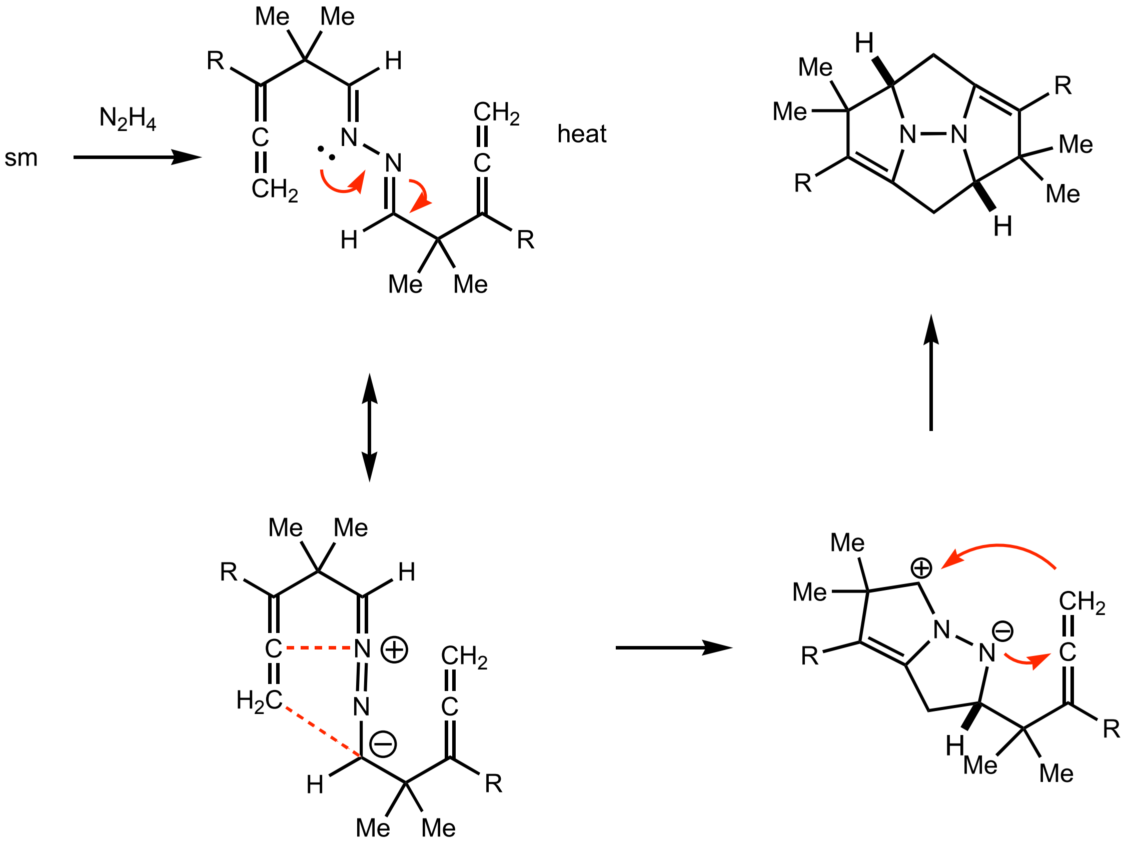


inverted stereocenters

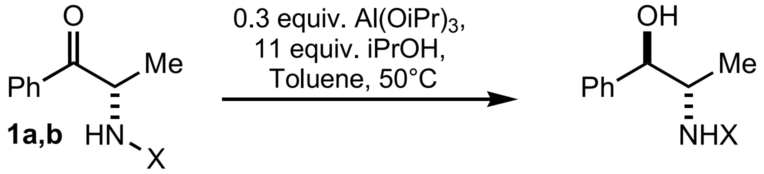
Now TS(1) is a preferred transition state

Question 5. (10 points). Provide a mechanism for the following reaction sequence recently published by the group of Potacek (*Eur. J. Org. Chem.* **2005**, 2548):





Question 6. (15 points). The Merck Research Laboratories have recently reported the following preparation of ephedrine analogues (*JOC* **2006**, *71*, 840):



1a,b

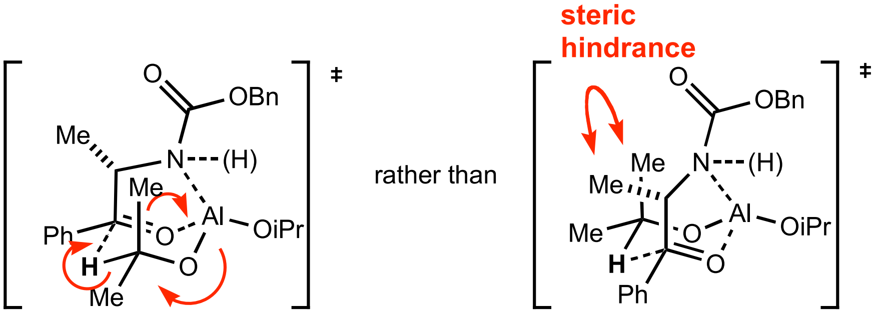
1a: X = BnO(C=O)-: dr > **99:1**
1b: X = *p*-MePhSO$_2$-: dr = 82:18

Part A (10 points): Explain the reactions of **1a-b** using clear 3D-drawings. Discuss the role of the nitrogen substituents. Note that **no racemization** was observed during the reaction!

- The highly diastereoselective reduction of **1a** can be explained by a transition state in which the nitrogen acts as a donor atom -> *chelate control.* The existing stereocenter determines the diastereoselectivity.

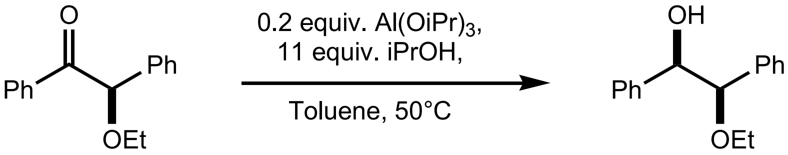
Meerwein-Ponndorf-Verley (MVP) reduction

transfer-hydrogenation in which IPA acts as the hydride source.



1b reacts less selectively. A tosyl group is a stronger acceptor compared to a Cbz-group reducing the donor strength of the nitrogen atom. Thus the chelate can be expected to be weaker.

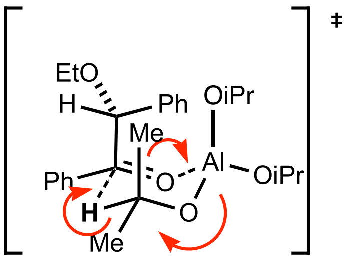
Part B (5 points): Subjecting ether **2** to the same conditions, the *syn*-product was obtained with high selectivity. Provide a 3D transition state drawing that explains this selectivity.



2

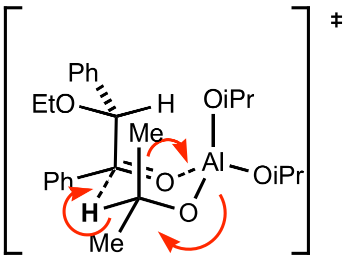
dr = 95.5:4.5

The high syn/anti ratio of this MVP is surprising as the alkoxide is a commonly used chelating group. However, the experimental outcome tells us, that it apparently does not chelate under the chosen reaction conditions (alcohol, elevated temperature). Thus, use the Cornforth (or Polar Felkin-Anh) model and envision the Al-IPA-reagent as a bulky hydride:



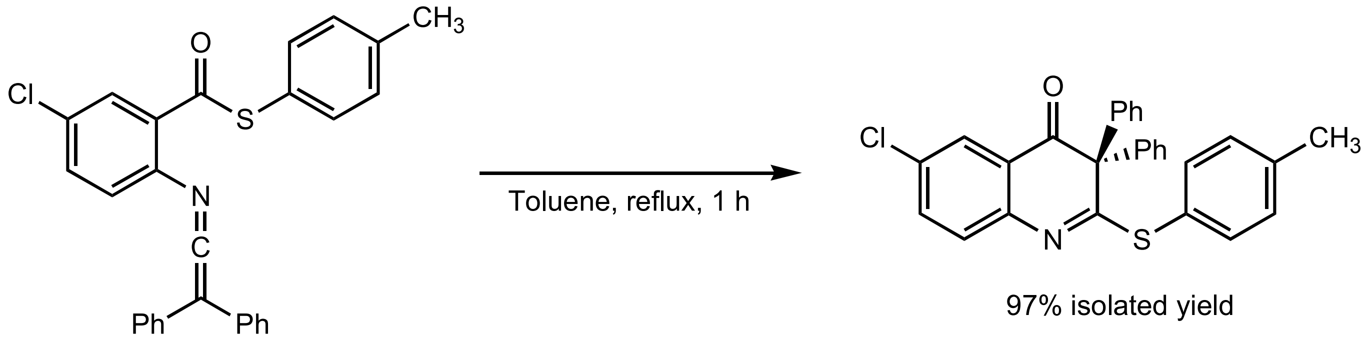
polar Felkin-Anh model

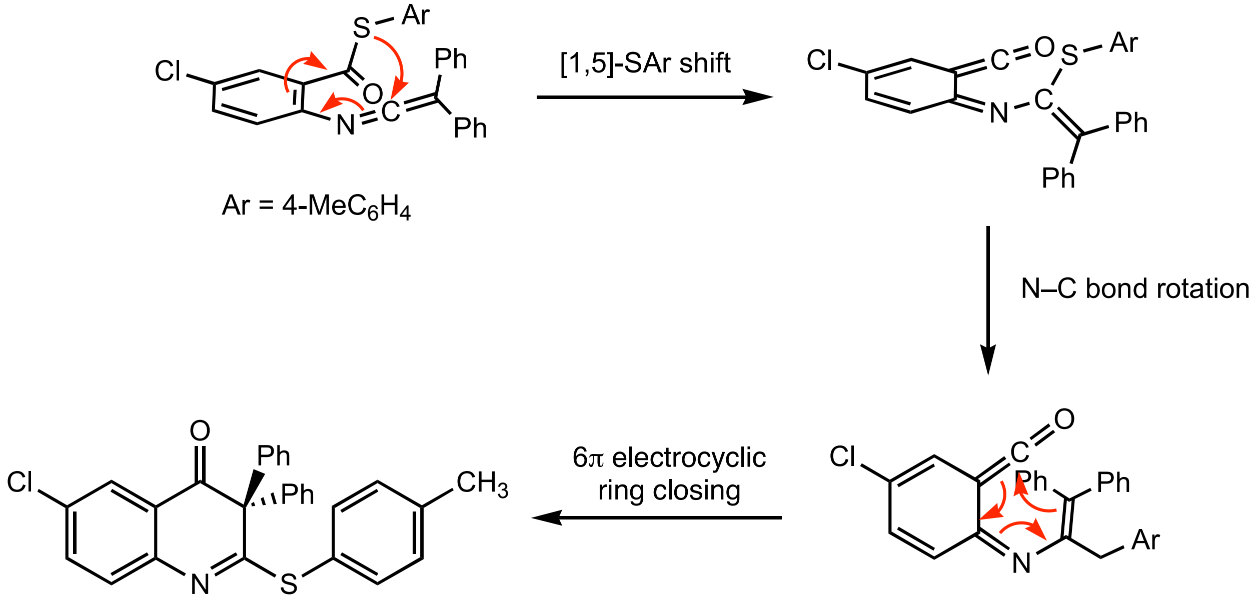
or



Cornforth model

Question 7. (10 points). The quinolinone synthesis depicted below was recently reported by Alajarín and coworkers (*J. Org. Chem.* **2006**, *71*, 8126-8139). Please provide a mechanism for this transformation.

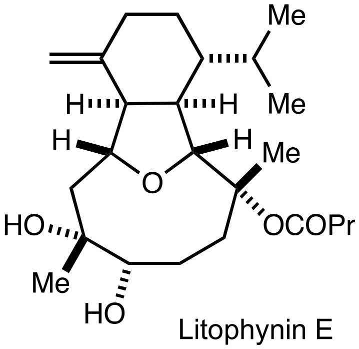




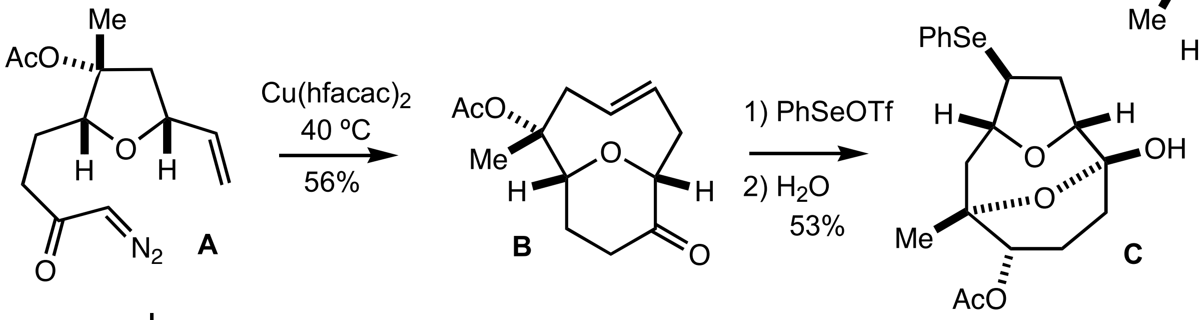
Tandem Pseudopericyclic Reactions: [1,5]-X Sigmatropic Shift/6π-Electrocyclic Ring Closure Converting *N*-(2-X-Carbonyl)phenyl Ketenimines into 2-X-Quinolin-4(3*H*)-ones. Alajarín, M.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, Á. *J. Org. Chem.* **2006**, *71*, 8126-8139.

Question 8. (15 points). In a recent report of the synthetic studies towards cladiellins (Clark *et al. Synlett* **2006**, *14*, 2191) the depicted below transformations were used to construct the macrocycle of litophynin E.

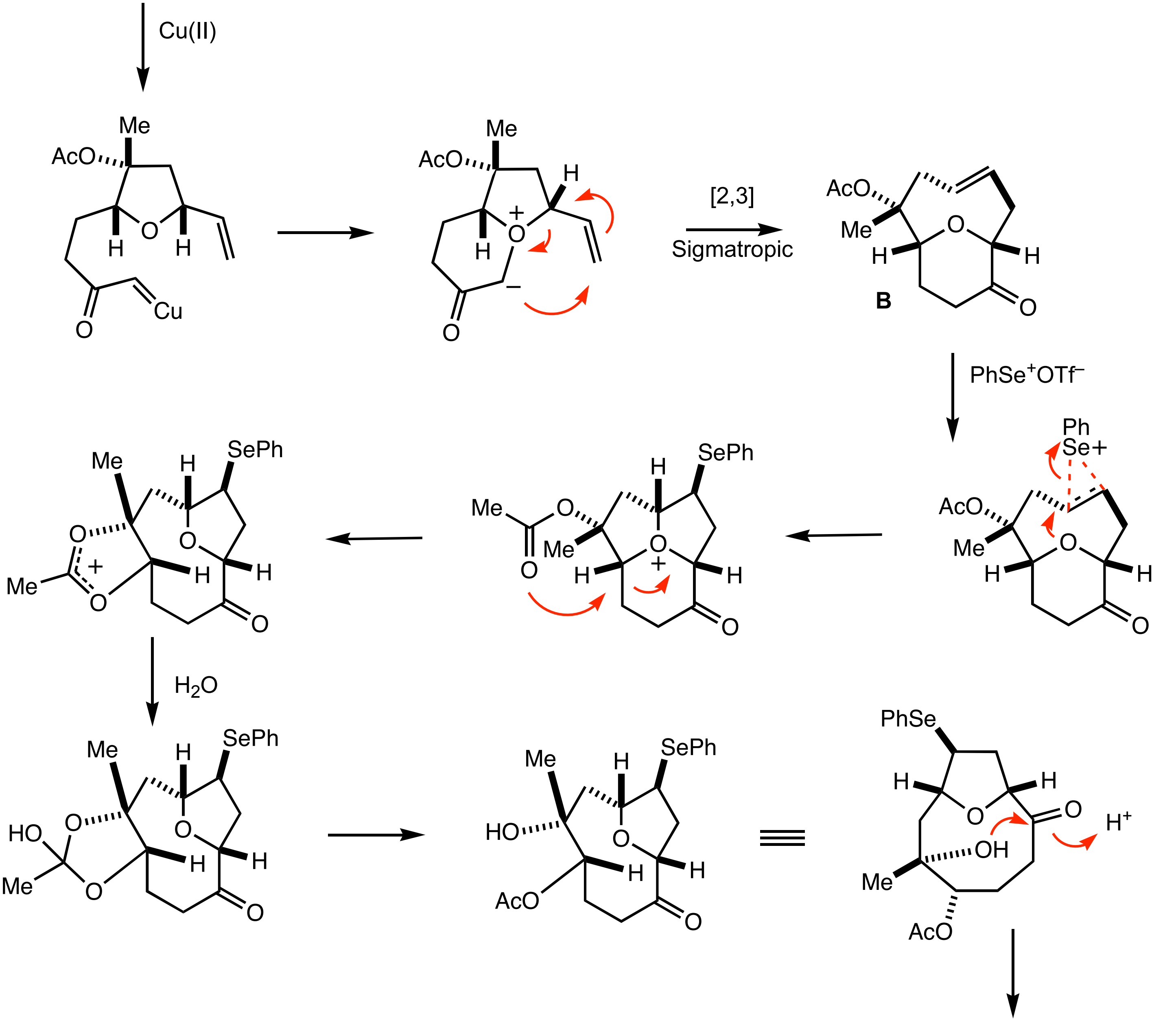
Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism for these transformations.



Litophynin E



A **B** **C**



C

Chemistry 206
Third Hour Examination

D. A. Evans

December 18, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (10)	______
No. 4 (10)	______
No. 5 (10)	______
No. 6 (20)	______
No. 7 (10)	______
No. 8 (15)	
Total (100)	

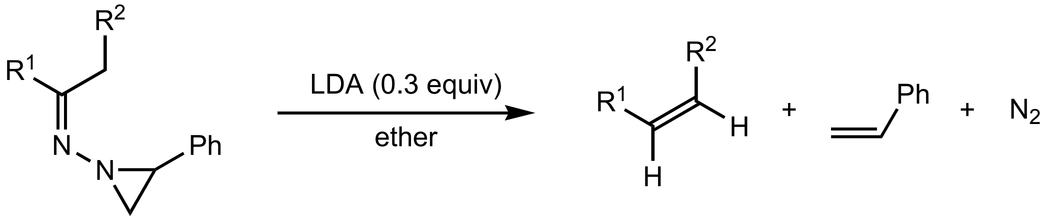
You have two hours to complete the exam
10:05 am to 12:05 pm

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

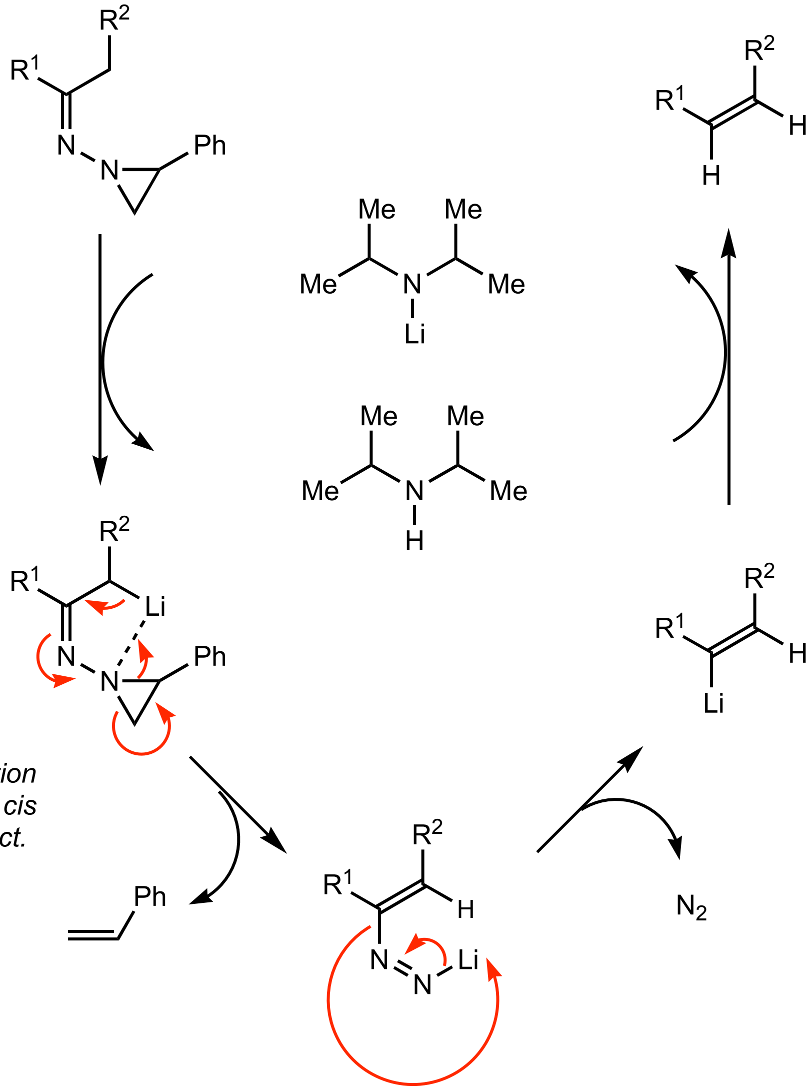
Be certain to address stereochemical and stereoelectronic issues where appropriate. This examination has nine pages.

Answer Key

Question 1. (10 points). In 1996, Maruoka and Yamamoto published the illustrated reaction of ketone phenylaziridinylhydrazones with catalytic amounts of lithium amides (*J. Am. Chem. Soc.* **1996**, *118*, 2289-2290).

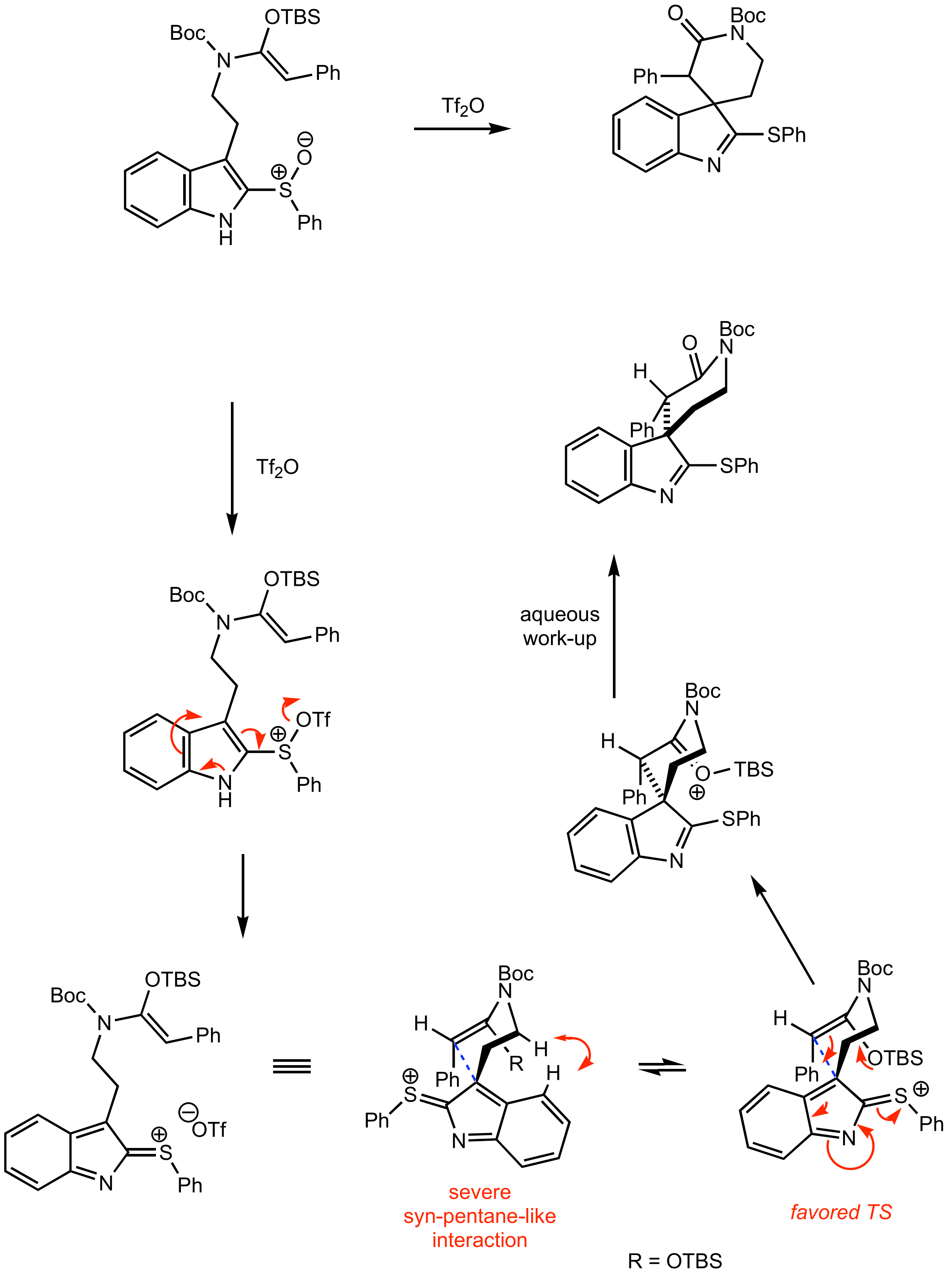


Provide a plausible mechanism that accounts for the observed *cis* selectivity and explain why 0.3 equivalents of LDA is enough to accomplish this transformation.

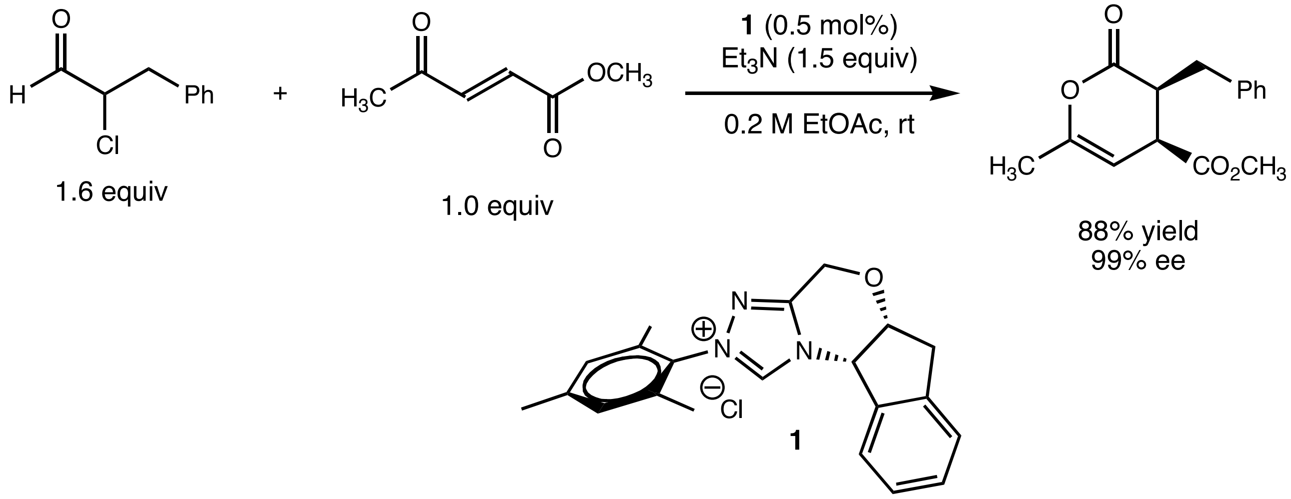


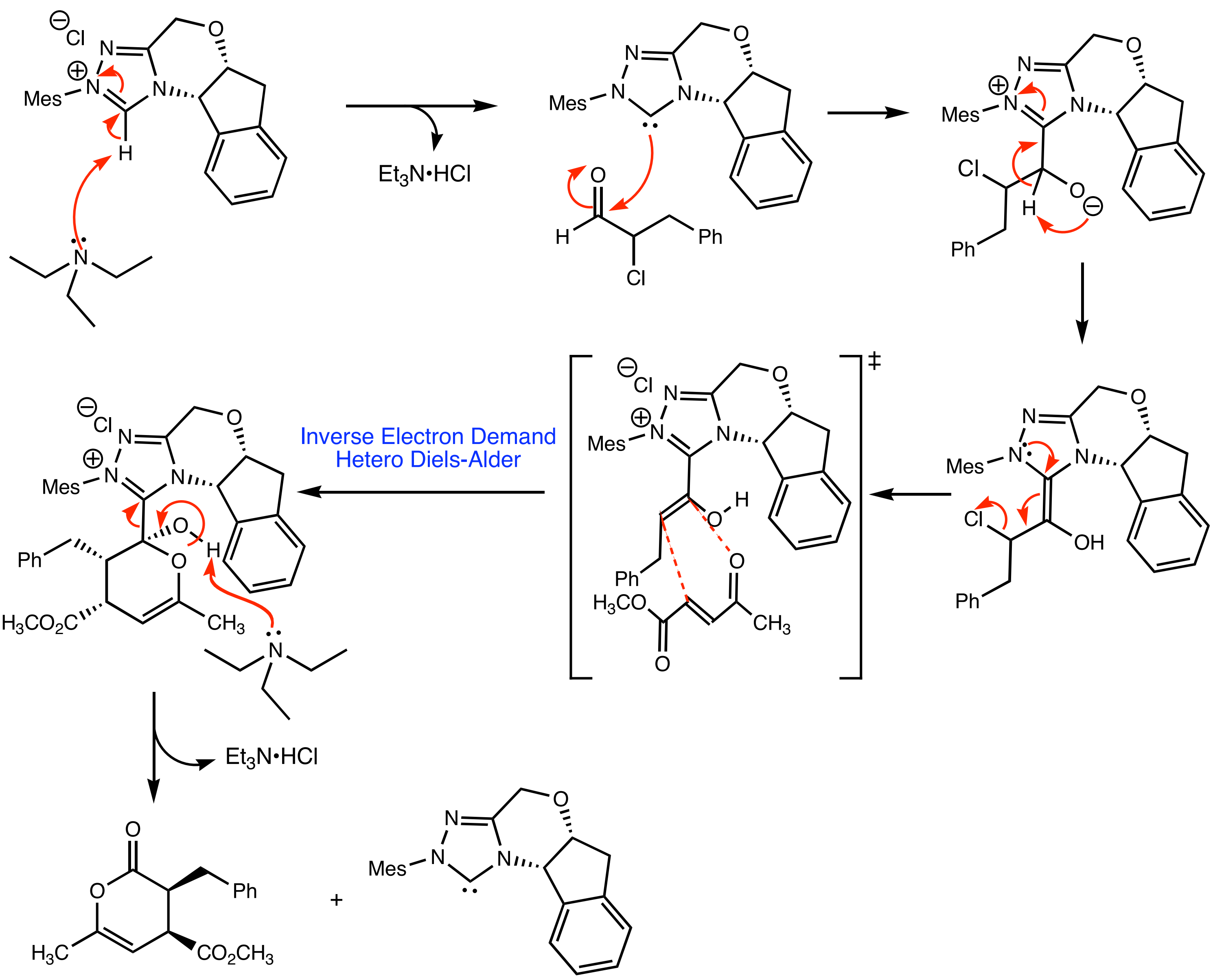
This internal chelation explains the excellent cis selectivity of the product.

Question 2. (15 points). In 2004, Feldman and coworkers published a construction of 3,3-spirosubstituted oxindoles. (*Org. Lett*. **2004**, *6*, 1869-1871). Provide the reaction mechanism and predict the relative stereochemistry of the product. Explain the origins of diastereoselectivity using clear 3D drawings.

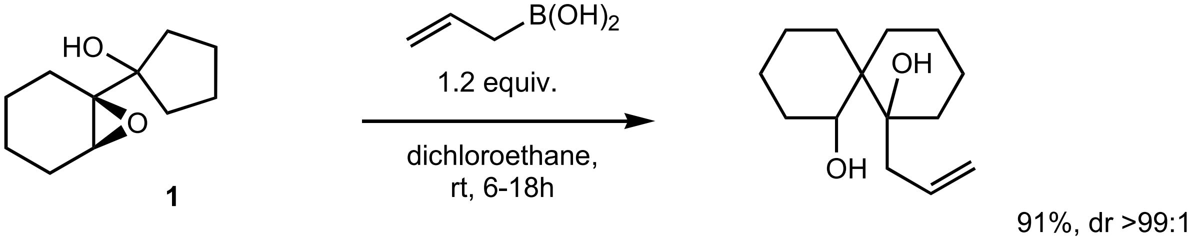


Question 3. (10 points). The transformation depicted below was recently reported by Bode and coworkers (*J. Am. Chem. Soc.* **2006**, *128*, 15088-15089.). Provide a mechanism for this transformation that accounts for the observed **relative** stereochemistry. **The absolute stereochemistry of the product does not need to be justified.**

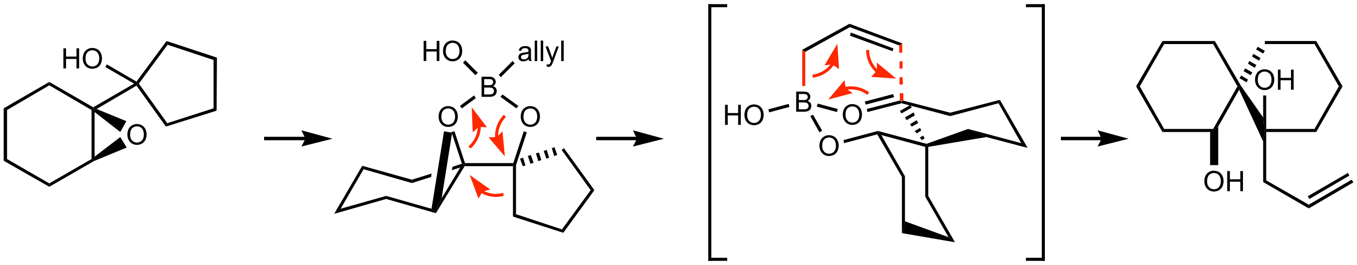




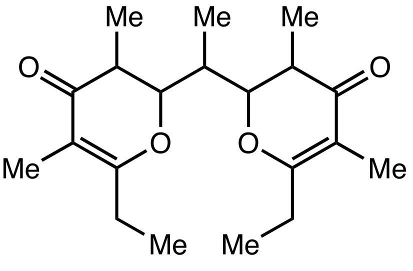
Question 4. (10 points). Tu *et al.* reported the following useful construction that could be used for a diastereoselective generation of the illustrated bicyclic structures with quaternary stereocenters. (*ACIEE* **2004**, *43*, 1702).



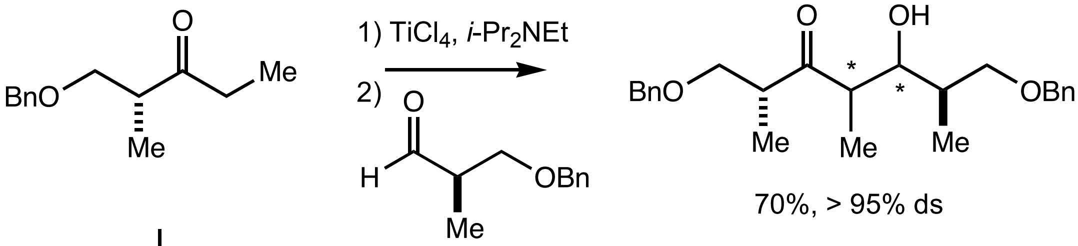
Please predict the absolute stereochemistry of the product and provide a mechanism that would support your predictions.



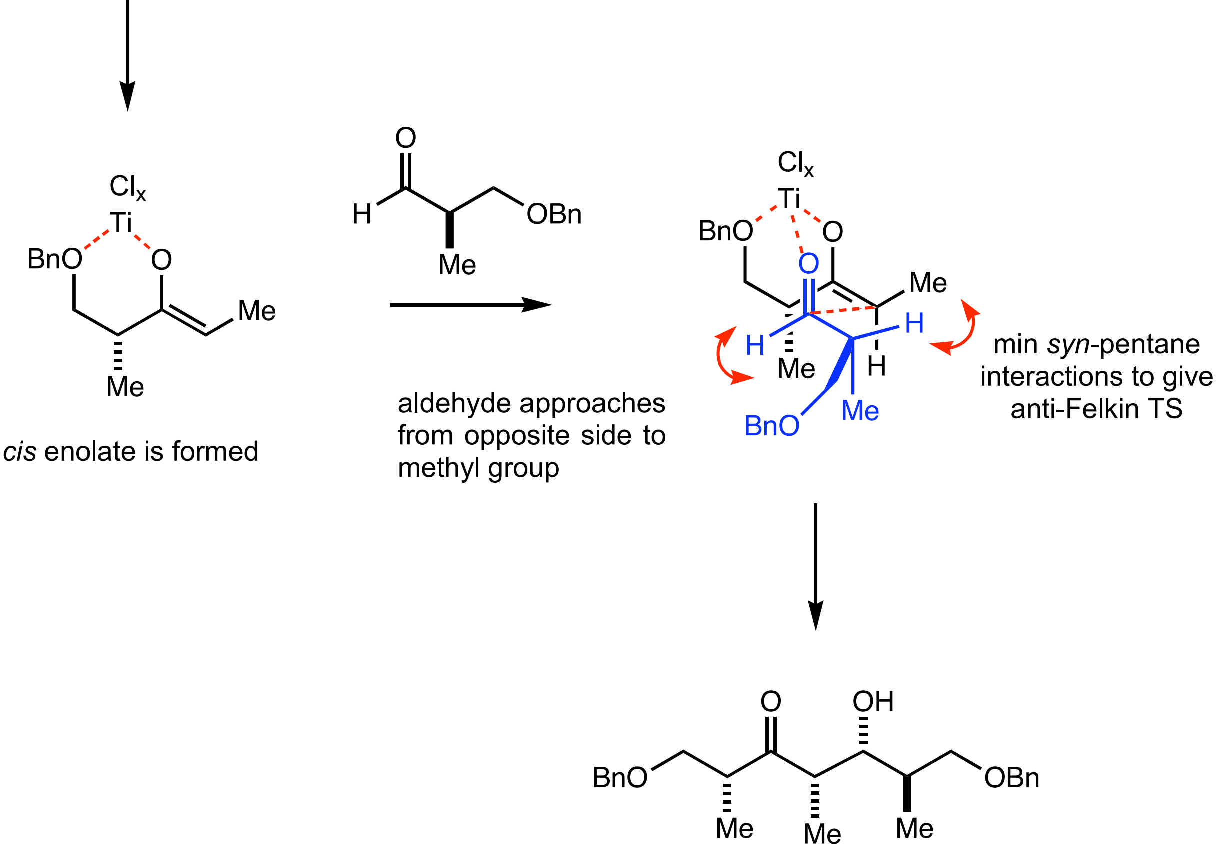
Question 5. (10 Points). The aldol addition reaction illustrated below was used to construct the core of the natural product (–)-membrenone-C (Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3*, 123-126). Provide the absolute stereochemistry of the product and show the transition state of this reaction with clear 3D drawings.



membrenone-C



70%, > 95% ds

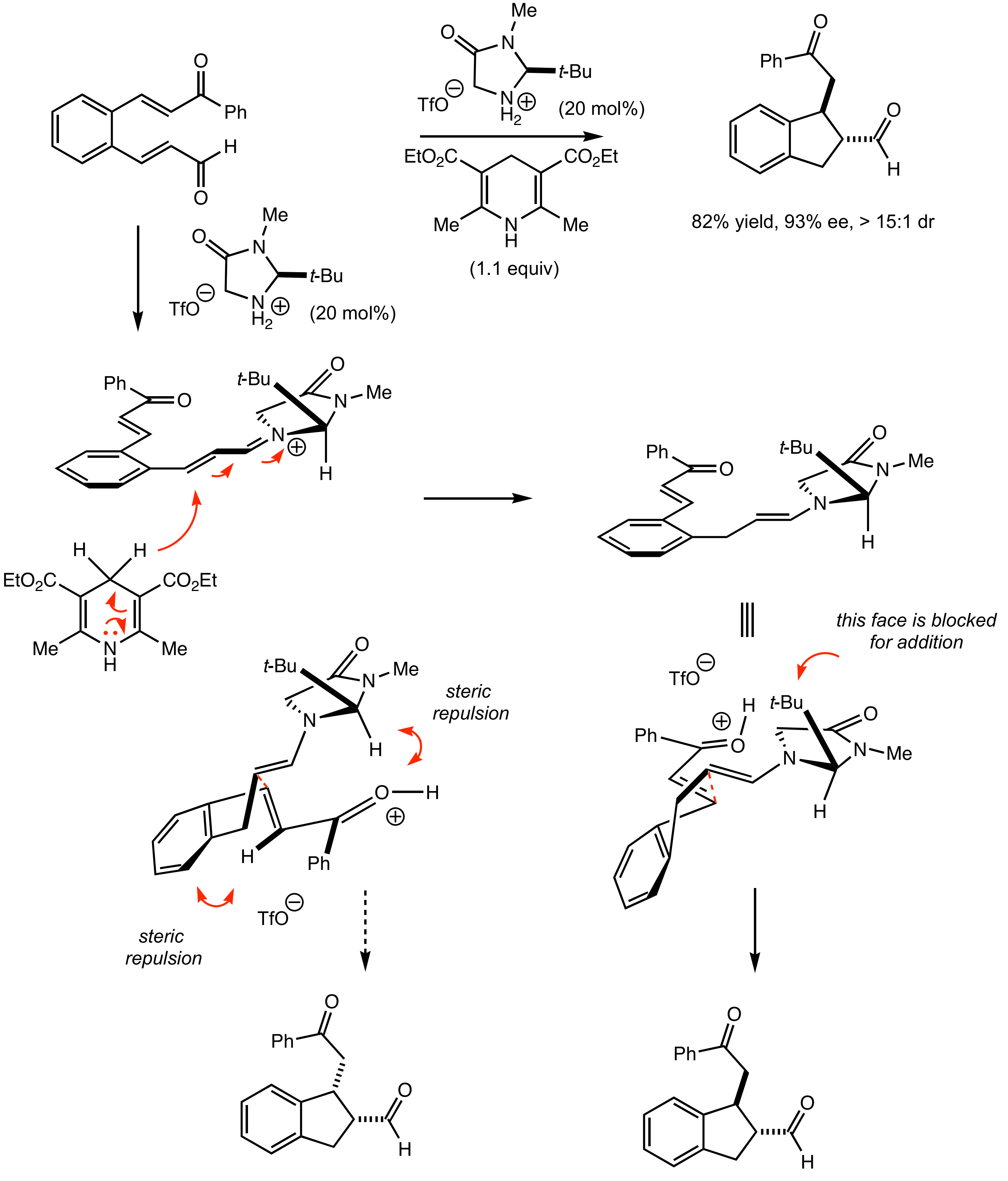


cis enolate is formed

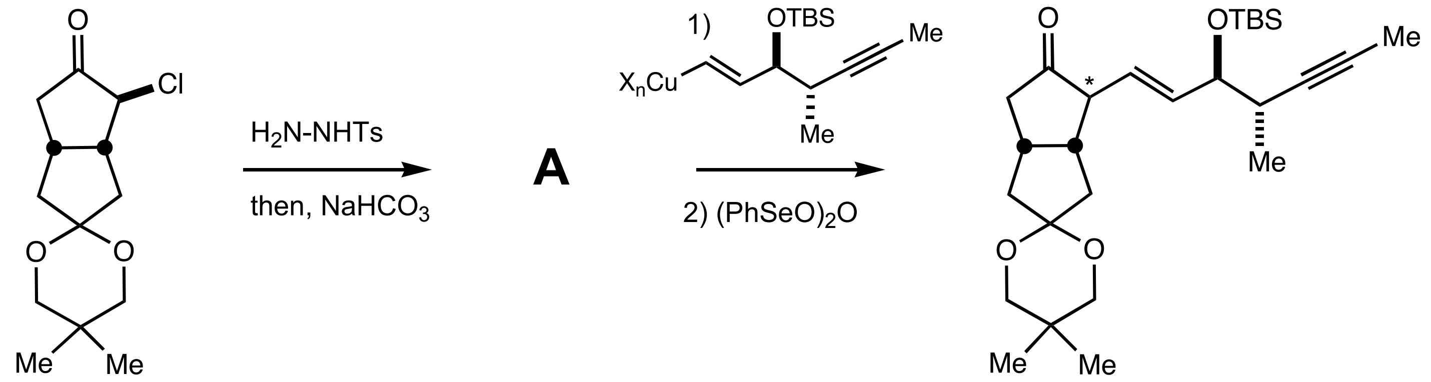
aldehyde approaches from opposite side to methyl group

min *syn*-pentane interactions to give anti-Felkin TS

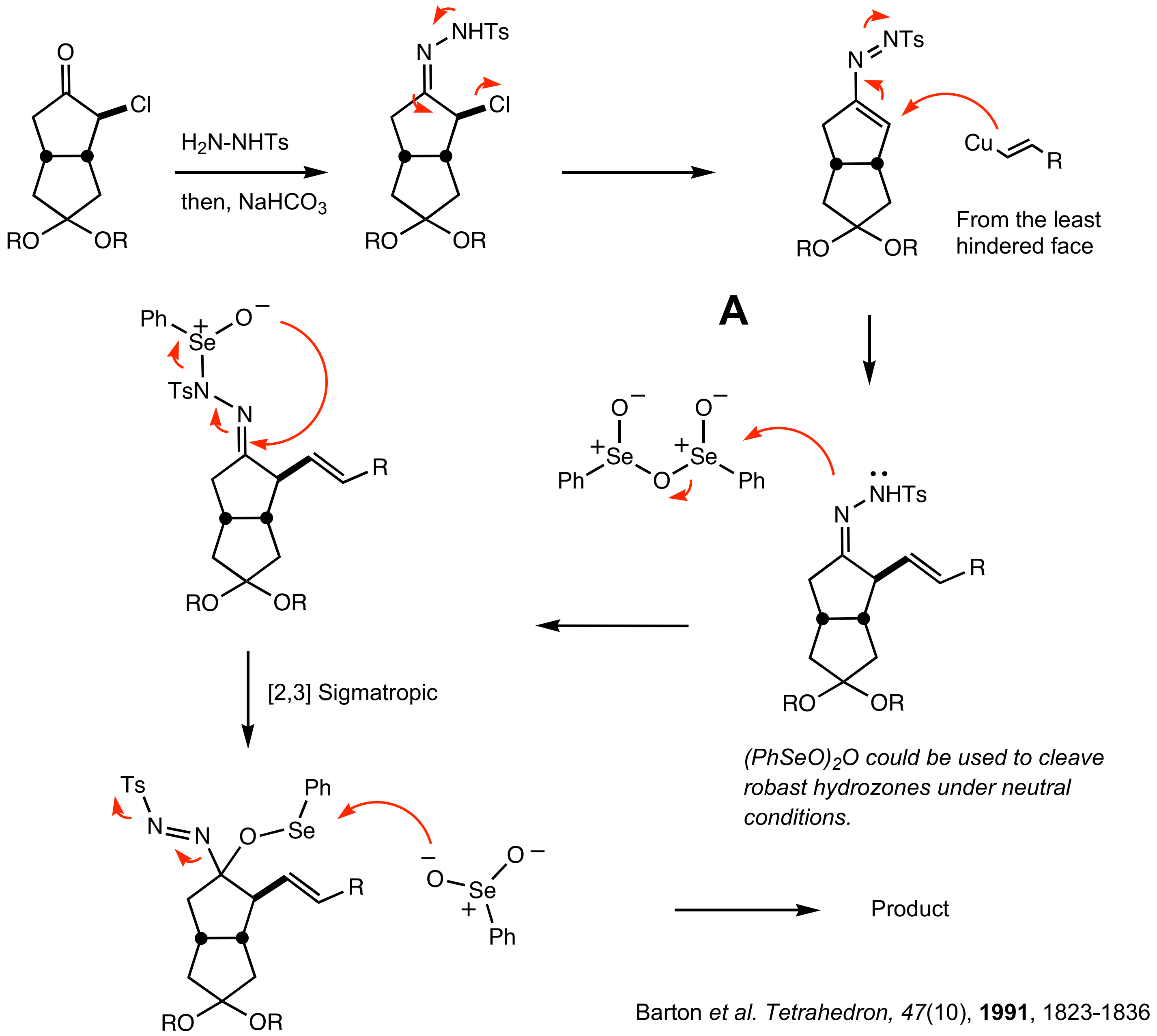
Question 6. (20 Points). The following tandem process was recently reported by the List group (*J. Am. Chem. Soc.* **2005**, *127*, 15036-15037). Please provide the mechanism for this transformation, predict the stereochemistry of the product and explain your predictions with clear 3D drawings.



Question 7. (10 points). The following sequence has recently been developed during the synthesis of Prostacyclin (Gais *et al. JACS* **2005**, *ASAP*).



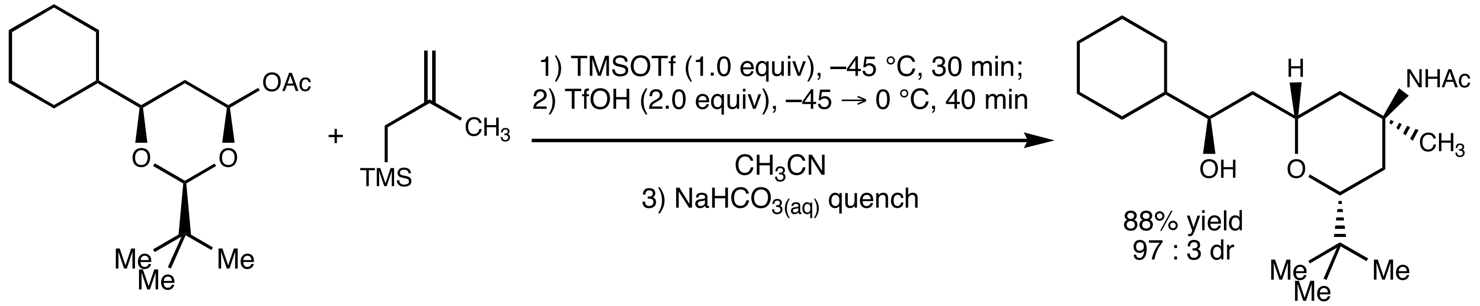
Please provide the structure of compound **A**, absolute stereochemistry of the product and mechanism for the transformation above. *You do not need to provide the mechanism for the $(PhSeO)_2O$ step.*

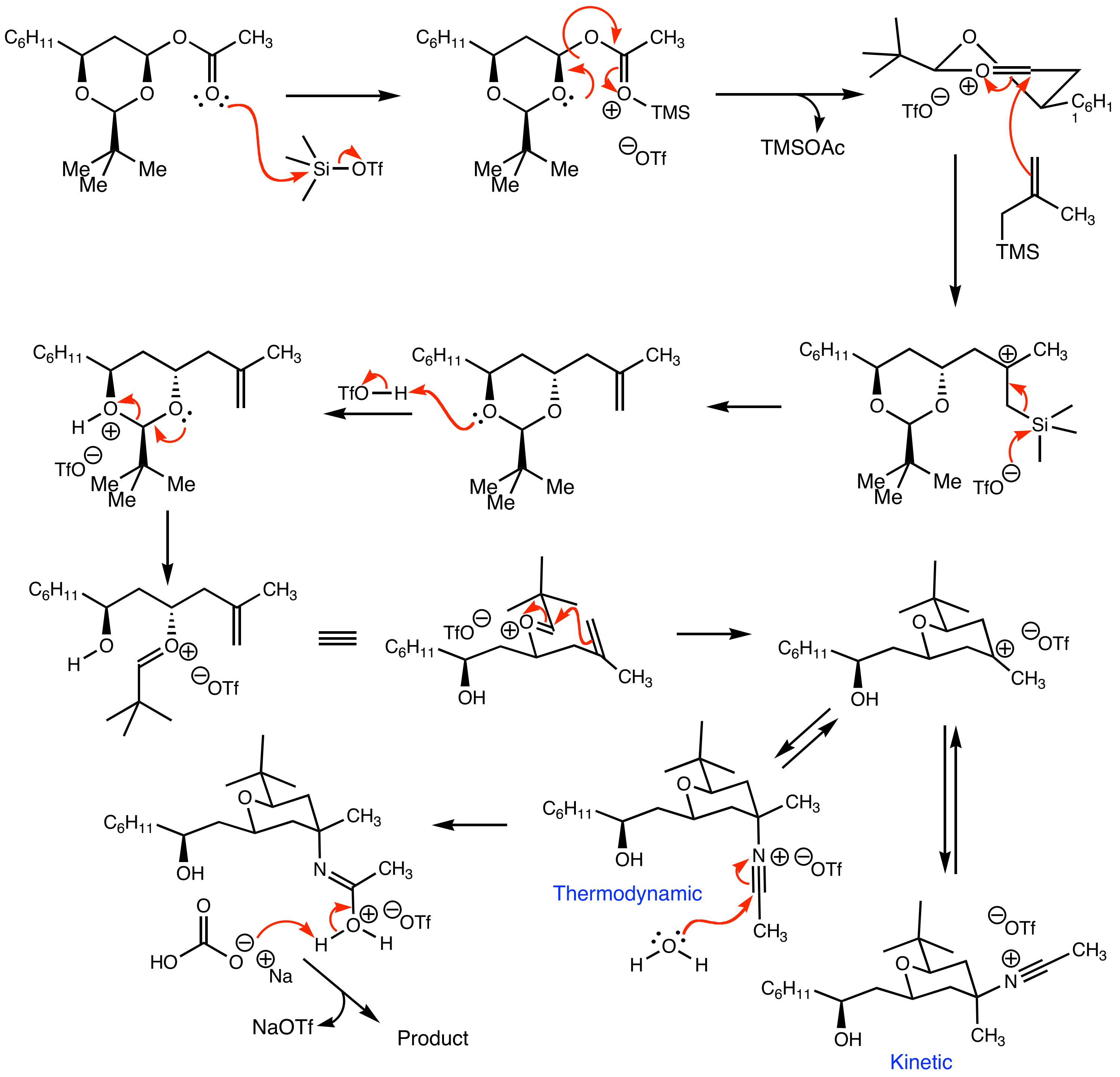


$(PhSeO)_2O$ could be used to cleave robast hydrozones under neutral conditions.

Barton *et al. Tetrahedron, 47*(10), **1991**, 1823-1836

Question 8. (15 points). The transformation depicted below was recently reported by Rovis and coworkers (Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, ASAP). Provide a mechanism for this transformation that accounts for the observed diastereoselectivity.


OAc
+
CH3
TMS
1) TMSOTf (1.0 equiv), –45 °C, 30 min;
2) TfOH (2.0 equiv), –45 → 0 °C, 40 min
CH3CN
3) NaHCO3(aq) quench
Me
Me
Me
H
NHAc
CH3
OH
O
88% yield
97 : 3 dr



Chemistry 206
Second Hour Examination

D. A. Evans

November 20, 2006

Name (please print): ______________________
last first initial

Signature: ______________________

Teaching Fellow: ______________________

Question (pts)	Score
No. 1 (15)	______
No. 2 (10)	______
No. 3 (10)	______
No. 4 (15)	______
No. 5 (10)	______
No. 6 (15)	______
No. 7 (10)	______
No. 8 (15)	
Total (100)	

You have two hours to complete the exam
10:05 am to 12:05 pm

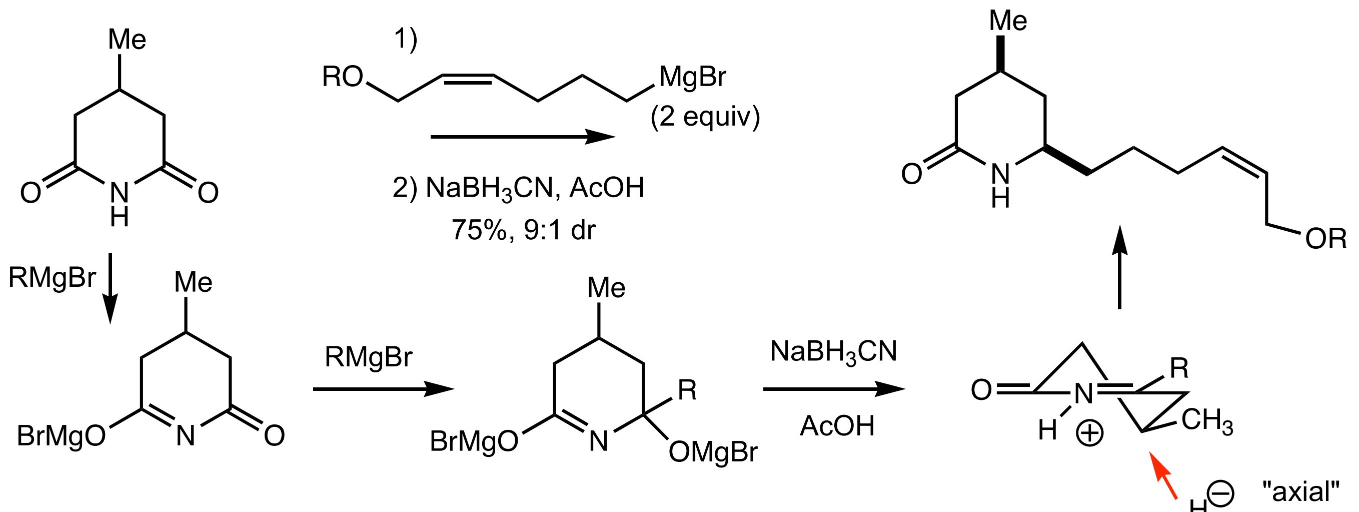
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate. This examination has nine pages.

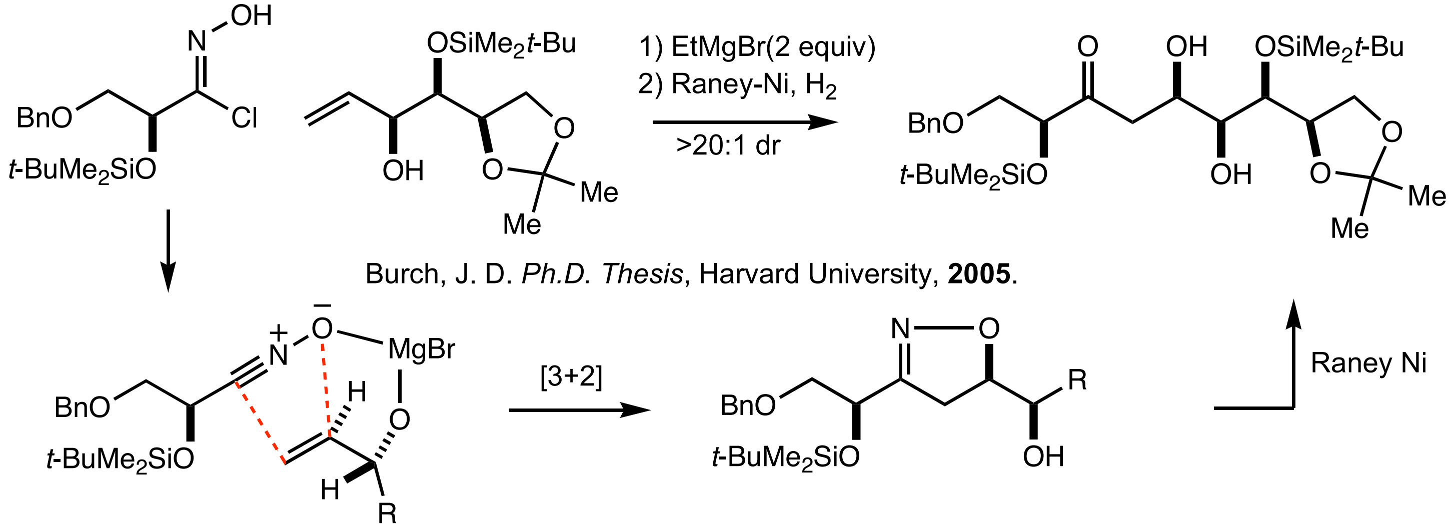
Evam Average: 62
High Grade: 98

Answer Key

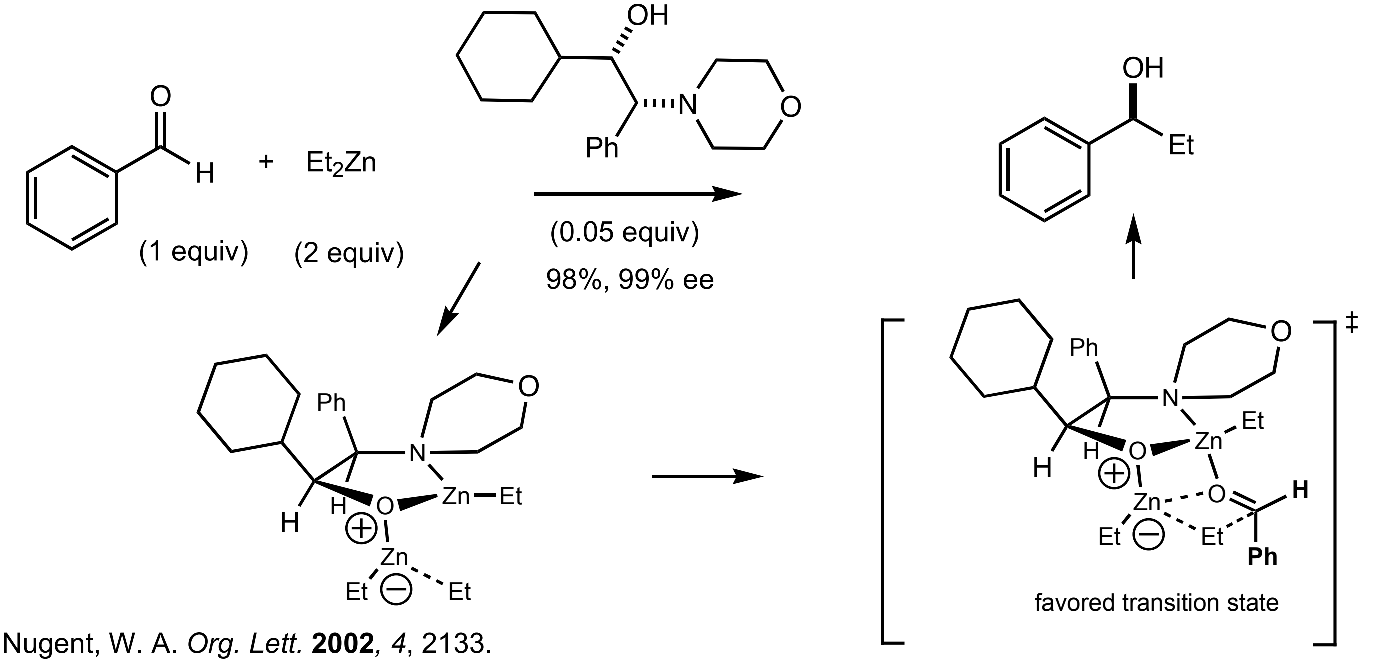
Question 1. (15 points). Predict the products for the transformations below. Also, provide mechanisms with the appropriate 3D models that explain your answer.



Gerasyuto, A. I.; Hsung, R. P. *Org.Lett.* **2006**, *8*, 4899-4902.

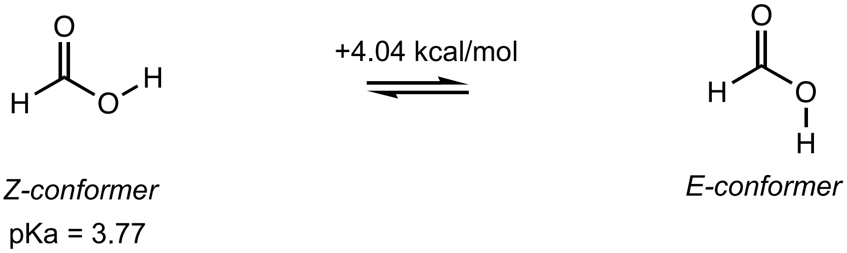


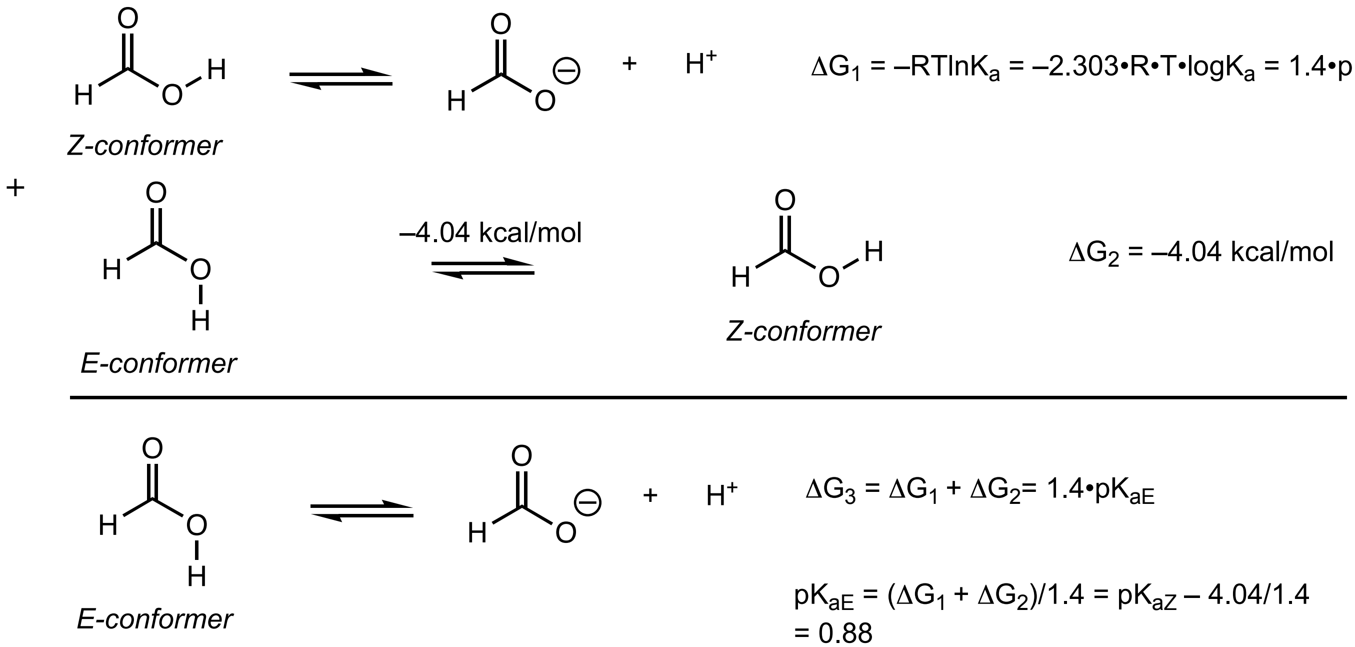
Burch, J. D. *Ph.D. Thesis*, Harvard University, **2005**.



Nugent, W. A. *Org. Lett.* **2002***,* *4*, 2133.

Question 2. Part A (7 points). A carboxylic acid can exist in two conformations *E* and *Z* that are different by the dihedral angle around the C–O bond. Recent theoretical calculations demonstrated that the *Z* isomer of formic acid is more stable by 4.04 kcal/mol (Ratajczyk *et al. Tetrahedron* **2004**, *60*, 179-185). Assuming that the pK_a of the *Z* isomer of formic acid is equal to 3.77 calculate the pK_a of the *E* isomer of formic acid. Assume that $\Delta G = 1.4\cdot pK_a$ kcal/mol.





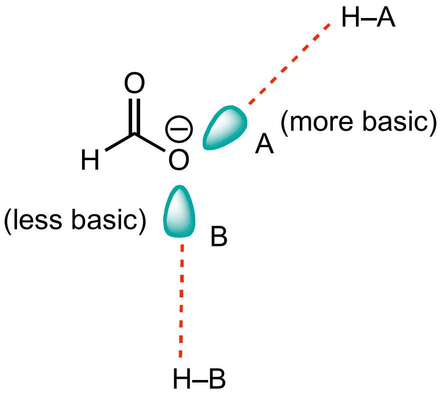
$\Delta G_1 = -RT\ln K_a = -2.303\cdot R\cdot T\cdot \log K_a = 1.4\cdot pK_{aZ}$

$\Delta G_2 = -4.04$ kcal/mol

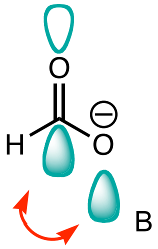
$\Delta G_3 = \Delta G_1 + \Delta G_2 = 1.4\cdot pK_{aE}$

$pK_{aE} = (\Delta G_1 + \Delta G_2)/1.4 = pK_{aZ} - 4.04/1.4$
$= 0.88$

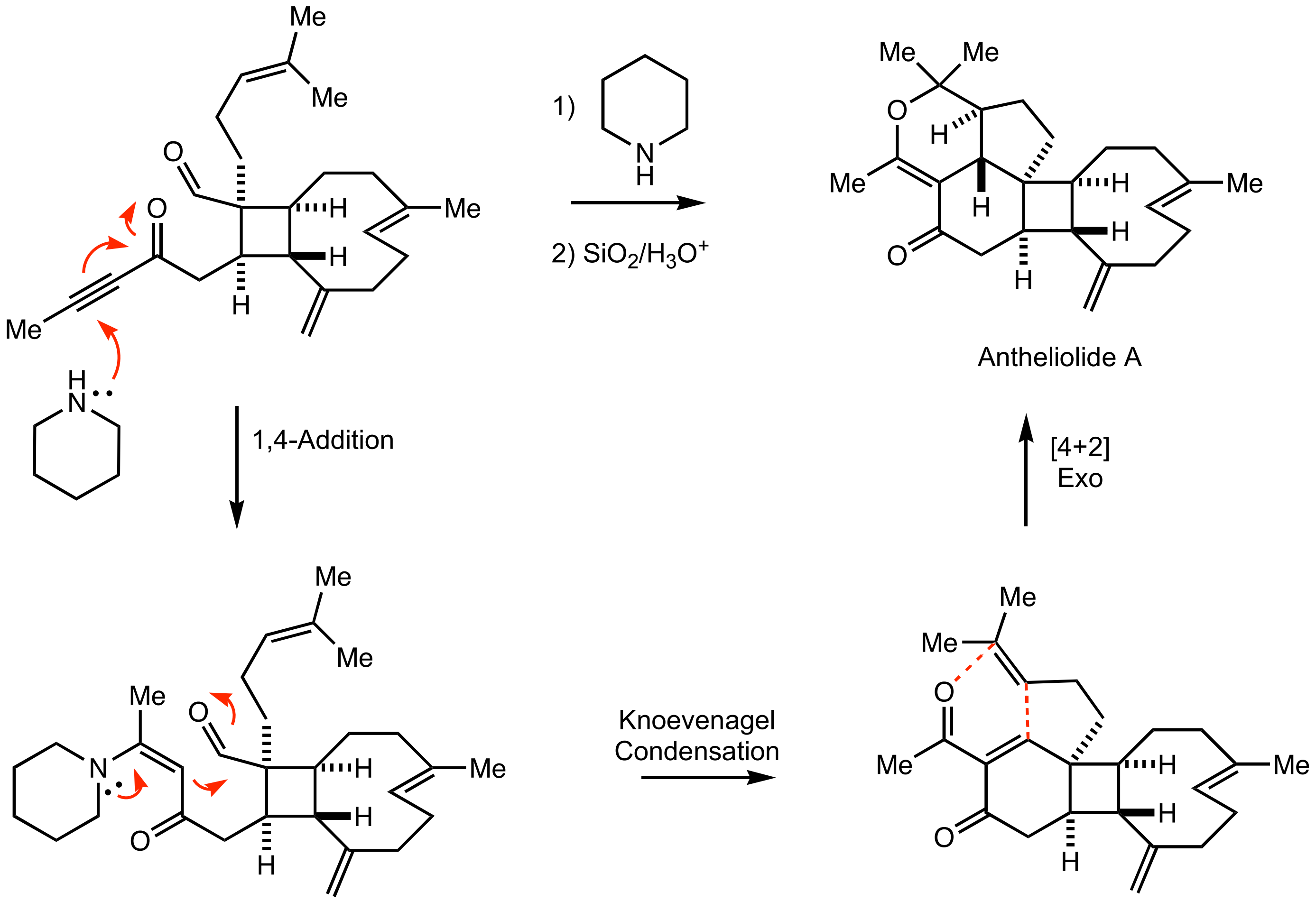
Part B (3 points). Based on your calculations propose which lone pair of the carboxylate anion shown below is going to be more basic. Is the FMO theory consistent with your answers?



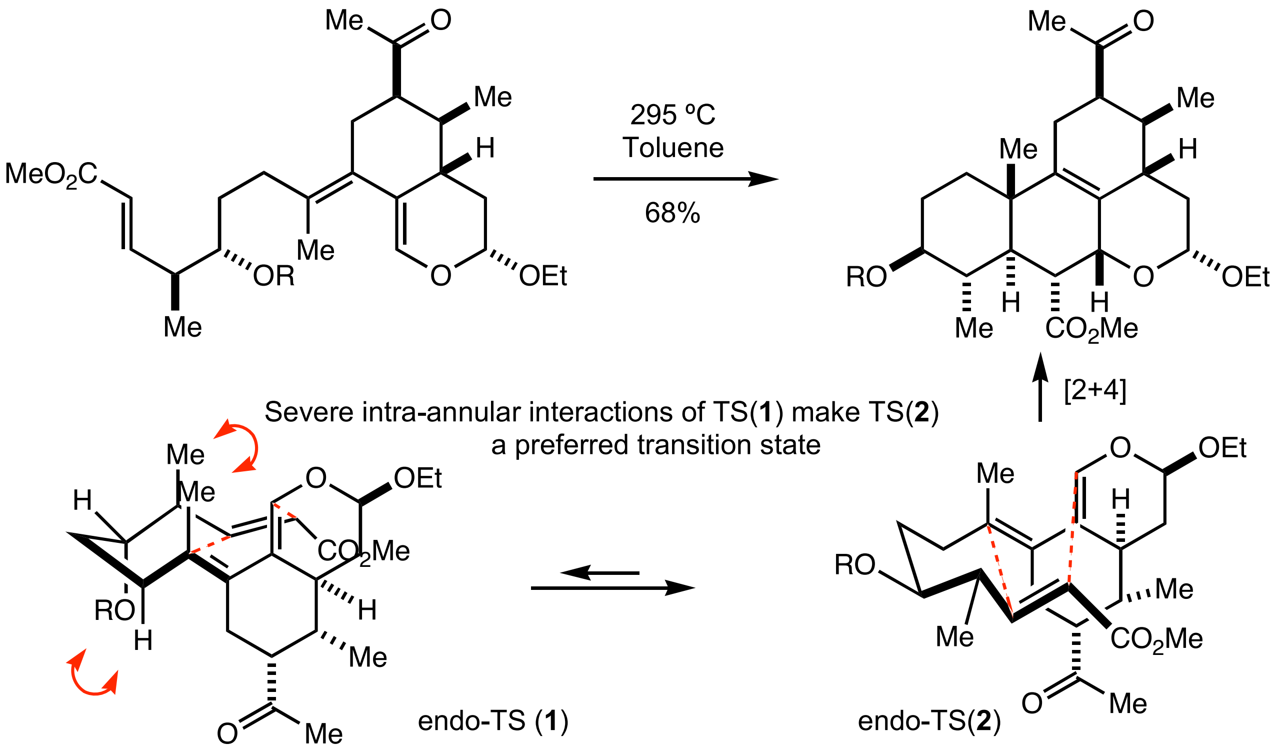
Our calculations are consistent with the FMO theory. Lone pair B can interact with σ^*(C=O) while lone pair A can overlap with σ^*(C–H). The former is a better acceptor that withdraws the electron density from the lone pair B and makes it less basic.



Question 3. (10 points). Recently, the sequence of reactions outlined below was used by Corey et al. (*JACS* **2006**, *128*, 14050) in their route to antheliolide A. Provide a mechanism for this reaction and explain the stereochemistry of the product.

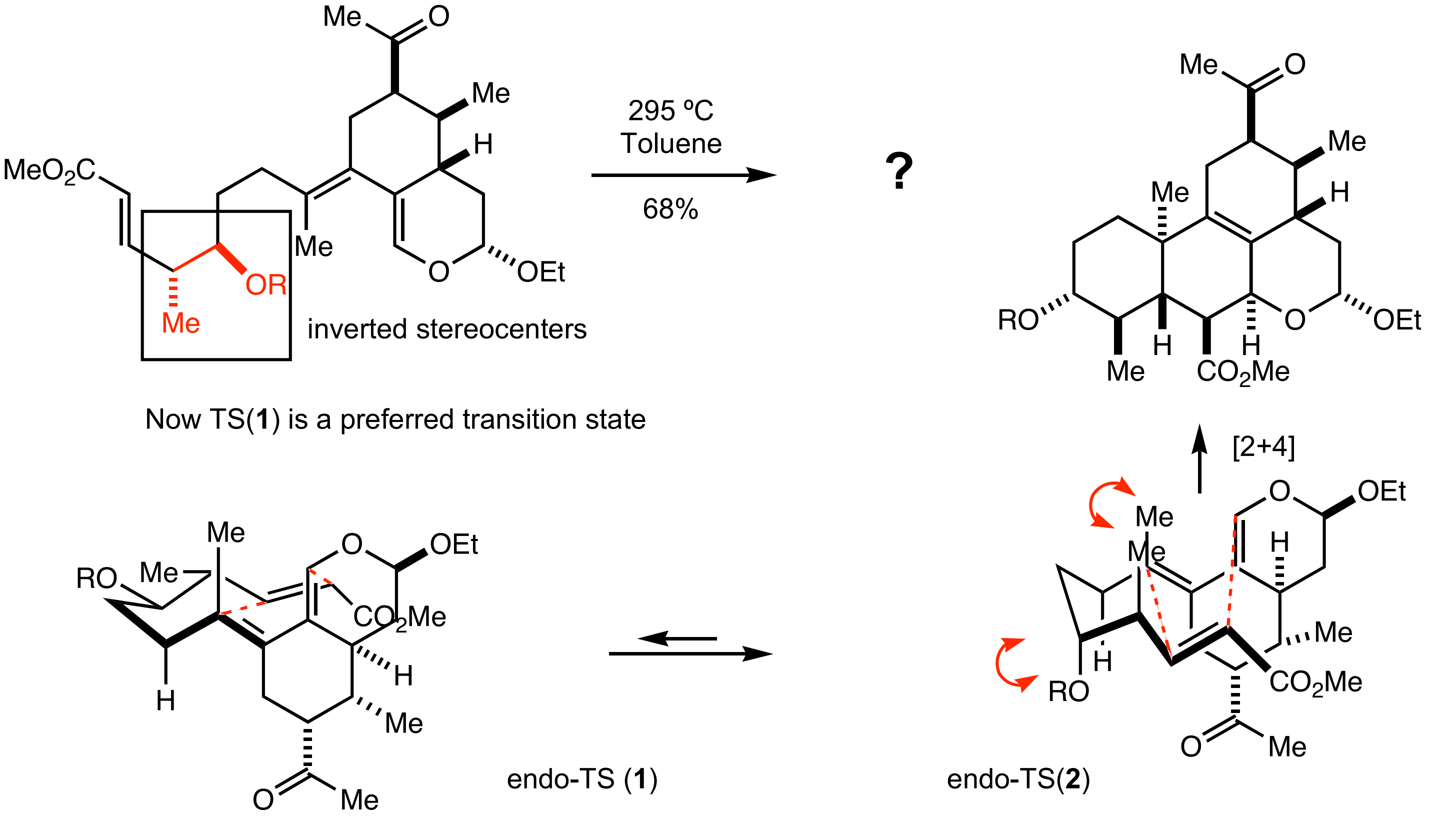


Question 4. Part A. (5 points). The following cycloaddition reaction was recently explored by Spino and Perreault (*Org. Lett.* ***2006***, *8*, 4385.) Provide a reasonable transition state that explains the stereochemistry of the product.



Severe intra-annular interactions of TS(**1**) make TS(**2**) a preferred transition state

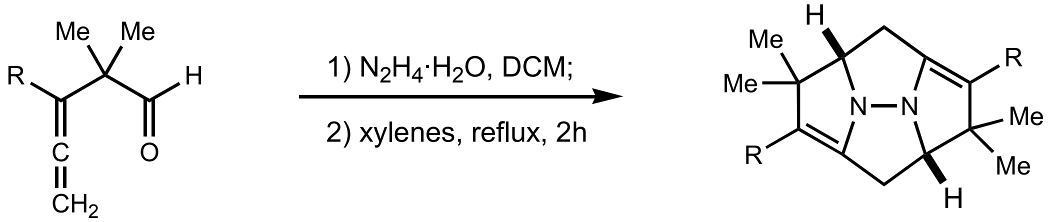
Part B. (10 points). Based on your solution above predict the stereochemical outcome of the cycloaddition carried out on the diastereomeric compound shown below. Use clear 3D drawing to explain your answer.

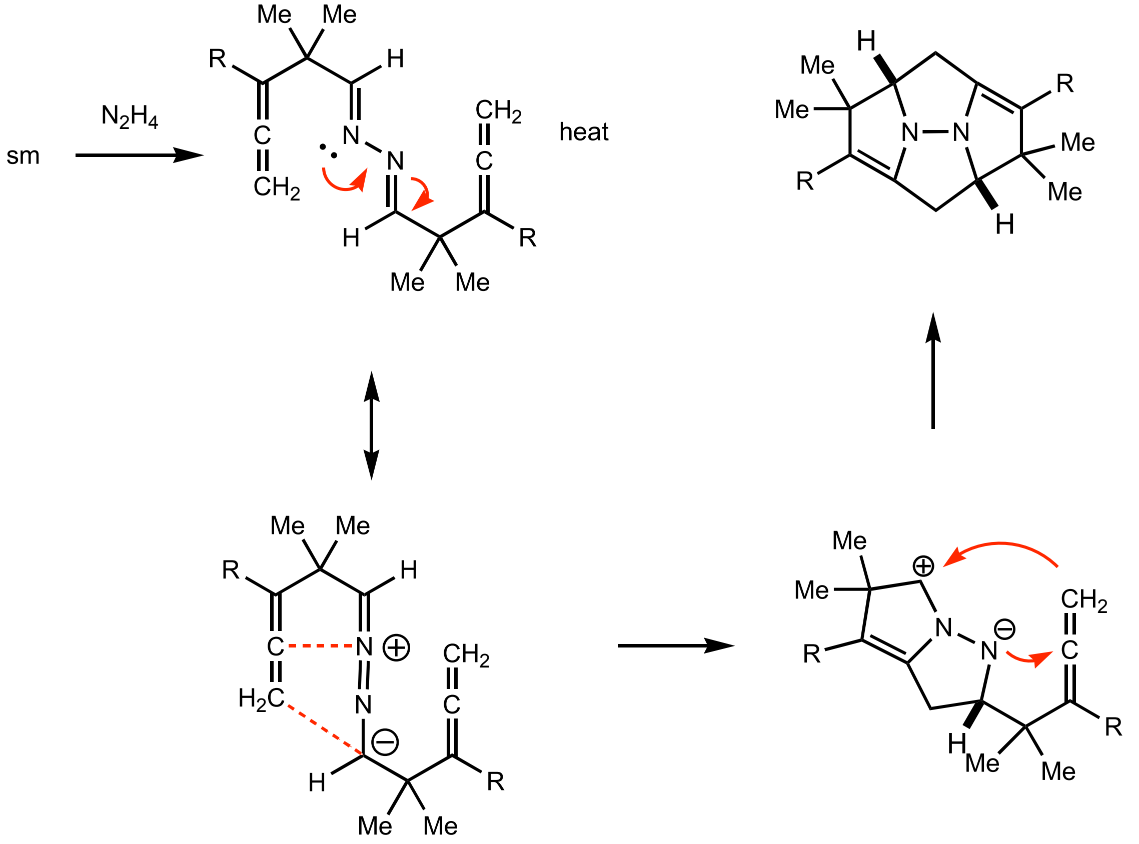


inverted stereocenters

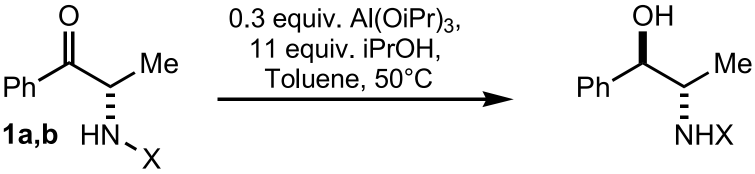
Now TS(**1**) is a preferred transition state

Question 5. (10 points). Provide a mechanism for the following reaction sequence recently published by the group of Potacek (*Eur. J. Org. Chem.* **2005**, 2548):





Question 6. (15 points). The Merck Research Laboratories have recently reported the following preparation of ephedrine analogues (*JOC* **2006**, *71*, 840):



1a,b

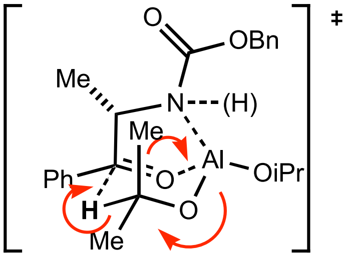
1a: X = BnO(C=O)-: dr > **99:1**
1b: X = *p*-MePhSO$_2$-: dr = 82:18

Part A (10 points): Explain the reactions of **1a-b** using clear 3D-drawings. Discuss the role of the nitrogen substituents. Note that **no racemization** was observed during the reaction!

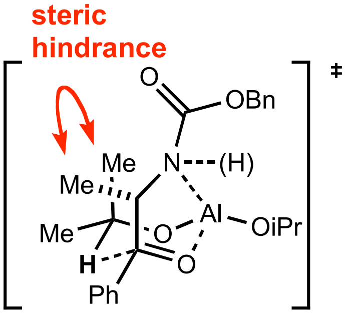
- The highly diastereoselective reduction of **1a** can be explained by a transition state in which the nitrogen acts as a donor atom -> *chelate control.* The existing stereocenter determines the diastereoselectivity.

Meerwein-Ponndorf-Verley (MVP) reduction

transfer-hydrogenation in which IPA acts as the hydride source.

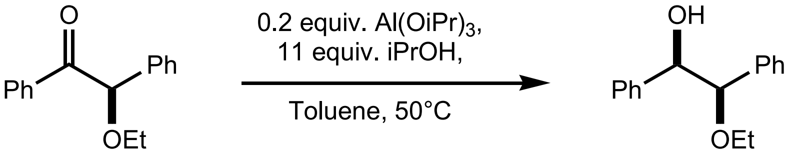


rather than



1b reacts less selectively. A tosyl group is a stronger acceptor compared to a Cbz-group reducing the donor strength of the nitrogen atom. Thus the chelate can be expected to be weaker.

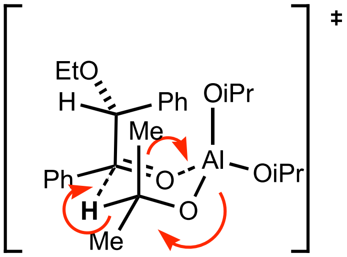
Part B (5 points): Subjecting ether **2** to the same conditions, the *syn*-product was obtained with high selectivity. Provide a 3D transition state drawing that explains this selectivity.



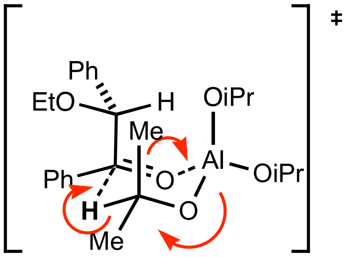
2

dr = 95.5:4.5

The high syn/anti ratio of this MVP is surprising as the alkoxide is a commonly used chelating group. However, the experimental outcome tells us, that it apparently does not chelate under the chosen reaction conditions (alcohol, elevated temperature). Thus, use the Cornforth (or Polar Felkin-Anh) model and envision the Al-IPA-reagent as a bulky hydride:



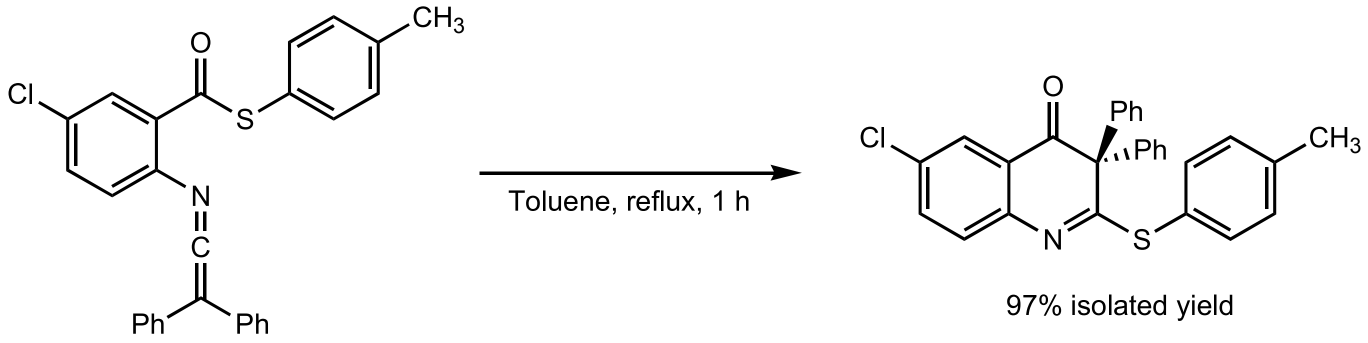
or

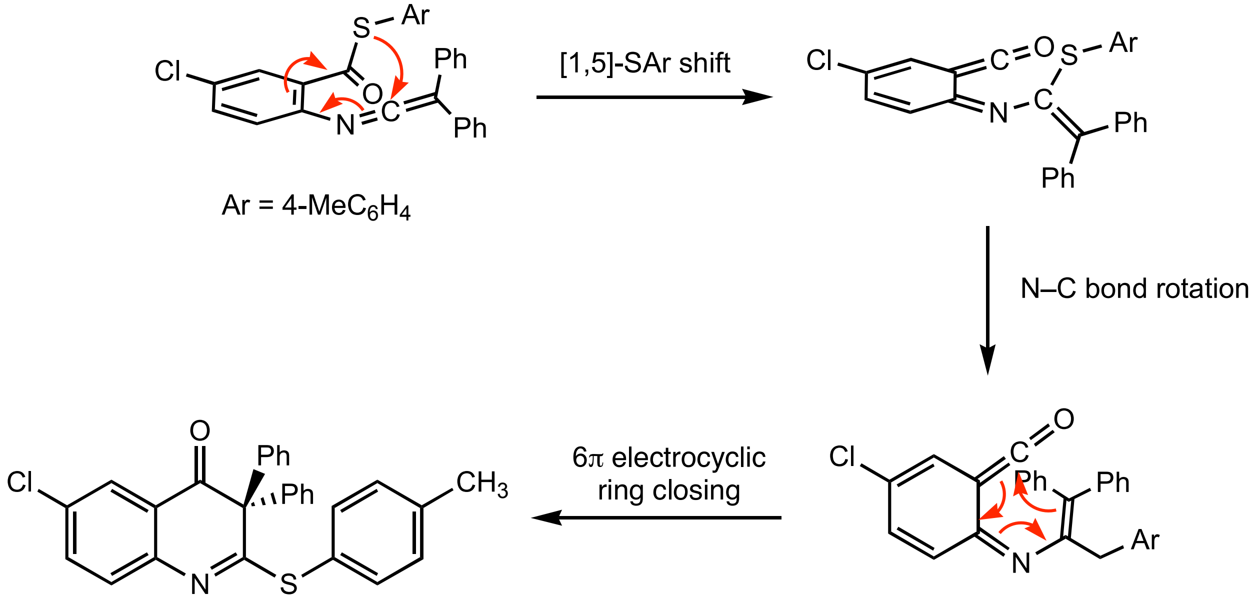


polar Felkin-Anh model

Cornforth model

Question 7. (10 points). The quinolinone synthesis depicted below was recently reported by Alajarín and coworkers (*J. Org. Chem.* **2006**, *71*, 8126-8139). Please provide a mechanism for this transformation.

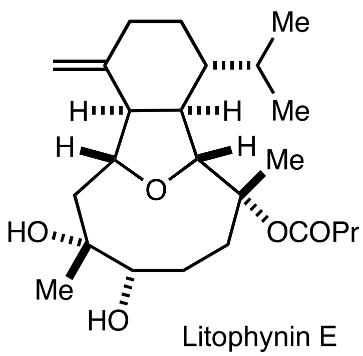




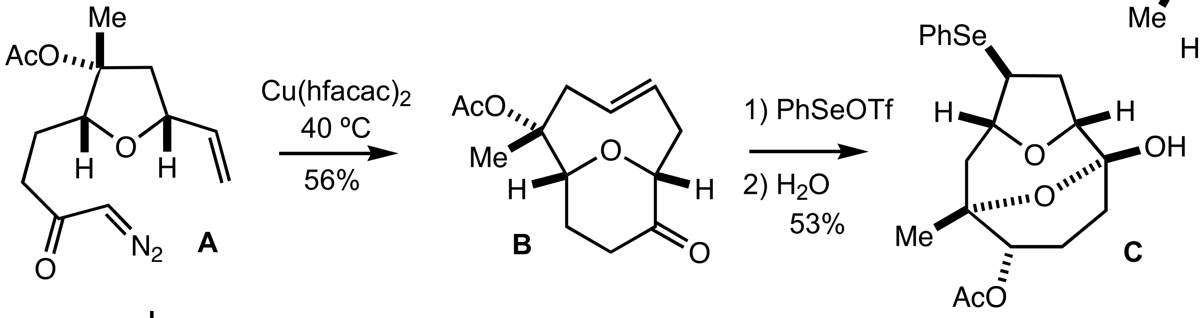
Tandem Pseudopericyclic Reactions: [1,5]-X Sigmatropic Shift/6π-Electrocyclic Ring Closure Converting *N*-(2-X-Carbonyl)phenyl Ketenimines into 2-X-Quinolin-4(3*H*)-ones. Alajarín, M.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, Á. *J. Org. Chem.* **2006**, *71*, 8126-8139.

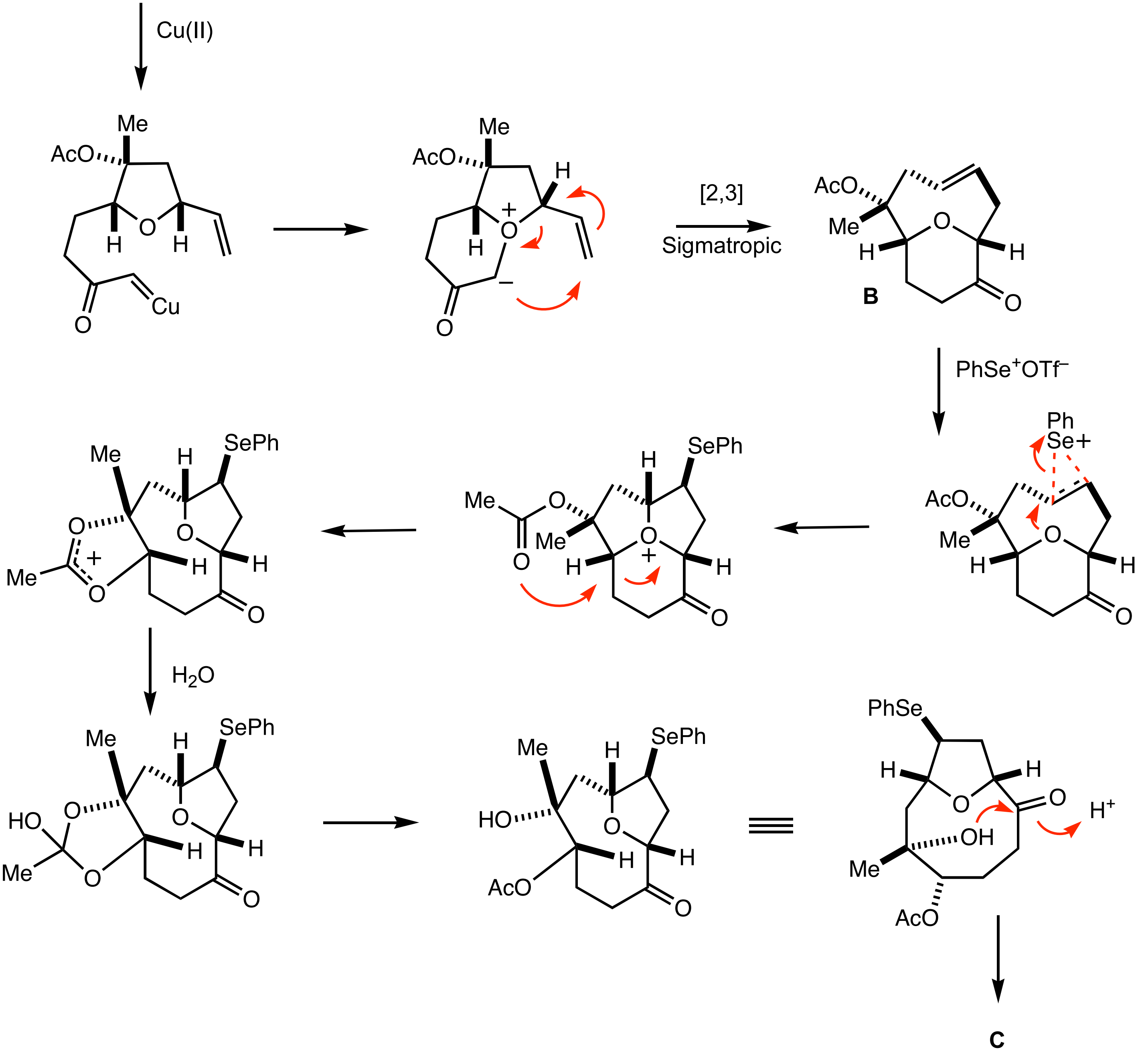
Question 8. (15 points). In a recent report of the synthetic studies towards cladiellins (Clark *et al.* *Synlett* **2006**, *14*, 2191) the depicted below transformations were used to construct the macrocycle of litophynin E.

Explain the formation of **B** from **A** and **C** from **B** by drawing a mechanism for these transformations.



Litophynin E





Chemistry 206
Final Examination

D. A. Evans
January 18, 2007

Name (please print): ______________________________
last first initial

Signature: ______________________________

Teaching Fellow: ______________________________

This examination contains **17** questions (17 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate.

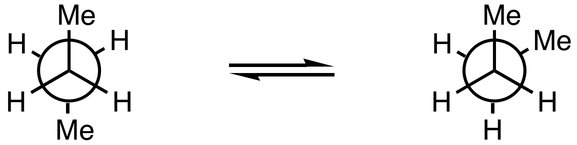
Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**15**)	______	No. 9 (**15**)	______
No. 2 (**15**)	______	No. 10 (**15**)	______
No. 3 (**20**)	______	No. 11 (**15**)	______
No. 4 (**20**)	______	No. 12 (**20**)	______
No. 5 (**20**)	______	No. 13 (**20**)	______
No. 6 (**20**)	______	No. 14 (**20**)	______
No. 7 (**20**)	______	No. 15 (**20**)	______
No. 8 (**15**)	______	No. 16 (**15**)	______
Subtotal (**145**)		No. 17 (**15**)	
		Subtotal (**155**)	

169

exam average

Total (300)

Question 1 (15 points). Estimate the relative percentage of *anti* and *gauche* *n*-butane conformers in the equilibrium shown below.



One gauche interaction is 0.88 kcal/mol.

$\Delta G = 1.4 \cdot pK_a$

$$K_{eq} = \frac{[gauche]}{[anti]}$$

$pK_{eq} = \Delta G/1.4 = 0.88/1.4 = 0.63$

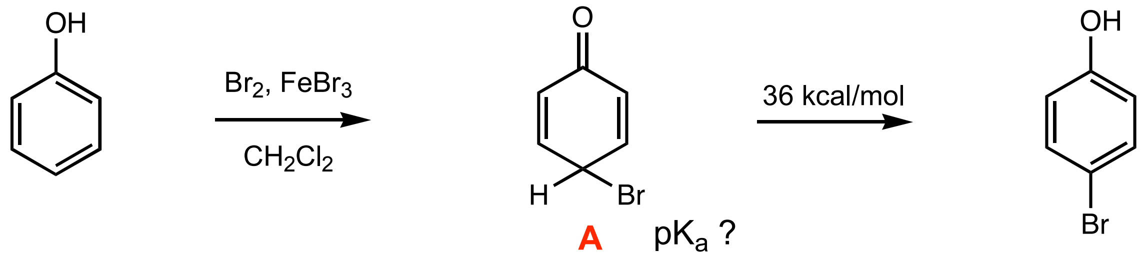
$K_{eq} = 10^{-0.63} = 0.234$

$$[gauche]_{\%} = \frac{[gauche]}{[anti] + [gauche]} \cdot 100\% = \frac{K_{eq}}{1 + K_{eq}} \cdot 100\% = 19\%$$

$[anti]_{\%} = 100 - 19 = 81\%$

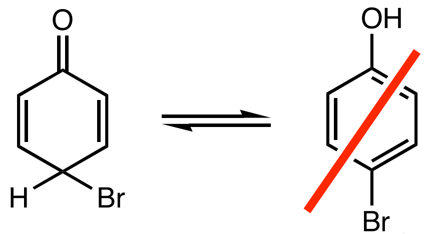
Compiler's note: The solution shown here neglects the statistical term $\Delta S^0 = R \ln 2$. Thus the computed percentage is incorrect. Taking this into account gives $K = 0.45$ or an *anti* : *gauche* ratio of 69% : 31% at 298 K.

Question 2. (15 points). The ferric bromide promoted bromination of phenol proceeds through σ-complex **A**. Estimate the pKa of **A** assuming that the bromophenol resonance energy is 36 kcal/mol.



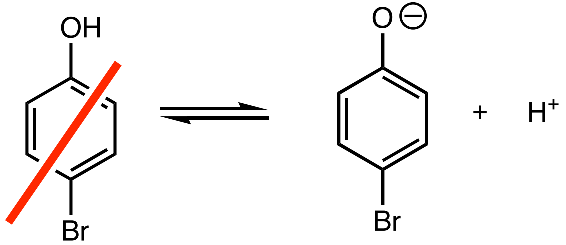
A pK_a ?

A



$\Delta G_1 = -36$ kcal/mol

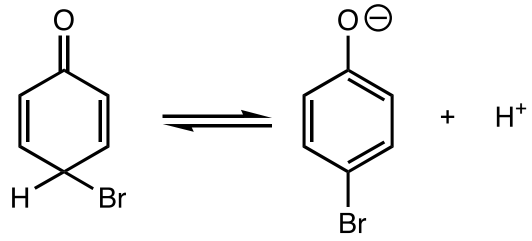
$pK_{eq} = \Delta G_1/1.4 = -25.7$



$pK_A = 18$ In DMSO

sum the pk values

A

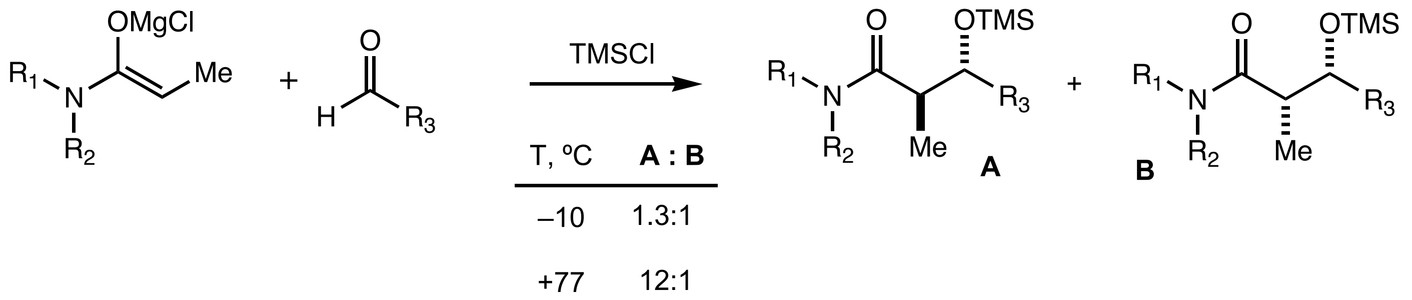


$pK_A = pK_{eq}$ (Resonance) + pK_A (phenol)

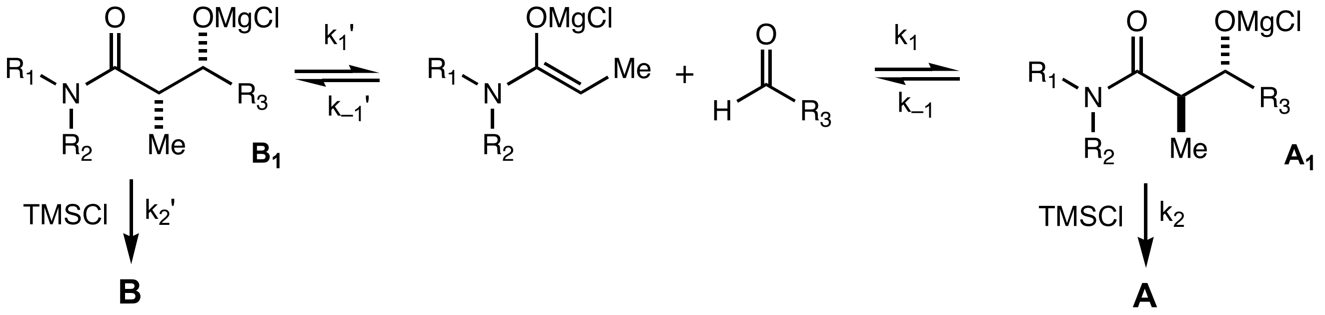
$pK_A = -25.7 + 18 = -7.8$

The pKa of HBr is roughtly the same!!

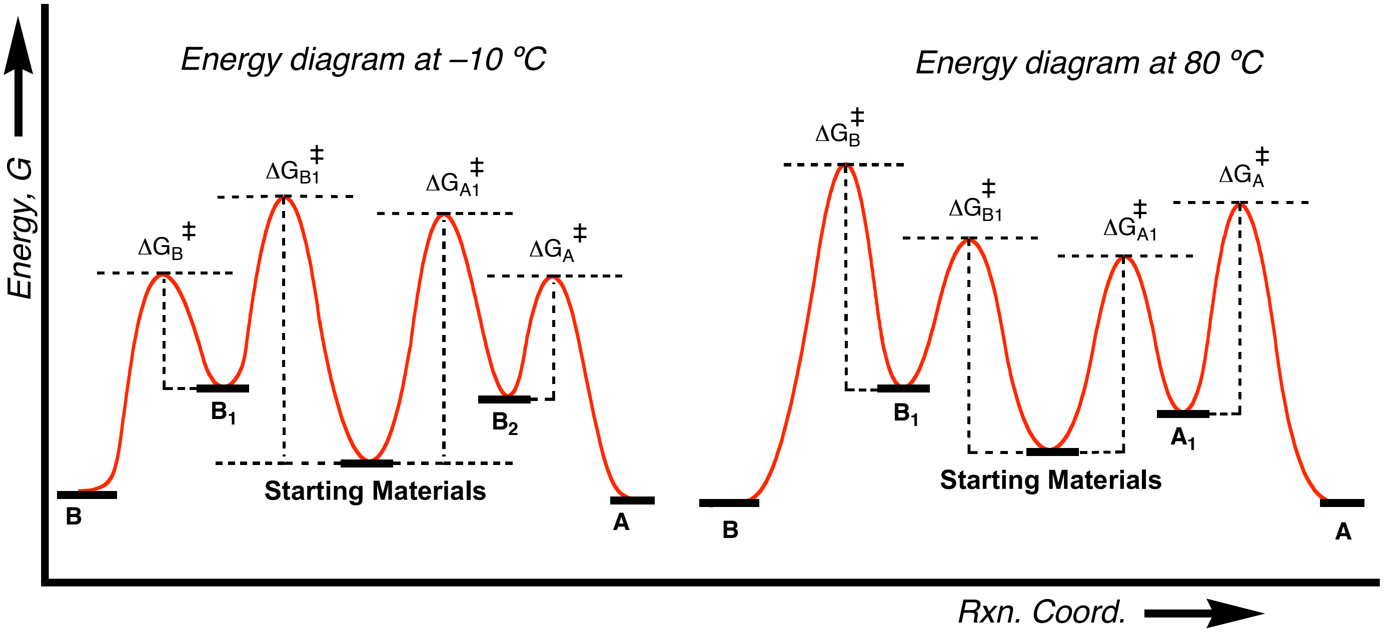
Question 3. (20 points). Consider an aldol addition reaction of the type illustrated below. It was found that the ratio of the diastereomeric products **A:B** increases with temperature. Assume that TMSCl is present at the beginning of the reaction.



T, °C	**A : B**
–10	1.3:1
+77	12:1

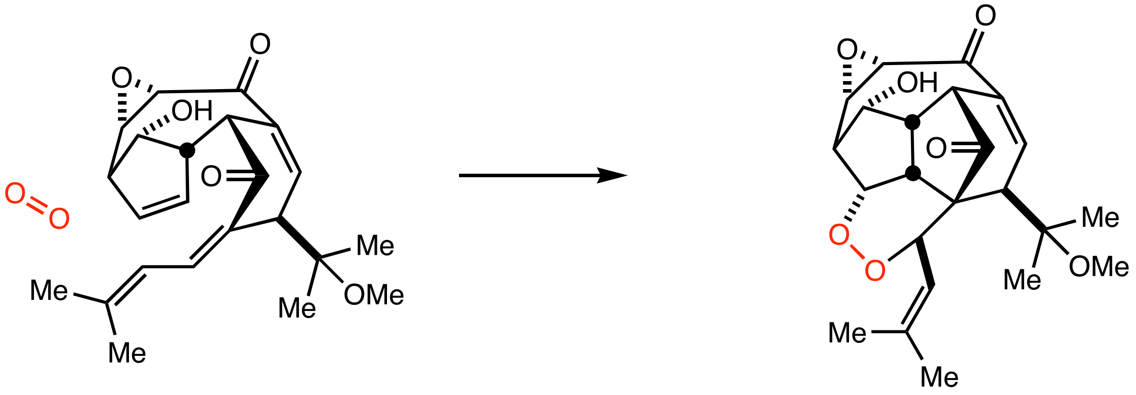


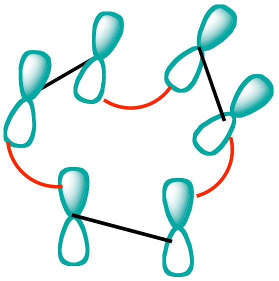
Using the mechanism provided draw a corresponding energy diagrams for –10 and +77 °C that would describe this situation. Comment on how rate constants should change with temperature in order for the illustrated effect to take place.



In order for the dr to increase with temperature, k_1 and k_1' (k_{-1} and k_{-1}') should increase with temperature faster than k_2 and k_2'

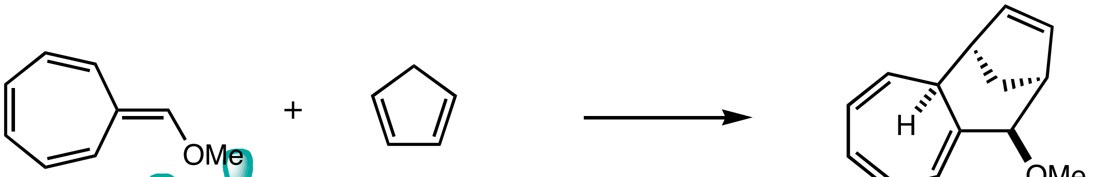
Question 4. Part A (10 points). Using Dewar-Zimmerman analysis predict whether this [2+2+2] cycloaddition with the participation of *singlet oxygen* is a thermally allowed pericyclic process.

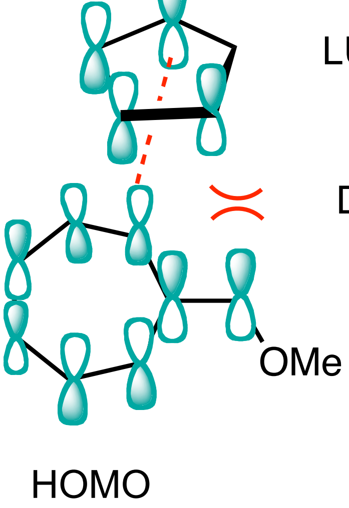




2 phase inversions, 6 π electrons,
Huckel topology, aromatic, thermally allowed

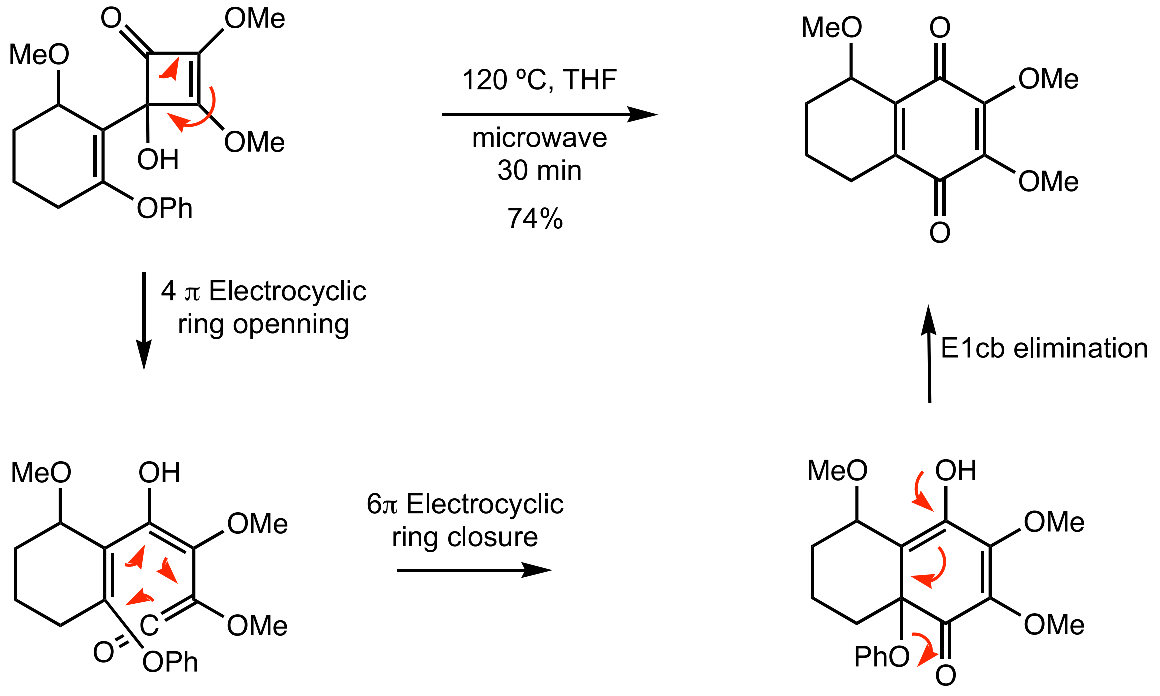
Part B (10 points). Using FMO analysis predict whether a cycloaddition illustrated below is a thermally allowed process.



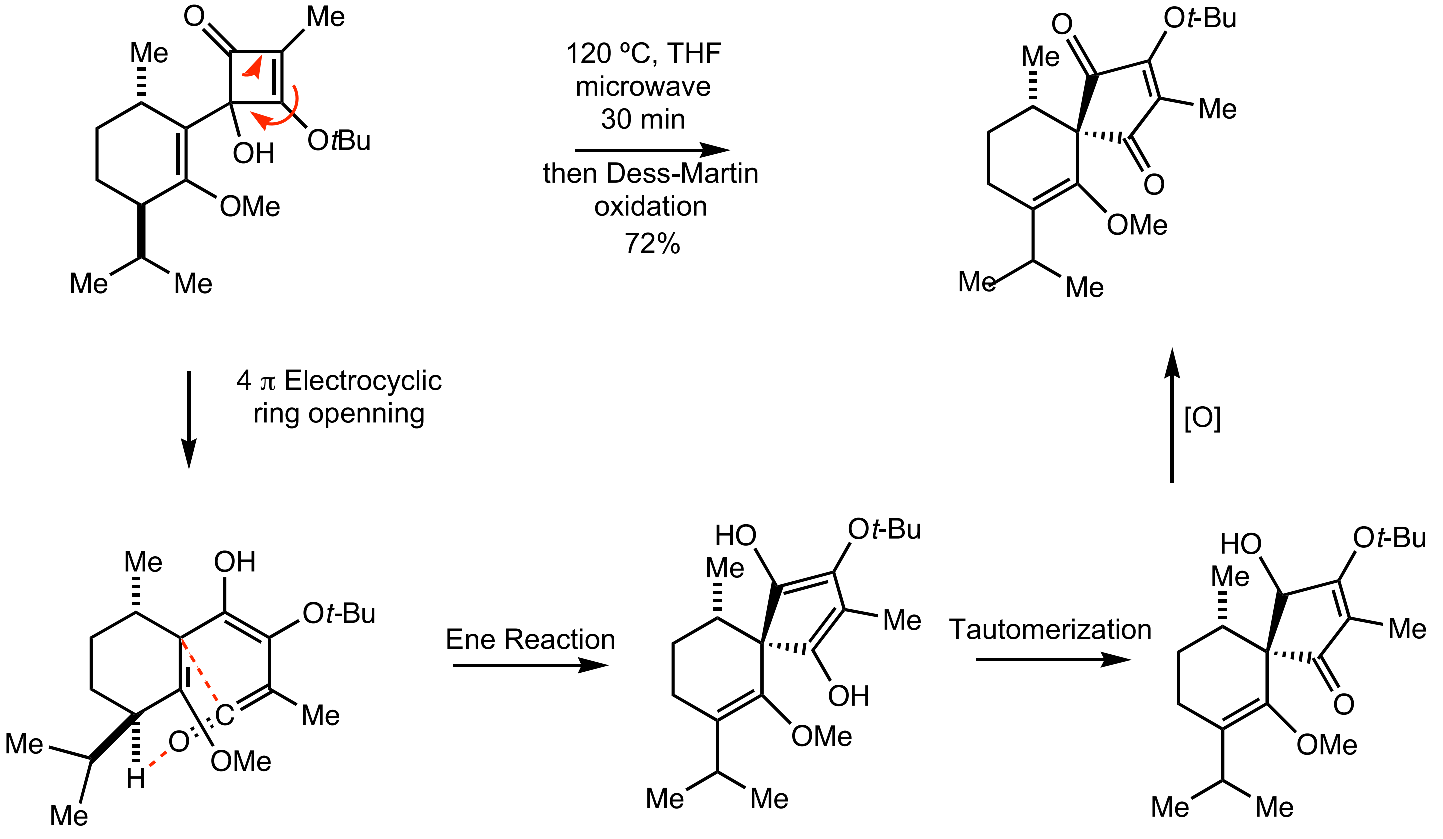


Distructive overlap, thermally forbidben

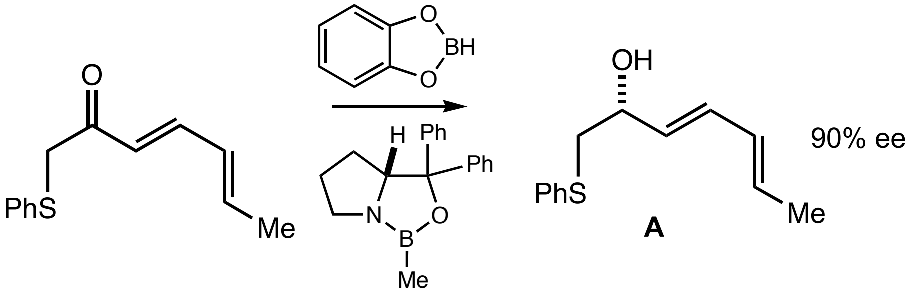
Question 5. Part A. (10 points). During a systematic study of thermally induced cyclobutenone rearrangements Harrowven discovered the illustrated transformation *(Angew. Chem. Int. Ed.* **2007**, *46*, 425-428) . Provide a detailed mechanism that accounts for the formation of the product.

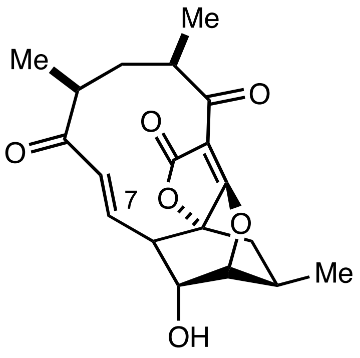

120 °C, THF
microwave
30 min
74%
4 π Electrocyclic ring openning
6π Electrocyclic ring closure
E1cb elimination

Part B (10 points). As illustrated below, it was also discovered that the substrate structure plays an important role in the rearrangement outcome. Provide the mechanism of this transformation and explain the diastereoselectivity of this reaction. *You do not need to provide the mechanism of Dess-Martin oxidation.*



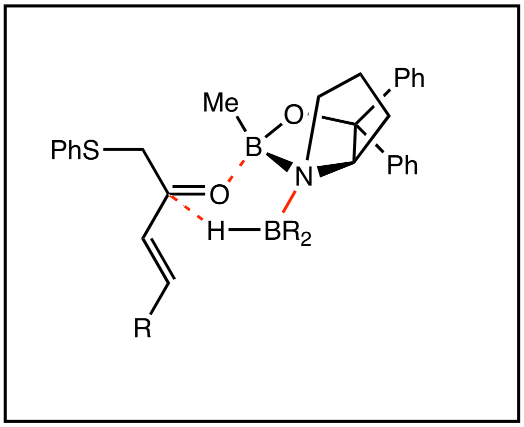
Question 6. (20 points). The following reaction sequence was used by the Nicolau group in their total synthesis of abyssomicin C (*JACS* **2007**, *129,* 429-440).



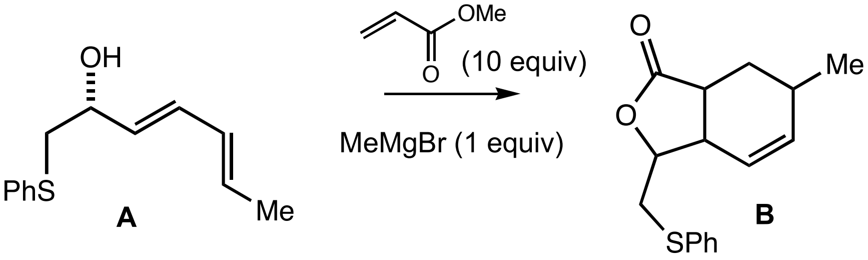


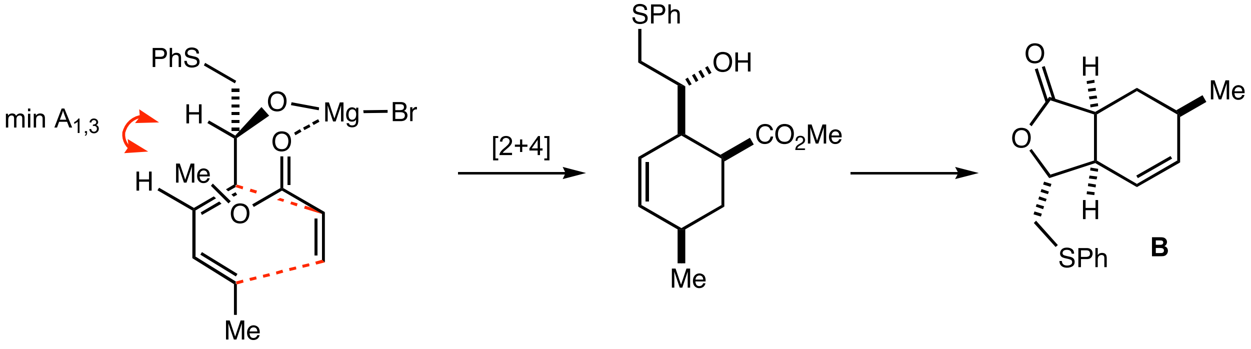
Abyssomicin C

Part A (10 points). Rationalize the stereochemical course of this reduction via the well-accepted transition structure.



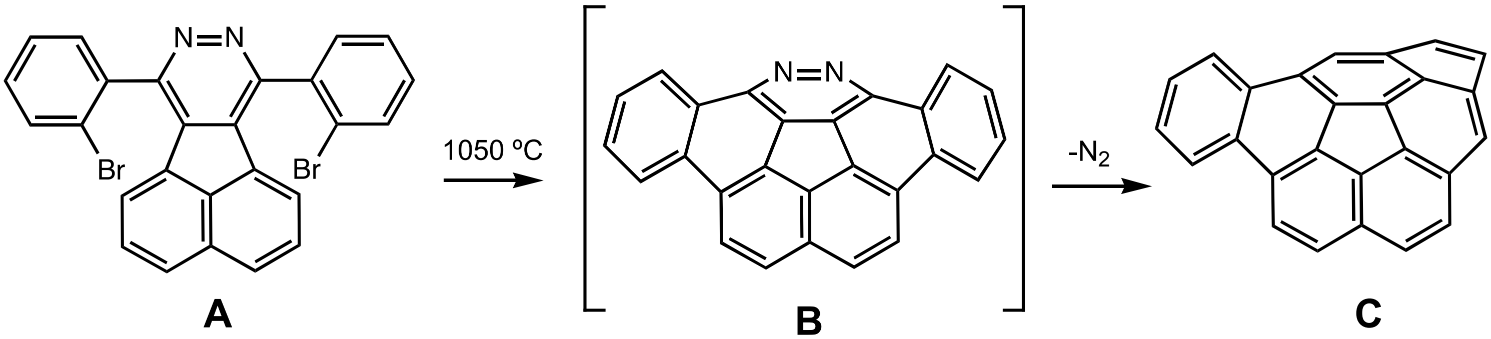
Part B (10 points). In the reaction below, product **B** is formed as a predominent diastereomer . Predict the absolute stereochemical relationships in **B** and explain your answer using clear drawings.



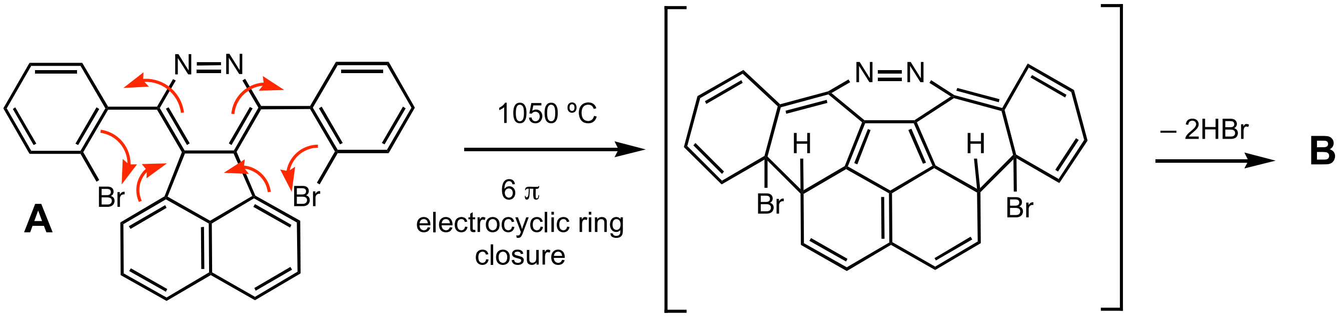


- Dienophile adopts *s*-trans conformation with a monodentate Lewis acid
- The dienophile delivery is mediated by a magnesium complex that binds to both diene and dienophile
- The facial selectivity is determined by minimized A1,3 strain

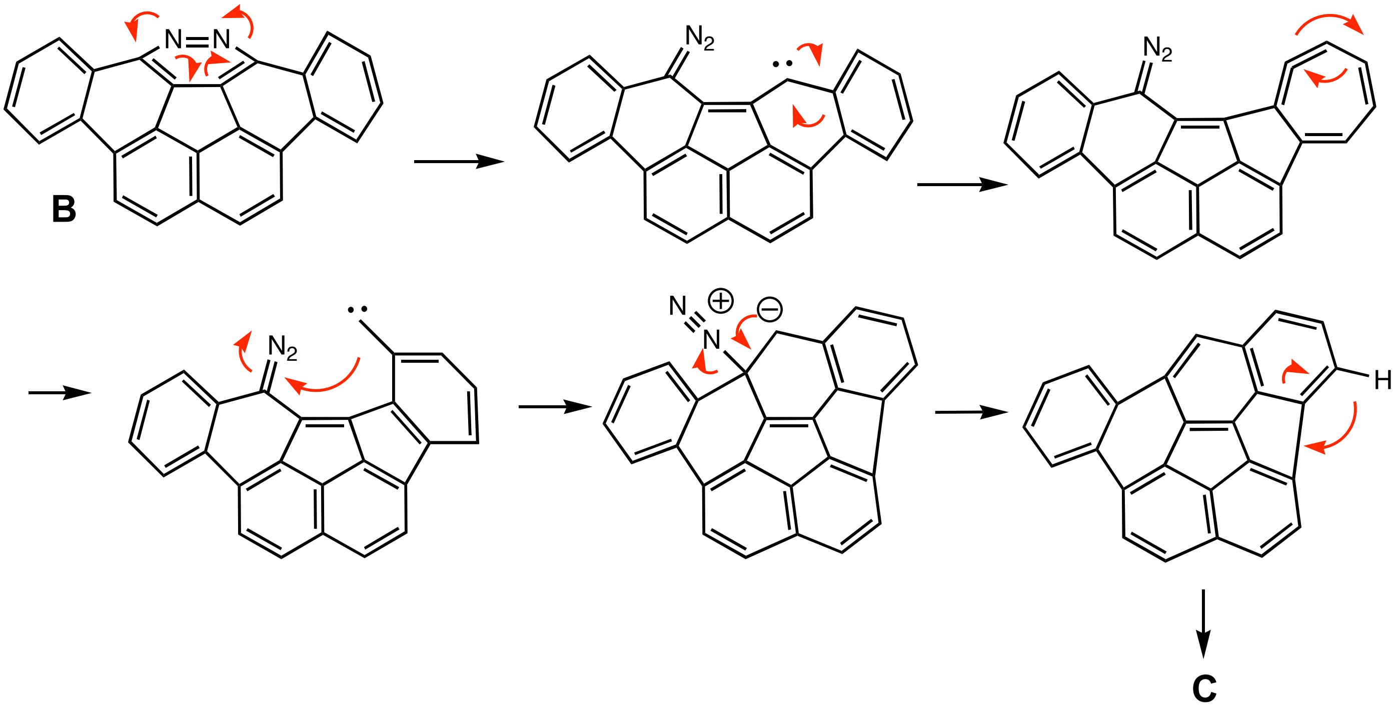
Question 7 (20 points). In their recent attempt to prepare compound **B** by the flash vacuum pyrolysis of dibromide **A**, Scott and Bodwell discovered the formation of the hydrocarbon **C** (*Org. Lett.* **2006**, *8*, 5195-5198). It was postulated that **C** is obtained by decomposition of **B** under the indicated reaction conditions.



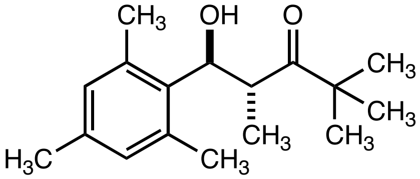
Part A. (10 points). Propose a reasonable mechanism for the transformation of **A** to **B**.



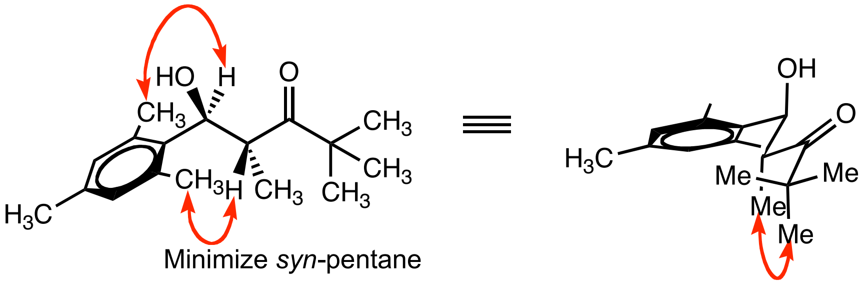
Part B. (10 points). Propose a reasonable mechanism for the transformation of **B** to **C**.



Question 8. (15 points). Draw what you would predict to be the most stable conformation of the product depicted below (*J. Org. Chem.* **2006**, *71*, 8835-8841).



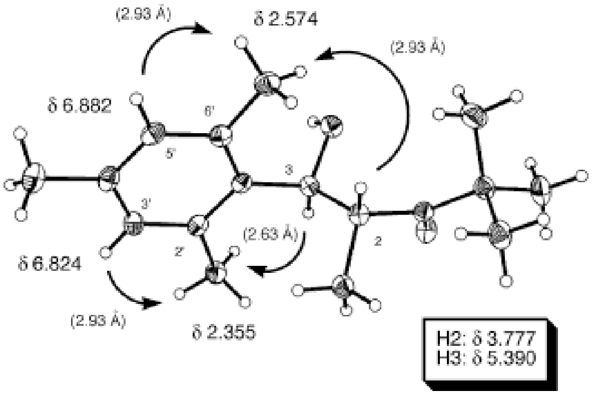
Minimize A(1,3)



Minimize *syn*-pentane

Hydrogens removed for clarity

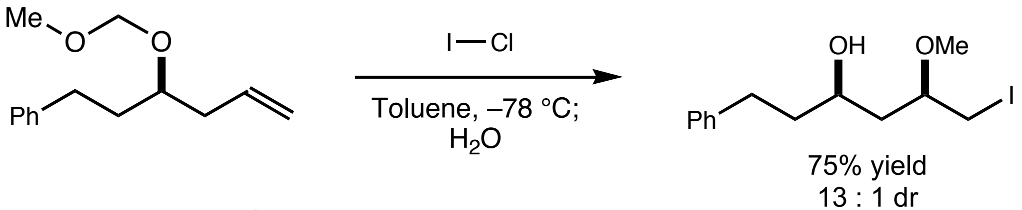
syn-pentane interaction alleviated by sp^2 carbonyl carbon (120° vs 109.5°). Further distortion occurs in the solid state (see crystal structure).



X-Ray Crystal Structure

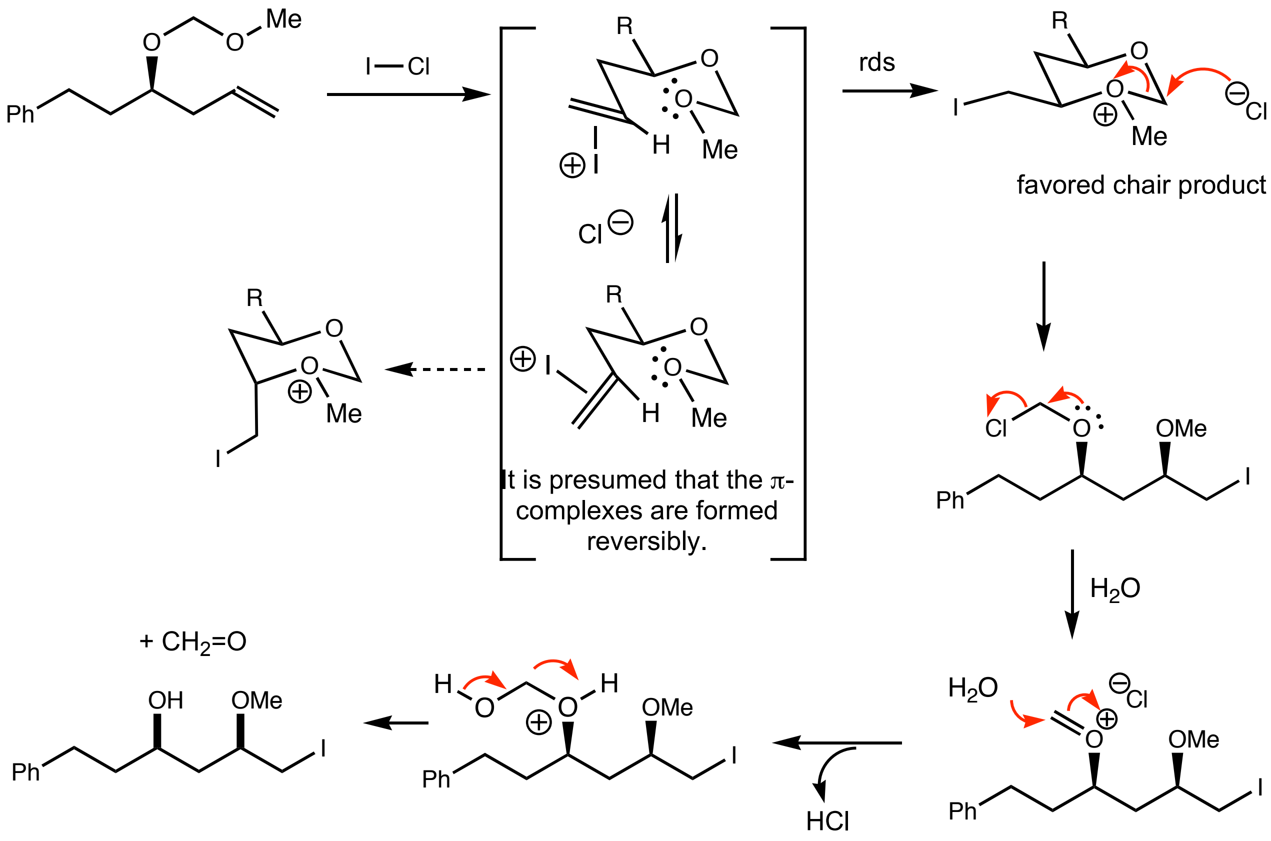
Effect of 2,6-Disubstituted Aryl Groups on Acyclic Conformation: Preference for an Antiperiplanar Orientation of the Geminal and Vicinal Hydrogens. Carlier, P. R.; Zhang, Y.; Slebodnick, C.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **2006**, *71*, 8835-8841.

Question 9 (15 points). The highly diastereoselective iodoetherification depicted below was recently published by Taylor and coworkers (*Org. Lett.* **2006**, *8*, 5393-5395).



75% yield
13 : 1 dr

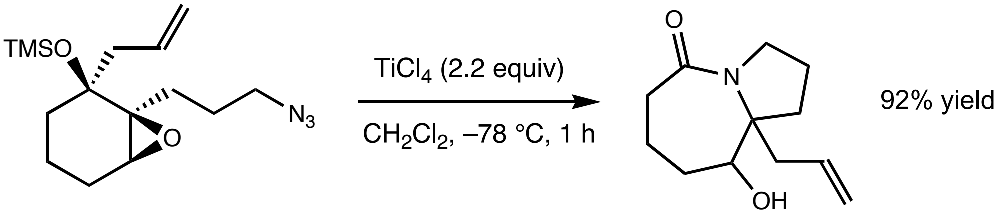
Provide a mechanism that accounts for the observed diastereoselectivity.



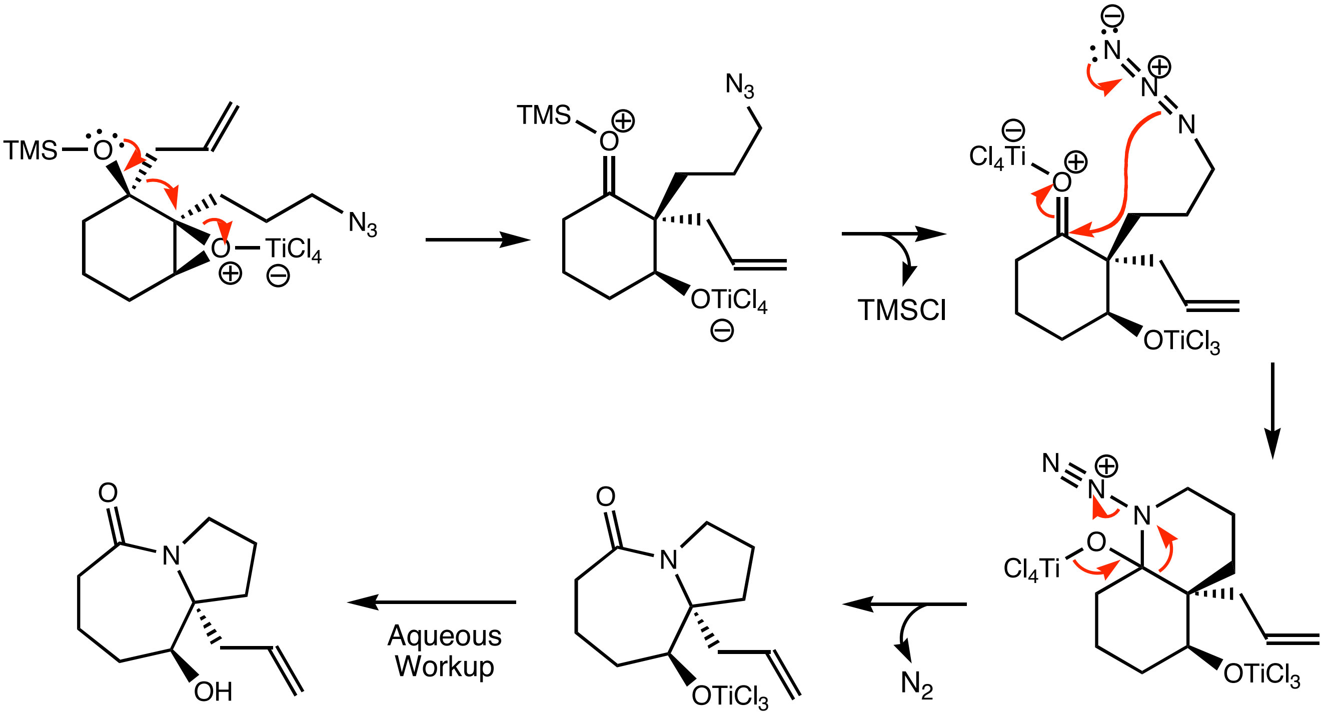
favored chair product

It is presumed that the π-complexes are formed reversibly.

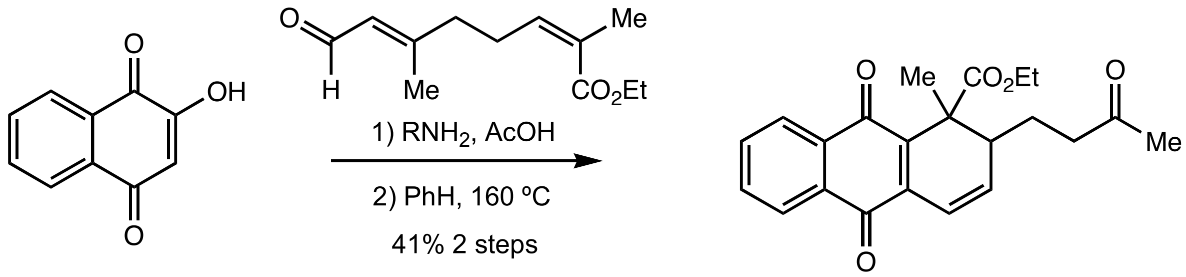
Question 10. (15 points). The transformation depicted below allows rapid access to azabicyclic ring systems (*Org. Lett.* **2006**, *8*, 5271-5273.).



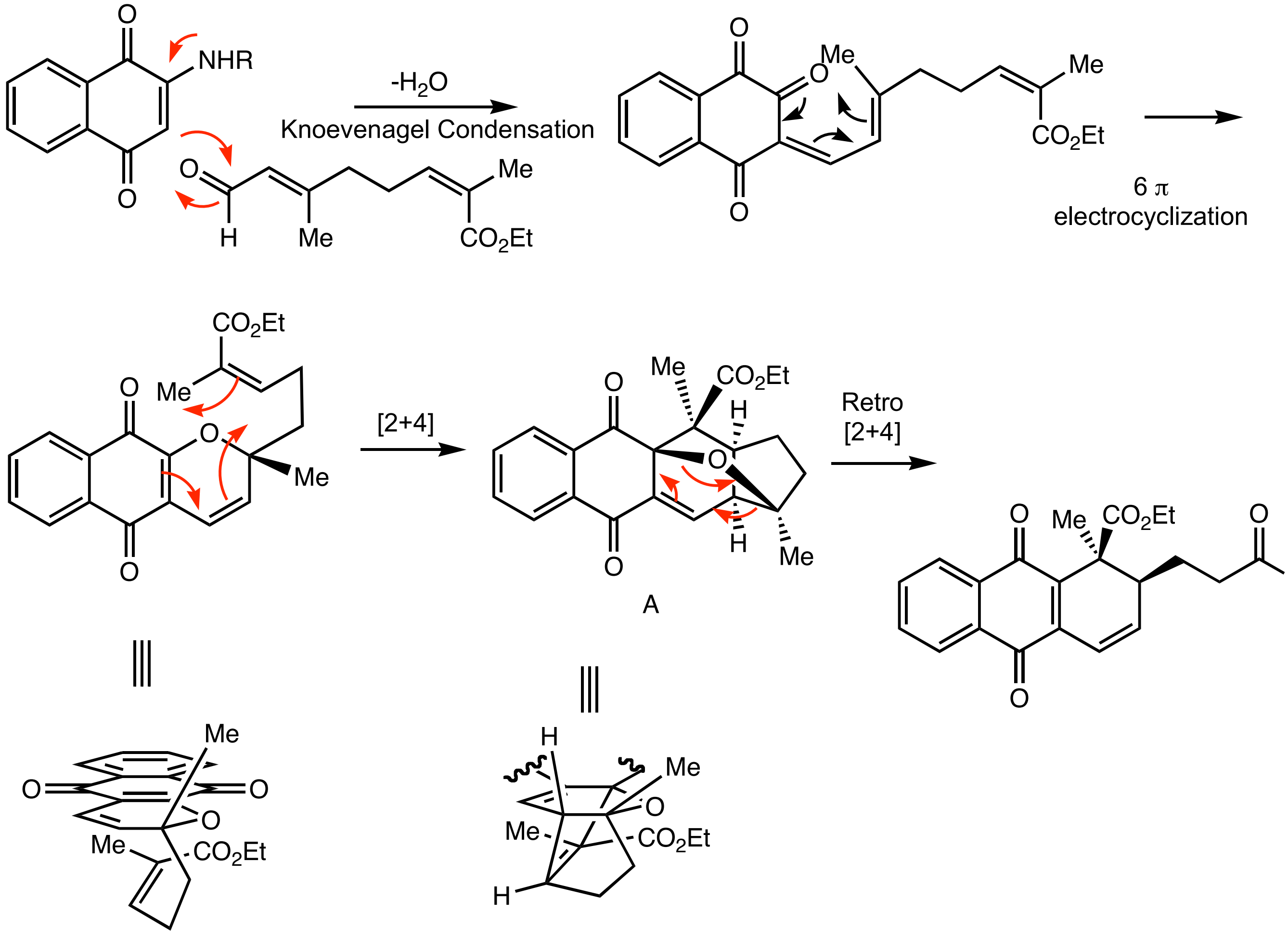
Provide a mechanism for this transformation and predict the stereochemistry of the product.



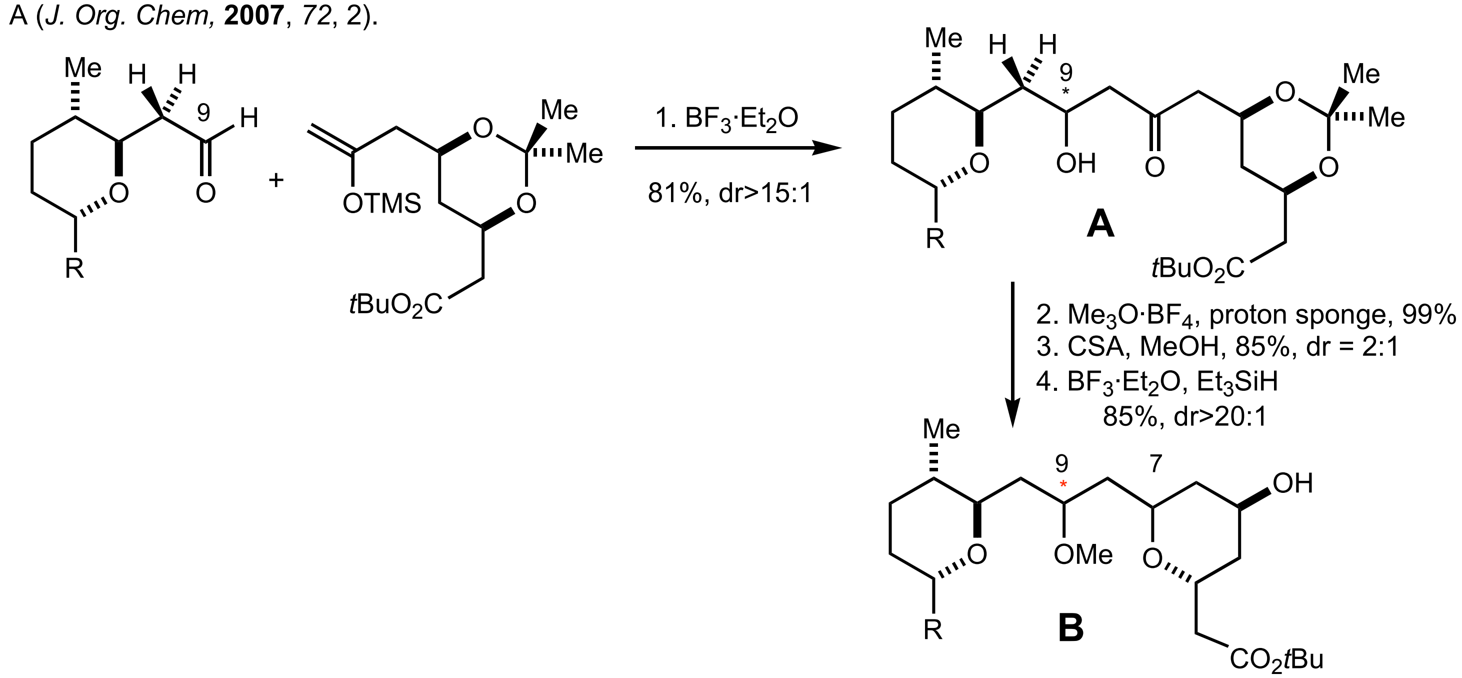
Question 11. (15 points). The following reaction cascade was recently employed by Trauner and coworkers (*JACS* **2005**, *127*, 6276).



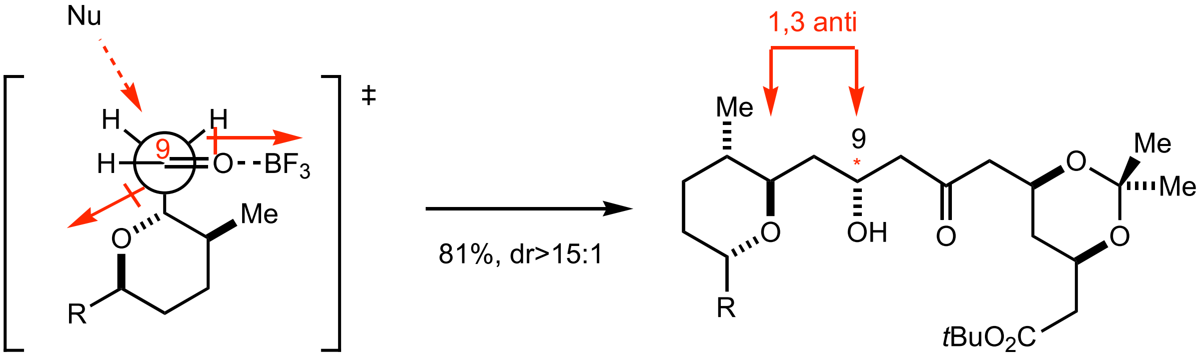
Please provide a mechanism for this transformation and predict the relative stereochemistry of the product.



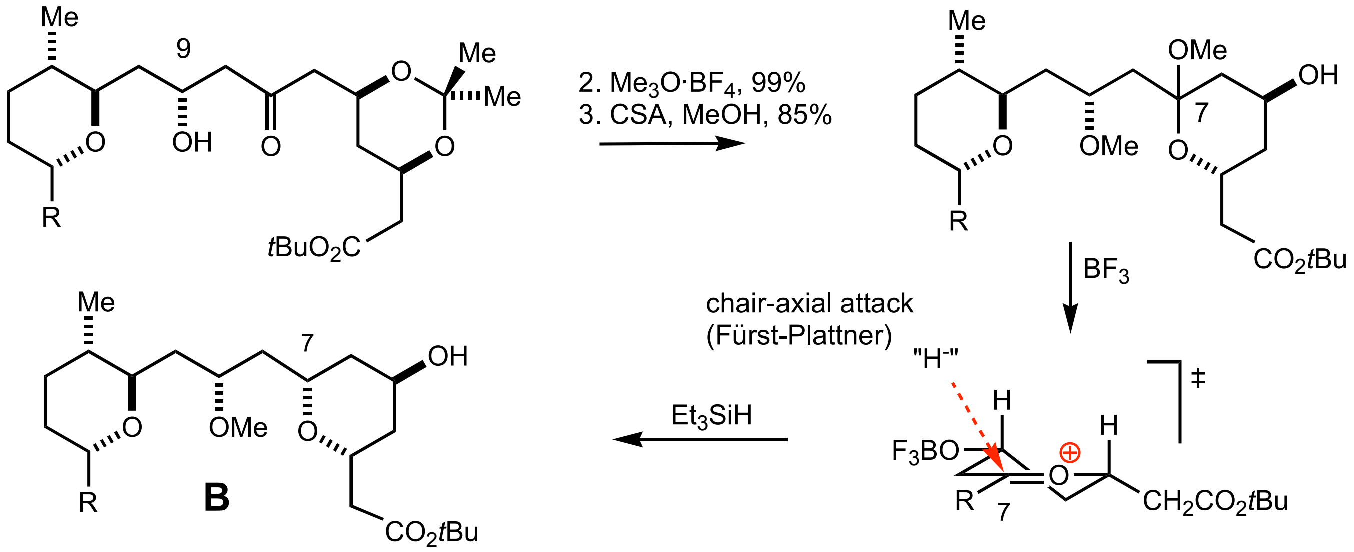
Question 12 (20 points). Below you see a short reaction sequence from Panek's recent synthesis of leucascandrolide A (*J. Org. Chem,* **2007**, *72*, 2).



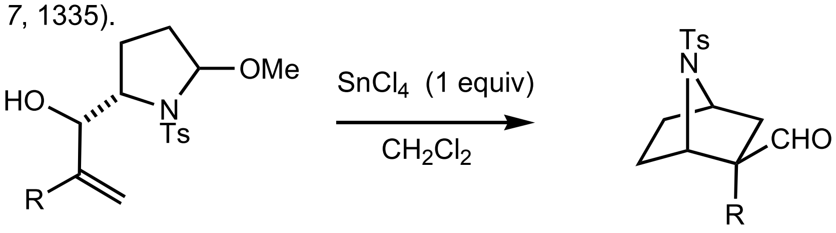
Part A (10 points): Please predict the stereochemistry of the product **A** and draw a clear 3D transition state picture to support your predictions.



Part B (10 points). Draw the absolute configuration of the product **B** and rationalize the stereochemistry at the C7 stereocenter using clear 3D drawings.

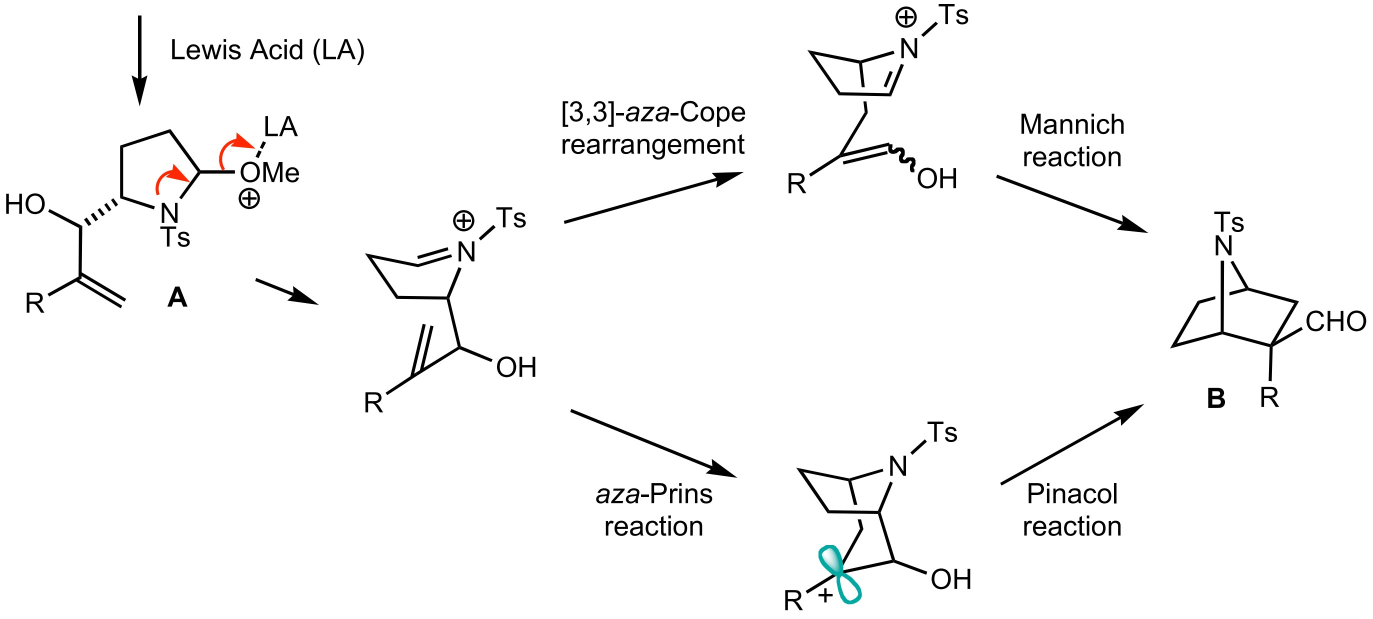


Question 13 (20 Points). The illustrated rearrangement was recently investigated by Armstrong and Shanahan (*Org. Lett.* **2005**, *7*, 1335).

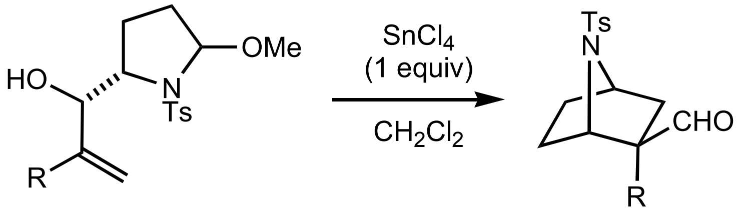


A **B**

Part A (10 points). Provide two possible mechanisms for the formation of B from A.



Part B (10 points). Given the following evidence, analyze which pathway is the more plausible of the two paths presented in **Part A** .

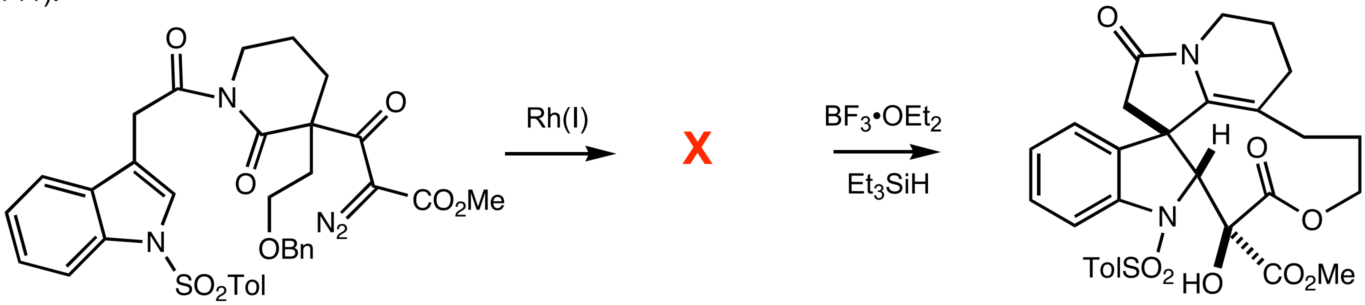


R	time	temp	yield
Ph	8 min	0 ºC	96%
Me	8 min	0 ºC	81%
H	14.5 h	20 ºC	32%
$PhSO_2$	–	–	NR

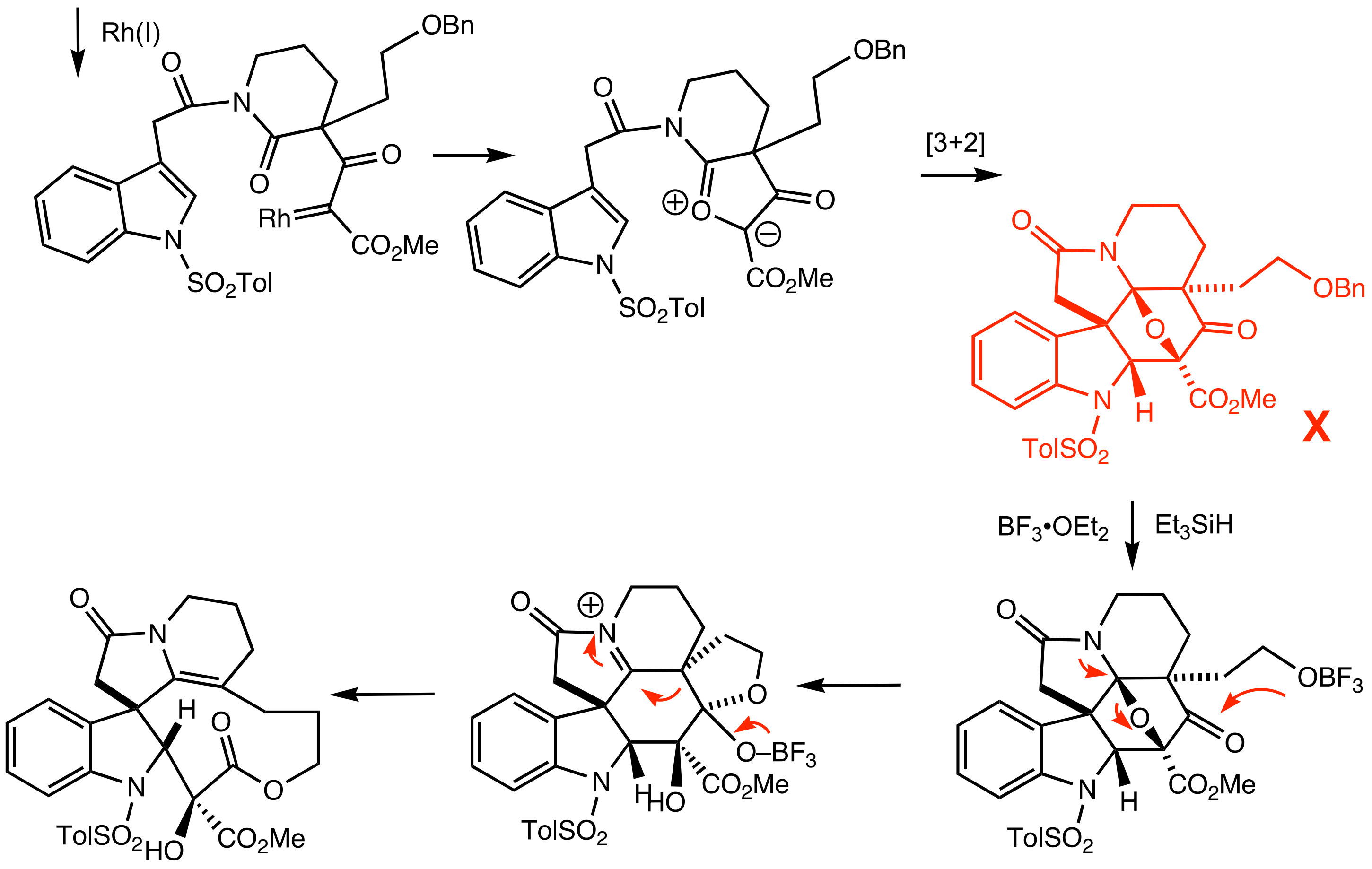
The above set of data support *aza*-Prins-Pinacol pathway.

When R = H, the less stable secondary carbocation has to be formed. This causes dramatic rate deceleration (14.5 hour at 20 ºC, compared to 8 min at 0 ºC from the more stable tertiary carbocation (R = Me or Ph)). When R is strongly electron-withdrawing group such as SO_2Ph, no rearrangement product was observed

Question 14. (20 points). The following reaction cascade was resently reported by Padwa et al. (*Org. Lett.* **2006**, *8*, 5141).

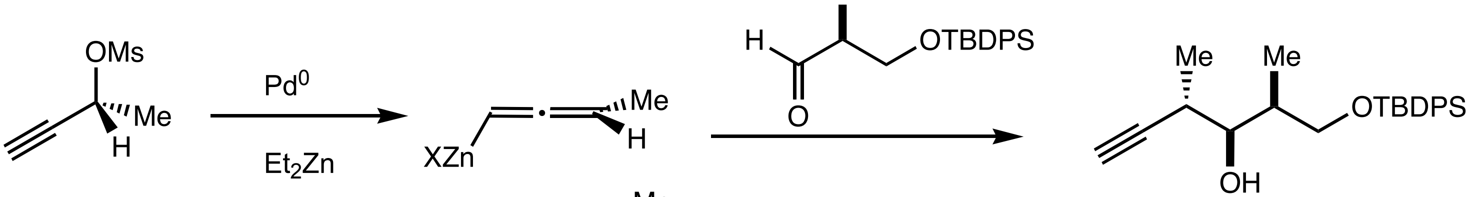


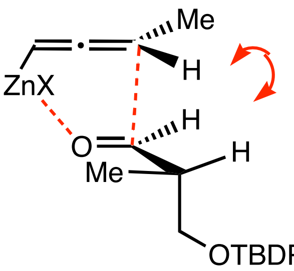
Provide the mechanism for this cascade and identify intermediate **X.**



Question 15 (20 points). Marshall and coworkers have reported the following diastereoselective addition of chiral allenylzinc reagents to aldehydes (*J. Org. Chem.* **1999**, *64*, 5201-5204).

Part A (10 points). Propose a mechanism (i.e. transition state structure) for the addition of the allenylzinc that accounts for the observed stereochemistry and classify the product as Felkin or Anti-Felkin. You need not show the mechanism for formation of the allenylzinc species.

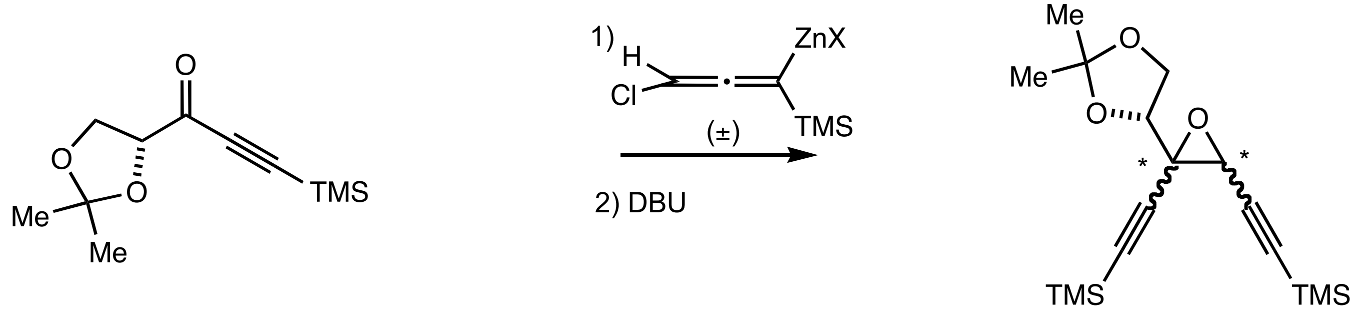




minimize eclipsing interactions

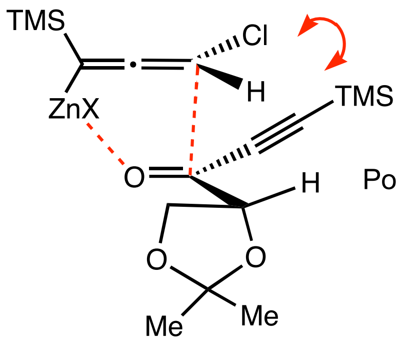
Felkin TS

Part B (10 points). The illustrated racemic allenylzinc reagent was recently used in the synthesis of the chiral epoxydiyne (Baker *et. al*, *Org. Lett.* **2007**, *9*, 45-48). Provide a plausible mechanism for this transformation and predict the relative stereochemistry of the resultant epoxide.

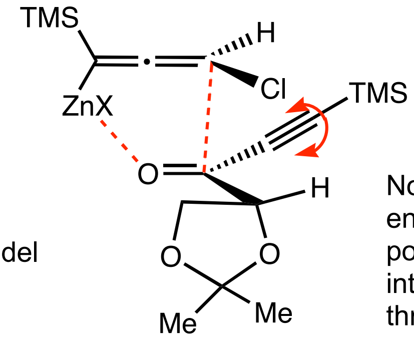


45%, >95:5 dr

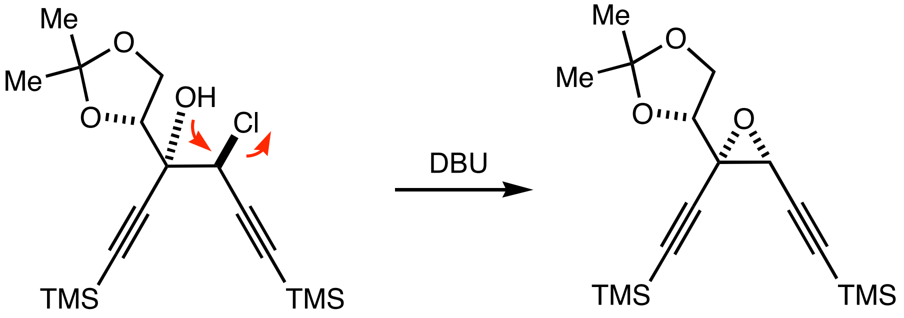
minimize eclipsing interactions



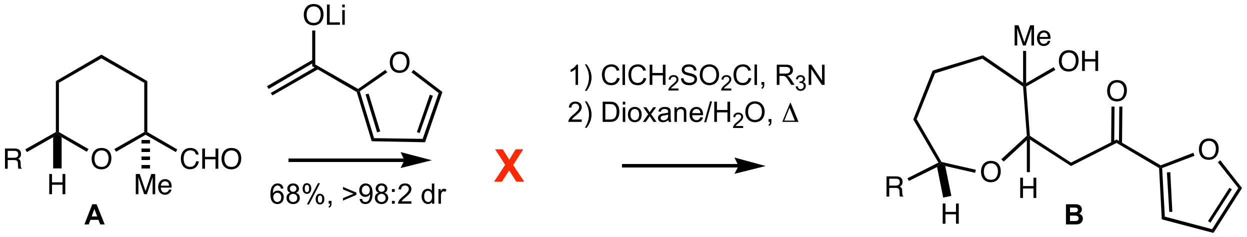
Polar Felkin Model



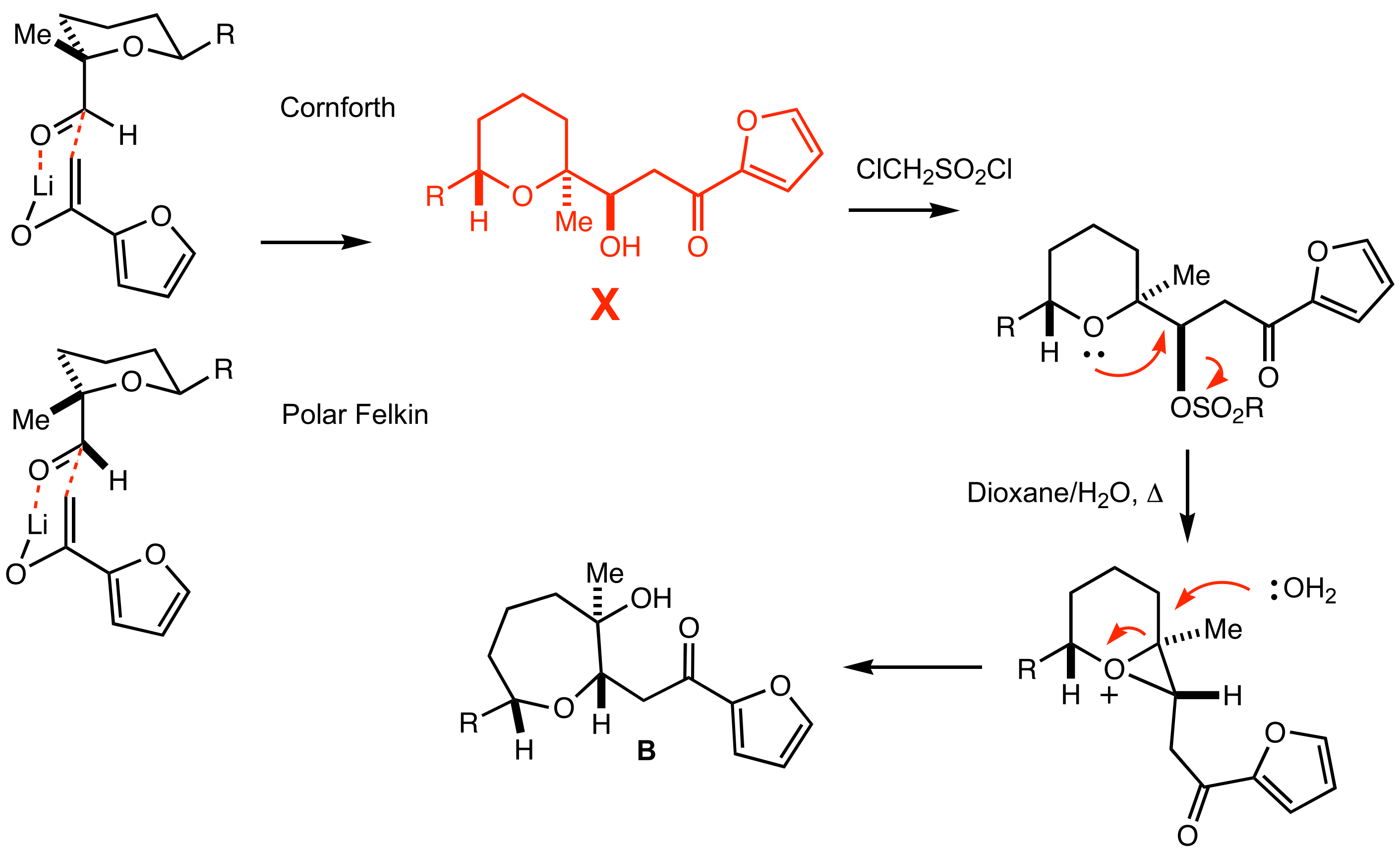
Note that the TS for the addition of the enantiomeric allenylzinc would possess a destabilizing eclipsing interaction in order to proceed through a polar Felkin TS.



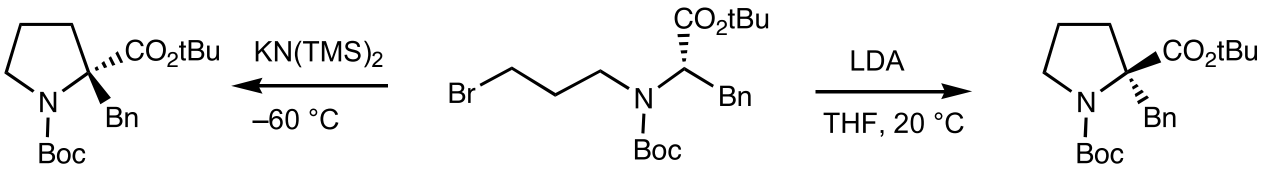
Question 16. (15 points). An interesting approach to oxepanes has been developed by Nelson *et al. (Org. Lett.* **2006**, *8*, 4231) in their studies directed toward the synthesis of brevetoxin B. Thus, oxepane **B** is constructed by a three-step procedure starting from aldehyde **A**.



Identify intermediate **X,** provide the mechanism of these transformations and predict the stereochemistry of **B.**



Question 17. (15 points). Kawabata has recently reported the rather remarkable enolate alkylation of the indicated (*S*)-phenylalanine derivative **1** *(JACS* **2006**, *128,* 15394-19395). The reaction is strongly counter ion dependent with the potassium enolate reacting with nearly complete retention whille the lithium enolate alkkylates with inversion.

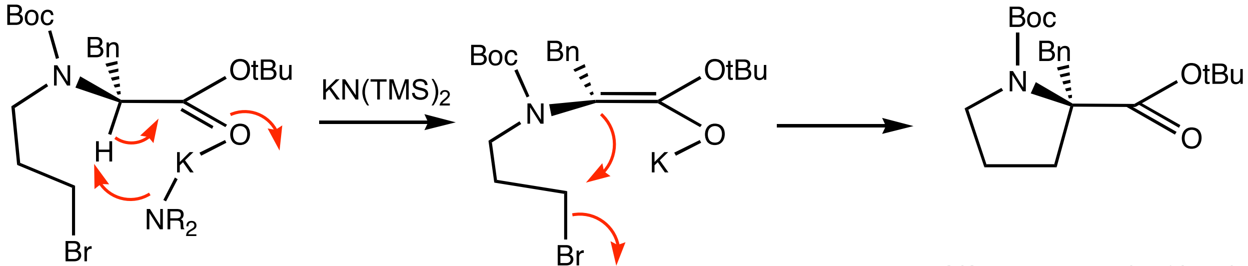


P-(*S*), Retention (98% ee)

1 (99% ee)

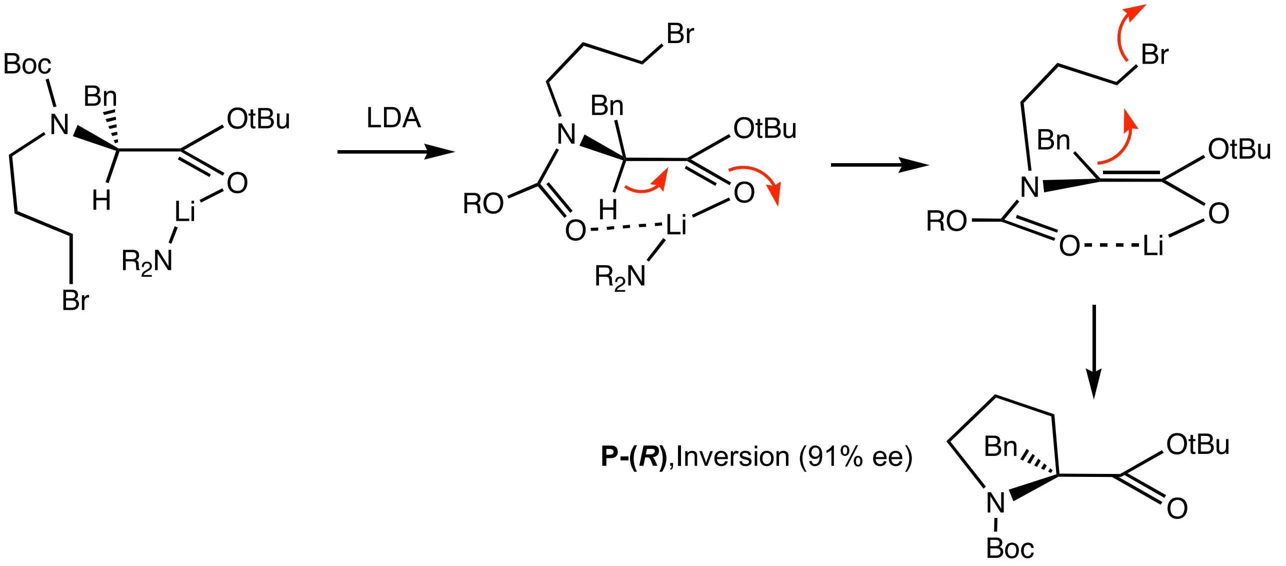
P-(*R*),Inversion (91% ee)

Part A. (10 points). Provide a rationalization for the transformation of **1** to **P-(*S*)**.



P-(*S*), Retention (98% ee)

Part B. (5 points). Provide a rationalization for the transformation of 1 to **P-(*R*)**.



P-(*R*),Inversion (91% ee)

Chemistry 206
Final Examination

D. A. Evans
January 23, 2000

Name (please print):______________________
last first initial

Signature:______________________

Teaching Fellow:______________________

This examination contains **19** questions for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

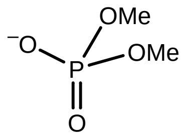
Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

Answer Key

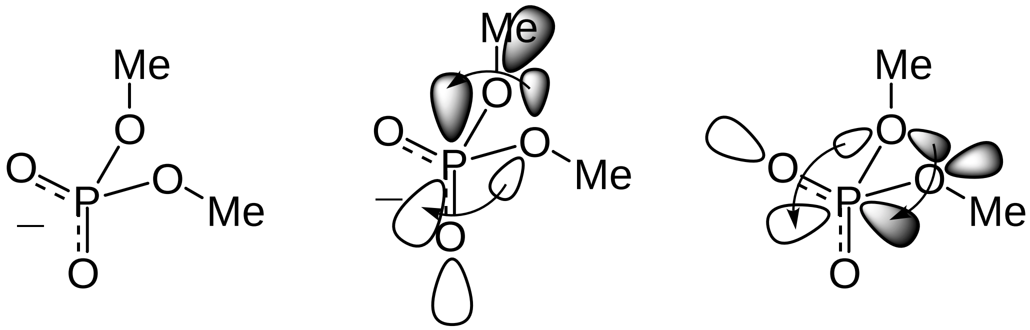
Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**10**)	______	No. 11 (**20**)	______
No. 2 (**10**)	______	No. 12 (**15**)	______
No. 3 (**10**)	______	No. 13 (**15**)	______
No. 4 (**15**)	______	No. 14 (**20**)	______
No. 5 (**10**)	______	No. 15 (**20**)	______
No. 6 (**10**)	______	No. 16 (**20**)	______
No. 7 (**15**)	______	No. 17 (**15**)	______
No. 8 (**20**)	______	No. 18 (**20**)	______
No. 9 (**15**)	______	No. 19 (**20**)	______
No. 10 (**20**)			
Subtotal (**135**)		Subtotal (**165**)	

Total (300)

Question 1 (10 points). As mentioned in class, the conformation of the sugar-phosphate backbone in DNA is found to exist in one principal conformation. Consider dimethyl phosphate anion, $[(MeO)_2PO_2]^-$, as a model for DNA. Draw a detailed 3D structure of the preferred conformation of $[(MeO)_2PO_2]^-$. Indicate the specific interactions responsible for your predicted geometry.



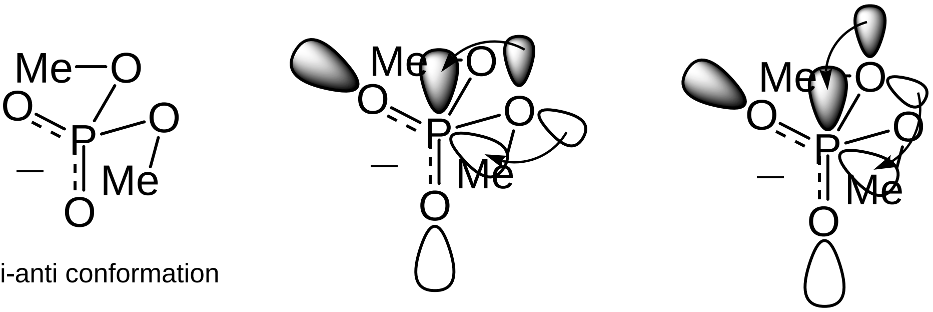
acceptor orbital hierarchy: σ^* P-OR > σ^* P-O$^-$



gauche-gauche conformation

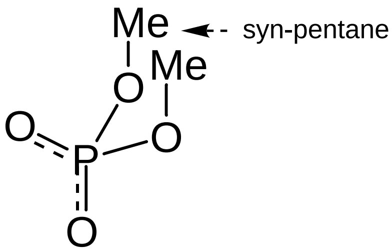
(preferred conformation)

two $n_o \rightarrow \sigma^*$ P-OR
two $n_o \rightarrow \sigma^*$ P-O$^-$



anti-anti conformation

four $n_o \rightarrow \sigma^*$ P-O$^-$

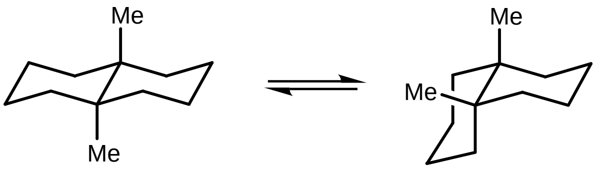


alternate gauche-gauche
disfavored on steric grounds

two $n_o \rightarrow \sigma^*$ P-OR
two $n_o \rightarrow \sigma^*$ P-O$^-$

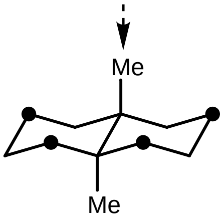
Question 2 (10 points). For each of the questions below, provide the requested information. When you are requested to estimate the relative energies of two conformers (**Parts A-B**), indicate: (1) the A-value(s) or A-value estimate(s) that you have employed; (2) the logic used to make the Δ G° estimate. If you follow this procedure, we may assign partial credit to those answers that are not completely correct.

Part A (5 points). Estimate the energy difference between these two decalin isomers.



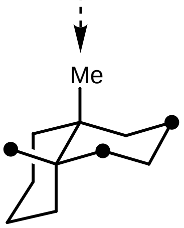
Δ skew interactions	Δ G° (kcal/mol) estimate
9-8=1	.88kcal/mol

interaction with this methyl

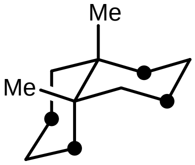


Each methyl has four such skew butane interactions for a total of 8

interaction with this methyl

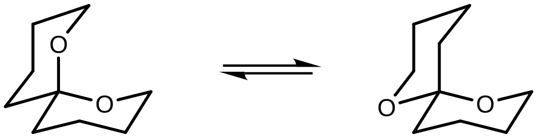


Each methyl has 3 skews for 6 total.



The cis decalin introduces 3 more skew interactions, bringing the total to 9.

Part B (5 points). Estimate the energy difference between these two dioxaspirane isomers.



Δ G° (kcal/mol) estimate +3.0 kcal/mol

2 anomeric oxygens

0 axial "ethyl" substituents

+2.4 kcal/mol

1 anomeric oxygens

1 axial "ethyl" substituents

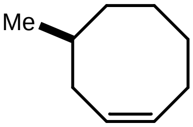
-0.6 kcal/mol

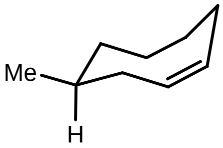
Δ G° (kcal/mol) estimate = +2.4 - (-0.6) = +3 kcal/mol

The A value for ethyl is about 1.8 kcal/mol. The anomeric stabilization of an axial α-oxy substituent is about 1.2 kcal/mol.

Question 3 (10 points).

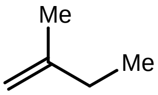
Part A (5 points). Draw the preferred conformation of this cyclooctene derivative.

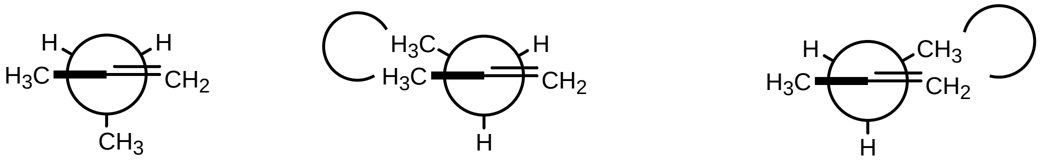




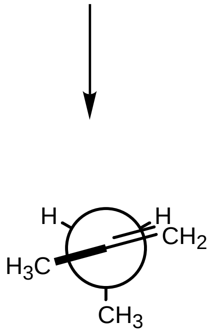
Equatorial methyl group, olefin is positioned so that transanuular interactions are minimized

Part B (5 points). Draw the lowest-energy conformation of 2-methyl-1-butene.



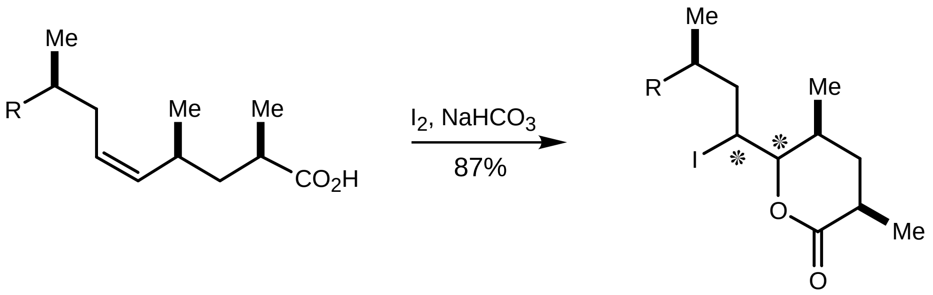


Methyl group placed in a position to avoid A1,2 and A1,3 interactions

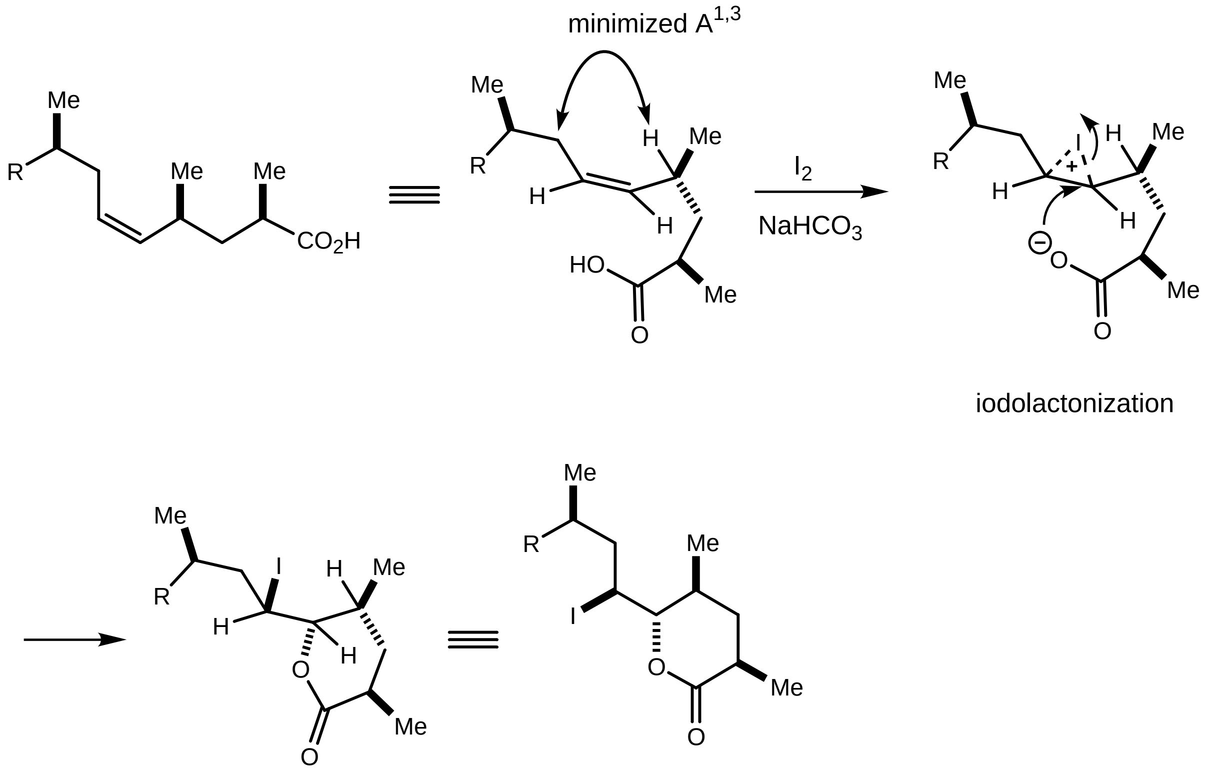


*σC-C is then aligned with π*C-C.*

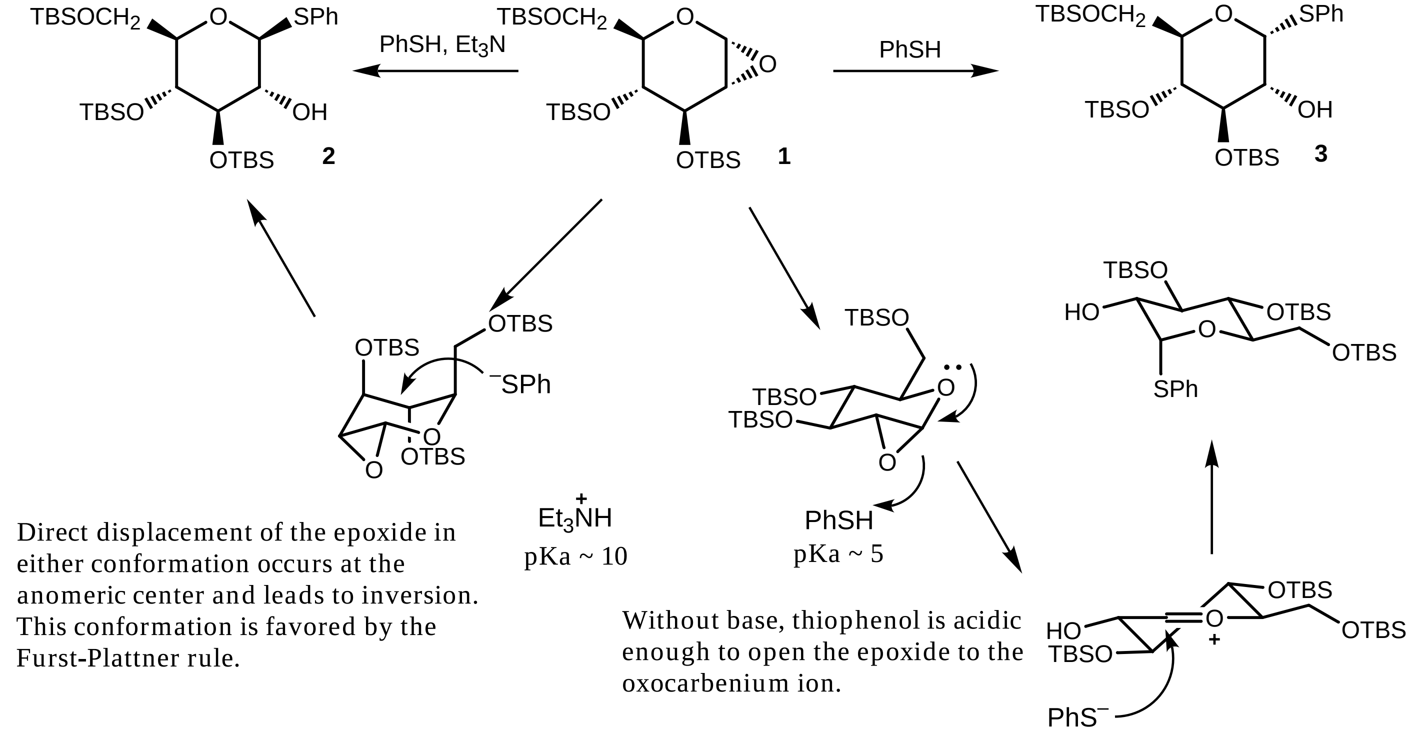
Question 4 (15 points). The Still synthesis of monensin (*JACS* **1980**, *102*, 218) features the diastereoselective iodo-lactonization shown below.



Provide a concise mechanism for this reaction in the space below. Be sure to identify all intermediates. In your answer, predict the stereochemical outcome of this transformation and identify the relevant stereochemical control element(s) operating in this reaction.



Question 5 (10 points). The illustrated glycal epoxide **1** reacts with thiophenol to afford in high selectivity either **2** or **3** depending on the reaction conditions (Jackson, *Chem. Commun.* **1997**, 1855).

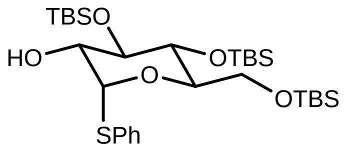


Direct displacement of the epoxide in either conformation occurs at the anomeric center and leads to inversion. This conformation is favored by the Furst-Plattner rule.

Without base, thiophenol is acidic enough to open the epoxide to the oxocarbenium ion.

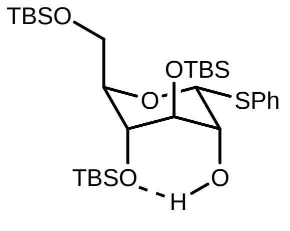
Stereoelectronically favored from bottom face to give chair conformation.

Question 6 (10 points). Draw the two chair conformations of **3** below. Based on an analysis of the vicinal ring ^{1}H-NMR coupling constants it is evident that the –SPh substituent is oriented in the equatorial position in the favored conformation of **3**. Explain why your conformation illustrated below possessing the equatorial substituent is more stable than the other illustrated conformer.



4 equatorial substituents
1 axial anomeric substituents

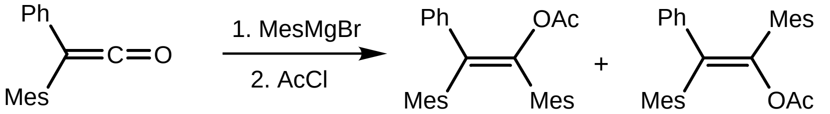
Steric crowding between adjacent equatorial OTBS groups destabilizes this conformation.



1 equatorial substituent
4 axial substituents

There are no destabilizing interactions between OTBS groups and there is a stabilizing hydrogen bond in this conformation. These factors override the normal preference for equatorial substituents

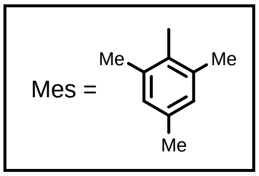
Question 7 (15 points). Rappoport has recently reported the transformation illustrated below (*JACS* **1996**, *118*, 12580). The kinetic stereochemical outcome of this reaction is superficially unanticipated in that the Grignard reagent adds to ketene **1** from the "more hindered" carbonyl π-face. This value judgement evolves from the assumption that the *mesityl substituent is more sterically demanding than the phenyl substituent*.



1

(*E*)-**2** (favored) (*Z*)-**2** (disfavored)

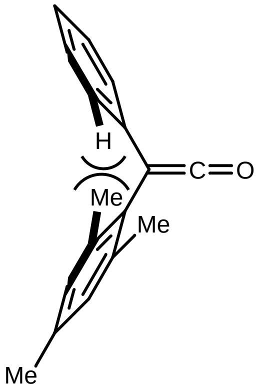
(*E*)/(Z) = 3:1 (kinetic ratio)



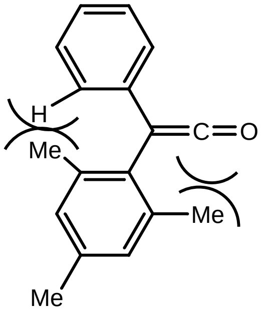
Provide a rationalization for this "contrasteric" ketene addition.

We start by analyzing the conformation of the ketene.

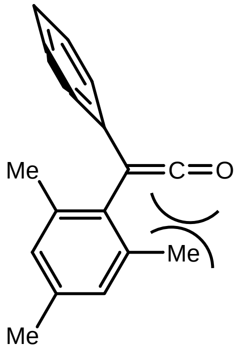
The all out-of-plane orientation has a steric clash between ortho substituents and also lacks any resonance stabilization from the phenyl groups



The all in-plane orientation of the aryl groups results in a very unfavorable clash between ortho groups

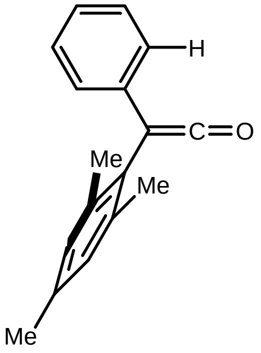


An in-plane orientation of the mesityl group has an unfavorable interaction between the methyl group and the ketene carbon

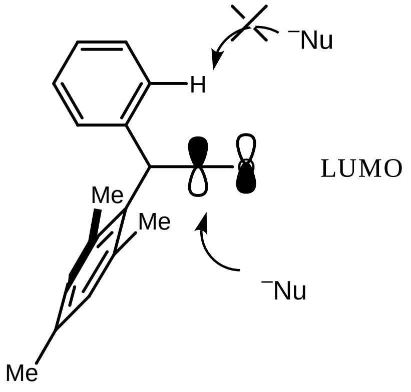


The in-plane orientation of the phenyl group provides some resonance stabilization and has no major steric clashes

FAVORED

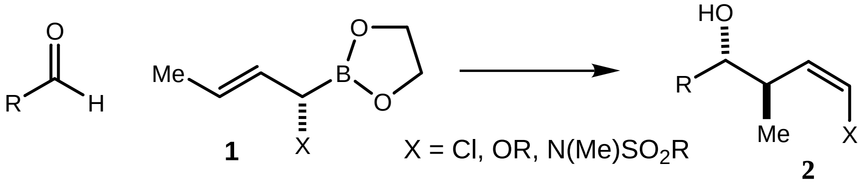


Now we analyze the addition.



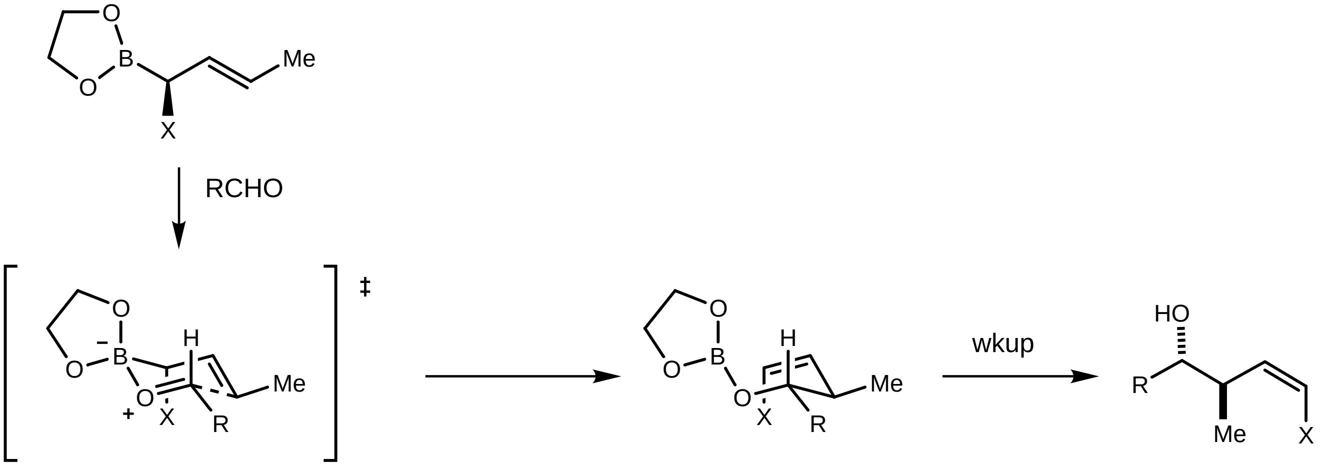
The LUMO of the ketene is in the plane of the substituents. Attack from the face syn to the phenyl group is blocked by the ortho hydrogen. Attack from the face syn to the mesityl is open because the mesityl group is out-of-plane.

Question 8 (20 points). A recent paper by Hoffmann (*Eur. J. Org. Chem.* **2001**, 323) highlights important advances made by this laboratory over the years in enantioselective aldehyde allylboration. A typical reaction developed by Hoffmann is illustrated below. In this case the enantiopure allylboronate **1** is transformed into the *anti* adduct **2** with high selectivities. The absolute stereochemical relationships of **1** and **2** are as illustrated.



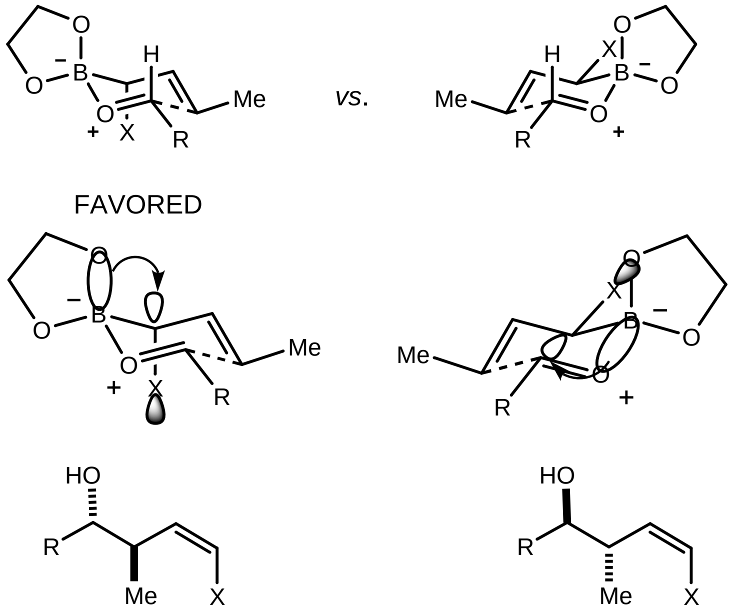
Anti/syn diastereoselection
> 15:1
enantioselection
> 95%

Part A (15 points). Draw the obligatory transition state for this transformation below. A carefully rendered three dimensional illustration is requested.



Part B (5 points). Identify those hyperconjugative effects, if any, that might be involved in transition state stabilization.

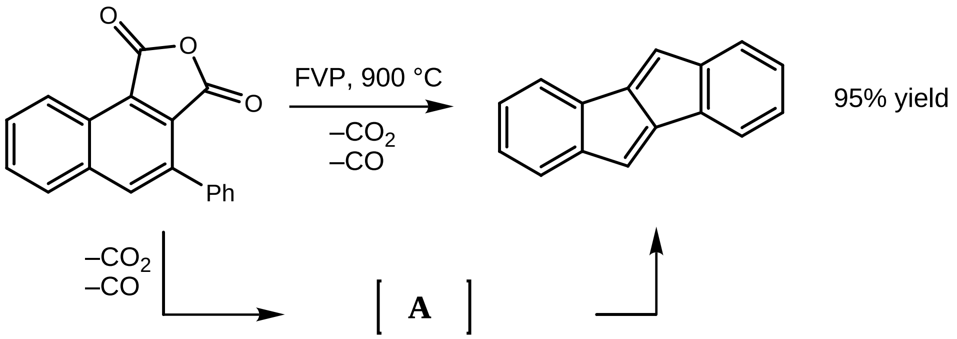
The complex undergoing allyl addition to the aldehyde prefers to have the R group of the aldehyde equatorial. This leaves two options for the position of the X group in the transition state.



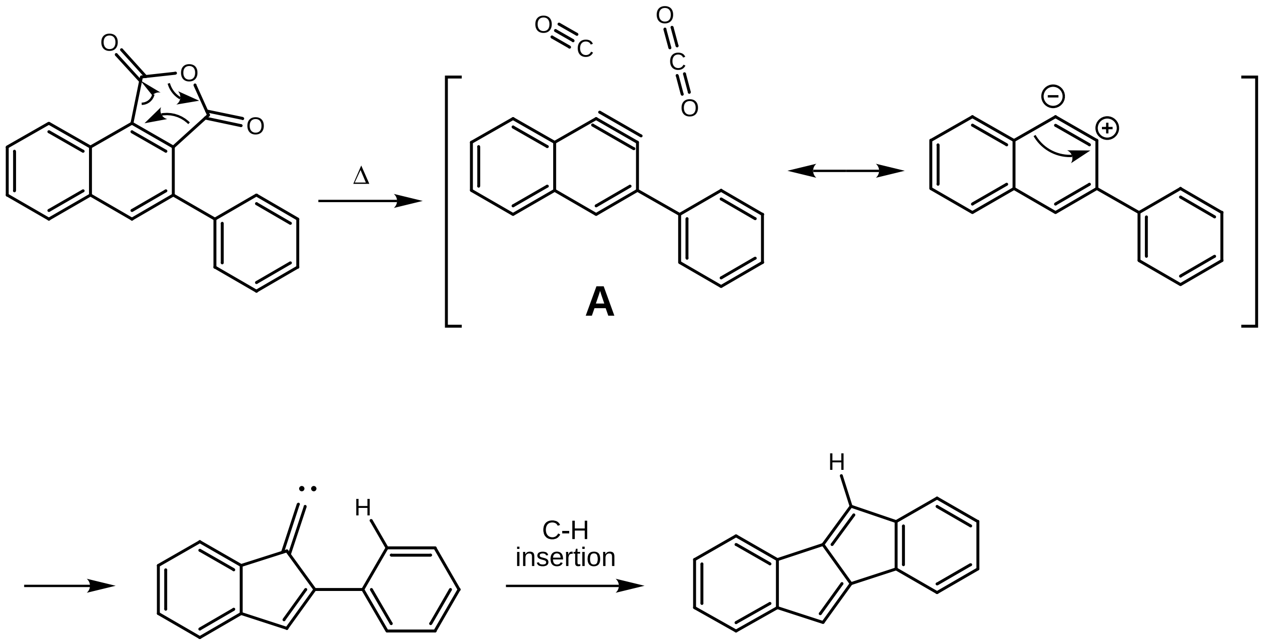
In this conformation, the X group is axial and the axial B-O bond can donate into C-X σ.*

In this conformation, the X group is equatorial and the B-O bond now capable of a hyperconjugative interaction is that of the carbonyl (a less electron rich B-O bond).

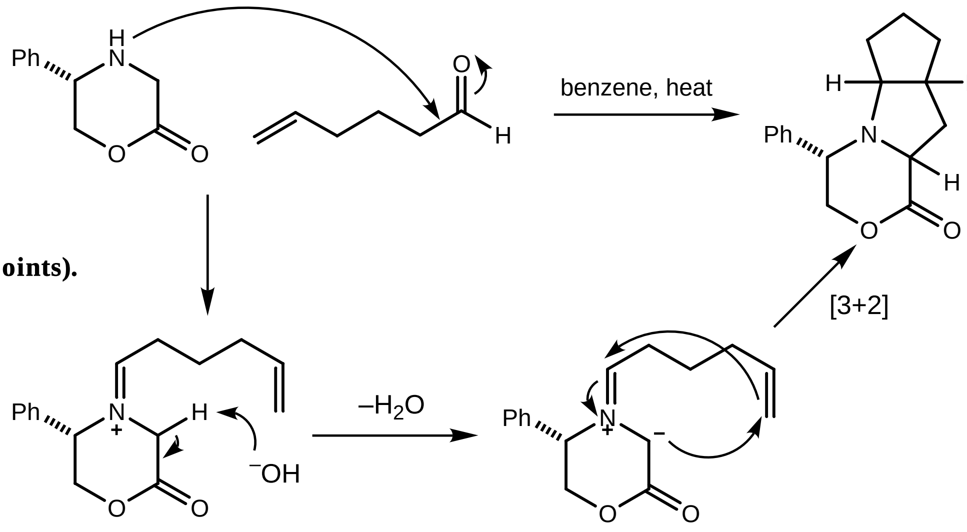
Question 9 (15 points). Anderson has reported the transformation illustrated below (*Aust J. Chem.* **1990**, *43*, 1137) which is implemented by flash vacuum pyrolysis (FVP) at the indicated temperature. As indicated, this reaction proceeds through intermediate **A**.



Provide a concise mechanism for this reaction in the space below and identify intermediate **A** in your answer.

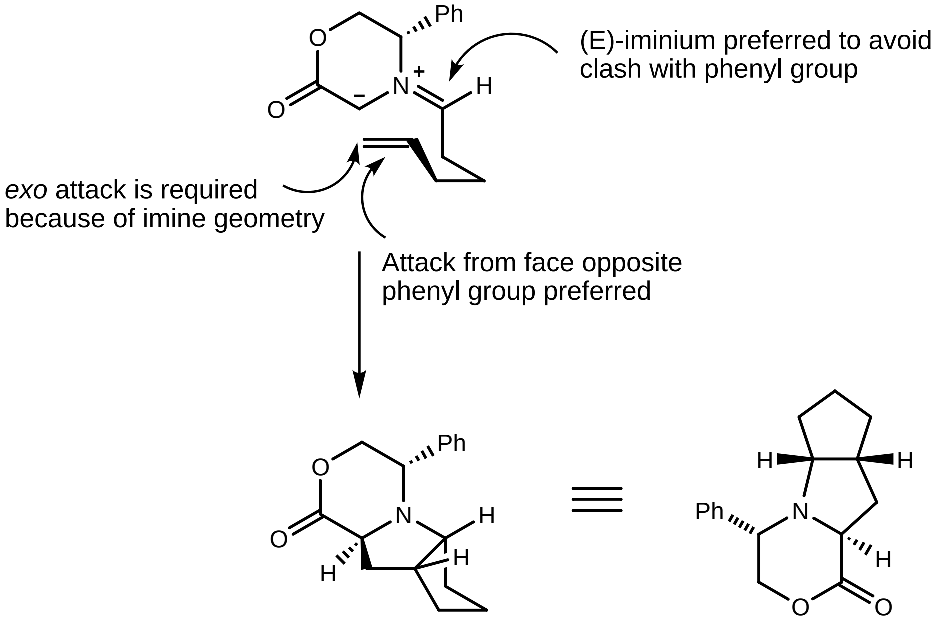


Question 10 (20 points). A recent paper by Harwood and Park highlights the rapidity which whch one may assemble complex architecture in a single chemical operation (*Tetrahedron Lett.* **1999**, *40*, 2907 and earlier cited references). The transformation in question is illustrated below. You are asked to address two aspects of this transformation.



Part A. (10 points).

Part B. (10 points). Predict the stereochemical outcome of the reaction at the three new stereocenters, and provide a three-dimensional drawing of the transition state wherein these centers are produced.

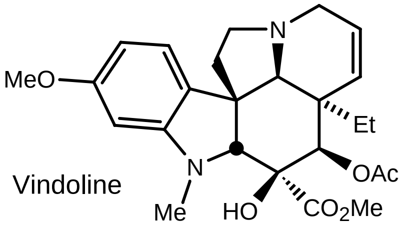


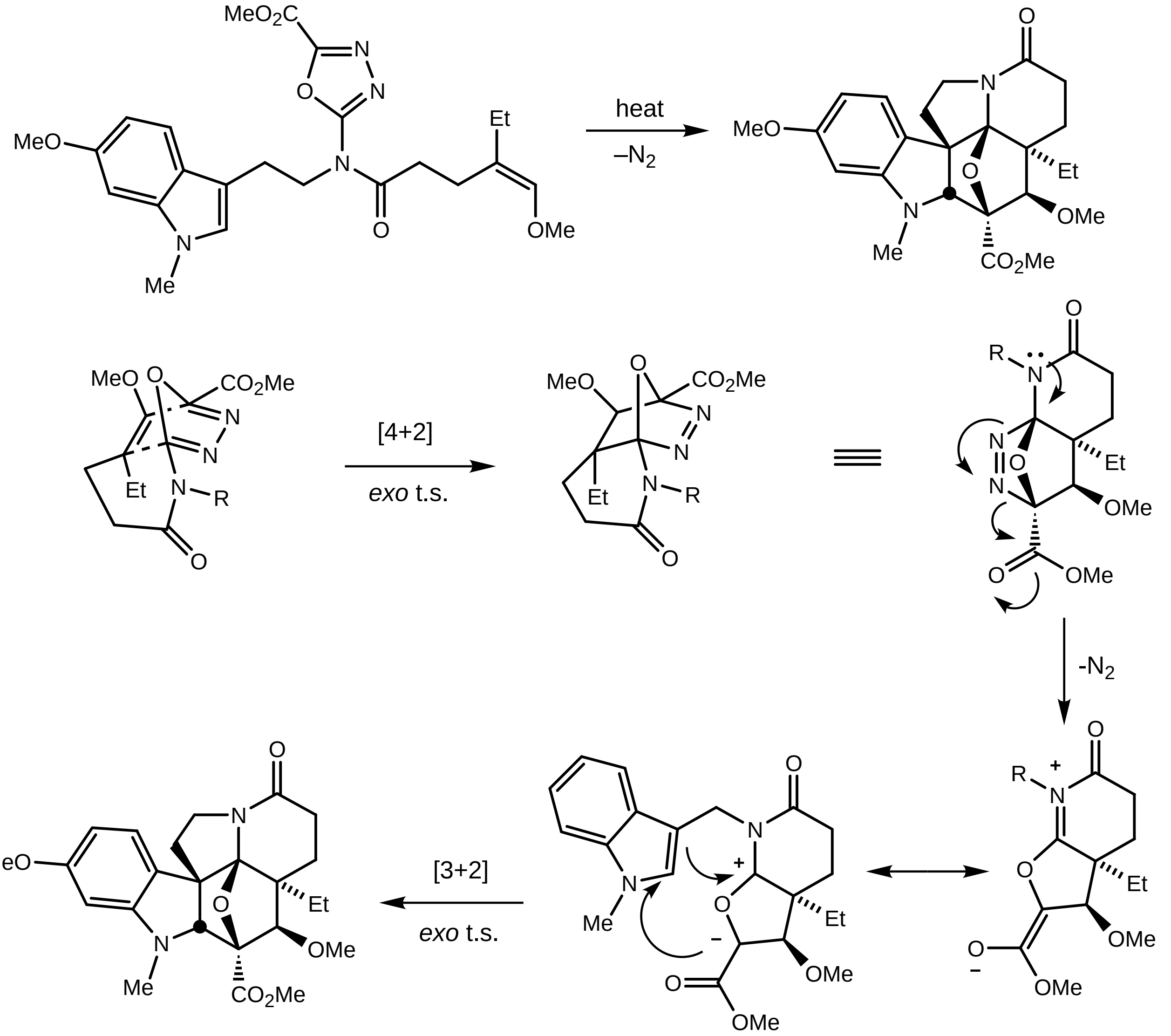
(E)-iminium preferred to avoid clash with phenyl group

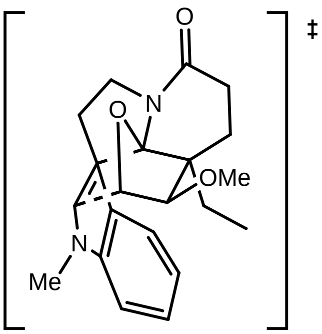
exo attack is required because of imine geometry

Attack from face opposite phenyl group preferred

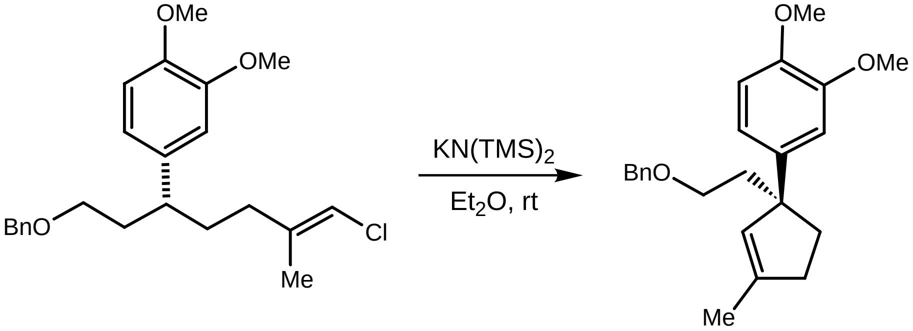
Question 11 (20 points). The indole alkaloid vindoline is an important subunit of the alkaloid vinblastine, an anticancer agent isolated from periwinkle. Boger has reported the transformation illustrated below (*C & E News* **2001**, 27) which has been designed to rapidly assemble the vindoline skeleton.


Vindoline

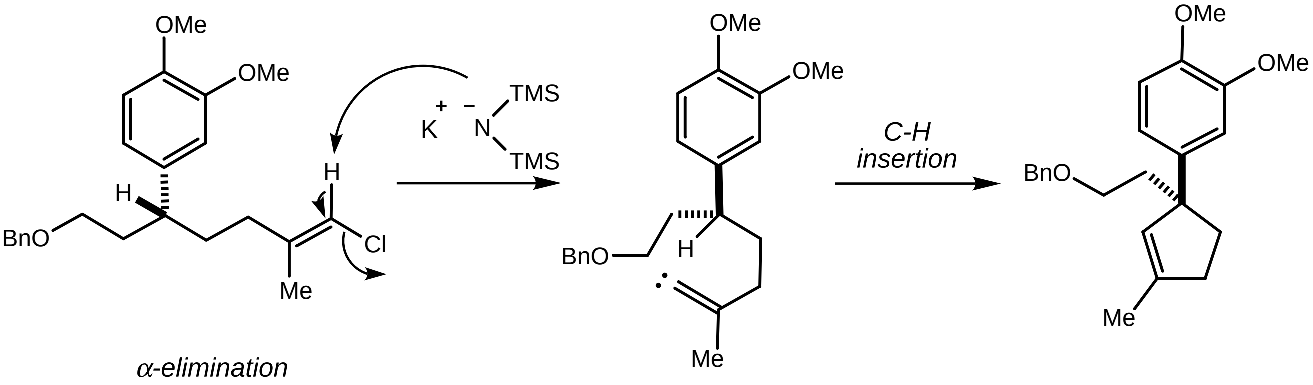




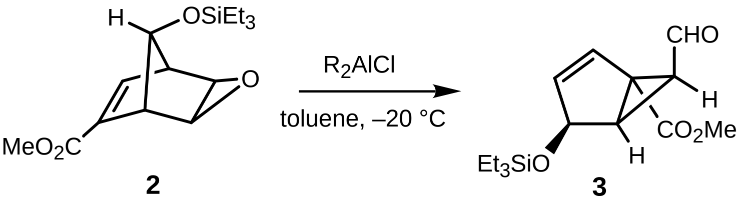
Question 12 (15 points). Taber has recently reported the transformation illustrated below (*J. Org. Chem.* **2001**, *66*, 143). The enantiopure starting material was transformed into the cyclopentene product with complete retention of stereochemical integrity.



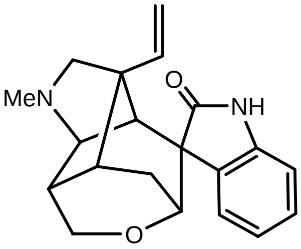
Provide a concise mechanism for this reaction in the space below.



Question 13 (15 points). Fukuyama has recently reported an elegant synthesis of gelsamine (**1**) (*Angew. Chem. Int. Ed.* **2000**, *39*, 4073). During the course of the synthesis, the rearrangement of **2** → **3** was reported (eq 1).

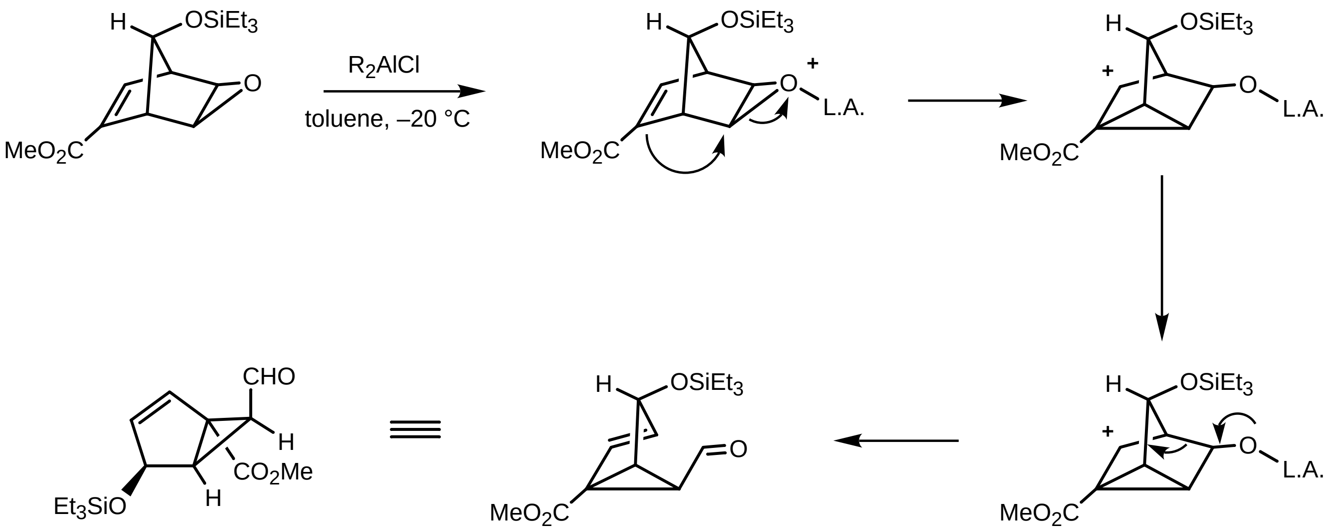


2 **3** (1)

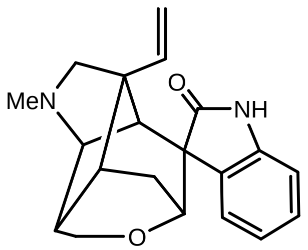


*gelsamine (**1**)*

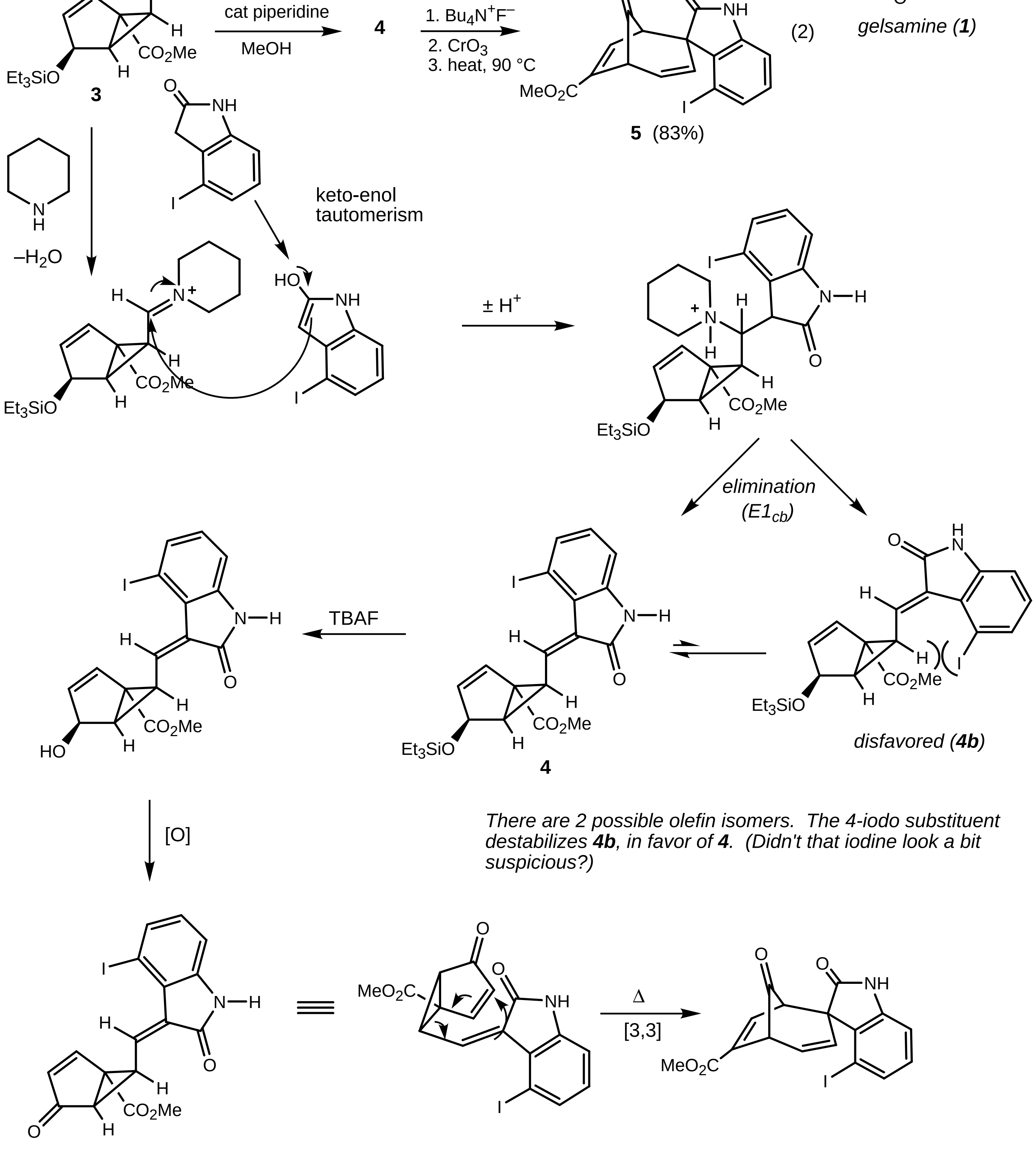
Provide a concise mechanism for this reaction in the space below.



Question 14 (20 points). In Fukuyama's gelsamine synthesis (*Angew. Chem. Int. Ed.* **2000**, *39*, 4073), the rearrangement product **3** was subjected to an aldol condensation with 4-iodooxindole to afford **4**. which, upon deprotection, oxidation, and heating afforded intermediate **5** in an 83% overall yield. Be sure to identify **4** in your answer, and identify any stereochemical ambiguity.



*gelsamine (**1**)*



3 → **4** → **5** (83%)

3

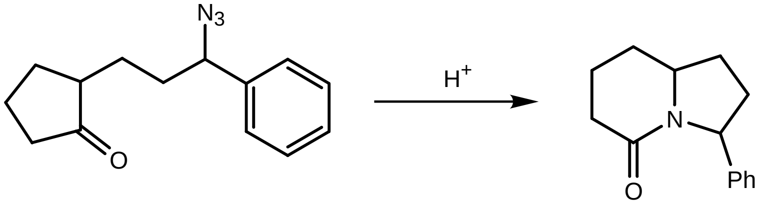
4

5 (83%)

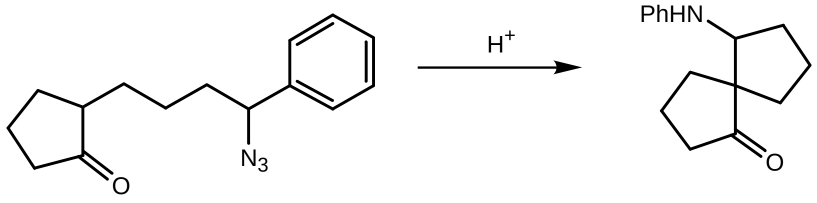
*disfavored (**4b**)*

*There are 2 possible olefin isomers. The 4-iodo substituent destabilizes **4b**, in favor of **4**. (Didn't that iodine look a bit suspicious?)*

Question 15 (20 points). Aube has recently reported the transformations illustrated below (*J. Org. Chem.* **2001**, ASAP). In this study he has documented that the observed product is dependent on the tether length between the azide and carbonyl functional groups.

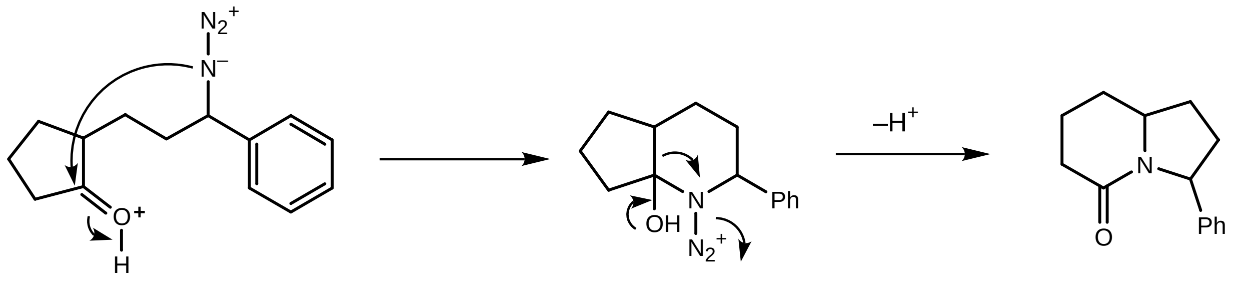


(eq 1)

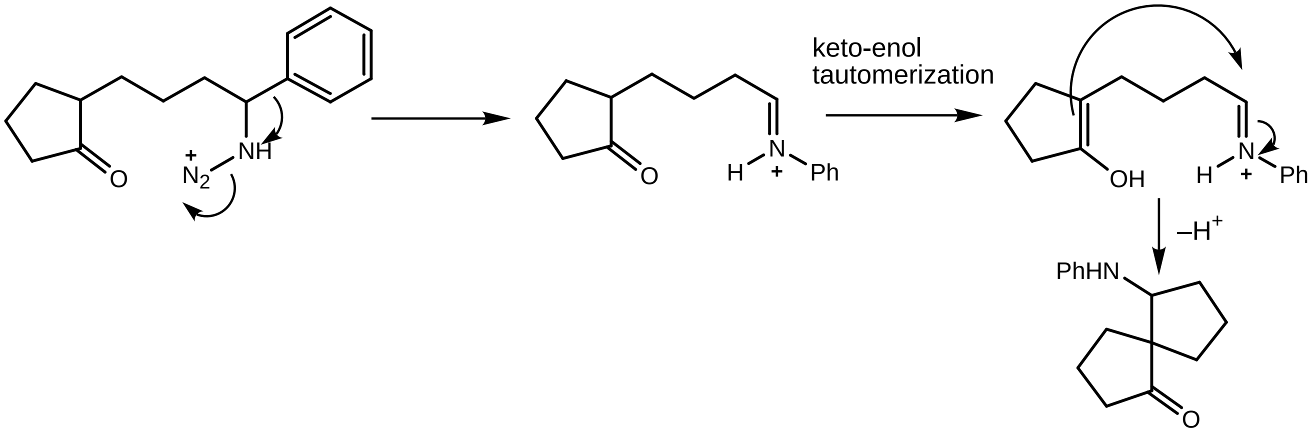


(eq 2)

Part A (8 points). Provide a mechanism for the transformation illustrated in Eq 1.



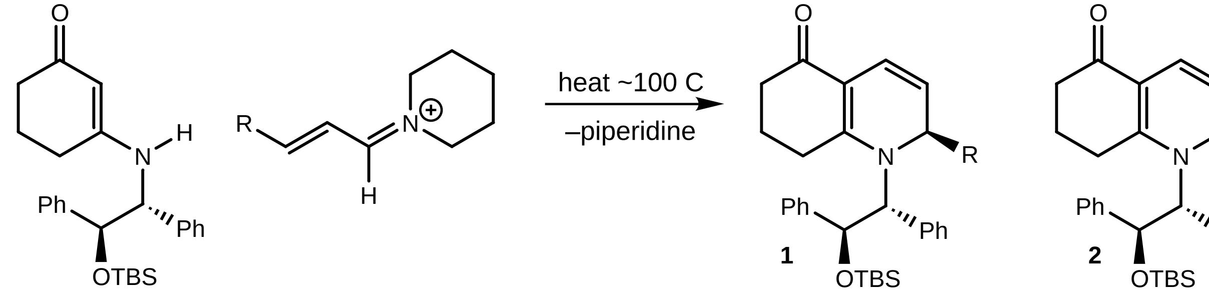
Part B (8 points). Provide a mechanism for the transformation illustrated in Eq 2.



Part C (4 points). Briefly rationalize the difference in reactivity.

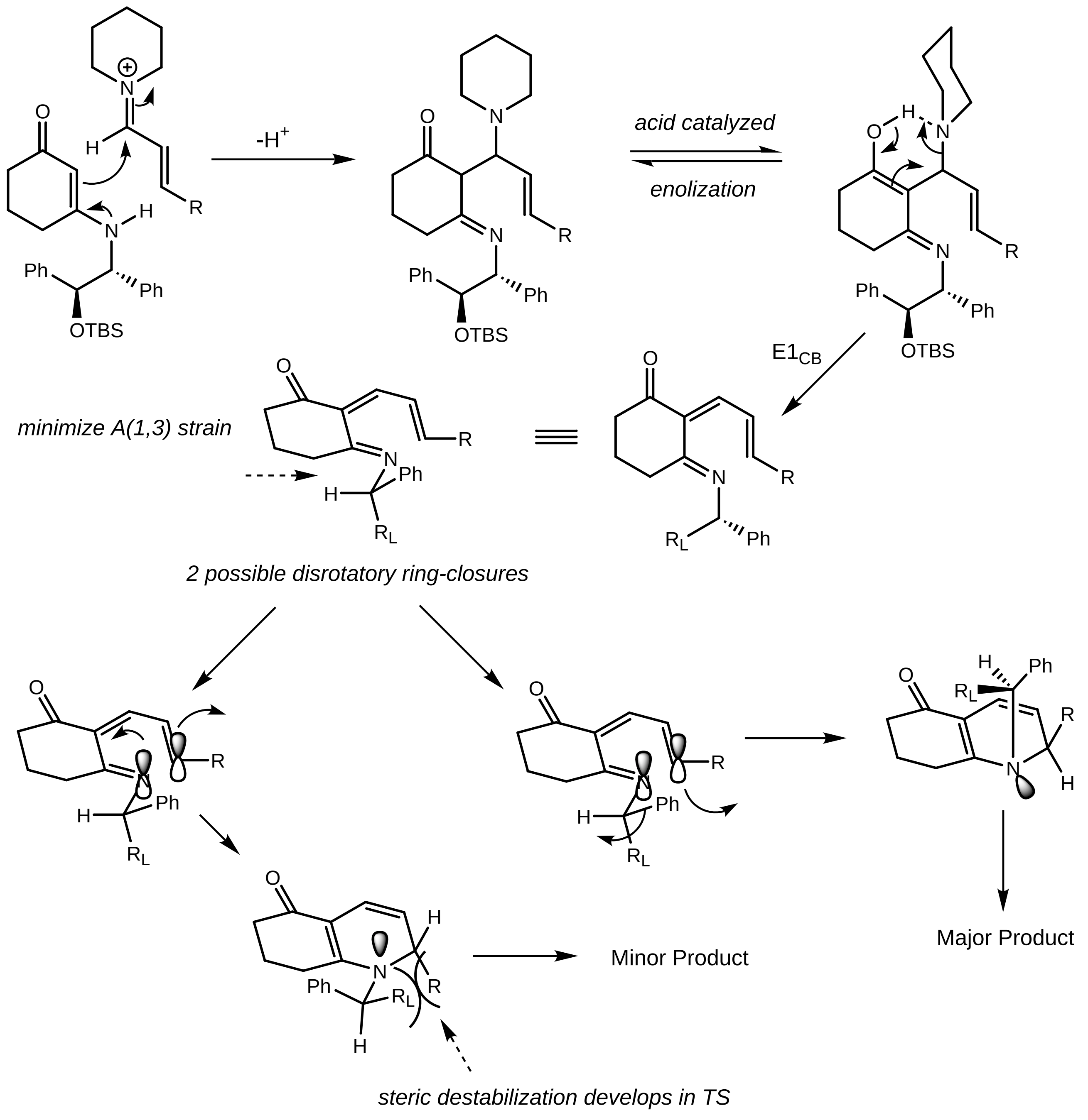
Cyclization of the azide onto the ketone in eq 1 forms a 6-membered ring and is therefore rapid. Cyclization of the azide onto the ketone in eq 2 would need to form a 7-membered ring, which is slow and allows the other reaction pathway to occur.

Question 16 (20 points).



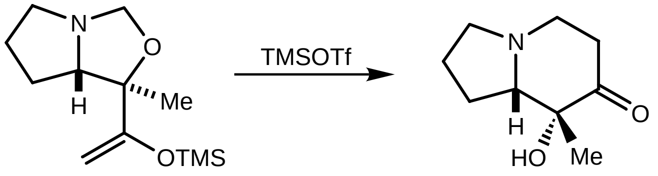
diastereoselection **1: 2** >10:1

Provide a concise mechanism for this reaction in the space below. Please rationalize the observed sense of asymmetric induction.



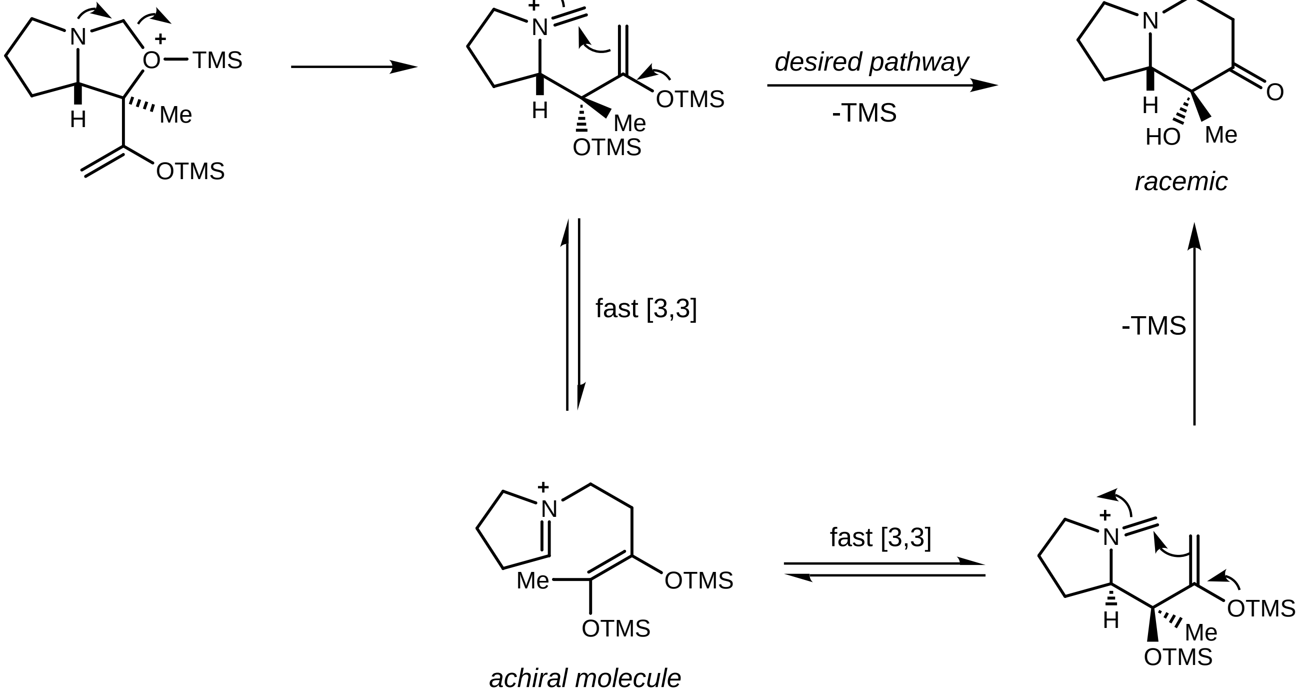
Question 17 (15 points). During the course of the synthesis of pumilotoxin (*J. Org. Chem.* **1992**, *57*, 1179) the indicated transformation was carried out with the expectation that the bicyclic ketone **2** would be enantiopure since the starting amine **1** was enantiomerically pure. Surprisingly, product **2** was obtained as a racemate.

1 *(enantiopure)*

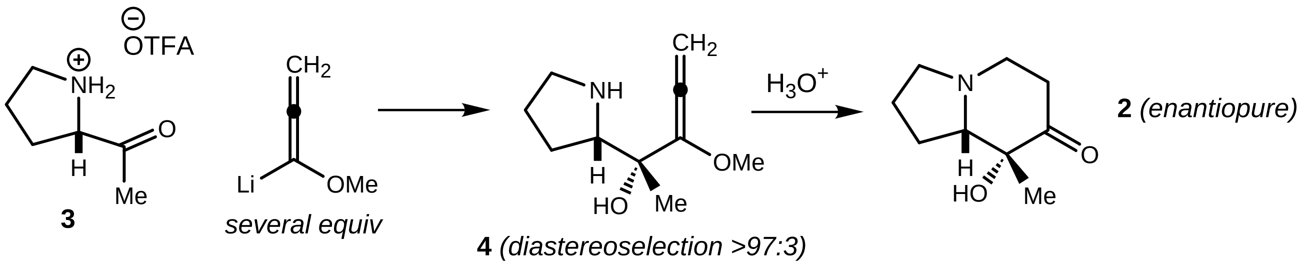


2 *(racemic)*

Provide a mechanism for this transformation that accounts for the illustrated stereochemical outcome.



Question 18 (20 points). The revised synthesis of enantiomerically pure **2** is illustrated below (*J. Org. Chem.* **1992**, *57*, 1179). Addition of **3** to several equivalents of the illustrated allenyllithium reagent afforded carbonyl adduct **4** as a single diastereomer. This intermediate was then transformed into enantiopure **2** under acidic conditions.



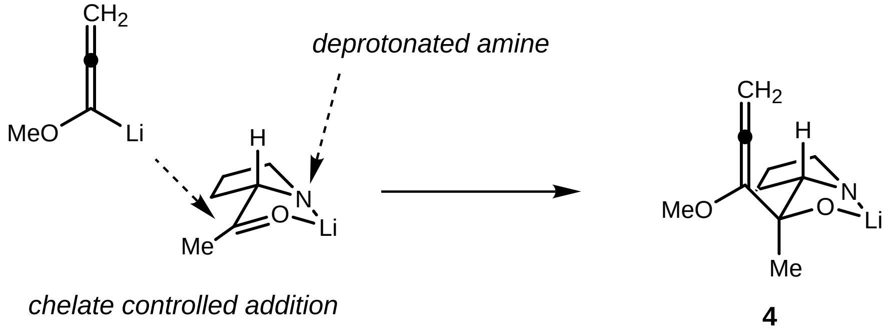
3

several equiv

4 *(diastereoselection >97:3)*

2 *(enantiopure)*

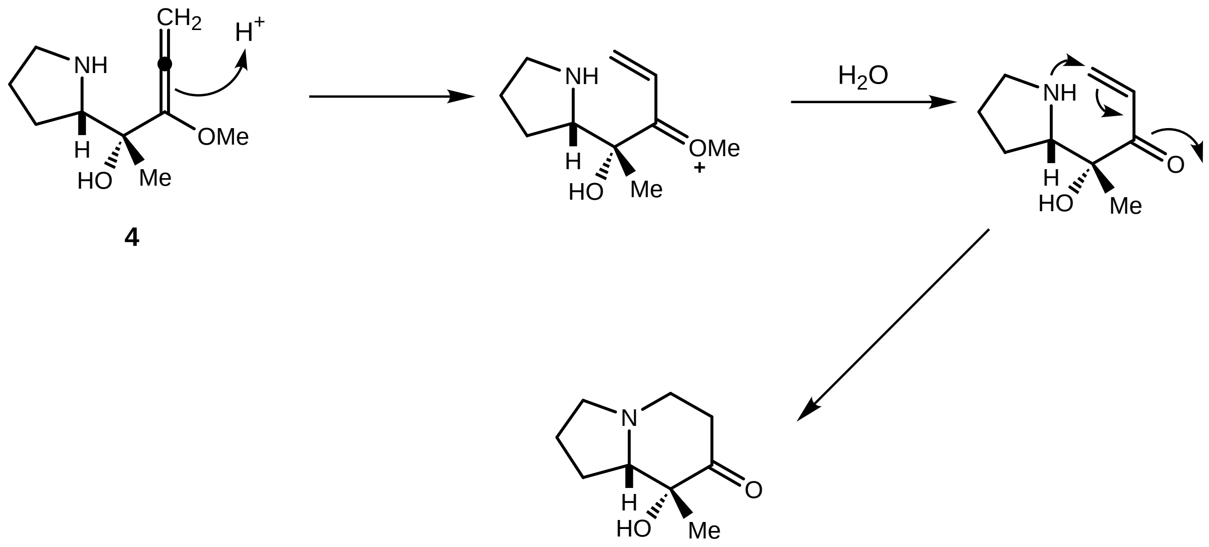
Part A. Provide an explanation for the high level of stereocontrol that is observed in the carbonyl addition step. A three dimensional drawing of the carbonyl addition transition state is requested in conjunction with this answer.



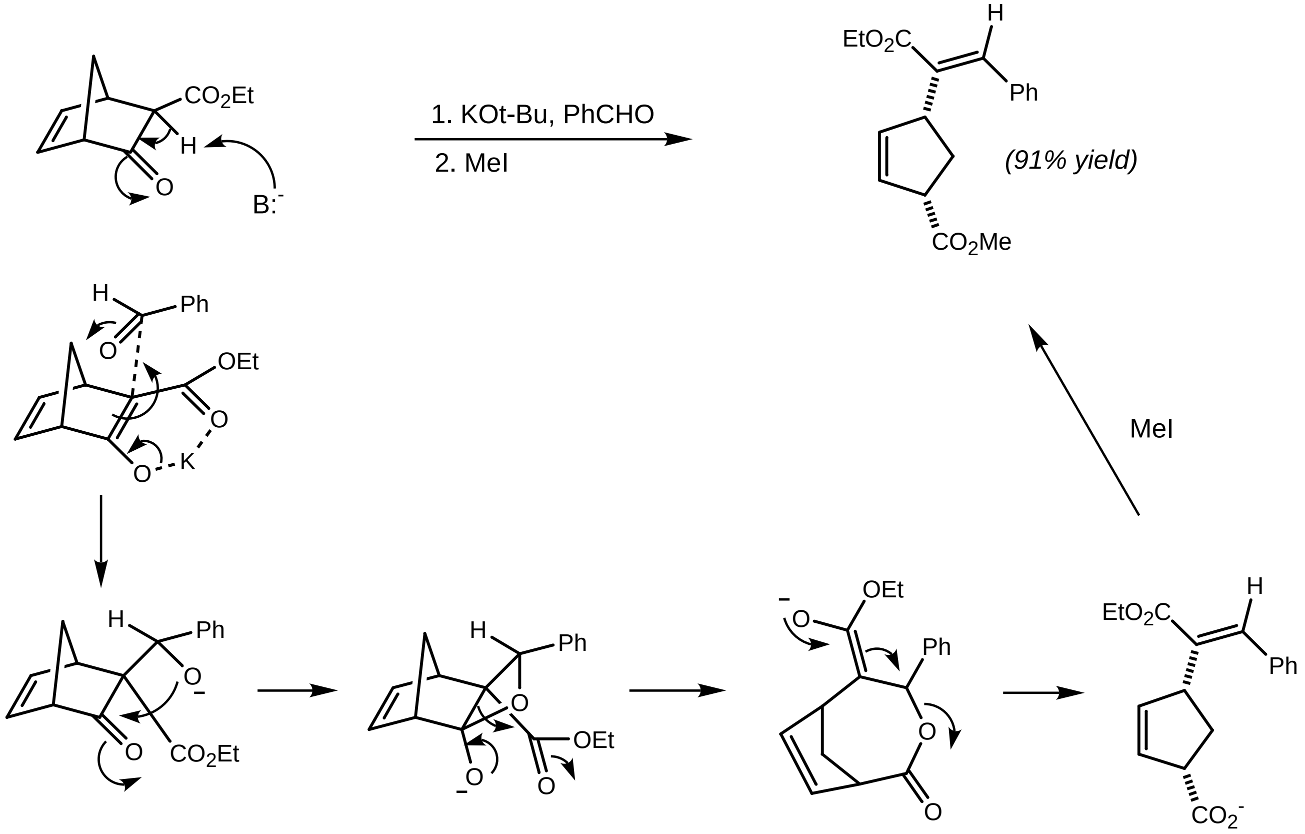
chelate controlled addition

4

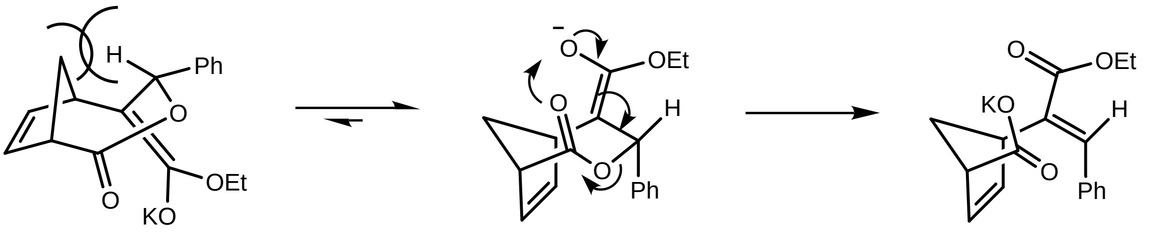
Part B. Provide a mechanism for the transformation of **4** to **2**.

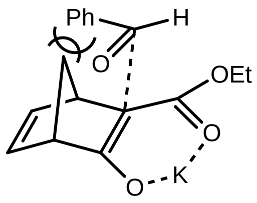


Question 19 (20 points). Rainer and Xiu (*Org. Lett.*, **1999**, 27) recently reported the remarkable fragmentation reaction illustrated below.



Part B: Provide an explanation for the observed olefin stereochemistry.





Attack on the norbornene system occurs from the top face. The diastereomer observed results from avoiding a steric interaction with the methylene bridge.

For elimination to occur, σ^* C-O must be aligned anti-periplanar to πC-C. There are two conformations of the seven-membered ring which satisfy this requirement. One places the phenyl group equatorial, but suffers from destabilizing transannular interactions. The other places the phenyl group axial, but avoids transannular interactions by placing sp^2 hybridized carbons at the 3 and 6 positions of the seven-membered ring. One could invoke a π-π stacking interaction between the necessarily axial olefin and the phenyl group.

Chemistry 206
Final Examination Answer Key

D. A. Evans
January 23, 2006

This examination contains **16** questions (16 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

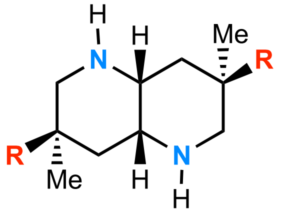
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**20**)	_______	No. 9 (**20**)	_______
No. 2 (**20**)	_______	No. 10 (**20**)	_______
No. 3 (**15**)	_______	No. 11 (**20**)	_______
No. 4 (**20**)	_______	No. 12 (**20**)	_______
No. 5 (**20**)	_______	No. 13 (**20**)	_______
No. 6 (**15**)	_______	No. 14 (**20**)	_______
No. 7 (**15**)	_______	No. 15 (**20**)	_______
No. 8 (**20**)	_______	No. 16 (**15**)	_______
Subtotal (**145**)		Subtotal (**155**)	

171 (57%)

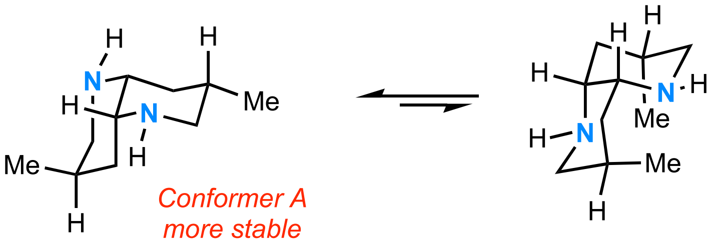
exam average

Question 1. (20 points). While investigating new diamine ligand scaffolds for asymmetric catalysis, Kozlowski and Xu (*J. Org. Chem.* **2002**, *67,* 3072) constructed a variety of 1,5-diaza-*cis*-decalins. They found that by altering substitution patterns on the parent scaffold, they could stabilize one conformer over the other. For example, when two addional methyl substituents were introduced onto the following dimethyl substituted 1,5-diaza-*cis*-decalin, the preferred ground-state conformer was altered.



R	Ratio (Conformer A:Conformer B)
H	80:20
Me	10:90

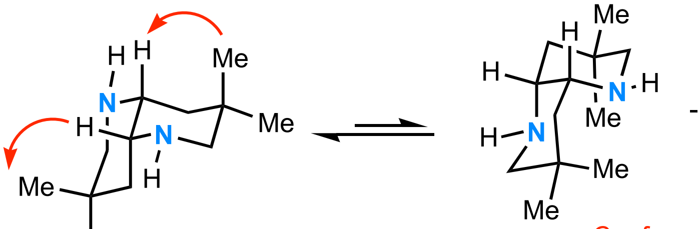
Part A (8 points). Please provide a clear 3-dimensional representation of both conformers when R = H. Identify the more stable conformer and the chief destabilizing interactions in the less stable conformer.



Conformer A more stable

-two 1,3 diaxial interactions (NH and Me)

Part B (8 points). Identify the new destabilizing interactions that occur on the more stable conformer from **Part A** when two additional methyl groups are introduced. Provide a clear 3-dimensional drawing of the most stable conformer in the geminal dimethylated case.

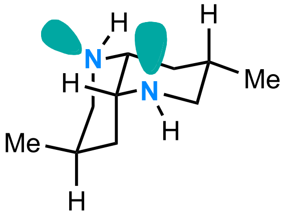


-now two additional 1,3 diaxial H-Me interactions which are more destabilizing than the corresponding N–Me interaction in Conformer B

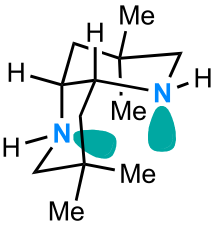
Conformer B more stable

-still two diaxial 1,3 interactions (NH and Me)

Part C.(4 points) Based on your analysis, which of the two systems (R = H or R = Me) should serve as a better metal chelating agent (ligand) for possible asymmetric catalysis?

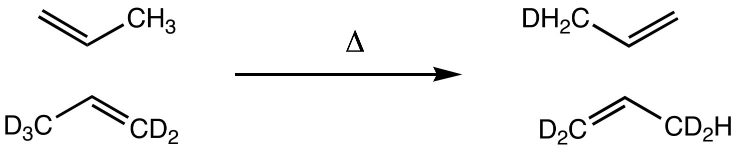


-axial lone pairs pointed away from each other and out of pocket formed by rings = poor chelating ligand



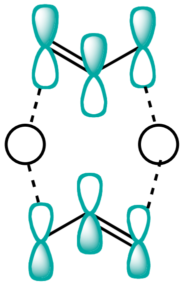
-axial lone pairs pointed into the pocket formed by the rings = able to chelate a metal well

Question 2. Part A (10 points). For the process indicated below please use either the Dewar Zimmerman or FMO analysis to predict whether isotope scrambling is allowed under thermal conditions.



Your Answer:

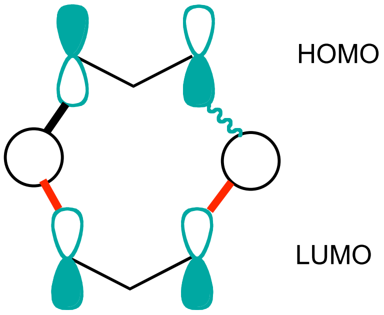
Dewar-Zimmerman



0 Phase inversions,
8 electrons, Huckel Topology,
Forbidden

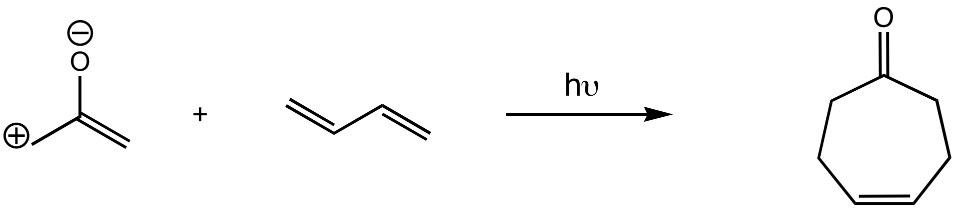
zero or even inversions:

FMO Analysis



Simultaneous bonding at both termini not possible
Forbidden

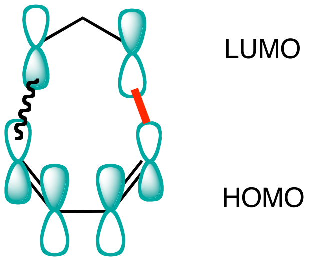
Part B. (10 points). Using FMO analysis, please predict whether the following cycloaddition is allowed under photochemical conditions.



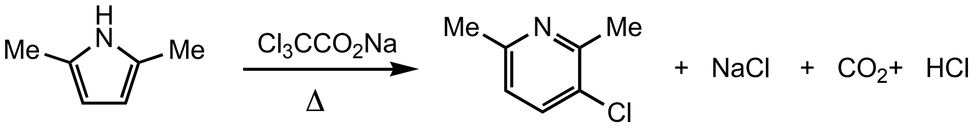
HOMO of diene is raised in energy. Hence, ψ_3 is the new HOMO

Using the raised HOMO of the cation with the LUMO of the diene gives the same answer.

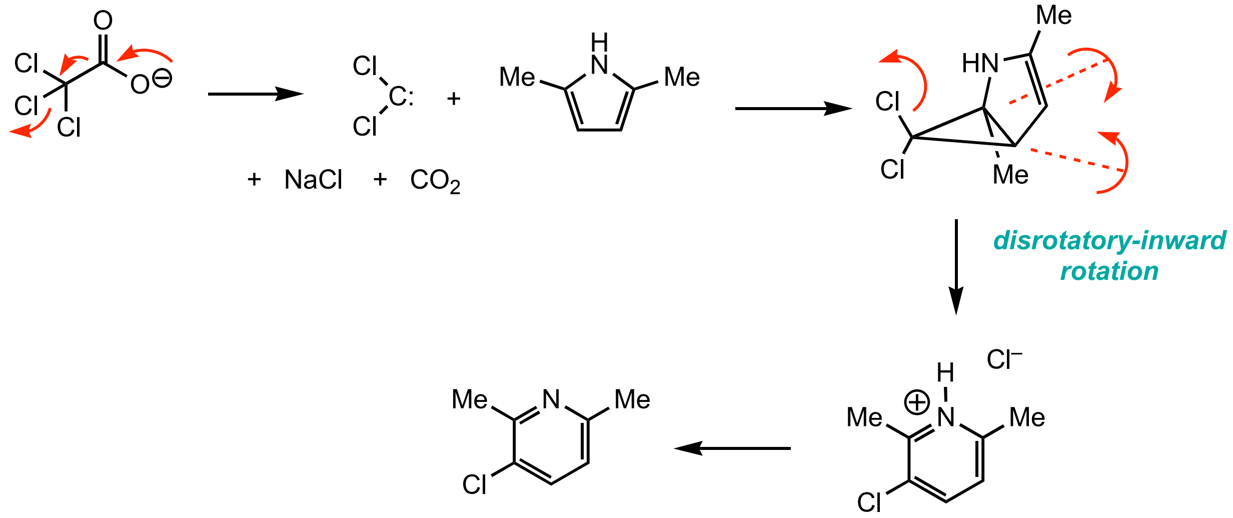
destructive overlap



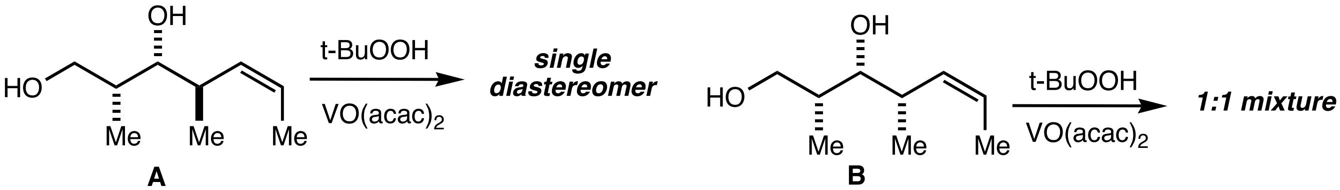
Question 3. (15 points). The following reaction was reported for the synthesis of substituted pyridines as shown below. Provide a reasonable mechanism for the transformation. Identify and describe any pericyclic processes that might be involved(Thomas L. Gilchrist, *Heterocyclic Chemistry.* 3rd Ed. Longman Press: England, **1997**).



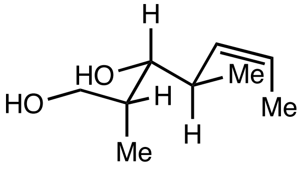
Your Answer:

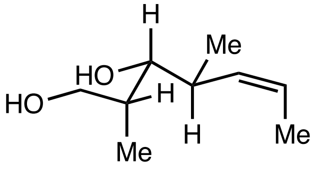


Question 4. (20 points). Sharpless expoxidation of diol **A** gives rise to a single product, while epoxidation of diol **B** affords a 1:1 mixture (*Eur. J. Org. Chem.* **1999**, 2929-2936).



Part A. (10 points). Please provide a clear 3-dimensional representation of the lowest energy conformer of both **A** and **B**. Be sure to indicate why these conformers are favored.

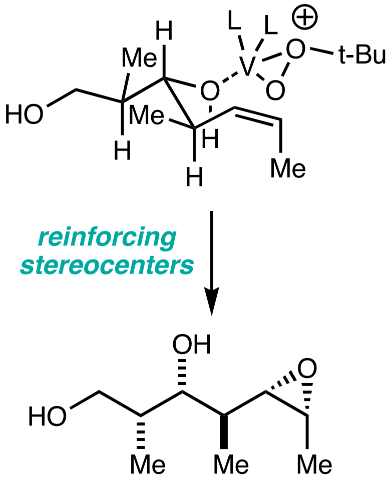




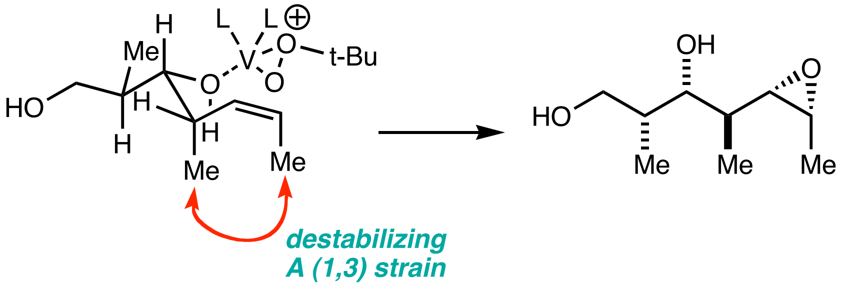
All Allyl strain and syn pentane interactions minimized

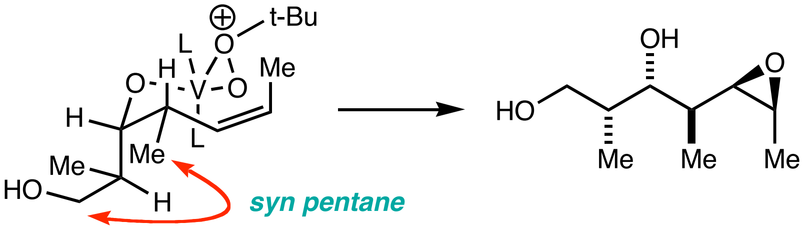
Part B. (10 points). Please predict the product formed by the epoxidation of **A**, and provide a clear rationale as to why **B** displays no diastereoselectivity. Indicate all relevant destabilizing interactions.

For A:



For B: Stereocenters are opposing each other

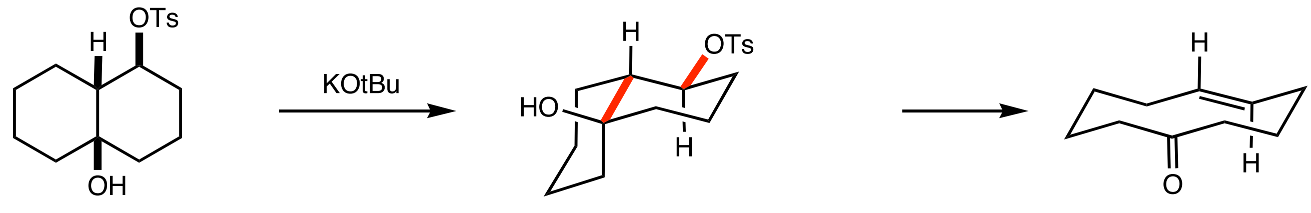




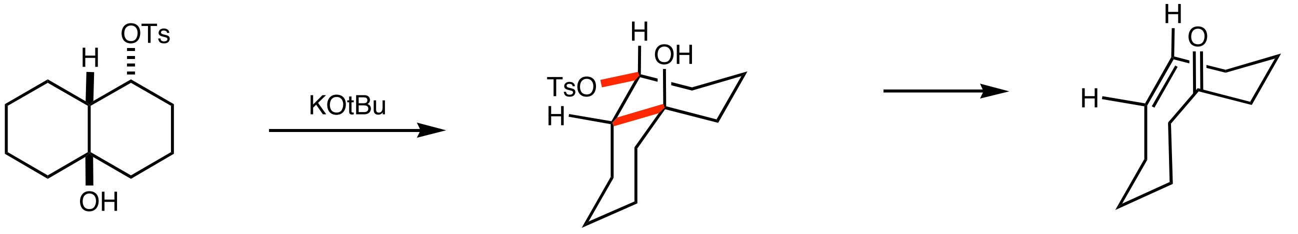
In this case reactions proceeding through either conformer are subject to severe destabilizing interactions. The results suggest that is little preference for one conformer.

Question 5. (20 points). The following alkoxide-induced reactions have been systematically studied by Wharton et al. (*J. Org. Chem.* **1965,** *30*, 3254 and prior citations). The illustrated substrates will undergo fragmentation to an olefinic ketone if the appropriate stereoelectronic constraints are met. If these constraints cannot be met, E2 elimination to the derived bicyclic olefinic alcohol will take place.

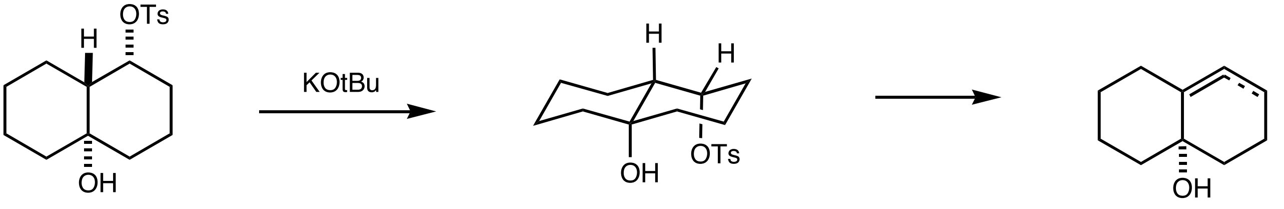
Predict the principal product observed in each instance (**B**) and draw the reactive conformation (**A**) that meets the stereoelectronic conditions for the reaction. Put your answers in the space provided.



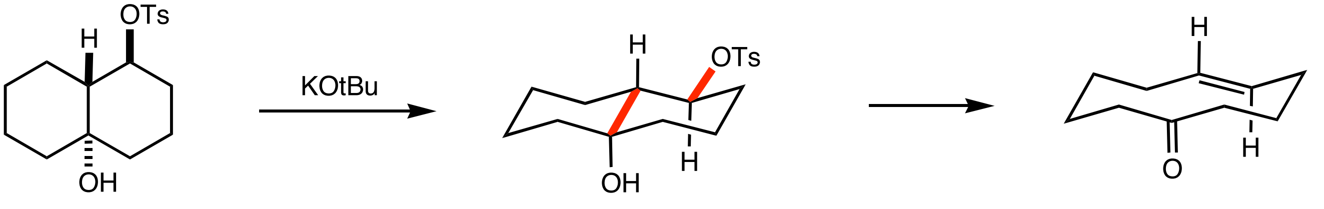
(A) *reactive conformation* **(B)** *product*



(A) *reactive conformation* **(B)** *product*

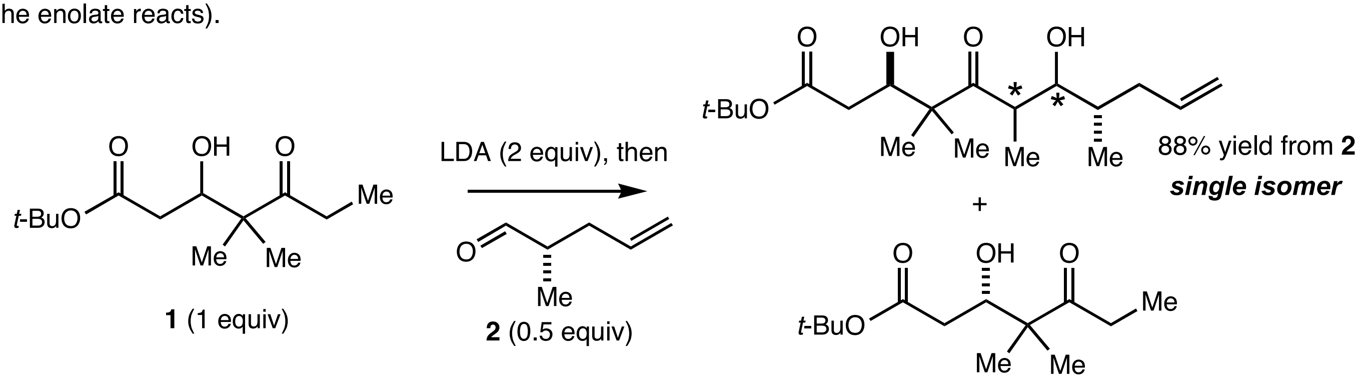


(A) *reactive conformation* **(B)** *product*



(A) *reactive conformation* **(B)** *product*

Question 6. (15 points). During the preparation of epothilone analogs, the following aldol reaction was investigated by Danishefsky and Zhang (Zhang, *PHD Dissertation*, **2003**). It was noted that if only 0.5 equivalents of the enantiopure aldehyde **2** was used then effective kinetic resolution of the racemic ketone **1** was achieved (*ie* only one enantiomer of the enolate reacts).

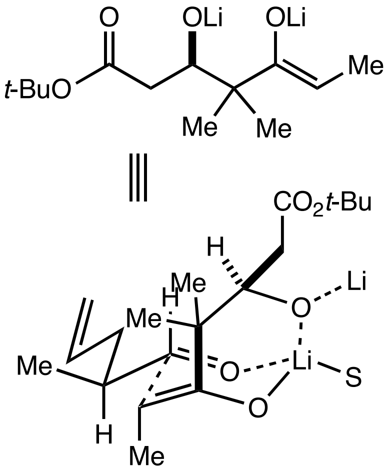


Using clear three dimensional representations please provide a rationale for the observed resolution and predict the relative stereochemistry of the aldol adduct (***HINT***: The enolate is likely to be chelated with the beta-alkoxy substituent).

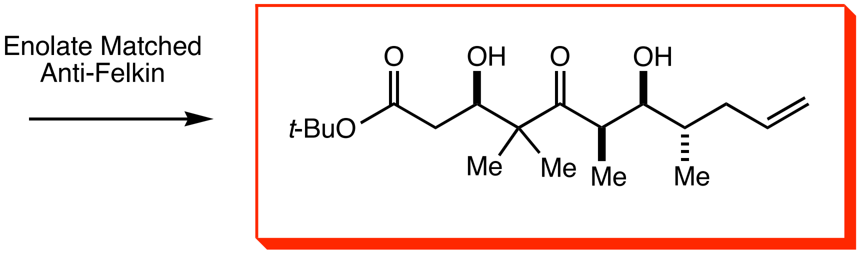
Your Answer:

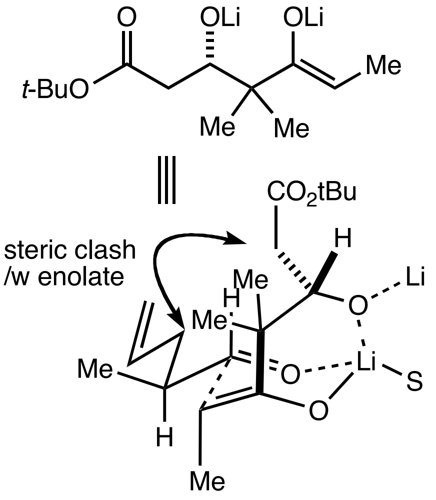
Z-enolate is formed (E-enolate would suffer severe A1,3 strain interactions). From four possible diastereomers, only the one that has the stereoreinforcing relationship of aldehyde and enolate is formed.

Z-enolates are inherently anti-Felkin selective as Felkin addition proceeds with a forming syn-pentane interaction.

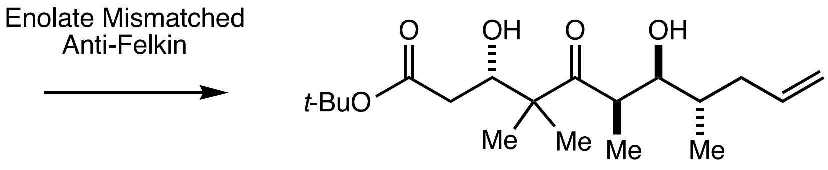


This is a matched case where we have favorable anti-Felkin addition across the least hindered face of the enolate.

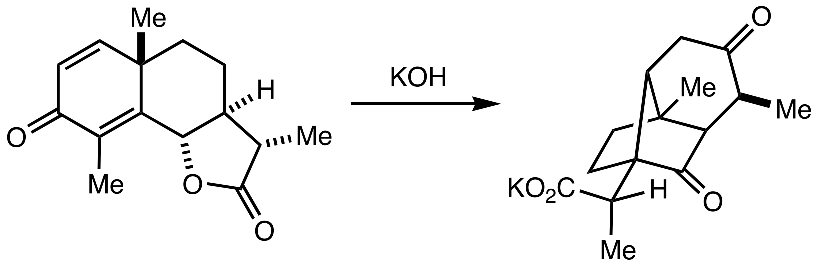




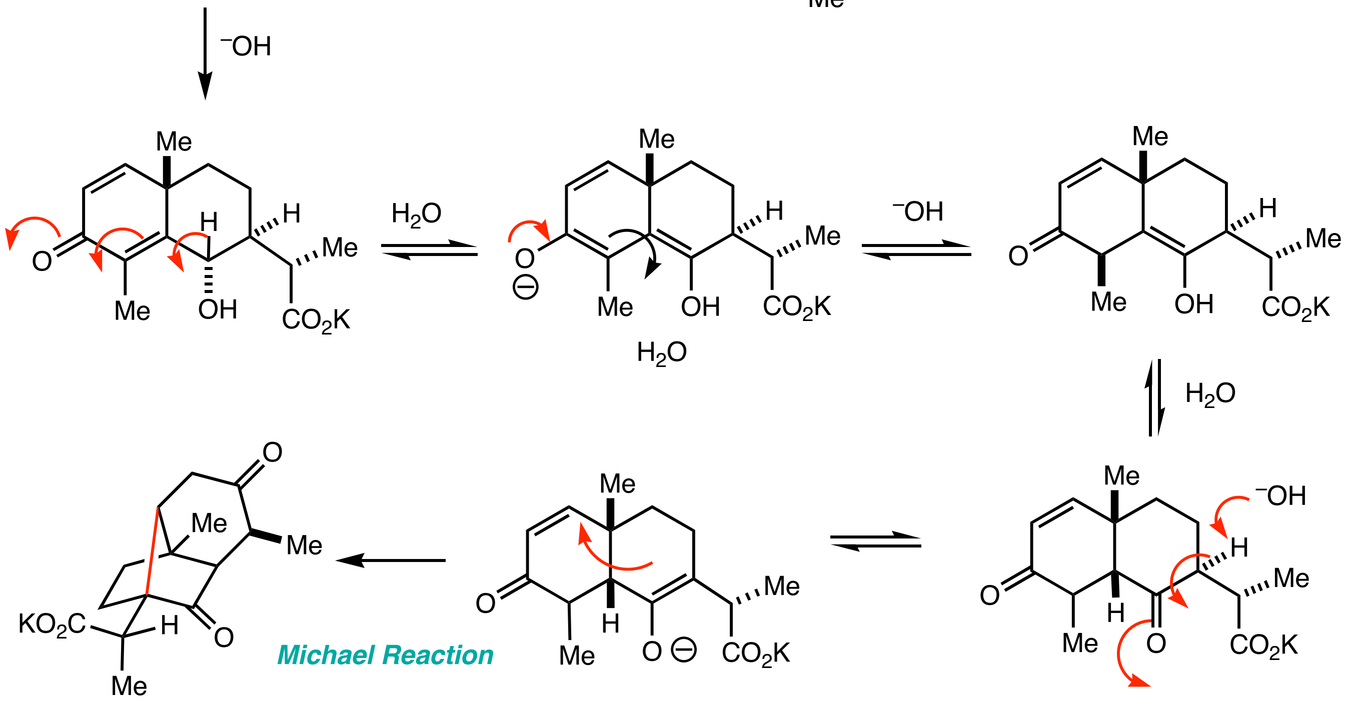
Reaction of this enantiomer in an anti-Felkin manner requires addition across the hindered face of the enolate - this is slow and hence this enantiomer does not react.



Question 7. (15 points). Woodward and coworkers reported the following base-promoted conversion of α-santonin into potassium santanoate as part of a classic natural product structural determination *(JACS* **1948,** *70*, 4216). In the space below please provide a concise mechanism for this intriguing rearrangement.
Hint: Work on the analysis of this transformation bi-directionally.

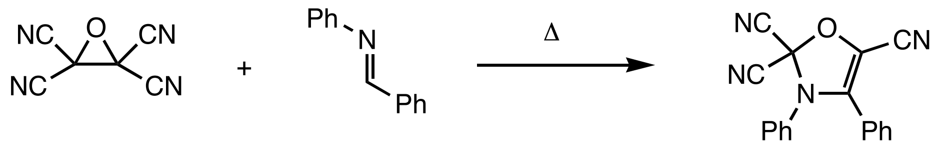


Your Answer:

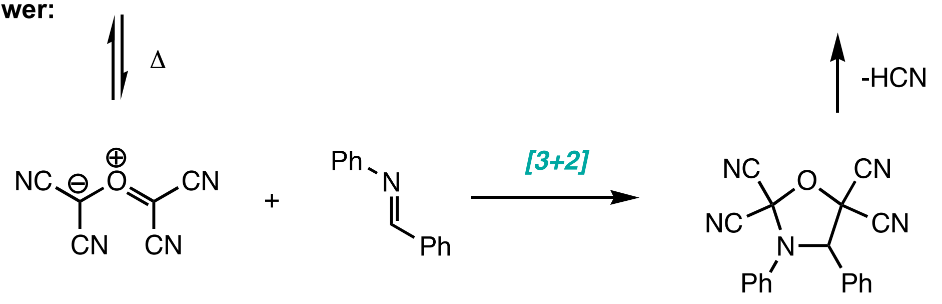


Question 8. (20 points). Many interesting and useful methods have been developed for the synthesis of heterocyclic molecules.

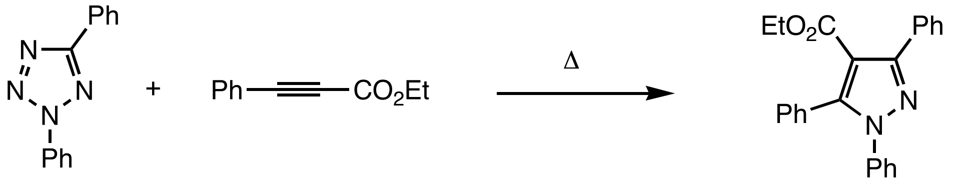
Part A. (10 points). The following reaction for the synthesis of oxazoles was developed by Linn and coworkers (*JOC* **1969**, 2146). Please provide a detailed mechanism for this reaction.



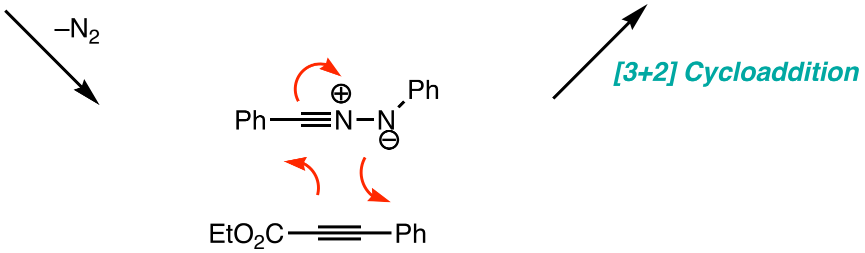
Your Answer:



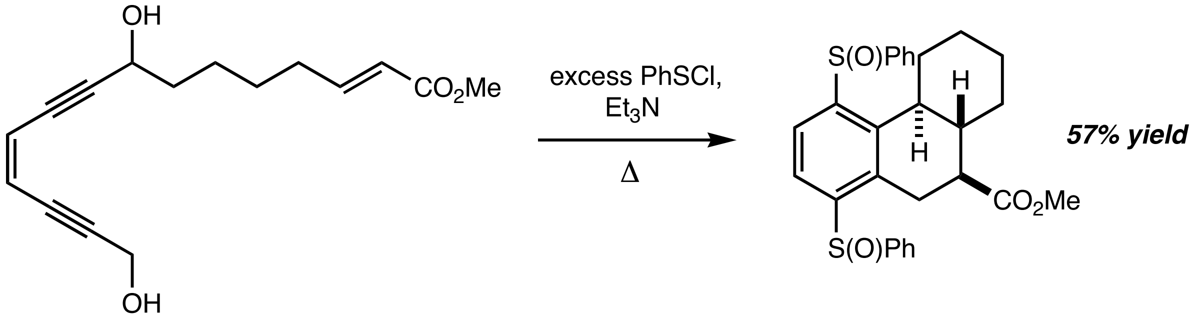
Part B. (10 points). Huisgen reported the use of tetrazoles as versatile precursors for the synthesis of substituted pyrazoles (*Tetrahedron* **1962**, *17*, 3). Please provide a detailed mechanism for this transformation.



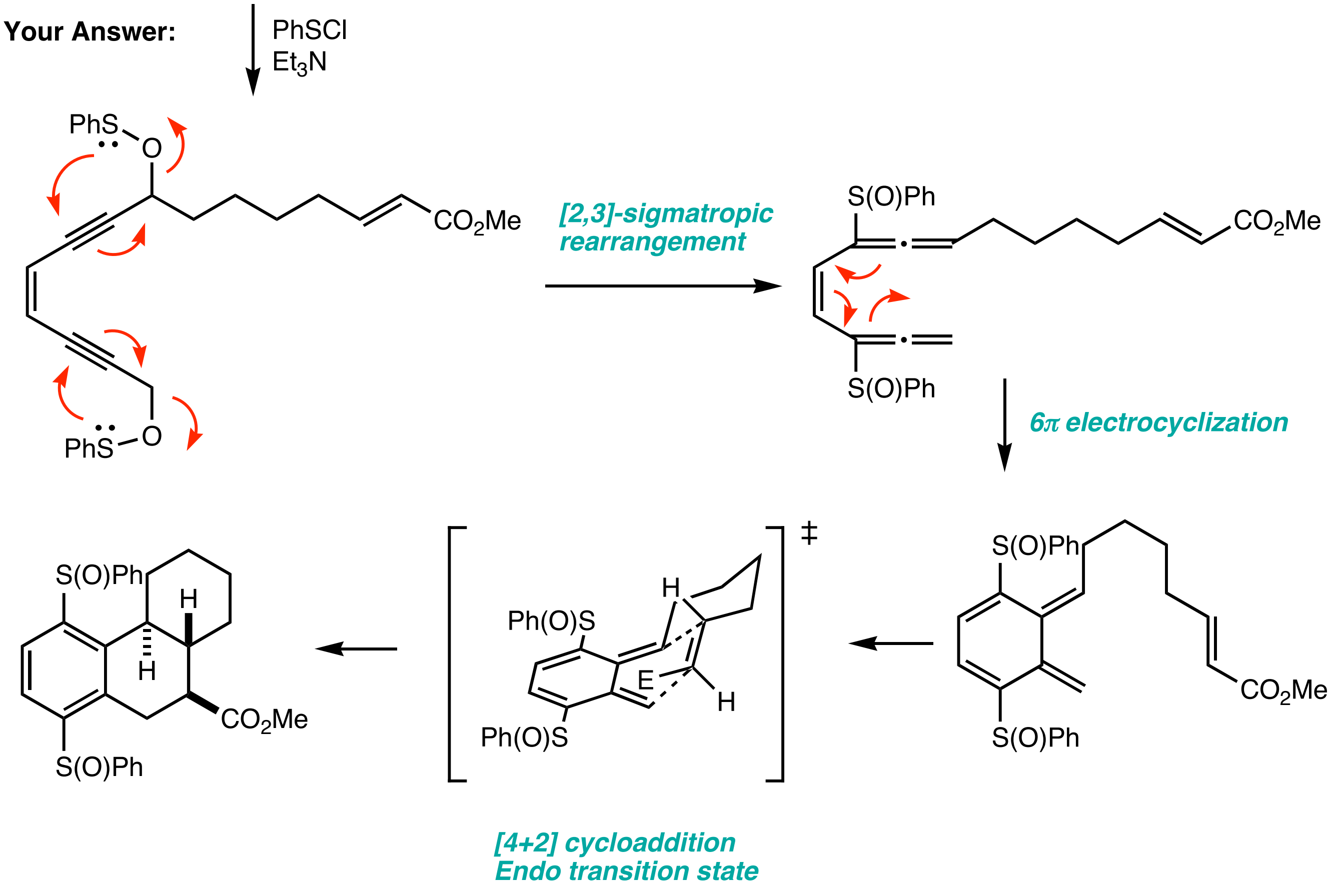
Your Answer:



Question 9. (20 points). The following cascade reaction to convert a linear precursor into a complex tricyclic structure was very recently reported (*Org. Lett.* **2006**, *8*, 95). In the space below please provide a detailed mechanism for this reaction. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.

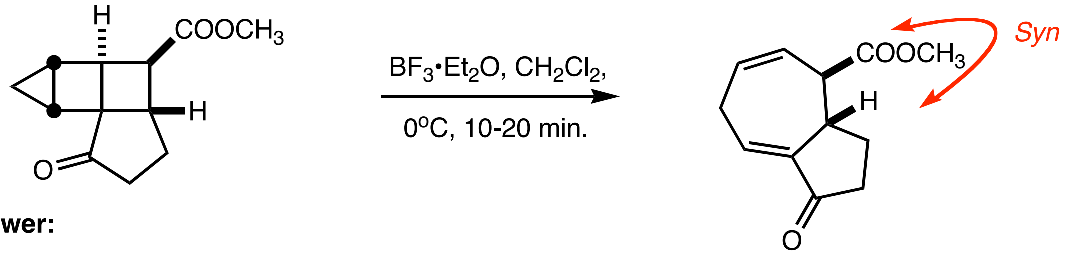


Your Answer:

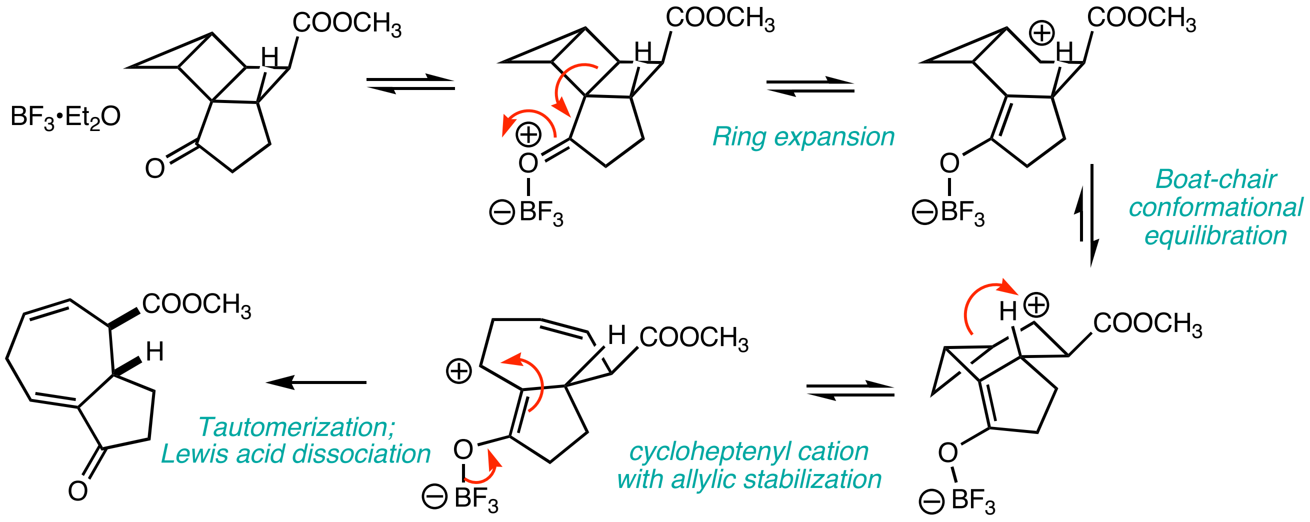


Question 10. (20 points). Snapper and co-workers have recently identified a mild, Lewis acid-mediated fragmentation of cyclobutane-containing adducts as a rapid entry into bicyclo[5.3.0]decane ring systems (*Org. Lett.* **2005**, *7*, 5785). They also noted that the stereochemical outcome of the acid-mediated fragmentations in such systems is complementary to the observed thermal ring expansions.

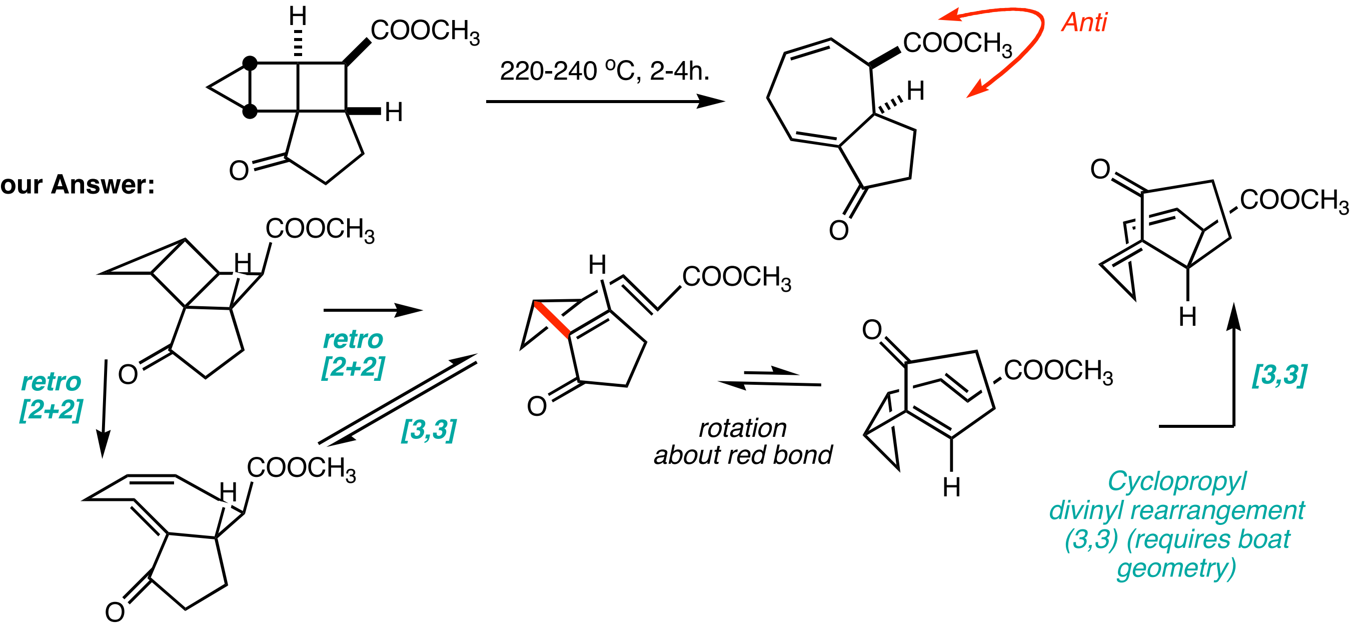
Part 1. (10 points). Please provide a plausible mechanism for the following Lewis acid-mediated transformation.



Your Answer:

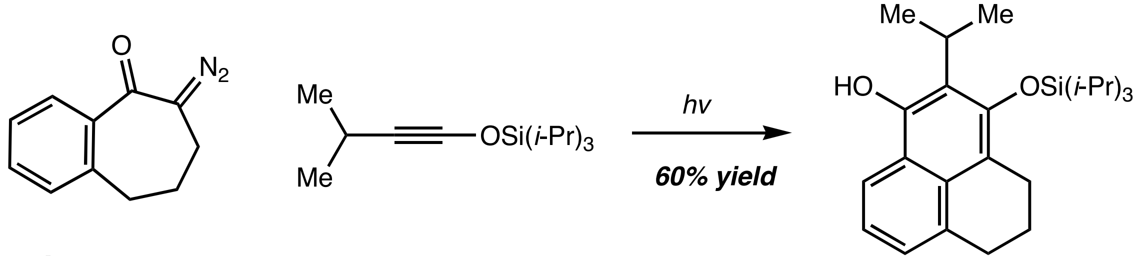


Part 2. (10 points). Propose a mechanism that rationalizes the complementry stereochemical outcome of the following thermal rearrangement.

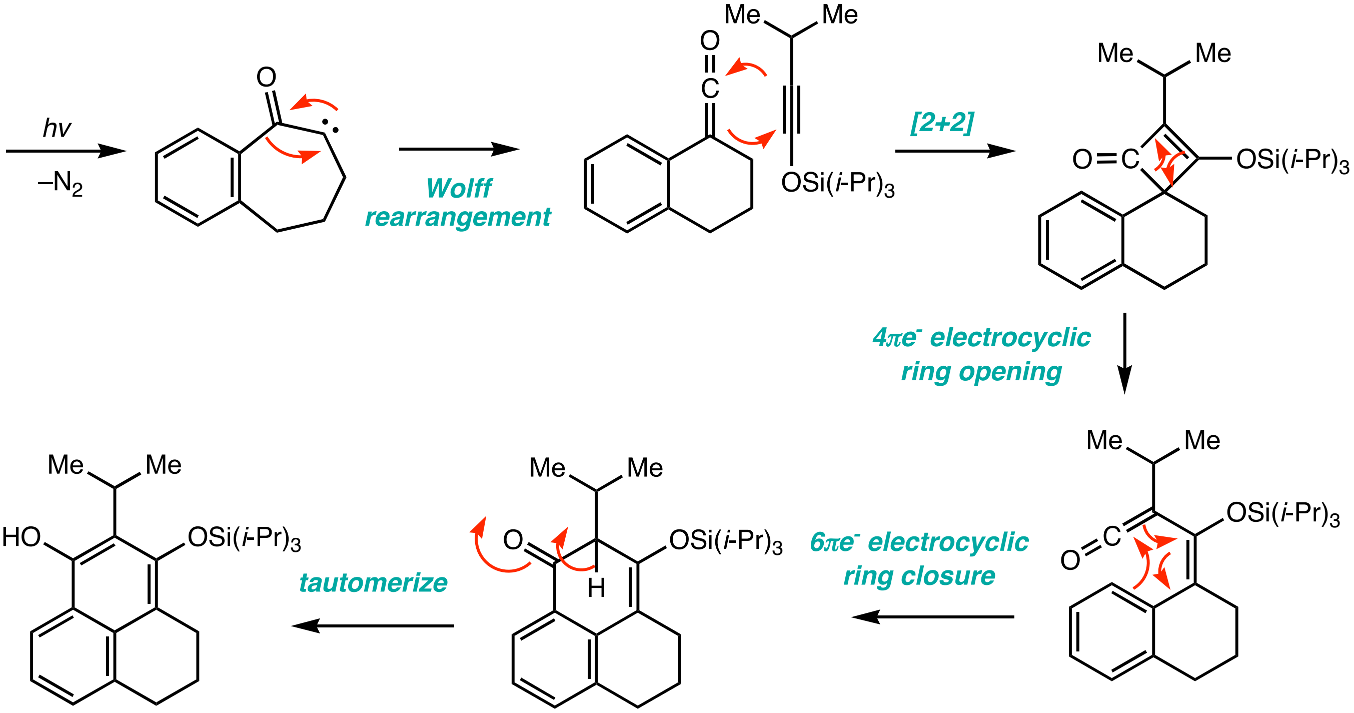


Your Answer:

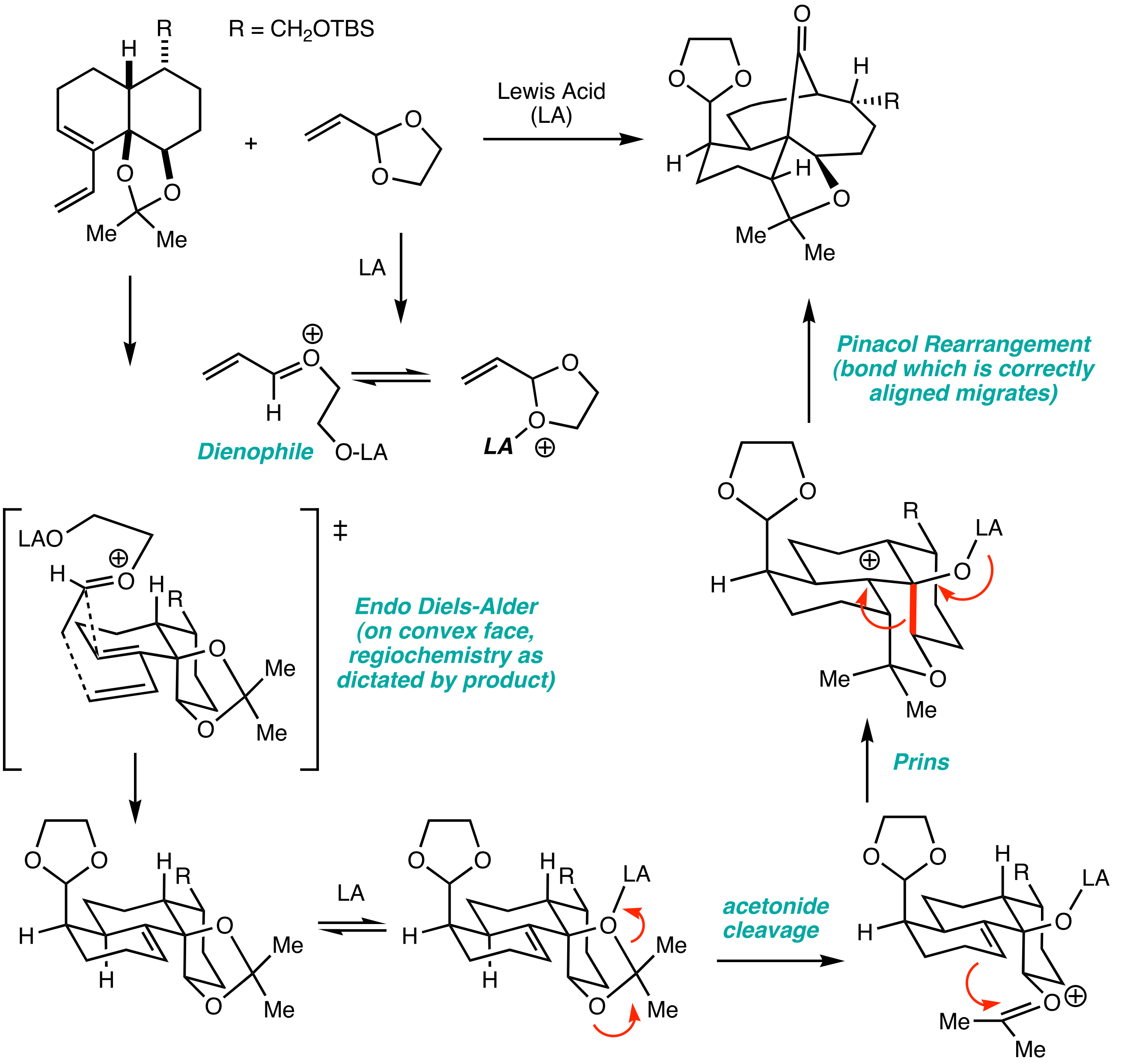
Question 11. (20 points). As part of a study directed towards the synthesis of the natural product Hyellazole, Danheiser and coworkers developed a clever route to the synthesis of complex fused polycyclic structures (*JACS* **1990**, *112*, 3093). Please provide a mechanism for the following rearrangement. Be sure to label all relevant pericyclic rarrangements.



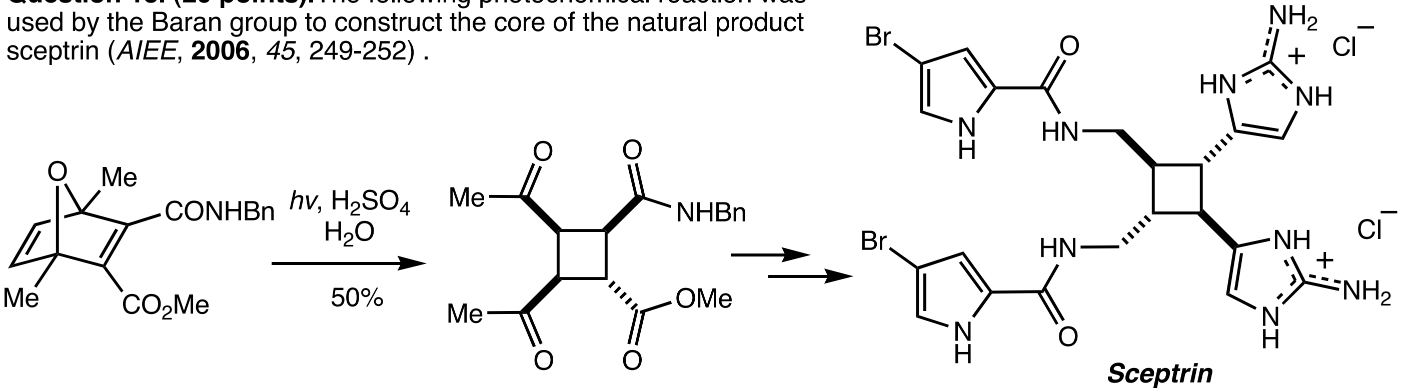
Your Answer:



Question 12. (20 points). Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones (*Org. Lett.* **2005**, *7*, 5921). Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.

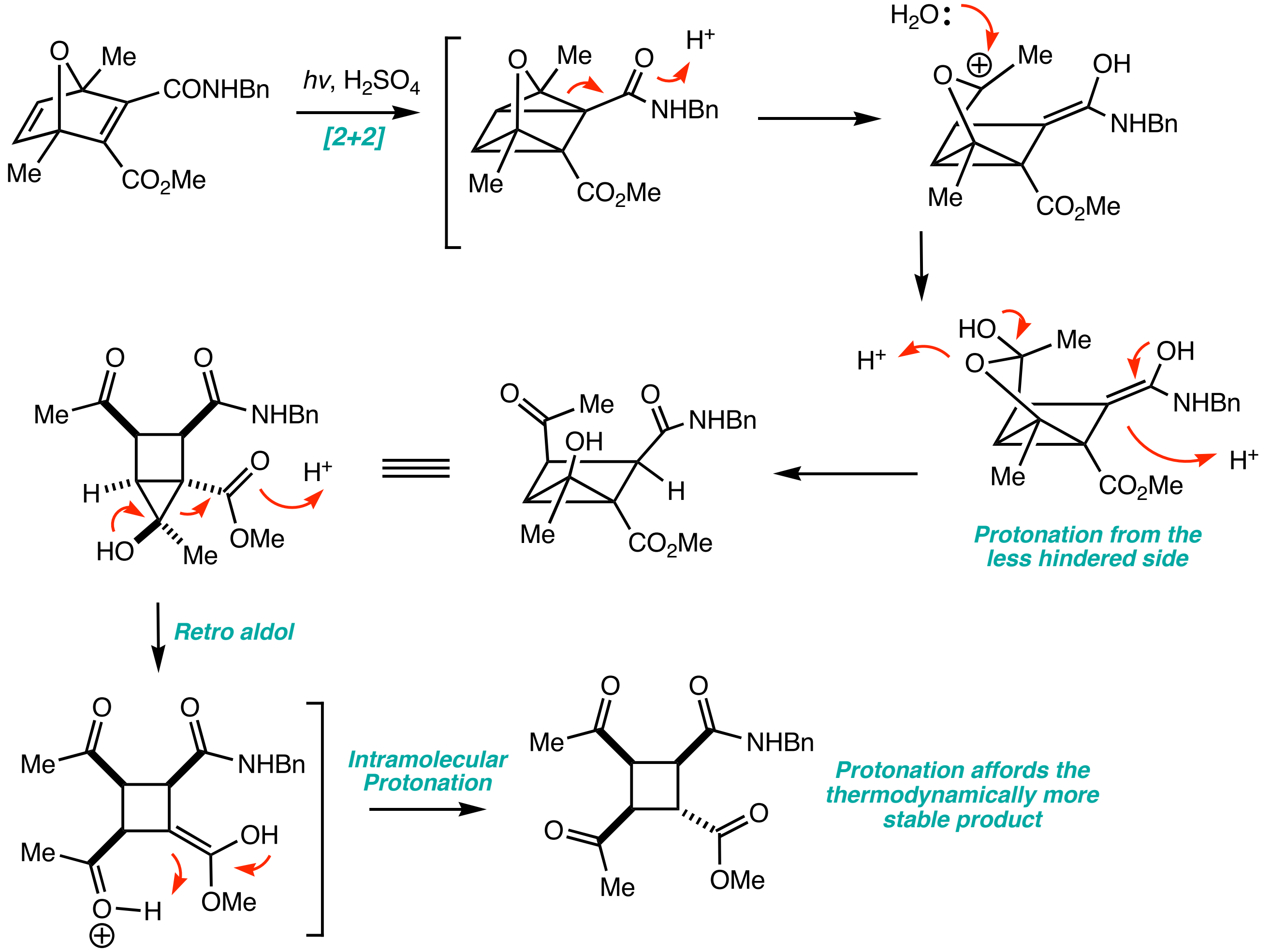

R = CH_2OTBS
Lewis Acid (LA)
LA
Dienophile
O-LA
LA
LAO
‡
Endo Diels-Alder (on convex face, regiochemistry as dictated by product)
LA
acetonide cleavage
Prins
Pinacol Rearrangement (bond which is correctly aligned migrates)
Me
Me
H
R
O

Question 13. (20 points). The following photochemical reaction was used by the Baran group to construct the core of the natural product sceptrin (*AIEE*, **2006**, *45*, 249-252) .

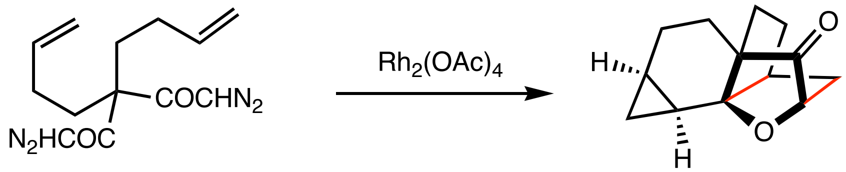


Sceptrin

In the space below please provide a reasonable mechanism for this powerful, multistep transformation.

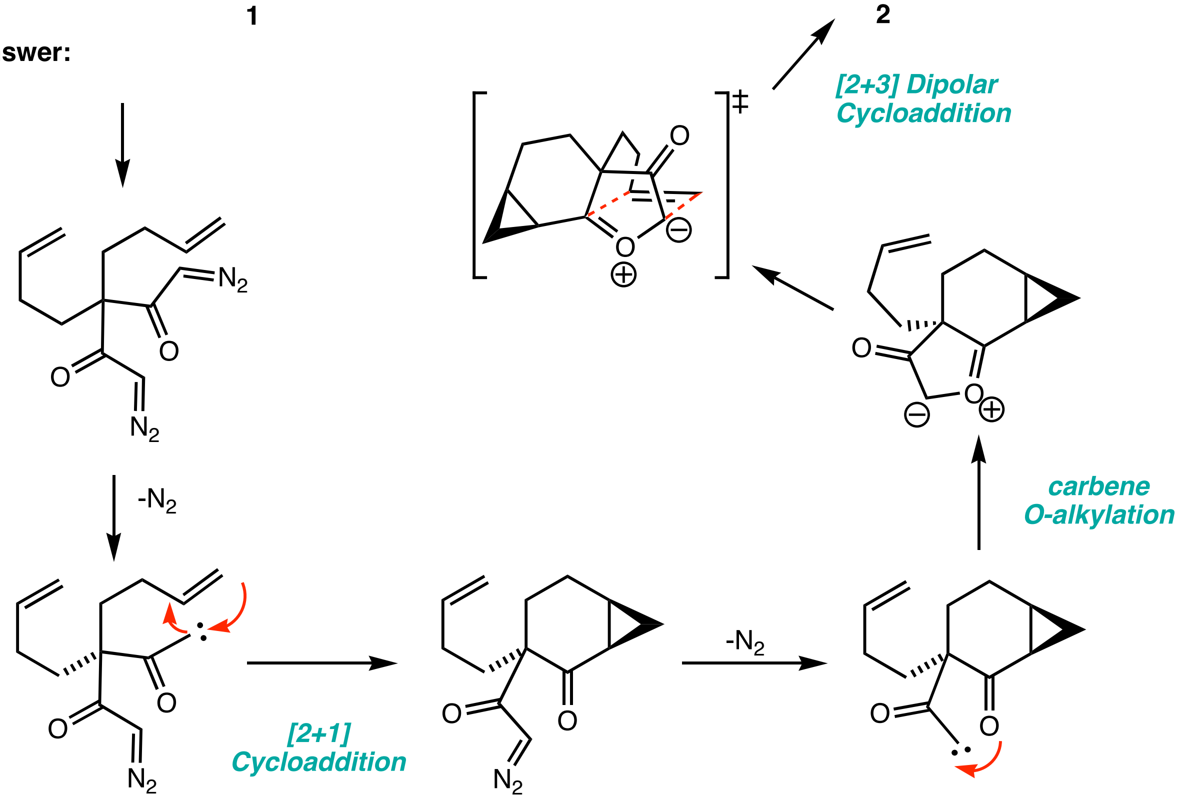

hν, H2SO4
[2+2]
H+
H2O:
OH
NHBn
Protonation from the less hindered side
HO
H+
OH
H
Retro aldol
Intramolecular Protonation
Protonation affords the thermodynamically more stable product

Question 14. (20 points). Bien and coworkers have reported the illustrated rhodium-catalyzed transformation of bis(diazo-ketone) **1** into the functionalized polycyclic product **2** (*Org. Lett.* **2005**, *7*, 5921). Please provide a mechanism for the following rearrangement that accounts for the observed relative stereochemistry. Be sure to label all relevant pericyclic processes.



1 **2**

Your Answer:



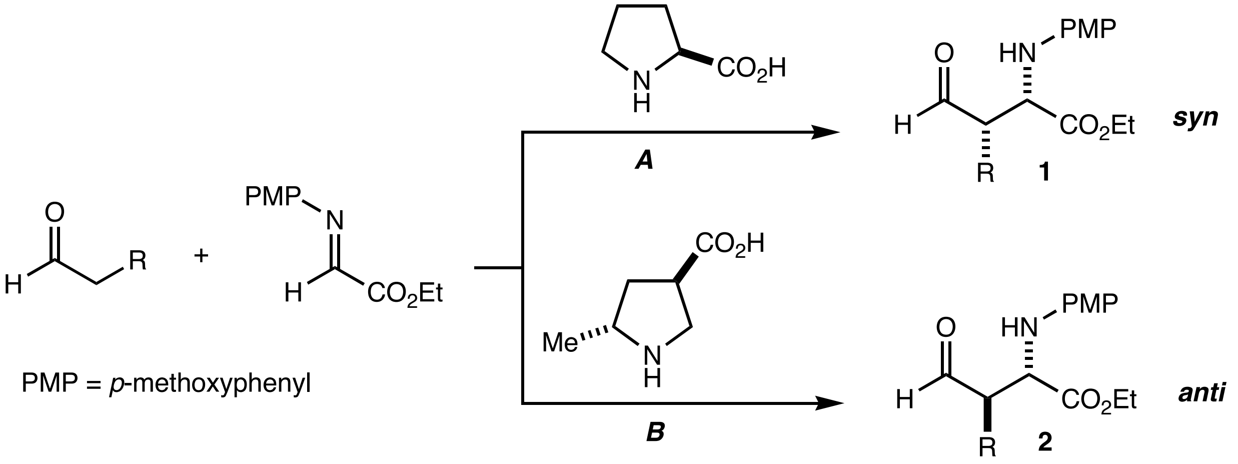
[2+3] Dipolar Cycloaddition

carbene O-alkylation

[2+1] Cycloaddition

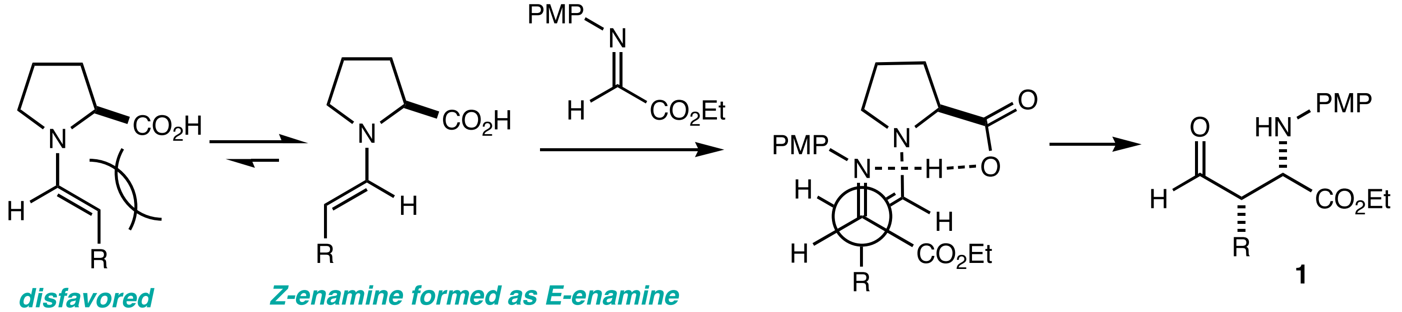
The stereochemical outcome of this step my only be deduced from the product structure.

Question 15. (20 points). The Mannich reaction catalyzed by proline (**A**) typically provides the **syn** adduct **1** with high levels of syn diastereocontrol. However, Barbas and coworkers have recently reported that catalyst **B** affords the corresponding **anti** adduct **2** with high selectivity (*JACS* **2006,** *128,* **ASAP**).



PMP = *p*-methoxyphenyl

Part A. (10 points). Please provide a clear depiction of the transition state leading to the formation of the observed syn adduct **1** when using **A**. Your answer should discuss the issues associated with the initially formed enamine intermediate, and identify all important control elements that determine enantio- and diastereoselectivity.

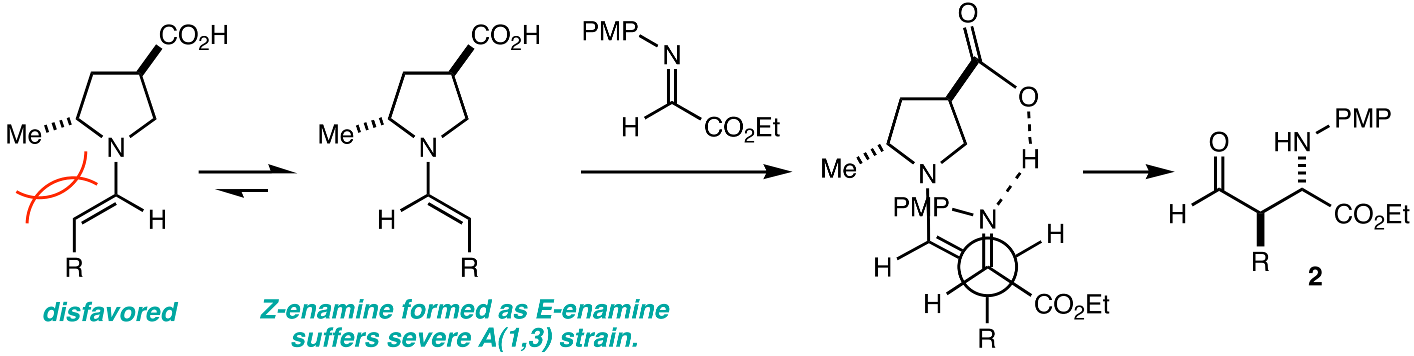


disfavored

Z-enamine formed as E-enamine suffers severe A(1,3) strain.

H-bond directs attack syn to acid substituent

Part B. (10 points). In contrast to above, please provide a clear depiction of the transition state leading to the formation of the observed anti product **2** when using **B**. Your answer should discuss the issues associated with the initially formed enamine intermediate and identify important control elements that determine enantio- and diastereoselectivity.



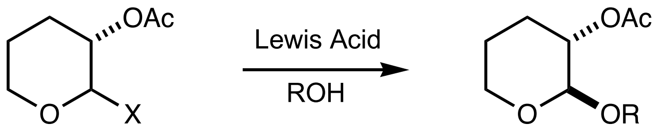
disfavored

Z-enamine formed as E-enamine suffers severe A(1,3) strain.

H-bond directs attack syn to acid substituent, the same as for A above, but now addition occurs across the opposite face of the enamine C=C bond. Thus, the anti adduct is formed.

Question 16. (15 points). Stereoselective formation of the glycosidic linkage is the principal challenge in the synthesis of biologically important oligosaccharides. Anchimeric assistance (neighboring group participation) can be a powerful tool for the selective construction of glycosidic bonds.

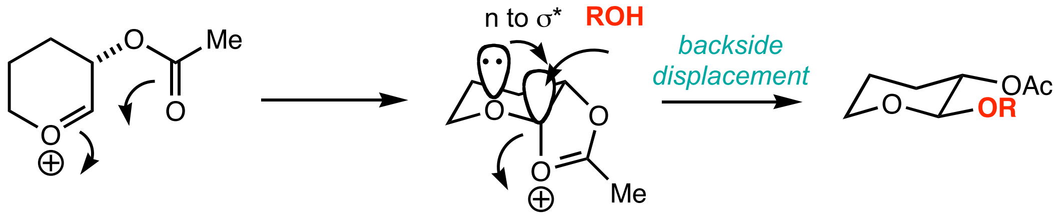
Part A. (5 points). For the following α-selective glycosylation please provide a clear mechanism, using three-dimensional representations, that accounts for the observed stereochemical outcome. Indicate all relevant orbital interactions.



X = activating group

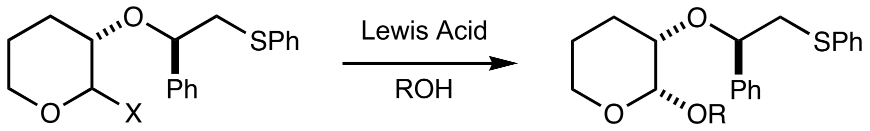
anti selective

Your Answer:



stereoelectronically favored intermediate

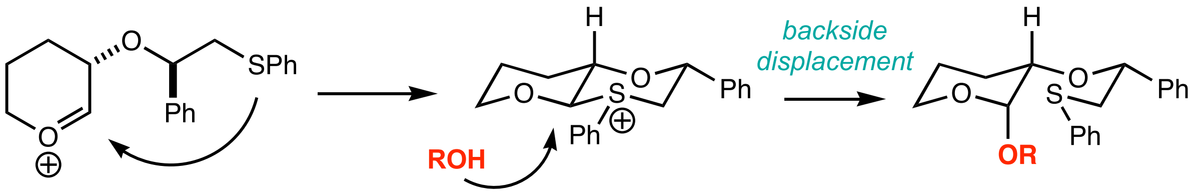
Part B. (10 points). Boons and coworkers (*JACS*, **2005**, *127*, 12090) have recently reported a highly selective synthesis of the corresponding syn di-substituted system by employing a participating phenyl-2-(phenylsulfanyl)ethyl moiety, as indicated below. Using clear three-dimensional drawings provide a rational mechanism for this interesting reaction. Be sure to indicate all favorable and unfavorable interactions, both steric and electronic. NOTE: This reaction is under ***kinetic** control.*



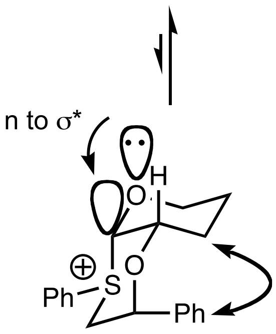
X = activating group

syn selective

Your Answer:



equatorial sulfonium ion favored



Although the axial conformer is favored by the better sigma acceptor ability of the sulfonium ion relative to H, the enforced Ph-ring interaction is highly destabilizing.

Destabilizing interaction

Chemistry 206
Final Examination

D. A. Evans
January 24, 2005

Name (please print):________________________________
last first initial

Signature:________________________________

Teaching Fellow:________________________________

This examination contains **15** questions (15 pages) for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**
No. 1 (**15**)	
No. 2 (**20**)	
No. 3 (**20**)	
No. 4 (**20**)	
No. 5 (**25**)	
No. 6 (**20**)	
No. 7 (**15**)	
No. 8 (**15**)	
Subtotal (**150**)	

Question (pts)	**Score**
No. 9 (**25**)	
No. 10 (**20**)	
No. 11 (**20**)	
No. 12 (**25**)	
No. 13 (**20**)	
No. 14 (**20**)	
No. 15 (**20**)	
Subtotal (**150**)	

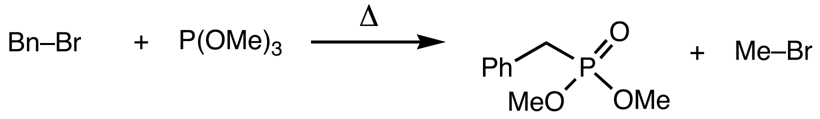
exam average

Total (300)

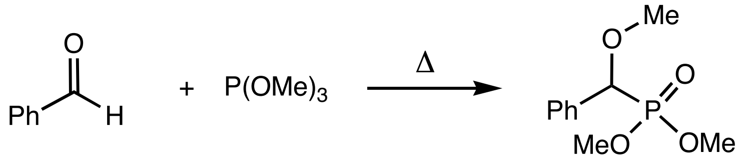
Answers
Answers
Answers
Answers
Answers
Answers

Question 1. (15 points). Equation (1) is a typical example of an Arbuzov rearrangement while Equation (2) is an Arbuzov variant carried out with an aldehyde.

(1)

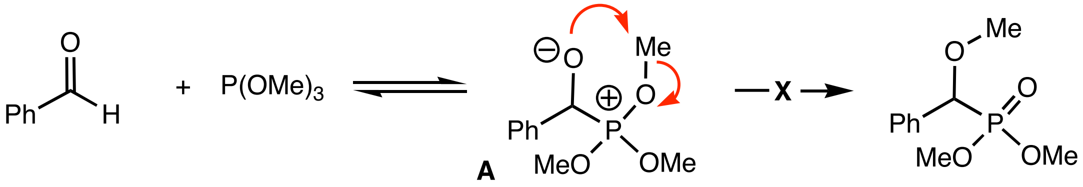


(2)

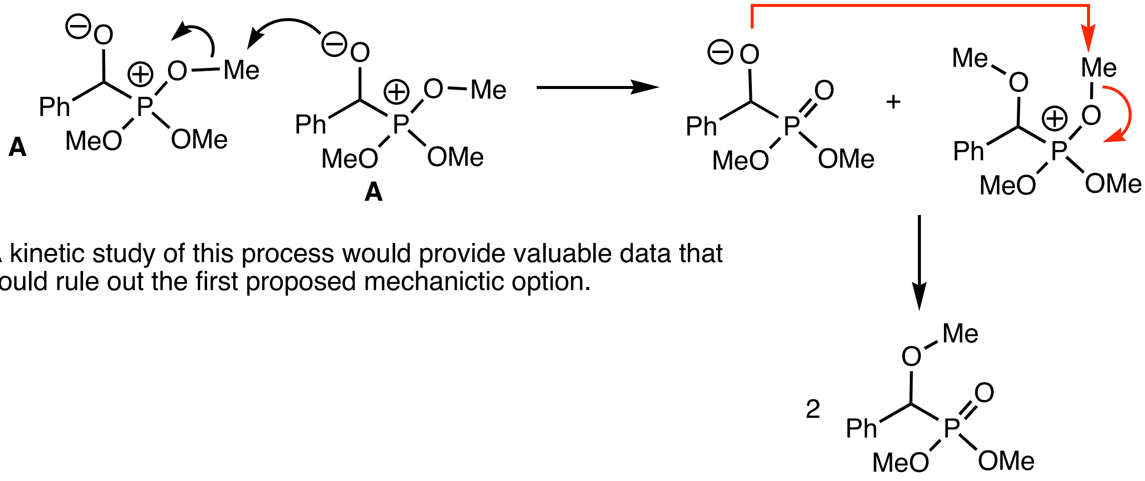


Please comment on the mechanism of the transformation in equation (2).

The obvious mechanism that involves an *intramolecular* methyl transfer in **A** cannot take place for geometric reasons. In Baldwin terminology this is a disallowed "5-endo tet substution (Baldwin, *Chem. Comm.* **1976**, 734–736.).

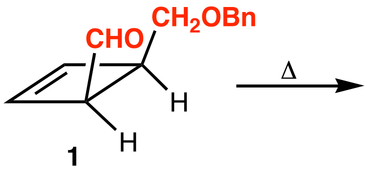


Accordingly, the transformation could involve the following alternative:



A kinetic study of this process would provide valuable data that could rule out the first proposed mechanictic option.

Question 2. (20 points). The ring opening of cyclobutene **1** is highly selective affording the isomeric dienes in a ratio >20:1. Please predict the structure of the major product and rationalize the stereochemical course of the transformation. It is suggested that your explanation employ orbital representations.

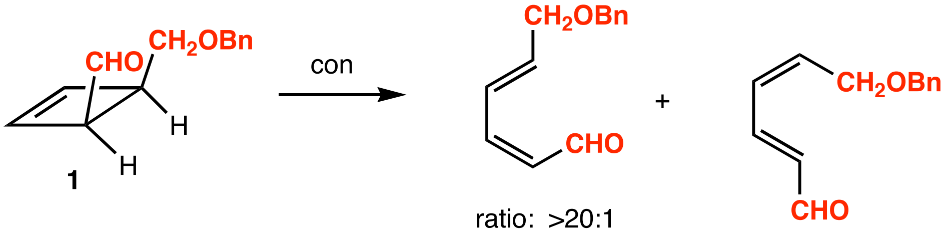


1

2 diene products, Ratio >20:1

Your Answer

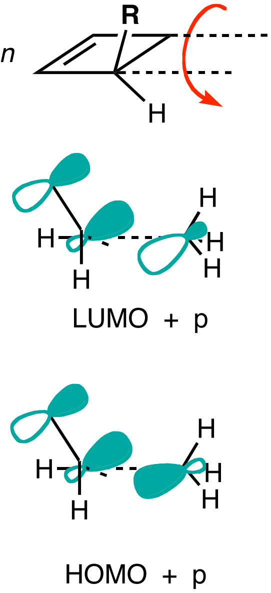
The prediction: Electron withdrawing groups prefer the con-in motion while alkyl groups sterically prefer the con-out motion. Accordingly, both steric and electronic effects reinforce the formation of the illustrate major product.



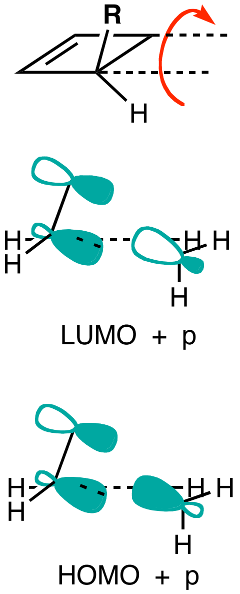
ratio: >20:1

Houk et al. *Acc. Chem. Res* **1996**, 29, 471

The rationalization:



A

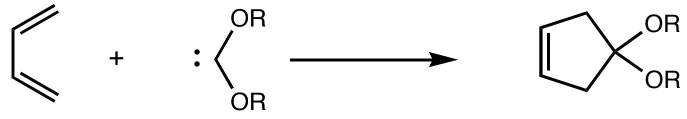


B

As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B**, is better in **B**. (Houk)

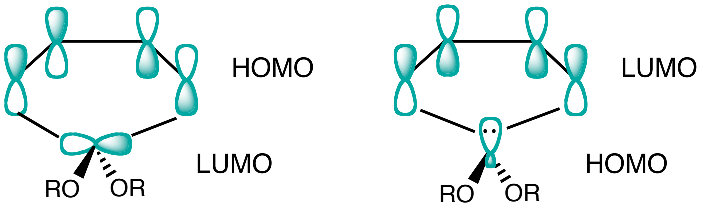
For the Inward motion: destabilizing 4 electron interation for donor substituents. On the other hand, there is a stabilizing 2 electron interation for acceptor substituents

Question 3. (20 points). A [4+1] cycloaddition between a diene and a carbene has recently been reported by Spino and co-workers (*JACS*, **2004**, *126*, 9926).



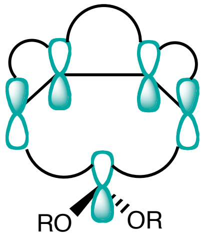
Part A. (10 points). Using a Dewar-Zimmerman or an FMO analysis, determine if this reaction is thermally allowed. Be sure to consider both the approach and the geometry of the carbene carefully.

FMO:



bonding interactions on both termini: the reaction is allowed thermally

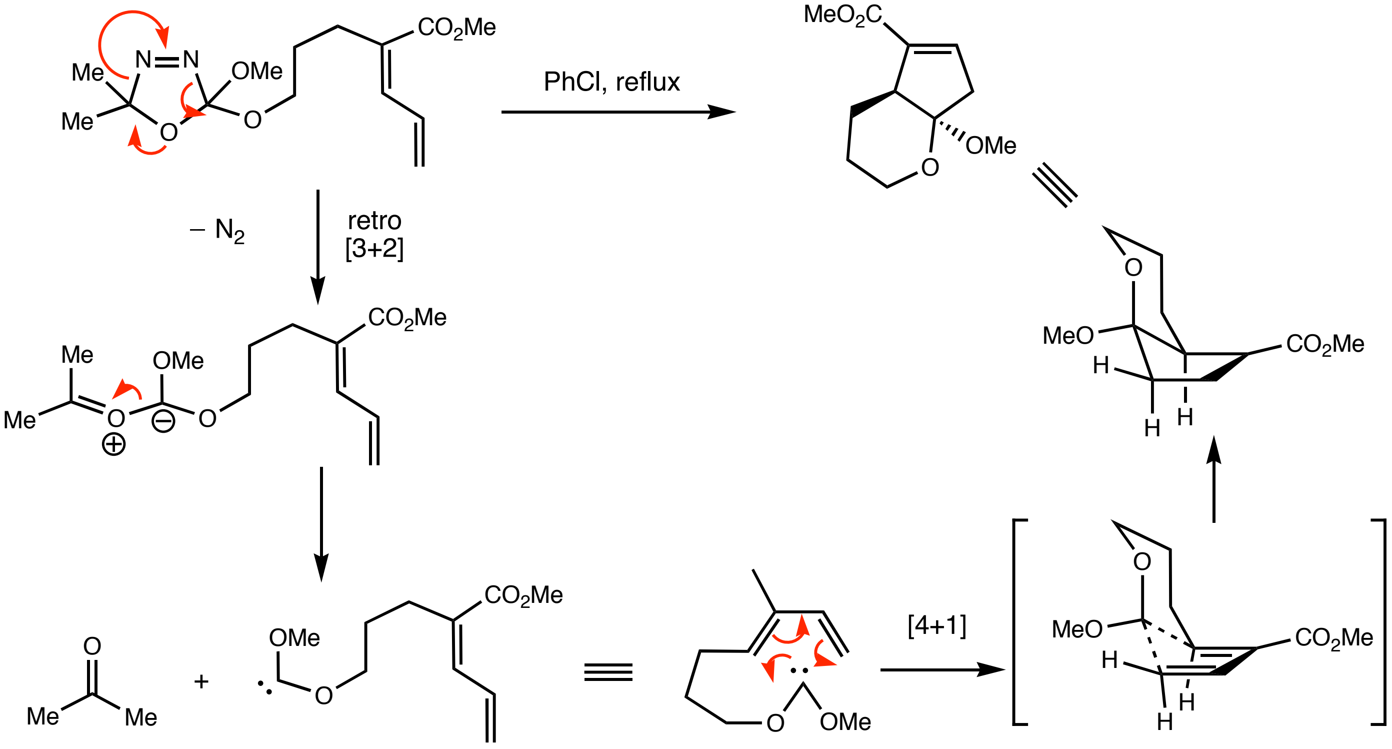
Dewar-Zimmerman:



2 phase inversions = Huckel topology

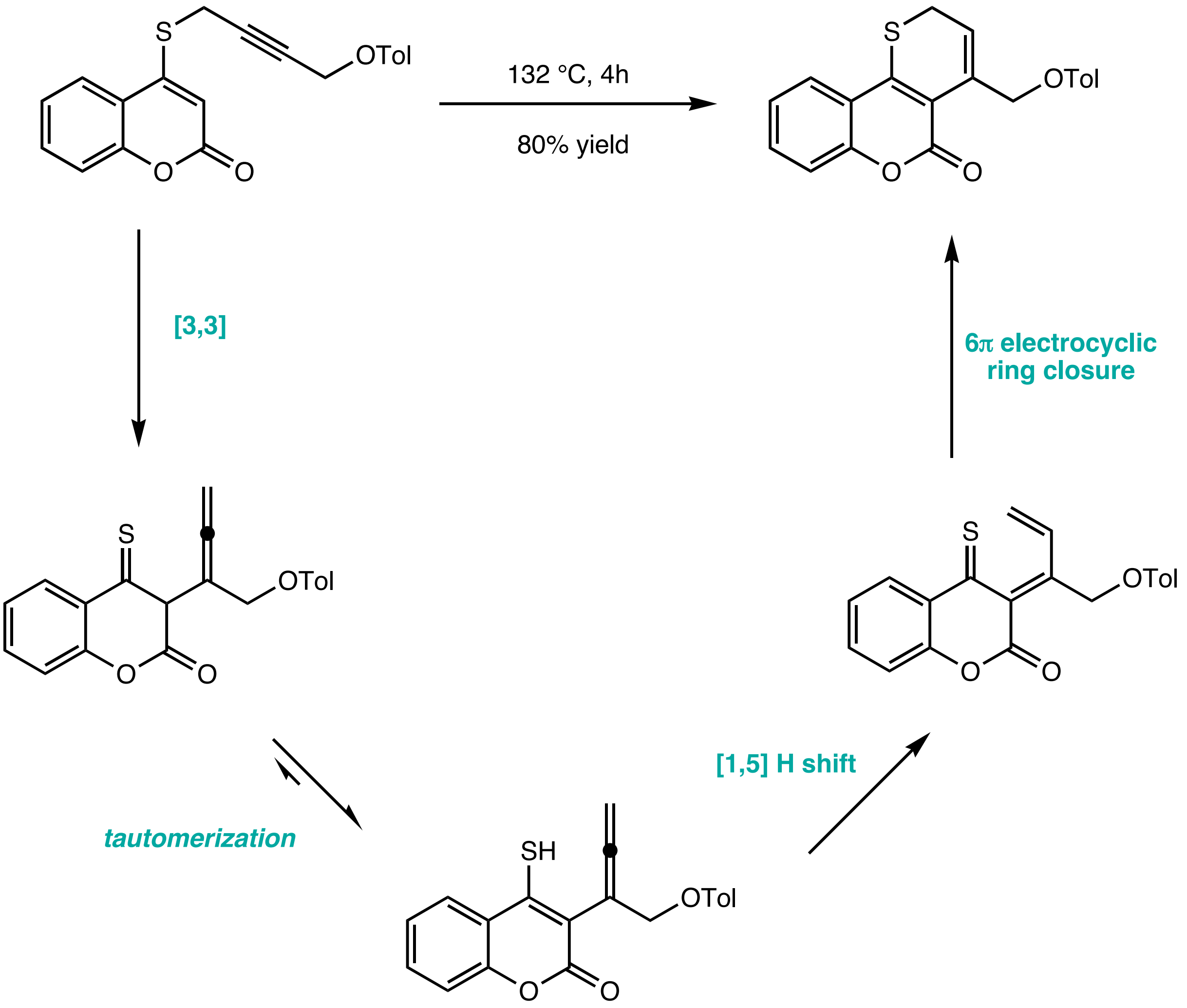
6 π electrons = aromatic, thermally allowed

Part B. (10 points). Provide a mechanism for the following reaction reported by Spino.

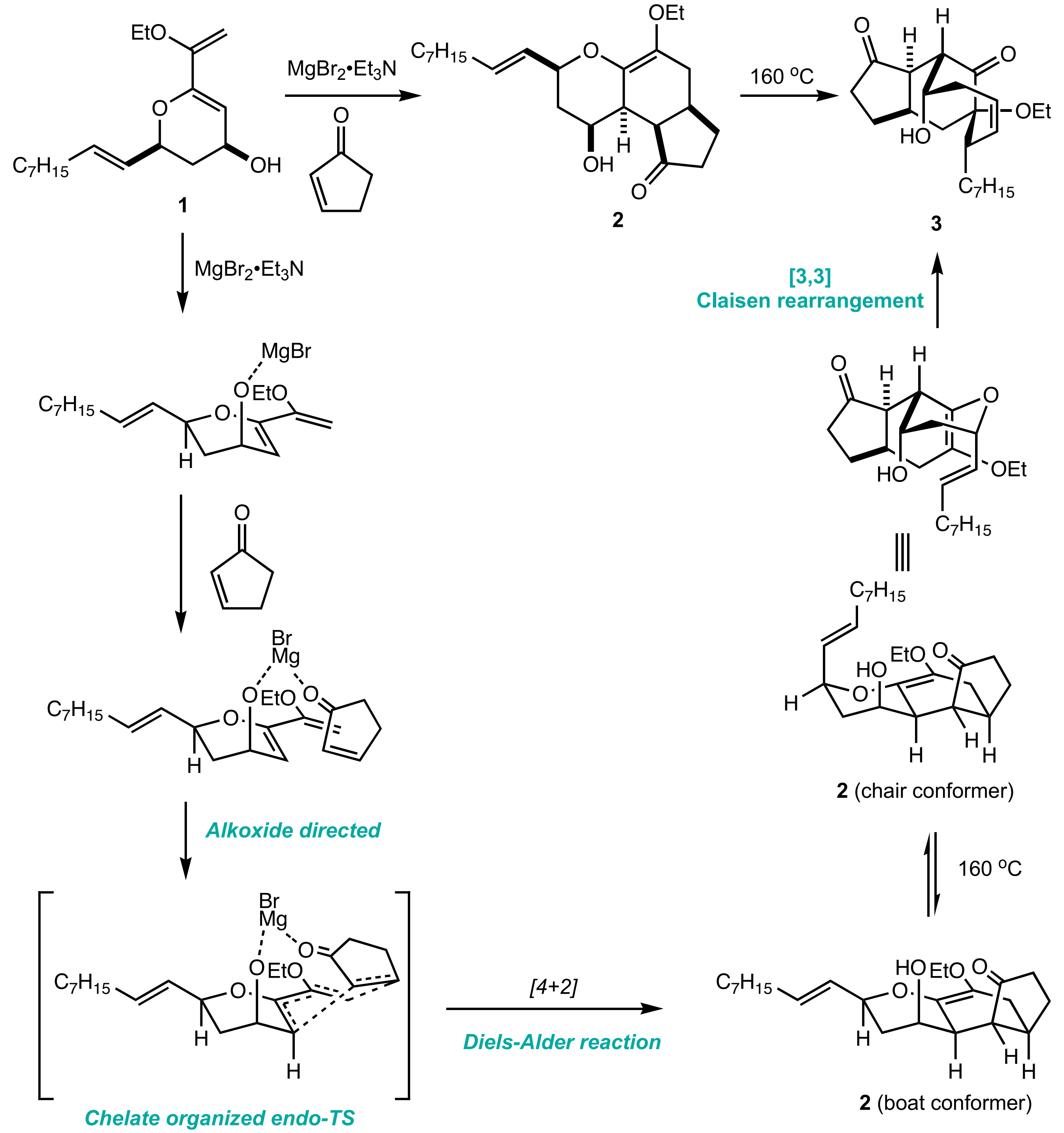


most stable TS has *cis* ring fusion

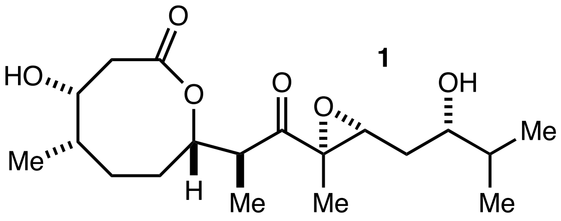
Question 4. (20 points). Please provide a mechanism for the following transformation (*Org. Lett.*, **2002**, 4, 2629.), being sure to classify any pericyclic processes that intervene.



Question 5. (25 points). The rapid assembly of the bicyclo[5.3.1]undecane core of penostatin F was recently reported by Barriault and coworkers (*Org. Lett.* **2004**, *6*, 1317). In this remarkable transformation dihydropyran **1** is converted to the highly complex tricycle **3** in only two operations. Please provide a detailed mechanism for this reaction sequence. Be sure to indicate all pericyclic reactions.

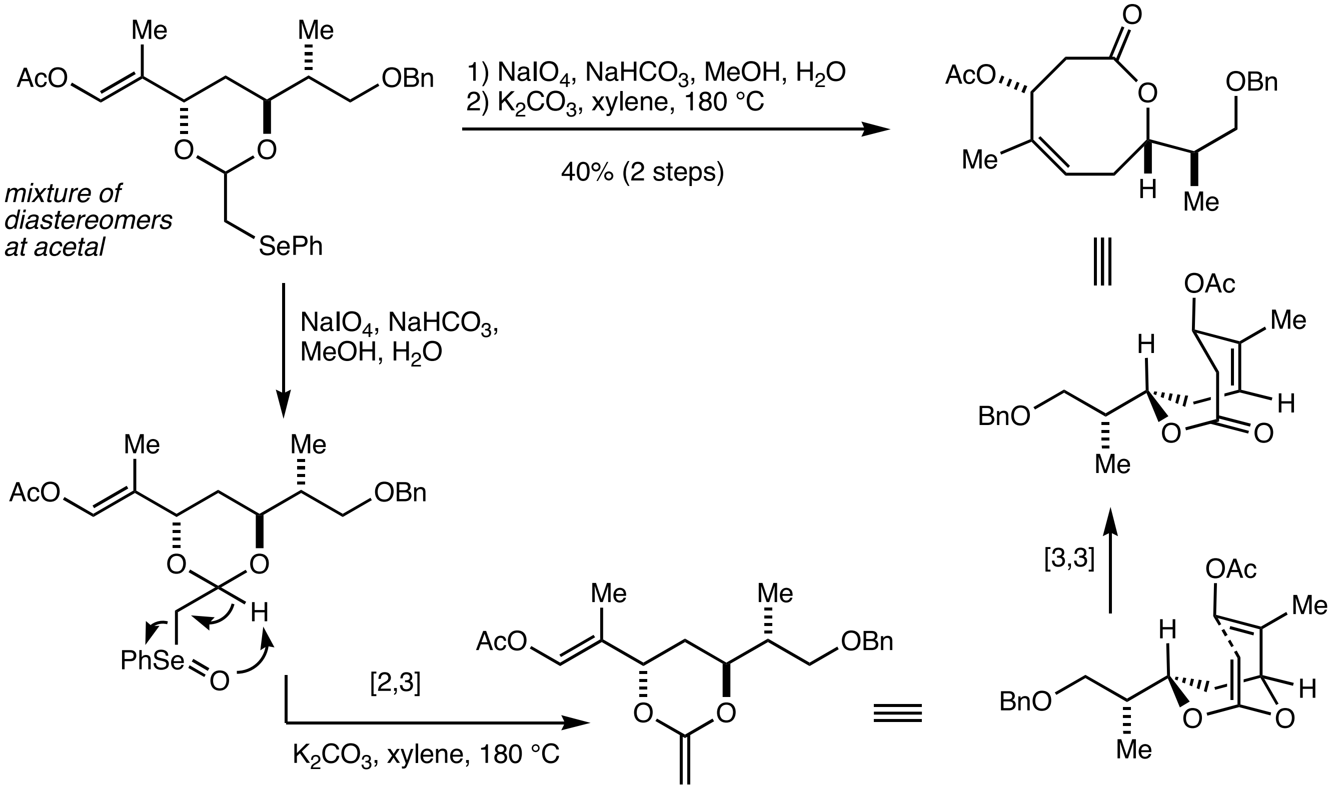


Question 6. (20 points). In 1991, Fenical and Clardy reported the isolation of eight-membered lactones, which were termed octalactins. The parent member, octalactin A (**1**), was recently synthesized by Holmes and co-workers (*JACS*, **2004**, *126*, 2194.).

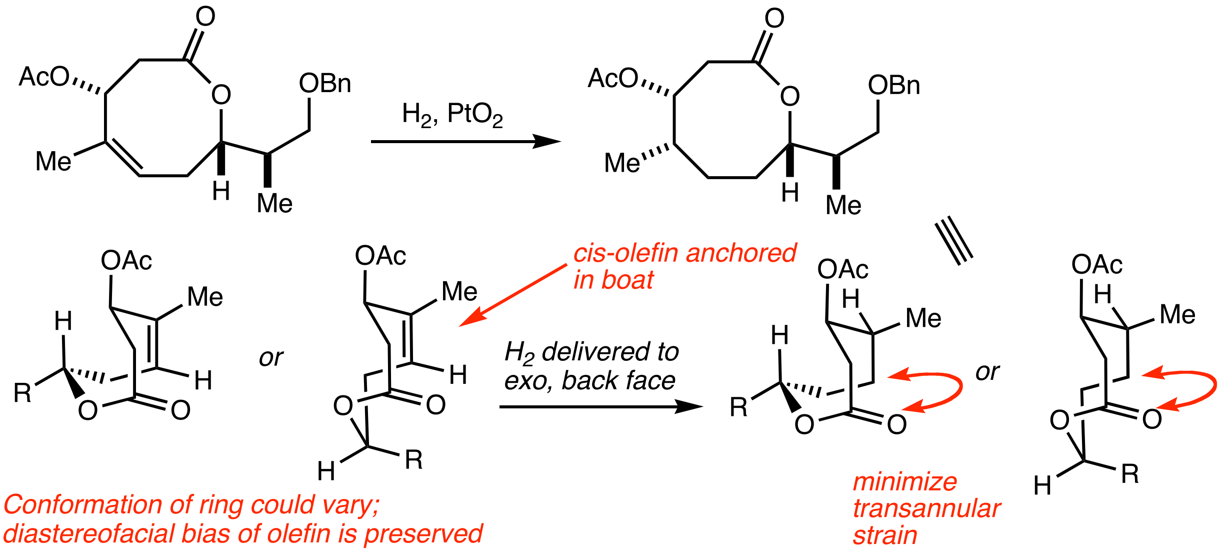


1

Part A. (15 points). Please provide a mechanism for the two-step sequence below that provides the eight-membered ring. Use 3-D illustrations in your explaination. *($NaIO_4$ is only an oxidant)*



Part B. (5 points). Please provide a rationale for the selective hydrogenation illustrated below.



cis-olefin anchored in boat

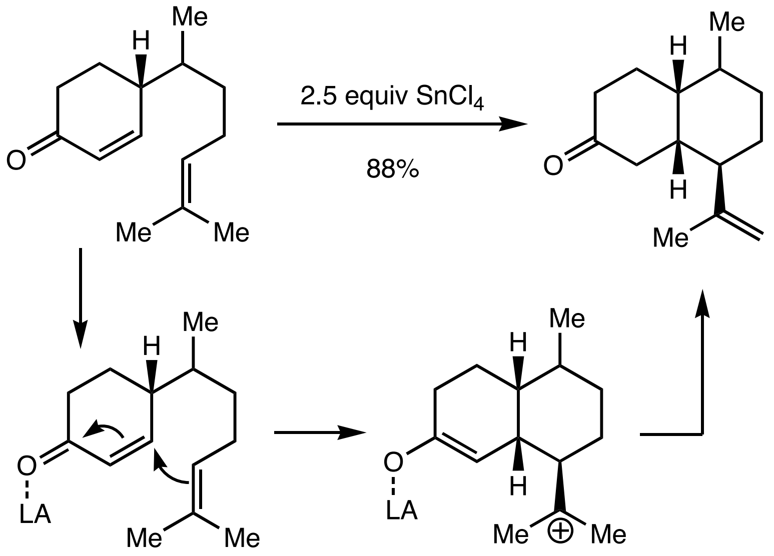
H2 delivered to exo, back face

minimize transannular strain

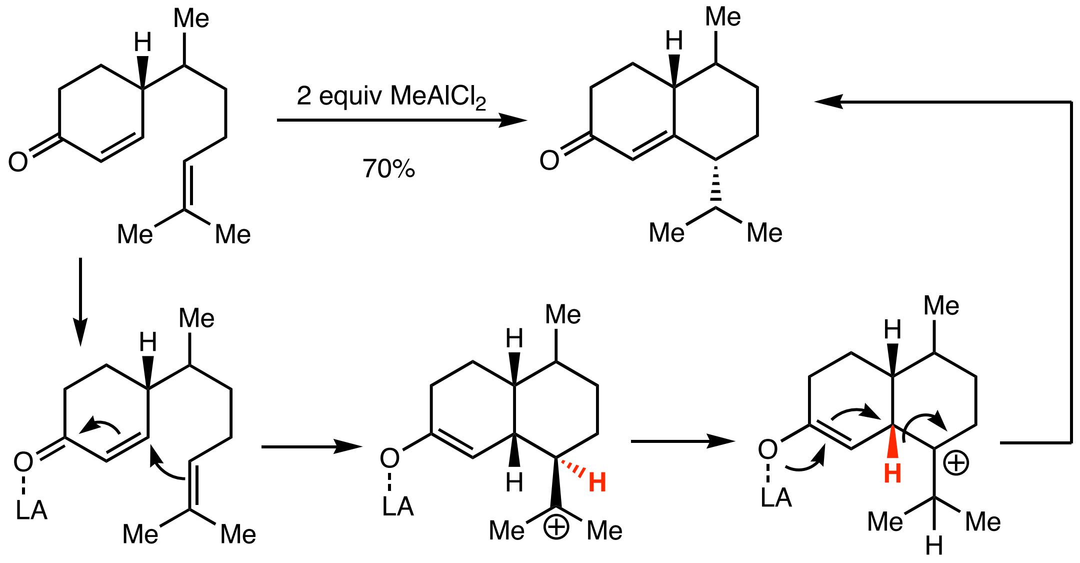
Conformation of ring could vary; diastereofacial bias of olefin is preserved

Question 7. (15 points). A recent report has investigated the cationic cyclization of olefins under Lewis acidic conditions (*ACIE*, **2005**, *44*, 99.). The examples below (**A-B**) are of increasing difficulty. The following question (8) will build on the foundation of this question. Please provide a mechanism for each part illustrated. Your answer can focus on the 2-D mechanistic analysis (3-D figures are not required).

Part A (5 points):

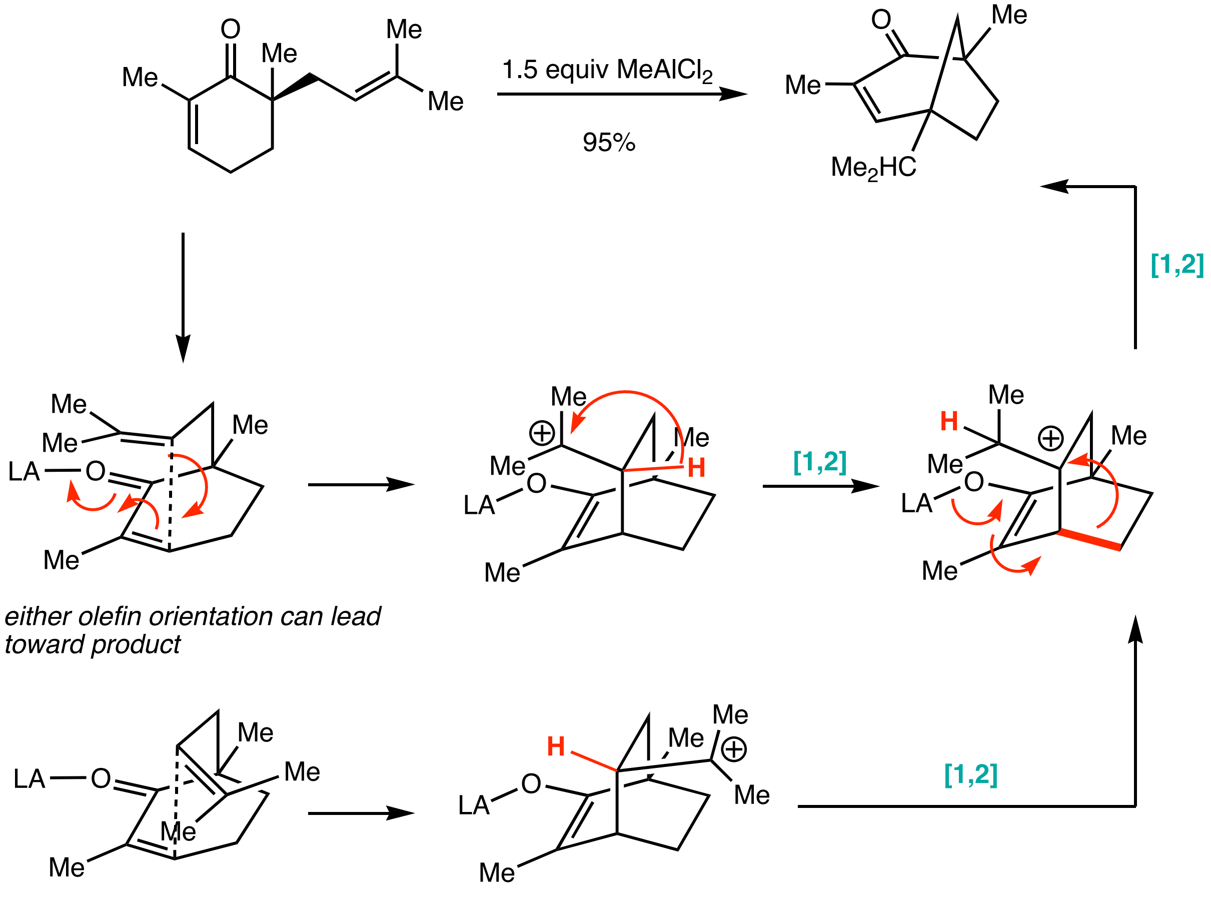


Part B (10 points):



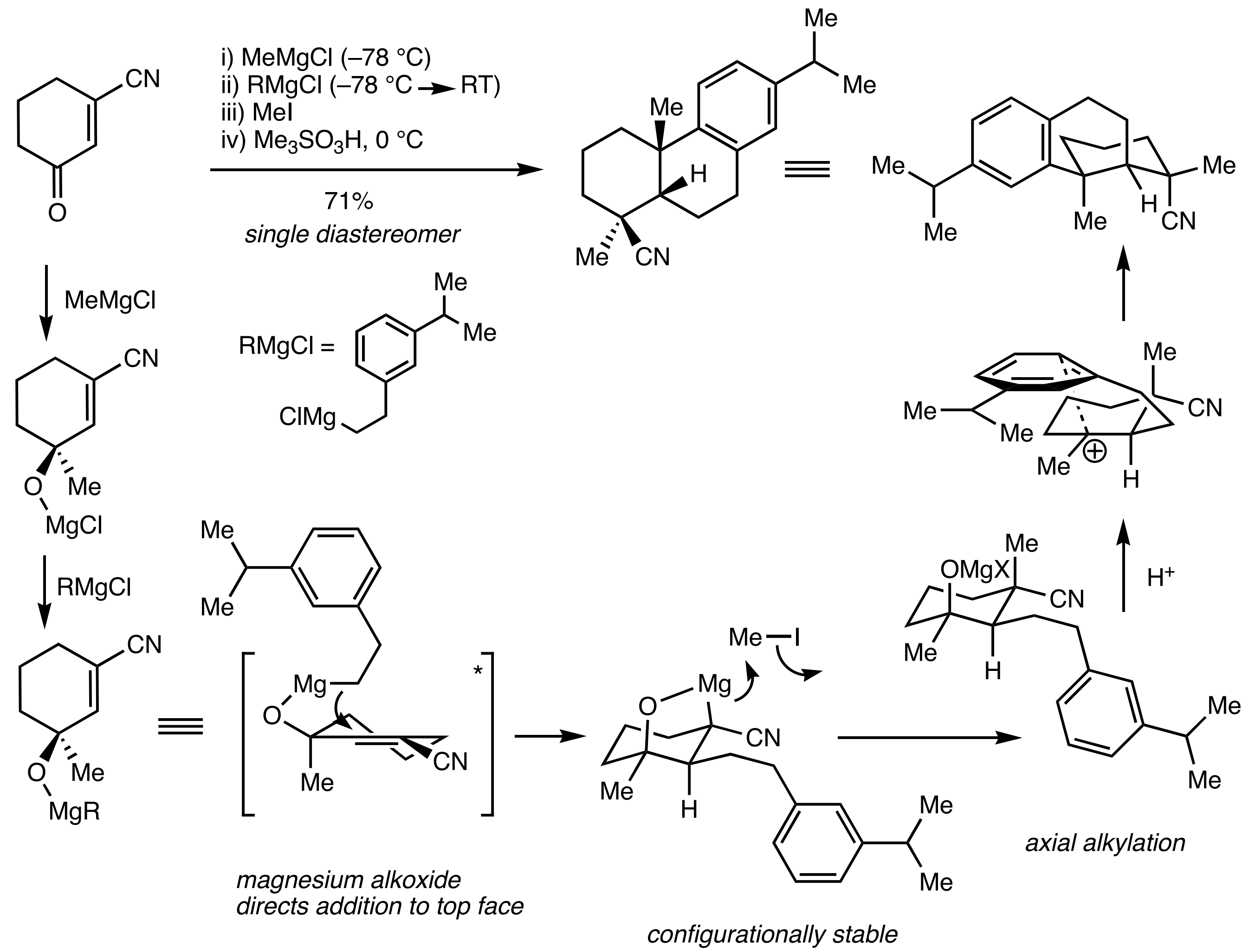
Question 8. (15 points). This question builds on the foundation of the previous question . Please provide a mechanism for the case illustated (ACIE, **2005**, 44, 99).

For this question please provide 3-dimensional representations.



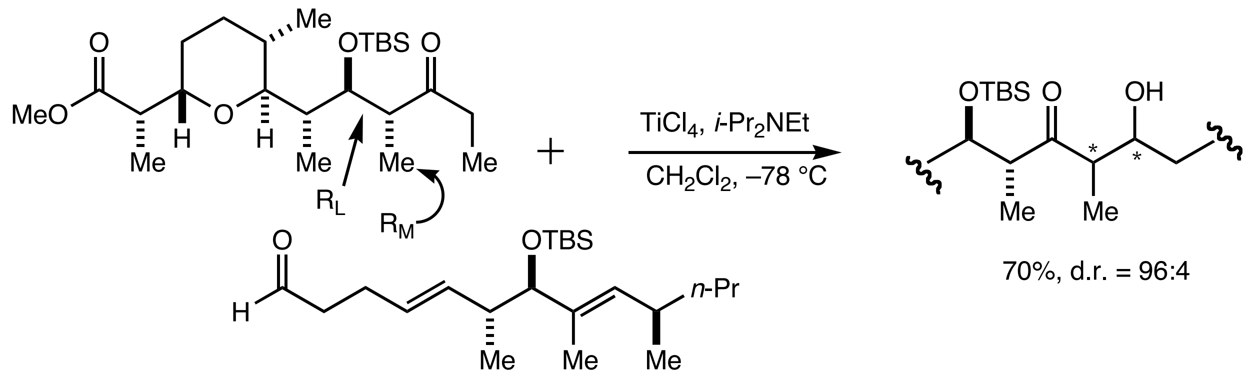
either olefin orientation can lead toward product

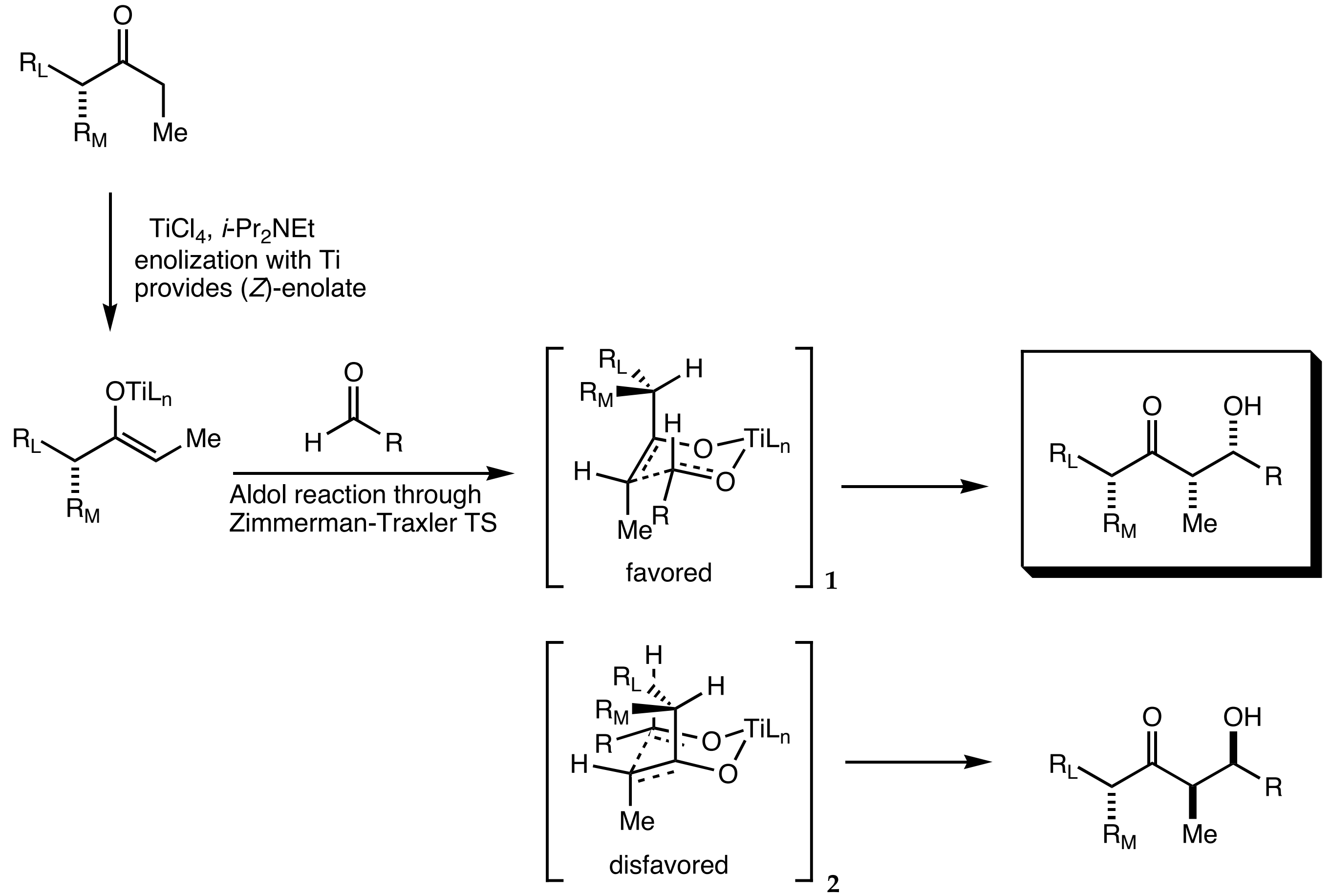
Question 9. (25 points). The following multi-component, one-pot reaction was recently reported by Fleming (*Angew. Chem. Int. Ed.* **2004**, *43*, 1126.). This is an impressive reaction for two specific reasons: 1) only a single diastereomer is observed; 2) the reaction appears to be general for an array of Grignard reagents and electrophiles.
Please provide a mechanism for the reaction that clearly explains the stereoselectivity for each step.
Please use 3-D representations. I recommend working on this problem bi-directionally from both product and starting material until you see the connecting transformations.



**six-membered directed addition is also valid*

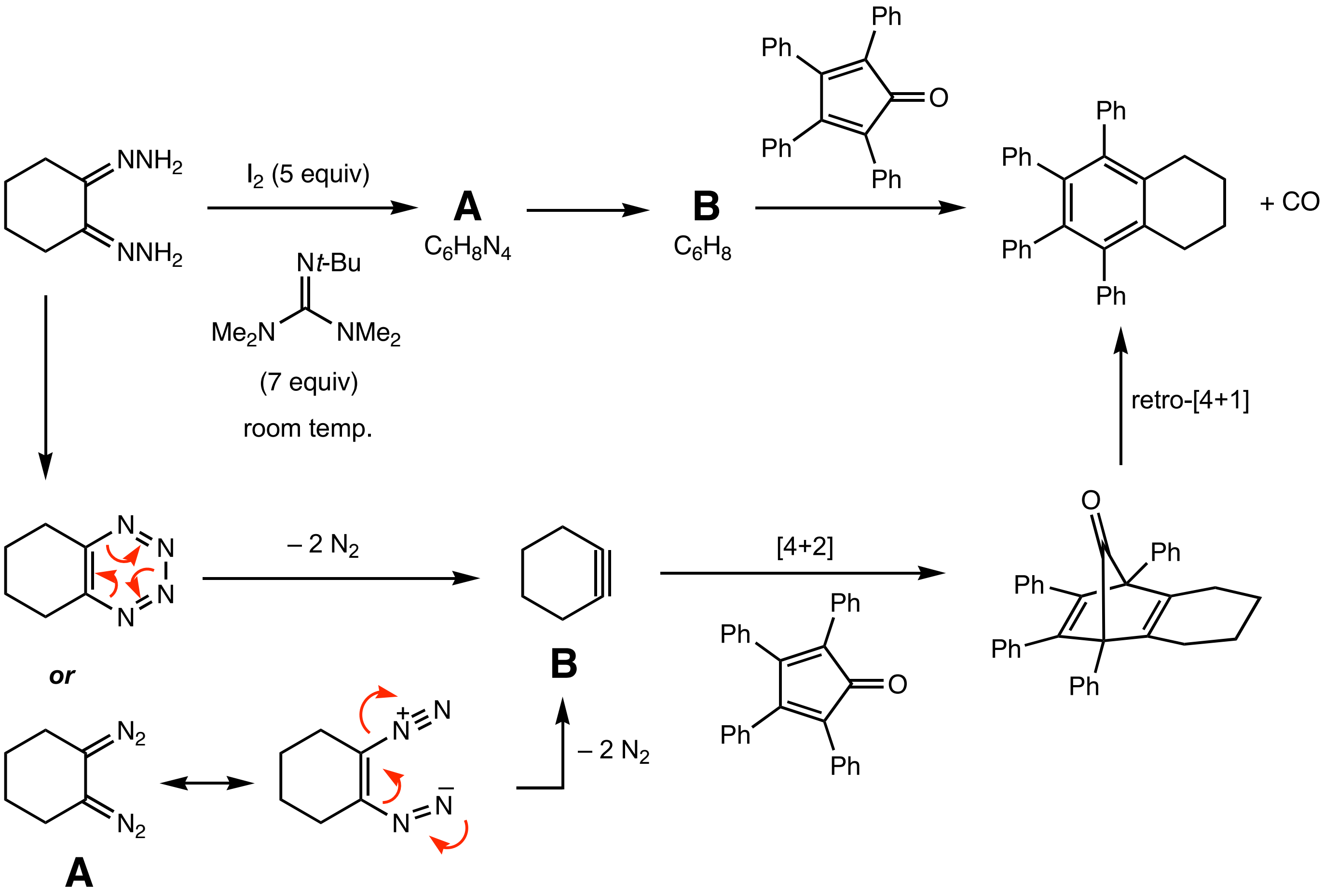
Question 10. (20 points). In a recent total synthesis of Zincophorin methyl ester (*Org. Lett.* **2003**, 4037), the following titanium-mediated aldol reaction was used to efficiently couple two large fragments. Predict the stereochemistry of the product and provide a stereochemical model to support your prediction.



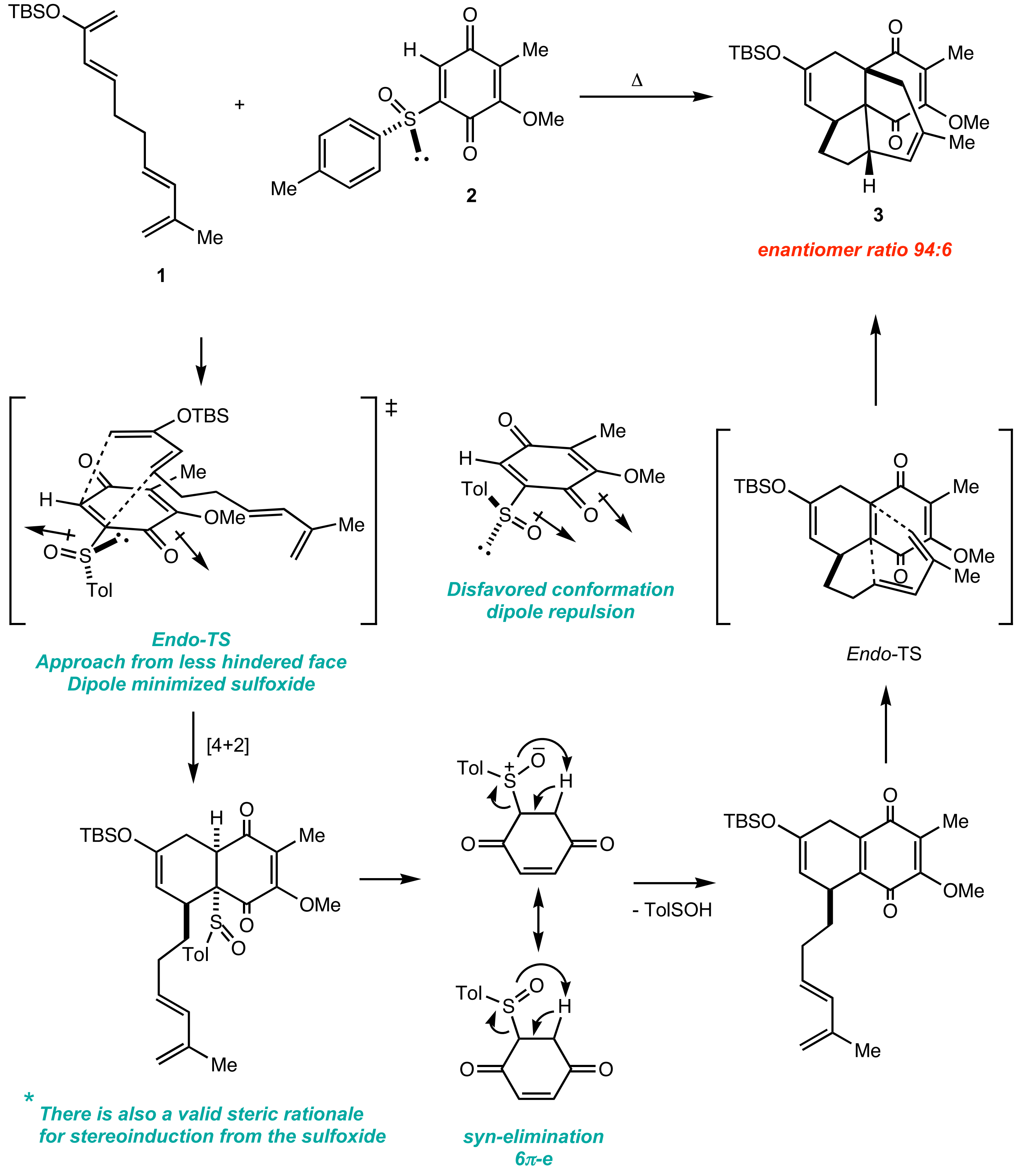


TS **1**, which orients R_M towards the aldehyde, is favored over TS **2**, where R_L is oriented towards the aldehyde.

Question 11. (20 points). During research into the chemistry of hydrazone derivatives, Barton and coworkers observed the interesting transformation shown below *(Tetrahedron,* **1988**, *44*, 147). Please provide a plausible mechanism for this reaction and identify intermediates **A** and **B**. (*NB: A and B are not isolable)*



Question 12. (25 points). Flynn and coworkers have reported the rapid construction of **3** from bisdiene **1** and chiral sulfoxide **2** (*Org. Biomol. Chem.* **2003**, *1*, 1842-1844).
Please provide a mechanism that accounts for the observed regiochemical and stereochemical outcome of this interesting transformation. Perspective drawings should be employed where relevant.



1

2

3

enantiomer ratio 94:6

Endo-TS
Approach from less hindered face
Dipole minimized sulfoxide

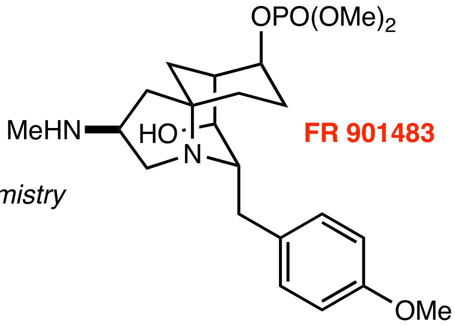
Disfavored conformation
dipole repulsion

Endo-TS

syn-elimination
6π-e

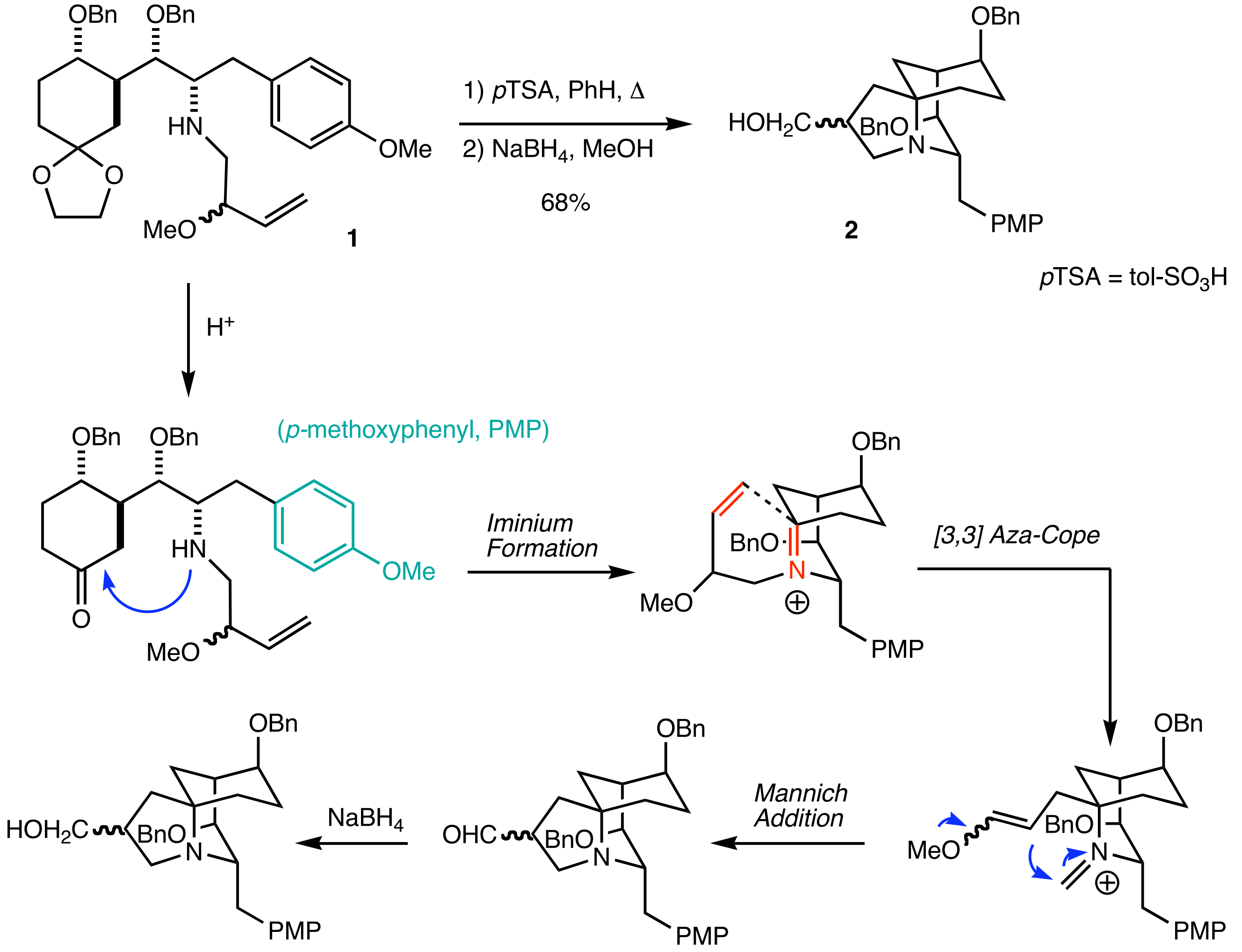
***** ***There is also a valid steric rationale for stereoinduction from the sulfoxide***

Question 13. (20 points). FR 901483 is an immunosuppressant developed by Fujisawa Pharmaceutical Company. Recently, a formal total syntheses of FR 901483 was disclosed that utilizes the transformation illustrated below (Brummond and Hong, *JOC,* **2004**, *ASA*P).



FR 901483

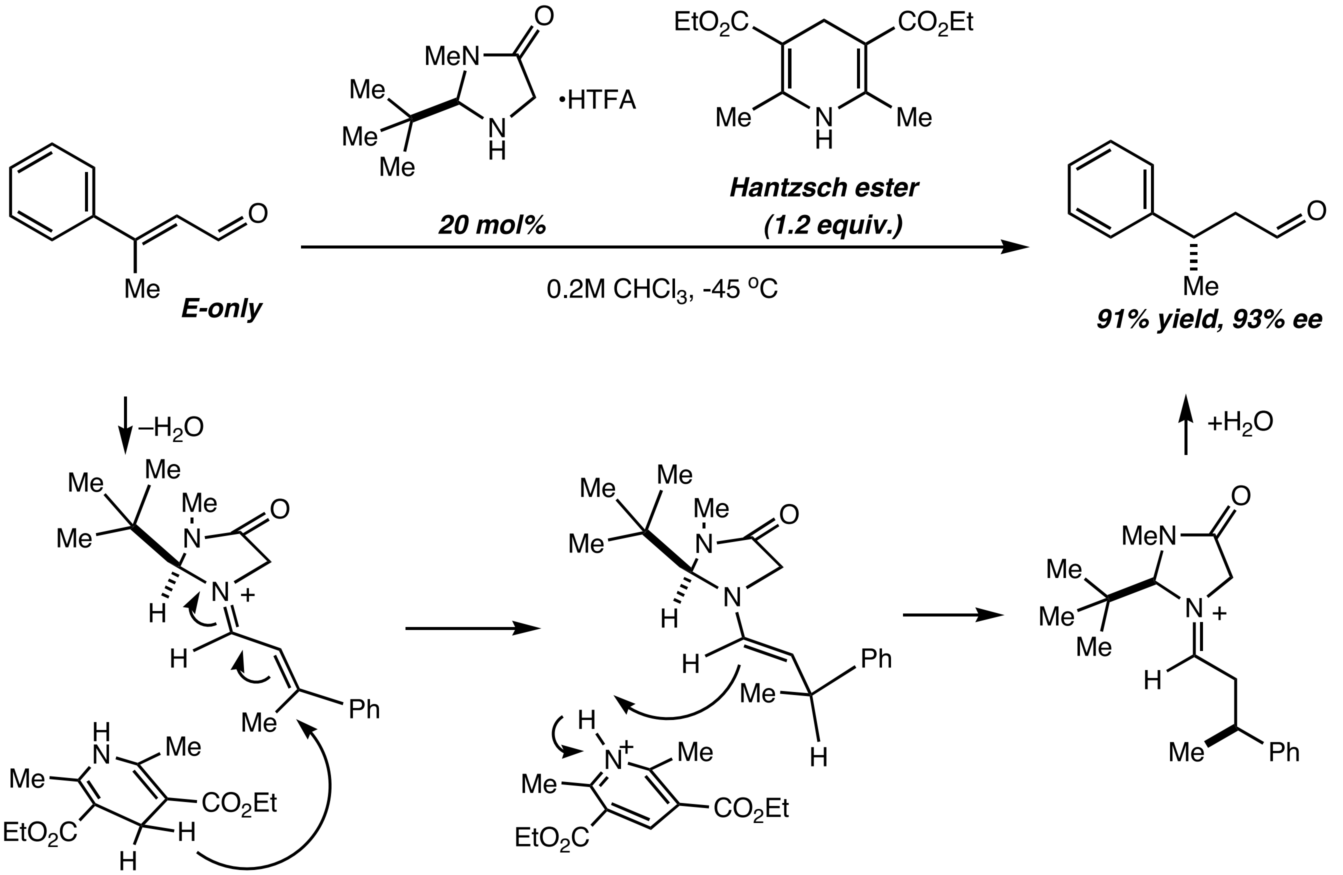
*Provide a mechanism for the conversion of **1** into **2** that explains the stereochemistry of the product. Utilize 3-D illustrations where necessary.*



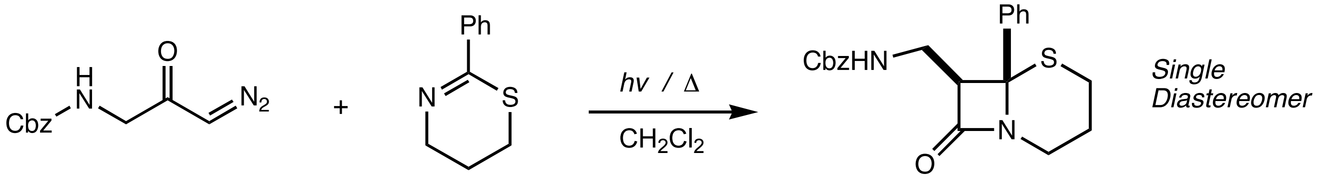
1 **2**

Question 14. (20 points). MacMillan and coworkers have recently reported the following enantioselective organo catalytic reduction of α,β-unsaturated aldehydes using a chiral iminium catalyst and the Hantzsch ester as the stoichiometric hydride source (*JACS,* **2005**, *127*, 32-33.).

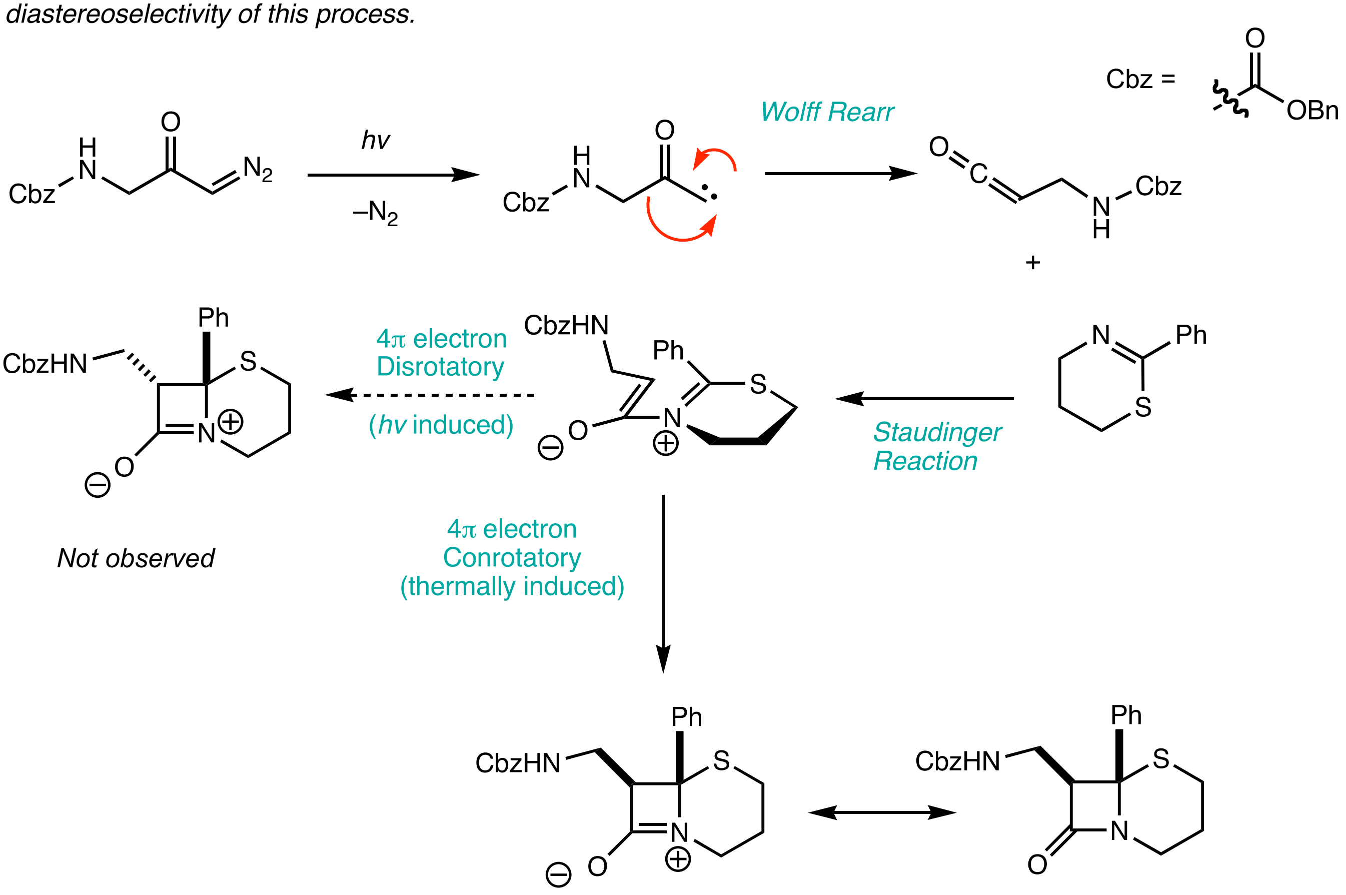
Please provide a detailed reaction mechanism for this reduction and rationalize the observed sense of absolute stereochemical induction.



Question 15. (20 points). α-Diazoketones are known to decompose to carbenes under photochemical excitation. It has recently been shown that in the presence of imines, the photo-decomposition of diazoketones provides β-lactams with good diastereocontrol (*JOC*, **2005**, *70*, 334-337).



Provide a mechanism for the above transformation. Your answer should include an explanation for the diastereoselectivity of this process.



Chemistry 206
Final Examination

D. A. Evans
January 23, 2004

Name (please print): **ANSWER KEY**
last first initial

Signature: ____________________

Teaching Fellow: ____________________

This examination contains **22** questions for which three hours are permitted. Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

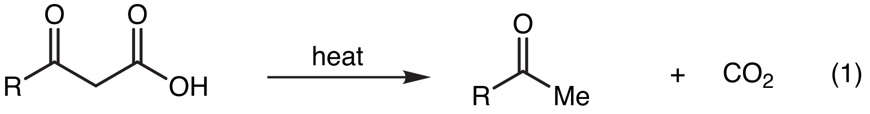
Be certain to address stereochemical and stereoelectronic issues where appropriate.

Question (pts)	**Score**	**Question (pts)**	**Score**
No. 1 (**15**)	______	No. 12 (**10**)	______
No. 2 (**10**)	______	No. 13 (**10**)	______
No. 3 (**20**)	______	No. 14 (**10**)	______
No. 4 (**20**)	______	No. 15 (**10**)	______
No. 5 (**15**)	______	No. 16 (**10**)	______
No. 6 (**20**)	______	No. 17 (**15**)	______
No. 7 (**15**)	______	No. 18 (**15**)	______
No. 8 (**15**)	______	No. 19 (**10**)	______
No. 9 (**10**)	______	No. 20 (**15**)	______
No. 10 (**10**)	______	No. 21 (**15**)	______
No. 11 (**15**)		No. 22 (**15**)	
Subtotal (**165**)		Subtotal (**135**)	

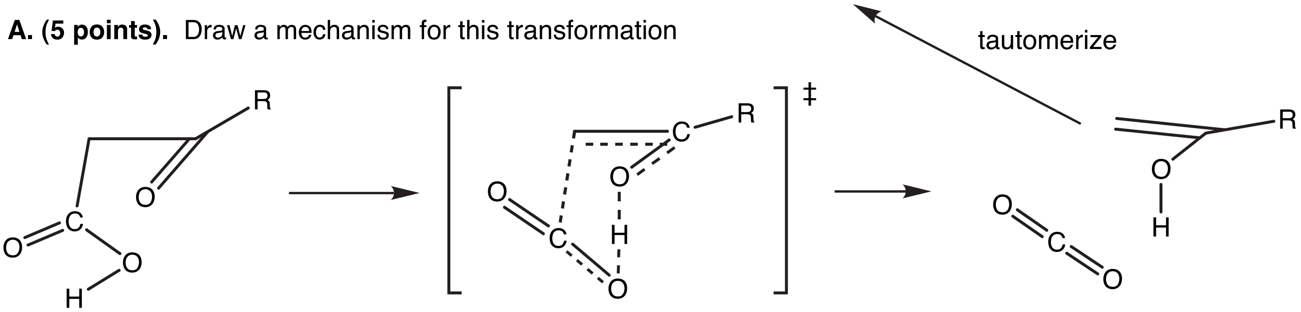
exam average

Total (300)

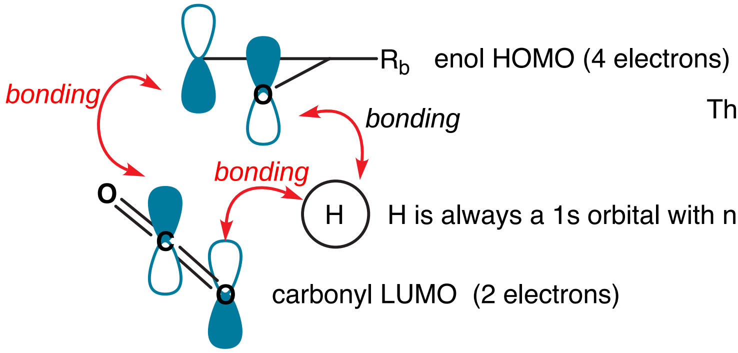
Question 1. (15 points). It is well-established that β-keto acids undergo thermal decarboxylation (Eq 1).



Part A. (5 points). Draw a mechanism for this transformation



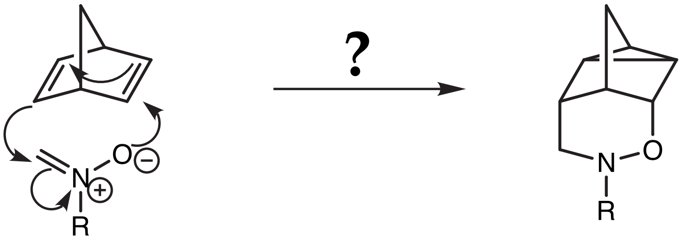
Part B. (10 points). Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.


R_b
enol HOMO (4 electrons)
bonding
O
bonding
bonding
H
H is always a 1s orbital with no electrons in this case
O
C
O
carbonyl LUMO (2 electrons)

The reaction should be thermally allowed

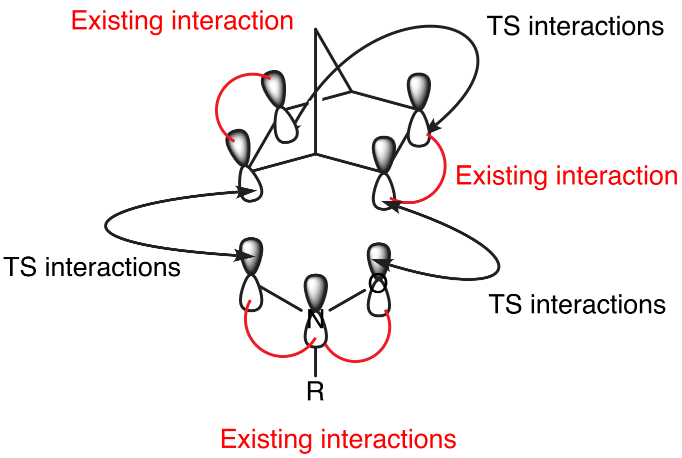
View the ene TS as a 3-component cycloaddition

Question 2. (10 points). Is the following cycloaddition allowed thermally? Please justify your answer with an FMO **or** Dewar-Zimmerman analysis.



This reaction is an eight electron, supra, supra, supra cycloaddition and is thermally forbidden.

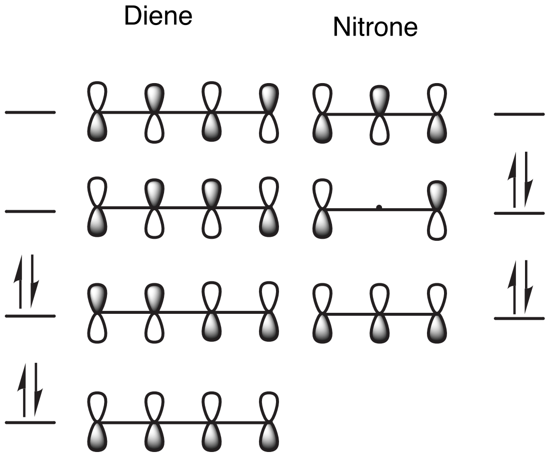
Dewar-Zimmerman Analysis

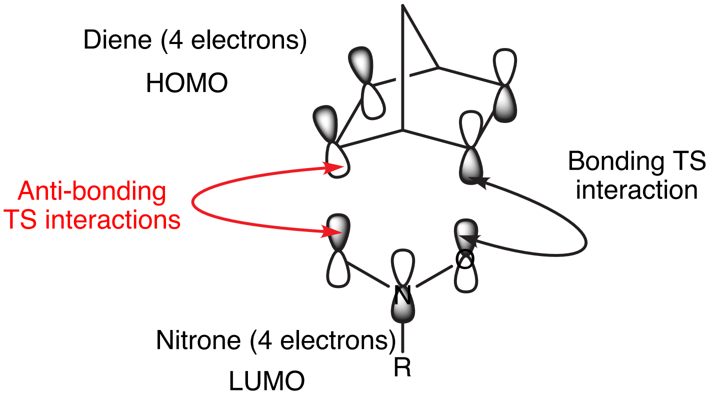


2 Phase inversions
Huckel topology
8 electrons
Anti-aromatic
thermally forbidden

FMO Analysis

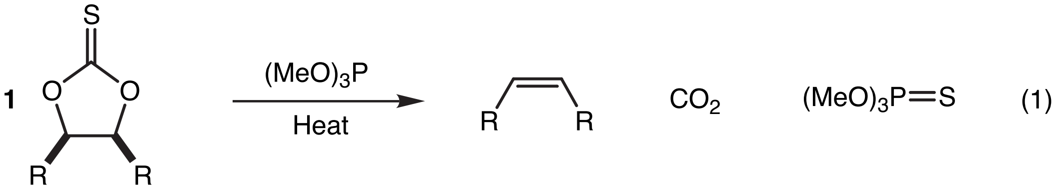
The FMO analysis is complicated because the reaction involves three independent pi components. The simplest thing to do is to treat the norbornadiene as a butadiene and construct the molecular orbitals in that fashion.





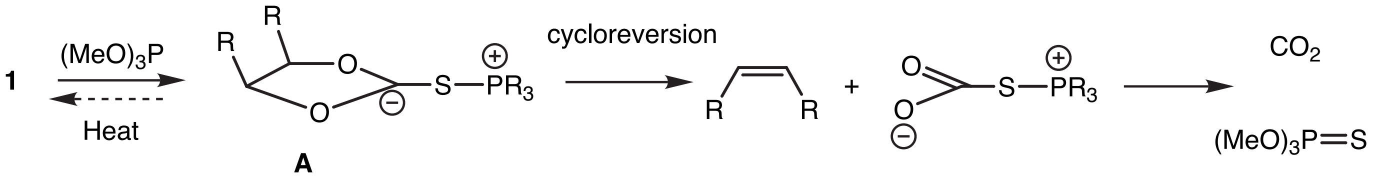
Reaction is forbidden because simultaneous bonding interaction at the termini is not possible.

Question 3. (20 points). In the Corey-Winter olefin synthesis, diol-derived thionocarbonates such as **1** are transformed *stereospecifically* to olefins when heated in the presence of phosphites (Eq 1) (*JACS* **1963**, *85*, 2677).

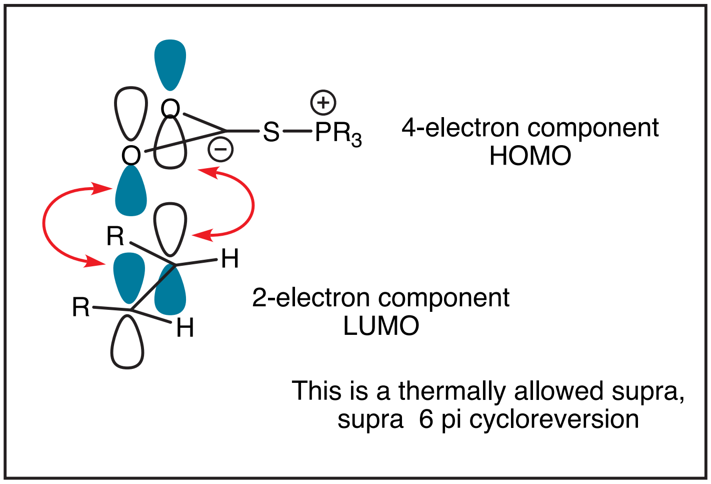


Part A. (5 points). Draw a mechanism for this transformation that accounts for the reaction specificity.

A plausible mechanism is provided below. It is not known whether A is an intermediate, or whether the cycloreversion is merged into the phosphite addition step. It is important to be aware of the fact that the reaction is stereospecific.

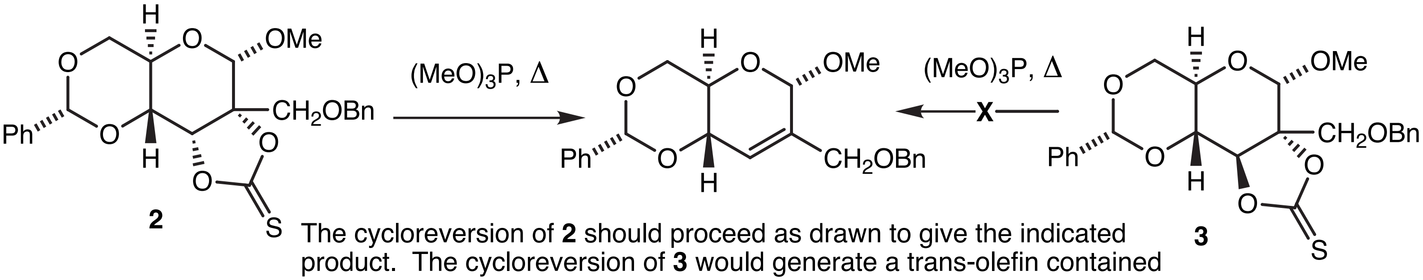


Part B. (10 points). Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.

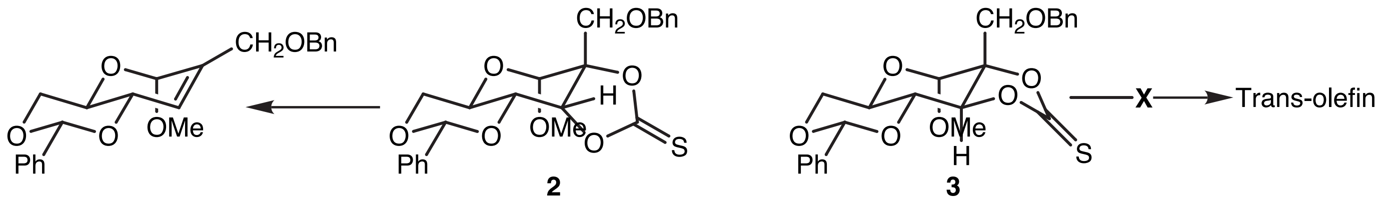


This is a thermally allowed supra, supra 6 pi cycloreversion

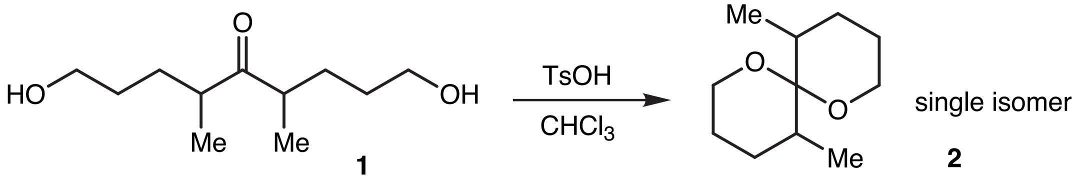
Part C. (5 points). Explain why thionocarbonate **2** undergoes the illustrated reaction smoothly while **3** does not. A good answer will include clear 3-D drawings of all relevant structures. (*Can. J. Chem.* **1994**,*72*, 69)



The cycloreversion of **2** should proceed as drawn to give the indicated product. The cycloreversion of **3** would generate a trans-olefin contained within the 6-membered ring. For this reason, the deoxygenation does not take place.



Question 4. (20 points). A 1:1 mixture of meso and *d/l* isomers of the hydroxyketone **1** is converted to a single stereoisomer (racemic, of course) of spiroketal **2**.



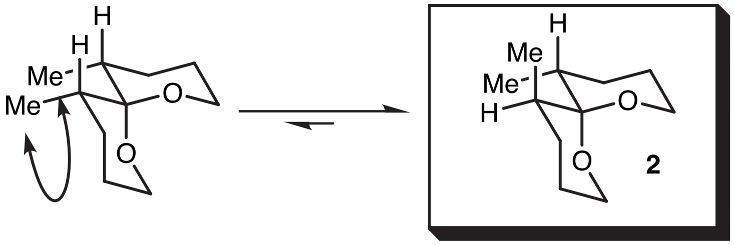
1

single isomer

2

Part A. (10 points). Please provide a 3-D drawing of spiroketal **2** clearly indicating its relative stereochemical configuration. Indicate specific factors responsible for the preferential formation of this isomer. Please also provide a mechanism for the equilibration of both stereoisomers of **1** to spiroketal **2**.

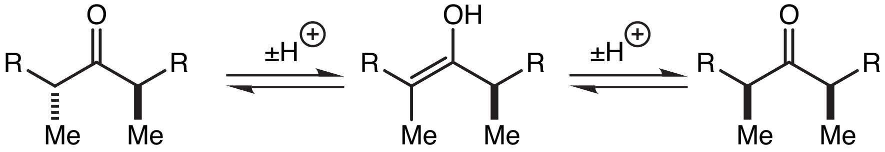
This spiroketal has two anomeric effects, but the syn-pentane interaction destabilizes it relative to its epimer.



2 anomeric effects

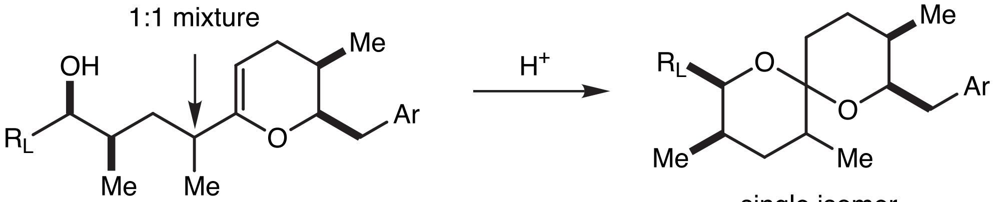
Methyl groups are equatorial on the THP rings

Avoidance of syn-pentane interactions



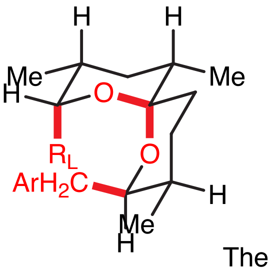
The α centers can be equilibrated via the enol tautomer.

Part B. (10 points). In the Evans' synthesis of calcimycin (*JACS* **1979**, *101*, 6789) a 1:1 mixture of methyl stereoisomers was converted to a single spiroketal diastereomer. Please provide a clear 3-D drawing of the resultant spiroketal. Please also provide a mechanism for the equlibration of both stereoisomers to a single isomer



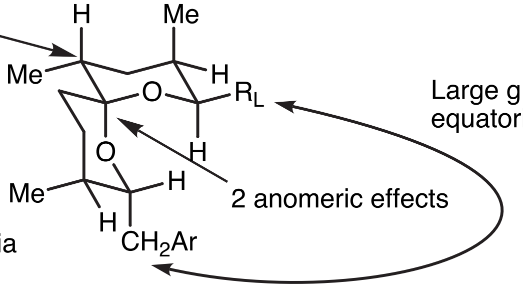
single isomer

Alternate spiroketal with 2 anomeric effects suffers from severe non-bonding interactions.



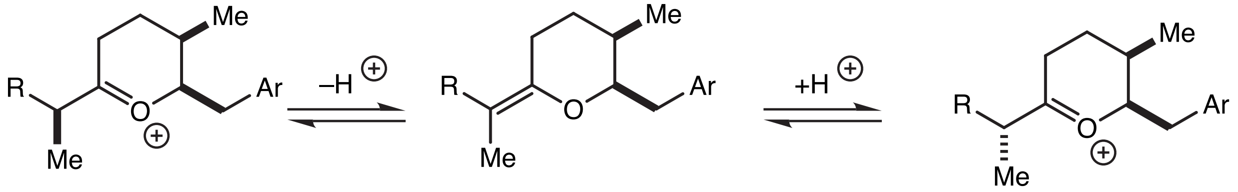
Preferred isomer

Epimerizable methyl group in equatorial position

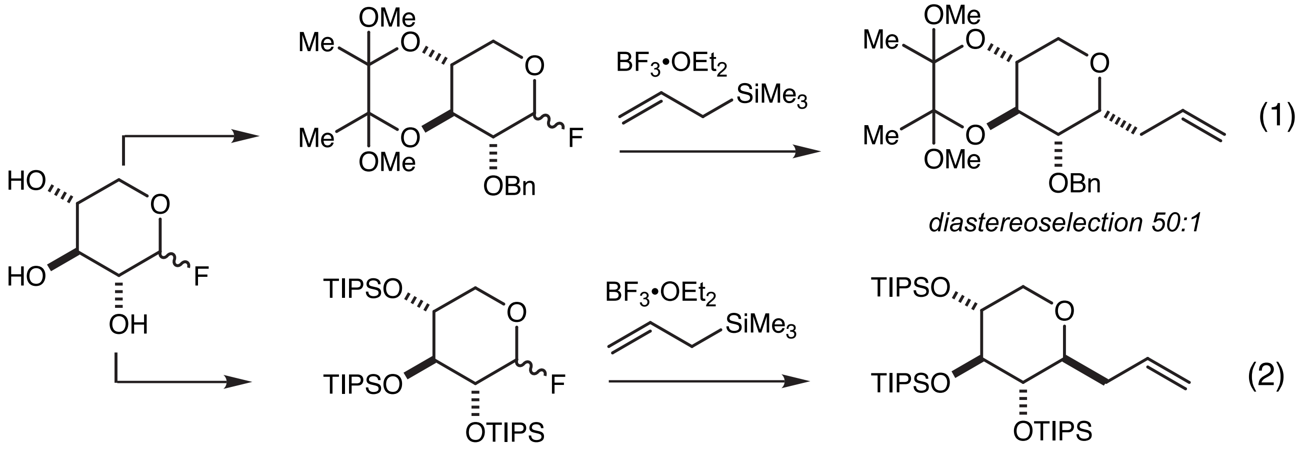


Large groups in equatorial positions

The α centers can be equilibrated via the exocyclic enol ether.



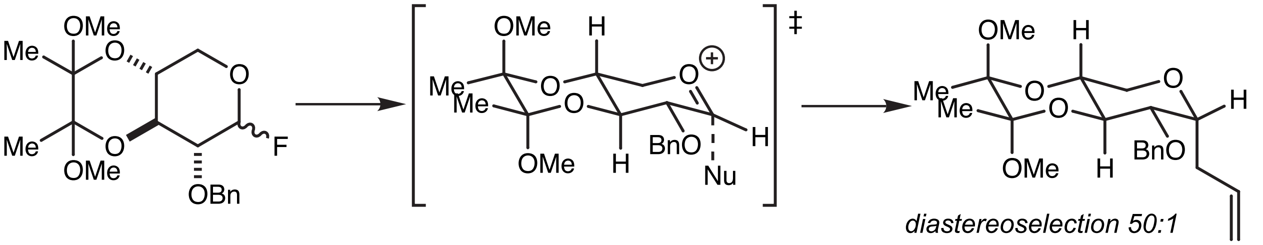
Question 5. (15 points). The stereochemical course of C-glycosidation may be controlled by the judicius choice of protecting groups (*Angew. Chem. Int. Ed.* **2003**, 1021-3).



diastereoselection >99:1

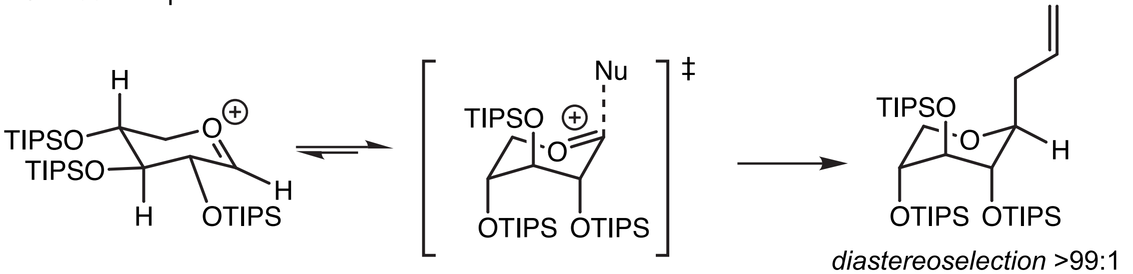
TIPS = (triisopropyl)silyl, a sterically demanding oxygen protecting group

Part A. (7 points). Using conformational drawings, rationalize the stereochemical outcome of of the allylation illustrated in Eq 1.



This substrate is conformationally locked.
Axial attack on oxocarbenium ion is stereoelectronically favored as is syn attack to the vicinal cis OBn substituent (Woerpel, *JACS* **2000**, *122*, 168).

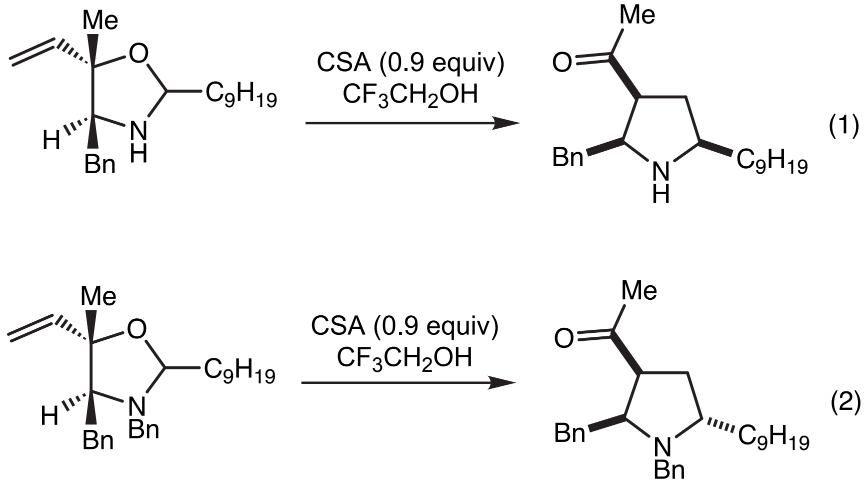
Part B. (8 points). Using conformational drawings, rationalize the stereochemical outcome of of the allylation illustrated in Eq 2.

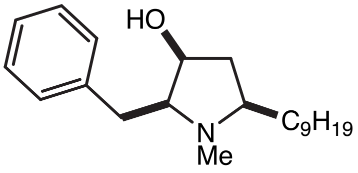


diastereoselection >99:1

Vicinal bulky diequatorial silyl ethers cannot are less stable than their diaxial counterparts accomodated diequatorially; forced diaxial alignment and stereoelectronically favored axial nucleophilic addition

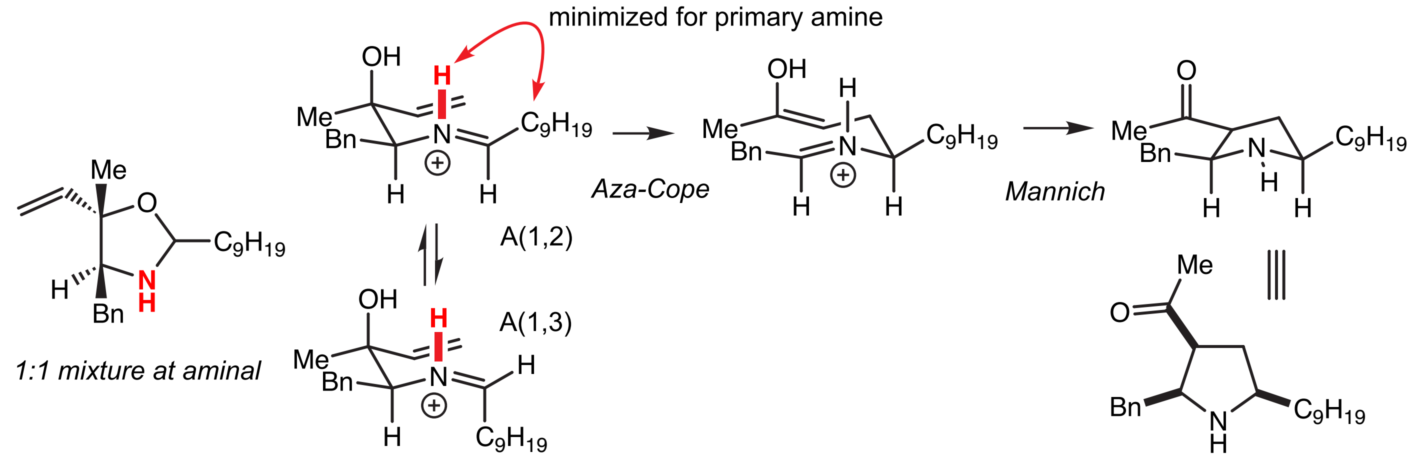
Question 6. (20 points). An elegant enantiodivergent synthesis of the potent anti-fungal reagent Preussin was reported by Overman (*JACS* **1994,** 11241.).



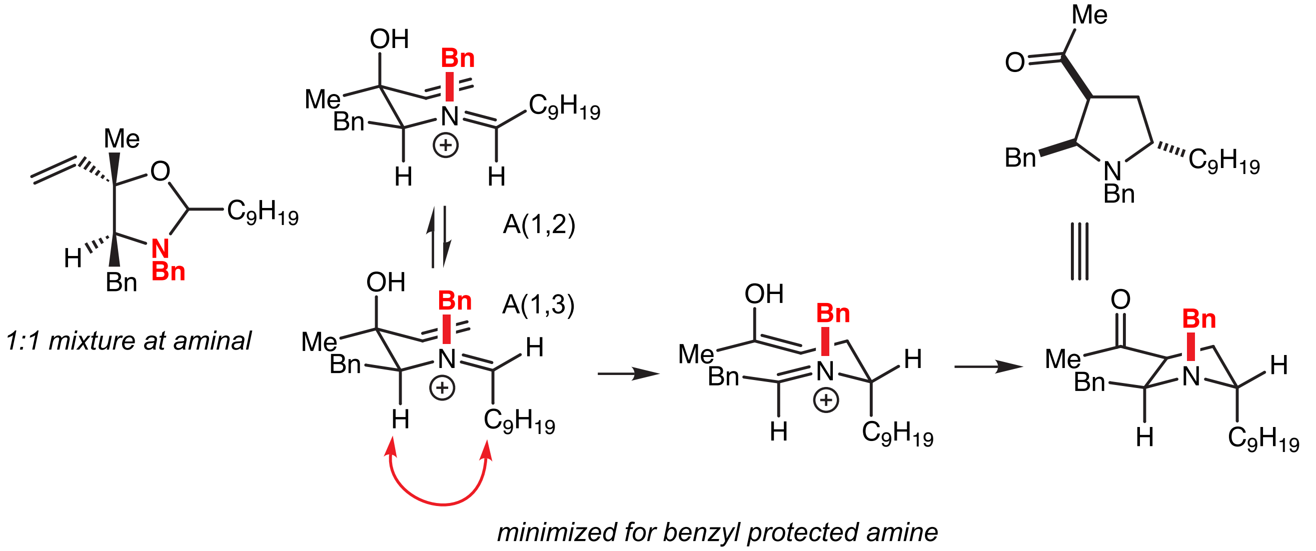


(+)-Preussin
natural configuration

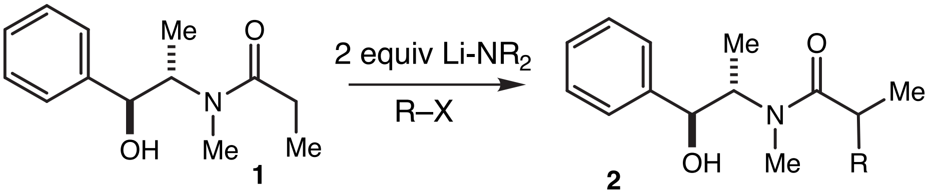
Part A. (10 points). Provide a mechanism for the transformation illustrated in Eq 1. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.



Part B. (10 points). Provide a mechanism for the transformation illustrated in Eq 2. Where stereochemicasl issues are involved, 3-dimensional drawings should be employed.

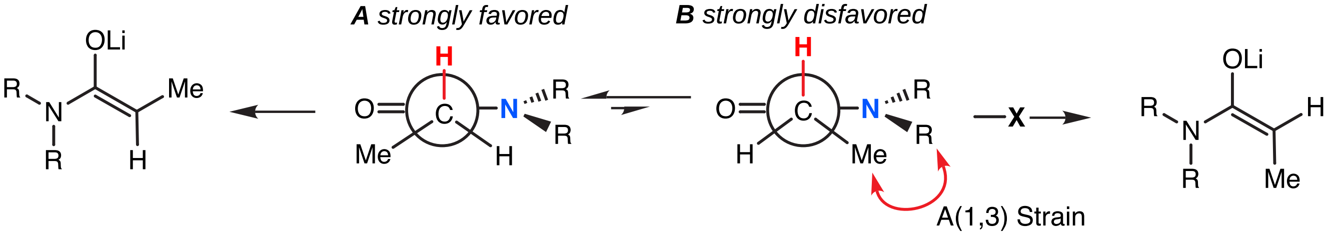


Question 7. (15 points). The pseudoephedrine-derived propionamide **1,** upon successive enolization with LiN(I-Pr)$_2$ (LDA) and alkylation with alkyl halide R–X, affords **2** with high diastereoselection (Myers, *JACS* **1997**, *119*, 6496).

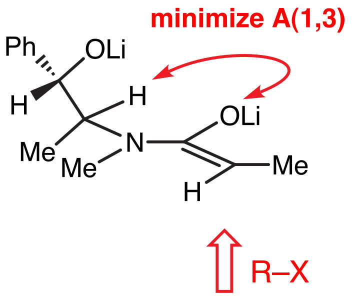


Part A. (5 points). Enolization of **1** with LDA affords a single enolate geometry. Provide an analysis of this enolization event and draw the enolate thus produced.

Allylic Strain controls Enolate Geometry. In the deprotonation of conformer **B,** developing A(1,3) strain strongly disfavors the formation of the (E) enolate.



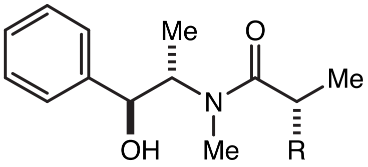
Part B. (5 points). Provide a 3-dimensional drawing of the transition state for this reaction in **Box-1.** *Hint: In answering this question, you do not need to assume that chelation is involved. Rather, a suitable transition state model may be derived purely from the consideration of non-bonding interactions.*



Box-1

5 points

Part C. (5 points). Provide the absolute stereochemistry of the alkylation product **2** of this reaction in **Box-2**.

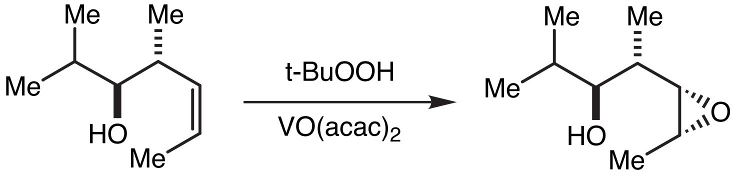


Box-2

5 points

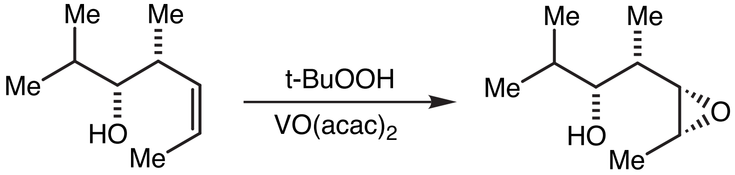
Question 8. (15 points). Mihelich has carried out an elegant study on the vanadium (V) hydroxyl-directed epoxidation of homoallylic alcohols (*JACS* **1981**, *103*, 7690). Two examples taken from this study are illustrated below (Eq 1, 2).

Anti isomer: (1)



dr = 400:1 (1)

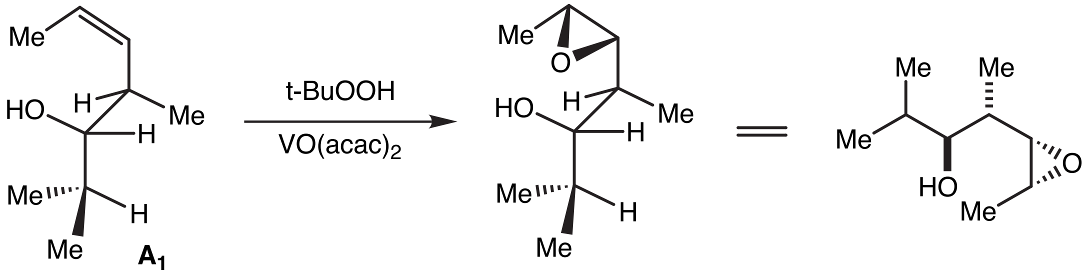
Syn isomer: (2)



dr = 2:1 (2)

Part A. (7 points). Illustrate the low-energy conformation of alcohol **1** that apparently leads to the observed epoxidation product.

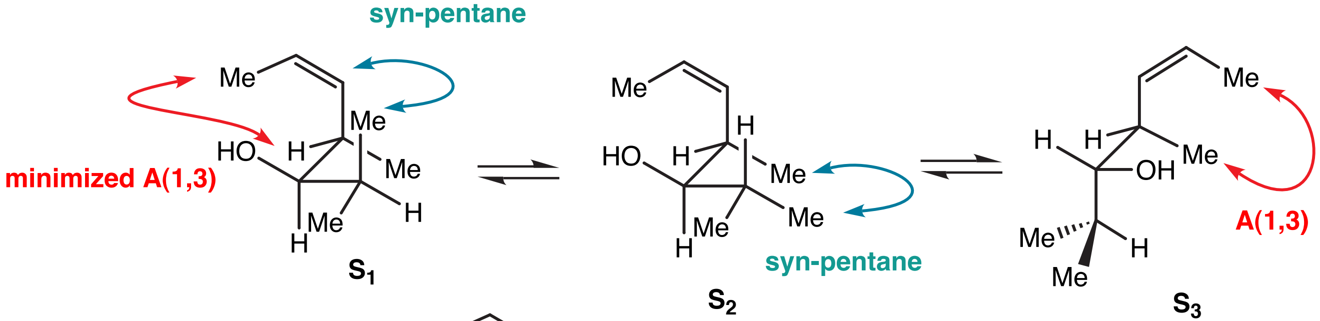
Anti isomer: (1)

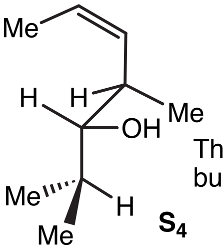


In conformation **A$_1$**, there are no destabilizing A(1,3) or syn-pentane interactions.

Part B. (8 points). The syn alcohol **2** is poorly diastereoselective in the directed epoxidation. Illustrate the connformations of **2** that should exhibit hydroxyl directivity and identify the principal destabilizing interation.

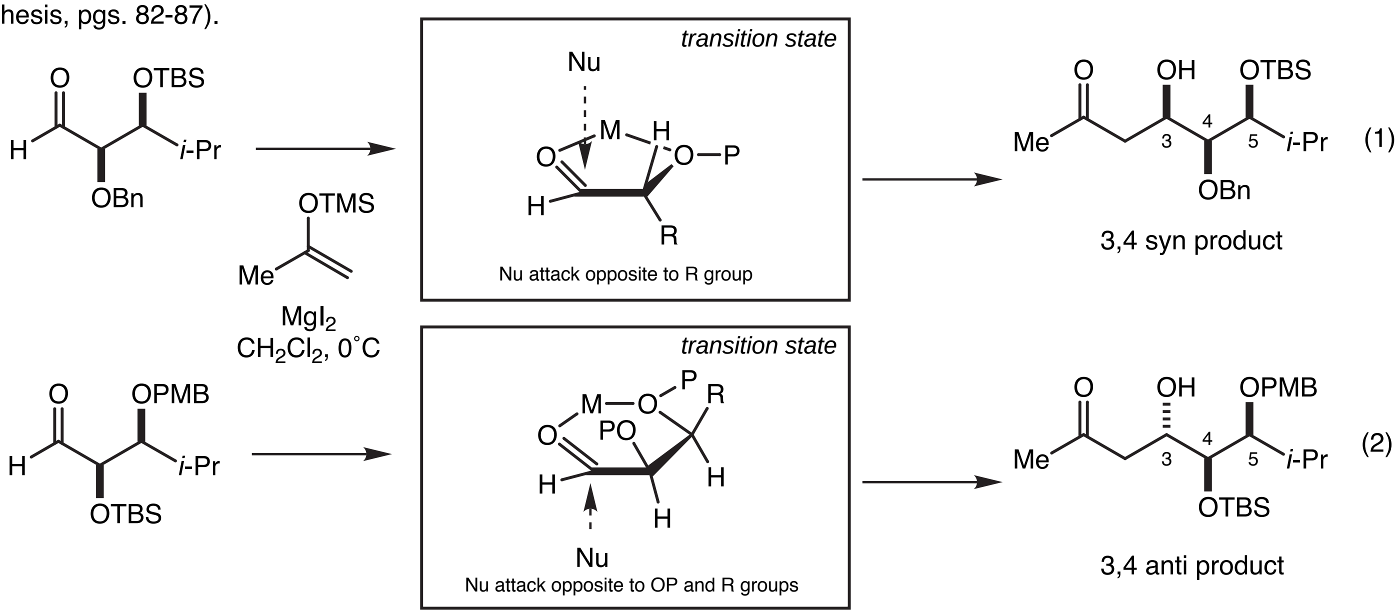
Each conformer has either a syn-pentane or A(1,3) destabilizing interaction, consequently epoxidation face selectivity is low





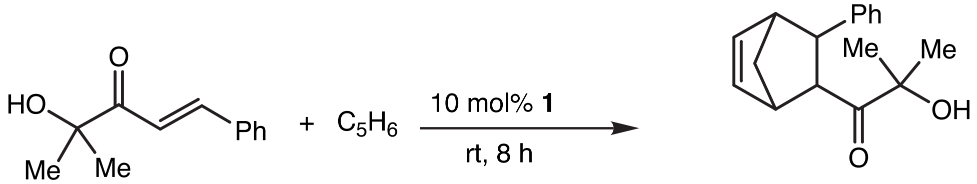
This conformation has all nonbonding interactons minimized but apparently the hydroxyl-olefin orientation is not optimal.

Question 9. (10 points). The two illustrated MgI_2–promoted Mukaiyama aldol reactions occur with high diastereoselectivity (Eq 1, 2). In contrast, only poor selectivity is observed in both reactions when MgI_2 is replaced with $BF_3 \cdot OEt_2$. Provide a transition state model that explains the formation of the 3,4 syn product in (Eq 1) and the 3,4 anti product in (Eq 2). Assume that the Bn and PMB protecting groups are chemically equivalent. (Victor Cee, Ph.D. Thesis, pgs. 82-87).

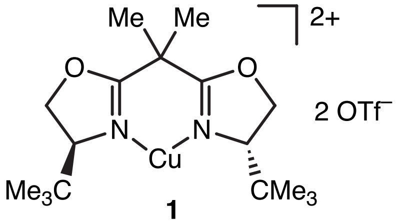


When the chelating protecting group is in the alpha position (Eq1), a five member chelate is formed and incoming nucleophile attacks from pi face opposite to the R group (TS-1). In contrast, a six-membered chelate is formed when the chelating protecting group is in the beta position and the nucleophile approaches from the face away from both the OP and R groups. The observation that $BF_3 \cdot OEt_2$ gives poor selectivity implies that the reaction is not simply under Felkin control, as one may predict for Eq 2.

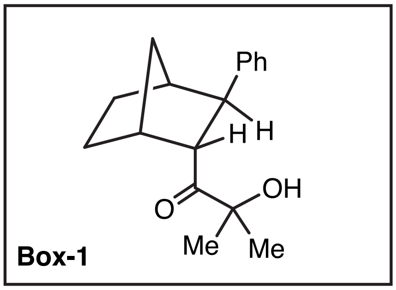
Question 10. (10 points). The C_2-symmetric cationic Cu(II) complex **1** is a chiral Lewis acid catalyst that exhibits good chelating potential. Palomo has reported the utilization of **1** in the catalyzed Diels-Alder reaction is illustrated below (*JACS*, **2003**, *125*, 3943).



99% ee, 90% yield
endo/exo: 91:9

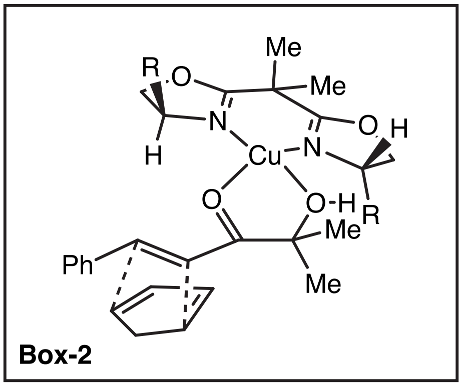


1



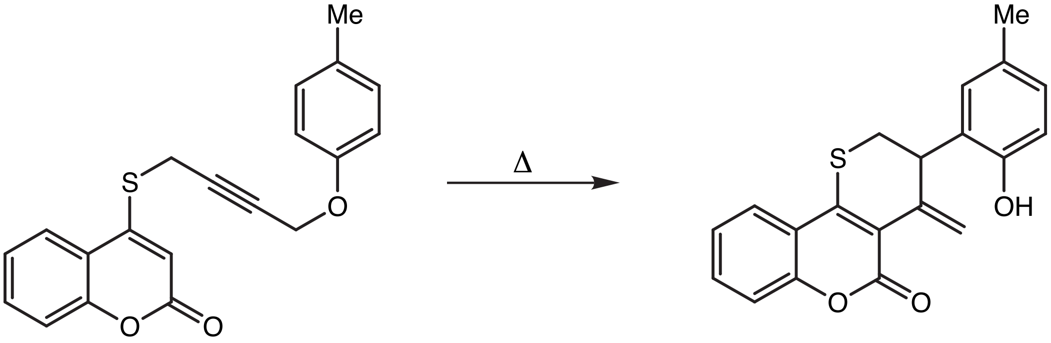
(5 points)

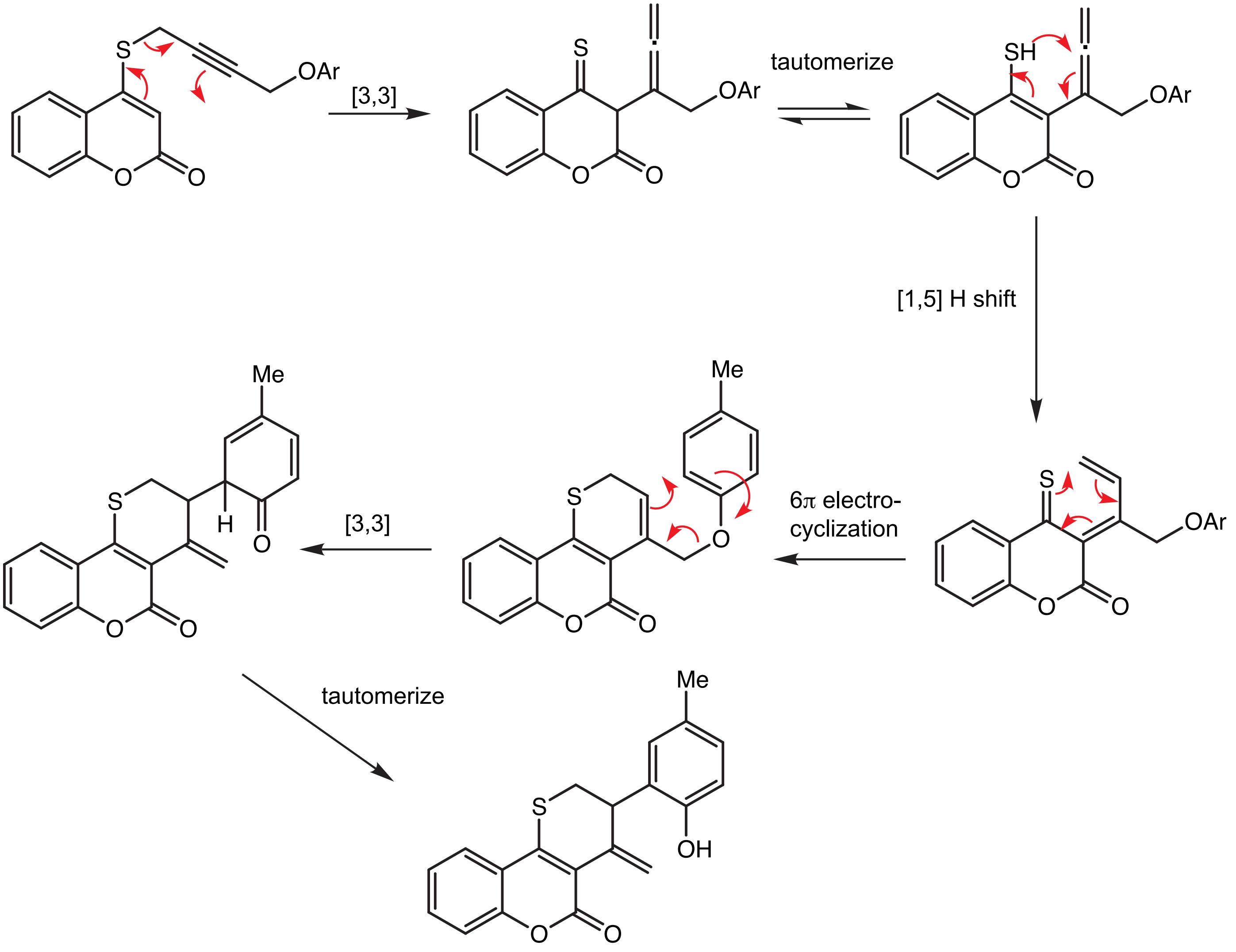
Provide the absolute stereochemistry of the product of this reaction in **Box-1**.
Provide a 3-dimensional drawing of the transition state for this reaction in **Box-2**.
Hint: Cu(II) complexes strongly prefer square-planar geometries



(5 points)

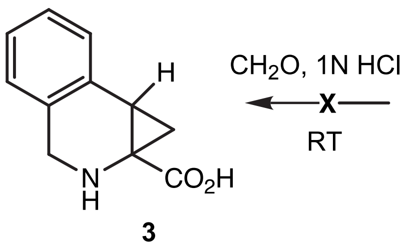
Question 11. (15 points). A recent paper by Majumdar and co-workers reported the transformation illustrated below (*Organic Lett* **2002**, *4*, 2629). Please provide a mechanism for this process. Feel free to use trace quantities of HX when needed.



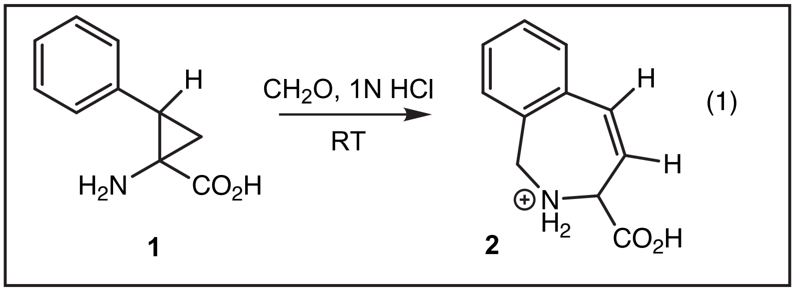


Question 12. (10 points). A recent paper by Martens (*JOC*. **2001**, *66*, 2884) reported the reaction shown below (Eq 1). Please provide a mechanism for the conversion of **1** to **2**. It is noteworthy that the Pictet-Spengler of 1 does not give **3**.

(2)

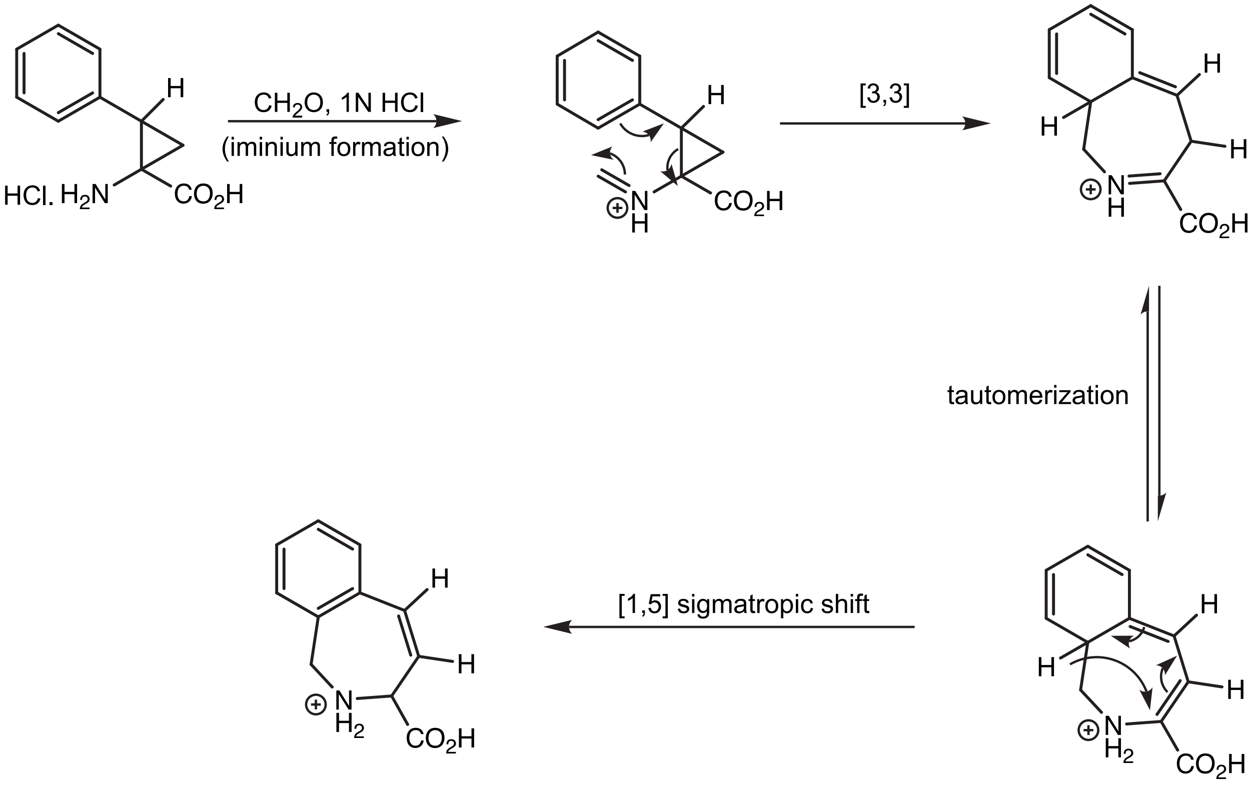


3

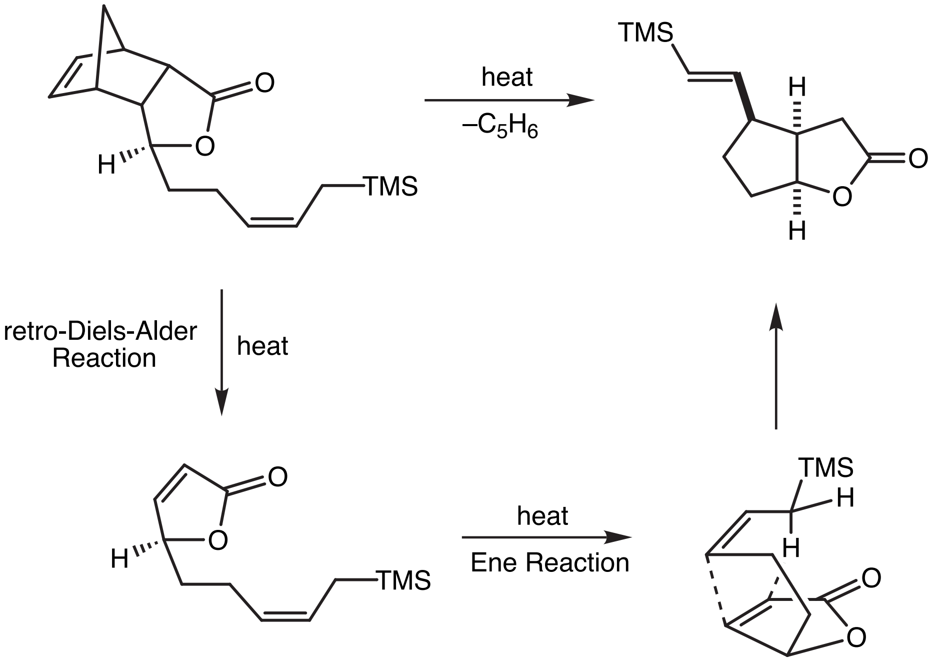


1 **2**

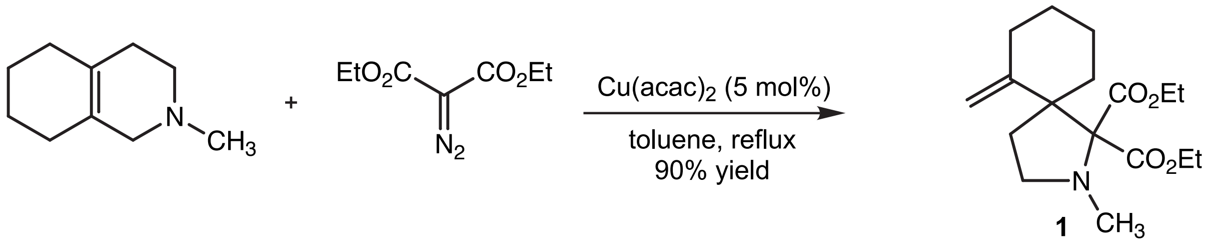
(1)

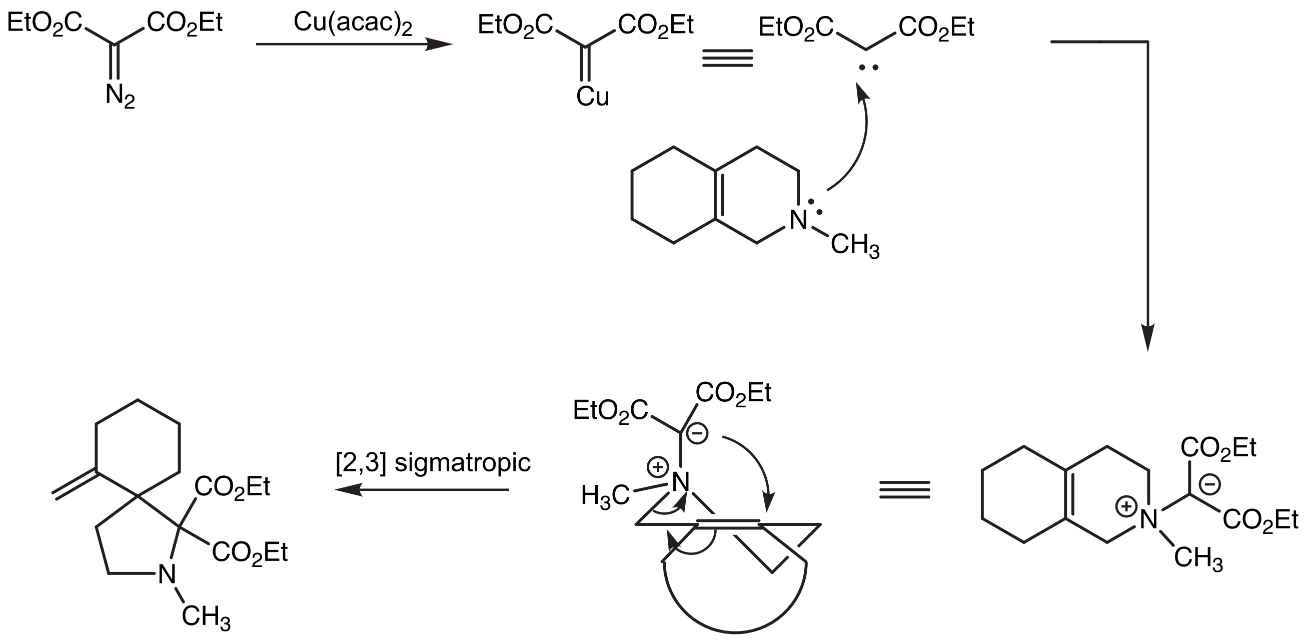


Question 13. (10 points). Inomata has reported the interesting thermal process in the context of methyl jasmonate (*Organic Lett.* **2004**, ASAP). Provide a mechanism for this overall transformation. Be sure to account for the stereochemical details of this process with the judicous use of 3-dimensional drawings.

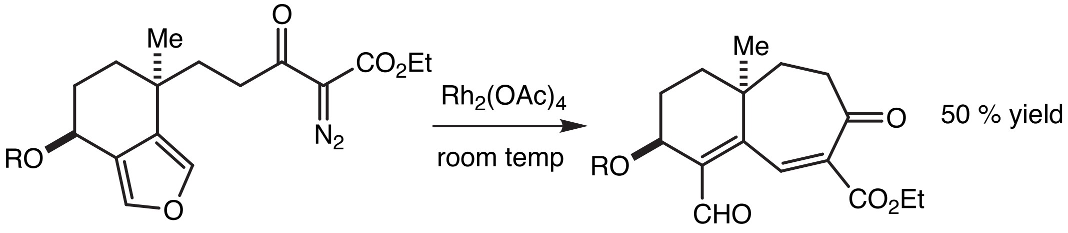


Question 14. (10 points). A recent paper by Workman and co-workers (*Org. Lett*. **2003**, *5*, 4775) describe an efficient reaction for the formation of spiro-heterocycle **1**. Propose a mechanism for the formation of **1**.

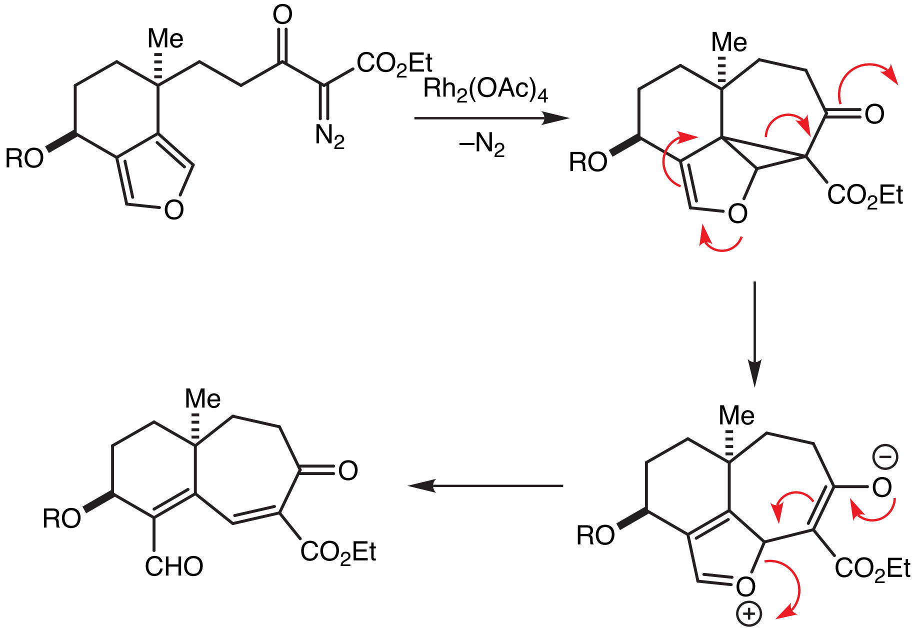




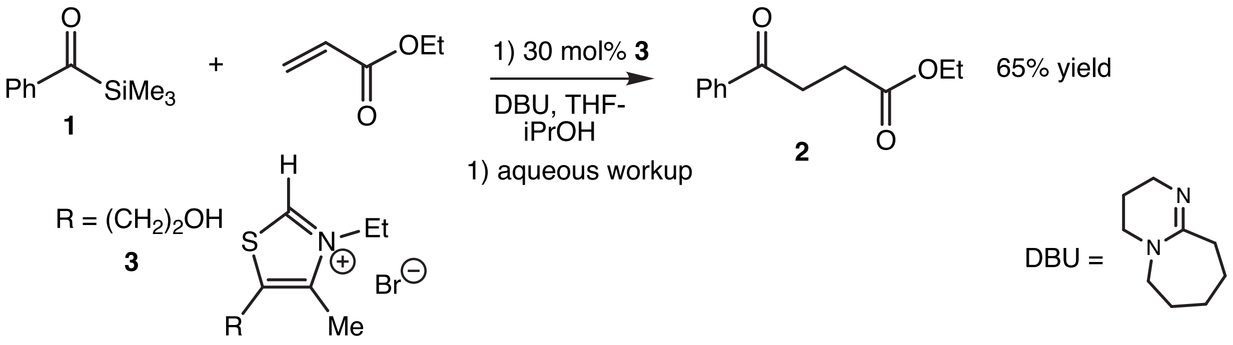
Question 15. (10 points). The following transformation was recently reported by Trauner and co-workers (*Organic Lett.* **2003**, *5*, 4113) as a pivotal reaction in the synthesis of specific members of the guanacastepene diterpenes. These natural products have attracted interest as potent antiobiotics against *Staphylococcus aureus*.

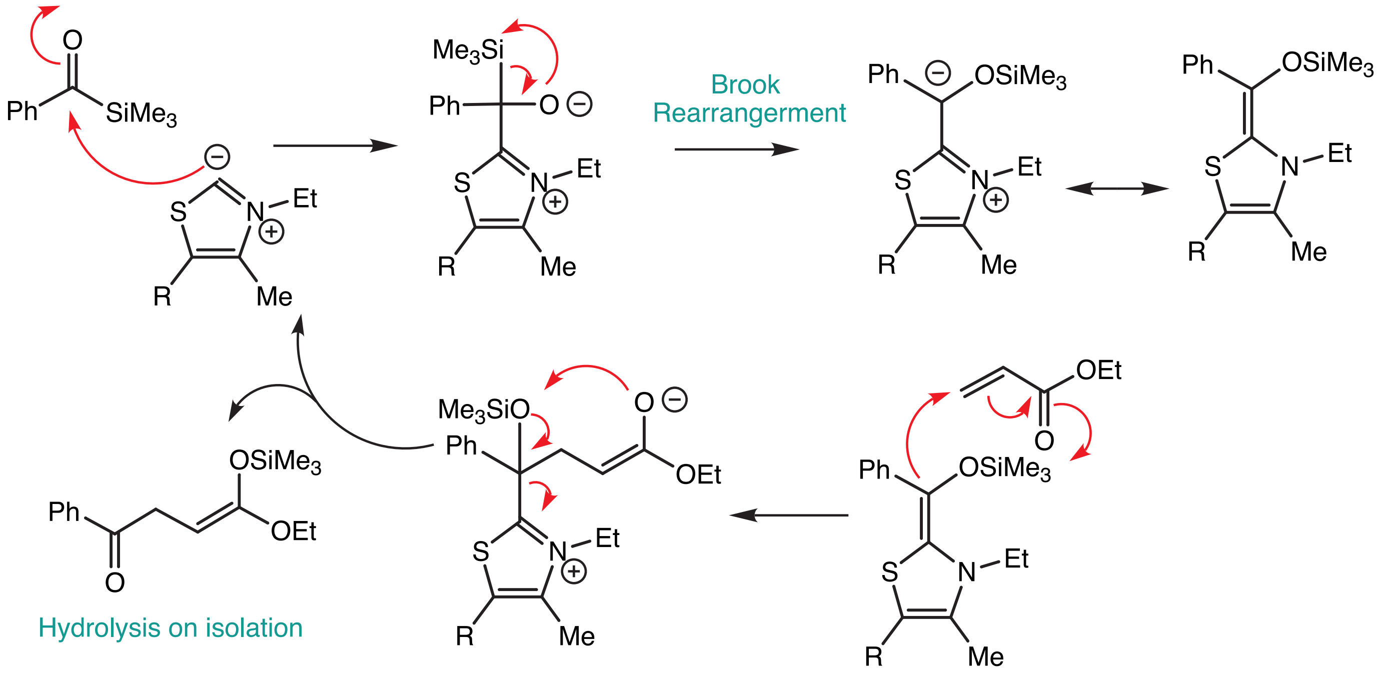


Provide a mechanism for the transformation illustrated above.

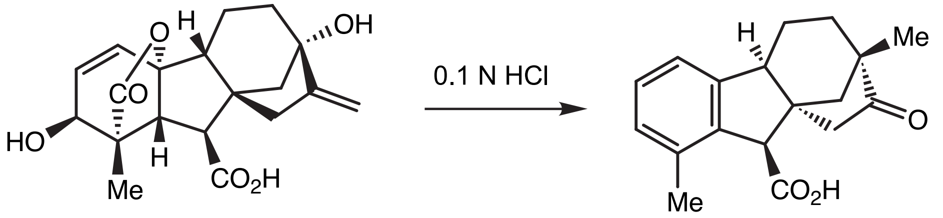


Question 16. (10 points). The first example of a "Silyl-Stetter reaction" will appear in the literature shortly (Scheidt, *JACS*, **2004**, 125, in press). Provide a mechanism for this transformation.



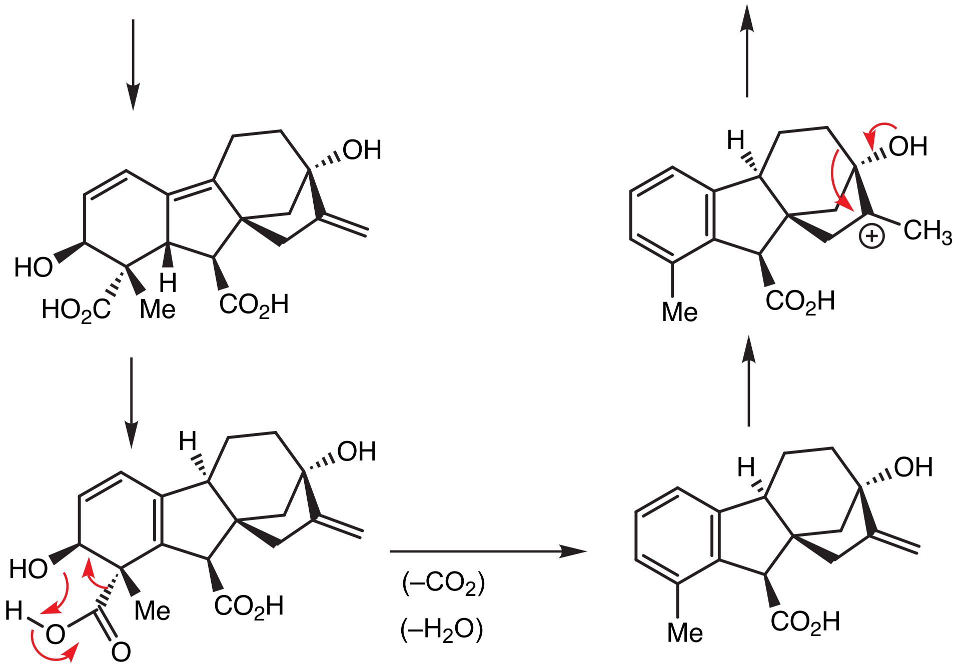


Question 17. (15 points). Gibberellic acid is a notoriously sensitive natural product. Rearrangement occurs readily in both acidic and basic conditions. Provide a mechanism for the illustrated rearrangement under dilute HCl.

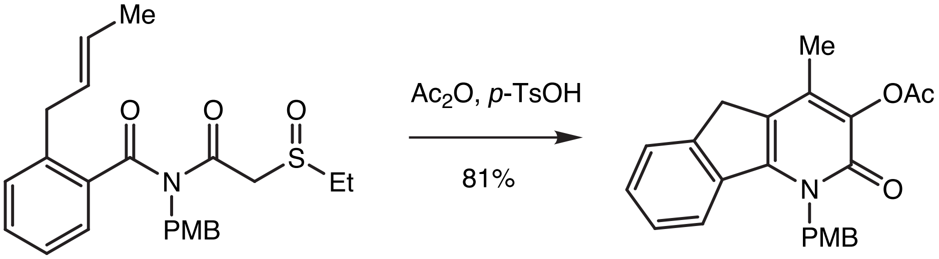


gibberellic acid

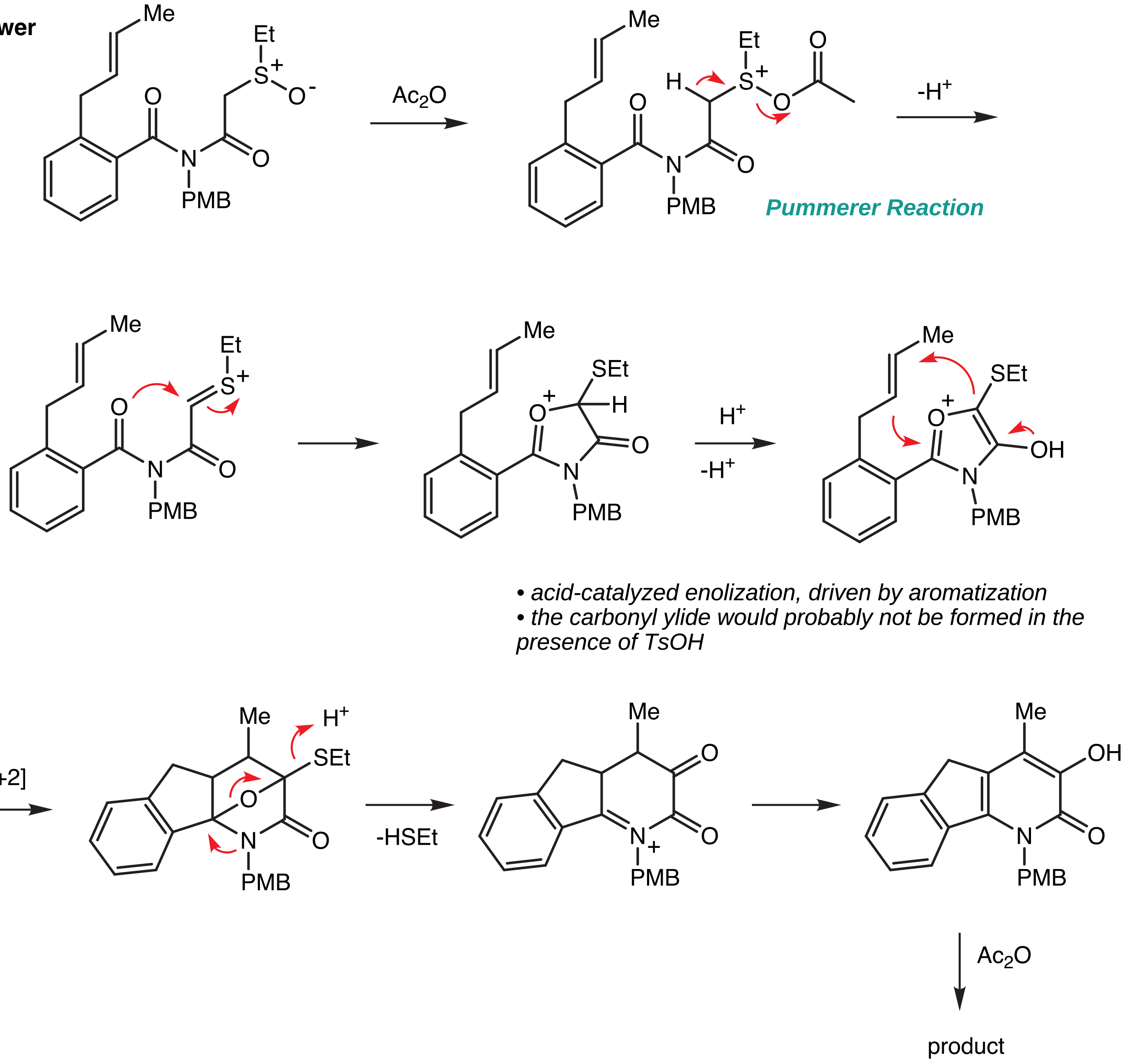
Answer



Question 18. (15 points). Padwa and co-workers recently reported this reaction cascade as an example of an efficient approach to the construction of a polycyclic piperidine ring system (*J. Org. Chem*. **2000**, *65*, 2368). Provide a mechanism for this complex transformation.

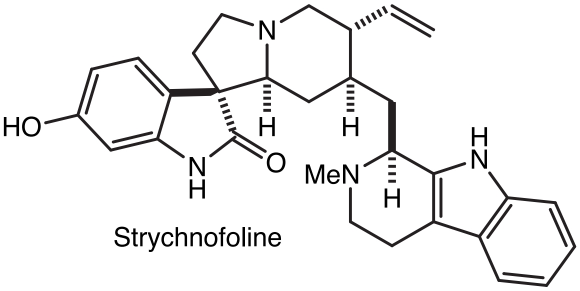


Answer

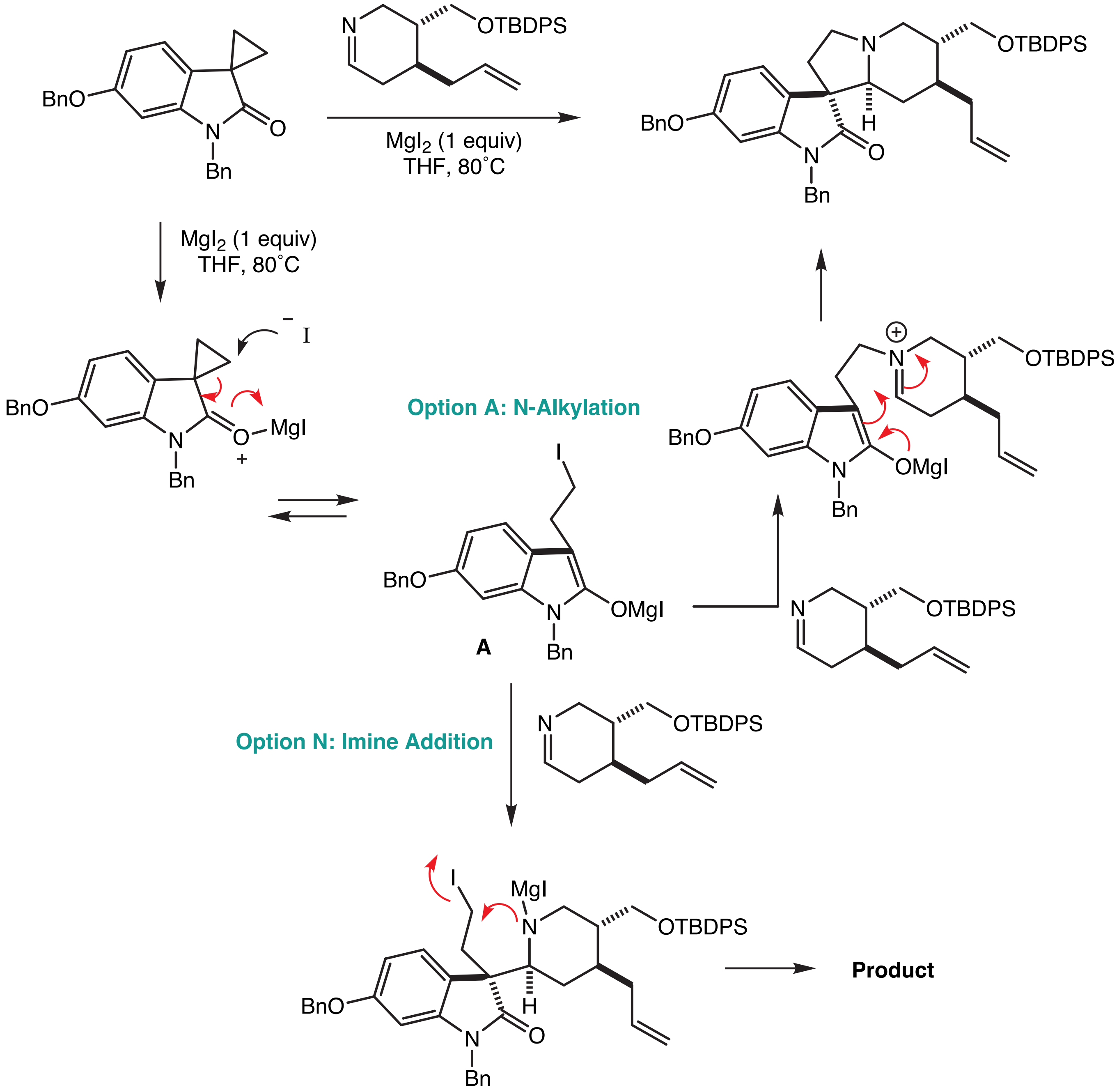


- *acid-catalyzed enolization, driven by aromatization*
- *the carbonyl ylide would probably not be formed in the presence of TsOH*

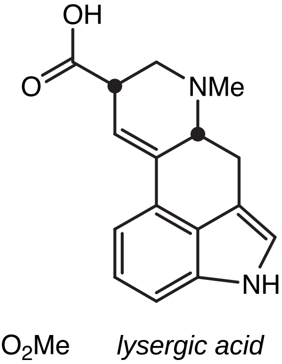
Question 19. (10 points). In conjunction with the total synthesis of *rac*-Strychnofoline (*JACS*, **2002**, *124*, 14826), Carreira utilizes the following MgI_2 catalyzed reaction to form the fused nitrogen heterocycle in one step. Provide a plausible mechanism for this transformation that accounts for the observation that *$Mg(OTf)_2$ does not catalyze this reaction.*



Strychnofoline

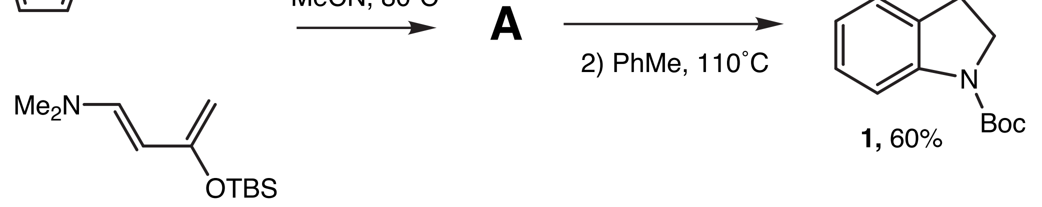


Intermediate A has two options for further reaction. Due to the low propensity for nucleophilic addition to imines, Option A represents the most probable reaction course.



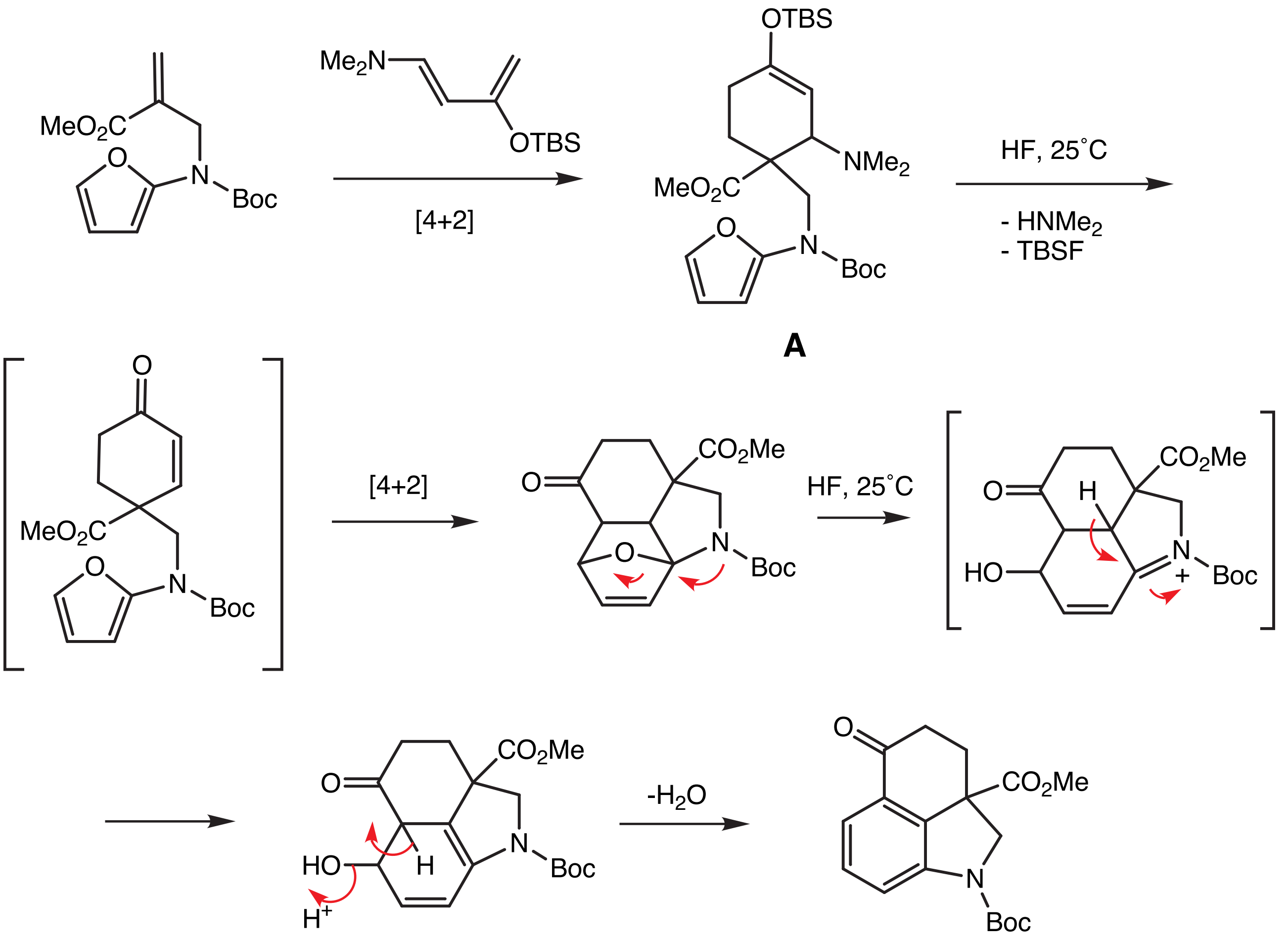
lysergic acid

Question 20. (15 points). Lysergic acid (**1**) and its numerous derivatives possess broad pharmalogical activity, arguably the broadest spectrum of activities found in any class of natural products. This has driven the pharmaceutical industry to agressively evaluate structural analogues of the lysergic acid skeleton. The reaction sequence illustrated below provides easy access to the tricyclic ketone **1**, a useful intermediate for further analogue studies (*Org. Lett.* **2002**, *4*, 4135).

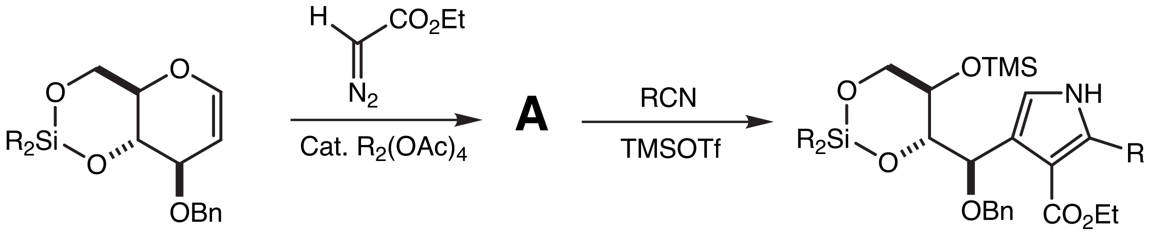


1, 60%

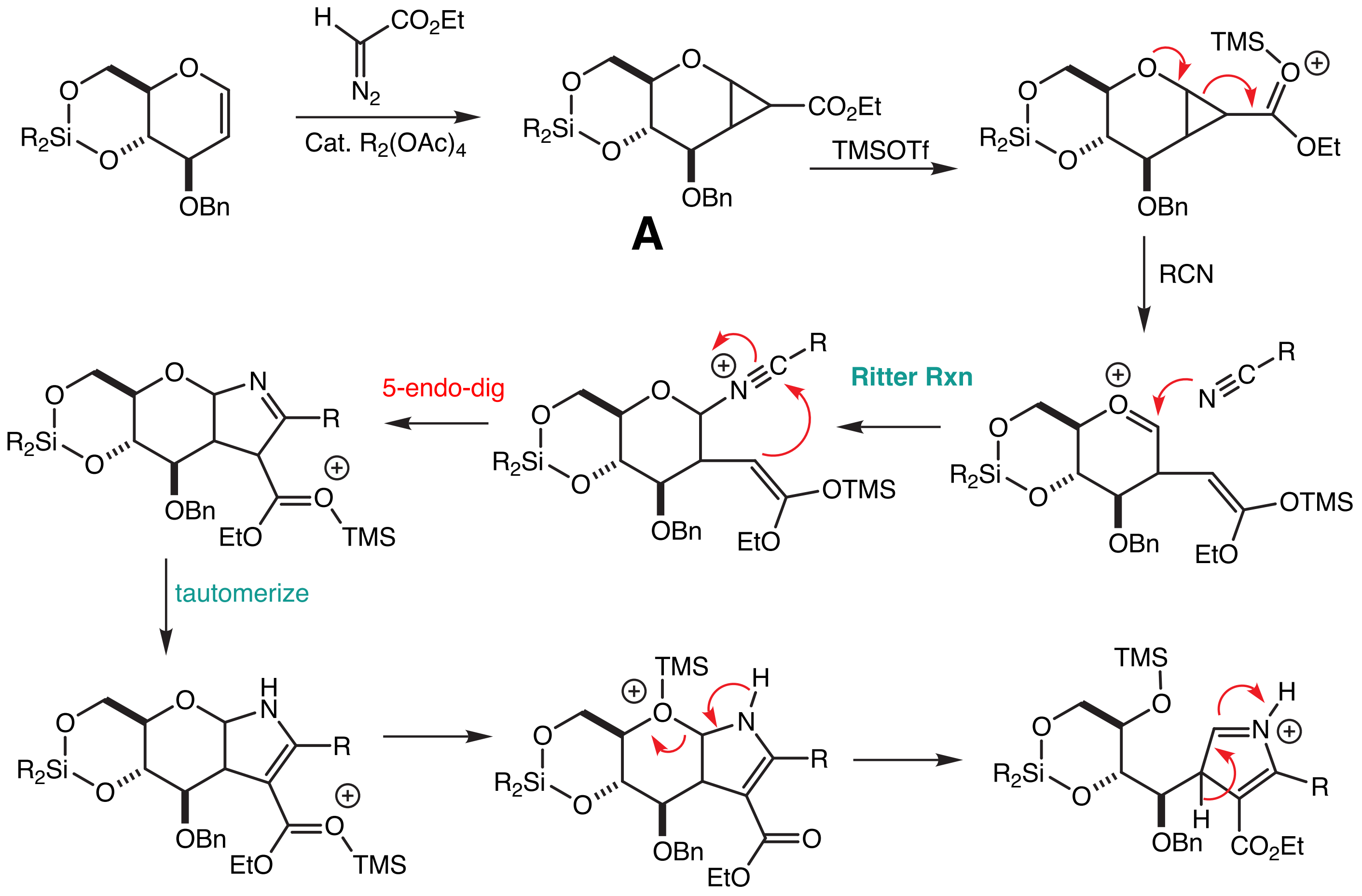
Provide a mechanism for the overall process and clearly identify intermediate **A**.



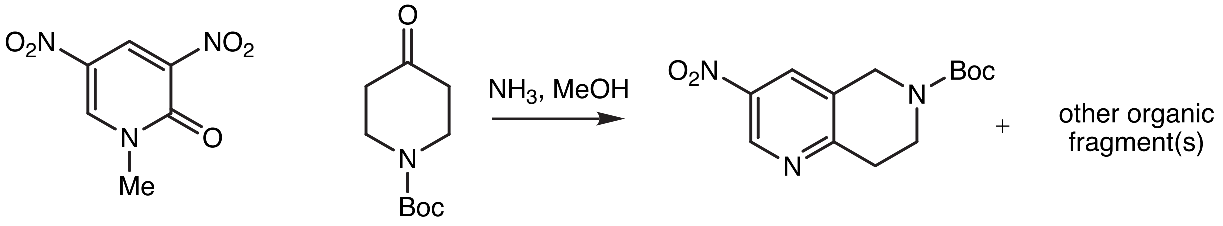
Question 21. (15 points). Pagendorf and Yu have recently reported a new "diversity-oriented" synthesis of pyrroles (*Org. Lett.* **2003**, *5*, 5099). The two-step process illustrated below will accomodate a range of "R" substituents.



Provide a mechanism for the overall process and clearly identify intermediate **A**.

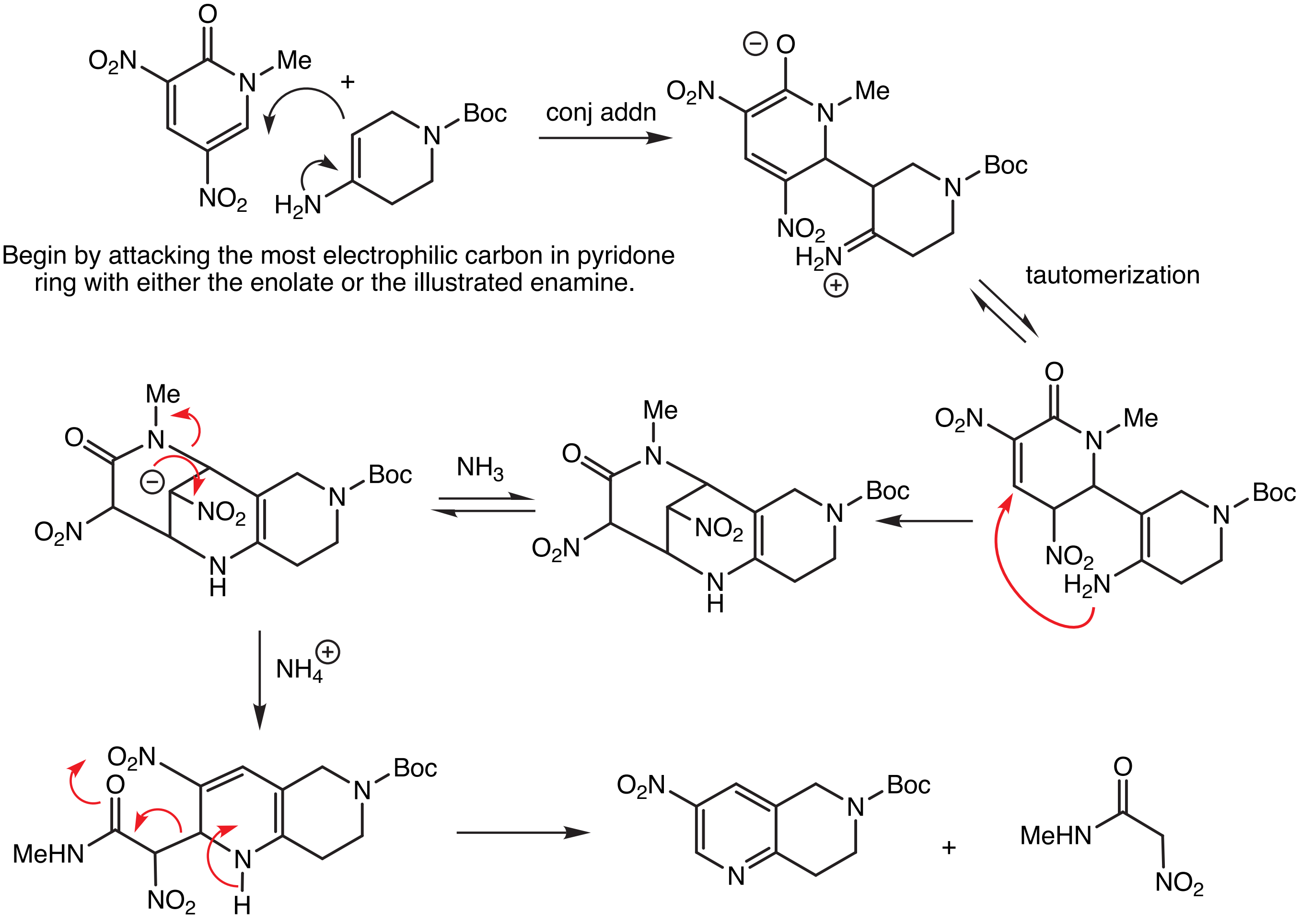


Question 22. (15 points). This is a classic problem in multistep electron pushing. The following pyridine synthesis has been reported by Tohda (*Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820-2827). Provide a plausible mechanism for this complex transformation. *Hint: To begin to solve a problem of this type, orient the two reacting components in such a fashion that they mirror their orientation in the observed product.*



Provide a mechanism for the overall process in the space below.

In this multistep transformation, the sequence of chemical events may not be unique. Let's now begin:



Begin by attacking the most electrophilic carbon in pyridone ring with either the enolate or the illustrated enamine.

Chemistry 206
Second Hour Practice Examination

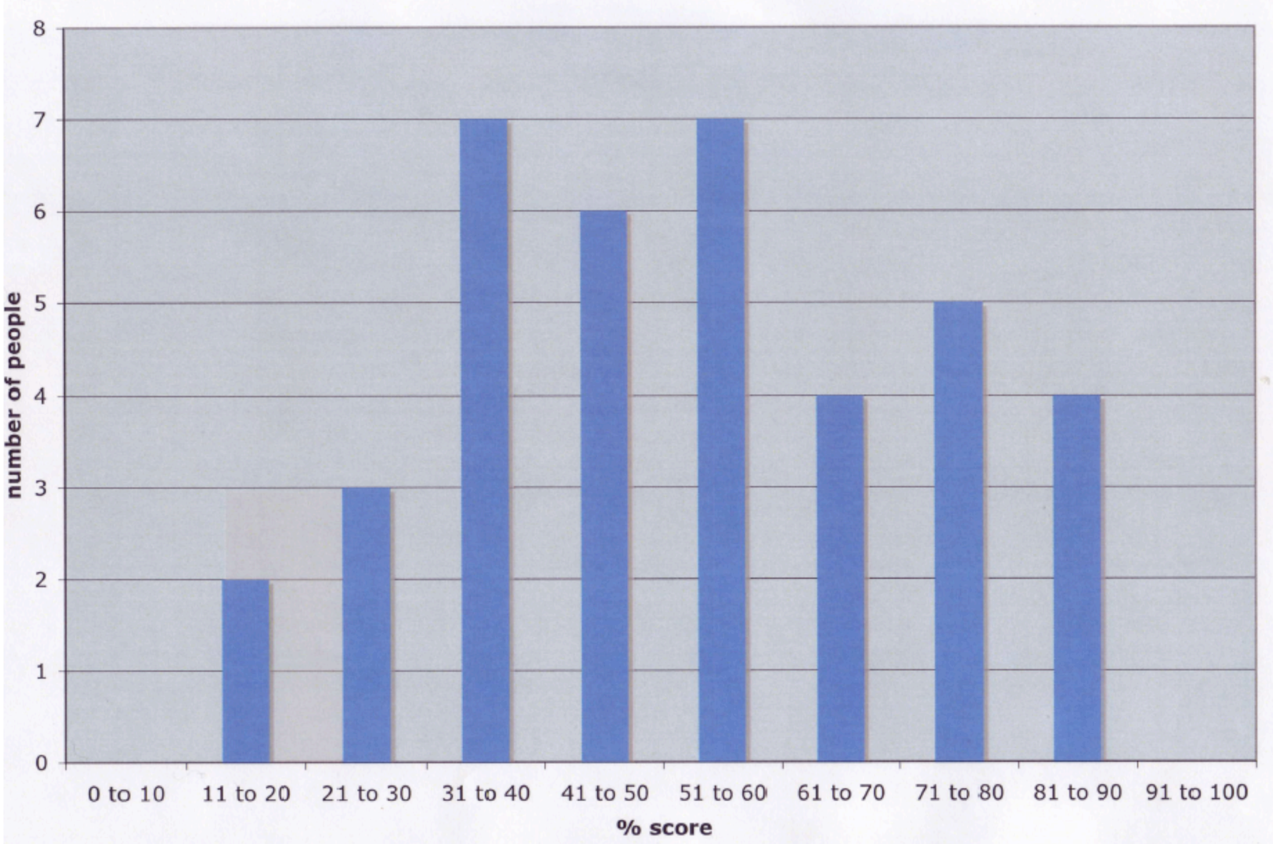
November 13, 2005

Answer Key

Chemistry 206
Second Hour Examination

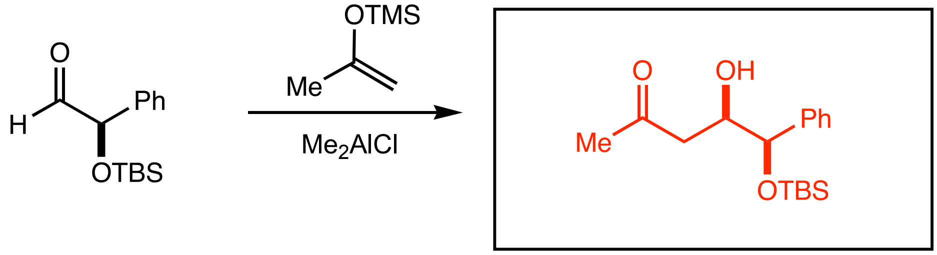
D. A. Evans
November 21, 2005

Examination Average: 52

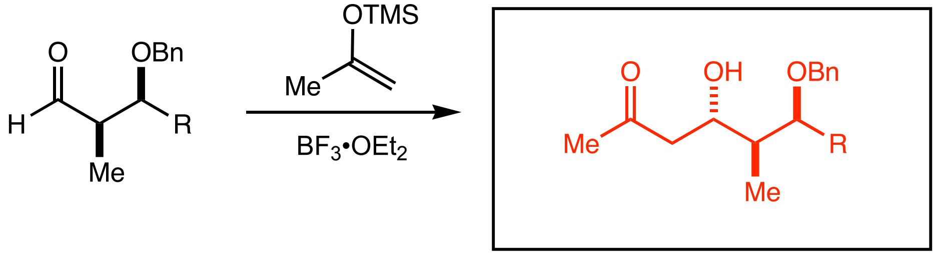


Question 1. (15 points). Predict the stereochemical outcome for each of the illustrated transformations. Draw the major product diastereomer in the box provided.

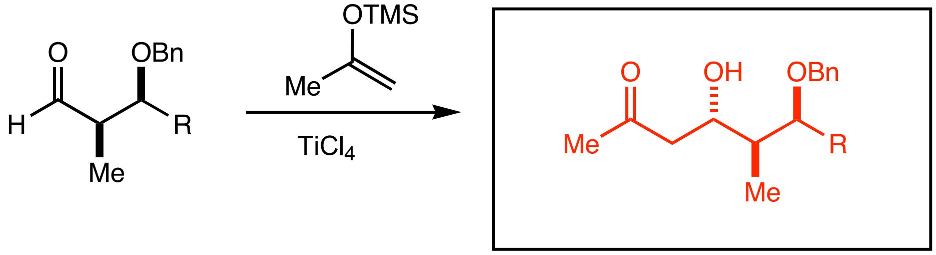
Part A: (3 points)



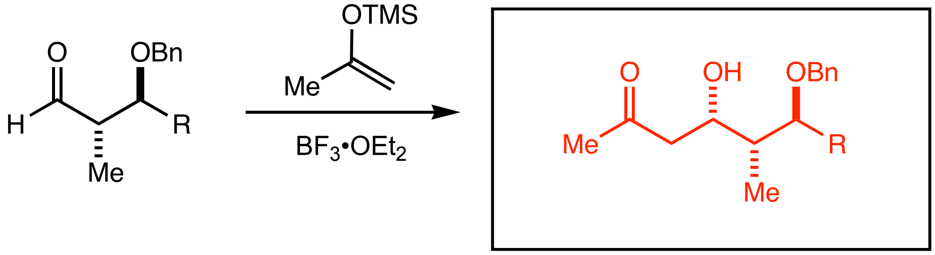
Part B: (3 points)



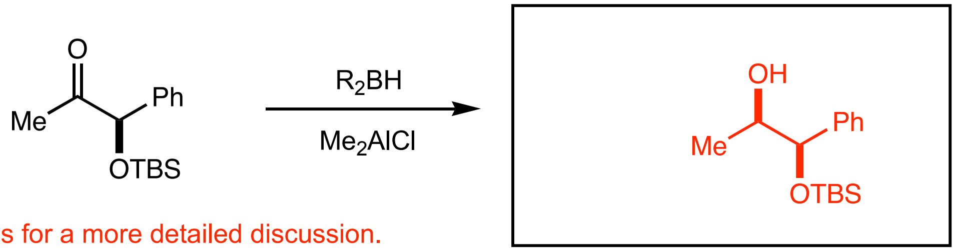
Part C: (3 points)



Part D: (3 points)



Part E: (3 points)



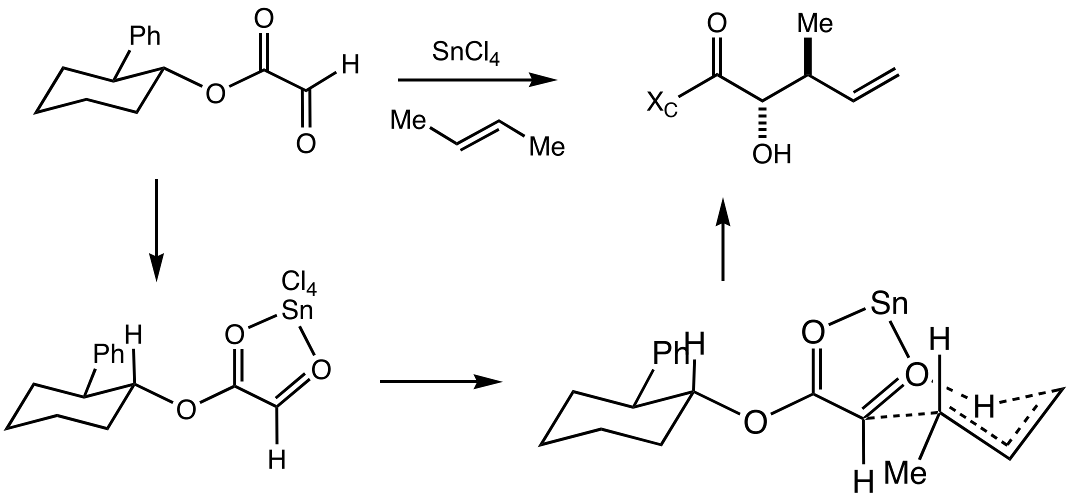
See the following references for a more detailed discussion.

"A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes.," Evans, D. A.et al. *JACS* **1996,** *118,* 4322-4343

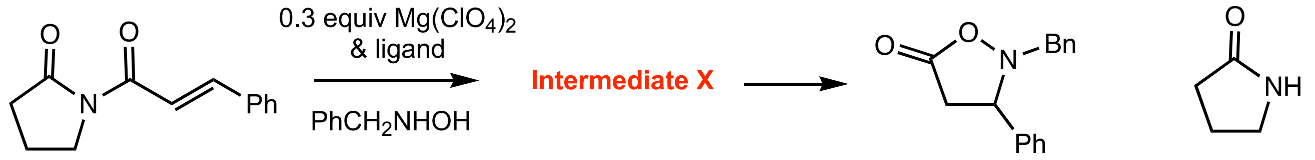
"The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride. The Merged Stereochemical Impact of a- andb- Stereocenters in Chelate-Controlled Carbonyl Addition Reactions with Enolsilane and Hydride Nucleophiles," Evans, David A., et al.*JACS* **2001**, *123,* 10840-10852

Question 2. (15 points). The following processes result in the transfer of chirality from either chiral auxiliary or catalyst to product. In each instance predict the absolute stereochemistry of the product and draw thetransition state that best rationalizes the sense of asymmetric induction.

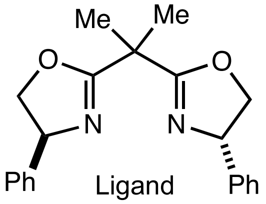
Part A. (7 points). The literature reference: Whitesell, et al. *Tetrahedron* **1986,** *42,* 2993-3001.
1: Predict the stereochemistry of the product; **2**: Draw the relevant transition structure.

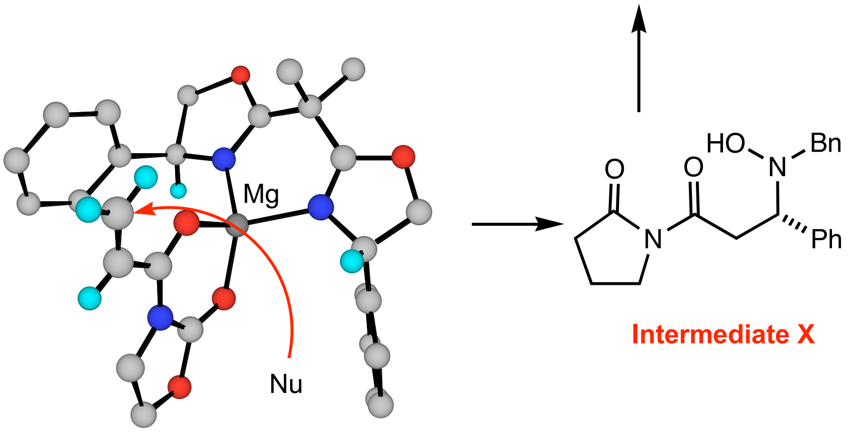


Part B. (8 points). The literature reference: Sibi et al. *Org Lett.* **2000**, *2*,3393-3396.
1: Predict the stereochemistry of the product; **2:** Draw the relevant transition structure for the stereodifferentiating step.

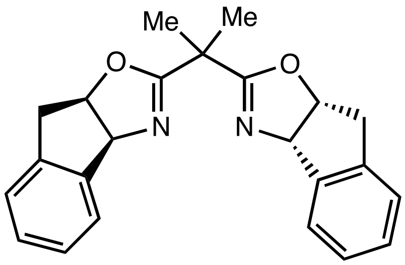


80% yield, 96% ee



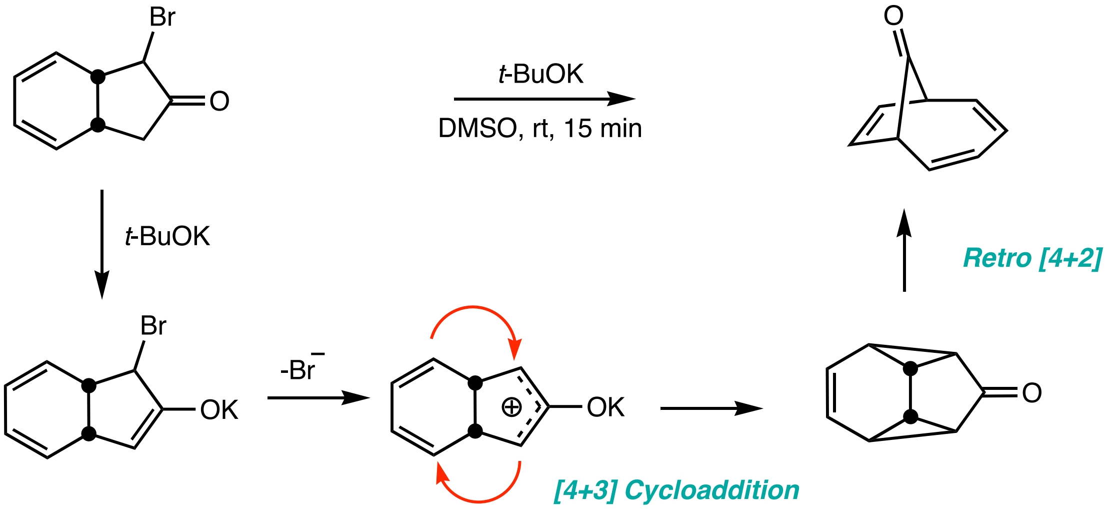


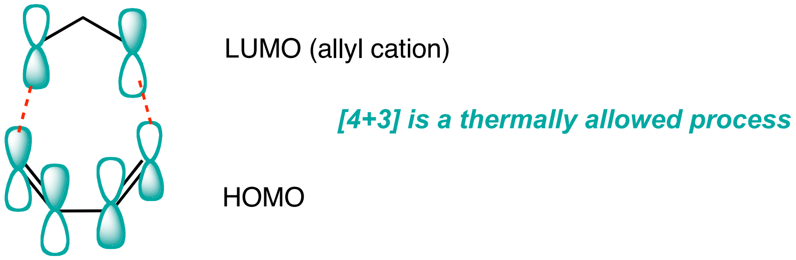
Metal Geometry for Mg: Tetrahedral



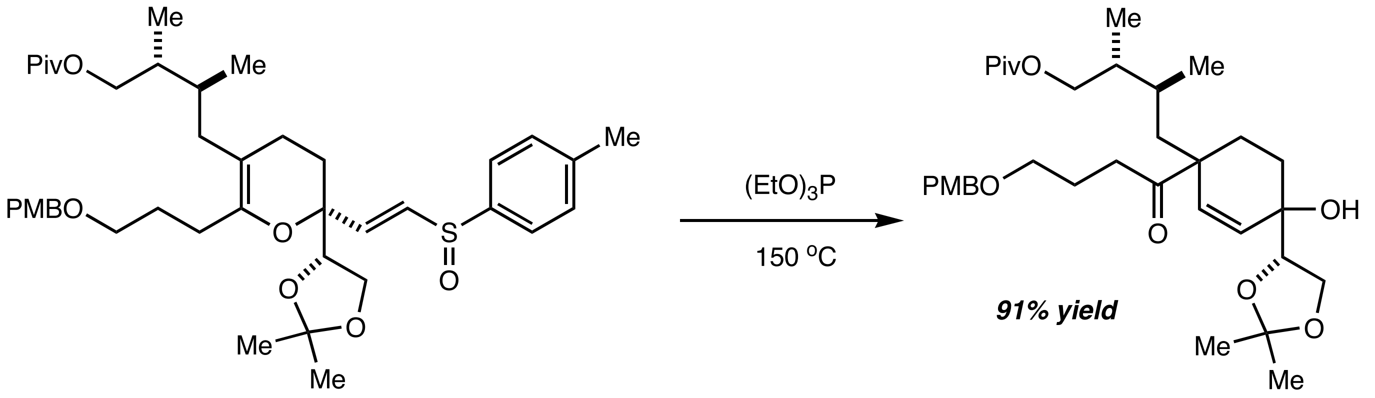
This was the actual ligand employed in this study

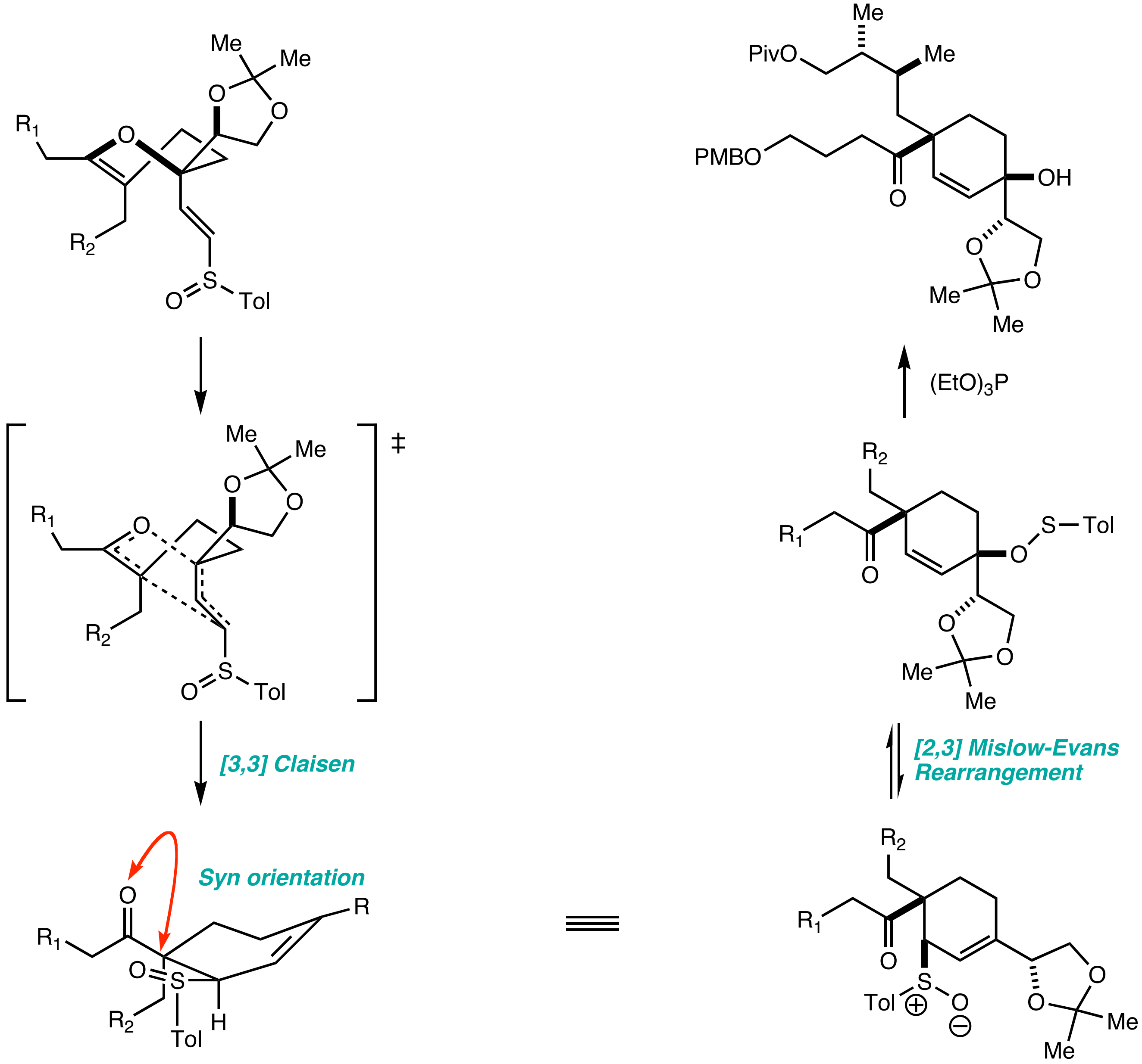
Question 3. (10 points). The following rearrangement was excecuted by Paquette and coworkers (*JACS*, **1973**, *95*, 2230). In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.



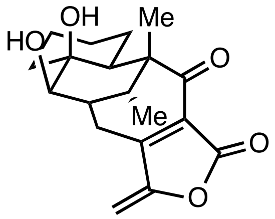


Question 4. (15 points). As part of a program directed toward the synthesis of the pinnatoxins, Pelc and Zakarian reported the single-pot conversion of sulfone **A** into cyclohexene **B** (*OL*, **2005**, *7*, 1629). Using clear three-dimensional representations please provide a concise mechanism for this transformation and predict the relative stereochemical outcome.

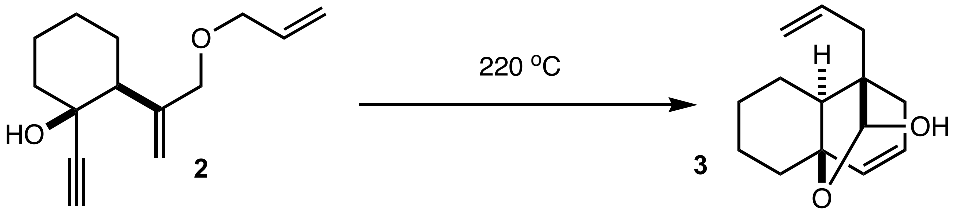




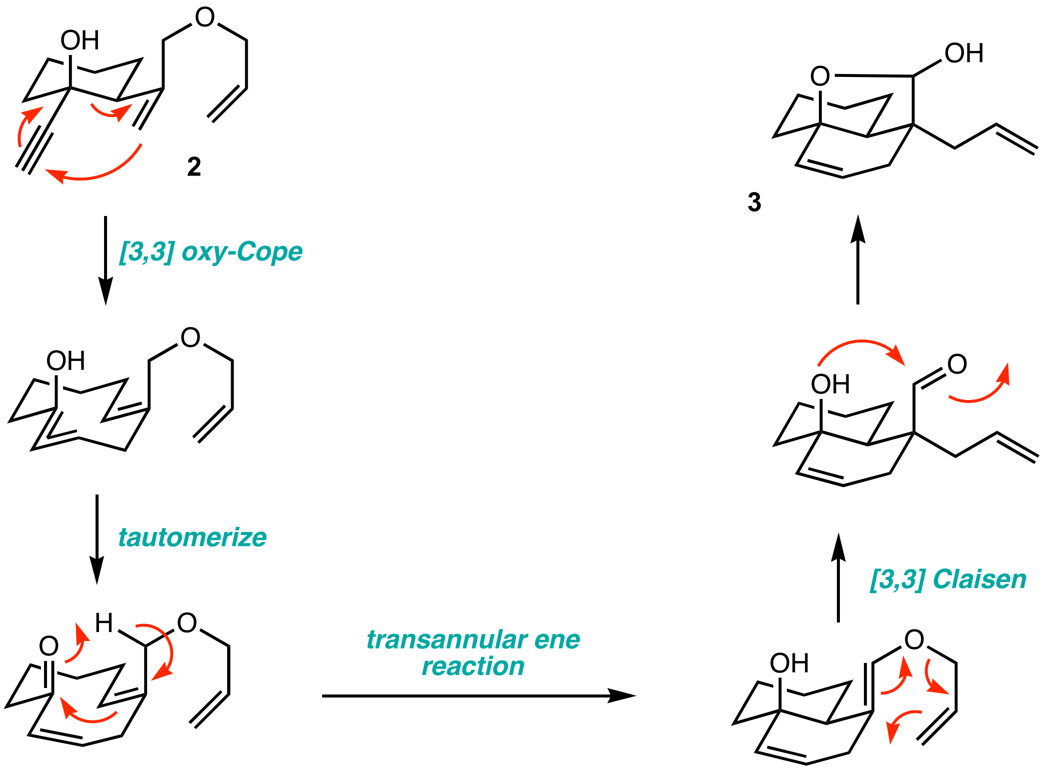
Question 5. (15 points). As part of a strategy directed towards the synthesis of tetradecamycin **(1),** Warrington and Barriault carried out the thermally induced rearrangement of **2** to synthesize the *trans-de*calin system **3** (*Org. Lett.* **2005**, *7*, 4589). Using clear three-dimensional drawings please provide a plausible mechanism for this transformation that is in accordance with the observed stereochemical outcome.



tetradecamycin (**1**)



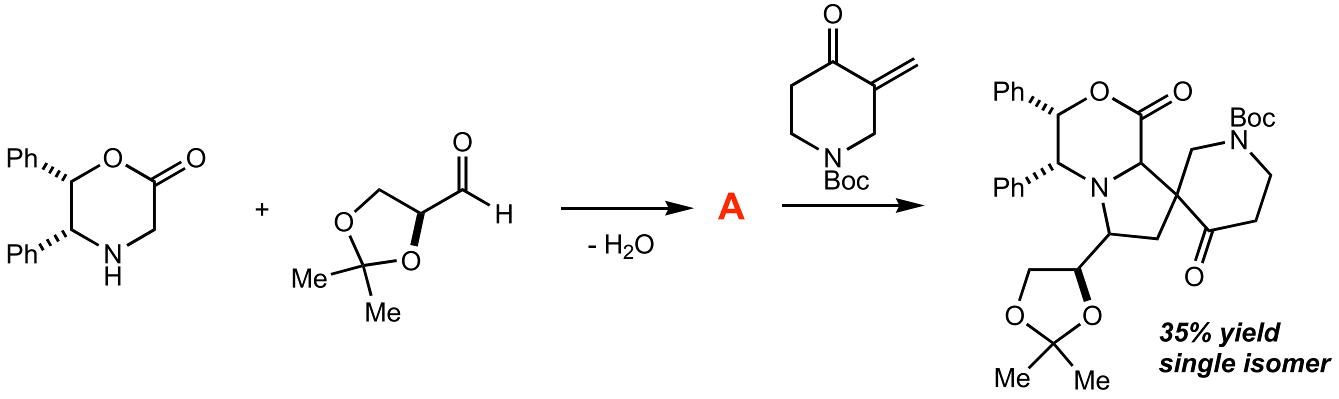
87% yield



Question 6. (15 points). As part of a effort towards the construction of Nakadomarin A, Williams and Ahrendt reported the following highly selective three-component reaction (*Org. Lett.* **2004**, *6*, 4539).

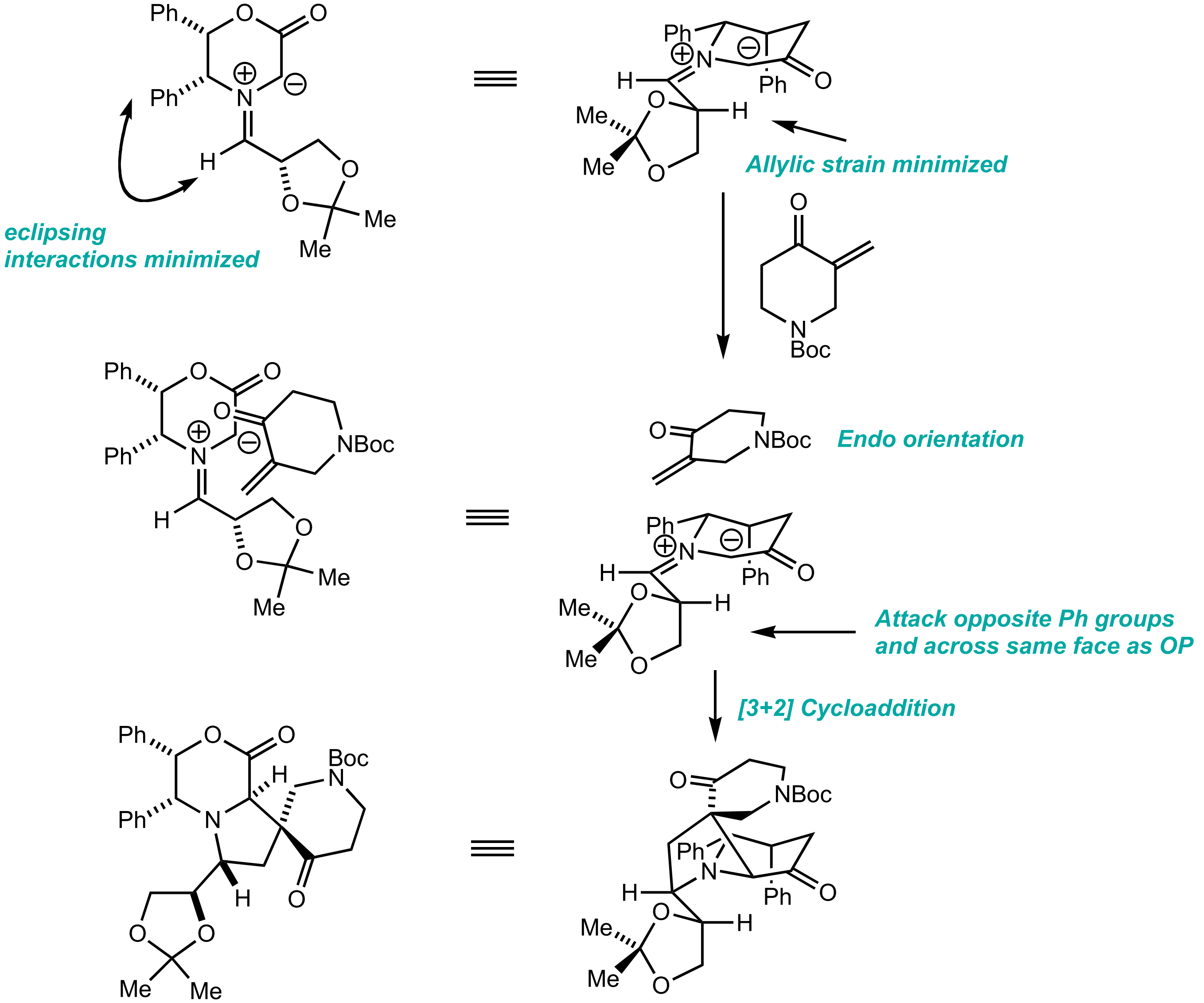
Part A. (X points). Please identify intermediate **A**, and clearly draw its low energy conformation.

Part B. (X points). Using clear three-dimensional drawings please provide a mechanism for the transformation of **A** into the product and predict the relative stereochemical outcome.



35% yield single isomer

Intermediate A:



eclipsing interactions minimized

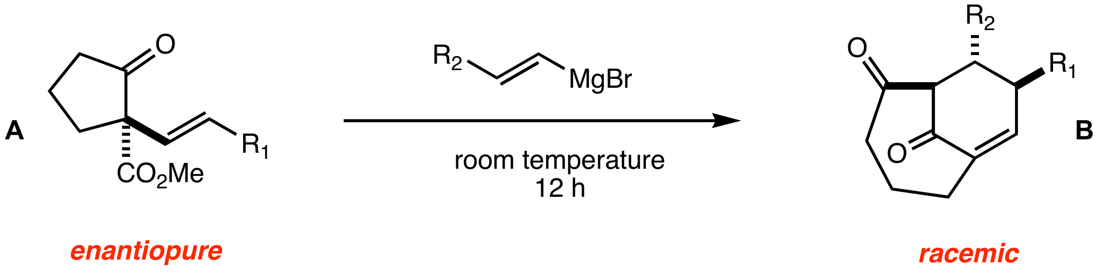
Allylic strain minimized

Endo orientation

Attack opposite Ph groups and across same face as OP

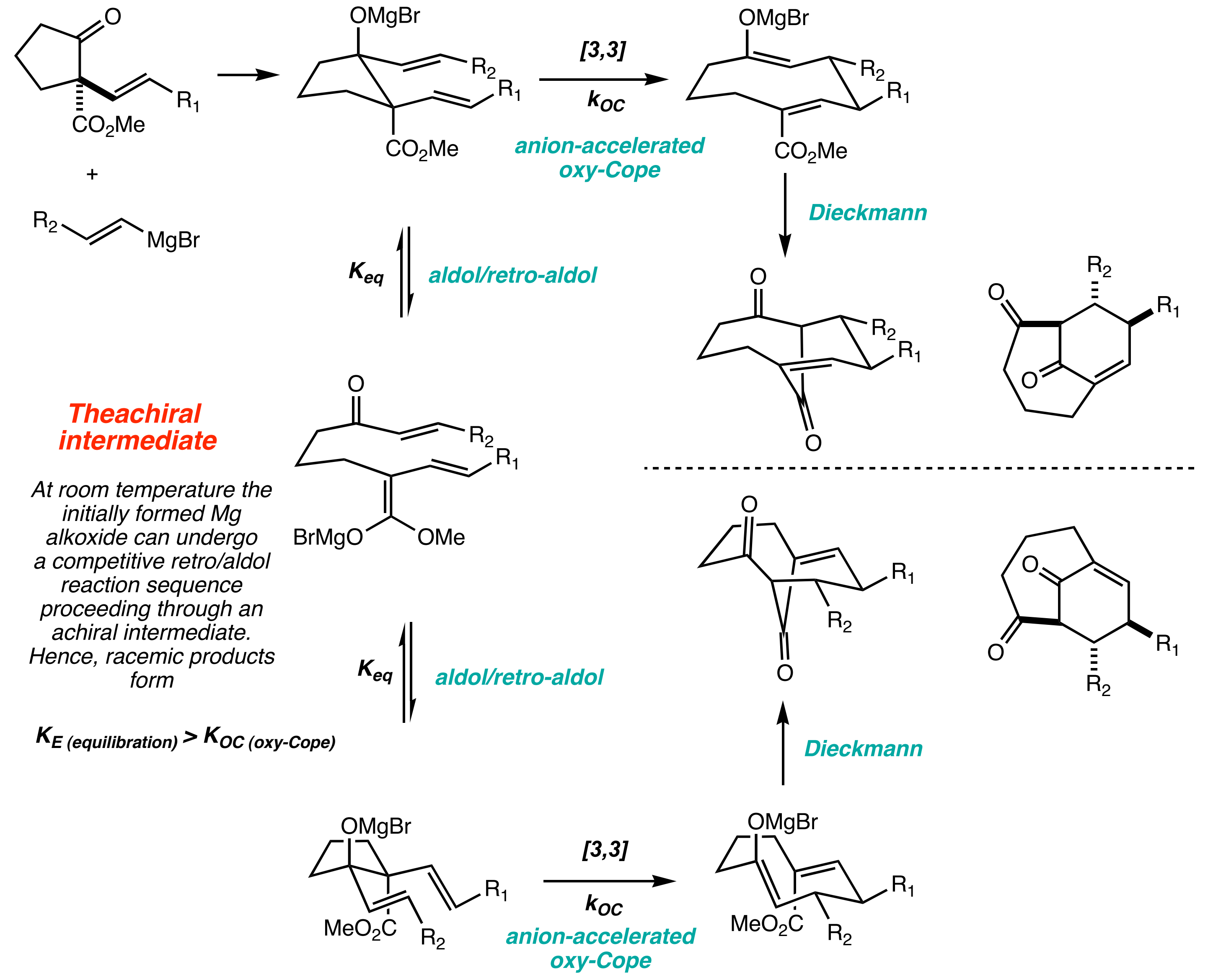
[3+2] Cycloaddition

Question 7. (15 points). The key step in Shair's total synthesis of CP-263-114 involved a one-pot synthesis of the bridged bicyclic system using a cascade sequence initiated by a Grignard addition to a β-keto ester. During the course of these studies it was found that if the reaction of enantiopure β–keto ester **A** was allowed to proceed at room temperature for 12 h then the product **B** was obtained as a single diastereomer but as a *racemic mixture.*



enantiopure ***racemic***

Using clear three-dimensional drawings provide an overall mechanism for the transformation shown above that accounts for both the observed diasteroselectivity as well as the formation of the product as a racemate.



Theachiral intermediate

At room temperature the initially formed Mg alkoxide can undergo a competitive retro/aldol reaction sequence proceeding through an achiral intermediate. Hence, racemic products form

$K_{E\ (equilibration)} > K_{OC\ (oxy\text{-}Cope)}$

Chemistry 206
Second Hour Examination

D. A. Evans
November 22, 2004

Name (please print): ____________________
last first initial

Signature: ____________________

Teaching Fellow: ____________________

Answer Key

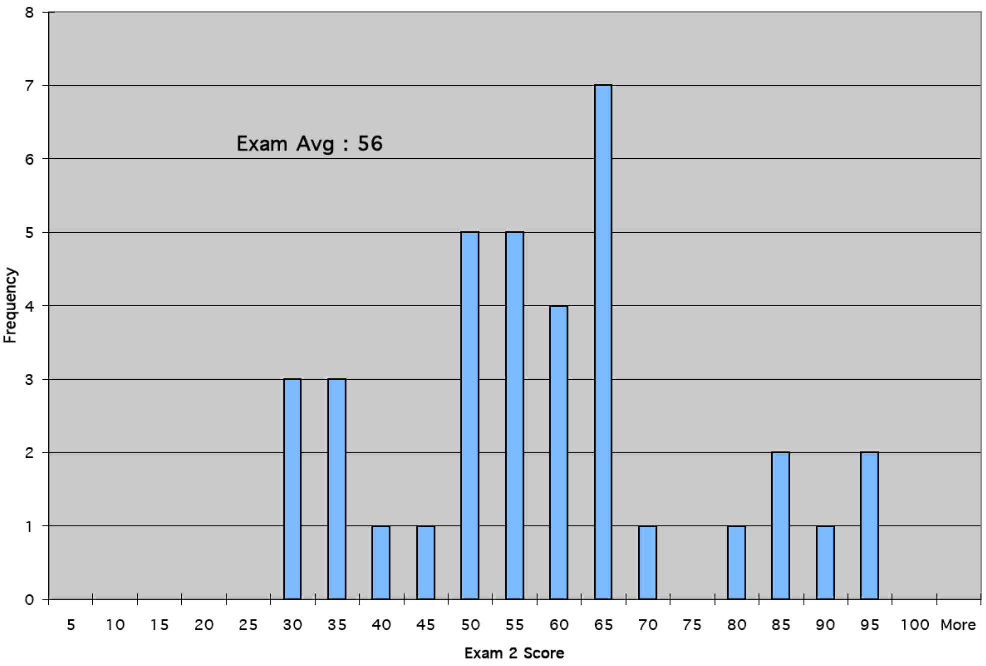
Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (15)	______
No. 4 (15)	______
No. 5 (15)	______
No. 6 (10)	______
No. 7 (10)	______
No. 8 (10)	______
Total (100)	

The exam will begin at 11:30 PM and end at 1:30.

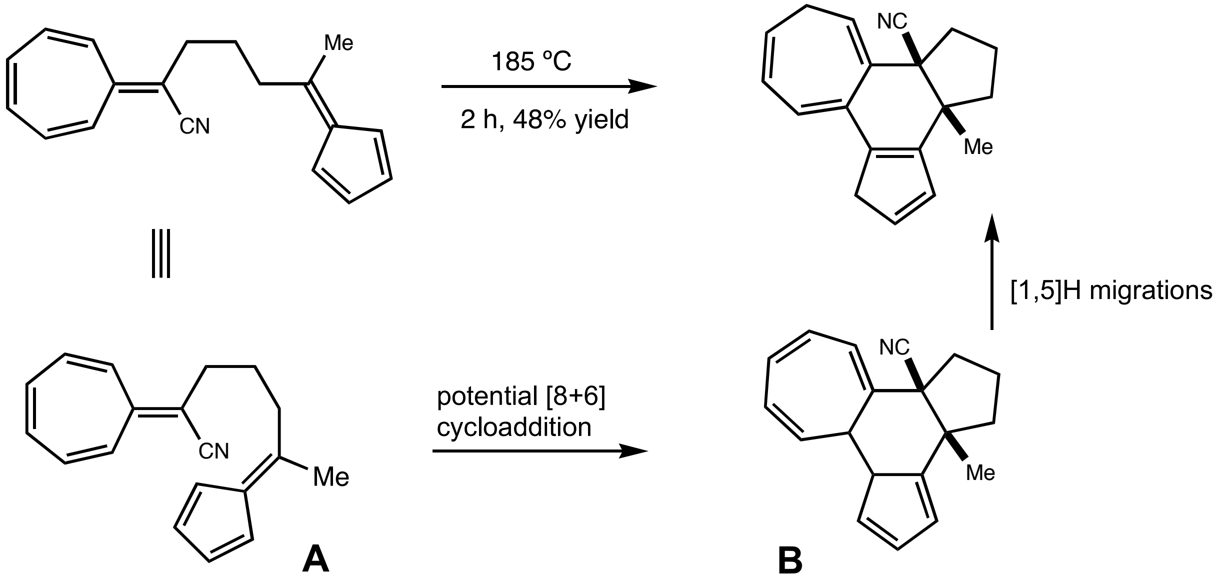
Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

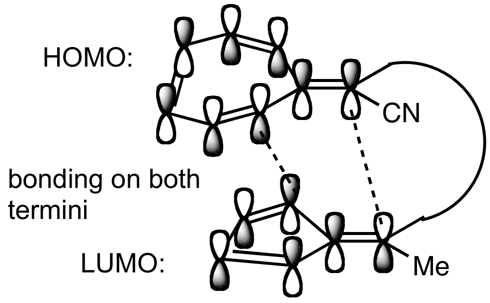
Exam Average: 56



Question 1. (10 points). The following reaction was reported (*Tet. Lett.*, **1986**, *27*, 4881.) The Authors propose a [8+6] cycloaddition for the conversion of **A** to **B**. Please analyze this proposed cycloaddition and determine using FMO or Dewar-Zimmerman analysis whether the ring-closing step is concerted or stepwise under the reaction conditions.

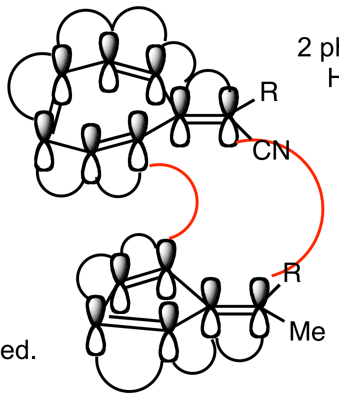


FMO analysis:



so, the [8+6] cycloaddition is allowed thermally and is concerted.

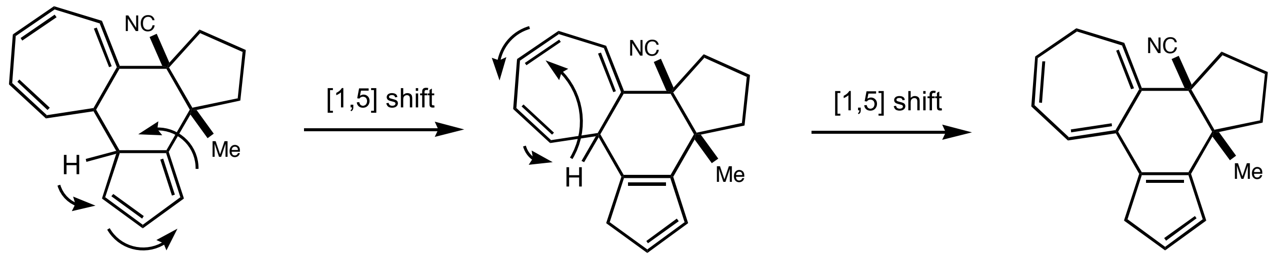
Dewar Zimmerman analysis:



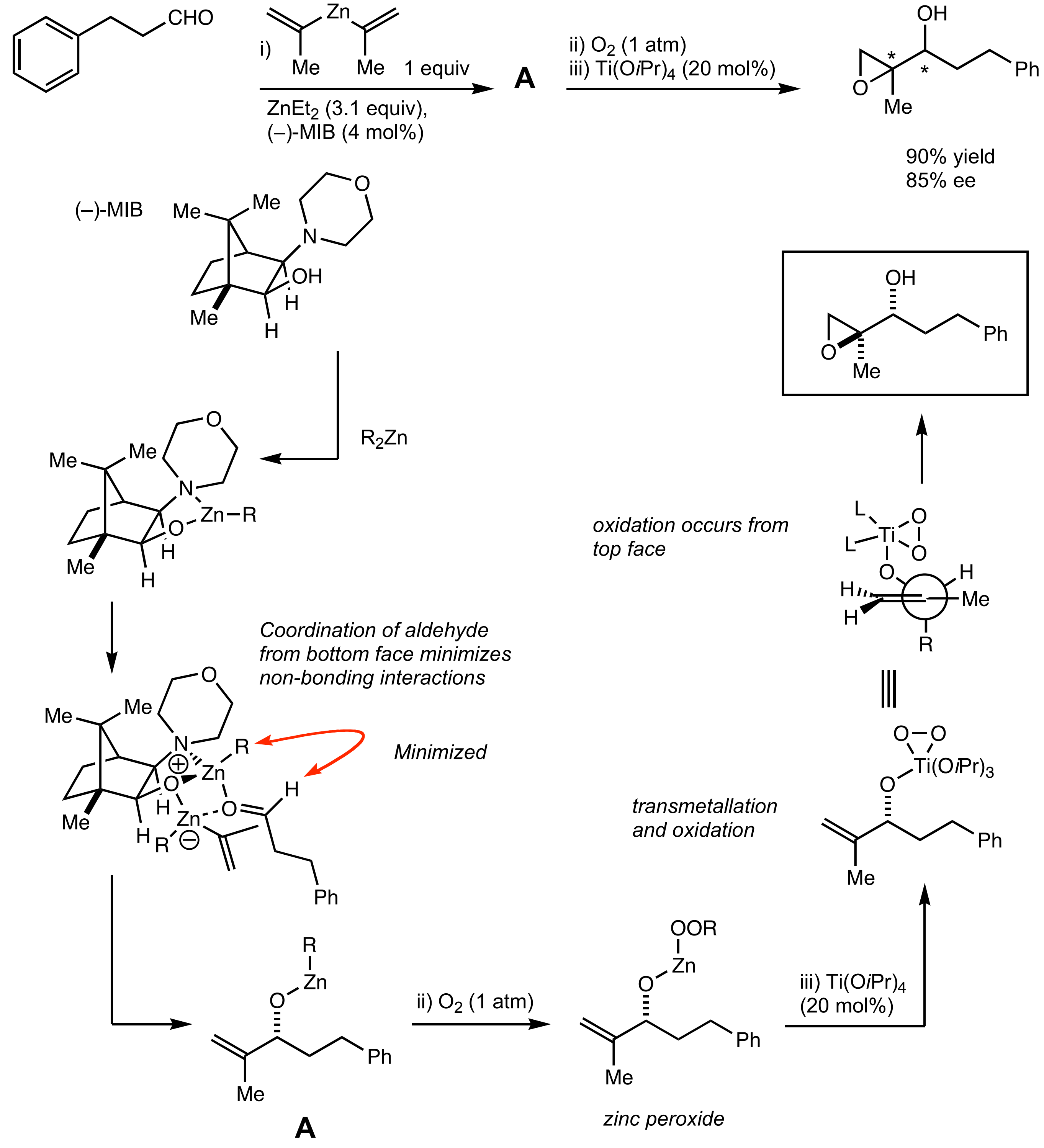
2 phase inversions ⇨
Huckel topology

14 electrons =
allowed

to obtain the product, two additional pericyclic reactions take place:



Question 2. (15 points). A one-pot procedure for the enantioselective addition / diastereoselective epoxidation was recently developed in the laboratories of Patrick Walsh (*JACS*, **2004**, *126*, 13608.). This methodology can directly prepare up to three contiguous stereocenters. Please provide a mechanism for this transformation and predict the stereochemistry of the product. Your anwser should use 3-D representations and highlight intermediate **A**. *(Hint: oxygen is known to insert into organozinc species, forming zinc peroxides and titanium can transmetallate with zinc. The organometallic aspects of this question may be de-emphasized in your answer.)*



Coordination of aldehyde from bottom face minimizes non-bonding interactions

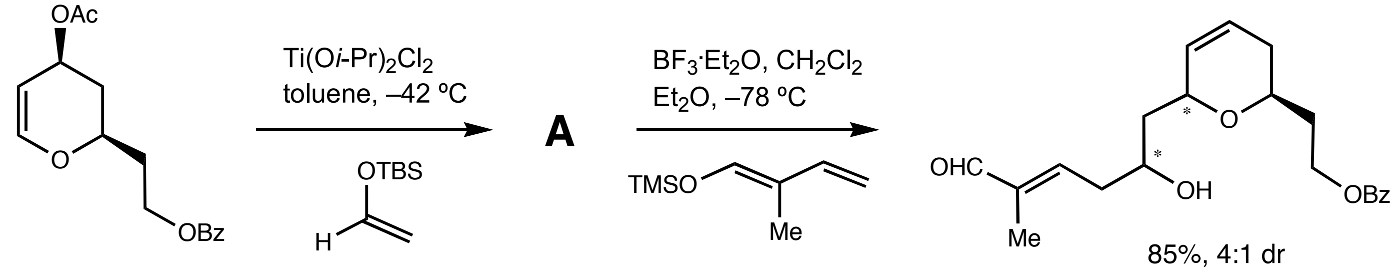
Minimized

oxidation occurs from top face

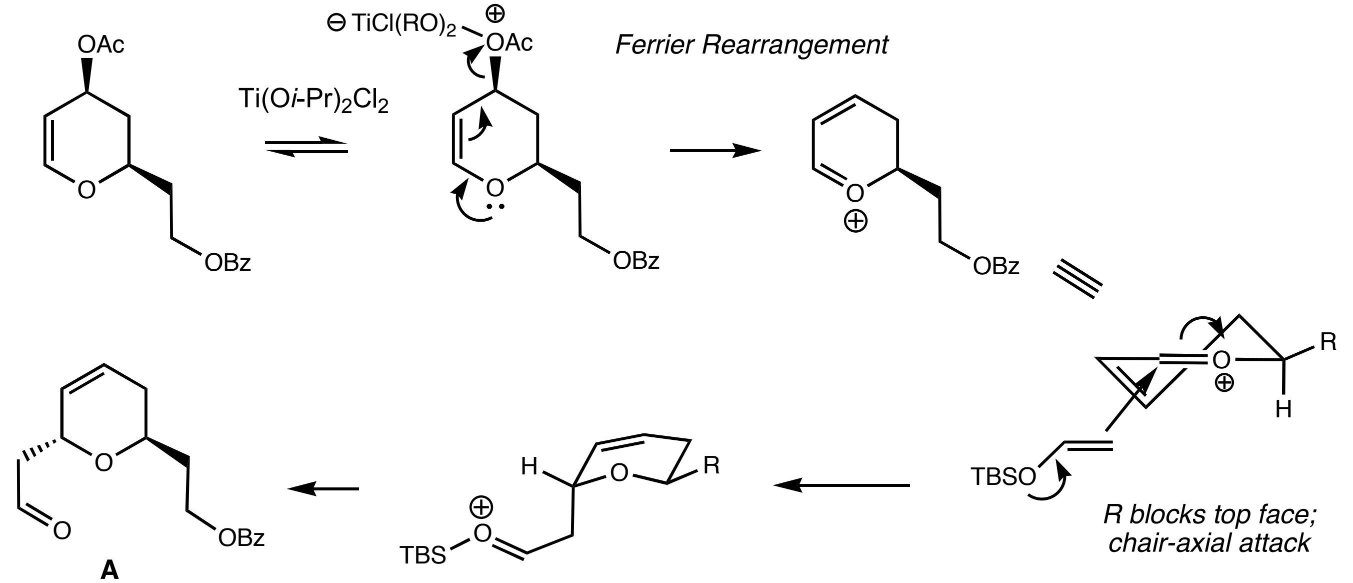
transmetallation and oxidation

zinc peroxide

Question 4. (15 points). The Paterson group utilized the following reaction sequence in a total synthesis of swinholide A (*Tetrahedron*, **1995**, *51*, 9413.):



Part a. Provide the structure of intermediate **A** and the mechanism for its formation. Predict and account for the stereochemistry of **A** in your mechanism. Include 3-D drawings when relevant.

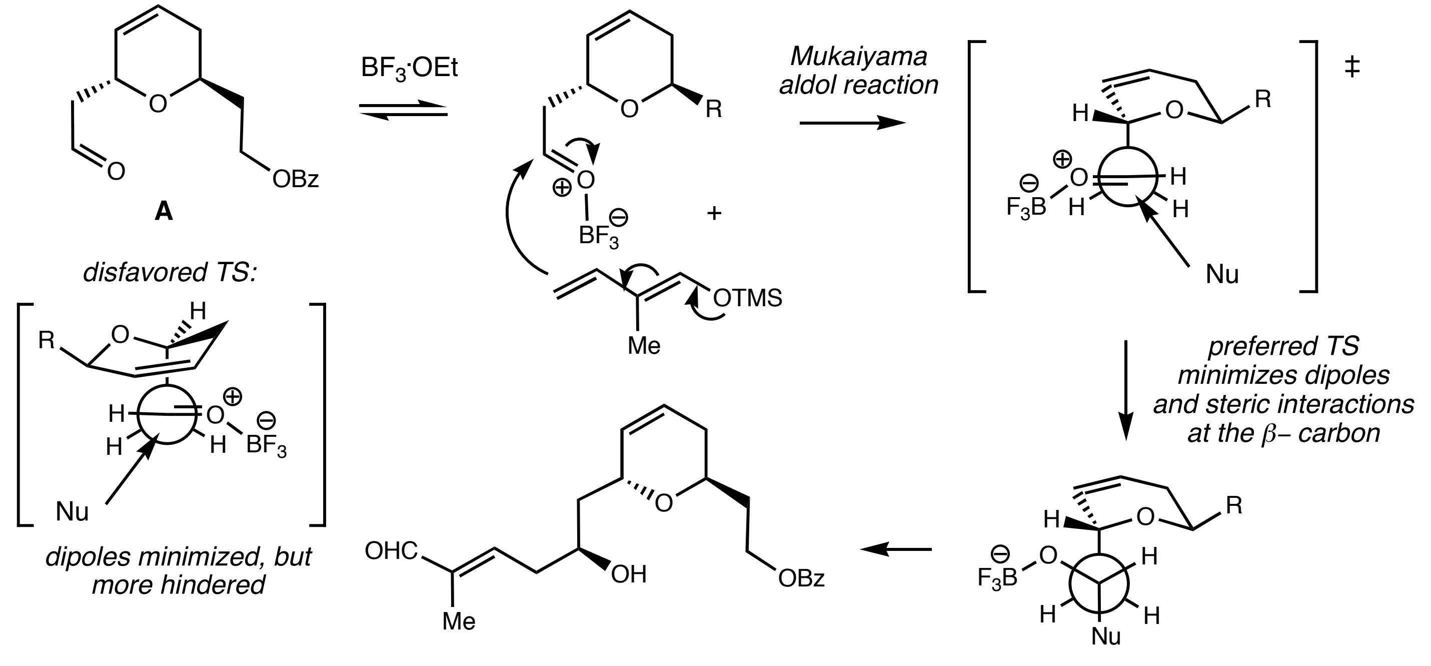


Ferrier Rearrangement

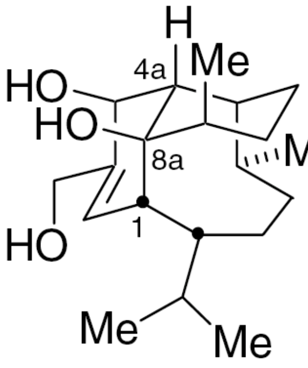
R blocks top face; chair-axial attack

A

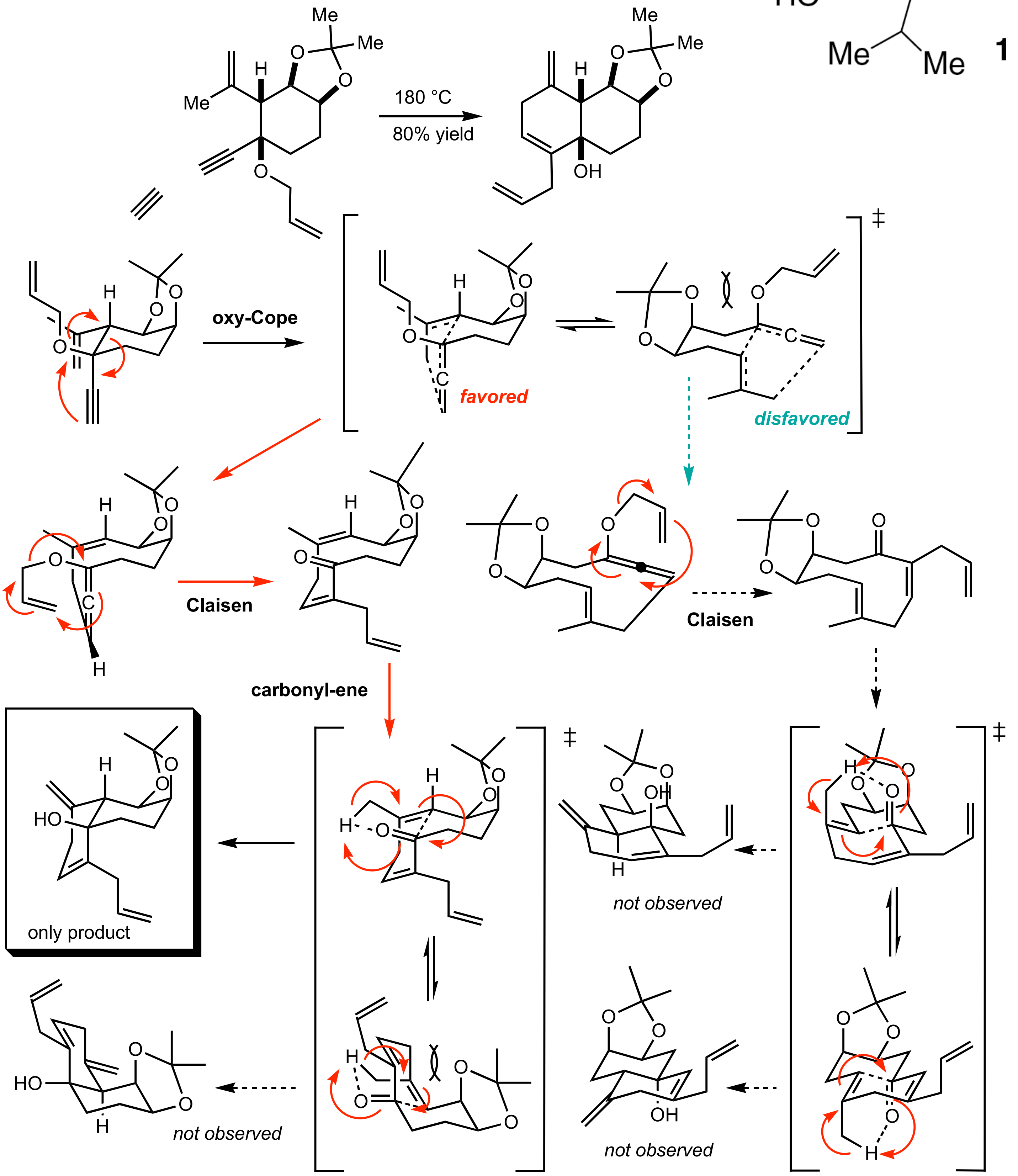
Part b. Provide a mechanism for the formation of the final product from intermediate **A**. Predict and account for the stereochemistry of the product in your mechanism. Include 3-D drawings when relevant.



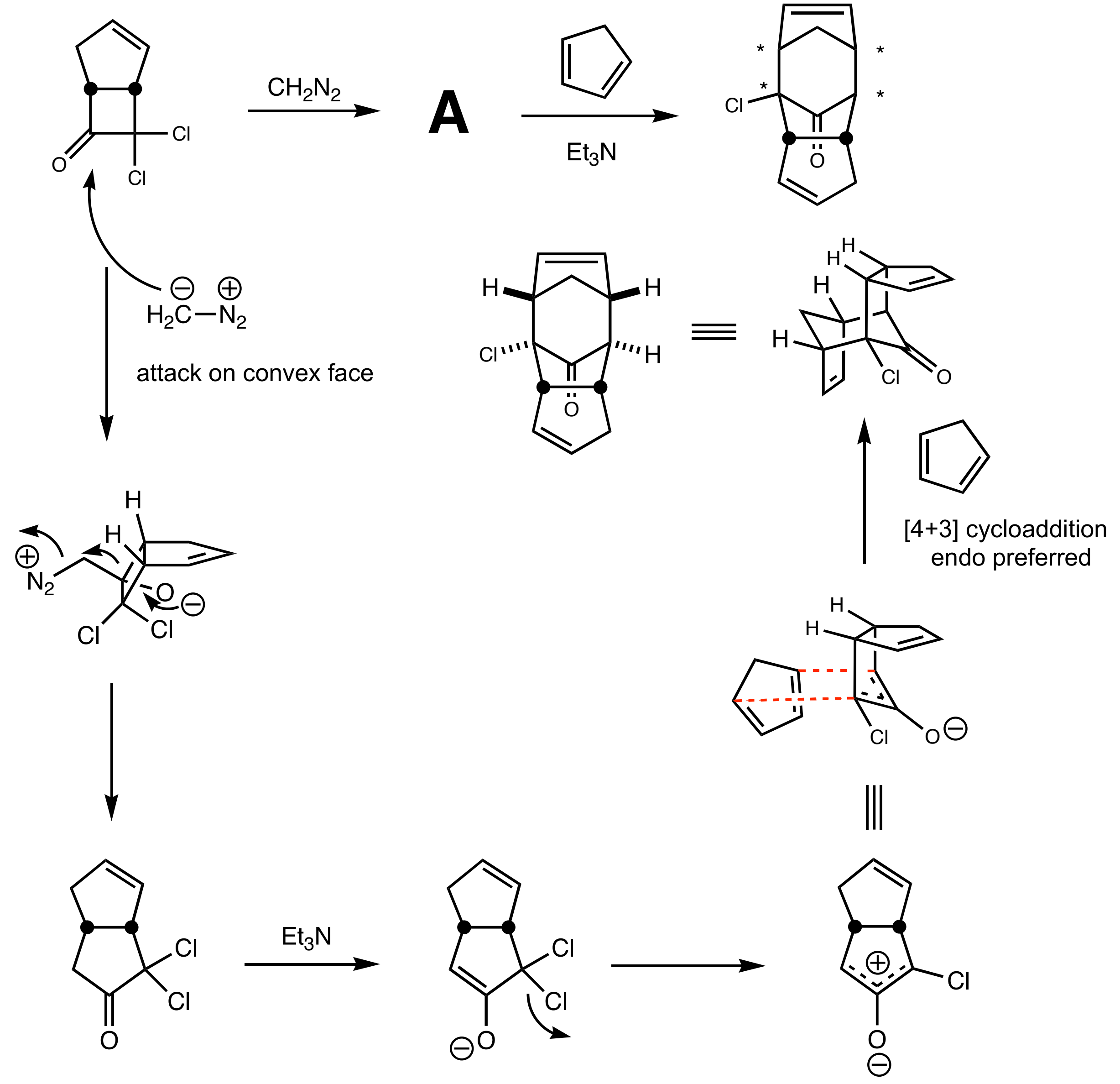
Question 5. (15 points). In a recent paper by Morency and Barriault (*Tet. Lett.* **2004**, *45*, 6105), the following transformation was reported. The series of thermally induced rearrangements afforded the cis decalin product as a single diastereoisomer in 80% yield. This transformation was reported as a model study for eventual application to the synthesis of vinigrol (**1**). Provide a plausible mechanism for this transformation and explain the selectivity



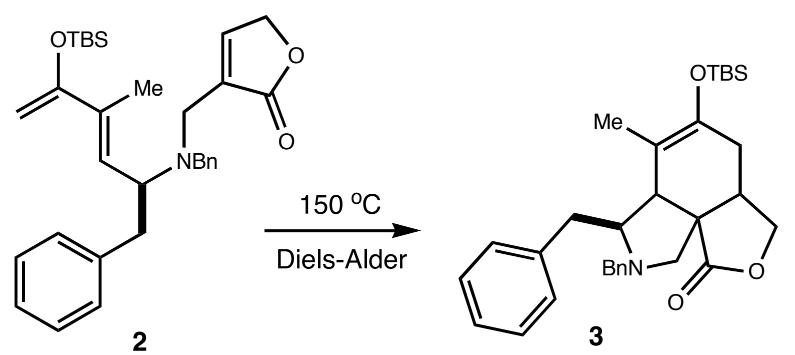
1

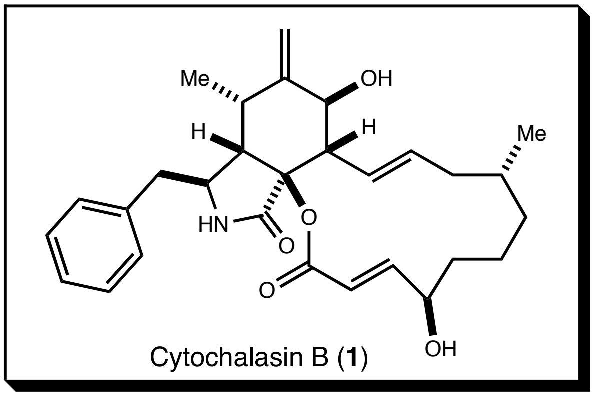


Question 6. (10 points). Harmata and co-workers reported the following interesting transformation (*Org. Lett.* **2001**, *3*, 2533.) Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product.



Question 7. (10 points). The intramolecular Diels-Alder reaction of **2** was recently employed in a total synthesis of the structurally complex natural product cyctochalasin B (**1**).



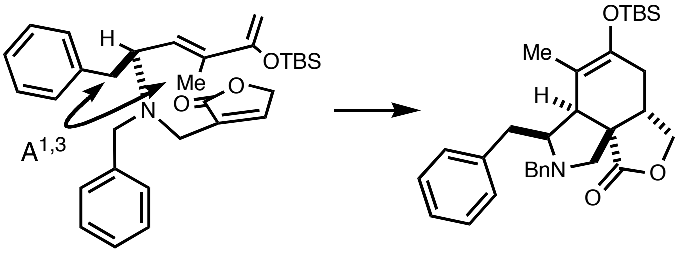


Cytochalasin B (**1**)

Please predict the major product **3** of this cycloaddition and provide clear three-dimensional drawings to illustrate your answer. Be sure to identify relevant control elements.

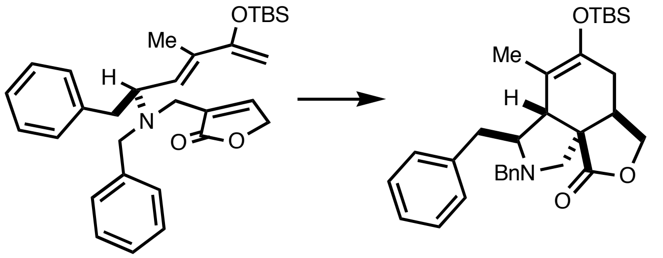
- Minimization of A 1,3-strain leads to either ***exo-2*** or ***endo-2***. The *endo* adduct is favored by better secondary orbital overlap.

exo-1



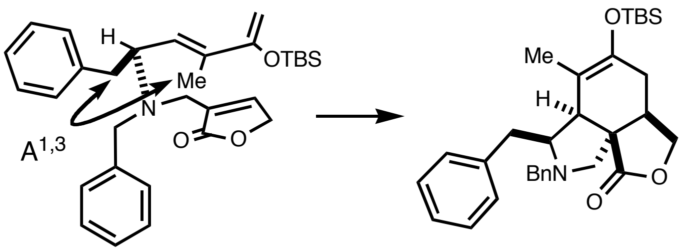
Not Observed

exo-2



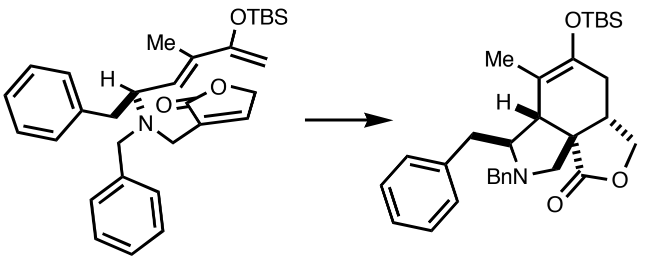
Minor (14% yield)

endo-1



Not Observed

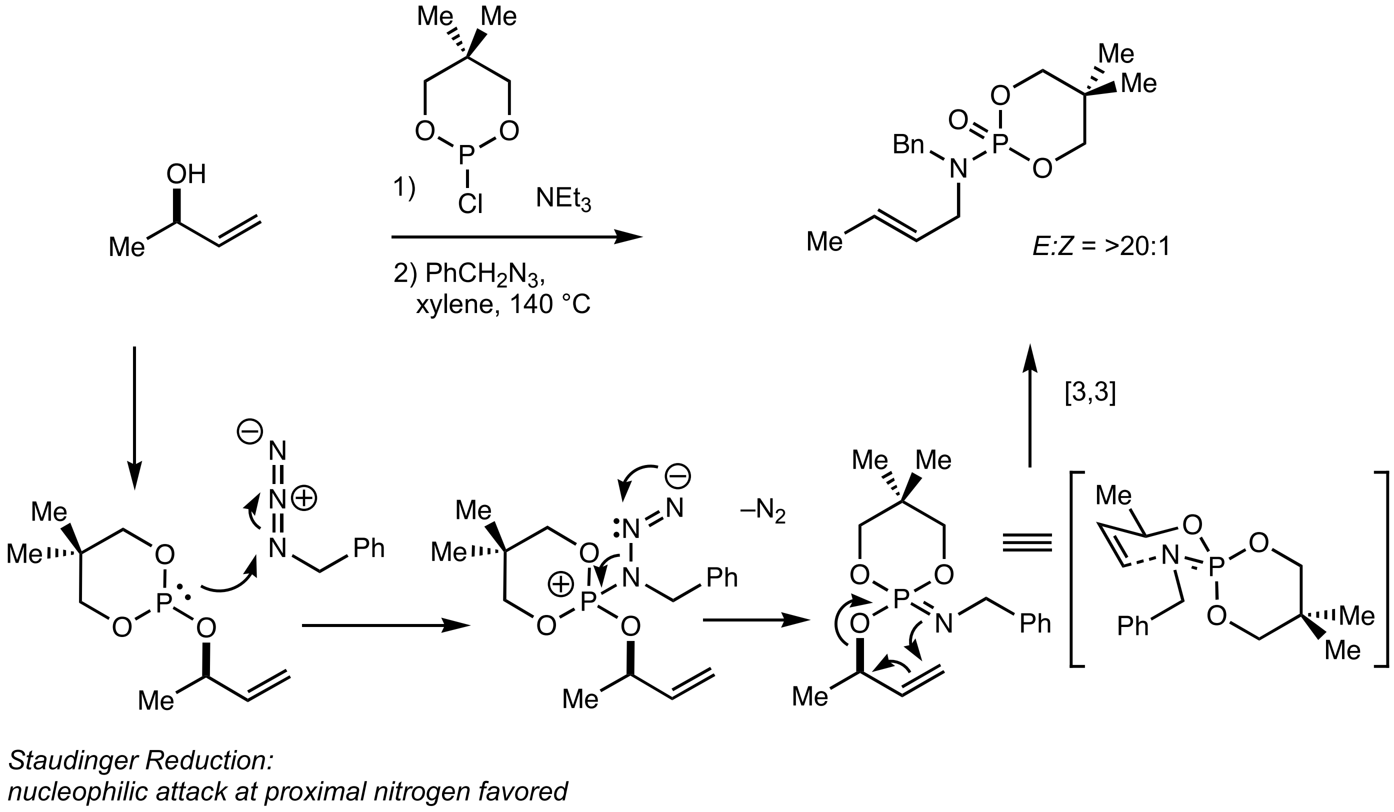
endo-2



Major (77% yield)

Haidle and Myers, *PNAS*, **2004**, *101*, 12048-12053

Question 8. (10 points). Mapp and co-workers disclosed a unique synthesis of allylic amines (*JACS*. **2004**, *126*, 5364.). Please provide a mechanism for the process that accounts for the observed the olefin selectivity.


1)
NEt$_3$
2) PhCH$_2$N$_3$, xylene, 140 °C
E:Z = >20:1
[3,3]
–N$_2$
Staudinger Reduction:
nucleophilic attack at proximal nitrogen favored

Chemistry 206
Second Hour Examination

D. A. Evans
November 14, 2003

Name (please print): ____________________
last first initial

Signature: ____________________

Teaching Fellow: ____________________

Question (pts)	Score
No. 1 (15)	
No. 2 (10)	
No. 3 (15)	
No. 4 (15)	
No. 5 (15)	
No. 6 (15)	
No. 7 (15)	
Total (100)	

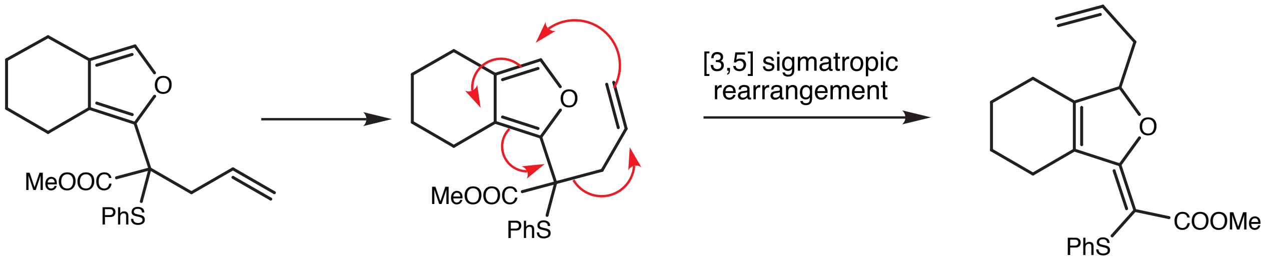
The exam will begin at 9:05 AM and end at 11:00.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

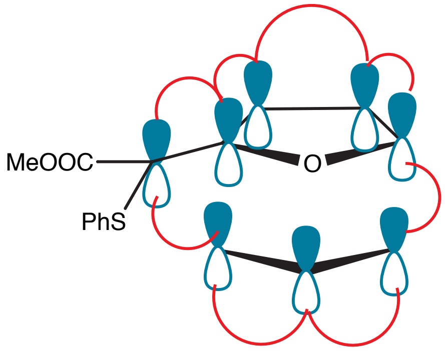
Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

Answer Key

Question 1. (15 points). The furan shown below rearranges on standing at room temperature to the isomeric form shown (*Org. Lett.* **2003**, *5*, 2619). The mechanism proposed in the article for this isomerism is a [3,5] sigmatropic rearrangement.



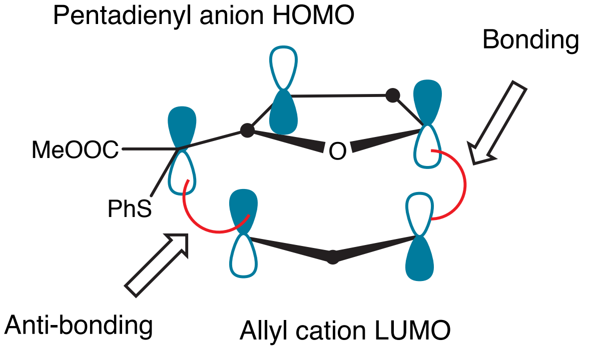
Part A (7 points). Please provide a Dewar-Zimmerman **and** an FMO analysis that illustrates why this is **not** a plausible mechanism.



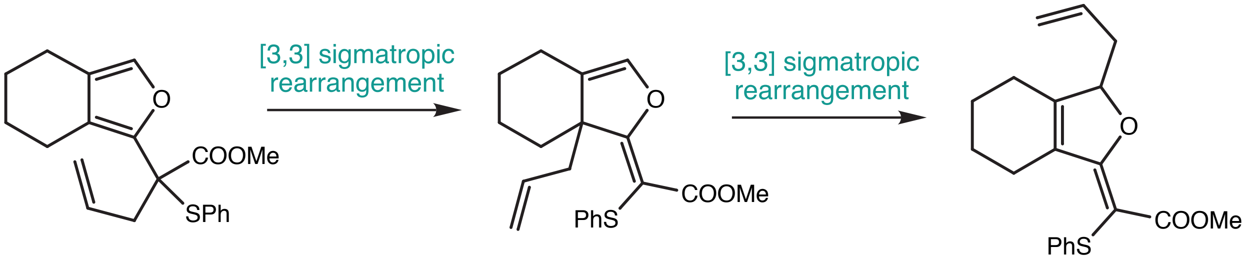
Dewar-Zimmerman Analysis
2 phase inversions
Huckel topology
8 electrons
Anti-aromatic and disallowed

FMO Analysis

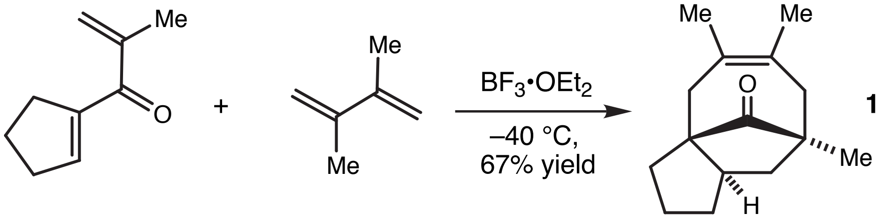
Imagine breaking the fragments into a cation/anion pair (or a pair of radicals) and allow the HOMO and LUMO to interact.



Part B (8 points). Please provide a mechanism for this rearrangement that is more consistent with the rules of orbital symmetry. You do not need to provide a justification for the step(s) of your mechanism.

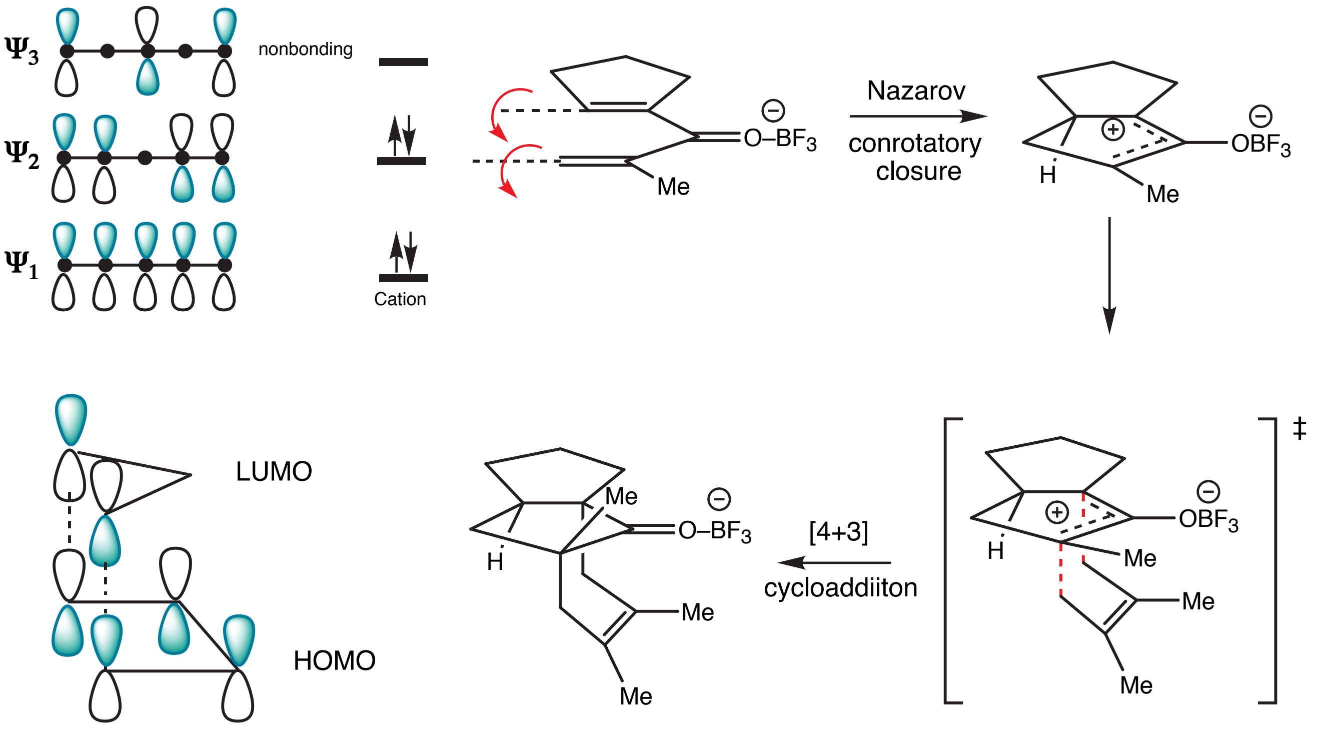

O
COOMe
SPh
[3,3] sigmatropic rearrangement
O
PhS
COOMe
[3,3] sigmatropic rearrangement
O
PhS
COOMe

Question 2. (10 points). The illustrated transformation reported this year by West and co-workers (*Org. Lett*. **2003**, *5*, 2747-2750) rapidly facilitates the construction of the complex tricyclic ketone **1** in 67% yield.



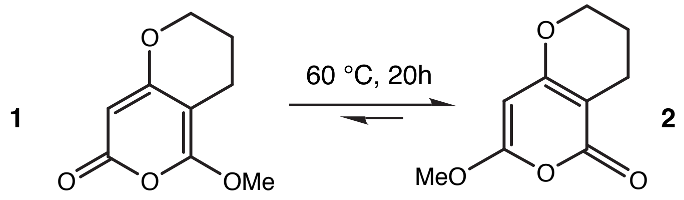
1

Please provide a concise mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.



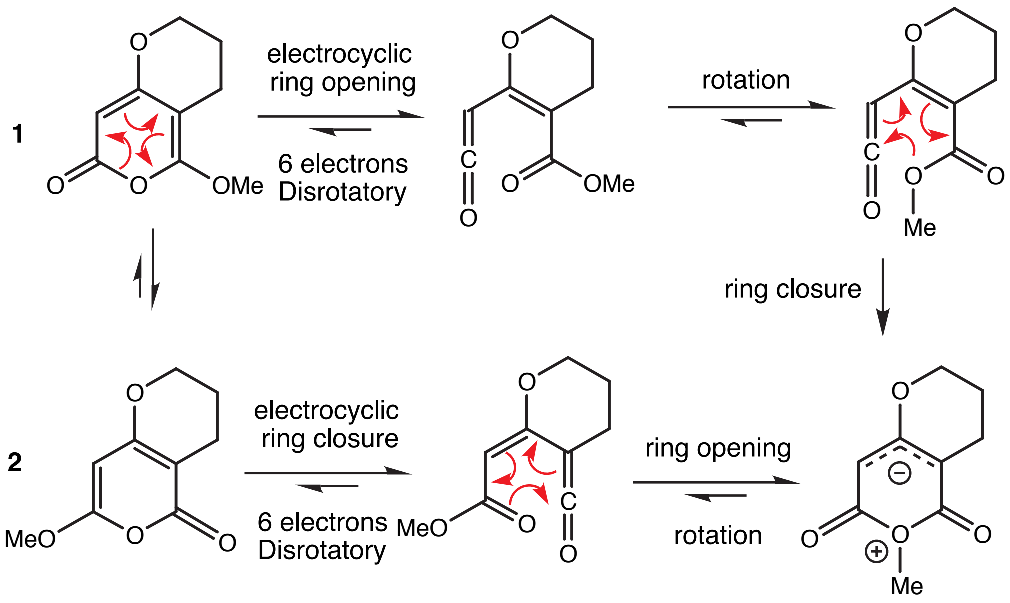
The cycloaddition

Question 3. (15 points). In 1989, Cha reported a study on the thermal isomerization of alkoxypyrones (*Tet. Lett.* **1989**, *30*, 3509-3512). One of the cases studies was the rearrangement of **1**→**2**.



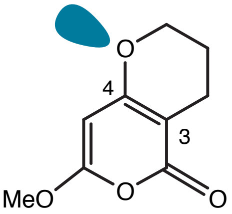
2:1 > 20:1

Part A. (10 points). Provide a mechanism for this rearrangement in the space below.



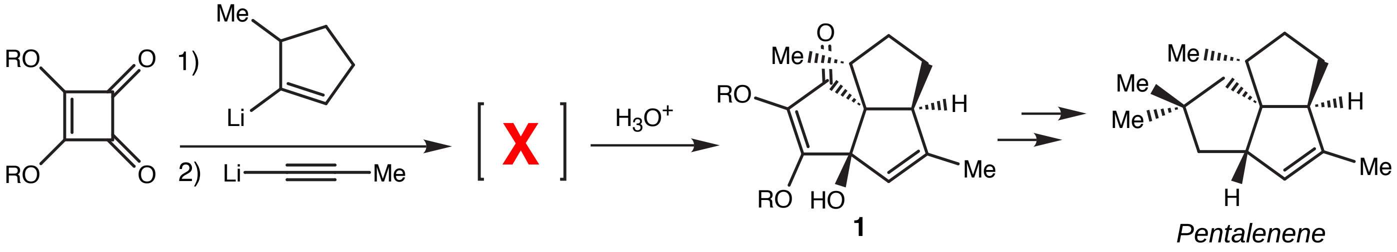
Part B. (5 points). At equilibrium, **2** is strongly favored over **1** (**2:1** > 20:1). Please rationalize product stability on the basis of the anomeric effect as was done by the authors.

The authors suggest that the added anomeric effect of the indicated oxygen lone pair donating into the polarized σ* C–C 3-4 is consistent with the noted the difference in stability

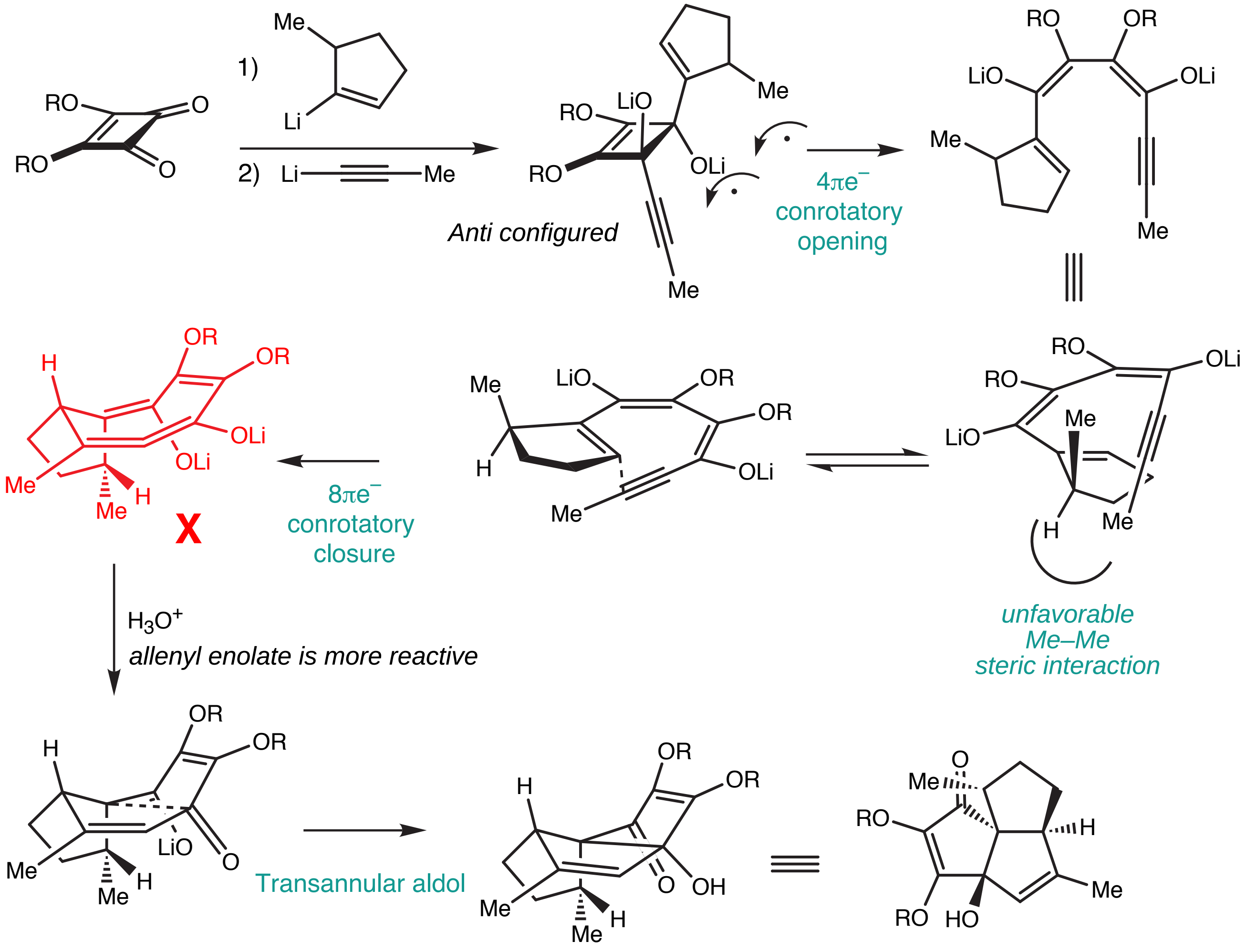


2

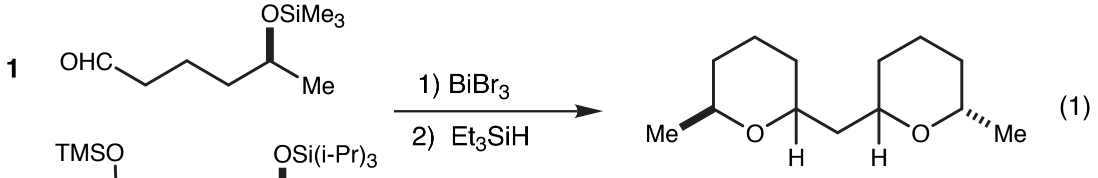
Question 4. (15 points). A synthesis of the hydrocarbon pentalenene was recently disclosed by Paquette and co-workers (*Org. Lett*. **2002**, *4*, 4547-4549). The pivotal reaction cascade that affords the pentalenene core **1** is illustrated below.



Please provide a mechanism for the reaction cascade that results in the production of the tricyclic core **1**. Your answer should include clear 3-D drawings where relevant and should clearly identify intermediate **X**.

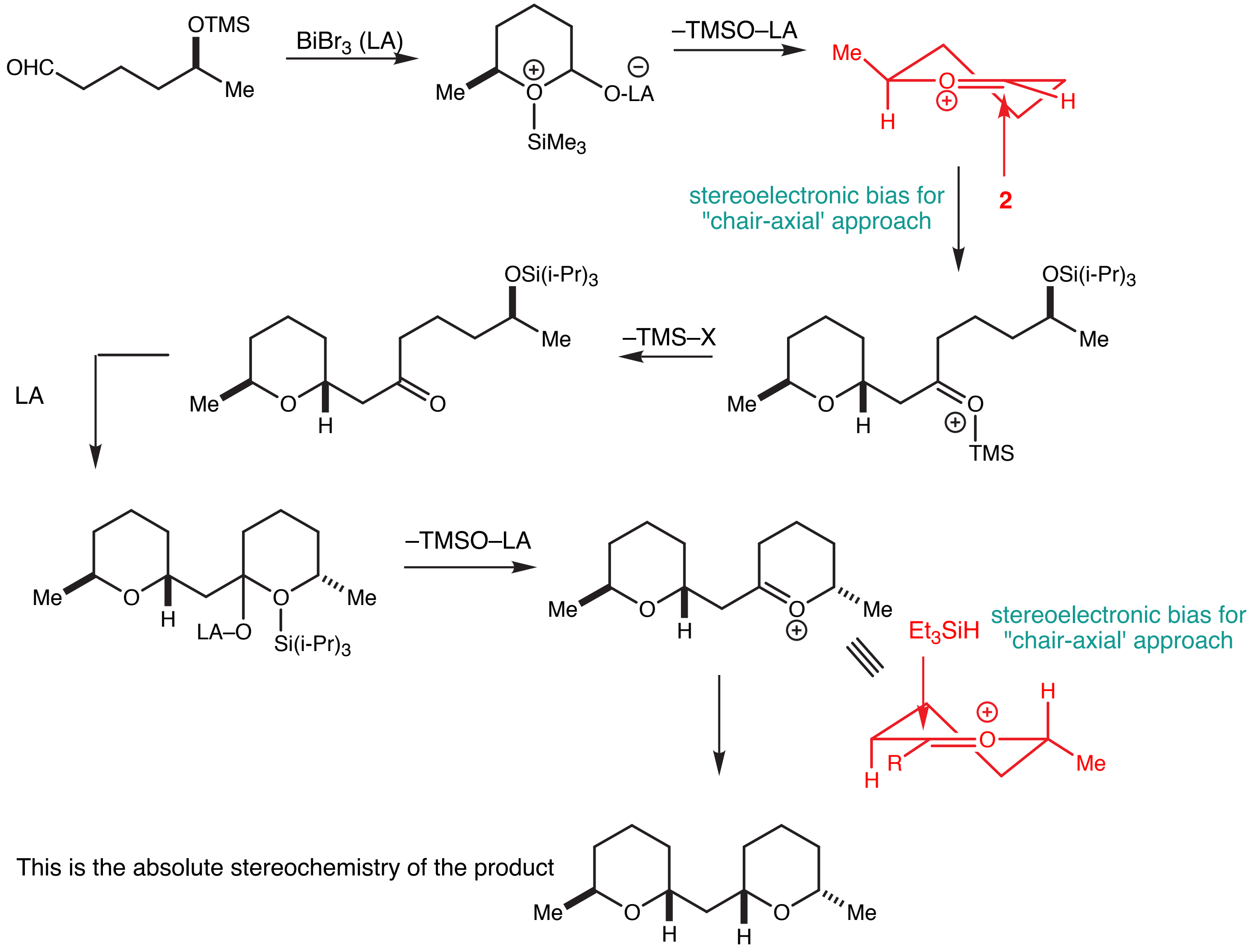


Question 5. (15 points). P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans (*JACS* **2003**, *125*, 11456-11457). One of their cases is illustrated in Eq 1. In this transformation $BiBr_3$ is employed as a mild Lewis acid.



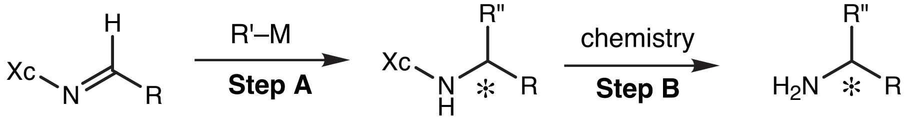
A single diastereoisomer
diastereoselection ≥95:5 (73% yield)

Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

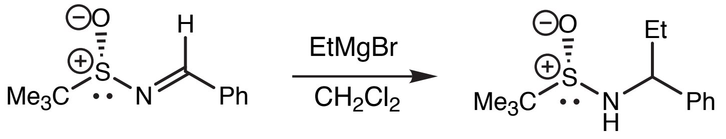


This is the absolute stereochemistry of the product

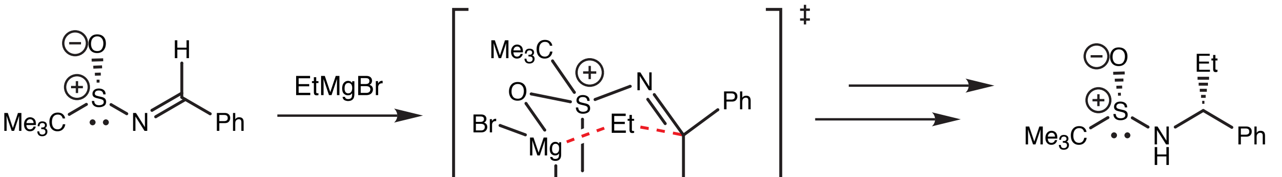
Question 6. (15 points). Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of lthe chirality transfer process.



Part A. (9 points). Provide a mechanism for the following transformation reported by Ellman and co-workers. (*Tet*, **1999**, 8883). Include a clear transition state representation that predicts the major product diastereomer. Clearly illustrate the the absolute stereochemistry of the product.

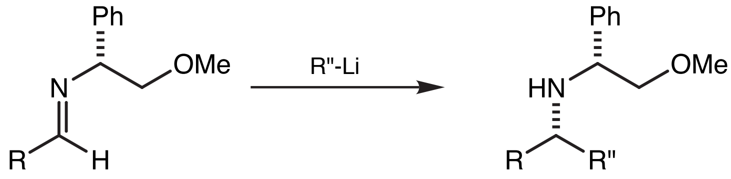


diastereomer ratio 92:8

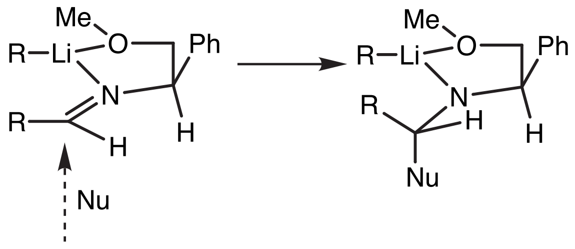


prod. stereochem: (R)

Part A. (6 points). The following stereoselective transformation has been reported by Fujisawa (*Chem.Lett.* **1991**, 1555). Given the stereostructure of the product, rationalize the stereochemical outcome.



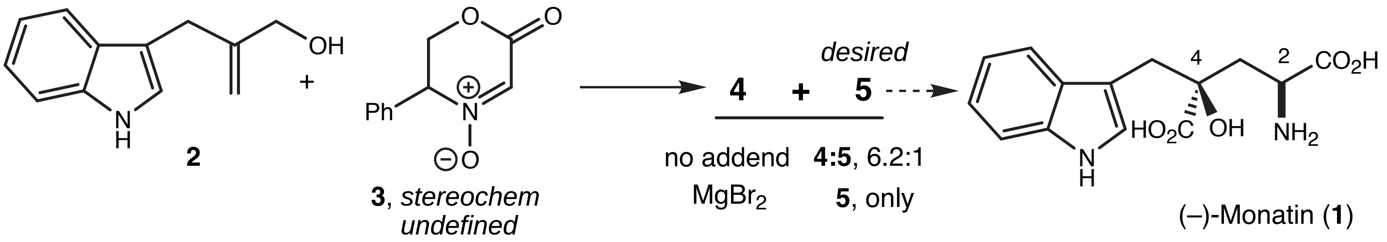
diastereomer ratio >97:3



Sterically preferred C=N diastereoface

The stereochemical outcome of this reaction has been rationalized by Fujisawa through the chelate-organized imine complex shown on the left. In this study diastereoface selectivity was noted to be strongly dependant on the nature of the organometallic reagent.

Question 7. (15 points). In 1992, (–)-monatin (**1**) was isolated from the bark and roots of *Schlerochiton ilicifolius*. This natural product was found to be a powerful sweetening agent (>1000X sucrose). Recently a stereoselective, nitrone-based synthesis of this natural product was reported by Tamura and co-workers (*Chem. Commun*. **2003**, 2678).

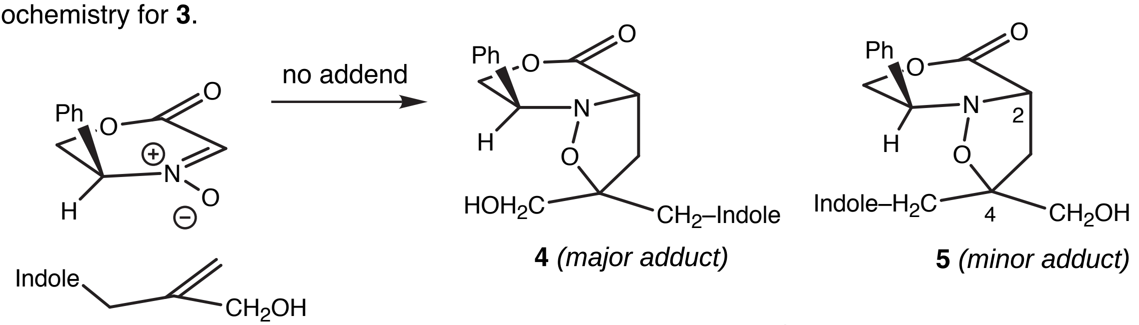


2

3, *stereochem undefined*

(–)-Monatin (**1**)

Part A. (8 points). In the initial study, the reaction of **2** and **3** afforded at 6.2:1 mixture of diastereomeric cycloadducts **4** and **5** respectively where the minor cycloadduct **5** was the desired product. Provide 3-dimensional absolute stereochemical representations of **4** and **5** below. Do not concern yourself at this point with a rationalle for this selectivity. In this exercise, you must work backwards to the two cycloadducts and then deduce the required absolute stereochemistry for **3**.



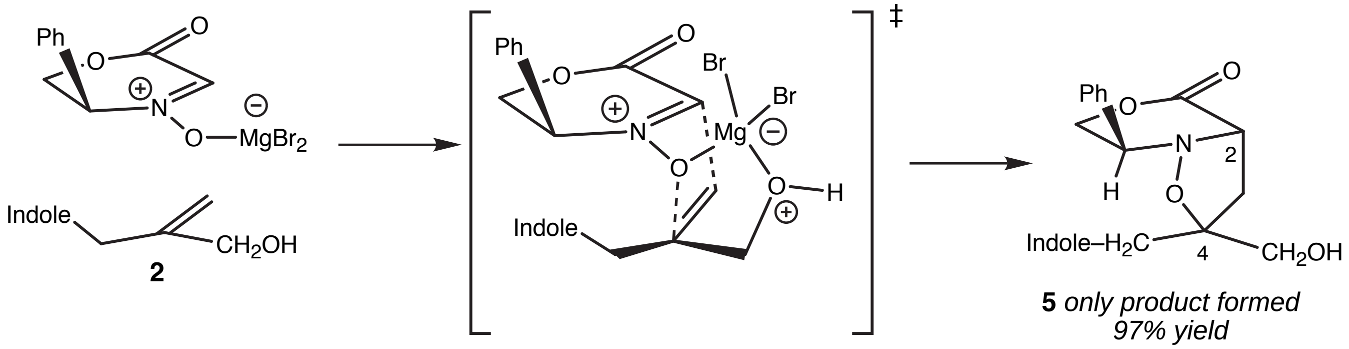
4 *(major adduct)*

5 *(minor adduct)*

2

4 is preferred on steric grounds since **CH_2–Indole** is more sterically demanding than **CH_2OH**. Stereochemistry at positions 2 & 4 in **1** requires cycloadduct **5** have this absolute and relative stereochemistry. Therefore the phenyl substituent must be (S) configured as drawn.

Part B. (7 points). When the reaction of **2** and **3** was carried out in the presence of 1.5 equiv of $MgBr_2$, the exclusive formation of the desired cycloadduct **5** was observed in 97% yield. Provide a 3-dimensional representation of the transition state leading to **5** that illustrates the role of $MgBr_2$.



2

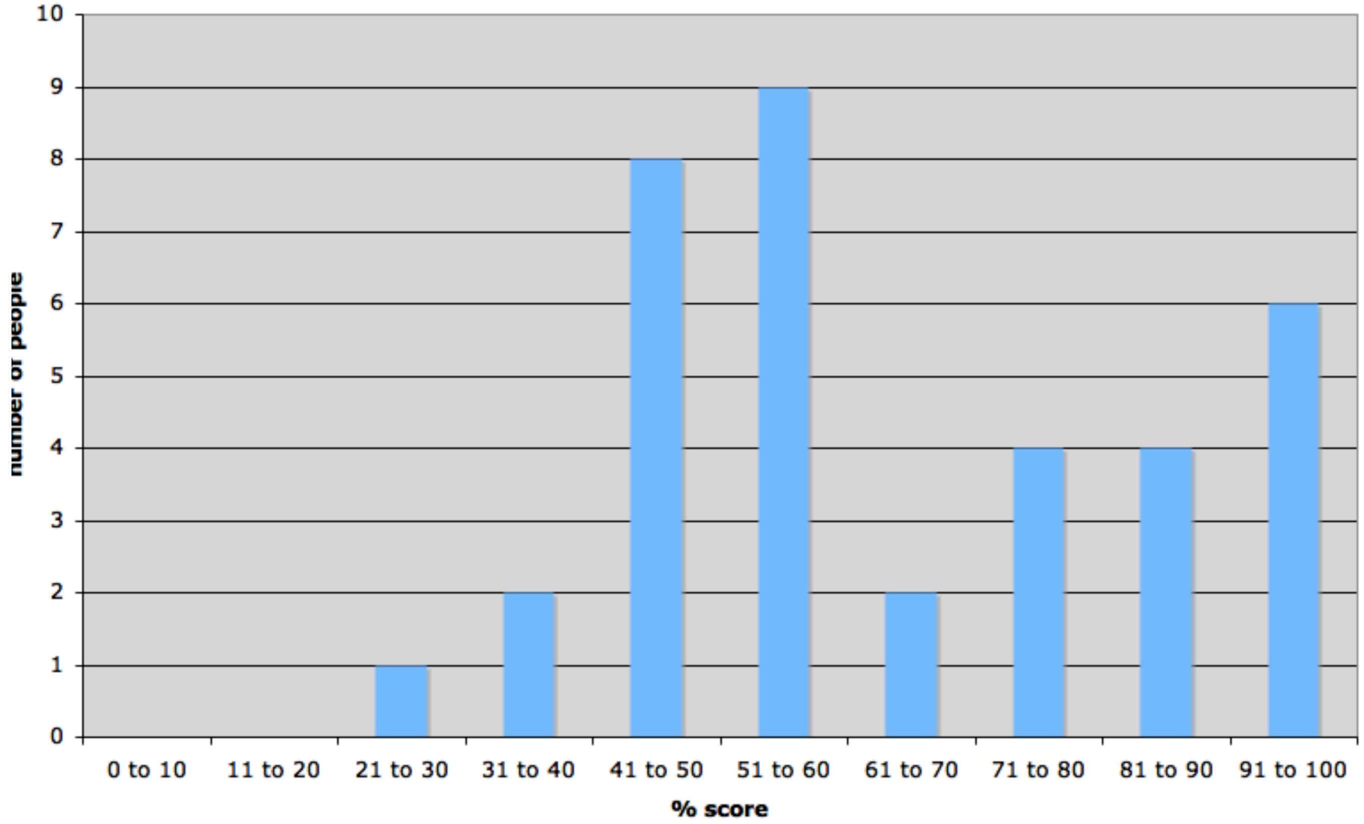
5 *only product formed*
97% yield

The experimental results are consistent with a chelate-organized transition state that constrains the Lewis basic hydroxyl moiety in the allylic alcohol and the nitrone oxygen to be syn-aligned as illustrated.

Chemistry 206
Third Hour Examination

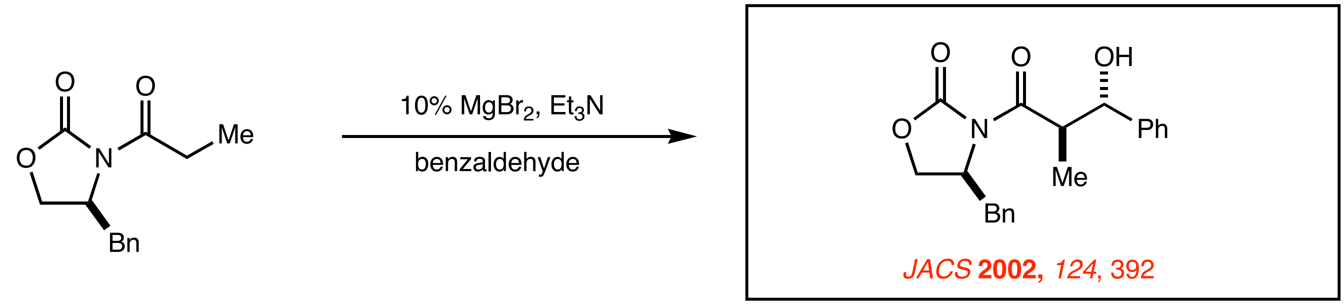
D. A. Evans
December 16, 2005

The Answer Key

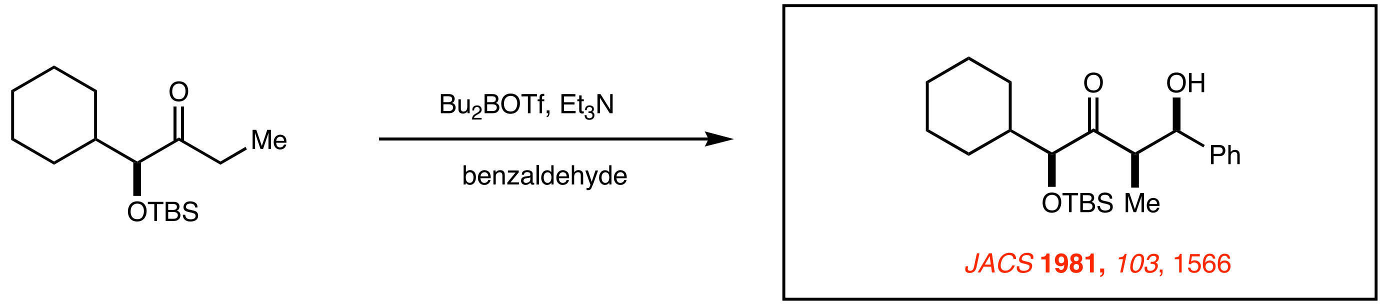


Examination Average: 62.5

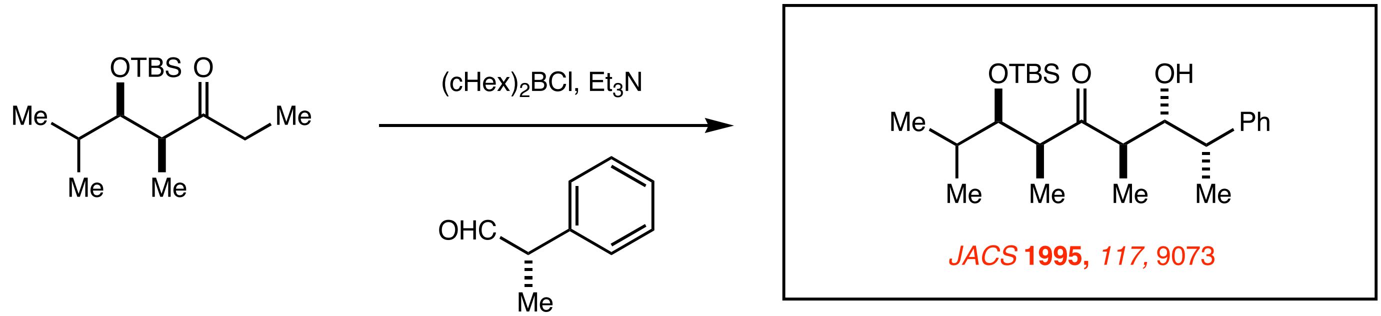
Question 1. (20 points). For each of the following aldol reactions provide the major product that you would expect to form under the given conditions. Provide the expected stereochemical outcome



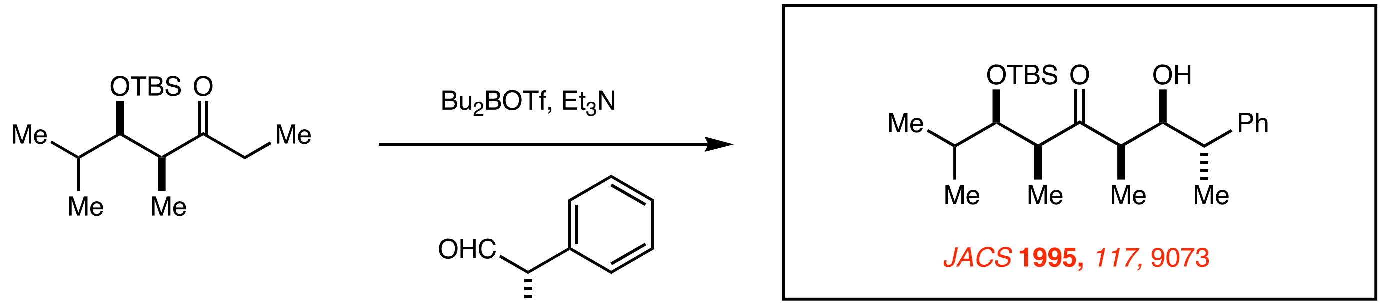
JACS **2002,** *124*, 392



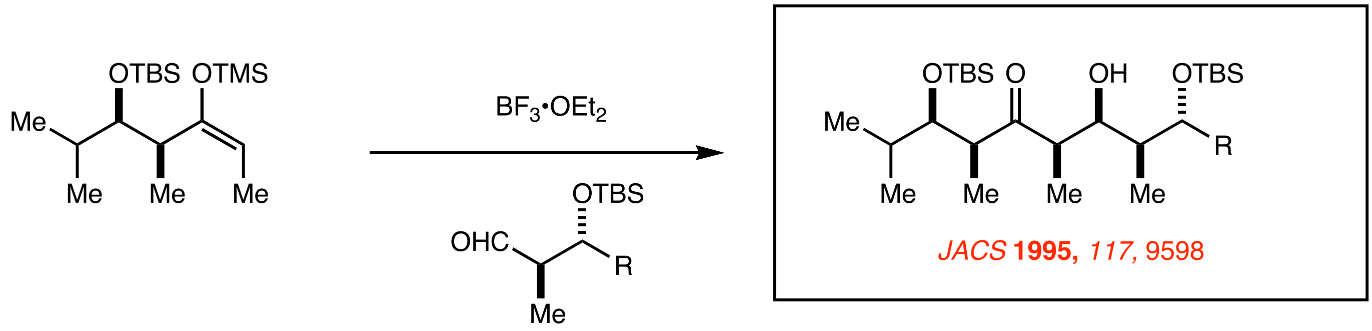
JACS **1981,** *103*, 1566



JACS **1995,** *117,* 9073

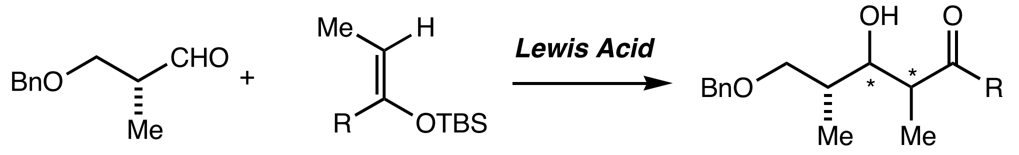


JACS **1995,** *117,* 9073



JACS **1995,** *117,* 9598

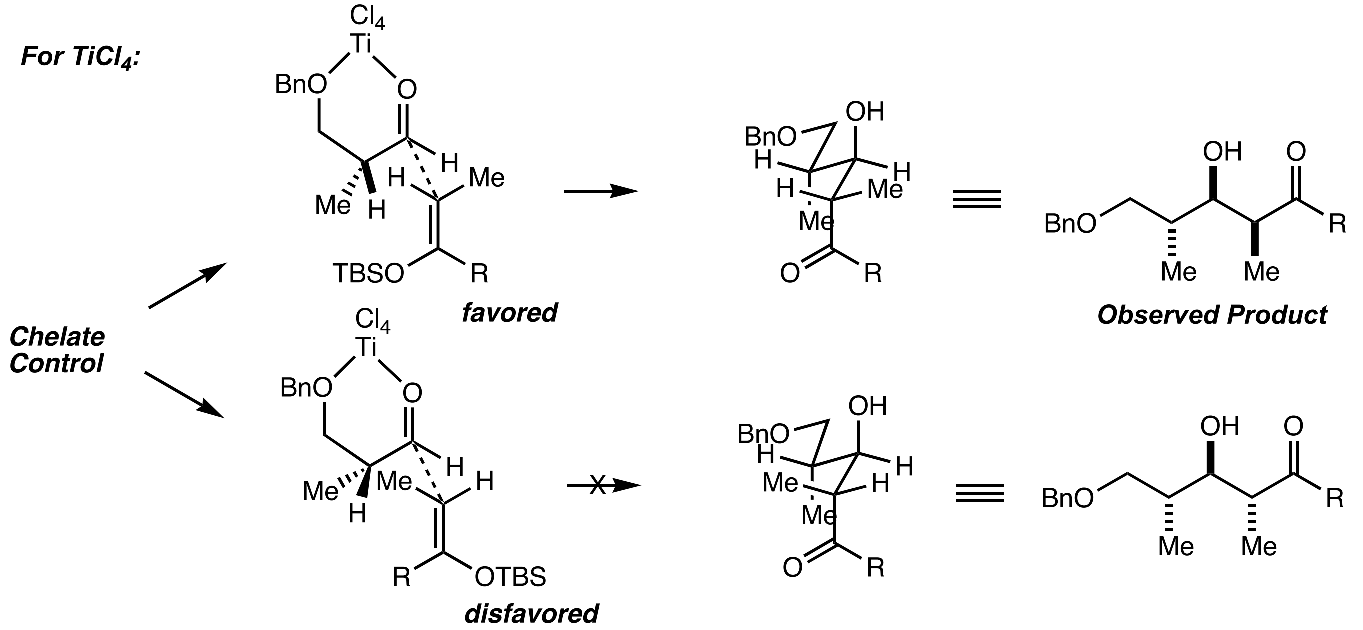
Question 2. (15 points). Using clear 3-dimensional transition state representations, predict the expected stereochemical outcome for the following Mukaiyama aldol reactions when using each of the two indicated Lewis acids.

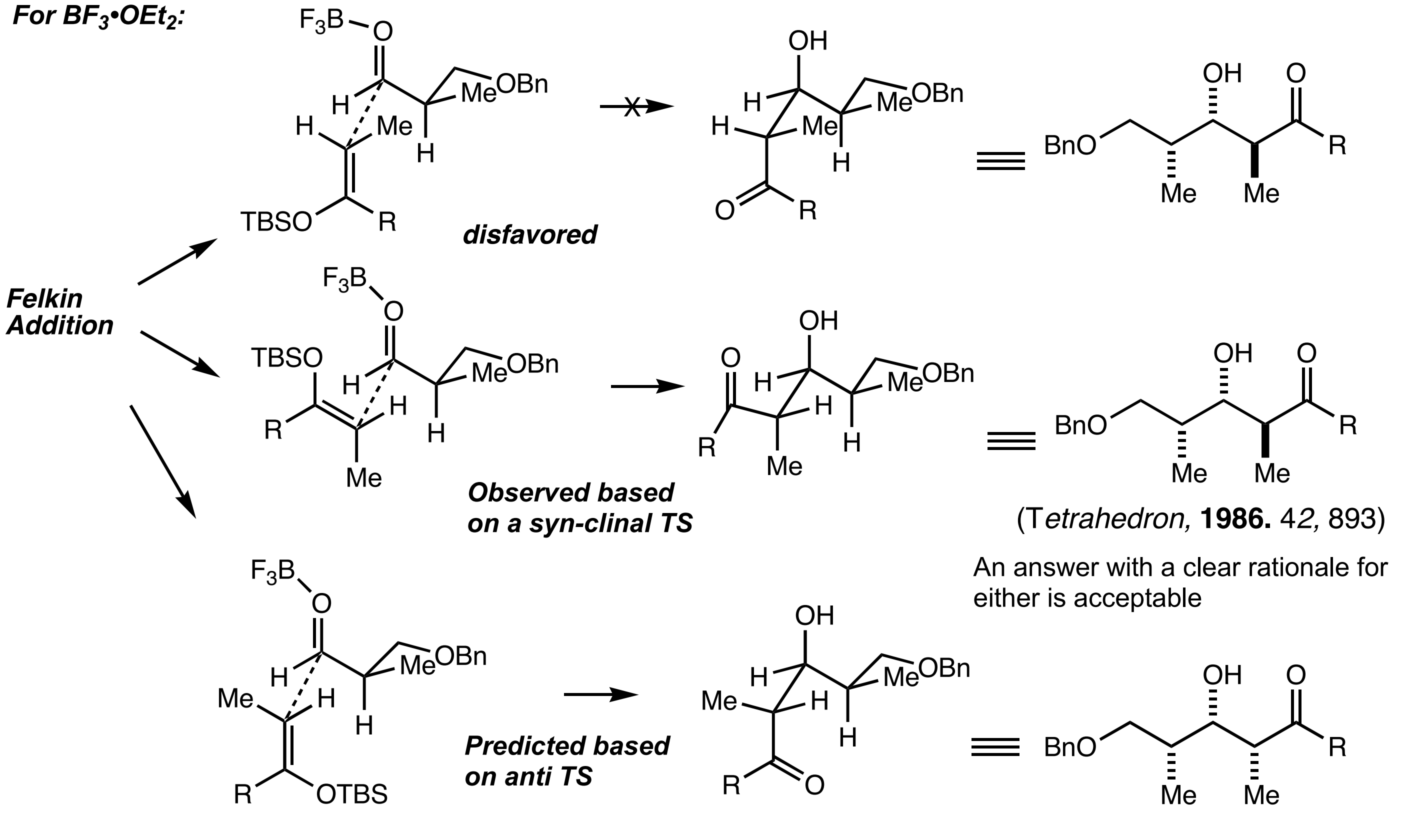


Lewis Acid

$TiCl_4$

BF_3•OEt_2





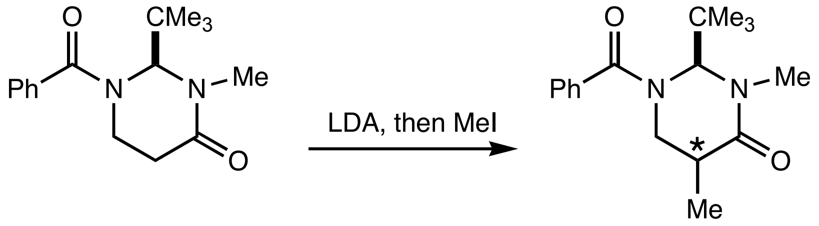
(T*etrahedron,* **1986.** 4*2,* 893)

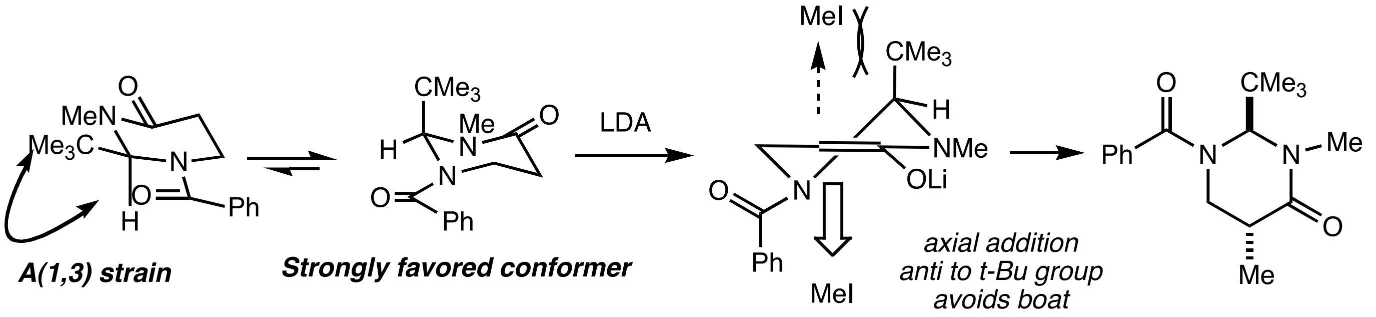
An answer with a clear rationale for either is acceptable

Question 3. (20 points). Predict the major product of each of the following alkylations. Be sure to provide clear three-dimensional representaions of the relevant transition states and to clearly identify any dominant steric or electronic effects. An answer without an explanation will not receive any credit.

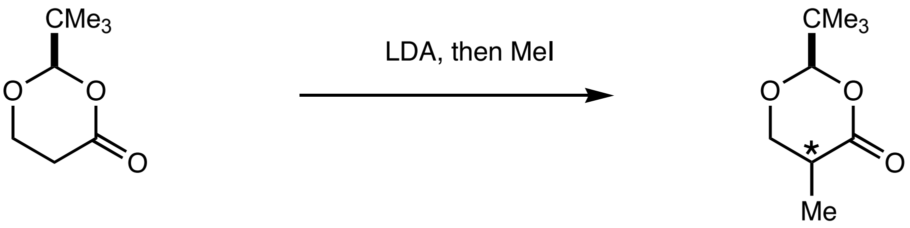
Part A. (10 points).

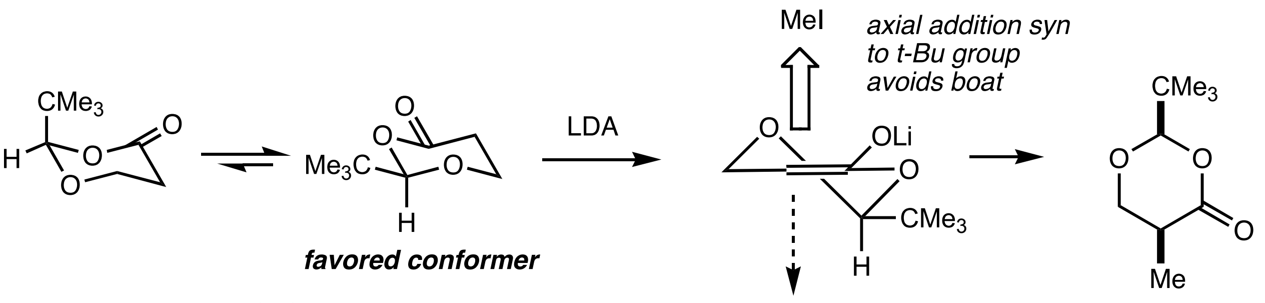
Seebach, *J. Org. Chem.* **1991**, *56*, 2557





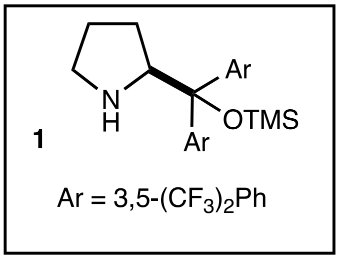
Part B. (10 points).

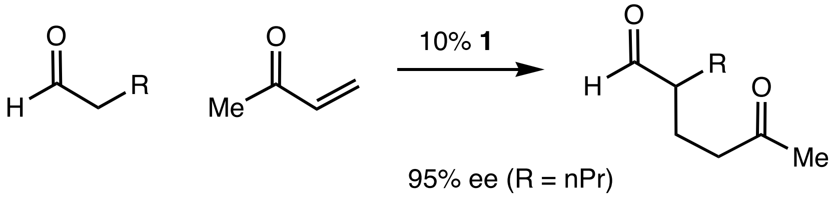




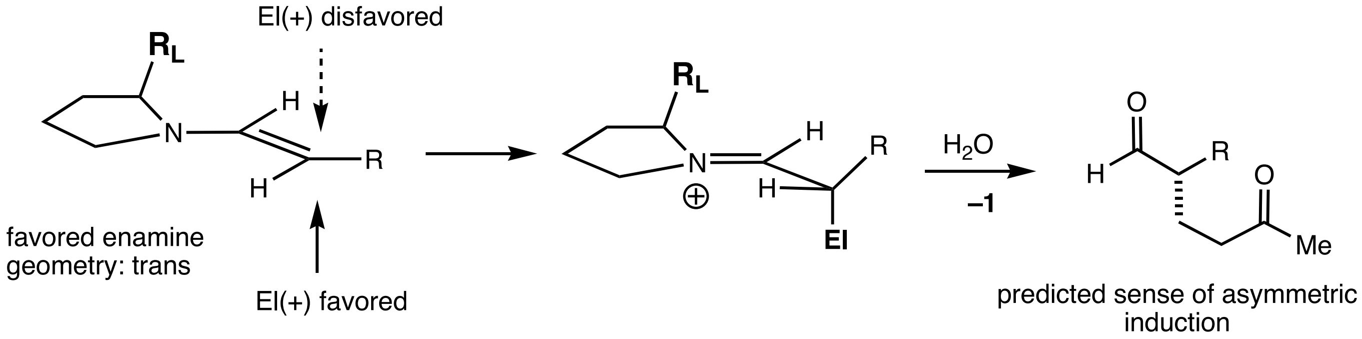
In the absence of A(!,3) strain the t-Bu group will be equatorially disposed.

Question 4. (15 points). In a *JACS ASAP* article that recently appeared on the web, Jorgensen and co-workers have reported that amine **1** is an excellent catalyst for the enantioselective α-functionalization of aldehydes with electrophiles. In all instances, the sense of asymmetric induction is the same. A typical reaction is shown below:

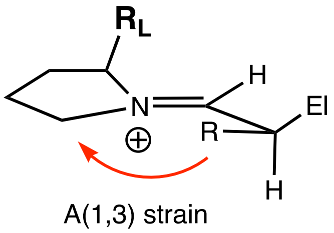




Part A. (10 Points). Precict the sense of asymmetric induction and provide a 3-dimensional drawing to support your prediction

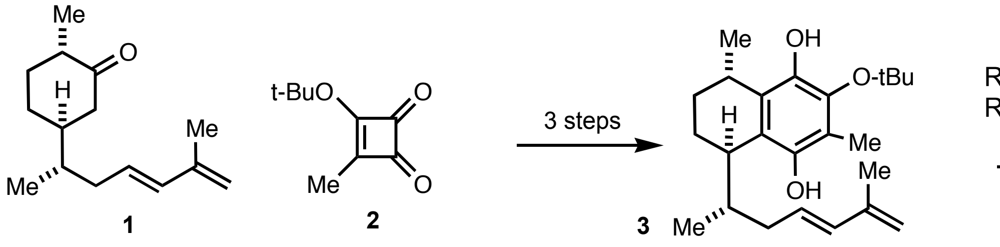


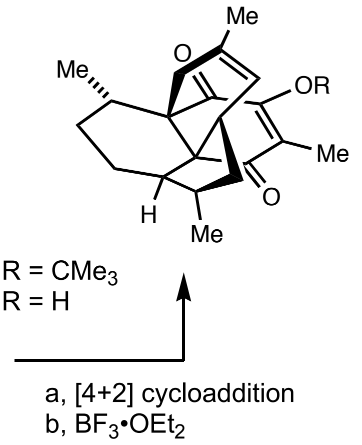
Part B. (5 Points). Explain why the iminium ion intermediate does not racemize under the reaction conditions. Illustrate your answer with a graphic.



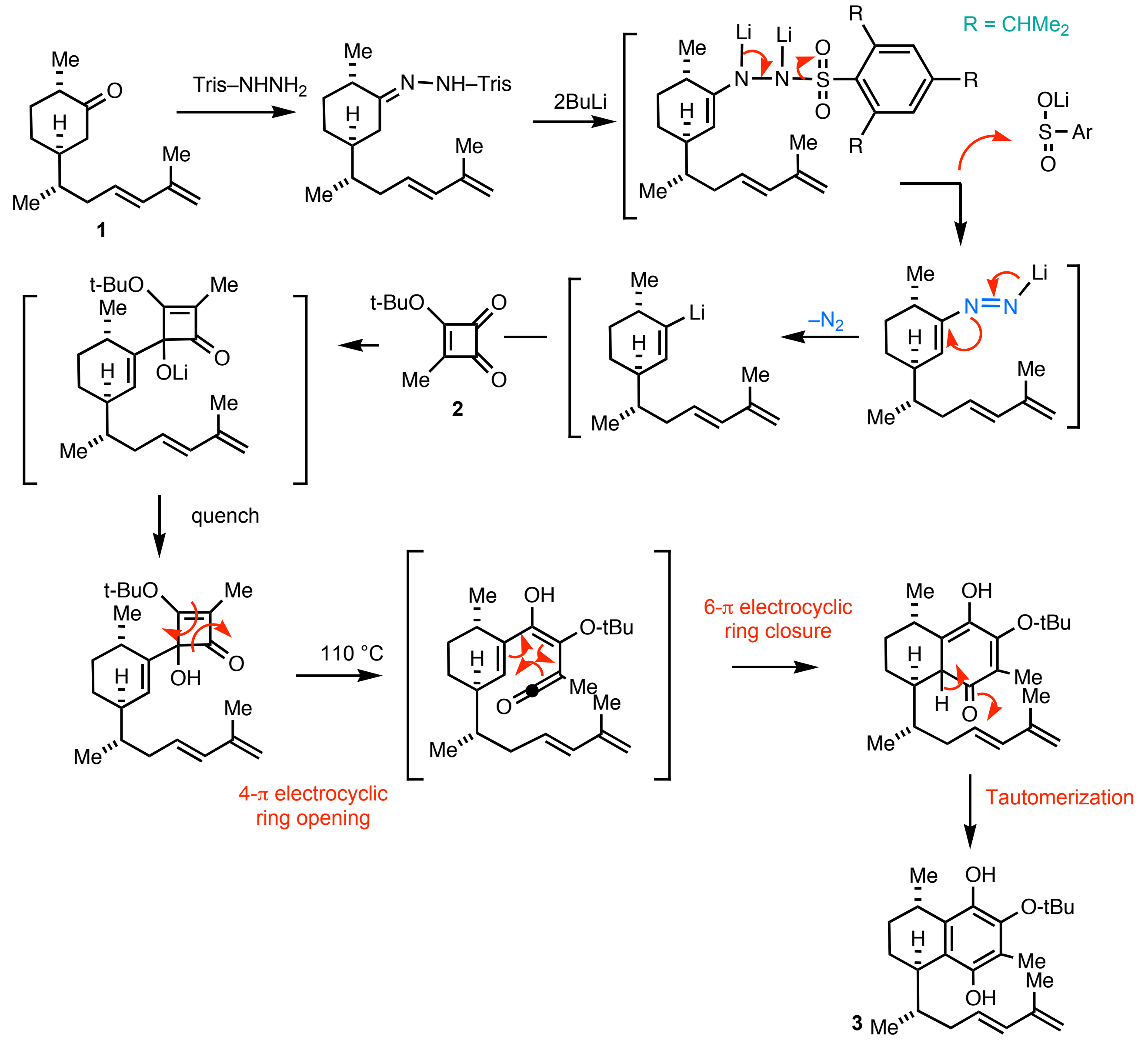
The required geometry that meets the stereoelectronic condition for deprotonation is strongly disfavored by A(1,3) allylic strain as illustrated. Hence, hydrolysis is favored over racemization.

Question 5. (15 points). Harrowven and so-workers recently reported the synthesis colombiasin (*Angew. Chemie Int. Ed.* **2005**, *44,* 1221-1222). The first series of steps begins with the union of the carvone-derived ketone **1** and squarate **2** to form hydroquinone **3** (eq 1). Upon oxidation,and subsequent heating **3** is transformed into colombiasin.

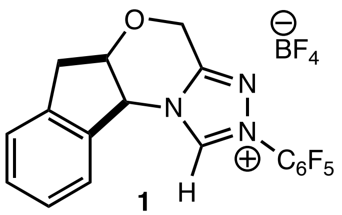




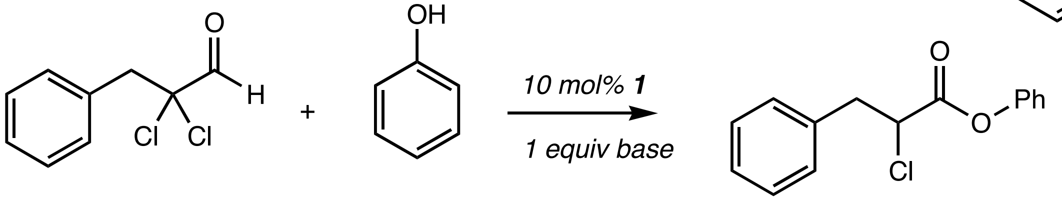
Using your general knowledge of organic chemistry, illustate the reactions and reagents needed to transform **1** and **2** into **3**. Please provide reasonable mechanisms for each of the steps



Question 6. (15 points). Reynolds and Rovis recently reported the following clever approach to the synthesis of enantiopure α-chloro esters from α,α-dichloroaldehydes (*JACS*, **2005**, *127*, 16406). Please provide a general mechanism for this reaction and predictthe stereochemical outcome.

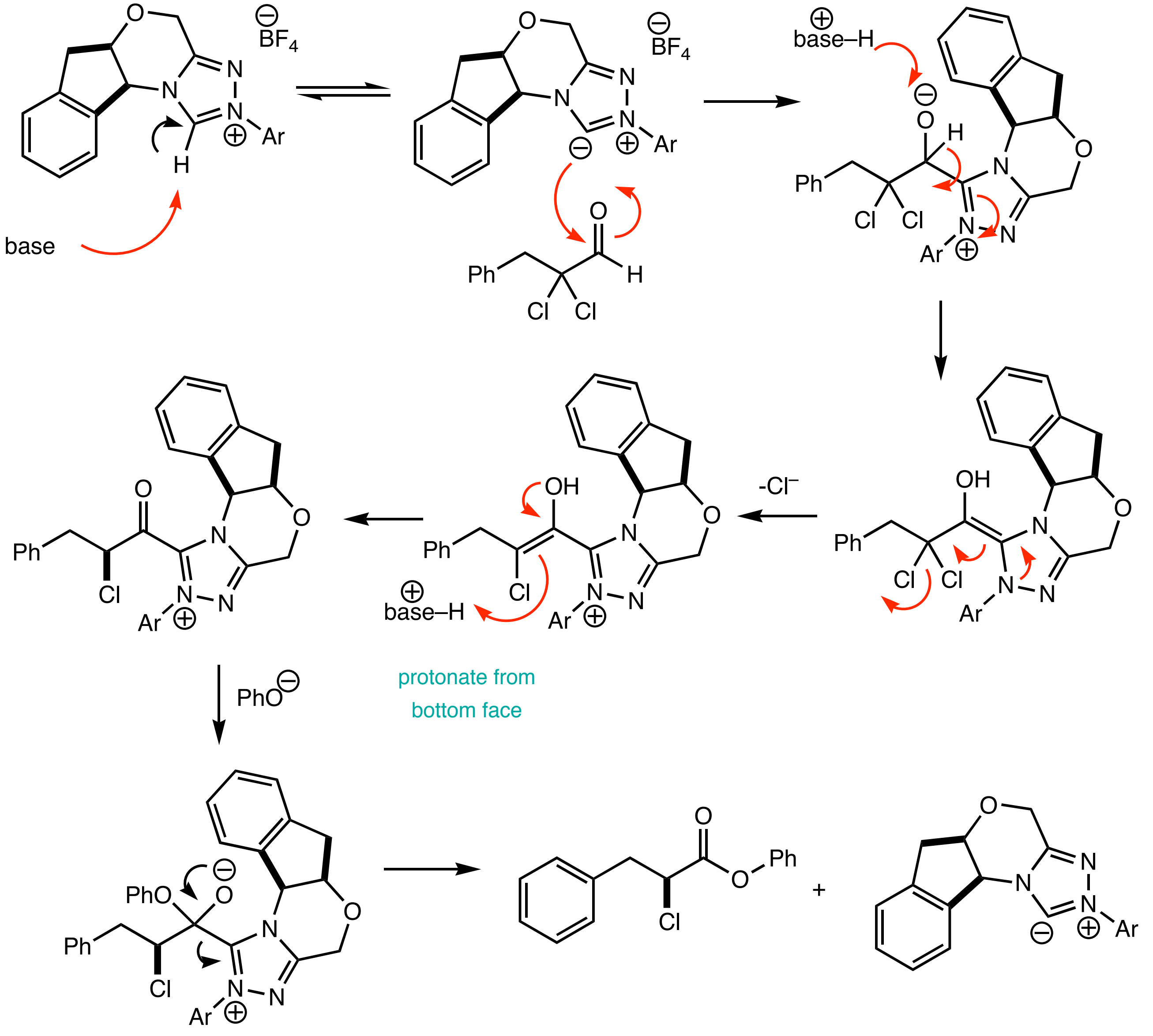


1



79% yield
93% ee

Your Answer:



Chemistry 206
Third Hour Examination

D. A. Evans
December 20, 2004

Name (please print): Answer Key
last first initial

Signature: ____________________

Teaching Fellow: ____________________

Question (pts)	Score
No. 1 (15)	_______
No. 2 (10)	_______
No. 3 (15)	_______
No. 4 (15)	_______
No. 5 (15)	_______
No. 6 (15)	_______
No. 7 (15)	_______
Total (100)	

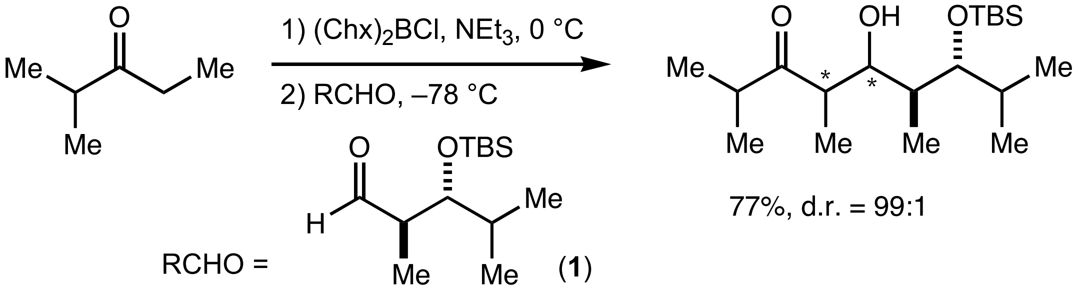
The exam will begin at 10:05 AM and end at 12:00 PM.

Please record your answers in the space provided on this examination. It is strongly recommended that the answers be worked out on scratch paper and then transferred to the examination.

Be certain to address stereochemical and stereoelectronic issues where appropriate and classify all pericyclic reactions.

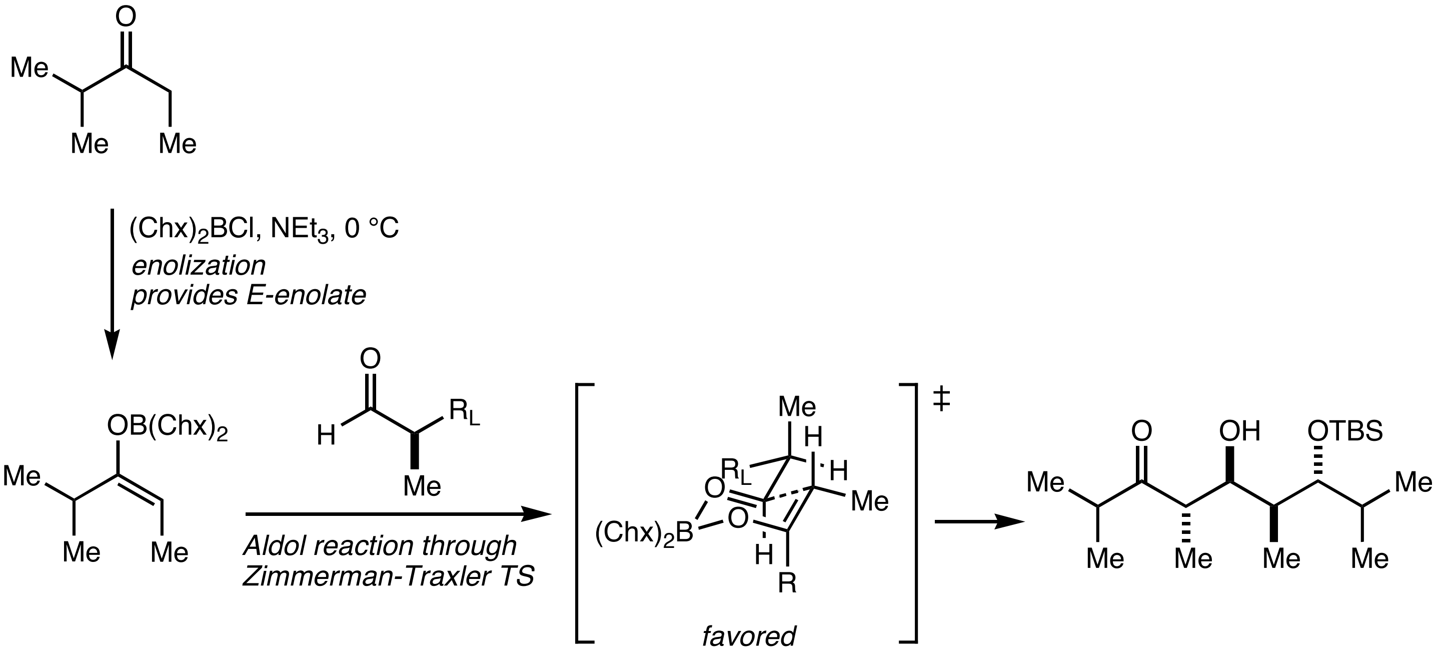
Exam Ave: 50
High Grade: 82

Question 1. (15 points). In the Ph.D. thesis of Dart (Harvard Univ. 1995), a systematic study of double stereodiffentiating aldol reactions was undertaken. The anti-configured chiral aldehyde (**1**) showed impressive selectivity (d.r. = 99 : 1) for the aldol addition of the dicyclohexyl boron enolate derived from ethyl isopropyl ketone (Eq 1).



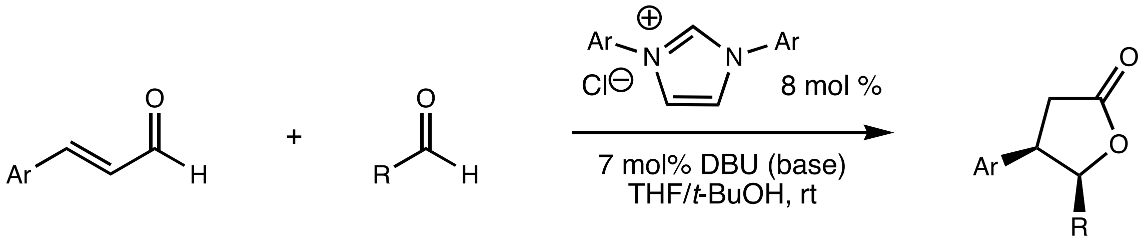
(Eq 1)

Please predict the major diasteromer and provide a rationale for the selectivity. Use of 3-D drawings is required.

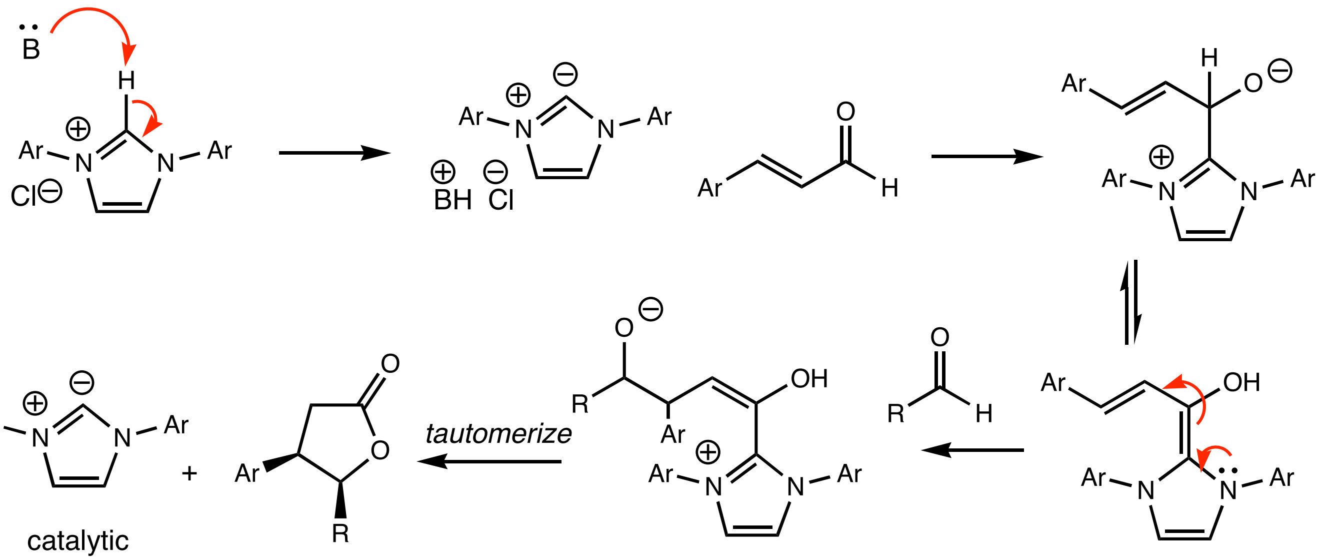


Felkin transition state
anti-aldol adduct

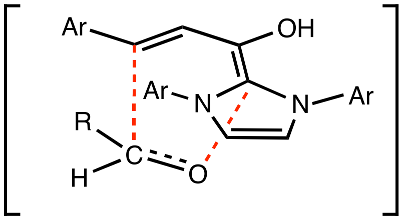
Question 2. (10 points). Bode and co-workers recently reported a new method for forming γ–butyrolactones from α,β-unsaturated aldehydes in the presence of catalytic amounts of bisarylimidazolium salts and base (*JACS*, **2004**, *126*, 14379).



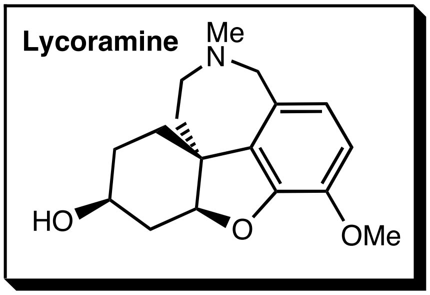
Propose a mechanism for this transformation that accounts for the use of catalytic amounts of salt . You do not need to explain the observed product stereochemistry in your answer.

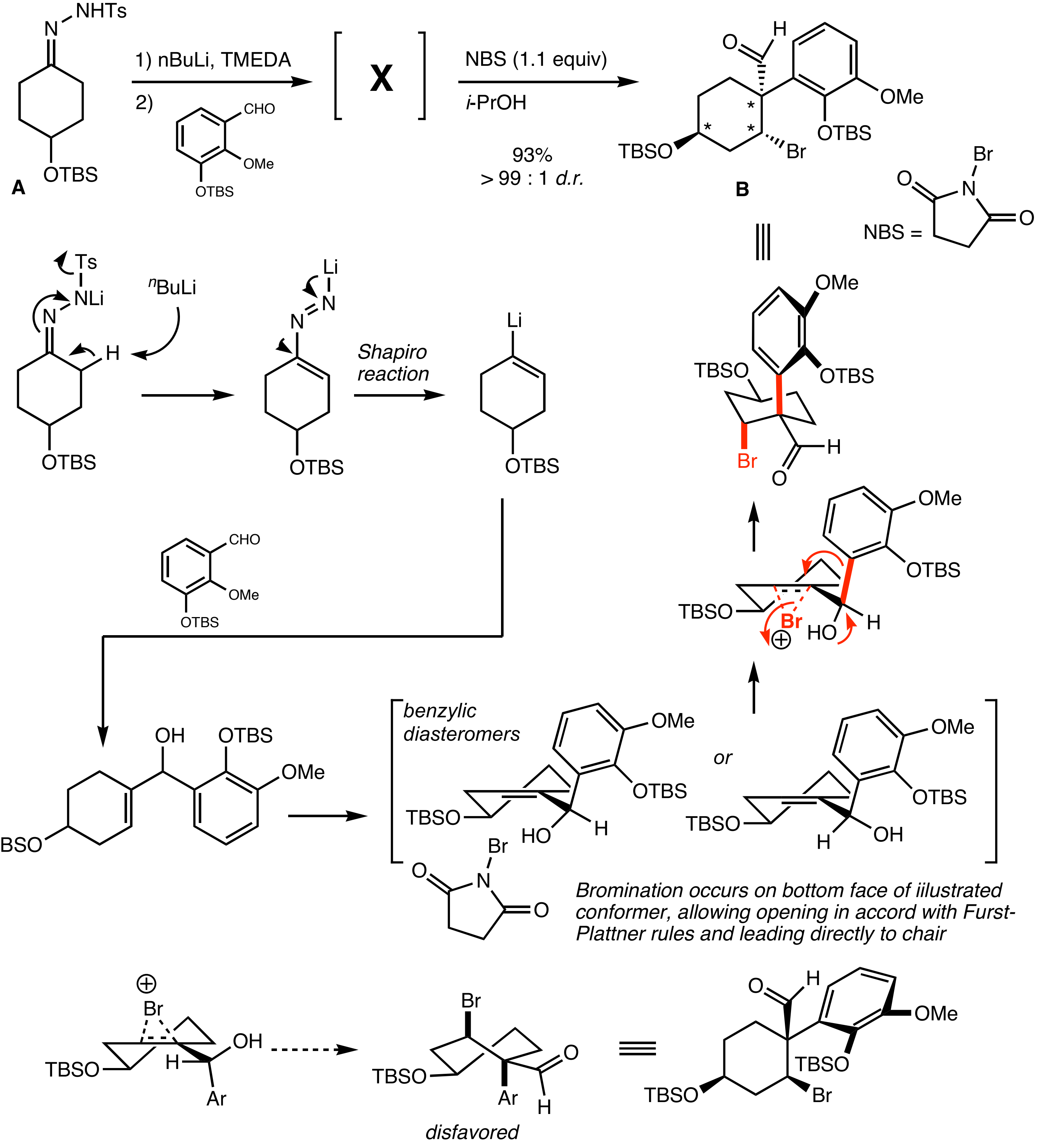


This transition state could explain the observed reaction stereochemistr.y



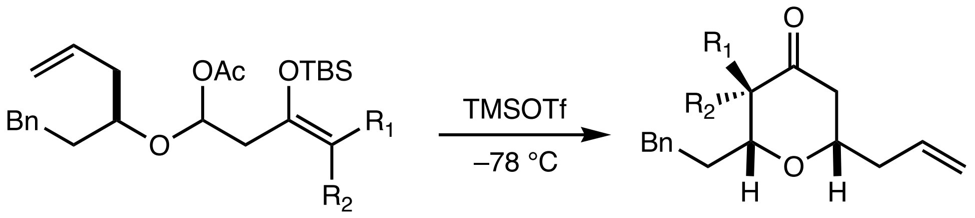
Question 3. (15 points). A synthesis of lycoramine was recently published (Tu, *Org. Lett.* **2004**, *6*, 4691.). A sequence from the report is provided below. Please provide a mechanism for the overall transfomation (**A** to **B**) that explains the high diastereoselectivity of the process. Your answer should highlight intermediate **X**.





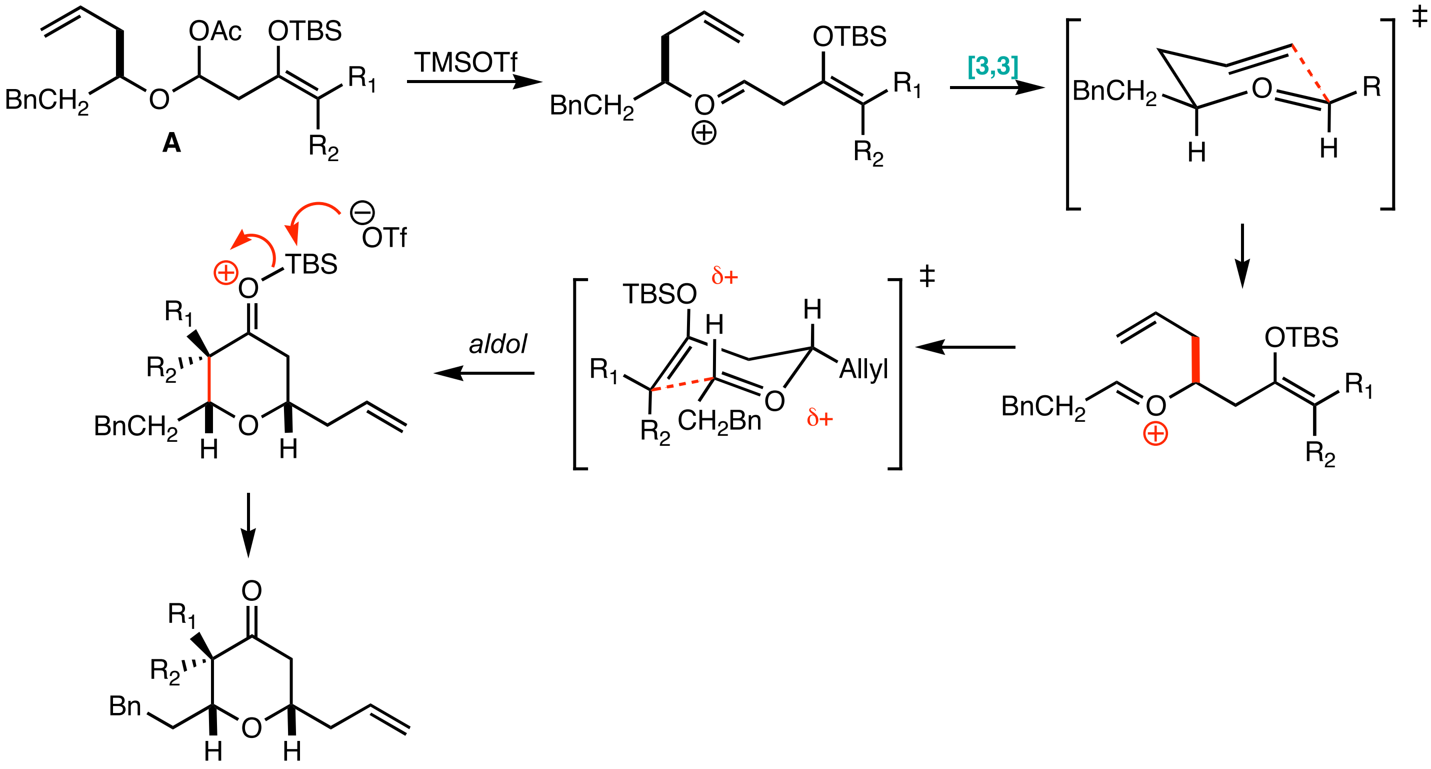
Bromination occurs on bottom face of iilustrated conformer, allowing opening in accord with Furst-Plattner rules and leading directly to chair

Question 4. (15 points). Rychnovsky and Dalgard *(JACS* **2004,** *126,* 15652) have reported the new diastereoselective pyranone synthesis illustrated below (Eq 1).

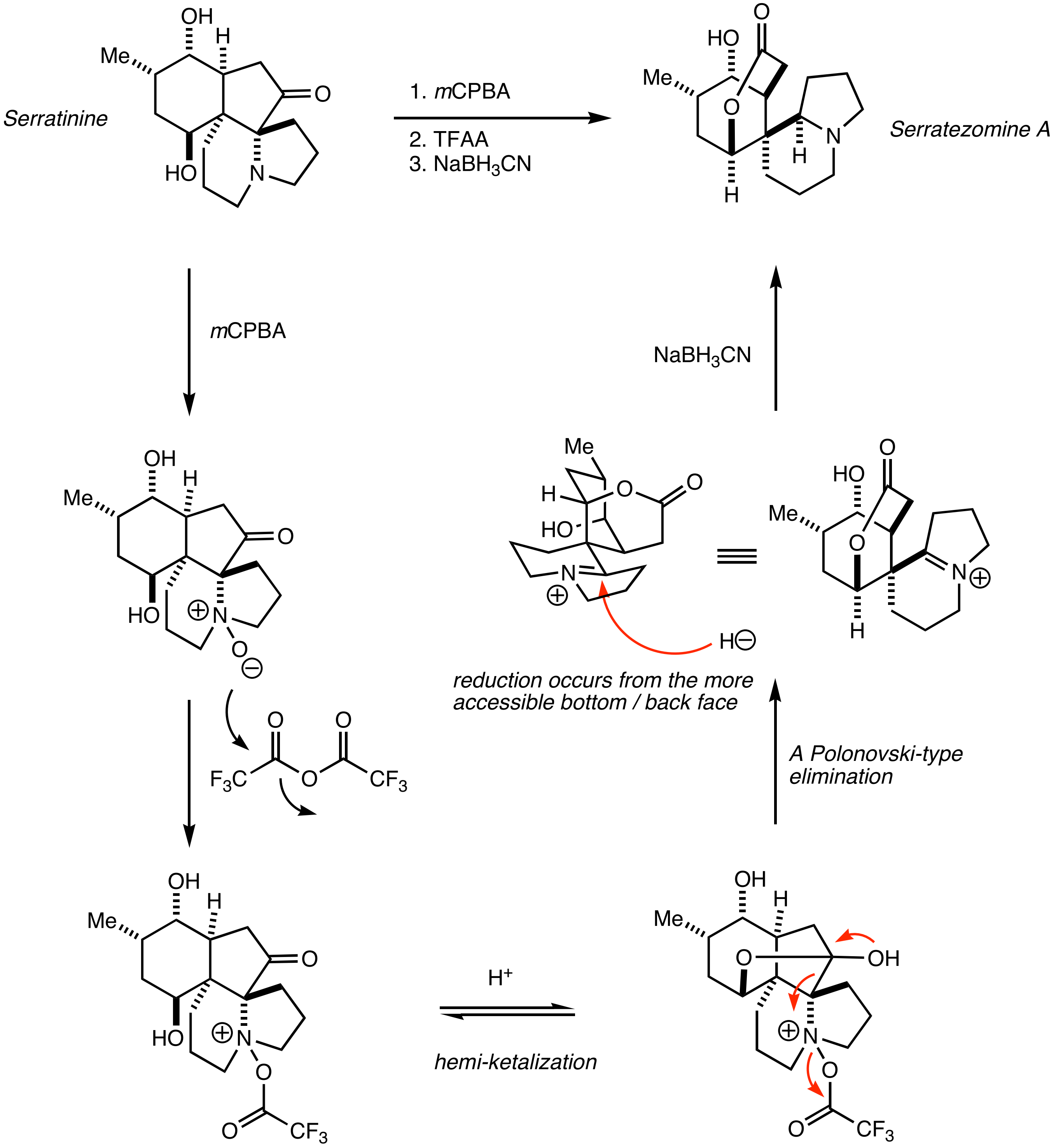


(Eq 1)

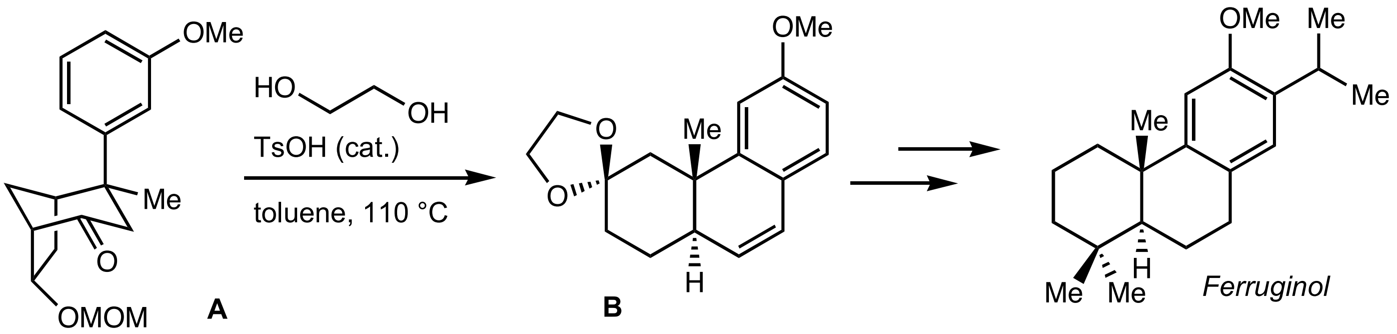
Please provide a mechanism for this rearrangement that accounts for the stereochemical outcome. Three-dimensonal representations are required for your rationalization the steps involving chirality transfer.



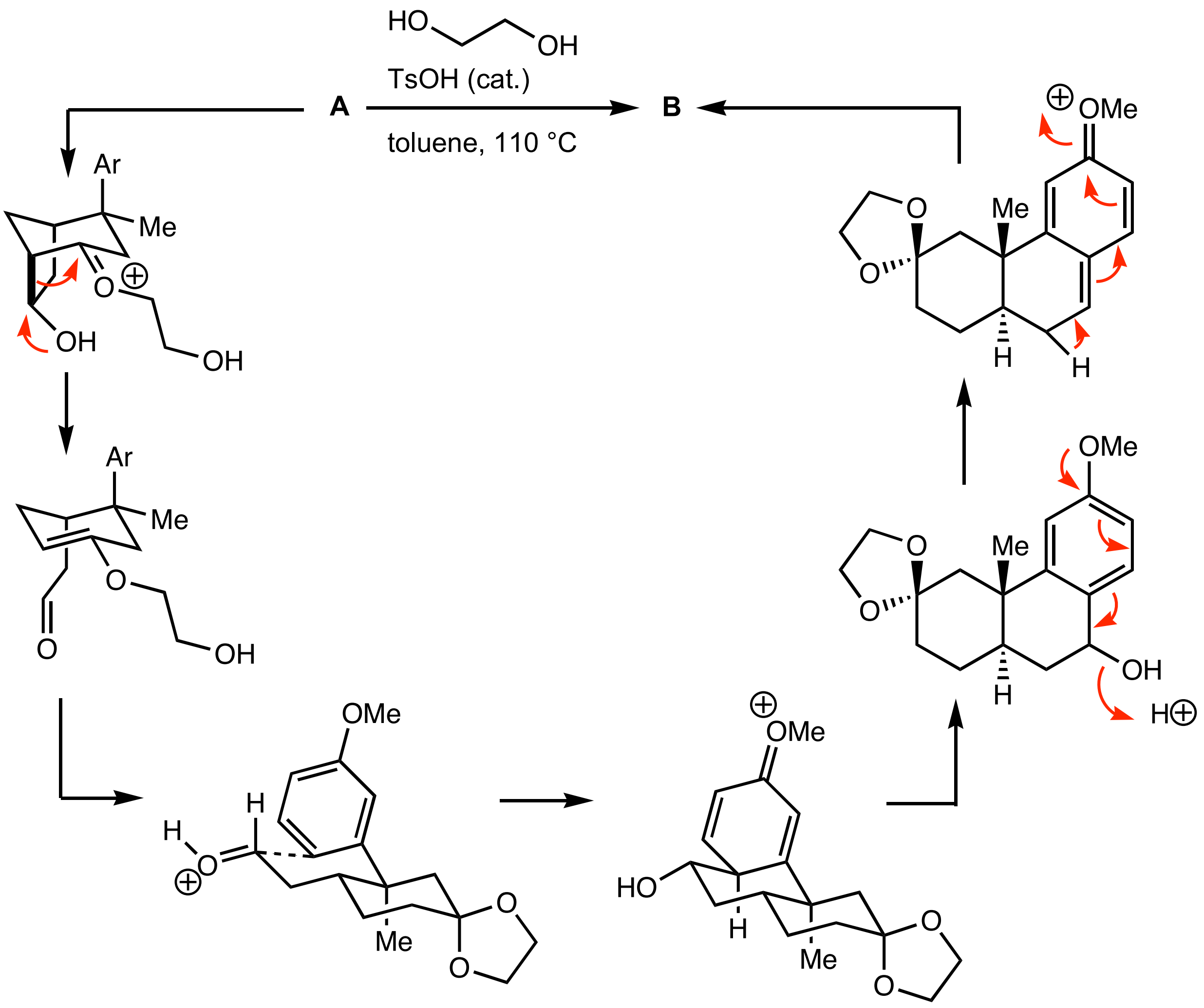
Question 5. (15 points). The following transformation of serratinine into serratezomine A was recently carried out in the laboratory to support the postulated biosynthesis of the *Lycopodium* alkaloid (*JOC,* **2002**, 67, 5378). Please provide a mechanism for the reaction.



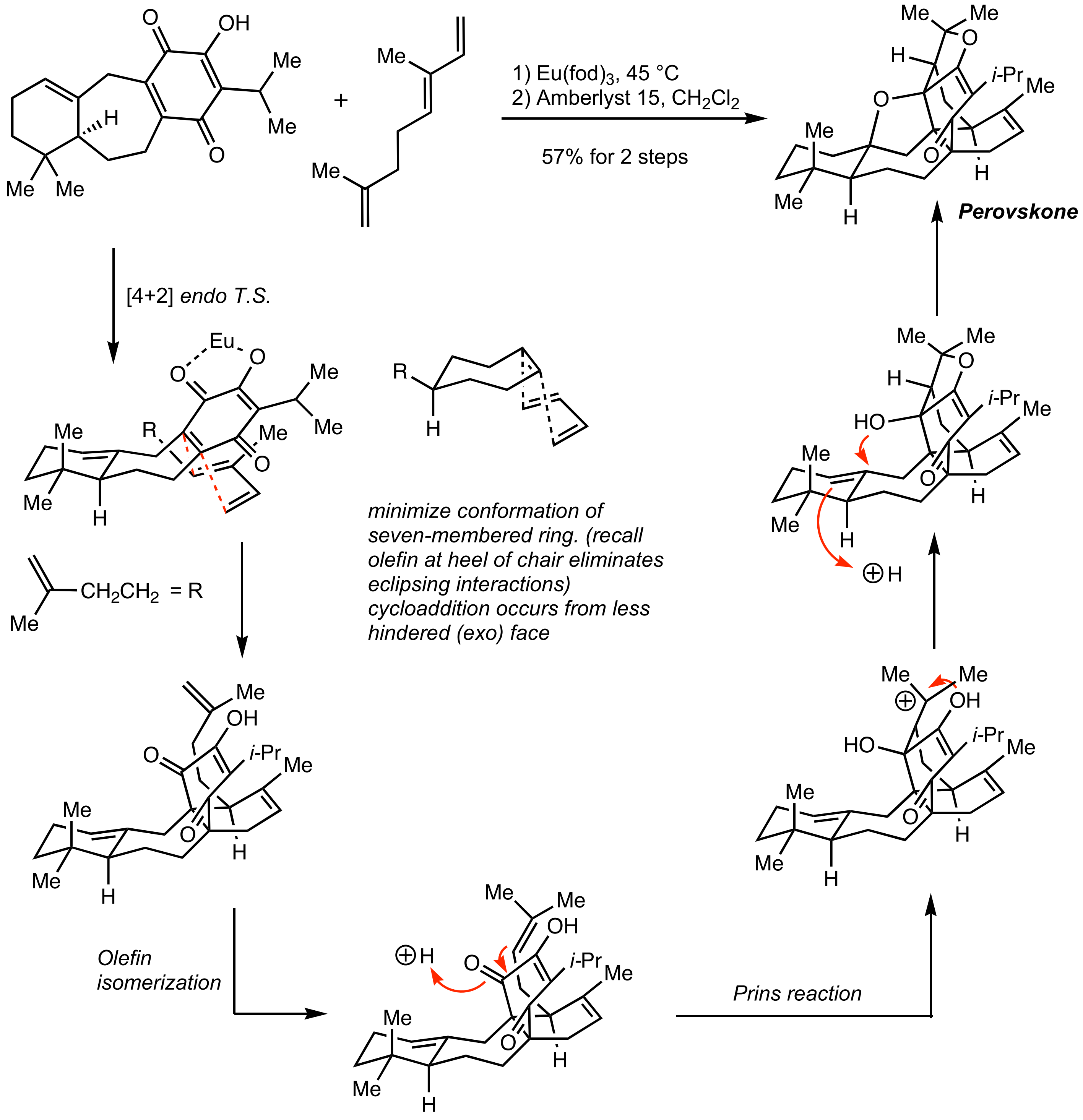
Question 6. (15 points). Ogasawara and co-workers have utilized the [3.2.1] bicyclic structure for the synthesis of a wide variety of terpene natural products. In the case at hand, [3.2.1] bicycle **A** was coverted to **B** in one operation (*Org. Lett.* **2001**, *3*, 1737) en route to (+)-ferruginol.



Please provide a mechanism for the conversion of **A** to **B**. Use 3-D pictures where relevant.



Question 7. (15 points). An elegant synthesis of the terpene perovskone has been reported (Majetich, *JACS.* **1994**, *116*, 4979.). Please provide a mechanism for this transformation making sure to explain relevant transition states with 3-D illustrations. (*nb: Eu (Europium) is functioning as a Lewis acid catalyst; Amberlyst-15 is a mineral protic acid)*



minimize conformation of seven-membered ring. (recall olefin at heel of chair eliminates eclipsing interactions) cycloaddition occurs from less hindered (exo) face

Chemistry 206
Third Hour Examination

D. A. Evans
December 17, 2003

Name (please print): ______________________
last first

Signature: ______________________

Teaching Fellow: ______________________

The exam will begin at 9:05 AM and end at 11:00.

Please record your answers in the space prov
on this examination. It is strongly recommend
the answers be worked out on scratch paper a
transferred to the examination.

Question (pts)	Score
No. 1 (10)	______
No. 2 (15)	______
No. 3 (10)	______
No. 4 (15)	______
No. 5 (10)	______
No. 6 (10)	______
No. 7 (10)	______
No. 8 (10)	______
No. 9 (10)	
Total (100)	

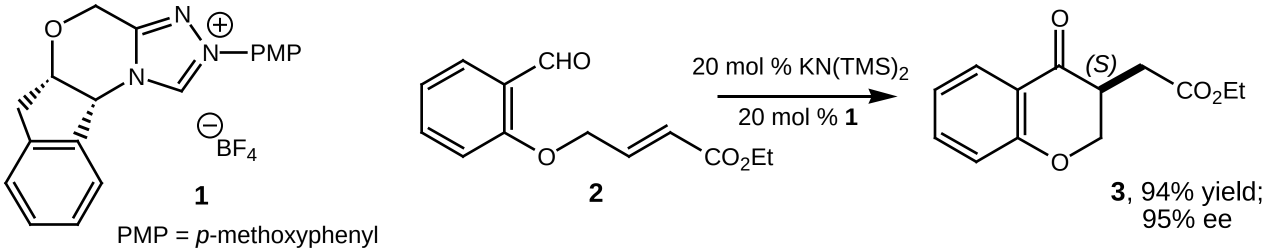
I HAVE WINGS, BUT I CAN'T FLY. SANTA'S REINDEER DO NOT HAVE WINGS, BUT THEY CAN FLY. CAN YOU EXPLAIN THIS TO ME????
VETERINARIAN
GLASBERGEN

© 1998 Randy Glasbergen. www.glasberg

☐ Check this box if you want us to email your score to you.

Answer Key

Question 1. (10 points). The development of chiral variants of the Stetter reaction is a current objective in the chemical literature. Such a study has been recently reported by Rovis and Co-workers (*JACS*, **2002**, *124*, 10298). In the presence of 20 mol percent of triazolium salt **1**, and an equal amount of $KN(TMS)_2$, **2** is transformed into **3** in 94% yield and 95% ee.

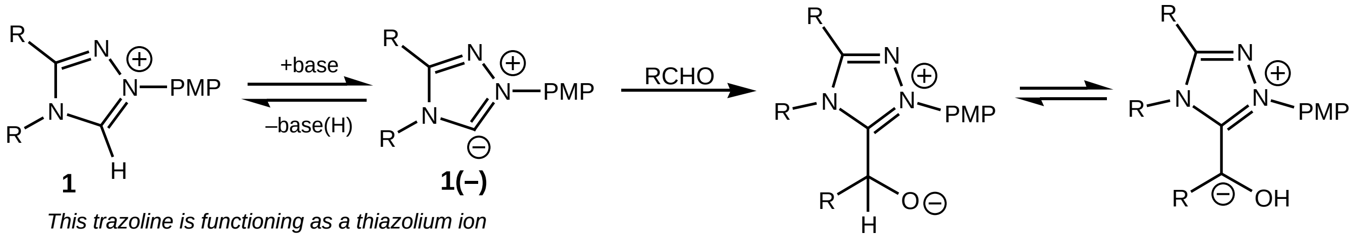


1
PMP = *p*-methoxyphenyl

2

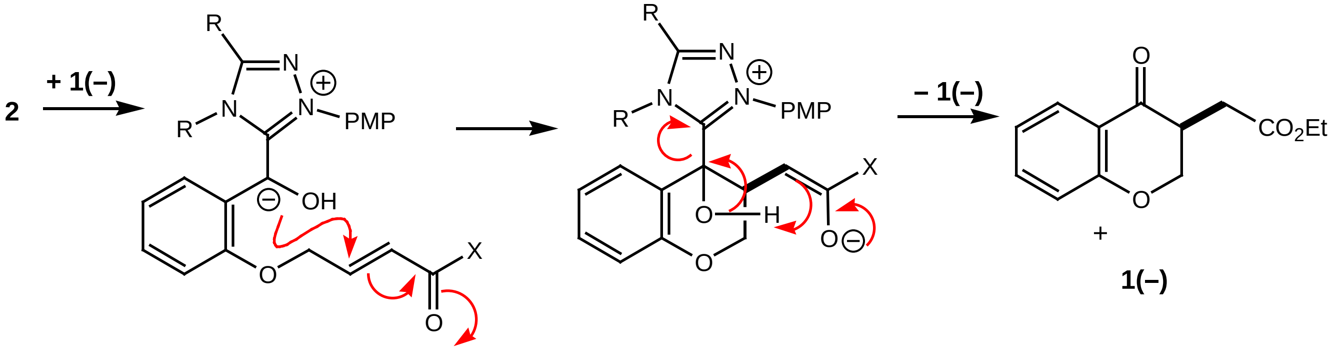
3, 94% yield;
95% ee

Provide a mechanism for this rearrangement in the space below. You do not need to account for the absolute stereochemical outcome of this reaction in your answer.

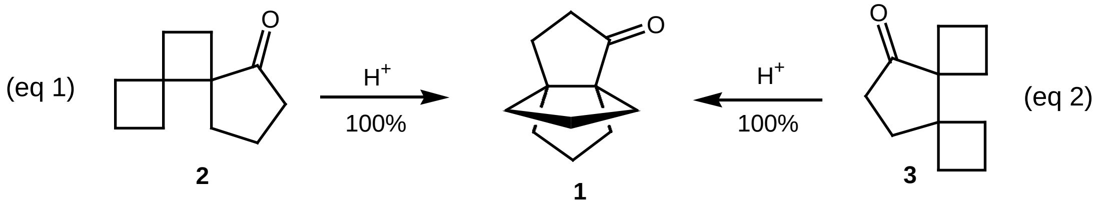


1 **1(–)**

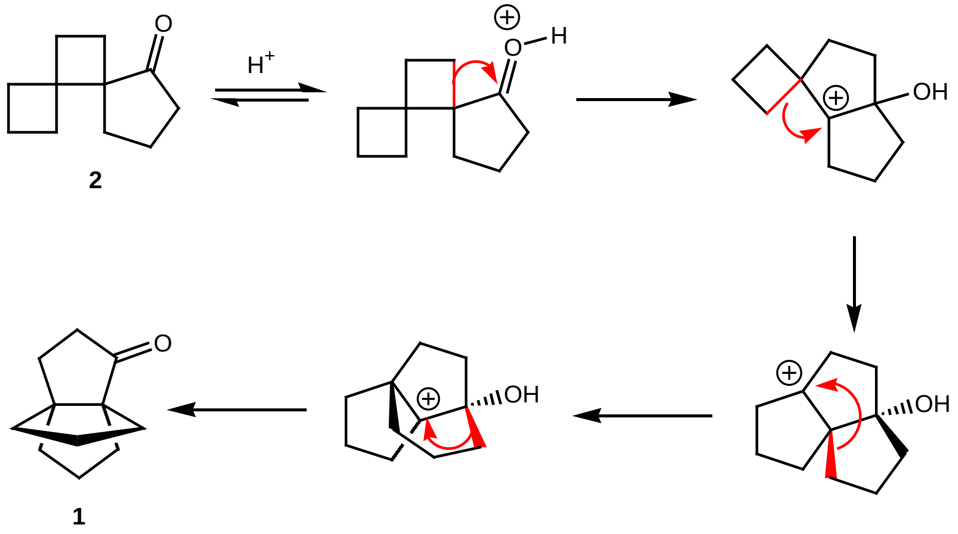
This trazoline is functioning as a thiazolium ion equivalent to generate an acylanion equivalent:



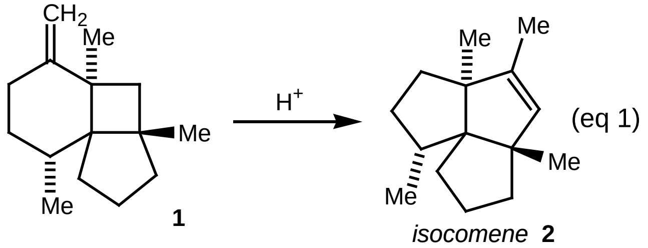
Question 2. (15 points). Fitjer and co-workers (***Tet. Lett.*** **1988**, ***129***, 263) have reported a very interesting approach to the [3,3,3]propellane **1**. This tricyclic ketone may be produced in quantitative yield through acid-catalyzed rearrangement of either ketones **2** or **3**.

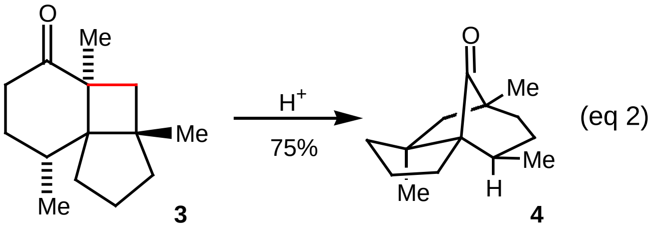


Please provide a plausible mechanism for the rearrangement **2**→**1** (eq 1). Use 3-dimensional representations where appropriate to illustrate your answer.

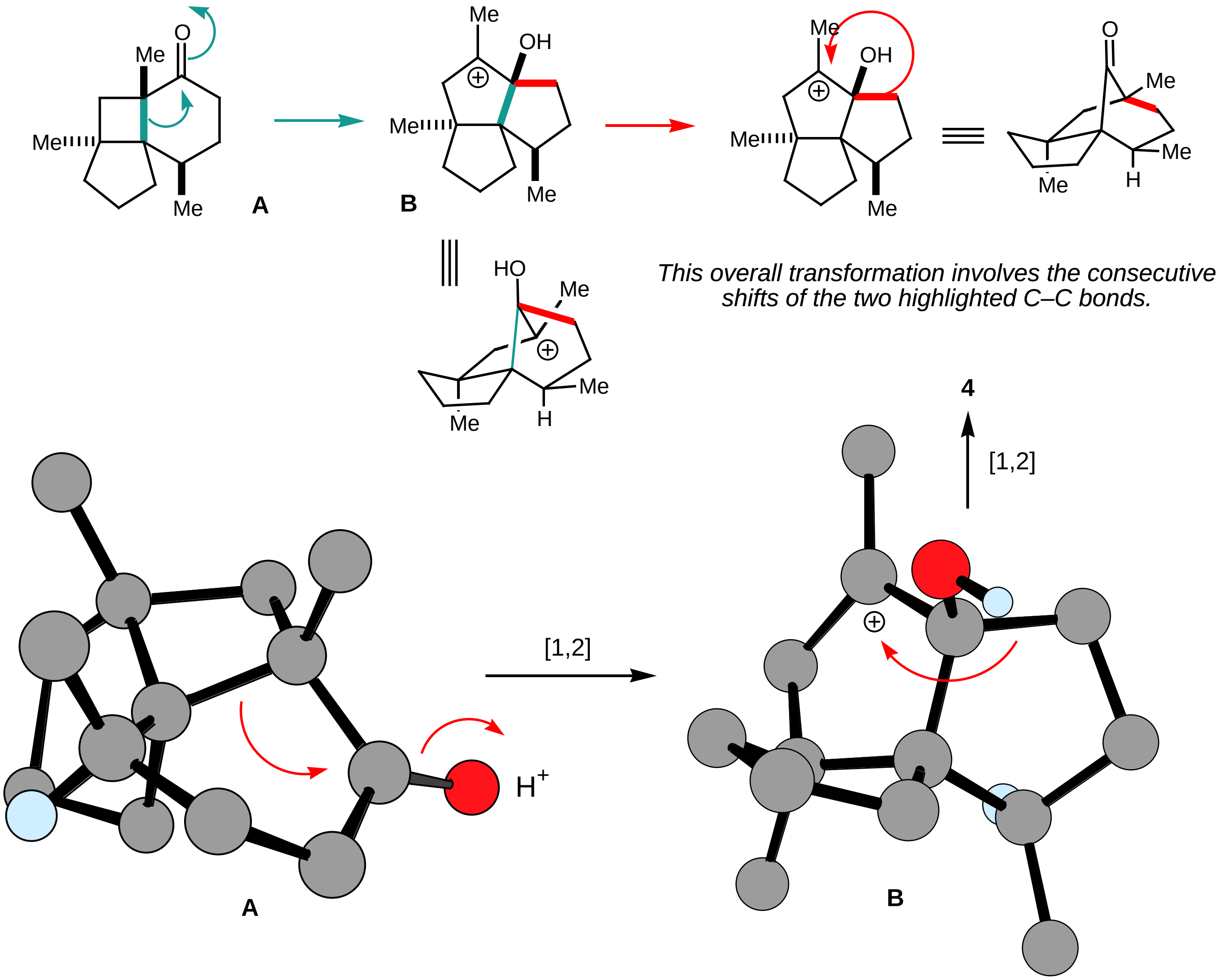


Question 3. (10 points). We have discussed the Pirrung approach to the synthesis of isocomene (**2**) (*JACS* **1982**, *103*, 82-87) that features the acid catalyzed rearrangement illustrated below (eq 1). In the Pirrung study the rearrangement of ketone **3** was also reported (eq 2).



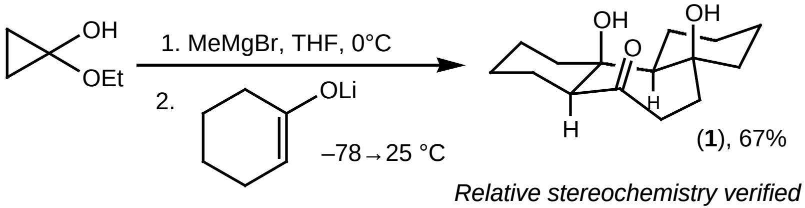


Please provide a plausible mechanism for the rearrangement **3**→**4** (eq 2). Use 3-dimensional representations where appropriate to illustrate your answer.



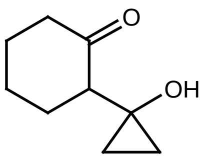
This overall transformation involves the consecutive shifts of the two highlighted C–C bonds.

Question 4. (15 points). Helquist has reported the interesting enolate-based ring-forming process illustrated below (*JACS* **1986**, *108*, 8313). In this experiment, the MeMgBr was added to the cyclopropanone hemiketal. The cyclohexanone enolate (2 equiv) was then cannulated into the reaction vessel. In addition to the indicated product **1**, ~14% of the cyclopropanone aldol adduct **2** was obtained. If **2** is treated under the stated reaction conditions, an 80% of **1** is obtained. The selection of Mg(II) to mediate the stereochemical outcome of this reaction is important.



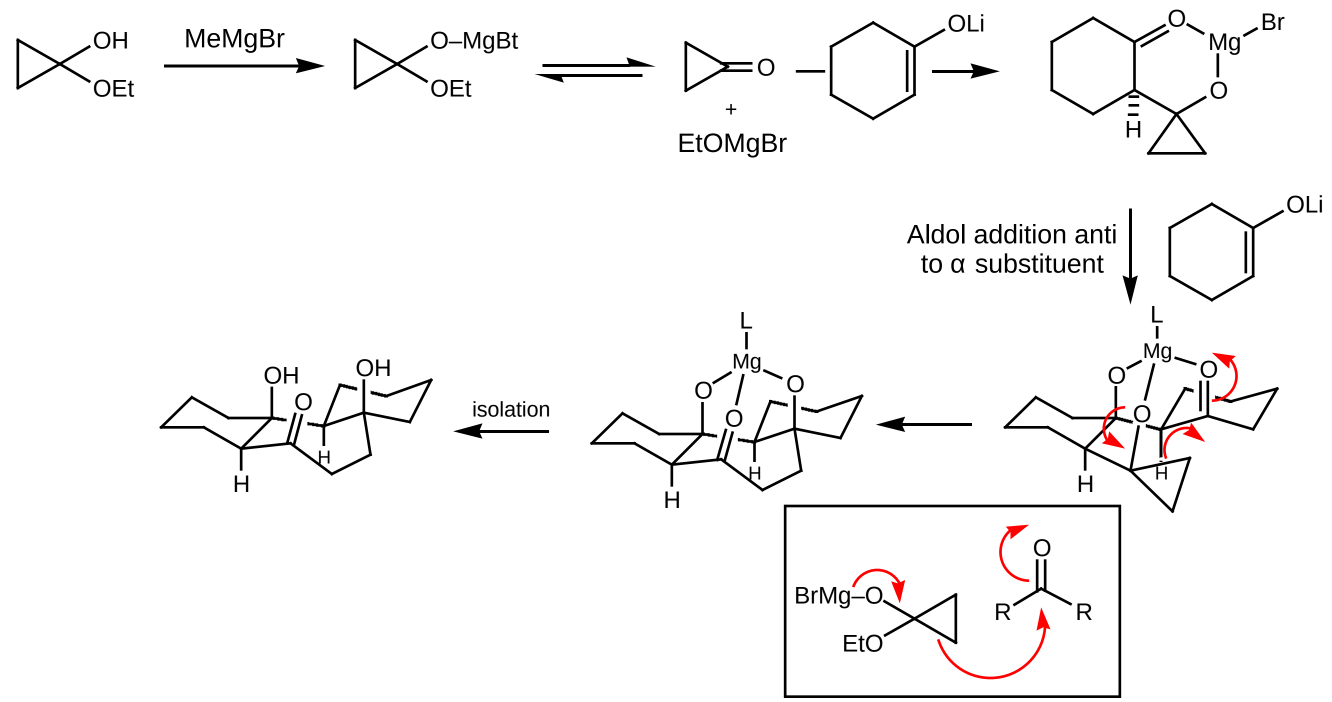
(**1**), 67%

Relative stereochemistry verified by x-ray crystallography

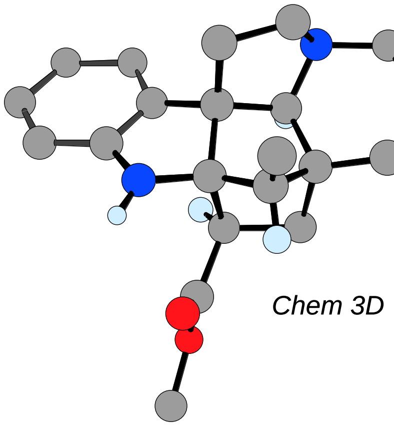


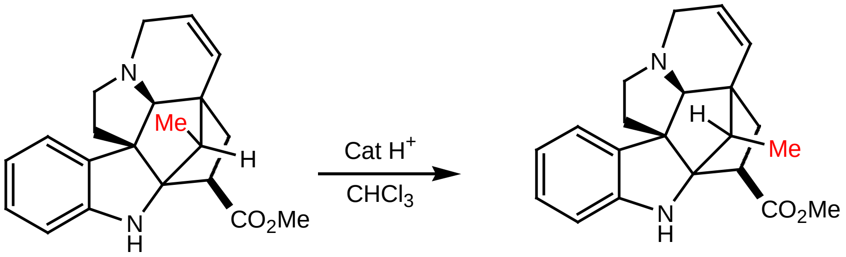
(**2**), 14%

Please provide a plausible mechanism for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer.



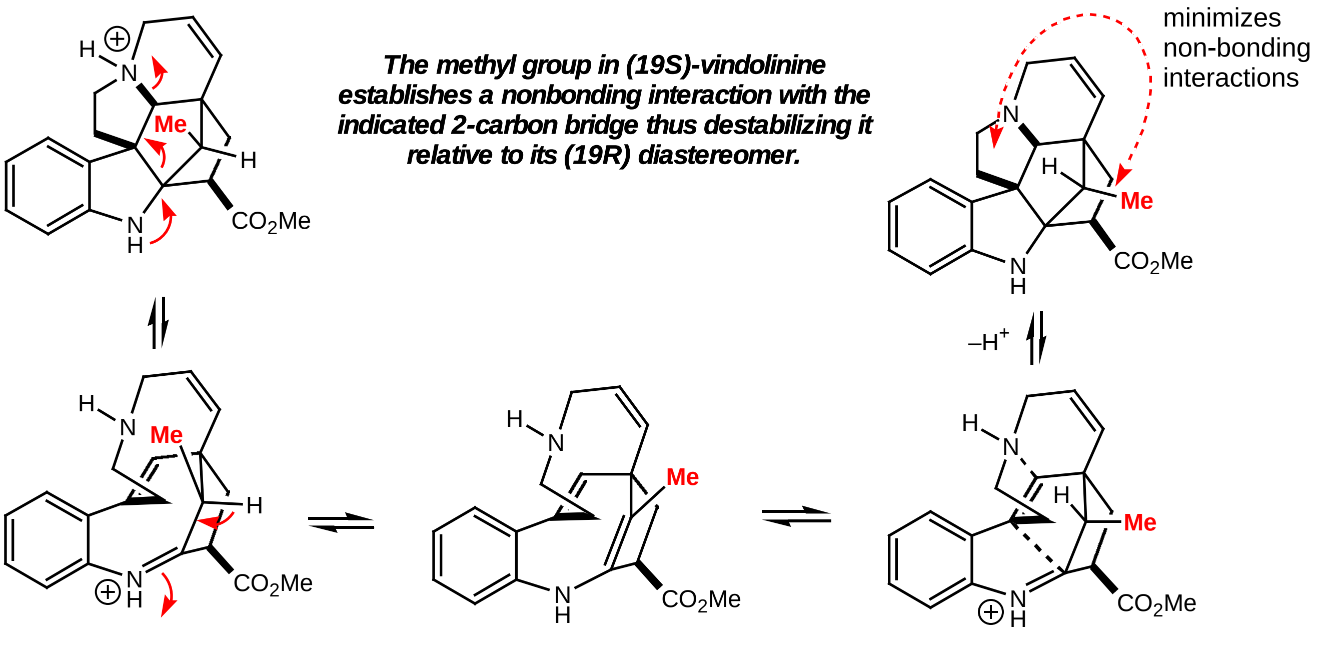
Question 5. (10 points). The indole alkaloid ***(19S)-***vindolinine readily isomerizes into its (***19R***) diastereomer under the influence of trace amounts of acid present in chloroform (Atta-ur-Rahman Z. ***Naturforsch*** **1986**, 386).





(19S)-vindolinine ***(19R)-vindolinine***

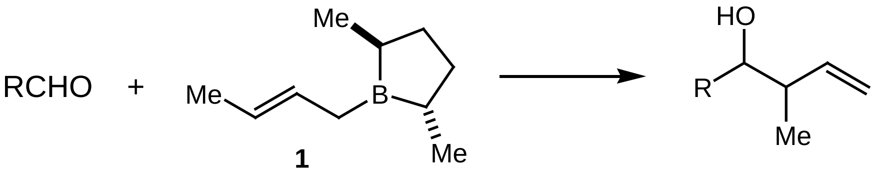
Provide a mechanism for this rearrangement in the space below. Explain why (19R) isomer is more stable than (19S).

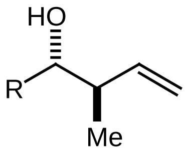


The methyl group in (19S)-vindolinine establishes a nonbonding interaction with the indicated 2-carbon bridge thus destabilizing it relative to its (19R) diastereomer.

minimizes
non-bonding
interactions

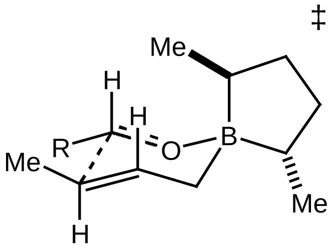
Question 6. (10 points). The C_2-symmetric allylborane **1** introduced by Masamune (*J. Org. Chem.* **1987**, *52*, 4831) has had an important impact on the design of chiral aldol and allylation catalysts.





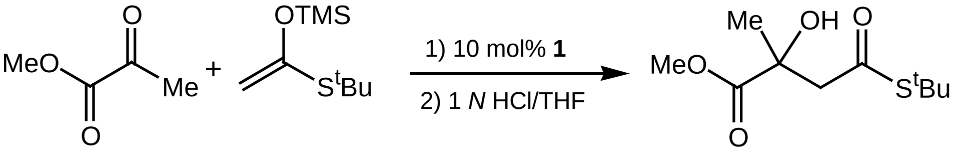
Box-1

Provide the absolute stereochemistry of the product of this reaction in **Box-1**.
Provide a 3-dimensional drawing of the transition state for this reaction in **Box-2**.

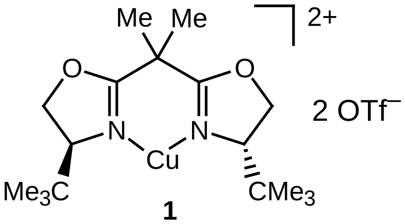


Box-2

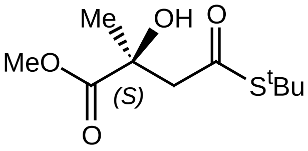
Question 7. (10 points). The C_2-symmetric cationic Cu(II) complex **1** is a chiral Lewis acid catalyst that exhibits good chelating potential. The utilization of **1** in the catalyzed Mukaiyama aldol addition is illustrated below (*JACS*, **1999**, *121*, 686).



99% ee, 95% yield

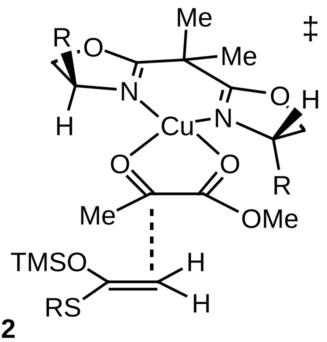


1



Box-1

(5 points)



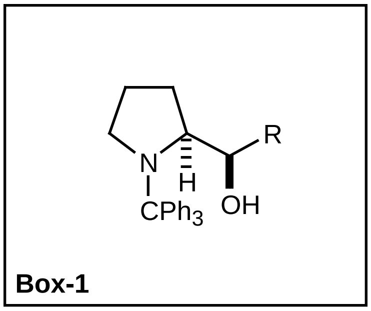
Box-2

(5 points)

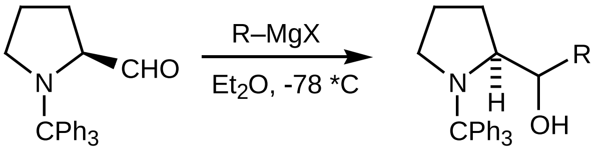
Provide the absolute stereochemistry of the product of this reaction in **Box-1**.
Provide a 3-dimensional drawing of the transition state for this reaction in **Box-2**.

Hint: Cu(II) complexes strongly prefer square-planar geometries

Question 8. (10 points). The illustrated stereoselective Grignard additions to trityl-protected prolinal have recently been reported (*JOC*, **2003**, *68*, 9747). These additions proceed with exceptional stereochemical control. A clue as to the operational mechanism for stereocontrol follows from the observation that the allylation product produced by Grignard addition has the same stereochemistry as the allylation product produced by the addition of allylsilane/BF_3•OEt_2.



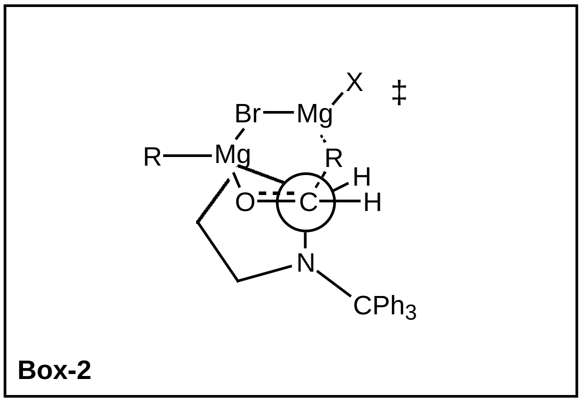
(5 points)



distereoselection >98:2

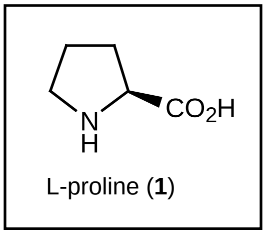
Please draw the absolute stereochemistry of the product in **Box-1**. In **Box-2** provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereoselection for this process. Briefly identify the transition state stereochemical control element(s) below.

Since these additions could operate by either a chelate-controlled or a Felkin-controlled process, the provided clue substantiates that Felkin control is operational and that the trityl-protected nitrogen does not participate in chelate organization. This is actually one of the points brough out in the paper. the transition structure should: A) adhere to the Felkin Model; B) should exhibit the bimetallic addition motif.

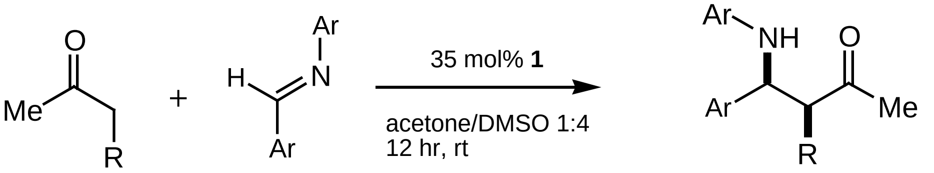


(5 points)

Question 9. (10 points). The illustrated proline-catalyzed Mannich reaction was recently reported by B. List (*JACS*, **2002**, *124*, 827). This reaction proceeds with exceptional stereochemical control.



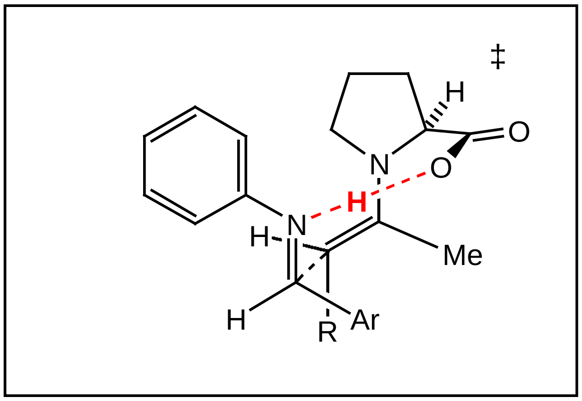
L-proline (**1**)



92 yield, dr >20:1, ee >99%

Provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereo and enantioselection for this process. Briefly identify the transition state stereochemical control elements.

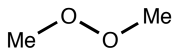
Transition state control elements include intramolecular H–bonding activation of the C=N bond. This interaction defines the reactive pi-face of the enamine C=C. The anti-imine geometry plus the H-bonding activation of the C=N lone pair establishes the reaction diastereoselectivity.

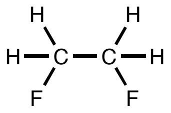


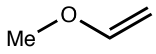
Problem Set 1 *Name*______________________

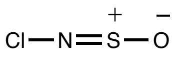
General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1. For each of the molecules shown below, hyperconjugative, rather than steric factors, dictate the geometry of the structure. Draw the most stable conformation or geometric isomer and clearly label all dominant hyperconjugative interactions (e.g. σ C–C ´ σ* C–O).



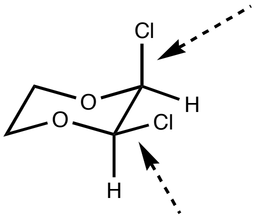






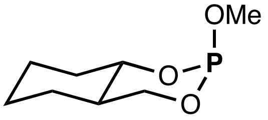
$$Cl-N=\overset{+}{S}-\overset{-}{O}$$

Question 2A. X-ray crystallographic analysis of the illustrated dichlorodioxane shows that the lengths of the 2 C-Cl bonds are different. One is 1.781Å while the other is 1.819 Å. Identify which C–Cl bond (axial or equatorial) should be the longer of the two. Explain the difference using FMO theory.

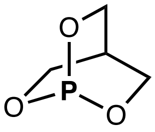


Question 2B. The three phosphites illustrated below exhibit a **750-fold span in reactivity** with a test electrophile (eq 1).

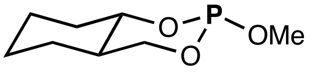
$$(RO)_3P \quad + \quad El(+) \longrightarrow (RO)_3\overset{+}{P}\text{–}El \qquad (1)$$



A



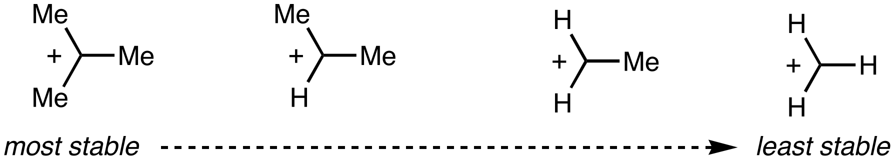
B



C

Rank the phosphites from the least to the most nucleophilic and provide a concise explanation for your predicted reactivity order.

Question 3. Carbonium ions are stabilized by alkyl substitution.

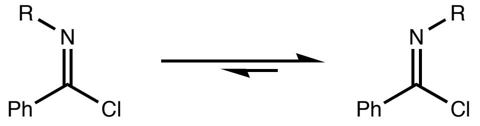


a. Using frontier MOs explain how increased alkyl substitution leads to the observed stability order.

b. Identify the interacting MOs.

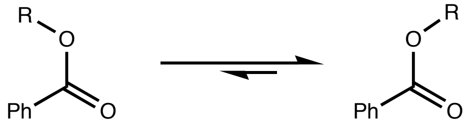
c. What is the stereoelectronic requirement for alkyl group stabilization?

Question 4. Based on your understanding of frontier molecular orbital theory, identify the dominant HOMO-LUMO (hyperconjugative) interaction which provides the critical stabilization for the major isomer in each instance.



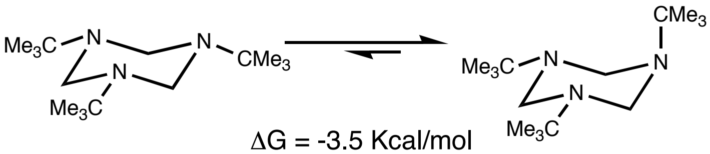
(E) (Z)

>99% at equilibrium



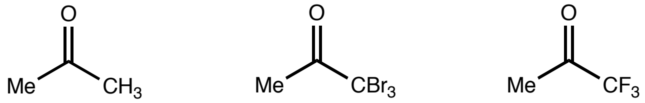
(E) (Z)

>99% at equilibrium



ΔG = -3.5 Kcal/mol

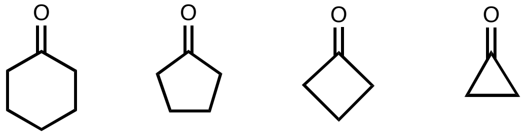
Question 5A. Increasingly electronegative substituents adjacent to the C=O group cause a high frequency shift of the IR C=O stretching frequency.



$\bar{\nu}_0$ (cm $^{-1}$) 1720 1750 1780

Identify the principal HOMO-LUMO interaction which you think might be responsible for this trend.

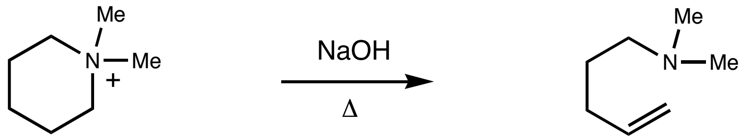
Question 5B. Ring strain dramatically affects the carbonyl infrared stretching frequency. Using FMO, show how increased ring strain might be responsible for an increased force constant for the C=O bond.



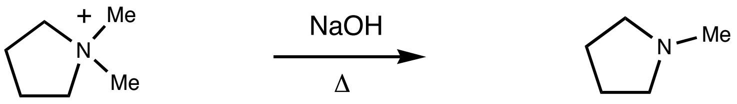
$\bar{\nu}_0$ (cm $^{-1}$) 1715 1745 1788 1813

Question 6. Explain the divergent reactivity of the following two quaternary ammonium salts:

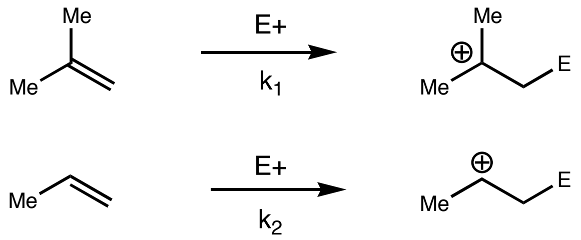
a)



b)



Question 7. Alkyl groups enhance the nucleophilicity of double bonds in reactions with electrophiles.

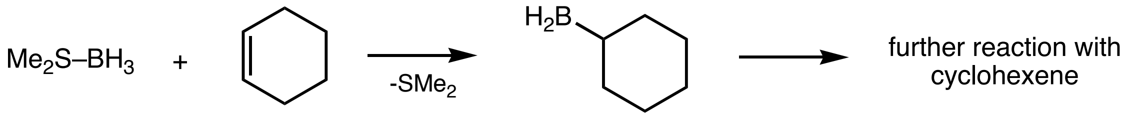


$k_1/k_2 = 2.5 \times 10^4$

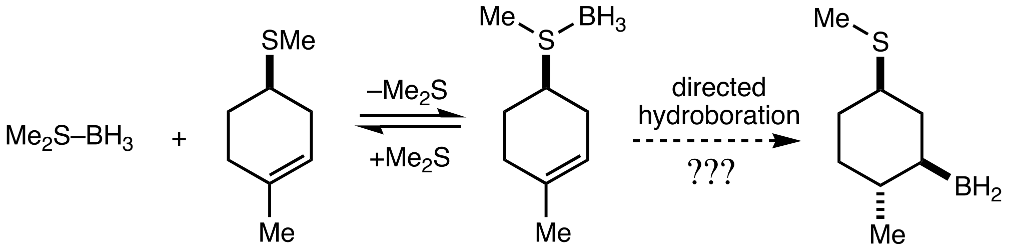
Part A. Identify and draw the principal orbital interaction that contributes to this observation.

Part B. Use orbital energy diagrams to explain why the interaction which you have identified causes an increase in nucleophilicity of C=C.

Question 8. The following is an idea that has been proposed to you by a fellow student. The proposal is based on the fact that borane–methyl sulfide complex is an effective hydroboration reagent (eq 1). It is proposed that allylic sulfides such as that illustrated below should be capable of "directing" the hydroboration process from this substituent through the borane-substrate complex.



(1)

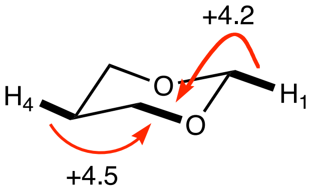


(2)

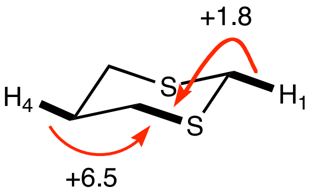
Part A. In order to begin your critique, you must possess a good working knowledge of the details of the hydroboration of olefins with borane–methyl sulfide. Provide a clear depiction of the transition state for the hydroboration process using ethylene as the olefinic substrate and borane–methyl sulfide as the hydroborating agent.

Part B. Now, based on your knowledge of the hydroboration reaction and the principles learned thus far in Chem 206, critique the idea proposed in Eq 2. You must concisely state the logic upon which you base your assessment. *Pictures speak a thousand words.*

Question 9. Natural bond order (NBO) analysis is a powerful computational tool that allows one to quantitatively estimate the energy of hyperconjugative effects. The stabilizing interactions for the H_1 and H_4 equatorial hydrogens for 1,3-dioxane and 1,3-dithiane are provided below. It is interesting that the two indicated hyperconjugative interactions in dioxane are approximately the same (4.5 vs 4.2) but that the same interactions in dithiane are quite different (6.5 vs 1.8). In fact, the authors refer to C–S bonds as "one directional" acceptor orbitals.



σC–H → σ^*C–O



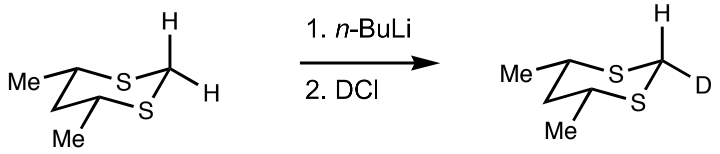
σC–H → σ^*C–S

numbers refer to interaction energies in kcal/mol at the B3LYP/6-31+G*** level

There is one quite reasonable qualitative argument that can rationalize the "one directional" character of σ^*C–S. Please provide your argument in the space provided below.

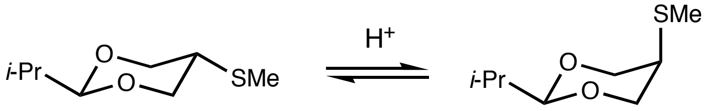
Problem 10. Many factors influence the reactivity and conformational bias of cyclic systems including steric, electronic, and stereoelectronic effects. For each of the following cases involving a six-membered heterocycle, provide a rationalization for the observed selectivity, including clear 3-dimensional representations where relevant.

Part A. Eliel and co-workers disclosed that the successive deprotonation of conformationally **1** and trapping with an electrophile occurs with high selectivity at the equatorial position.



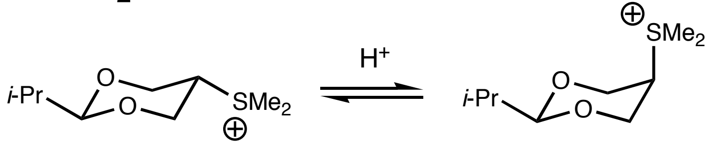
1

Part B. Eliel has also reported that the acid-catalyzed equilibrium of dioxane **2** favors the equatorial isomer, while the related equilibration of dioxane **3** prefers the axial isomer. Please provide a rationalization of these observations that is based on stereoelectronic arguments.



2

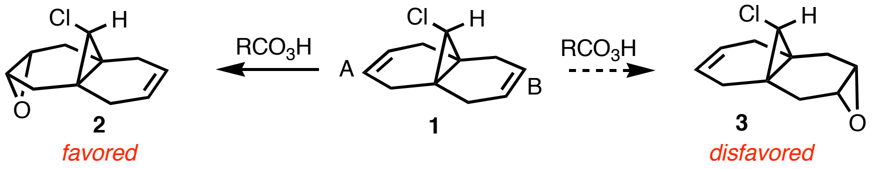
$\Delta G = +1.1$ kcal/mol



3

$\Delta G = -2$ kcal/mol

Problem 11. The following publication (*J. Org. Chem.* **1991**, *56,* 5553) reported the surprisingly selective olefin epoxidation illustrated below. In this reaction, olefin B in **1** was found to be much less reactive than olefin A.



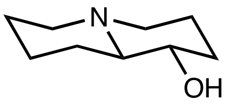
Using your knowlege of stereoelectronic effects, provide an explanation for the reduced reactivity of olefin B in diene **1**.

Chem 206 *Due: Friday, Sept. 29th*

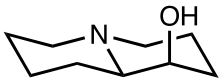
Problem Set 2: Conformational Analysis *Name:*__________________________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

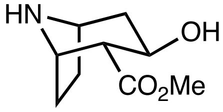
Question 1. The given below pairs of hydroxylated piperidines exhibit substential differences in pKa. These pKa differences could be attributed to stereoelectronic effects. Using FMO theory, provide an explanation that accounts for the different basicity of the diastereomeric piperidines below. Be sure to include 3D drawings to your explaination and clearly identify the interacting orbitals.



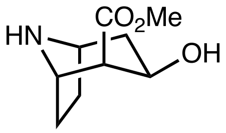
pKa 8.73



pKa 10.2



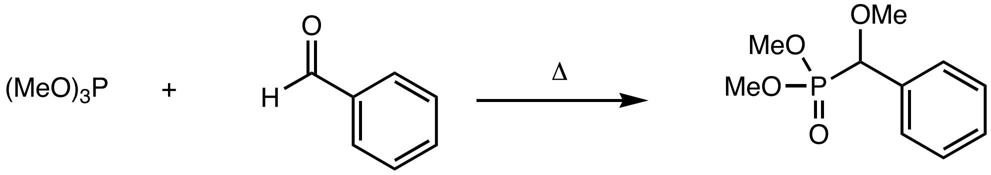
pKa 8.2



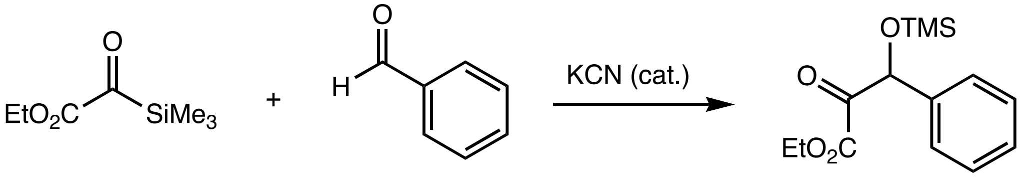
pKa 9.2

Question 2. For each of the following two transformations please provide a plausible reaction mechanism. Be sure to dicuss the relevant issues regarding orbital overlap requirements.

A.

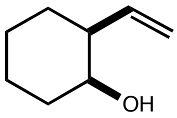


B.

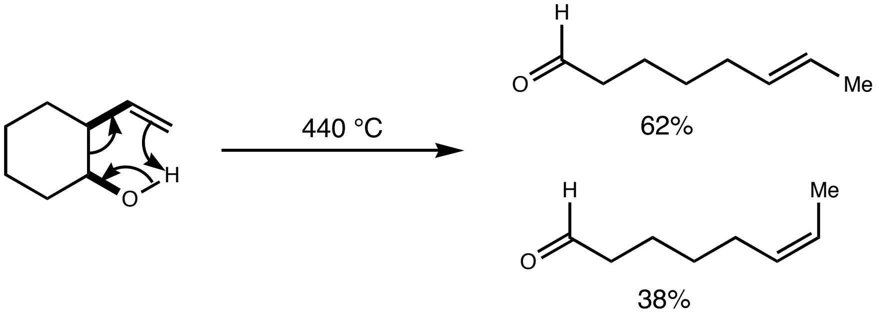


Question 3.

Part A. Draw the two chair conformers of the vinylcyclohexanol shown below. Based on A values, predict which of the two is the most stable.



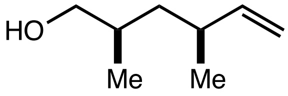
Part B. Vinylcyclohexanols undergo retro-ene reactions at high temperatures as shown below. Sketch out 3-D transition states leading to the two products.



Part C. Assuming A values are valid at 440 °C, can these be used to account for the product distribution? If not, can you think of another explanation?

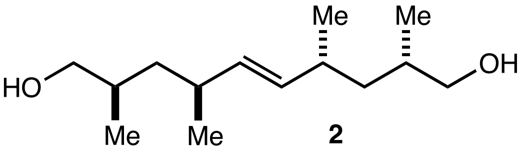
Question 4. The structural unit of β-turns is present in many proteins and bioactive peptides and has important implications for both structure and function. As such, the synthesis of β-turn mimics has been an intensive area of research. While most solutions to creating such turns have relied on covalent linkages, Hoffmann and coworkers have developed an approach based on acyclic conformational preferences (*Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1745-1747).

Part A. Please provide a clear 3-dimensional representation of the lowest energy conformer of **1**.

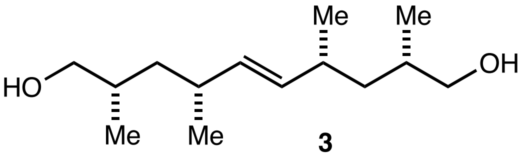


1

Part B. Based on your analysis of **1** please draw the low energy conformations of **2** and **3**, and comment on which structure you think could be used as a β-turn mimic. ***Note:*** A β-turn is a structural feature that creates a U-turn in a peptide, bringing the termini into proximity.

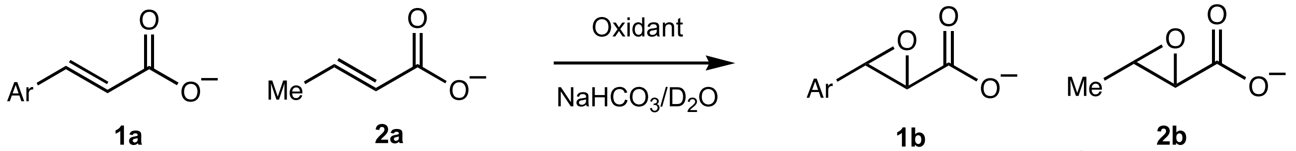


2

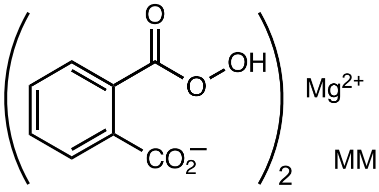


3

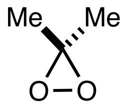
Question 5. The following epoxidation studies performed in aqeous medium have been reported by Breslow and Biscoe. It was noted that cinnamates **1a** have similar epoxidation rate as crotonates **2a** if MMPP is used for epoxidation. However, the oxidation of styrenes **1a** is faster if dimethyldioxyrane (DMDO) and oxaziridinium **3** are used as epoxidizing agents.



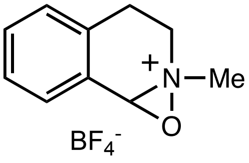
Ar	MMPP (**1b**:**2b**)	DMDO (**1b**:**2b**)	Oxaziridinium **3** (**1b**:**2b**)
p-CF_3Ph	16:84	22:78	92.7:7.3
Ph	44:56	61:39	96.5:3.5
2-Naphthyl	47:53	68:32	99.8:3.2



MMPP



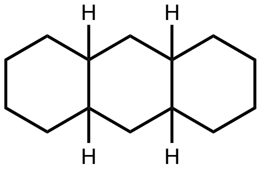
DMDO



3

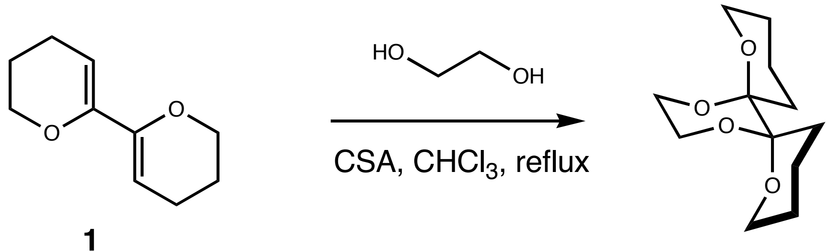
Using 3D drawings of the epoxidation transition states, eplain why oxaziridinium **3** shows the highest selectivity for the cinnamic acid epoxidation and MMPP--the lowest.

Question 6. Draw all possible diastereomers of this tricyclic ring system in 2D and 3D. Based on your 3D drawings, rank each structure in terms of energy. Clearly identify all gauche-butane and syn-pentane interactions.



2D Structure	**Corresponding 3D Structure**

Question 7. The dispiroketal (Dispoke) protecting group is of great utility for the selective protection of 1,2-diols. Provide a 3-D representation of the expected product for the acid-catalyzed reaction of *bis*-dihydropyran **1** with ethylene glycol.

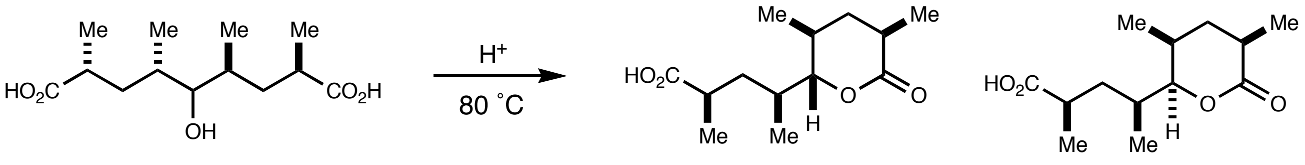


1

aa/aa

Question 8.

Part A. Rationalize the selectivity observed in the following thermodynamic cyclization:

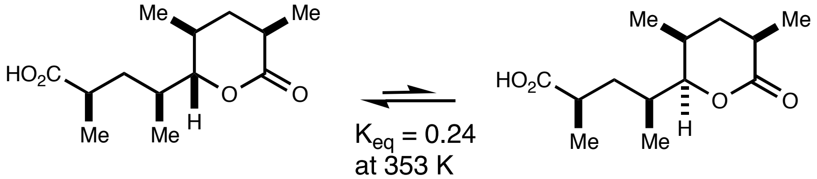


A/B =4.2:1

A

B

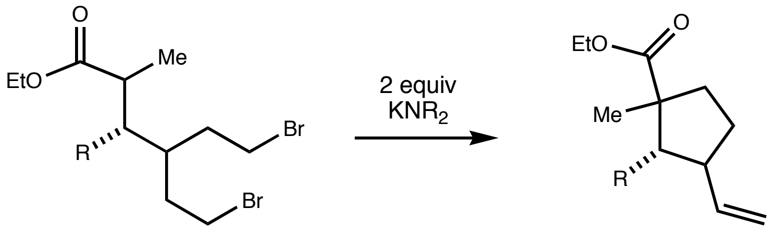
Part B. Assuming that equilibration between **A** and **B** is complete, calculate the energy difference between **A** and **B**.



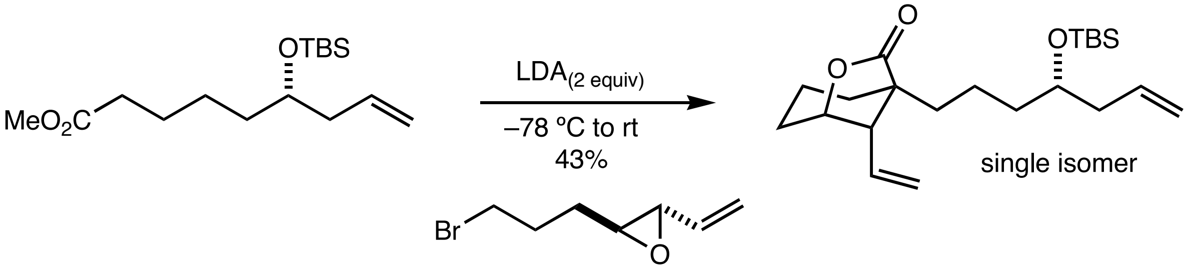
A

B

Question 9. Two new stereocenters have been generated in the illustrated transformation shown below. Based on your knowledge of conformational analysis, provide a mechanism for this transformation that predicts the stereochemistry of the product.



Question 10. The following cascade alkylation was employed by Stork and coworkers during their synthesis of histrionicotoxin alkoloids. Please propose a mechanism with clear 3D drawings that accounts for the formation of the indicated product and explains the diastereoselectivity.



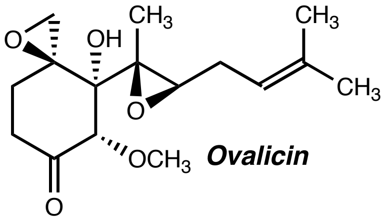
Chem 206 *Due: Wednesday, Dec. 13*

Problem Set 10

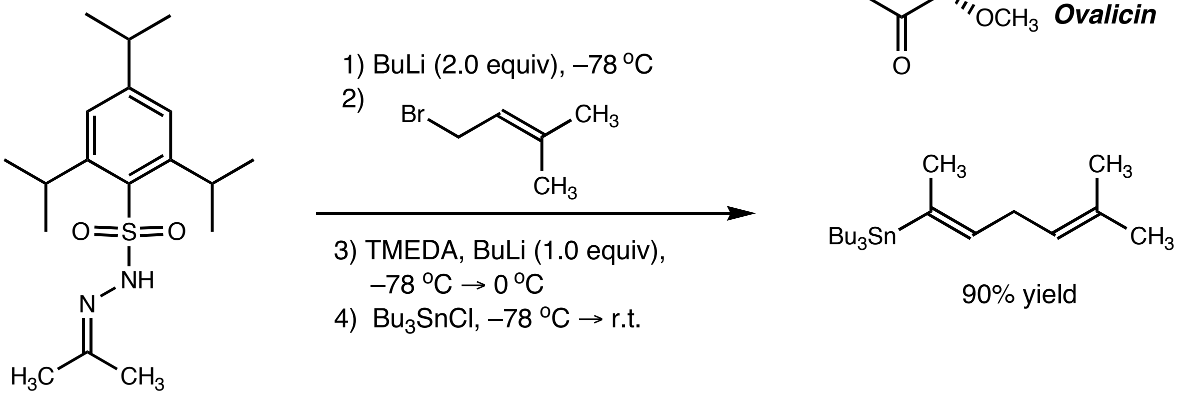
Name:______________ TF:_______________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1. Corey's synthesis of ovalicin required the use of the vinylstannane below as a coupling fragment. This fragment was synthesized from acetone trisyl hydrazone. Please provide a mechanism for this sequence of steps.



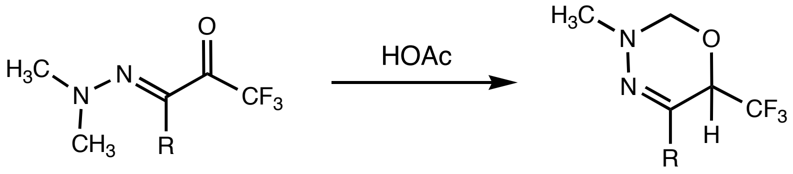
Ovalicin



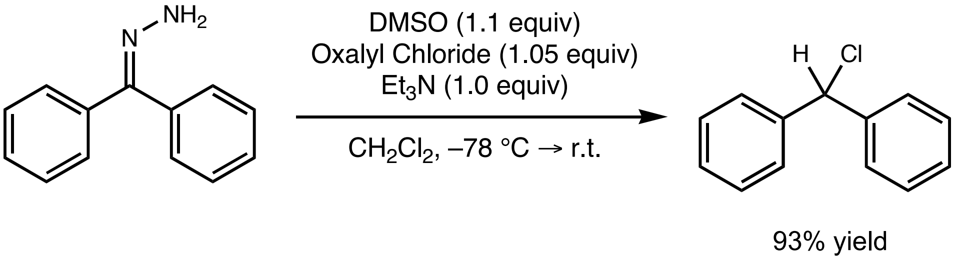
O=S=O
NH
N
H_3C
CH_3
1) BuLi (2.0 equiv), –78 °C
2)
Br
CH_3
CH_3
3) TMEDA, BuLi (1.0 equiv), –78 °C → 0 °C
4) Bu_3SnCl, –78 °C → r.t.
CH_3
CH_3
Bu_3Sn
CH_3

90% yield

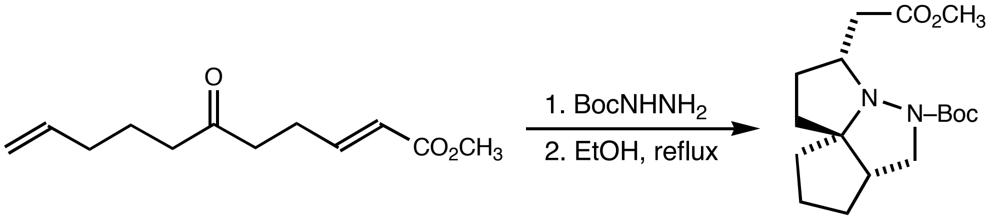
Question 2. Kamitori and coworkers have reported the acid catalyzed cyclization illustrated below. Provide a reasonable mechanism for this transformation.



Question 3. The interesting functional group interconversion depicted below was recently published by Matthias Brewer. Provide a mechanism for this transformation. Note that DMSO and oxalyl chloride are first mixed together and that hydrazone and triethylamine are added once gas evolution has ceased.



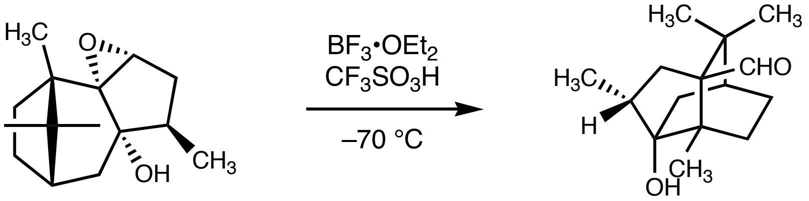
Question 4. A recent paper by Dolle highlights the rapidity with which one may assemble complex architecture in a single chemical operation. The transformation in question is illustrated below.



75% yield, one diastereomer

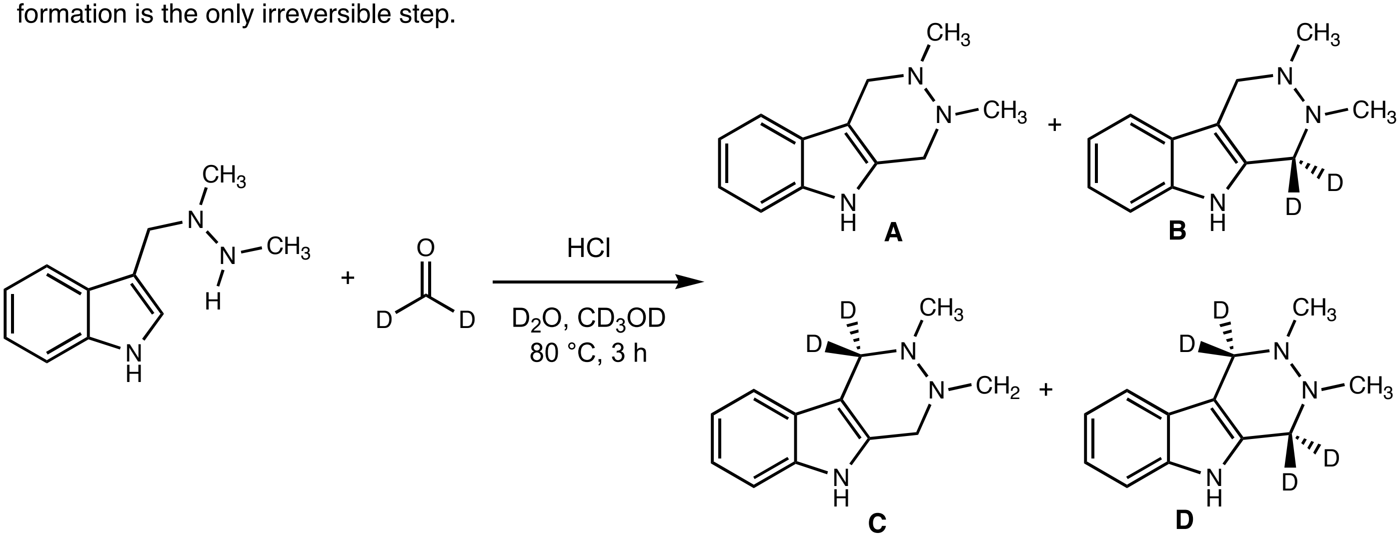
Provide a concise mechanism for the indicated transformation. In that step where the complex stereochemical relationships are established, a carefully rendered three dimensional illustration is requested.

Question 5. Using clear 3D representations, provide a mechanism for the transformation below.



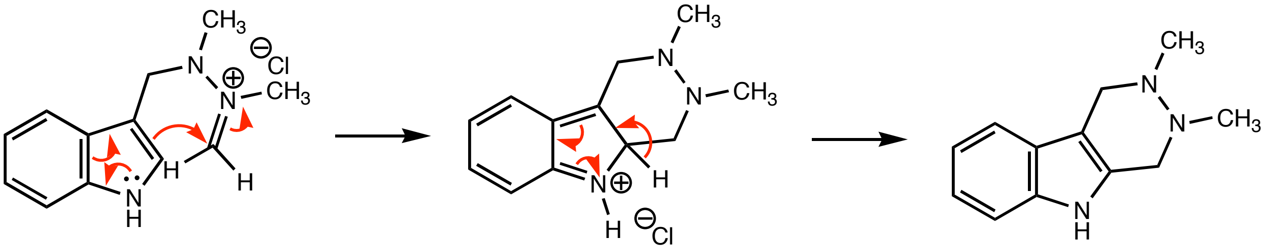
Question 6. The experiment depicted below was conducted in order to determine whether or not a spirocyclic intermediate is en route to product in the Pictet-Spengler reaction.

Part A. Provide a mechanism that accounts for the observed labelling pattern of the products. Assume that product formation is the only irreversible step.

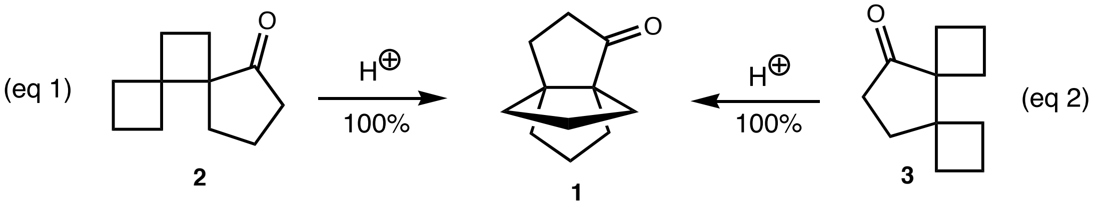


A : **B** : **C** : **D** ~ 1 : 1 : 1 : 1

Part B. Bailey concluded that the above experiment was proof that a spirocycle was involved in the pathway leading to product formation in the Pictet-Spengler reaction. However, he does note that the experiment does not rule out a mechanism where product formation occurs via direct attack of the indole 2-position on the iminium ion as shown below (i.e. the pathway leading from starting material to product does not include a spirocycle)? Explain why this is in fact the case.

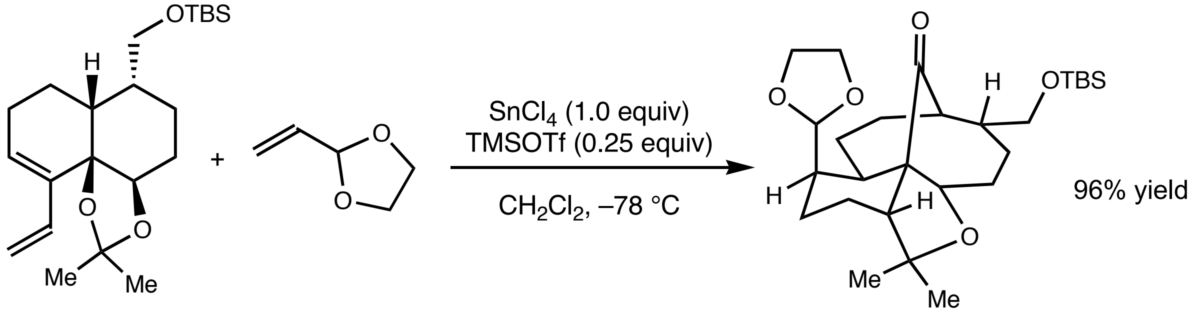


Question 7. Fitjer and co-workers have reported a very interesting approach to the [3,3,3]propellane **1**. This tricyclic ketone may be produced in quantitative yield through acid-catalyzed rearrangement of ketones **2** or **3**.

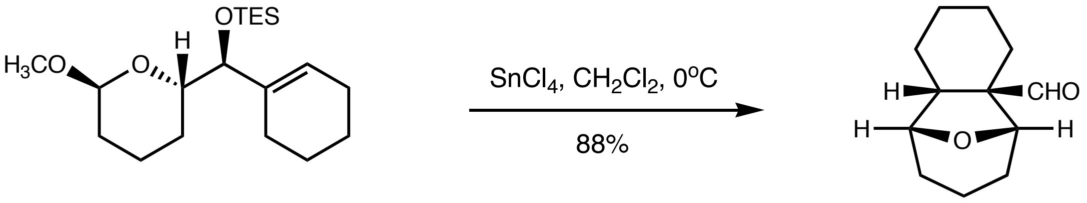


Please provide a plausible mechanism for the rearrangement **2→1** (eq 1). Use 3-dimensional representations where appropriate to illustrate your answer.

Question 8. Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones. Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.



Question 9. Using clear 3D representations, provide a mechanism for the transformation below.



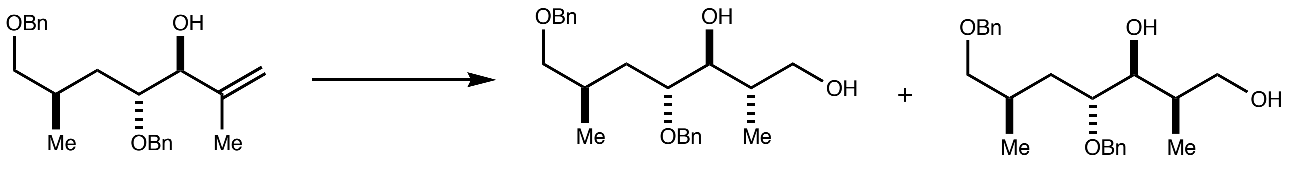
Chem 206 Due: Friday, Oct. 6

Problem Set 3

Name:____________________TF:_______________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

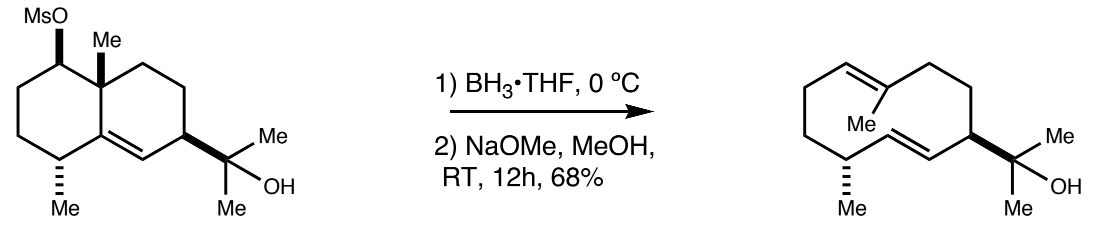
Question 1. Rationalize the following outcome of the two hydroboration reactions shown below.

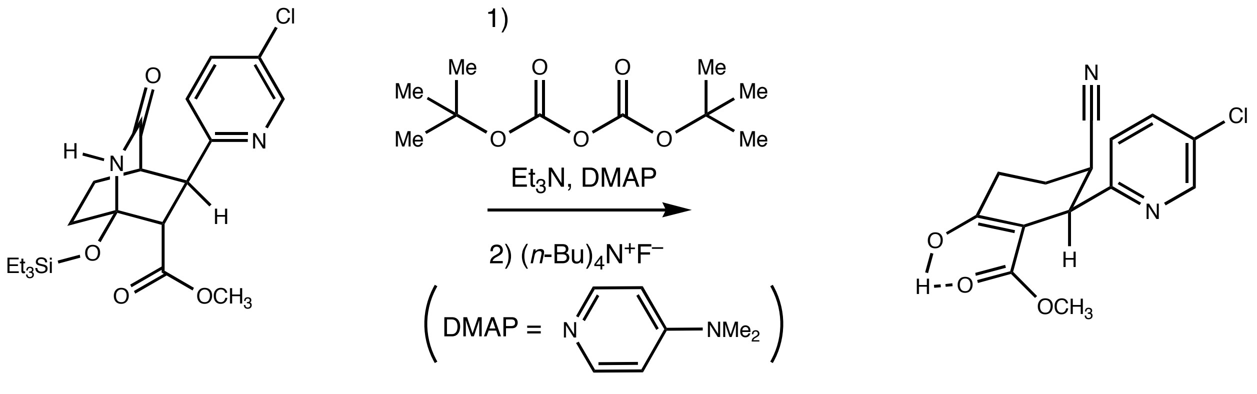


anti *syn*

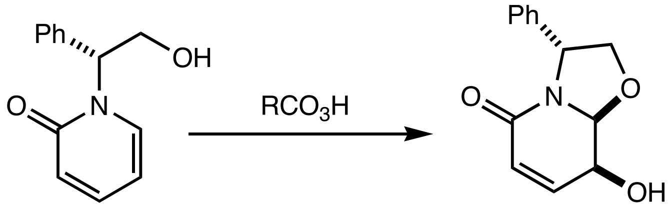
	anti : syn	yield
9-BBN	82 : 18	70%
BH3•THF	16 : 84	84%

Question 2. Please provide the mechanisms with clear 3D drawing that expain the products of the following reactions:



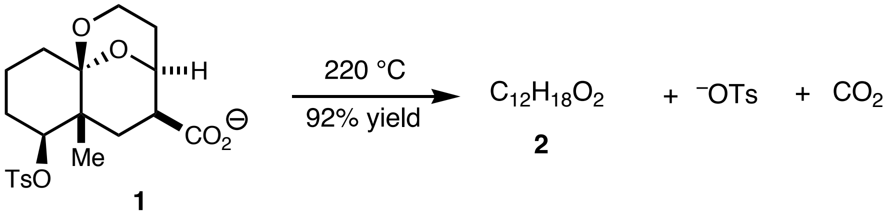


Question 3. Provide a mechanism for the following reaction which is consistent with the product stereochemistry. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.



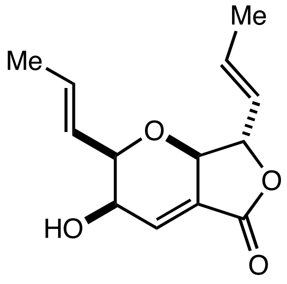
Question 4. Carboxylate **1** undergoes a complex fragmentation-decarboxylation cascade upon heating to 220 °C. The product **2**, $C_{13}H_{20}O_2$, contains two double bonds and an ester/lactone moiety based on IR and NMR data.

Predict the structure of **2** including the stereochemistry of both double bonds. Identify the stereoelectronic requirements that must be met in this transformation.

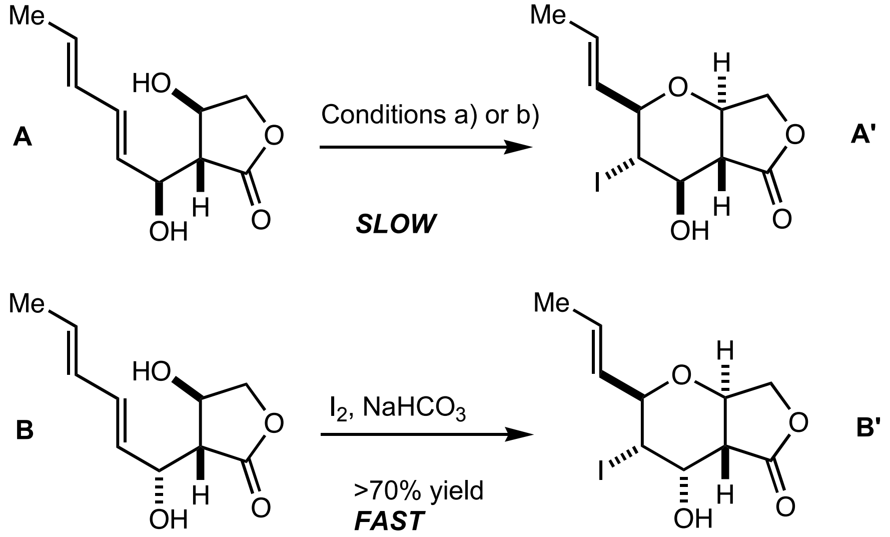


1

Question 5. During the synthesis of the anti-tumor agent Waol A, Snider (*Org. Lett*. **2003**; 5(4); 451-454) and coworkers prepared the diastereomeric aldol adducts **A** and **B**. These substrates underwent iodoetherification at vastly different rates. In fact, to achieve sufficient conversion a more reactive iodonium reagent (bis(sym-collididne) AgPF$_6$) was necessary. *Please provide a mechanism for the reactions (**A** to **A'** and **B** to **B'**) that accounts for the observed selectivity and difference in rate. 3-dimensional representations are required.*



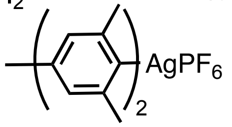
Waol A (FD-211)



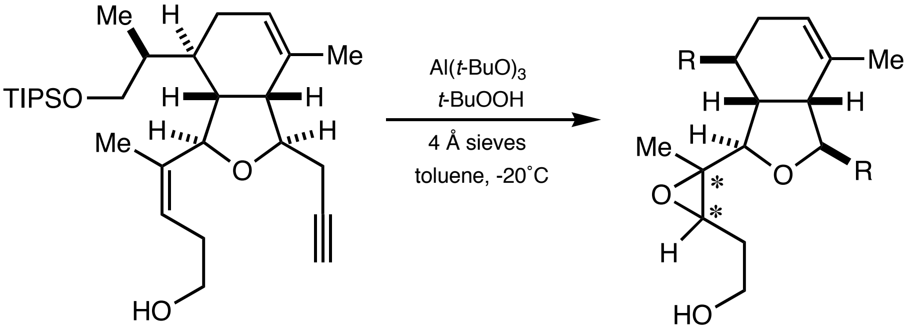
Conditions:

a) I$_2$, NaHCO$_3$ = 5% conv

b) I$_2$ = 88% yield



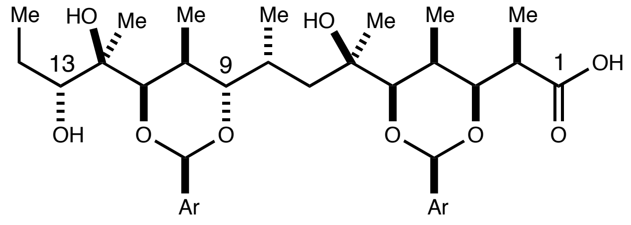
Question 6. Overman and co-workers recently reported the indicated selective epoxidation in conjunction with a synthesis of briarellins A and E, a new family of diterpenes**.** It should be noted that the $Al(t\text{-}BuO)_3$/(t)-BuOOH reagent system is both highly diastereoselective and site selective. It is also relevant to the mechanism of the reaction that the ring-trisubstituted olefin lacking an allylic oxygen substituent would normally be more prone to epoxidation with a peracid than the acyclic trisubstituted olefin.



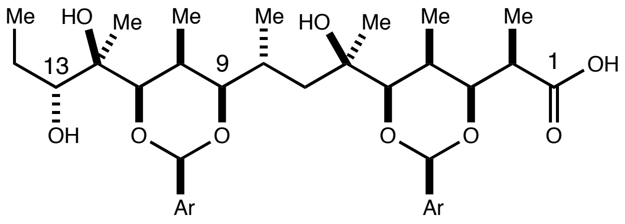
Part A. Provide a general mechanism illustrating how the $Al(t\text{-}BuO)_3$/(t)-BuOOH reagent epoxidizes olefins (see Sharpless V^{5+} epoxidation). Three-dimensional drawings are recommended.

Part B. Provide a general mechanism illustrating how the above epoxidation proceeds and provide the stereochemistry (*) of the product epoxide along with a stereochemical analysis of the noted face selectivity.

Question 7. Woodward's synthesis of erythromycin uncovered an interesting relationship between the configuration at C9 and the facility of macrolactonization with the C13 hydroxyl (In the natural product C9 is a ketone). Draw the lowest energy conformation of the C8-C13 region of both diastereomers, and determine why compounds of the 9(S) configuration readily cyclize while those of the 9(R) configuration do not.



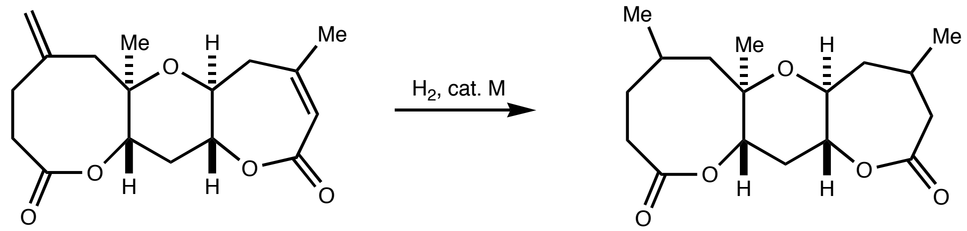
9(S) - macrolactonization possible



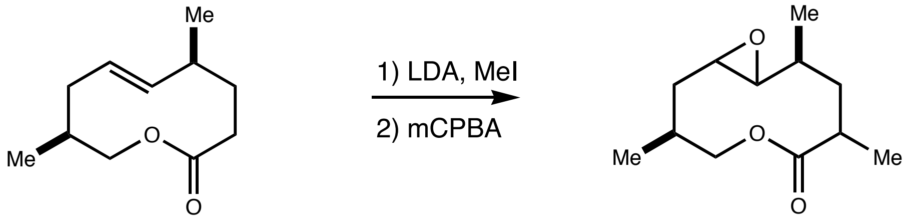
9(R) - macrolactonization impossible

Question 8.

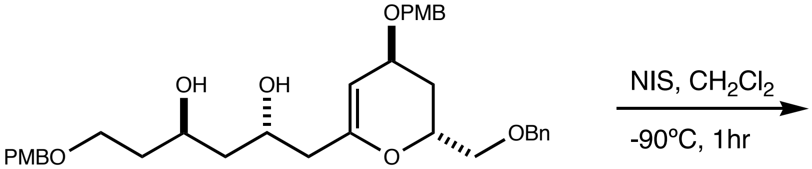
Part A. Predict the major diastereomer obtained from the following reduction assuming that the ground-state conformation is translated into the transition state one without changes:



Part B. Identify the correct diastereomer obtained from the following sequence:

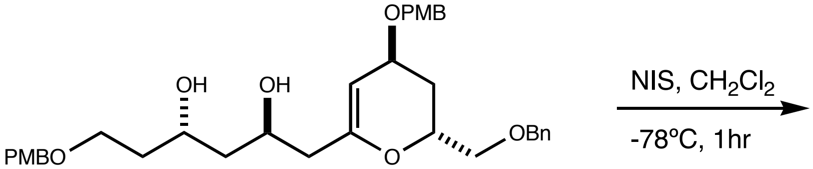


Question 9. Provide three-dimensional representations of the major diastereomeric addcuts arising from the following **kinetic** iodo-spiroketalizations of diols **1** and **2**. Be sure to provide an explanation for the observed diastereoselectivities in each case.



1

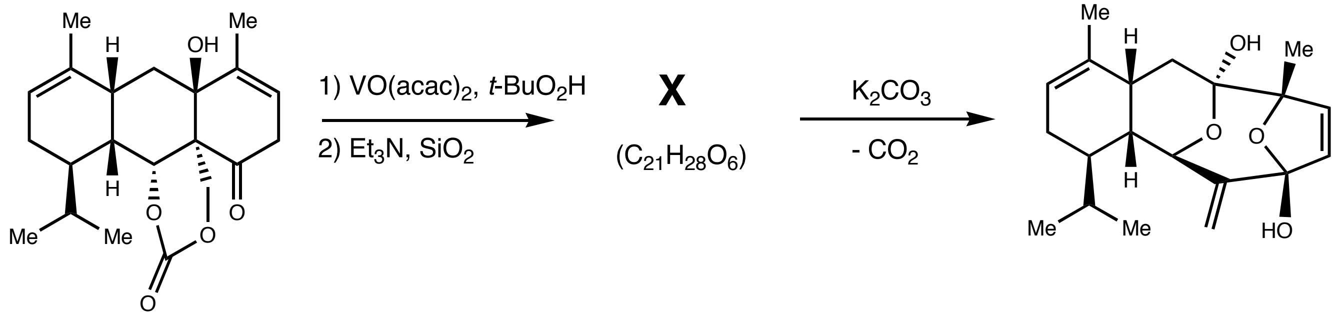
8:1 diastereoselectivity



2

single diastereomer

Question 10. Please provide a mechanism for the following transformation, including a three-dimensional representation of intermediate **X**.

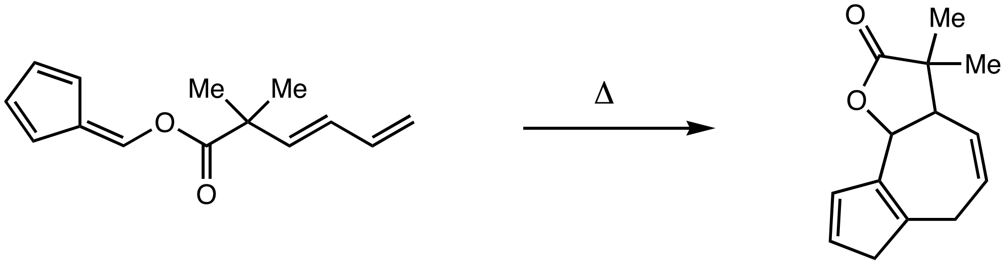


Chem 206 *Due: Friday, Oct. 20*

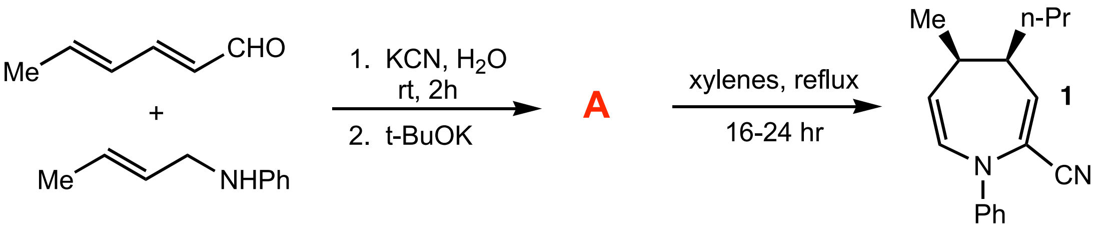
Problem Set 4 *Name:________________TF:___________*

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

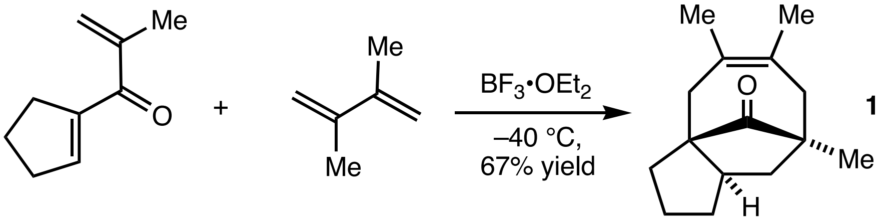
Question 1. Provide a mechanism for the following transformation with clear representation of FMO and Dewar-Zimmerman analysis. Be sure to label any pericyclic processes. Also, assign the expected relative stereochemistry in the product.



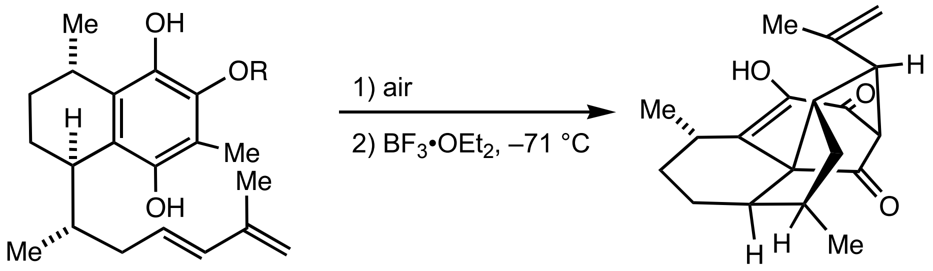
Question 2. The indicated three-step process leads to the production of enamine **1**. Propose a mechanism for the overall transformation that includes the structure of intermediate **A**. Be sure to label any pericyclic processes.



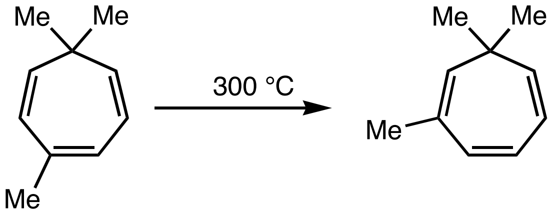
Question 3. Please provide a concise mechanism with FMO analysis for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer. Be sure to label any pericyclic processes.



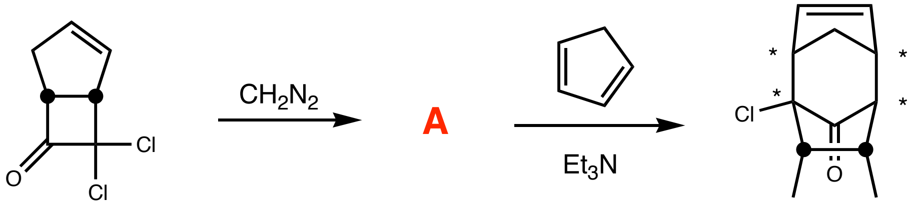
Question 4. Provide a mechanism for this transformation. Determine whether the reaction might be concerted. Also, carry out the relevant FMO analysis. Be sure to label any pericyclic processes.



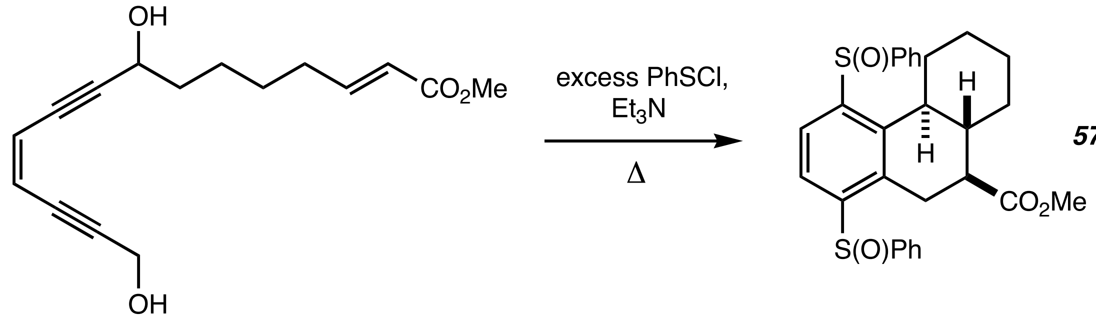
Question 5. Provide a rationalization of these results with brief FMO analysis. Be sure to label any pericyclic processes. Three-dimensional drawings are recommended.



Question 6. Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product. Be sure to label any pericyclic processes.

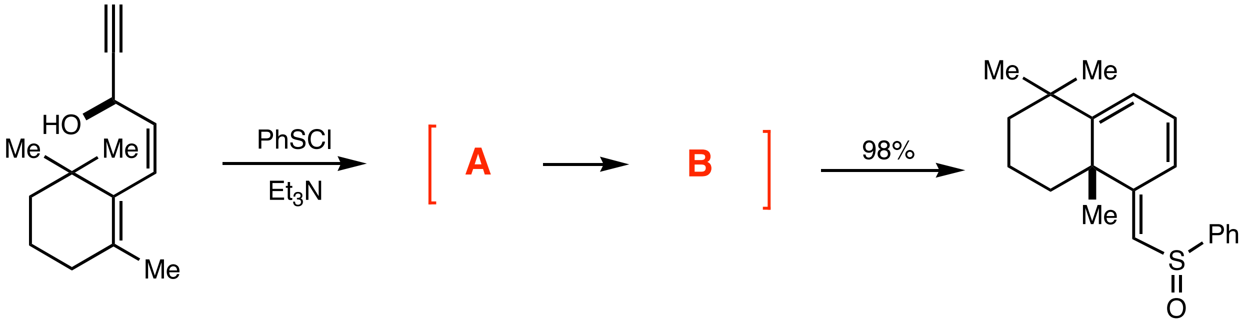


Question 7. In the space below please provide a detailed mechanism for this reaction. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.

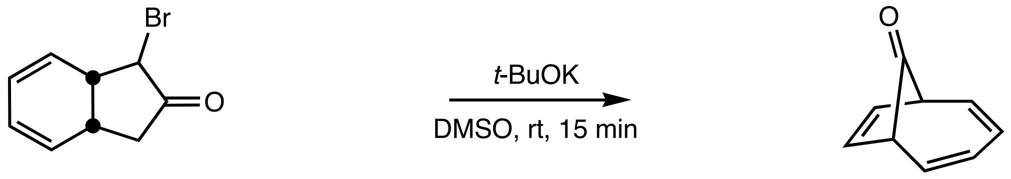


57% yield

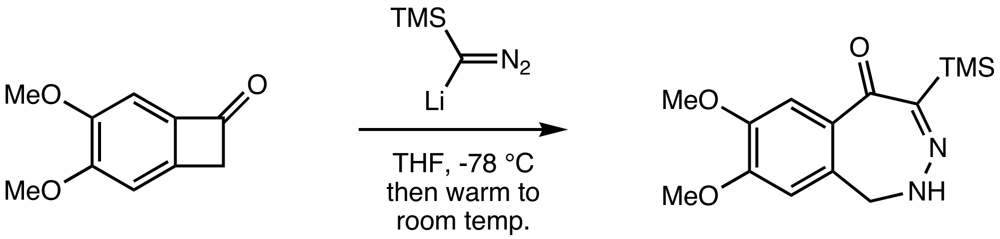
Question 8. Provide a mechanism for the following transformation. Identify **A** and **B** in your reaction sequence.
Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.



Question 9. In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.



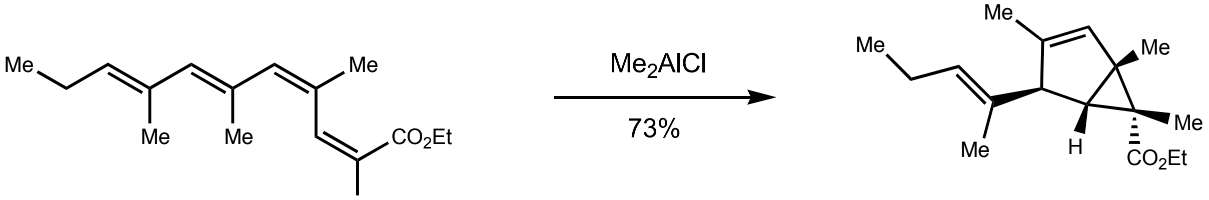
Question 10. In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.



Problem Set 5 Name:_______________ TF:__________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

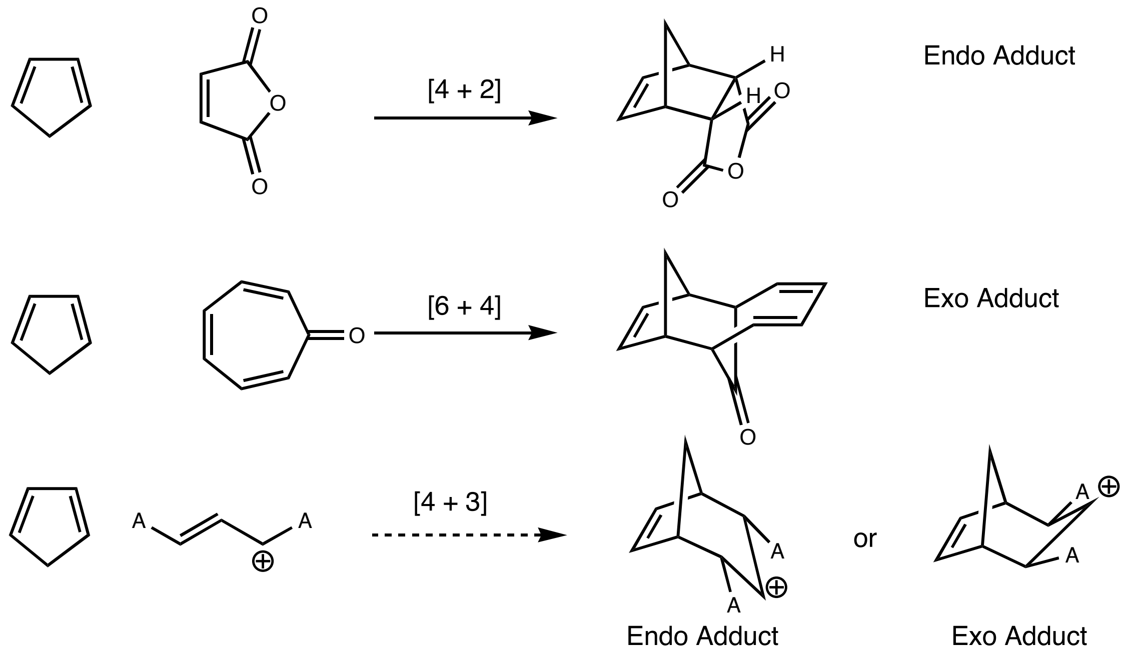
Question 1. As it has been disclosed byTrauner *et al*, the following transformation is possible under Lewis Acid catalysis conditions. To explain the formation of the product, authors propose that this transformation could be either concerted or stepwise.



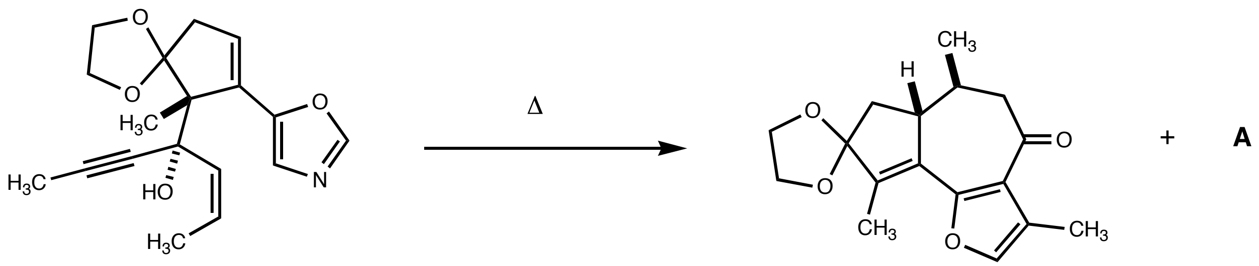
Only Isomer

Please provide one stepwise and one concerted mechanism that would account for the stereochemistry of the product. Please, label and classify all of the pericyclic processes involved. Using the FMO analysis predict whether the proposed concerted mechanism is allowed.

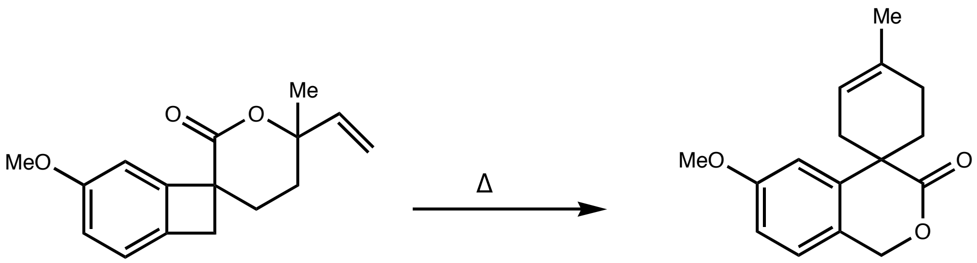
Question 2. While the Dewar-Zimmerman, Woodward-Hoffman and Frontier Molecular Orbital theory are quite good at predicting which cycloadditions are allowed and which are forbidden, only FMO theory is able to explain some observed phenomena. For example, when cyclopentadiene reacts with maleic anhydride, the predominant mode of additions is endo, as shown below. When cyclopentadiene reacts with tropanone, the predominant mode of addition is exo, also shown below. Please rationalize this selectivity using FMO theory. What mode of addition would you expect for the allyl cation plus cyclopentadiene?



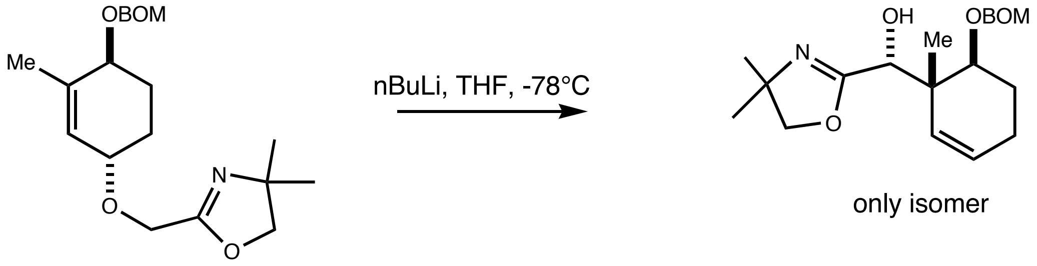
Question 3. Propose a mechanism for the following transformation. Note that in addition to the product shown, a stoichiometric amount of **A** is formed. What is **A**?



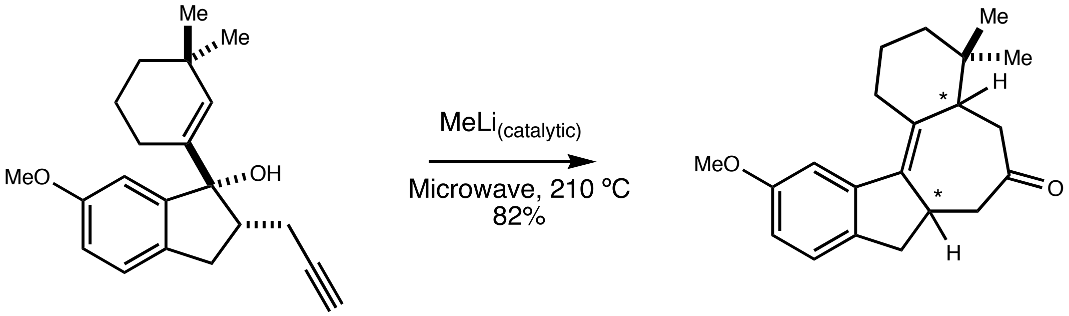
Question 4. Give a mechanism for this transformation labeling all pericyclic reactions.



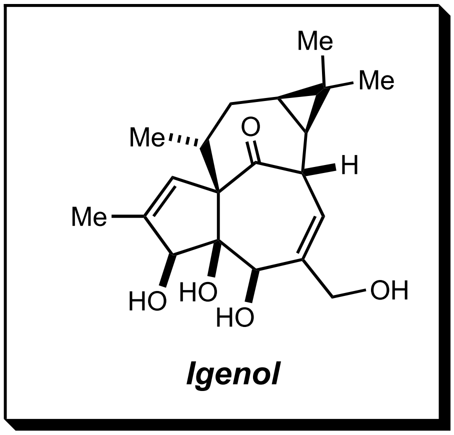
Question 5. Provide a mechanism for this transformation and explain the observed diastereoselectivity using clear, 3D transition state drawings.

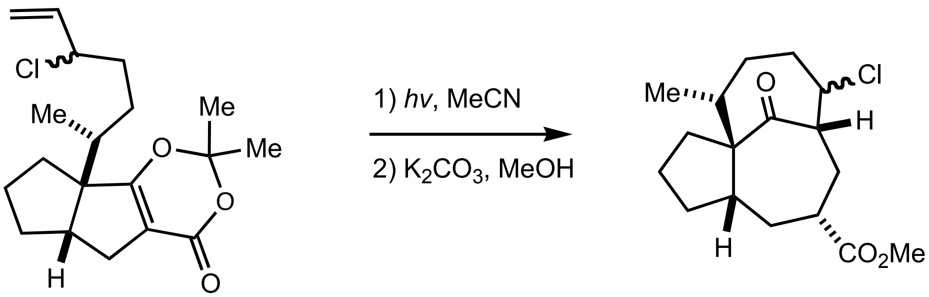


Question 6. The illustrated below transformation was recently developed by Ovaska Coworkers. Using *clear 3D drawings* provide a mechanism for this transformation and predict the stereochemistry of the product.

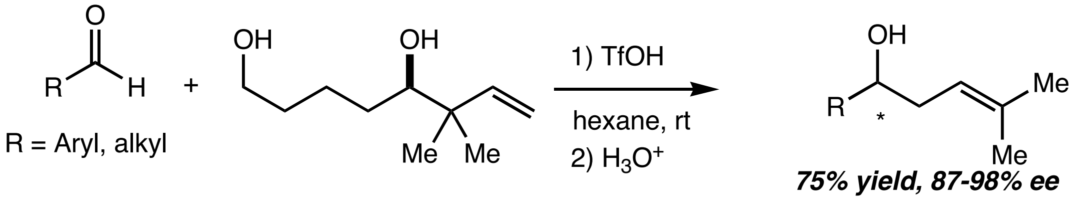


Question 7. The following reaction sequence was excecuted to construct the core of Ingenol by Winkler and Coworkers. Provide the mechanism of the indicated transformation below using clear 3D drawings. Explain the diastereoselectivity of this reaction.



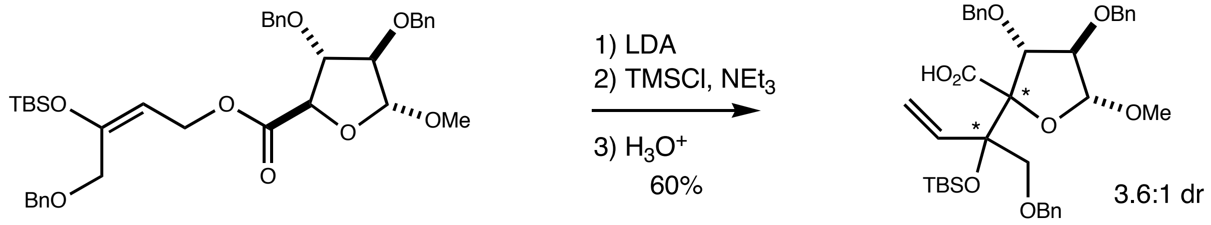


Question 8. The prenyl group is an essential unit in the biosynthesis of terpene natural products. Due to the large number of natural products that contain this moiety, methods for its selective introduction into molecules are highly useful. Loh and Cheng have descibed a general regioselective and highly enantioselective prenylation of aldehydes, as shown below.



Please provide a general mechanism for this interesting reaction and using clear three-dimensional drawings predict the absolute stereochemical outcome.

Question 9. The following transformation has been recently employed during the total synthesis of Zaragozic Acid C. Using clear 3D drawings provide the mechanism for this reaction sequence and predict the stereochemistry of the major diastereomer of the product.



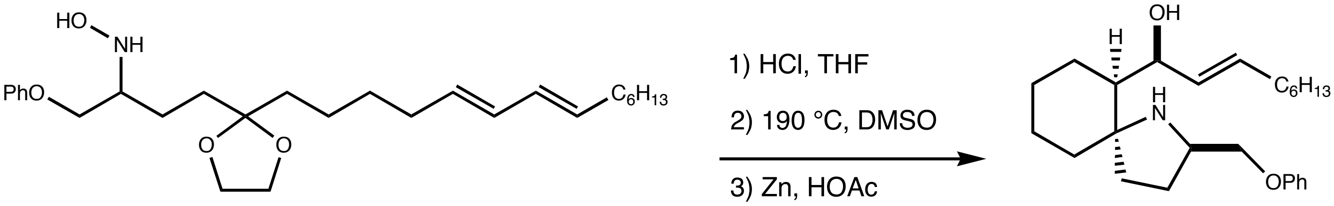
Problem Set 6

Name:____________ TF: ____________

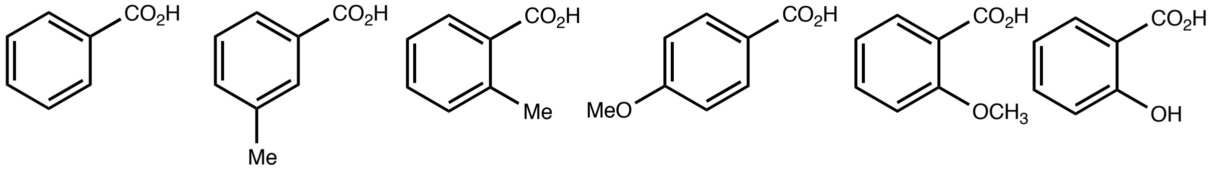
General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate. CLASSIFY ALL PERICYCLIC REACTIONS.

Question 1.

In the Weinreb synthesis of the proposed structure of lepadiformine the following synthetic sequence was executed. Please provide a mechanism and clear 3-D depictions of all relevant intermediates that explains the stereochemical outcome of the reaction.



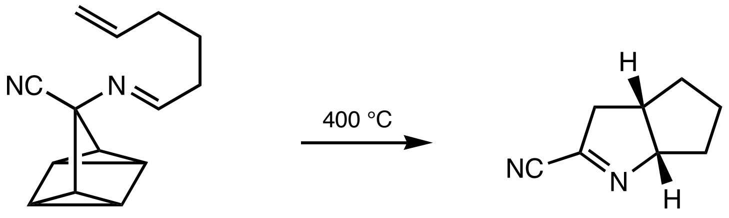
Question 2. For the set of carboxylic acids shown below, briefly rationalize the given pKa's.



pK_a 4.20 4.24 3.91 4.47 3.85 2.97

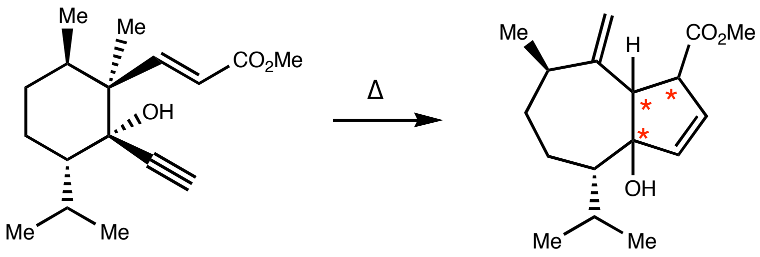
Question 3.

Hoffmann has reported the mechanistically interesting thermally induced transformation illustrated below



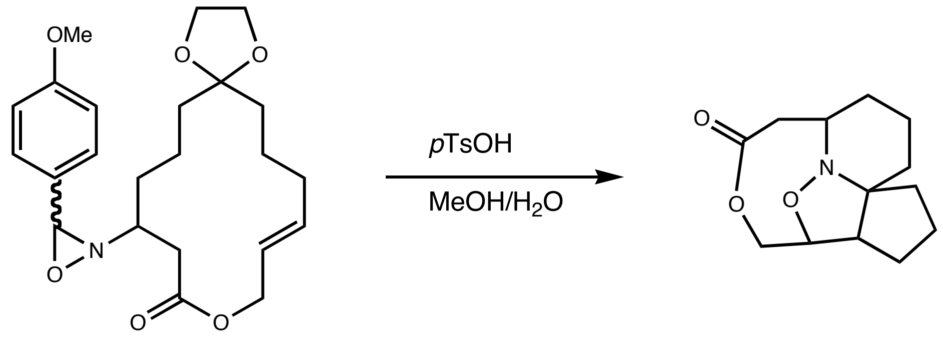
Provide a plausible mechanism for this reaction.

Question 4. Provide a mechanism that predicts the observed stereochemistry at the starred (*) carbon atoms. Draw the starting material, each intermediate, and the product clearly in 3D.



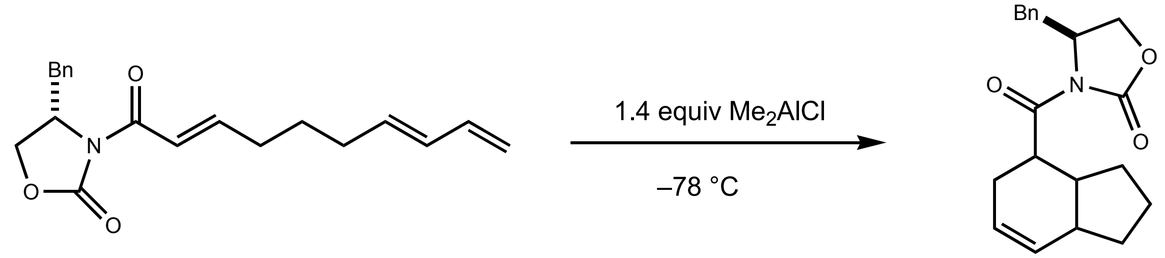
Question 5.

Please provide a mechanism for the following transformation and predict the stereochemistry of the product.



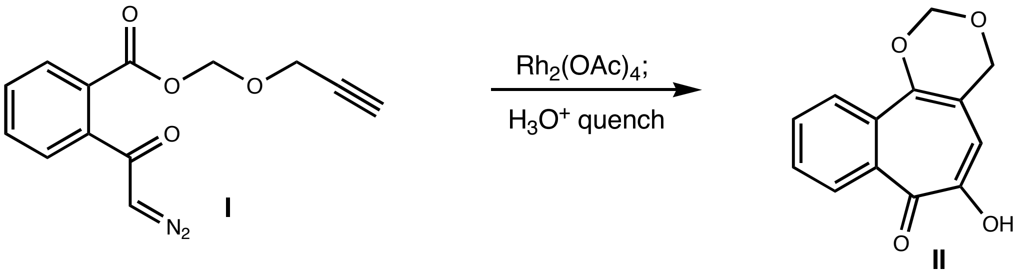
Question 6.

Provide a mechanism, including a clear 3-dimensional depiction of the transition state, which predicts the major product diastereomer for the following intramolecular Diels-Alder reaction.

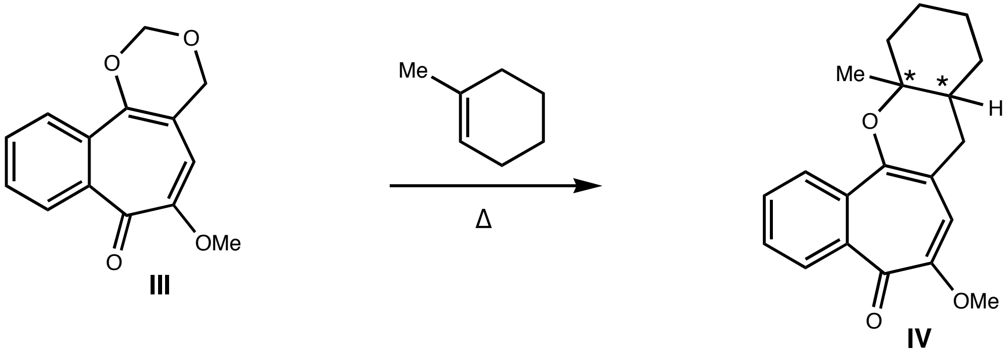


Question 7. This question is taken from recent work reported by Jack Baldwin.

Part A. Provide a mechanism for the conversion of **I** to **II**.



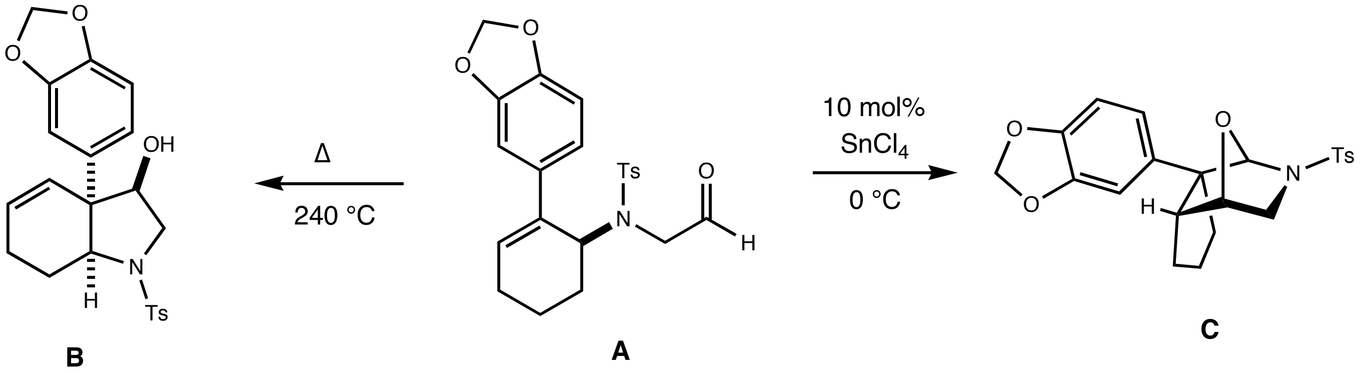
Part B. Compound **II** is protected as its methyl ether **III** and then transformed to **IV**. Provide a mechanism for the conversion of **III** to **IV**. Predict the relative stereochemistry at the starred (*) carbon atoms.



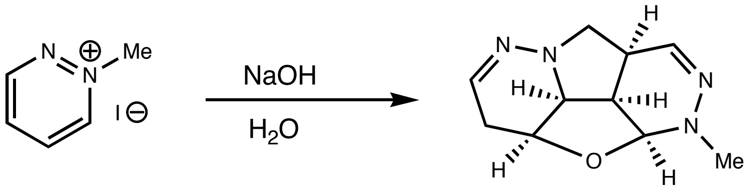
III

IV

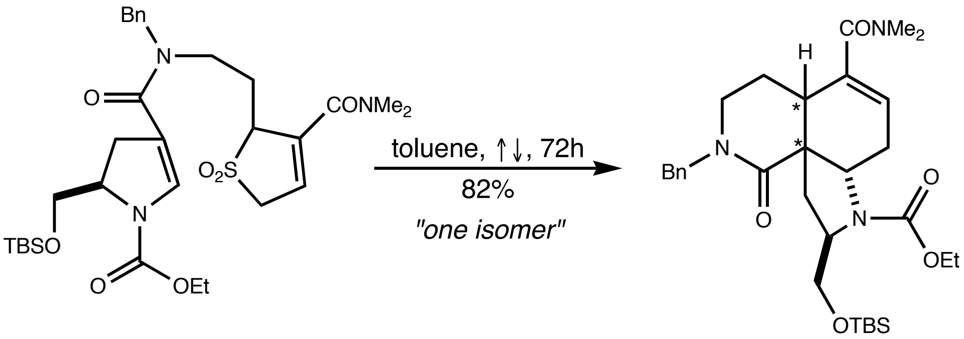
Question 8. Provide mechanisms that account for the stereoselective formation of the products obtained by subjection of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions.

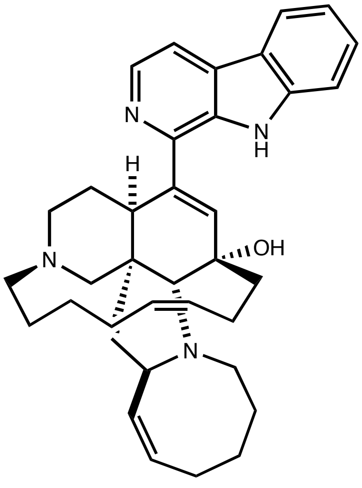


Question 9. Provide a mechanism for the following transformation.



Question 10. The following reaction was utilized in an approach to synthesize the core structure of the manzamines. Provide a mechanism for the transformation, and assign stereochemistry where appropriate.





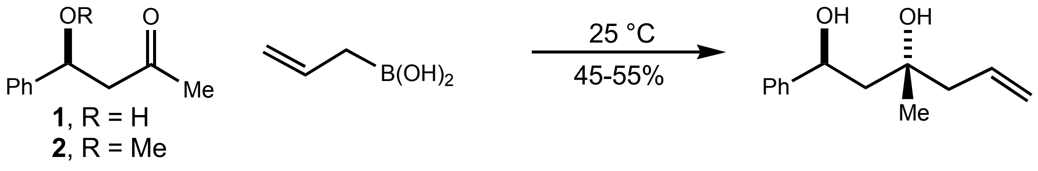
Manzamine A

Chem 206 *Due: Friday, Nov. 10*

Problem Set 7 *Name:______________* *TF:________________*

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1. The following transformation was recently reported by Kabalka. Treatment of **1** with allylboronic acid afforded the indicated adduct in high yield with 10:1 diastereoselection. On the other hand, the analogous reaction of **2** was nonstereoselective. Propose a mechanism for this transformation that accounts for the stereochemical outcome of the addition process.

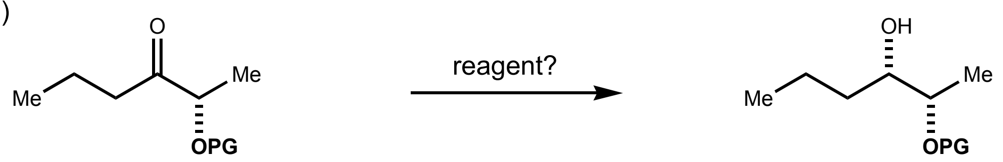


1, R = H
2, R = Me

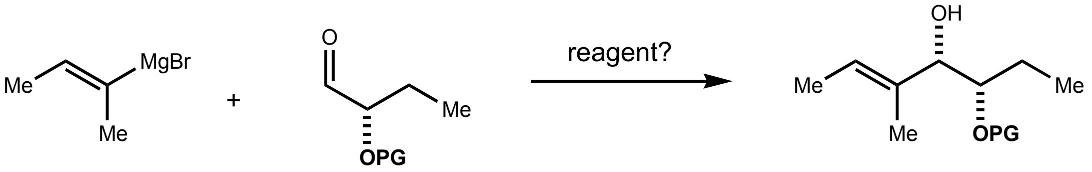
diastereoselection 10:1

Question 2. Give your choice of a protecting group and reagent, and justify your answer with 3D drawings:

a)

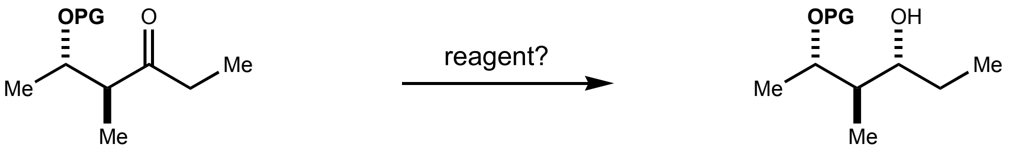


b)

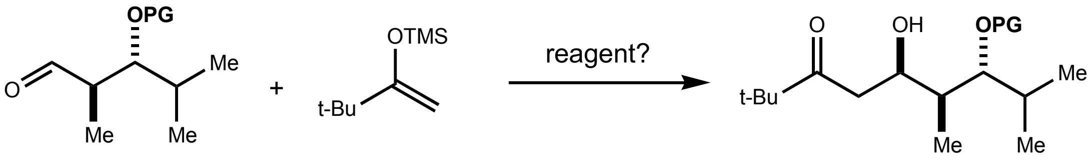


Question 2, continued

c)



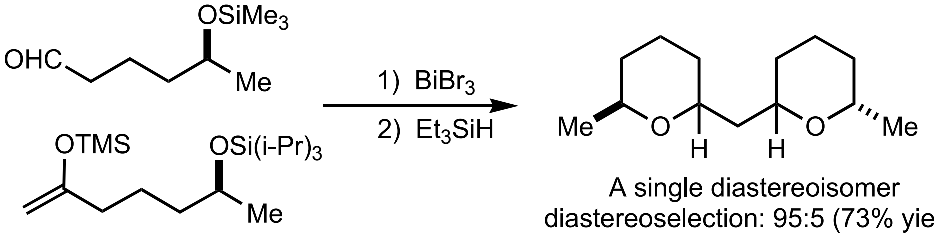
d)



Question 3. P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans. One of their cases is illustrated in Eq 1. In this transformation $BiBr_3$ is employed as a mild Lewis acid.

1

2

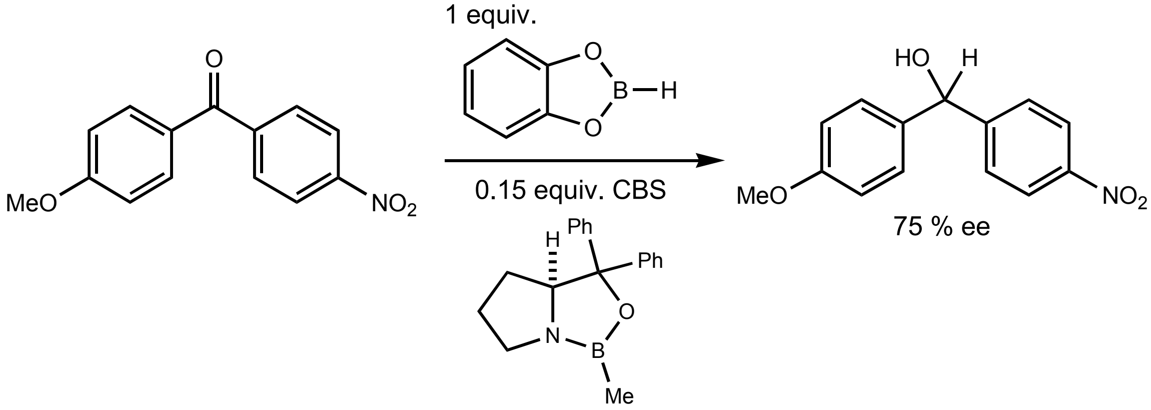


(1)

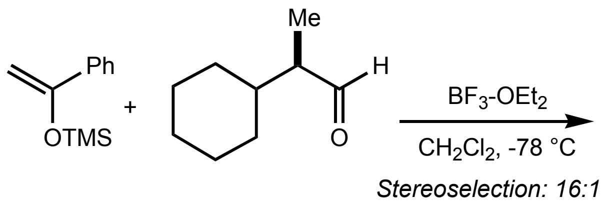
A single diastereoisomer
diastereoselection: 95:5 (73% yield)

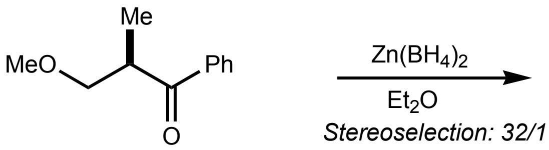
Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.

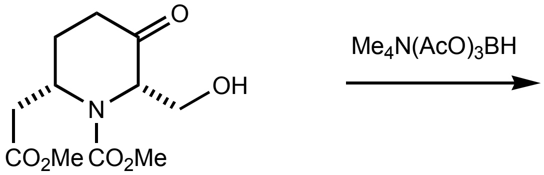
Question 4. Corey's CBS catalyst for ketone reduction often delivers high yields of enantioenriched secondary alcohols. Provide a clear illustration of the transition state which predicts the absolute stereochemistry of the product obtained in the illustrated reaction. Include an explanation of why the reduction of this practically symmetric ketone is selective.

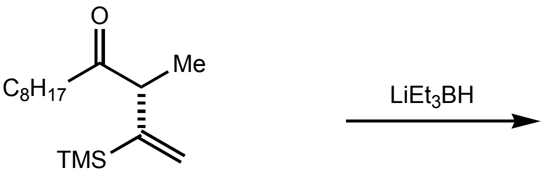


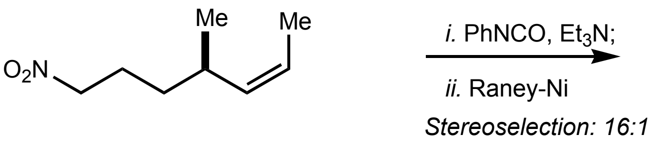
Question 5. In each of the following reactions, provide the stereostructure of the major product and rationalize the stereochemical outcome using clear 3D-drawings or Newman projections



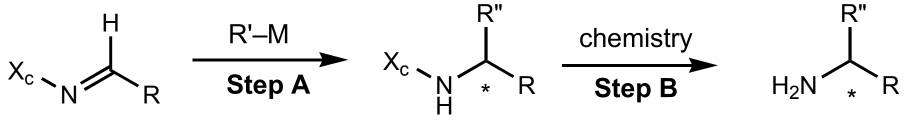




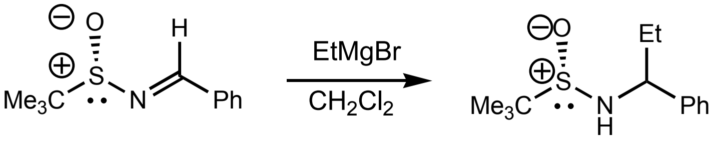




Question 6. Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of the chirality transfer process.

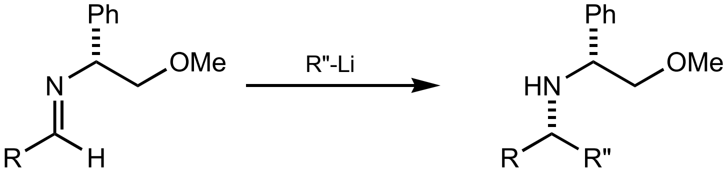


Part A. Provide a mechanism for the following transformation reported by Ellman and co-workers. Include a clear transition state representation that predicts the major product diastereomer. Clearly illustrate the absolute stereochemistry of the product.



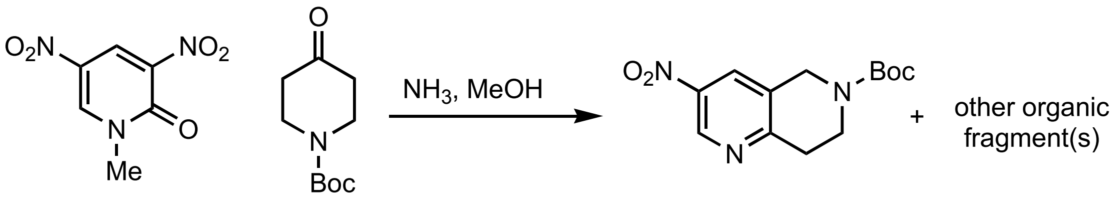
diastereomer ratio 92:8

Part B. The following stereoselective transformation has been reported by Fujisawa. Given the stereostructure of the product, rationalize the stereochemical outcome.

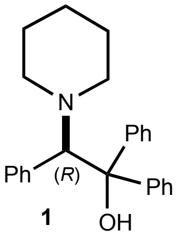


diastereomer ratio >97:3

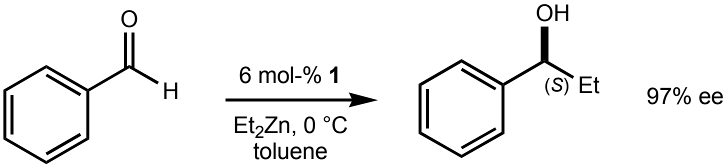
Question 7. This is a classic problem in multistep electron pushing. The following pyridine synthesis has been reported by Tohda. Provide a plausible mechanism for this complex transformation.



Question 8. Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational investigation that addresses the preferred transition state geometry for this addition process. It should be noted that, while **1** is not the actual catalyst, it is modified under the reaction conditions to the competent catalytic agent.

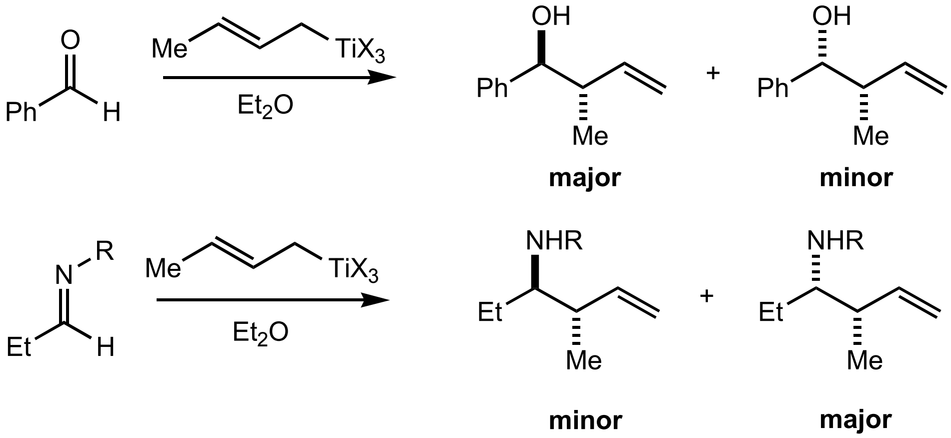


1



Provide a detailed mechanism for the overall transformation in the space below. Use three-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.

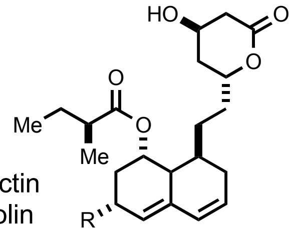
Question 9. Crotyltitanium reagents have been developed for addition to C=O and C=N bonds.



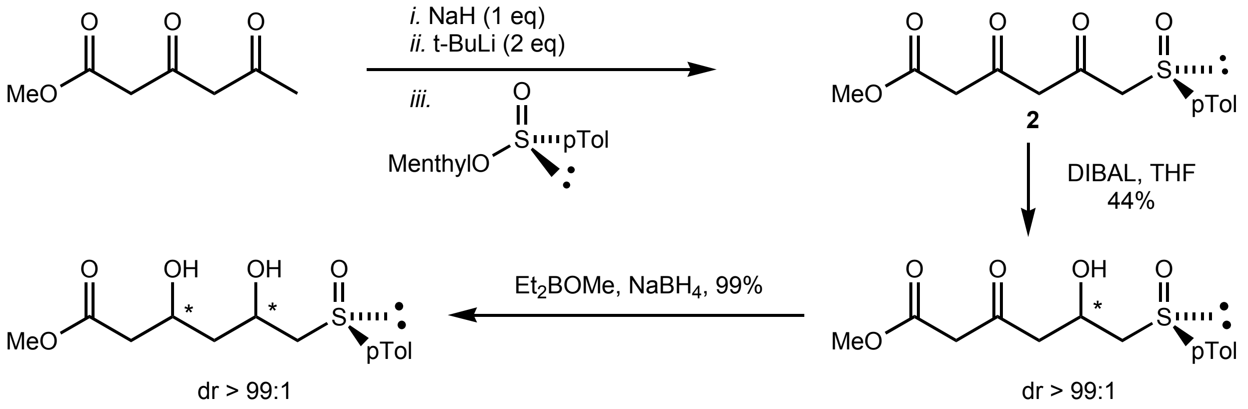
Part A. Provide an explanation, including clear 3D drawings of the transition states, which account for the divergent stereoselectivity observed in the addition reactions illustrated above.

Part B. The use of a chiral imine induces useful levels of asymmetric induction in this reaction. Provide an explanation, including a clear 3D drawing of the transition state, which accounts for the preferred production of the indicated diastereomer.

Question 10. Solladie has used a chiral sulfoxide as an auxiliary for the enantioselective synthesis of the lactonic moiety **1** of (+)-Compactin and (+)-Mevinolin**.**



R=H: (+)-compactin
R=Me: (+)-mevinolin



Explain which stereoselectivities are observed in the two reduction steps illustrated above. Use clear 3D drawings for the transition states. What happens when the $ZnCl_2$/DIBAL combination is used instead of DIBAL for the reduction of **2**?

Chem 206 *Due: Monday, Nov. 27*

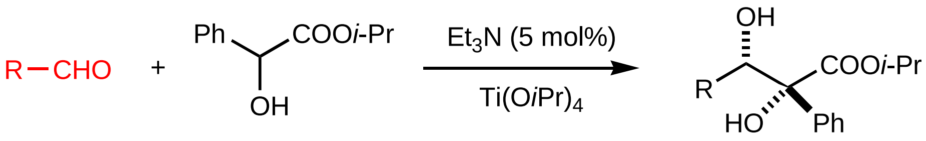
Problem Set 8

Name:________________TF:____________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1.

Part A. Rationalize the syn-selectivity of the following reaction with a clear 3-D representation of Zimmerman-Traxler transition state.

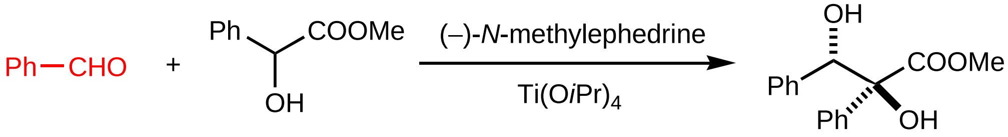


R	yield (%)	ration (syn/anti)
Me	70	55:45
Et	75	79:21
i-Pr	78	94:06

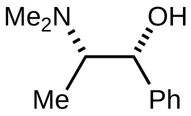
Answer:

Question 1.

Part B. Read the following results and observations and provide a plausible reaction mechanism and transition state for the high anti-selectivity and enantioselectivity of following reaction.



(–)-*N*-methylephedrine =



Observation

1) The enantio- and diastereoselection did not depend on the configuration of the mandelic acid esters used. The enantioselectivities found in these reactions depended only on the chirality of the *N*-methylephedrine used. (*S,S*)-product from (–)-*N*-methylephedrine and (*R,R*)-product from (+)-*N*-methylephedrin.

2) The reactions were completed after 1-2 h at room temperature. After that time, syn-aldol products were isolated in high yields. But no enantioselectivities were detected.

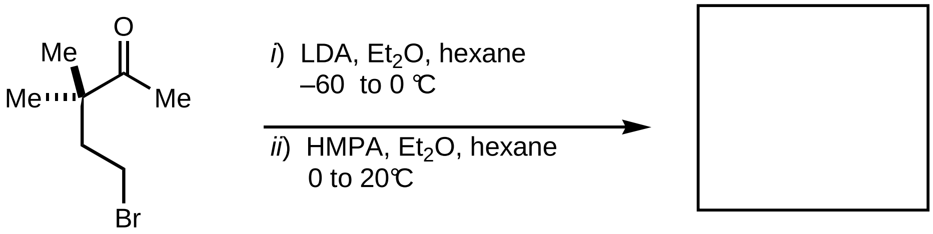
3) After 24 h at room temperature, anti-aldol products were isolated in high yields and high enantioselectivities. Only small amounts of syn-products were detected.

4) When racemic anti-aldol adduct was reacted with benzaldehyde in the presence of Ti(O*t*Bu)$_4$ and both (+) and (–)-*N*-Methylephedrine, both (*R,R*) and (*S,S*) products were isolated with a high degree of enantioselectivity.

Answer :

Question 2.

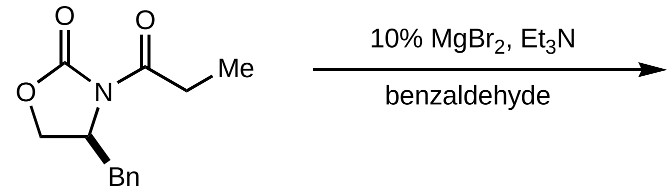
Predict the product of the reaction below. Include a rationalization based on a detailed analysis of competing transition state geometries with stereoelectronic argument.

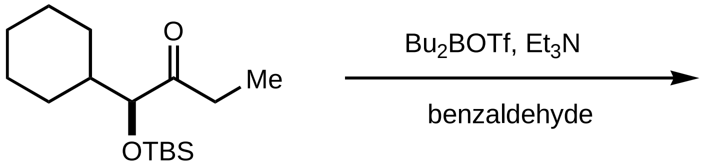


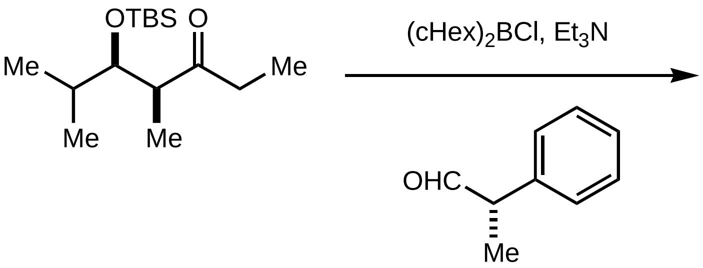
Answer

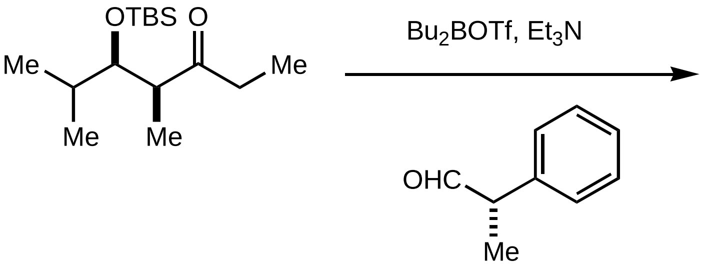
Question 3.

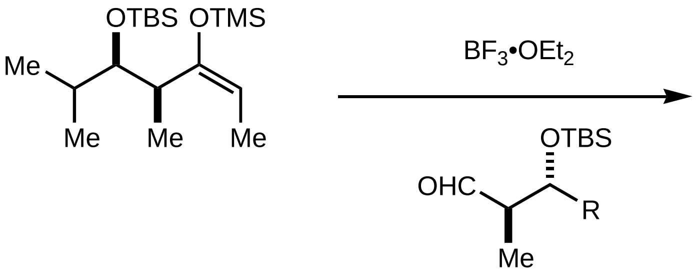
For each of the following aldol reactions provide the major product that you would expect to form under the given conditions. Provide the expected stereochemical outcome





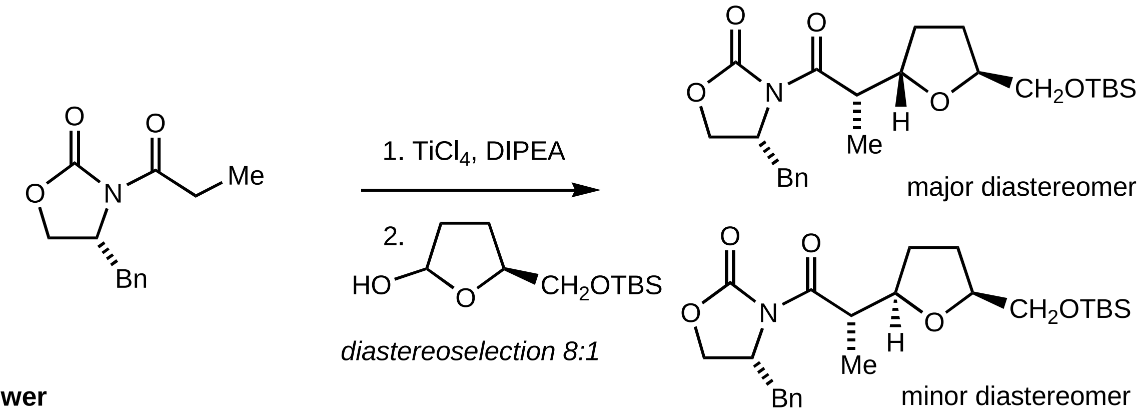






Question 4.

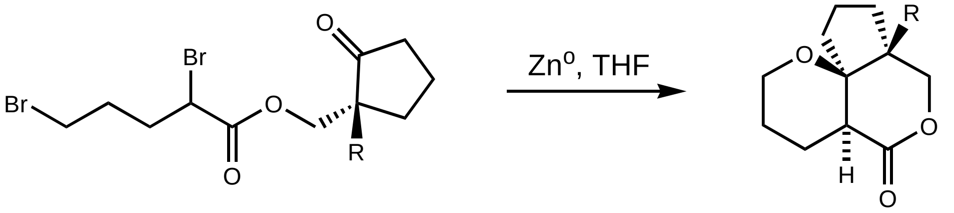
From your knowledge of the chemistry of the indicated *N*-acyloxazolidinone, provide a mechanism for the indicated transformation which is consistant with the observed stereochemistry at the two newly formed stereocenters.



Answer

Question 5.

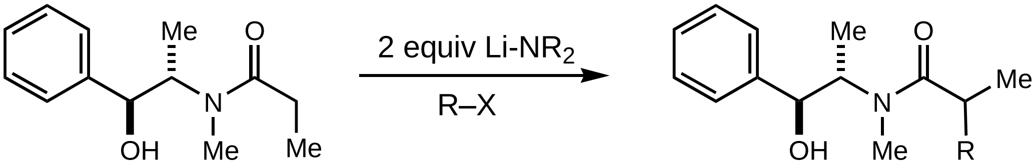
Provide a mechanism that accounts for observed stereochemistry of the illustrated transformation



Answer

Question 6.

The Myers pseudoephedrine-derived propionamide **1,** upon successive enolization with LiN(**I**-Pr)$_2$ (LDA) and alkylation with alkyl halide R–X, affords **2** with high diastereoselection .



1 **2**

Part A. Enolization of **1** with LDA affords a single enolate geomerty.
Provide an analysis of this enolization event and draw the enolate thus produced.

Part B. Provide a 3-dimensional drawing of the transition state for this reaction in **Box-1.** *Hint: In answering this question, you do not need to assume that chelation is involved. Rather, a suitable transition state model may be derived purely from the consideration of non-bonding interactions.*

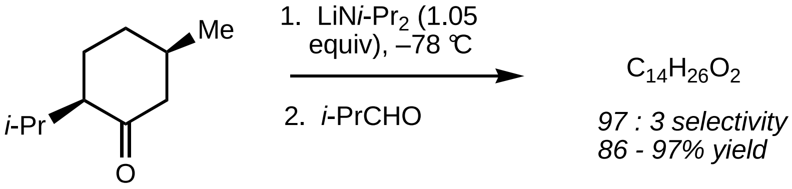
Box-1

Box-2

Part C. Provide the absolute stereochemistry of the alkylation product **2** of this reaction in **Box-2**.

Question 7.

Provide the product of the following reaction, including the stereochemistry at all relevant stereogenic centers. Draw a transition structure that clearly indicates how this stereoisomer is formed.

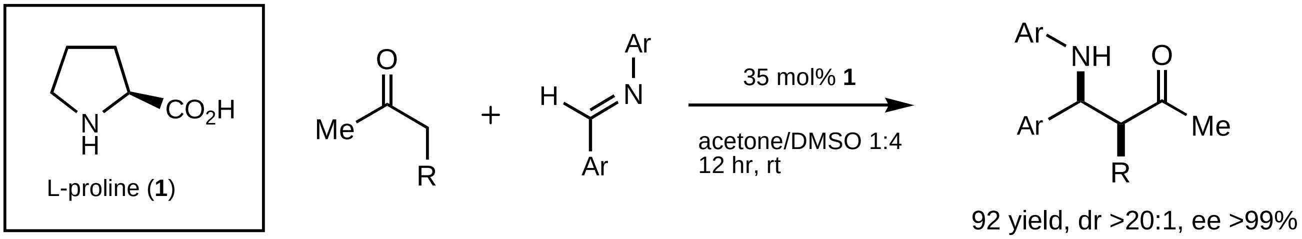


97 : 3 selectivity
86 - 97% yield

Answer

Question 8.

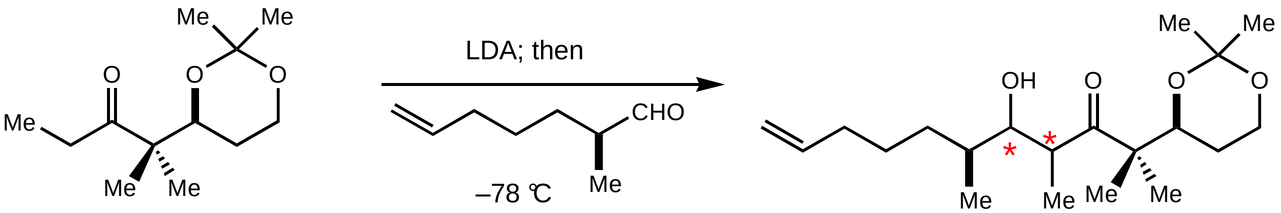
Provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereo and enantioselection for this process. Briefly identify the transition state stereochemical control elements.



Answer

Question 9.

Provide a mechanism which clearly predicts the product stereochemistry at the starred (*) carbon atoms . Provide a clear depiction of the transition state to support your answer.



Answer

Chem 206 *Due: Monday, Nov. 27*

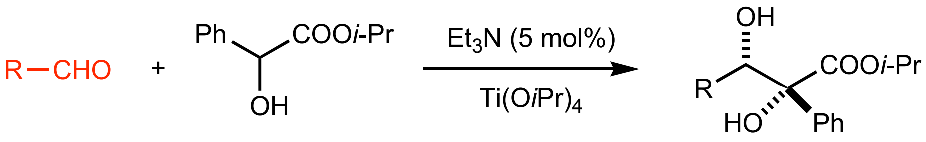
Problem Set 8

Name:______________TF:___________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1.

Part A. Rationalize the syn-selectivity of the following reaction with a clear 3-D representation of Zimmerman-Traxler transition state.



R	yield (%)	ration (syn/anti)
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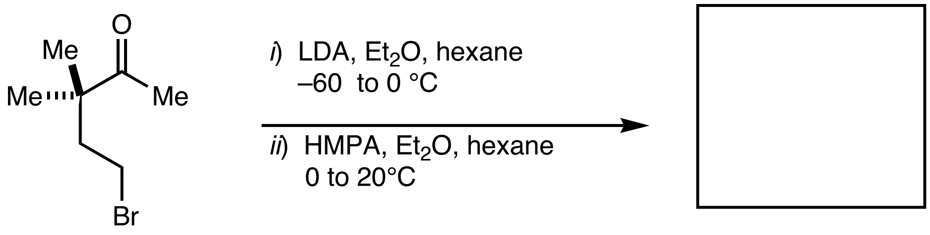
Et	75	79:21
i-Pr	78	94:06

Answer:

Question 2.

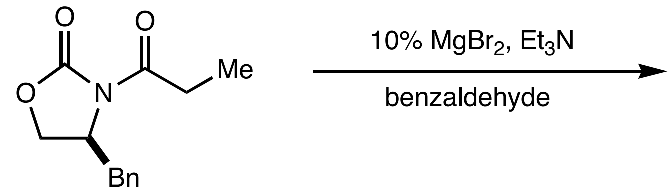
Predict the product of the reaction below. Include a rationalization based on a detailed analysis of competing transition state geometries with stereoelectronic argument.

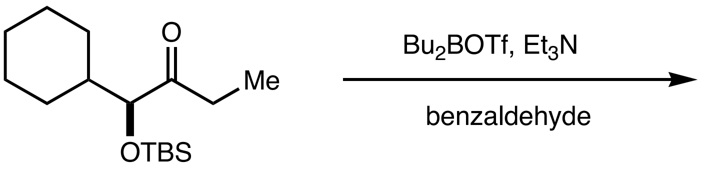


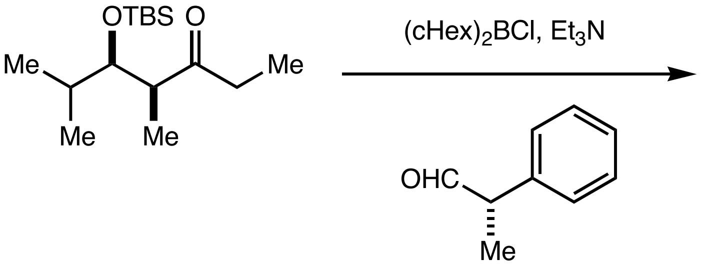
Answer

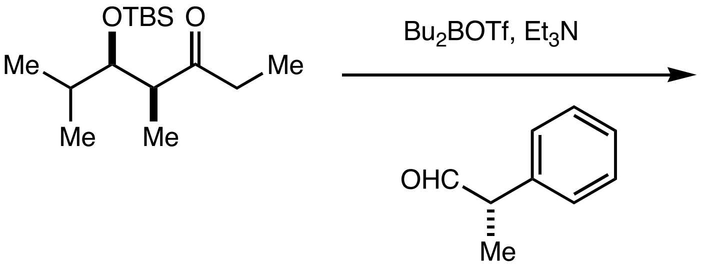
Question 3.

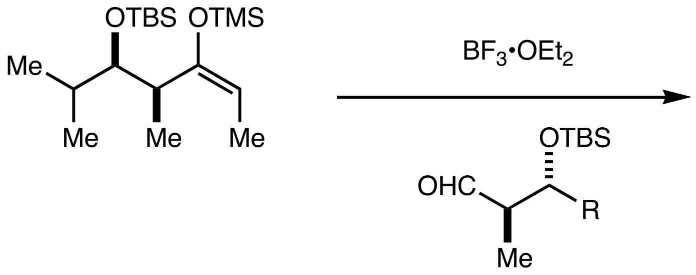
For each of the following aldol reactions provide the major product that you would expect to form under the given conditions. Provide the expected stereochemical outcome





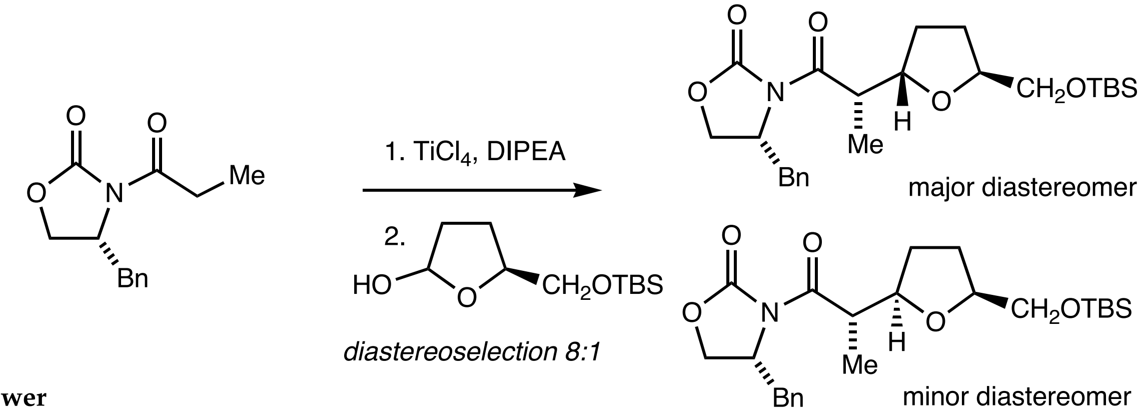






Question 4.

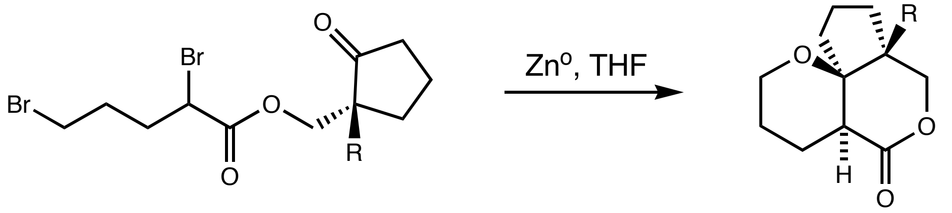
From your knowledge of the chemistry of the indicated *N*-acyloxazolidinone, provide a mechanism for the indicated transformation which is consistant with the observed stereochemistry at the two newly formed stereocenters.



Answer

Question 5.

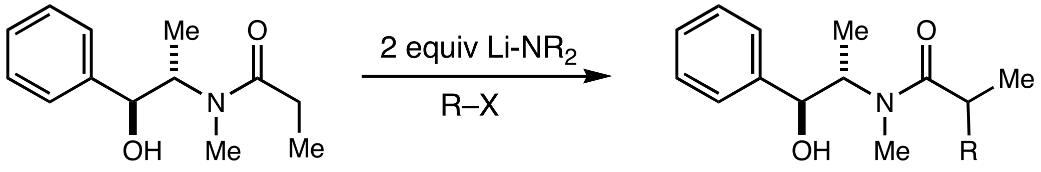
Provide a mechanism that accounts for observed stereochemistry of the illustrated transformation



Answer

Question 6.

The Myers pseudoephedrine-derived propionamide **1,** upon successive enolization with LiN(I-Pr)$_2$ (LDA) and alkylation with alkyl halide R–X, affords **2** with high diastereoselection .



1 **2**

Part A. Enolization of **1** with LDA affords a single enolate geomerty.
Provide an analysis of this enolization event and draw the enolate thus produced.

Part B. Provide a 3-dimensional drawing of the transition state for this reaction in **Box-1.** *Hint: In answering this question, you do not need to assume that chelation is involved. Rather, a suitable transition state model may be derived purely from the consideration of non-bonding interactions.*

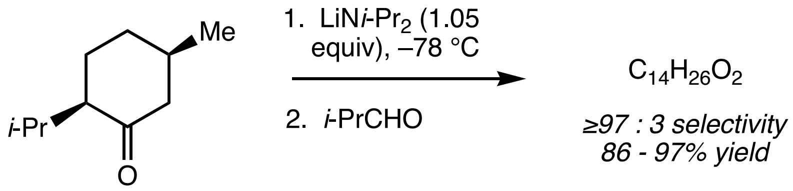
Box-1

Box-2

Part C. Provide the absolute stereochemistry of the alkylation product **2** of this reaction in **Box-2**.

Question 7.

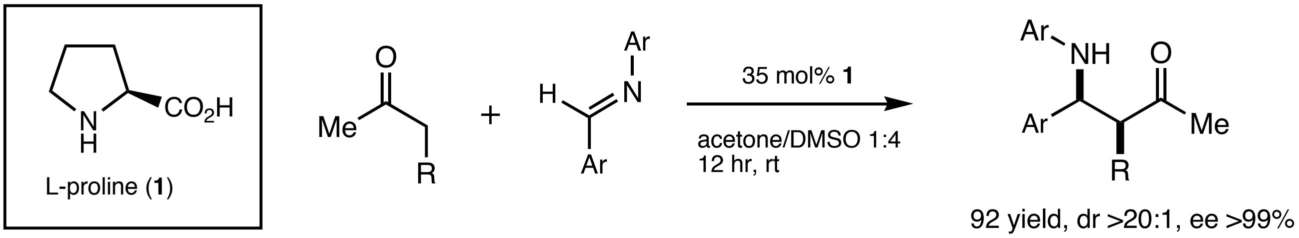
Provide the product of the following reaction, including the stereochemistry at all relevant stereogenic centers. Draw a transition structure that clearly indicates how this stereoisomer is formed.



Answer

Question 8.

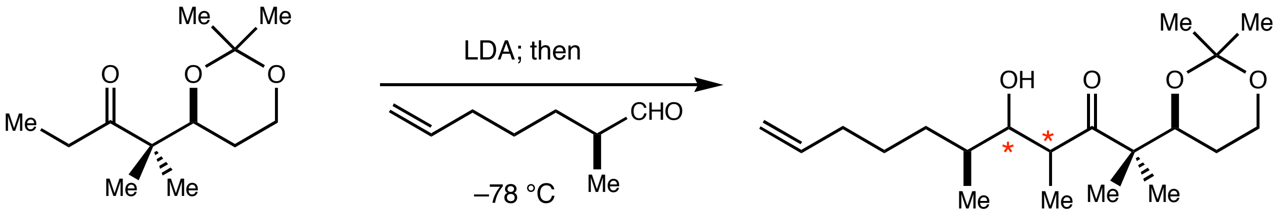
Provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereo and enantioselection for this process. Briefly identify the transition state stereochemical control elements.



Answer

Question 9.

Provide a mechanism which clearly predicts the product stereochemistry at the starred (*) carbon atoms .
Provide a clear depiction of the transition state to support your answer.



Answer

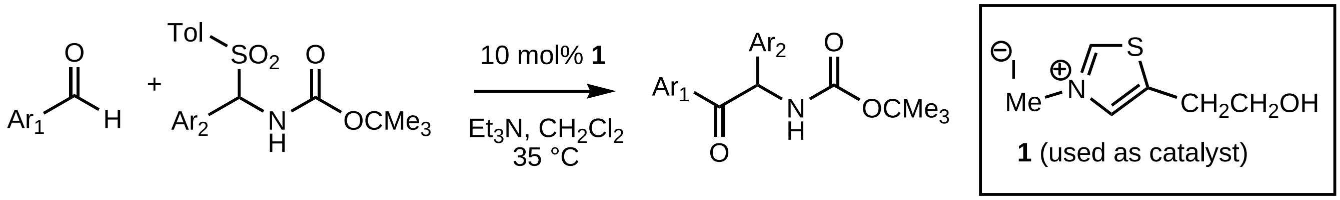
Problem Set 9

Name:_____________ TF:_______________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1.

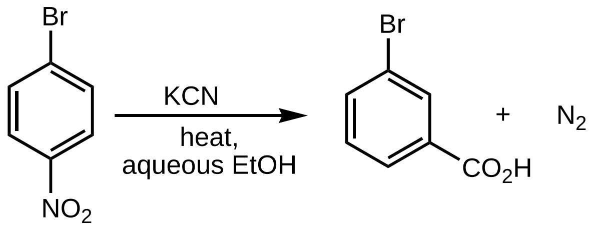
The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group. Provide a mechanism for this transformation in the space below.



1 (used as catalyst)

Question 2.

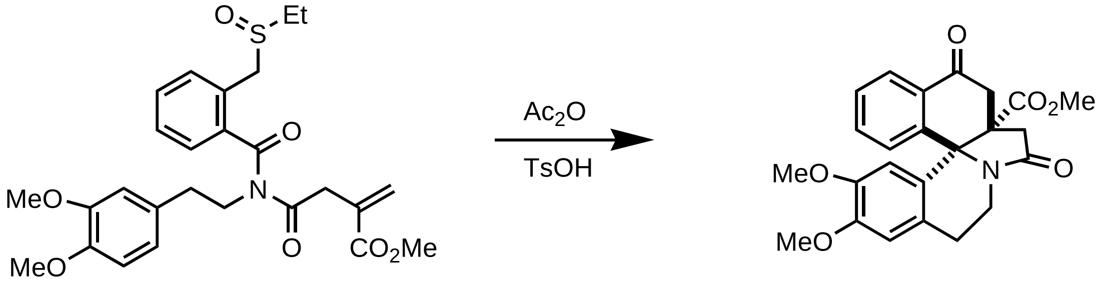
The **Von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If ^{15}N-labeled KCN is used, the N_2 formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.



Provide your answer in the space below:

Question 3.

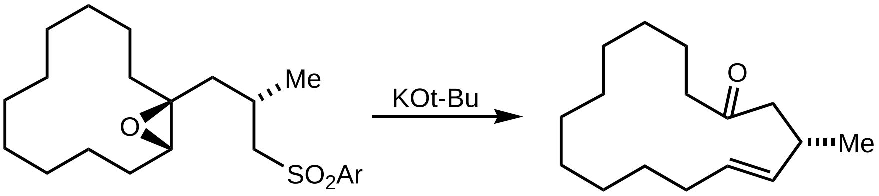
Padwa reported the interesting transformation shown below. Provide a detailed mechanism and identify any organic named reactions in this sequence.



ANSWER:

Question 4.

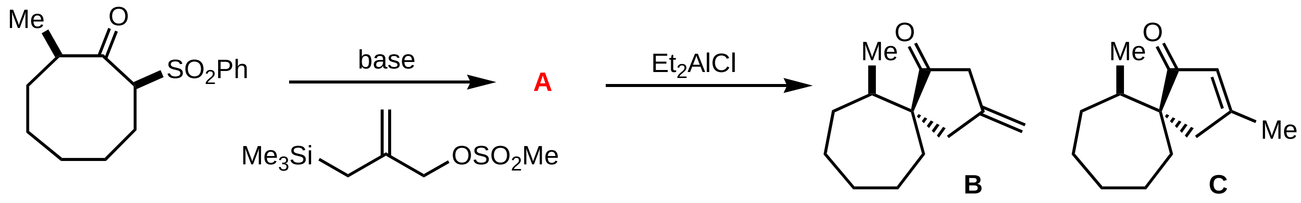
Fishli and Branca have reported the annulation reaction sequence shown below.



Provide a detailed mechanism for this transformation in the space below.

Question 5.

Trost and Adams have reported the interesting spiroannulation reaction sequence shown below. In the first step the enolate alkylation produces a single diastereomeric adduct **A**. Rearrangement of **A** under Lewis acidic conditions affords a mixture of **B** and **C**. As the reaction times are increased more **C** is produced by equilibration.

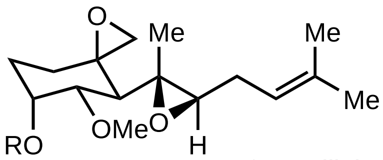


Part A. Using your knowledge of the conformations of eight-membered rings, predict the stereochemical outcome of the the alkylation and identify the full stereostructure of **A**.

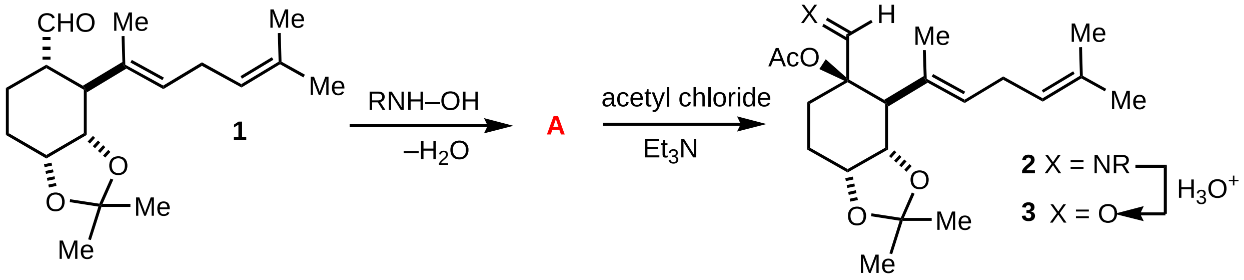
Part B. Provide a detailed mechanism for the transformation of **A** into **B** in the space below.

Question 6.

The fumagillin natural products possess several interesting biological properties including antibiotic activity against *Staphylococcus auereus*. In Sorensen's recent synthesis of fumagillol, intermediate **1** was transformed into its a-oxygenated counterpart **3** through the indicated reaction sequence.



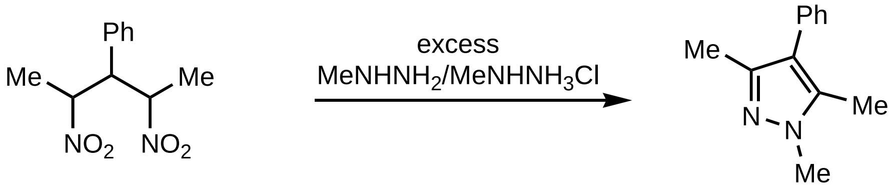
fumagillol



In the space below, identify the structure of intermediate **A** and provide a mechanism for the transformation of **1** into **2**.

Question 7.

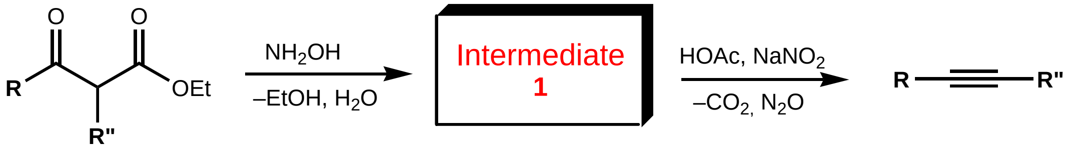
Here is a good exercise that deals with the verstility of the nitro group. Provide a detailed mechanism for the following reaction.



Answer

Question 8.

S. Zard has recently reported the very clever synthesis of acetylenes from β-keto esters illustrated below. In this article, he demonstrates that this transformation exhibits broad scope.

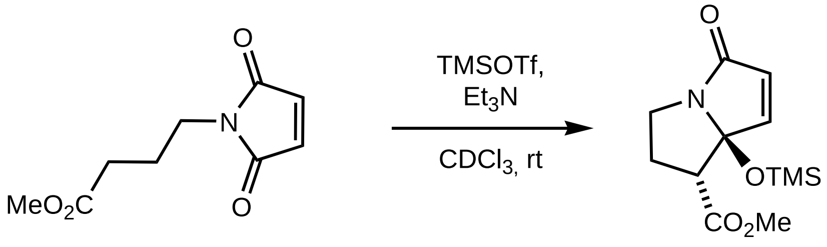


Provide a plausible mechanism for this transformation and identify intermediate **1** in the space below.

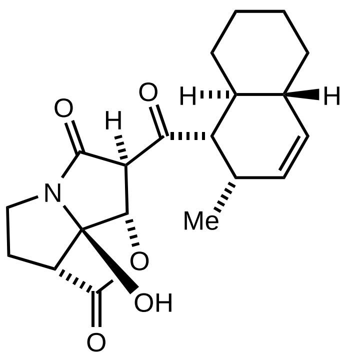
Question 9.

Hoye *et al.* studied the following silylative cyclization in the context of a construction of the telomerase inhibitor UCS1025A.

Part A: Rationalize the mechanism and explain the diastereoselectivity

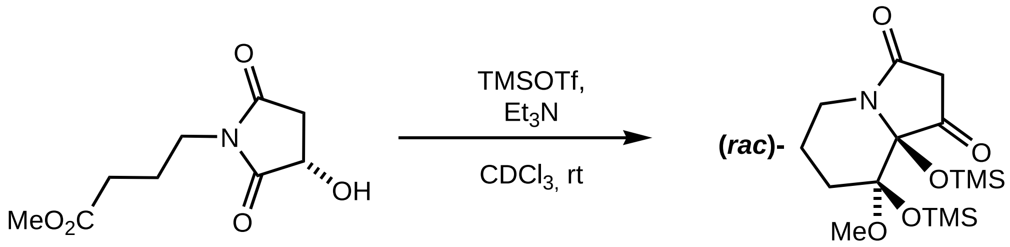


88%, dr 62:1



UCS1025A

Part B: The seemingly similar starting material derived from L-malic acid showed a different reaction course. Knowing about the outcome, you can definitely provide a good *a posteriori* explanation!



quant., 90% pure
by ^{1}H-NMR
(unstable on silica)

Chem 206 *Due: Friday, Dec. 1*

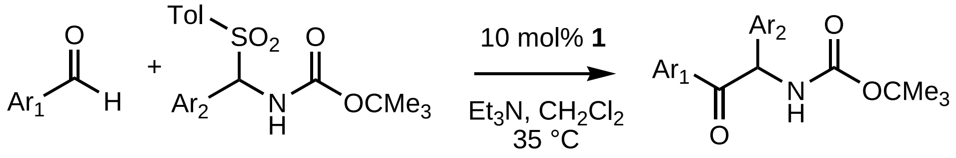
Problem Set 9

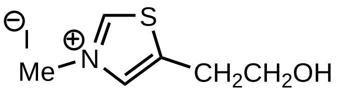
Name:_____________ TF:_______________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1.

The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group. Provide a mechanism for this transformation in the space below.

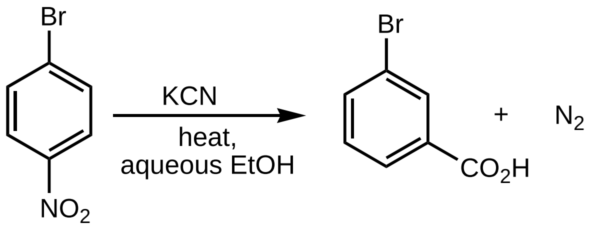




1 (used as catalyst)

Question 2.

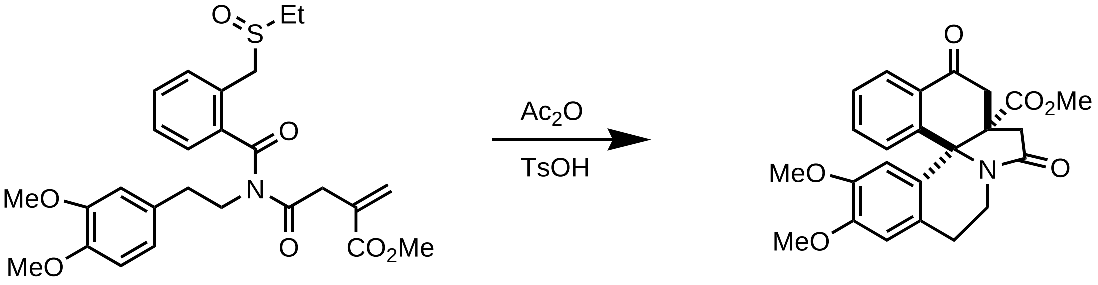
The **Von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If ^{15}N-labeled KCN is used, the N_2 formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.



Provide your answer in the space below:

Question 3.

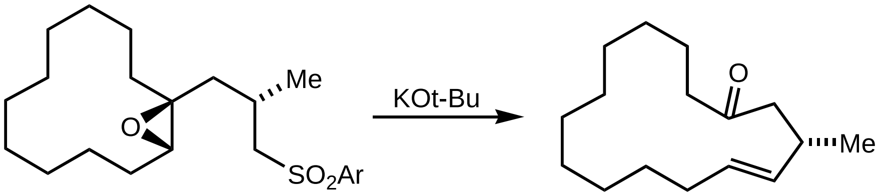
Padwa reported the interesting transformation shown below. Provide a detailed mechanism and identify any organic named reactions in this sequence.



ANSWER:

Question 4.

Fishli and Branca have reported the annulation reaction sequence shown below.



Provide a detailed mechanism for this transformation in the space below.

Question 5.

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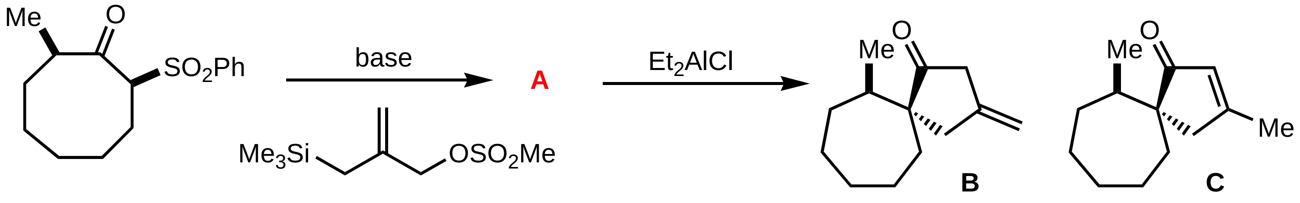

Part A. Using your knowledge of the conformations of eight-membered rings, predict the stereochemical outcome of the the alkylation and identify the full stereostructure of **A**.

Part B. Provide a detailed mechanism for the transformation of **A** into **B** in the space below.

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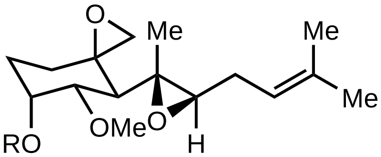
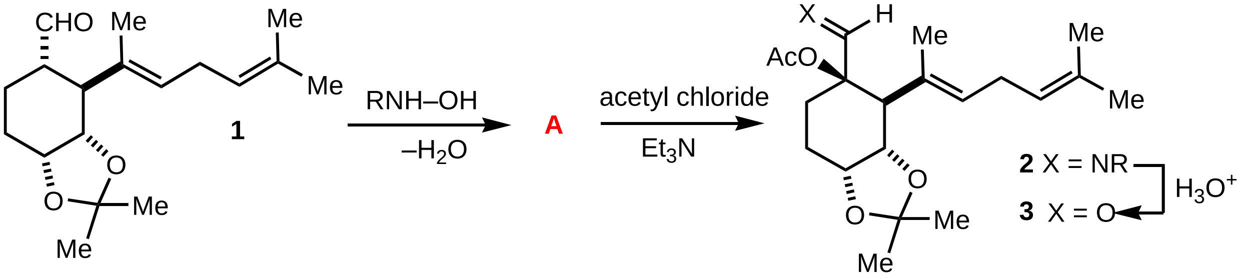


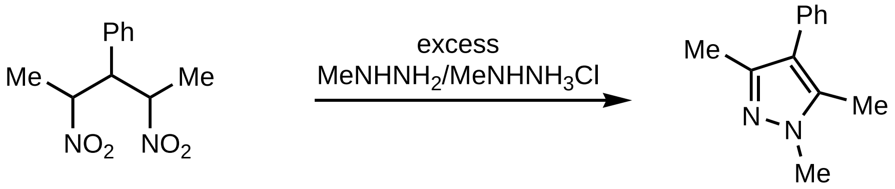
fumagillol



In the space below, identify the structure of intermediate **A** and provide a mechanism for the transformation of **1** into **2**.

Question 7.

Here is a good exercise that deals with the verstility of the nitro group. Provide a detailed mechanism for the following reaction.



Answer

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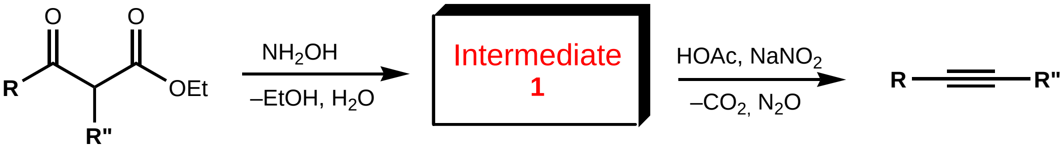

Provide a plausible mechanism for this transformation and identify intermediate **1** in the space below.

Question 9.

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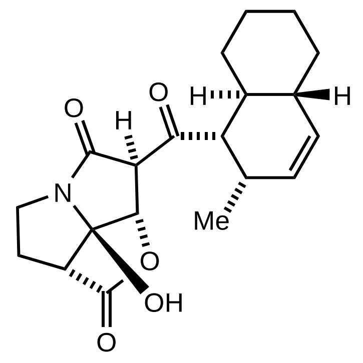
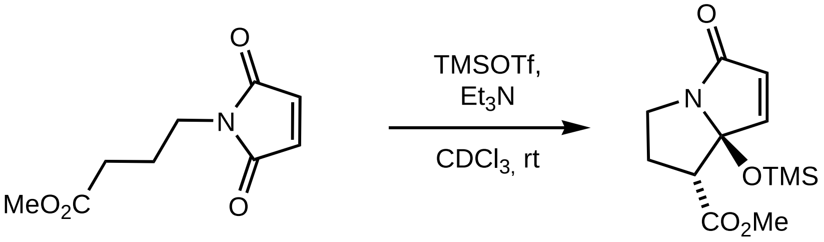


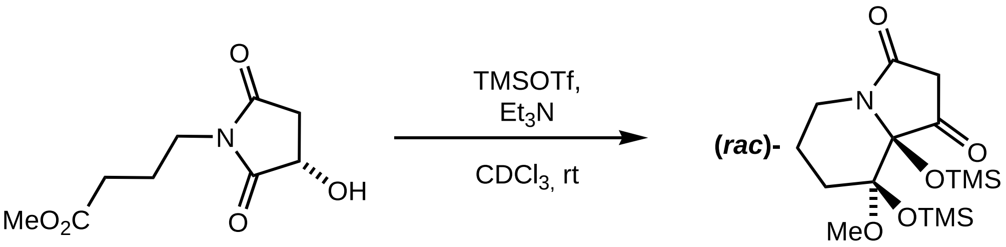
UCS1025A

Part A: Rationalize the mechanism and explain the diastereoselectivity



88%, dr 62:1

Part B: The seemingly similar starting material derived from L-malic acid showed a different reaction course. Knowing about the outcome, you can definitely provide a good *a posteriori* explanation!



quant., 90% pure
by ^{1}H-NMR
(unstable on silica)

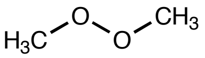
Chem 206 Due Friday, September 22

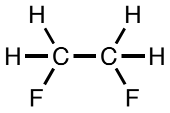
Name________________________

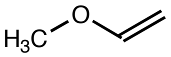
Problem Set 1

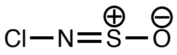
General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Problem 1. For each of the molecules shown below, hyperconjugative, rather than steric factors, dictate the geometry of the structure. Draw the most stable conformation or geometric isomer and clearly label all dominant hyperconjugative interactions (e.g. $\sigma_{C\text{–}C} \rightarrow \sigma^*_{C\text{–}O}$).



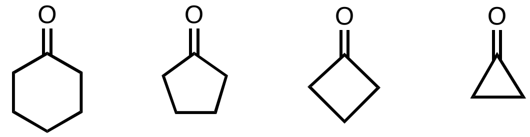






$Cl{-}N{=}\overset{\oplus}{S}{-}\overset{\ominus}{O}$

Problem 2. Ring strain dramatically affects the carbonyl infrared stretching frequency.

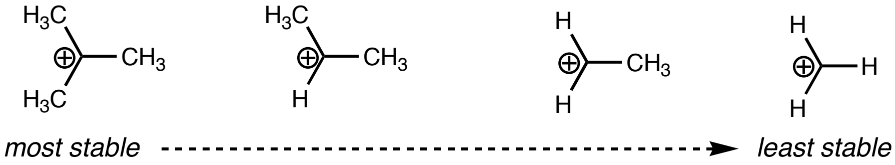


$\bar{\nu}_{C=O}$ (cm $^{-1}$) 1715 1745 1788 1813

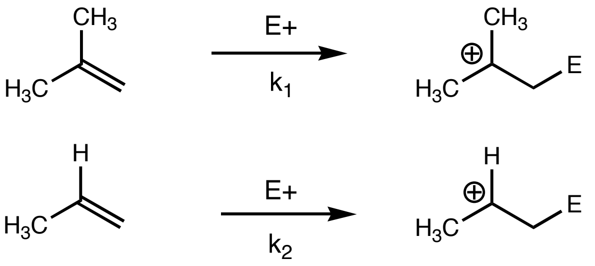
Part A. Explain the above trend using molecular orbital theory.

Part B. Can you find an alternative explanation for the above trend that relies on basic organic chemistry principles?

Problem 3. Carbocations are stabilized by alkyl substitution. Using frontier molecular orbitals, explain how increased alkyl substitution leads to the observed stability order. Identify the molecular orbitals (including the stereoelectronic requirement) involved in the stabilizing interaction.



Problem 4. Alkyl groups enhance the nucleophilicity of double bonds in reactions with electrophiles.

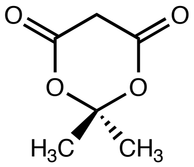


$k_1/k_2 = 2.5 \times 10^4$

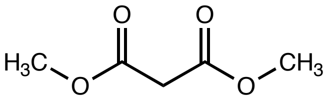
Part A. Identify and draw the principal orbital interaction that contributes to this observation.

Part B. Use orbital energy diagrams to explain why the interaction which you have identified causes an increase in the nucleophilicity of the carbon–carbon double bond.

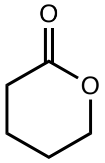
Problem 5. Gao and coworkers recently performed a variety of high level calculations on Meldrum's acid (**1**) in order to rationalize its enhanced acidity relative to dimethyl malonate (**2**). Upon calculating strain energies on the basis of the isodesmic reaction: Ester + Cyclohexane → Lactone + *n*-Heptane, the authors found that Meldrum's acid possessed a lower strain energy than 2-oxacyclohexanone (**3**). The result seemed rather counterintuitive given the presence of two ester functional groups in **1** versus a single ester functional group in **3**.



1
pKa = 7.3 (DMSO)



2
pKa = 15.9 (DMSO)



3

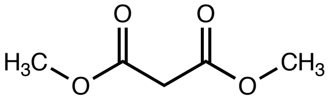
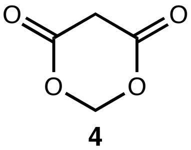
Computed Strain Energies at the B3LYP/aug-cc-pDVZ Level

Ester	Lactone	Strain Energy (Kcal/mol)
methyl pentanoate	2-oxacyclohexanone	9.8
methyl pentanoate anion	2-oxacyclohexanone anion	5.5
dimethyl malonate	Meldrum's acid	5.7
dimethyl malonate anion	Meldrum's acid anion	–7.9

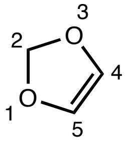
Part A. Identify a stabilizing effect that could account for the surprisingly low strain energy of **1** (it should be noted that the strain energy includes the cost of changing the ester conformation from *Z* to *E*).

Part B. The strain energy difference between neutal Meldrum's acid and its anion (7.9 Kcal/mol) does not entirely account for the 11.4 Kcal/mol difference in acidity calculated between **2** and **4**. Could the effect identified in part A account for the remaining 3.5 Kcal/mol of added acidity of **4** relative to **2**? If so, what must be assumed? Explain.

Gas Phase Acidities obtained from B3LYP/Aug-cc-pVDZ calculations

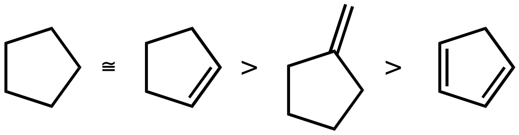
Compound	ΔG_{gas} (Kcal/mol)
 **2**	336.5
 **4**	325.1

Problem 6. Experiments involving IR and Raman spectroscopy indicate that 1,3-dioxole is puckered with a dihedral angle of 24° and an energy barrier to planarity of 275 cm^{-1}. The molecule was expected to be planar given the absence of torsional strain (see strain trend for 5-membered rings below).



1,3-dioxole
4-3-2-1 dihedral angle = 24°
energy barrier to planarity = 275 cm^{-1}

Strain trends:



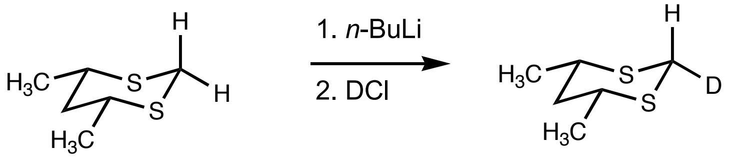
- Decrease in eclipsing strain more than compensates for the increase in angle strain.

Part A. Identify the dominant hyperconjugative interactions in a hypothetically planar 1,3-dioxole molecule.

Part B. Draw a molecular orbital diagram of the π-system of hypothetically planar 1,3-dioxole. Can you explain why the molecule is puckered? (Note that in the absence of a particular hyperconjugative interaction identified above, planar 1,3-dioxole has been calculated to be more stable than its puckered counterpart.)

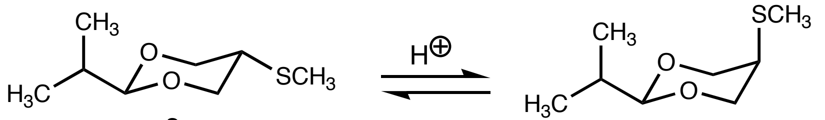
Problem 7. Many factors influence the reactivity and conformational bias of cyclic systems including steric, electronic, and stereoelectronic effects. For each of the following cases involving a six-membered heterocycle, provide a rationalization for the observed selectivity, including clear 3-dimensional representations where relevant.

Part A. Eliel and coworkers disclosed that the successive deprotonation of conformationally locked **1** followed by trapping with an electrophile occurs with high selectivity at the equatorial position (*J. Am. Chem. Soc.* **1974**, *96*, 1807.)



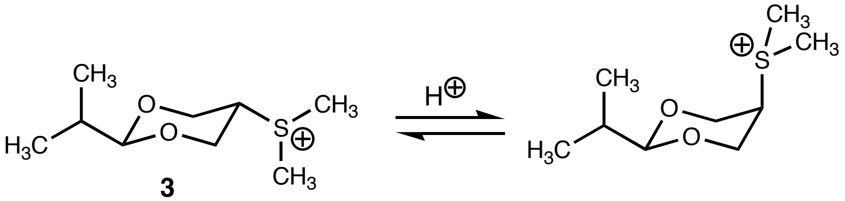
1

Part B. Eliel has also reported that the acid-catalyzed equilibrium of dioxane **2** favors the equatorial isomer, while the related equilibration of dioxane **3** prefers the axial isomer (*J. Am. Chem. Soc.* **1974**,*96*, 1939). Please provide a rationalization of these observations that is based on stereoelectronic arguments.



2

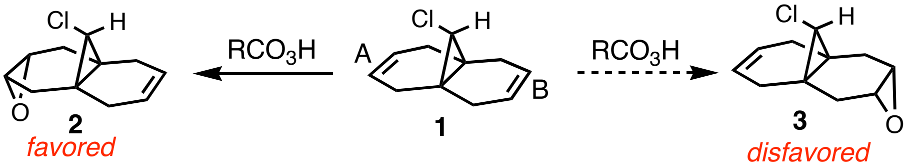
ΔG = +1.1 kcal/mol



3

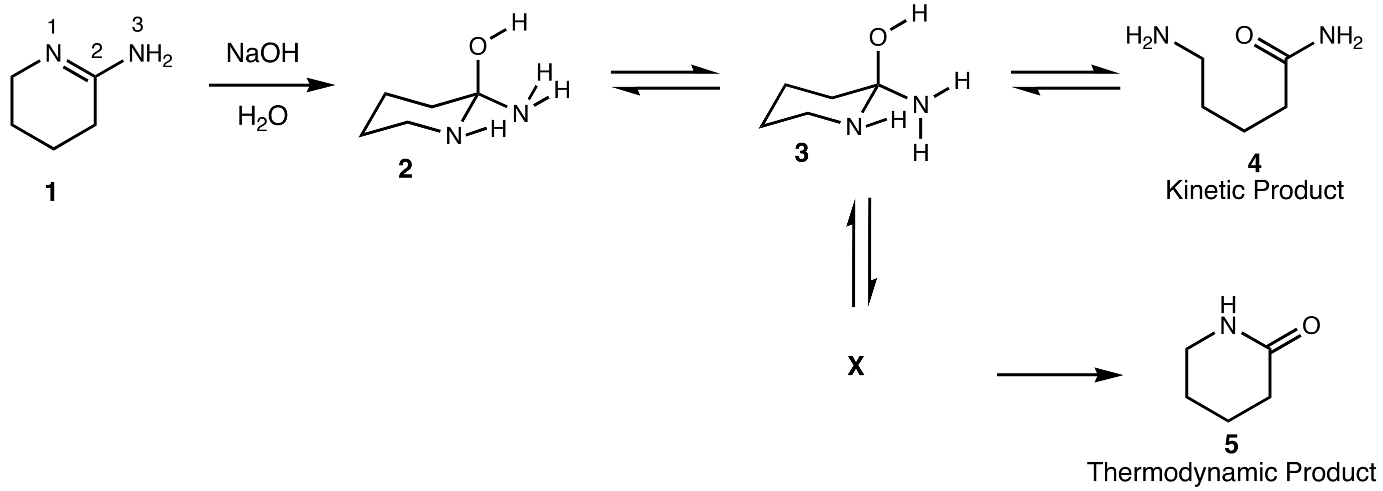
ΔG = –2.0 kcal/mol

Problem 8. The following publication (*J. Org. Chem.* **1991**, *56,* 5553) reported the surprisingly selective olefin epoxidation illustrated below. In this reaction, olefin B in **1** was found to be much less reactive than olefin A.



Using your knowledge of stereoelectronic effects, provide an explanation for the reduced reactivity of olefin B in diene **1**.

Question 9. Hydrolysis of amidine **1** with sodium hydroxide initially produces kinetic product **4** exclusively. As the reaction progresses, **4** is converted to the thermodynamic product **5**.



Part A. Identify the dominant hyperconjugative interactions in intermediate **2** (If you are looking for an extra challenge, try to explain why **2** was invoked as the first intermediate).

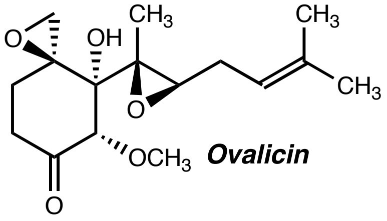
Part B. Explain why **4** is the kinetic product of the hydrolysis.

Part C. Draw the conformation of intermediate **X** (including lone pairs of electrons) which is most likely to lead to thermodynamic product **5**.

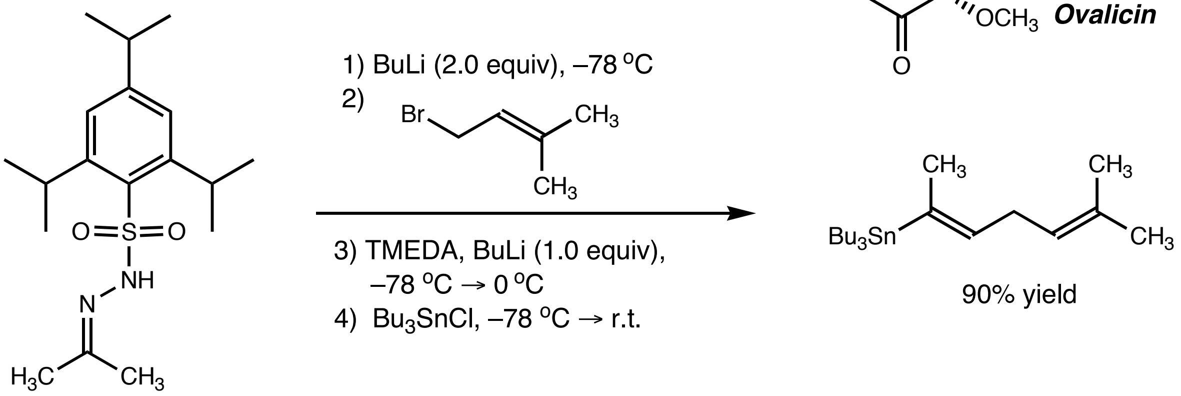
Problem Set 10 *Name:* **Answer Key** *TF:*________________

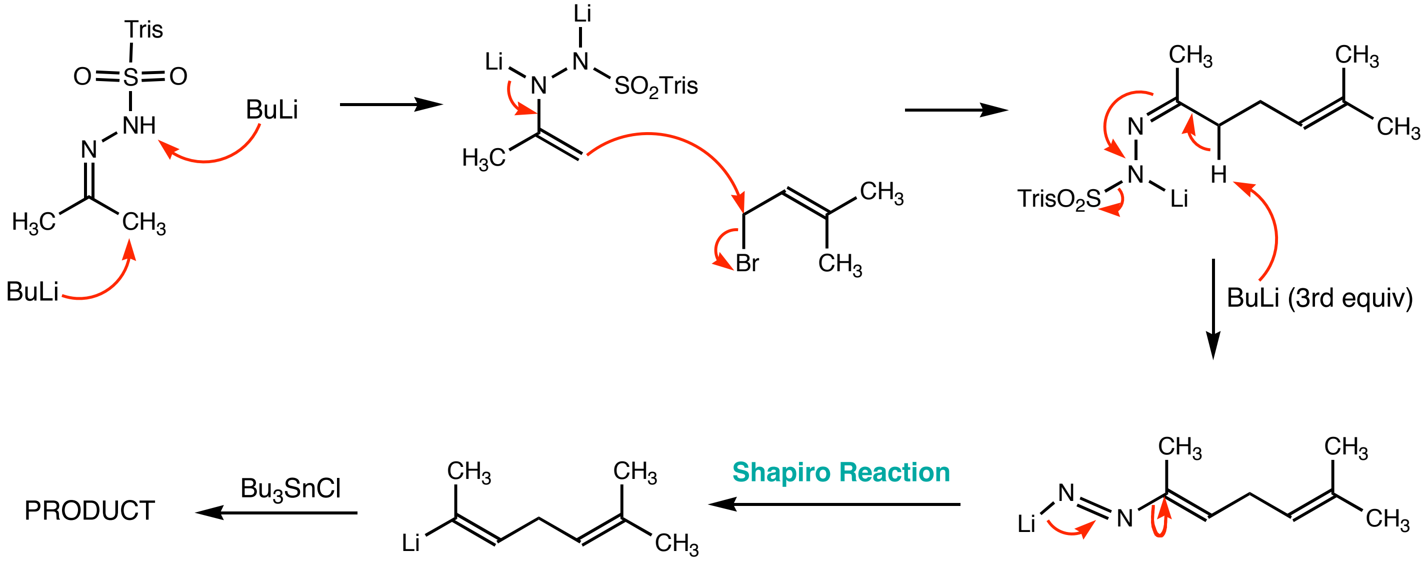
General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1. Corey's synthesis of ovalicin required the use of the vinylstannane below as a coupling fragment. This fragment was synthesized from acetone trisyl hydrazone. Please provide a mechanism for this sequence of steps.



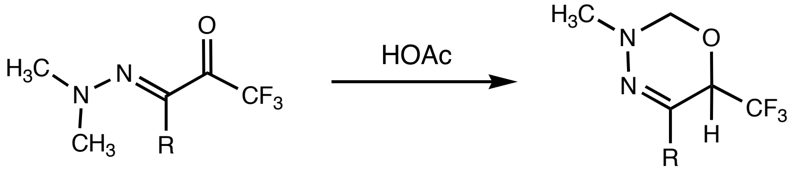
Ovalicin

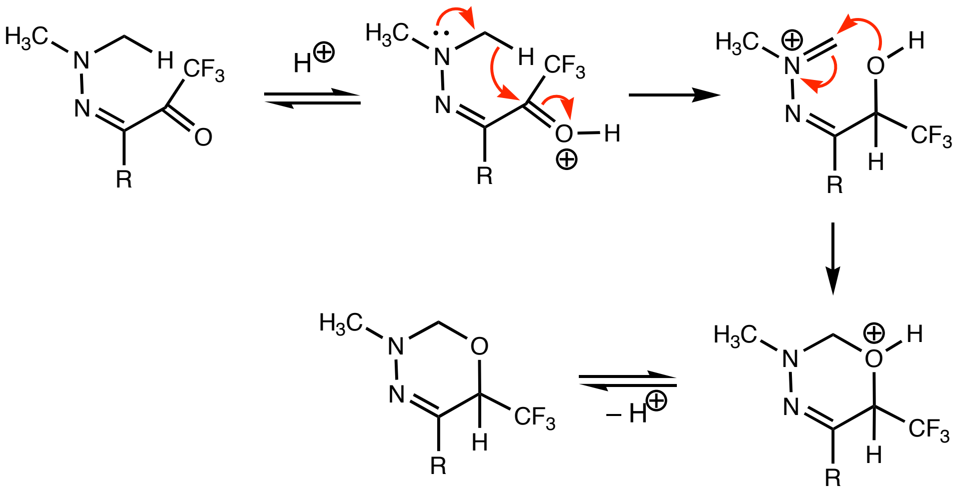

O=S=O
NH
N
H3C
CH3
1) BuLi (2.0 equiv), –78 °C
2)
Br
CH3
CH3
3) TMEDA, BuLi (1.0 equiv), –78 °C → 0 °C
4) Bu3SnCl, –78 °C → r.t.
CH3
CH3
Bu3Sn
CH3
90% yield



Total Synthesis of (±)-Ovalicin. Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985,** *107,* 256-257

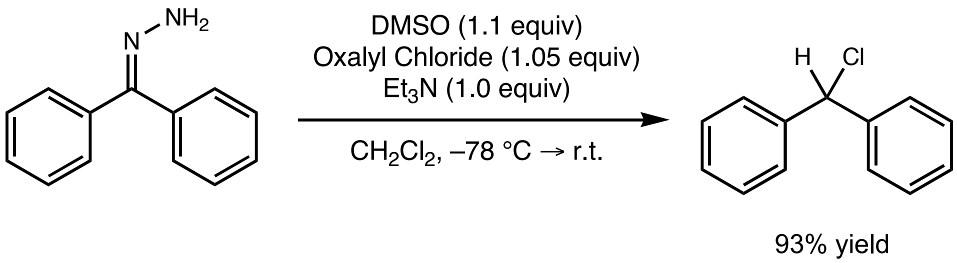
Question 2. Kamitori and coworkers have reported the acid catalyzed cyclization illustrated below. Provide a reasonable mechanism for this transformation.

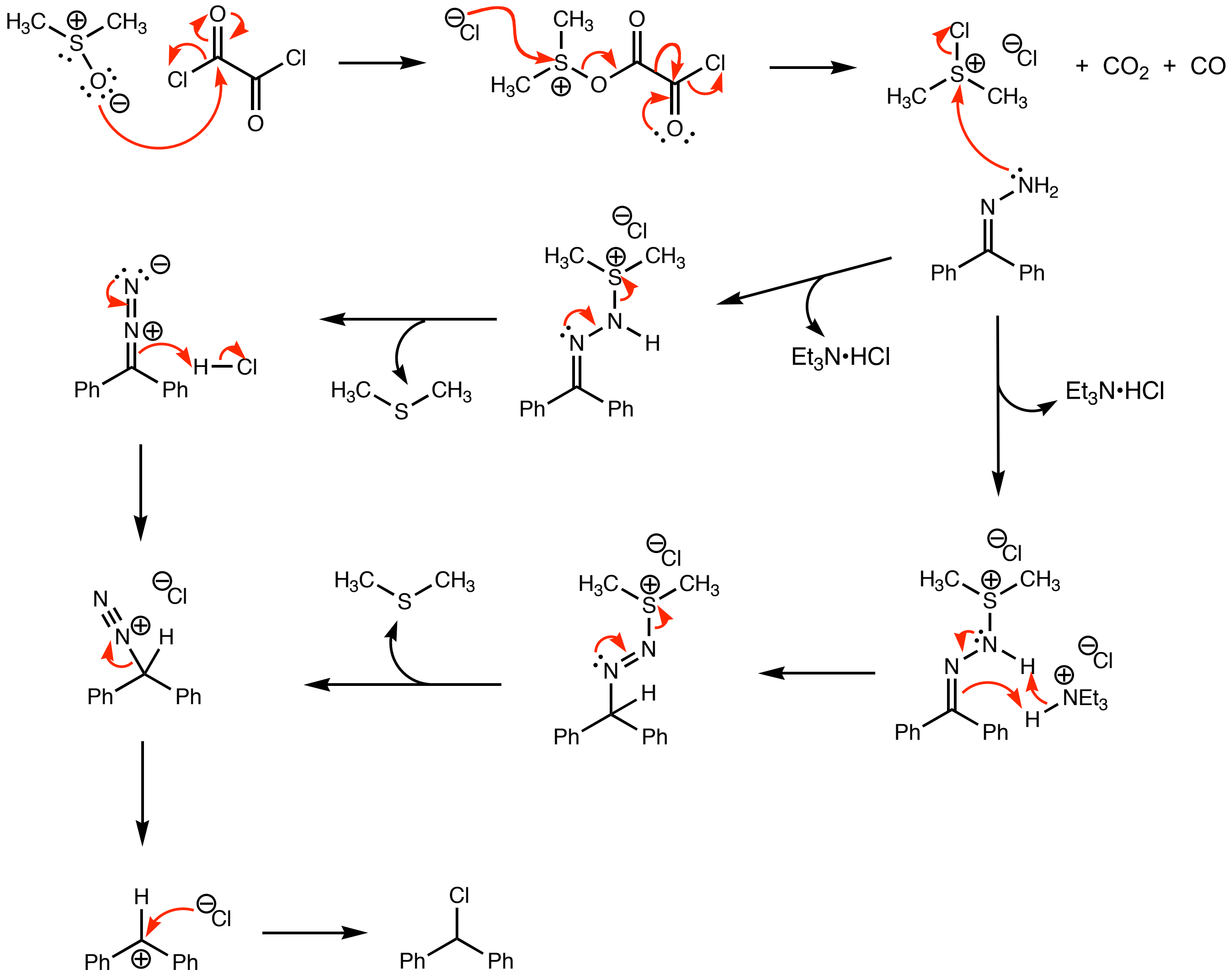




Acid-Catalyzed Cyclization Reaction of 3-Hydrazono-1,1,1-Trifluoro-2-Alkanones to 6-Trifluoromethyl-3,6-Dihydro-2H-[1,3,4]-Oxadiazines. Kamitori, Y.; Tomoko, S. *Heterocycles* **2005**, *65,* 2139-2150.

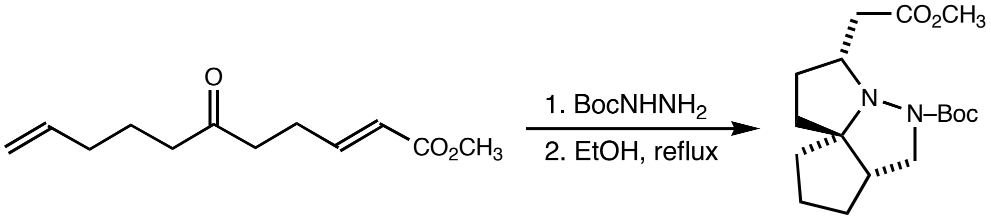
Question 3. The interesting functional group interconversion depicted below was recently published by Matthias Brewer. Provide a mechanism for this transformation. Note that DMSO and oxalyl chloride are first mixed together and that hydrazone and triethylamine are added once gas evolution has ceased.





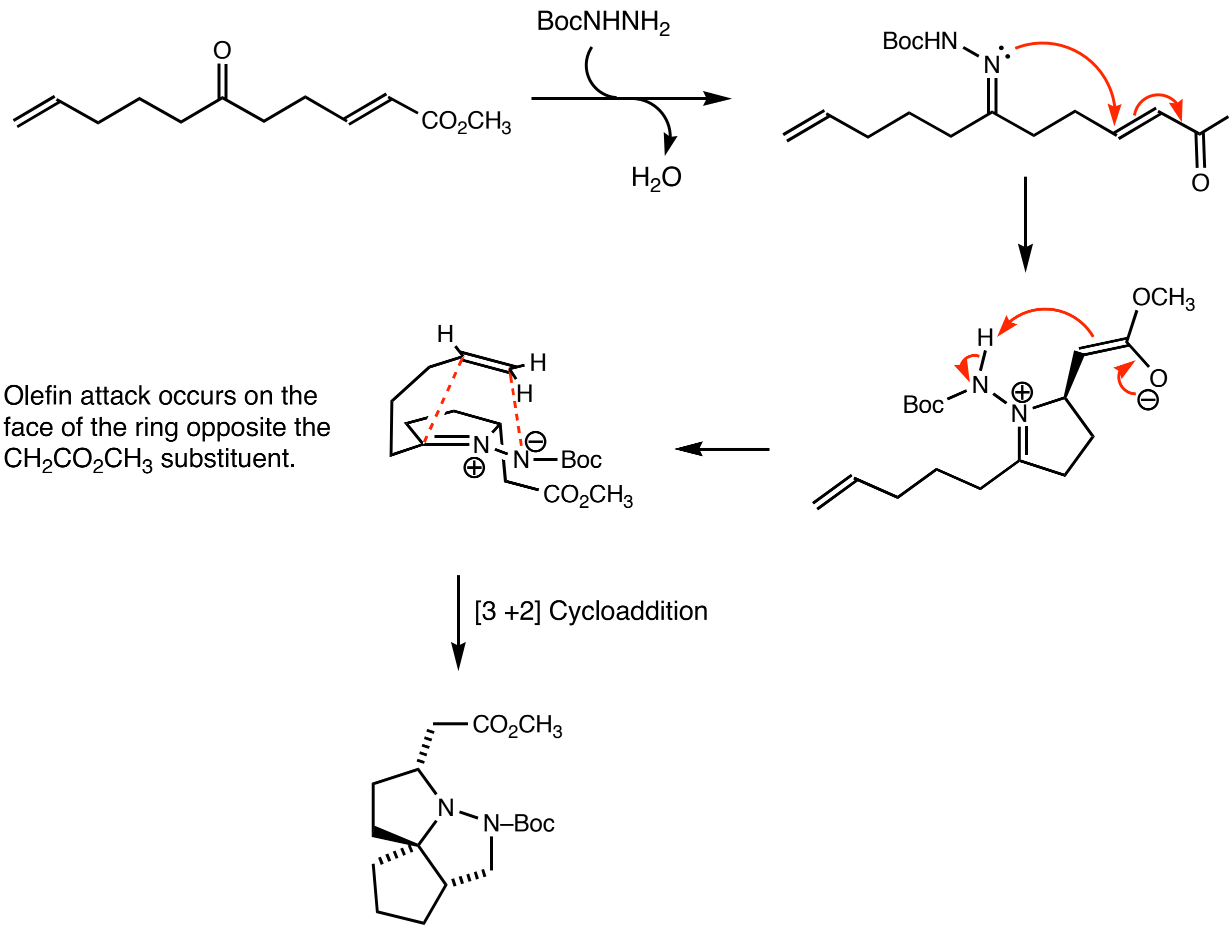
Conversion of Hydrazones to Alkyl Chlorides Under Swern Oxidation Conditions. Brewer, M. *Tetrahedron Lett.* **2006**, *47*, 7731-7733.

Question 4. A recent paper by Dolle highlights the rapidity with which one may assemble complex architecture in a single chemical operation. The transformation in question is illustrated below.



75% yield, one diastereomer

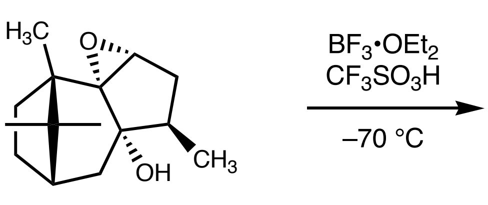
Provide a concise mechanism for the indicated transformation. In that step where the complex stereochemical relationships are established, a carefully rendered three dimensional illustration is requested.

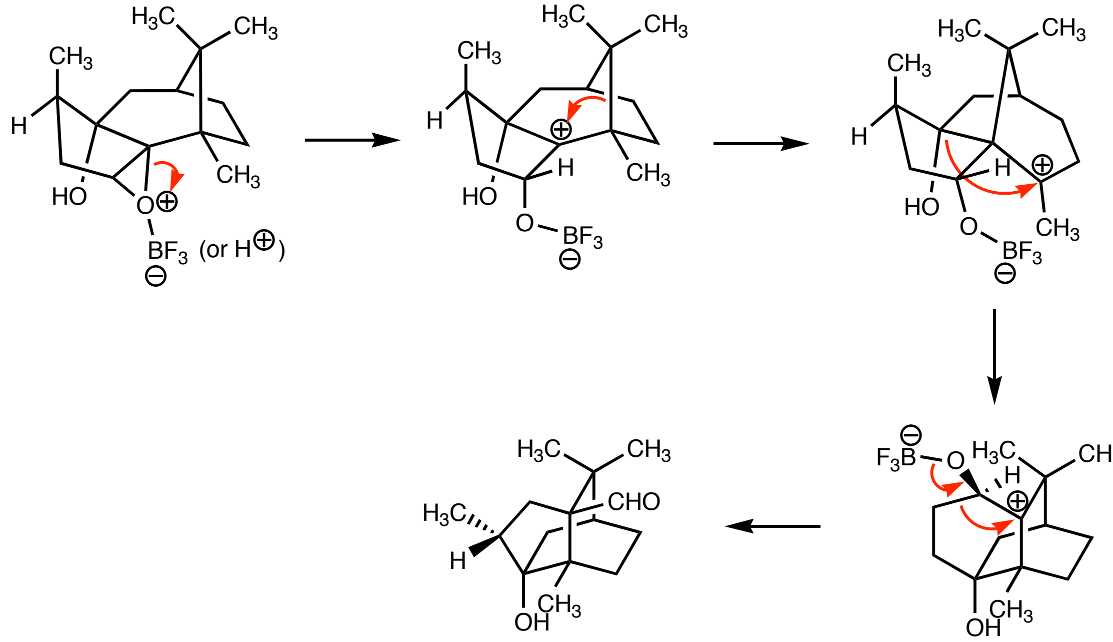


Olefin attack occurs on the face of the ring opposite the $CH_2CO_2CH_3$ substituent.

Application of the Intramolecular Azomethine Imine Cycloaddition to the Construction of a Novel, Orthogonally Protected Spirodiamino Acid Scaffold. Dolle, R. E.; Barden, M. C.; Brennan, P. E.; Ahmed, G.; Tran, V.; Ho, D. M. *Tetrahedron Lett.* **1999**, *40*, 2907-2908.

Question 5. Using clear 3D representations, provide a mechanism for the transformation below.

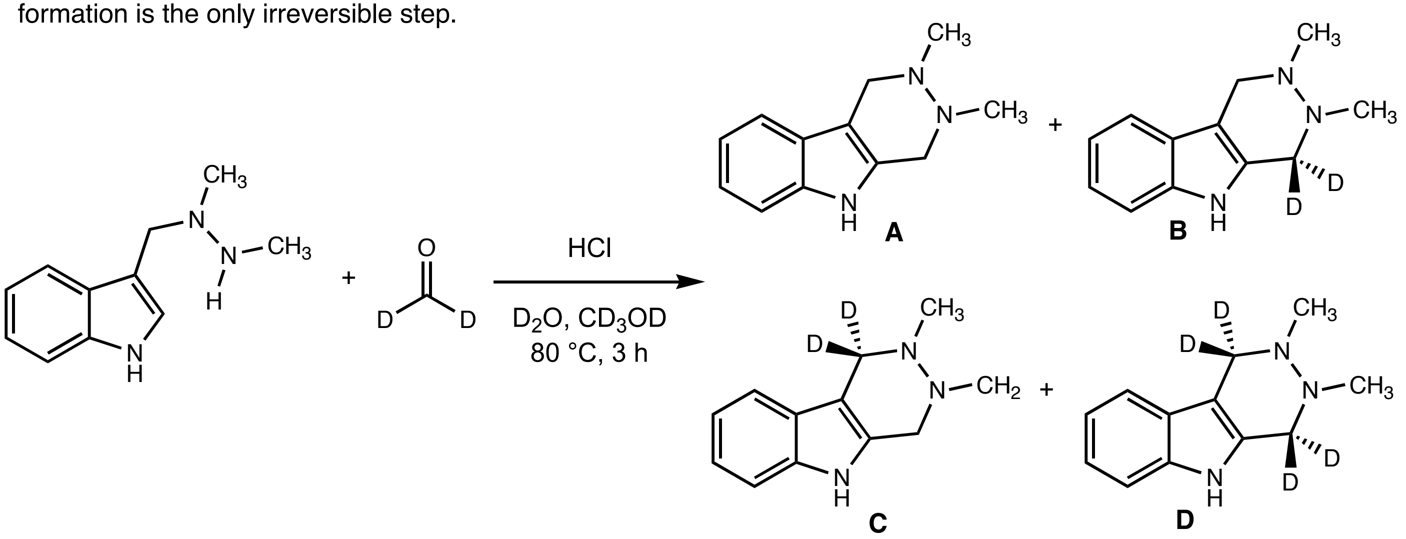




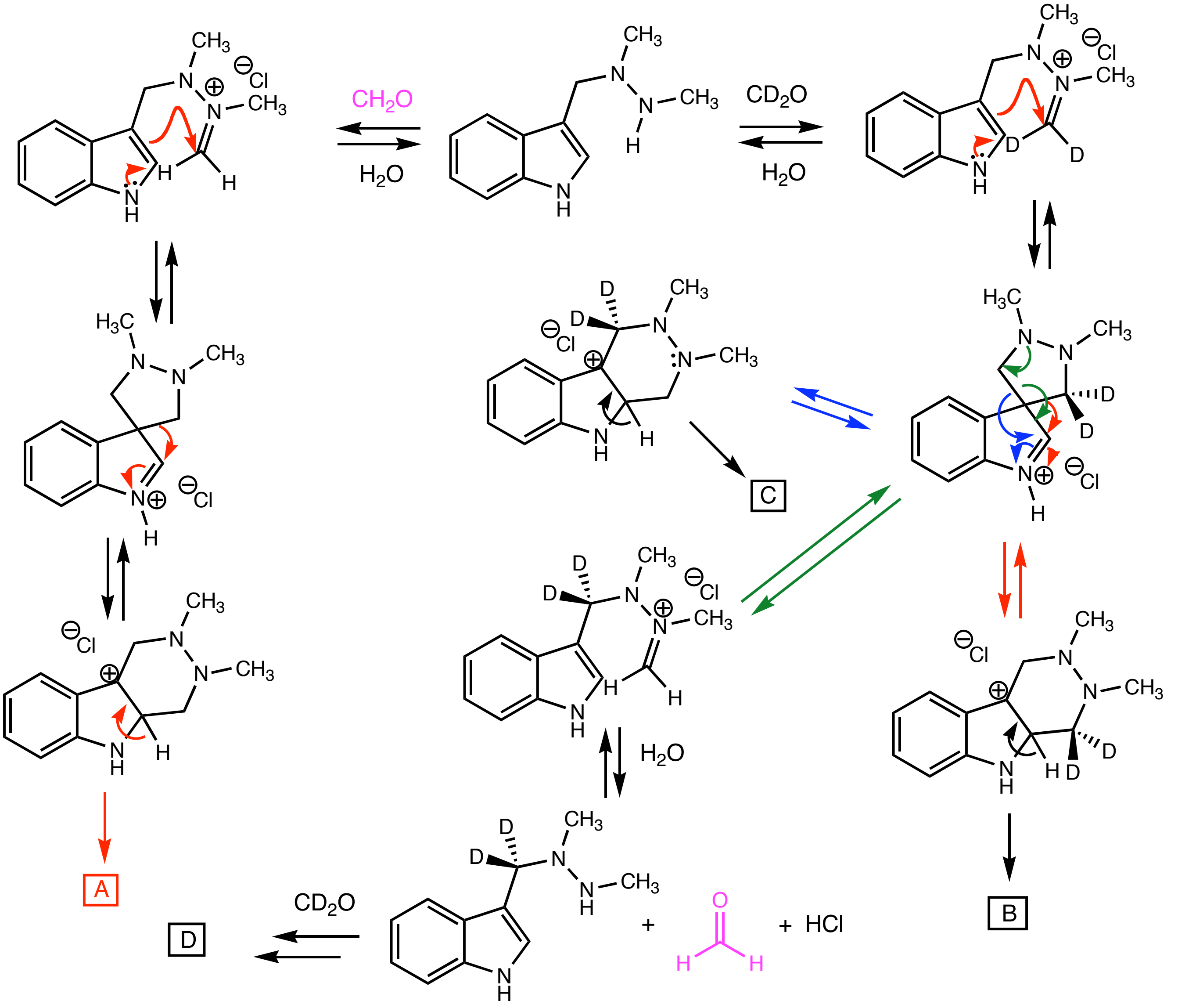
Strategies & Tactics in Org. Syn. **1991**, *3*, 165-198

Question 6. The experiment depicted below was conducted in order to determine whether or not a spirocyclic intermediate is en route to product in the Pictet-Spengler reaction.

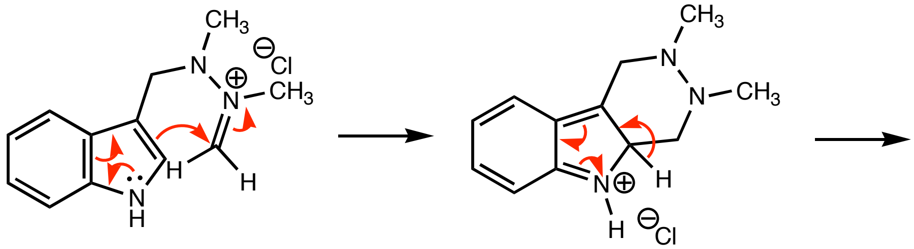
Part A. Provide a mechanism that accounts for the observed labelling pattern of the products. Assume that product formation is the only irreversible step.



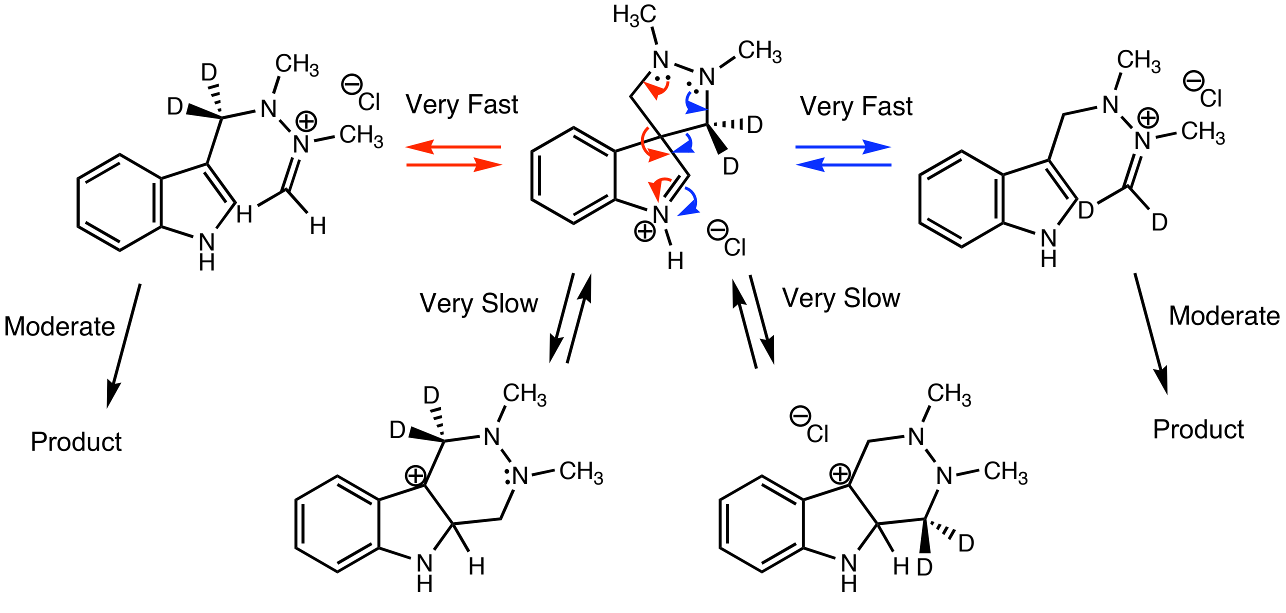
A : **B** : **C** : **D** ~ 1 : 1 : 1 : 1



Part B. Bailey concluded that the above experiment was proof that a spirocycle was involved in the pathway leading to product formation in the Pictet-Spengler reaction. However, he does note that the experiment does not rule out a mechanism where product formation occurs via direct attack of the indole 2-position on the iminium ion as shown below (i.e. the pathway leading from starting material to product does not include a spirocycle)? Explain why this is in fact the case.

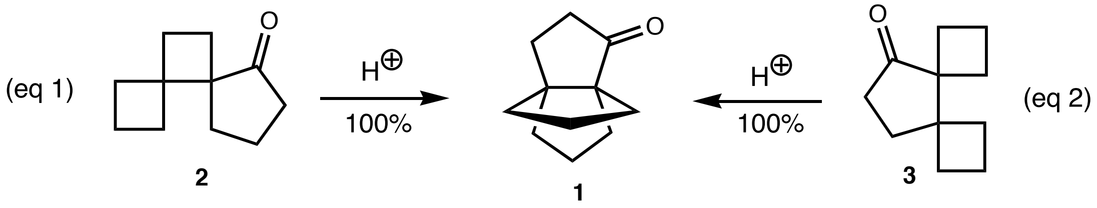


The labelling experiment does not rule out the following scenario: Spirocycle breakdown via iminium ion formation is faster than product formation via attack of the indole 2-position which in turn is much faster than product formation via C–C migration from the spirocycle intermediate (i.e. the latter is so slow it is not observed).

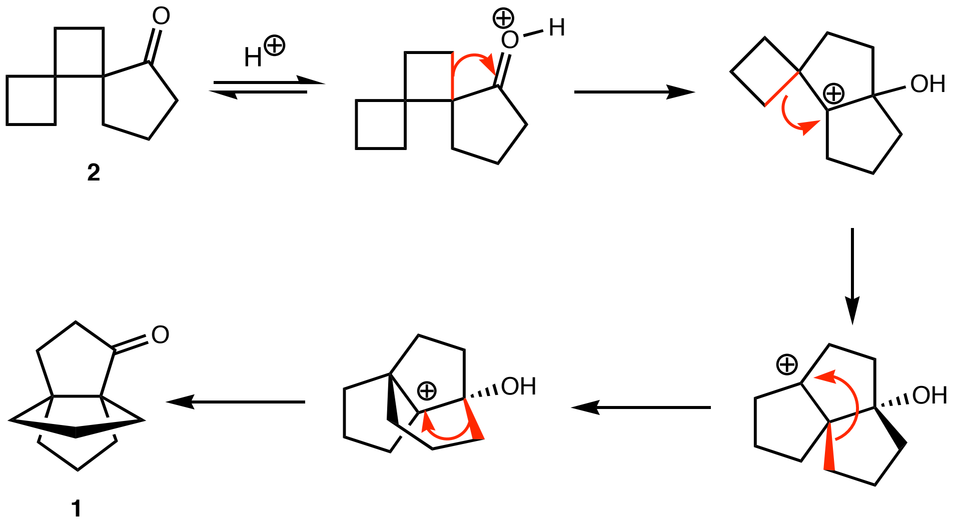


Direct Proof of the Involvement of a Spiro Intermediate in the Pictet-Spengler Reaction. Bailey, P. D. *J. Chem. Res.* **1987**, 202-203.

Question 7. Fitjer and co-workers have reported a very interesting approach to the [3,3,3]propellane **1**. This tricyclic ketone may be produced in quantitative yield through acid-catalyzed rearrangement of ketones **2** or **3**.

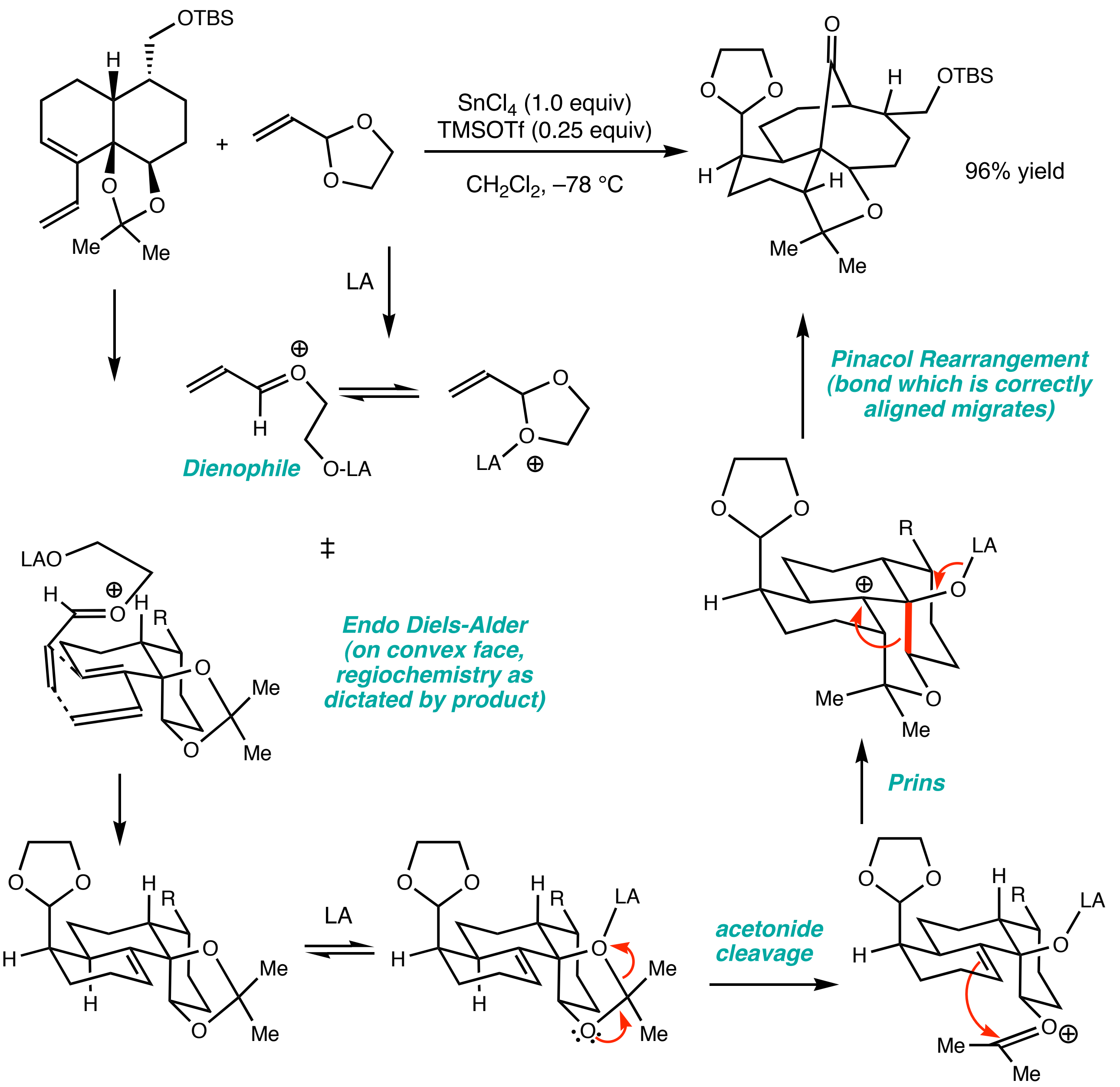


Please provide a plausible mechanism for the rearrangement **2**→**1** (eq 1). Use 3-dimensional representations where appropriate to illustrate your answer.



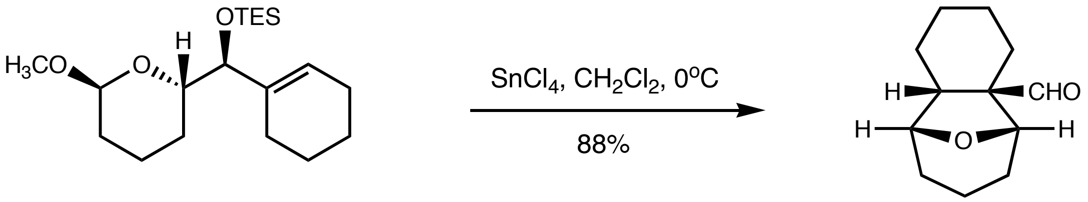
Towards A Synthesis of (±)Modhephene Via Cascade Rearrangement: Synthesis and Rearrangement of Dispiro[3.0.3.2]Undecane to [3.3.3]Propellanes. Fitjer, L.; Majewski, M.; Kanschik, A. *Tetrahedron Lett.* **1988**, *29*, 1263-1264.

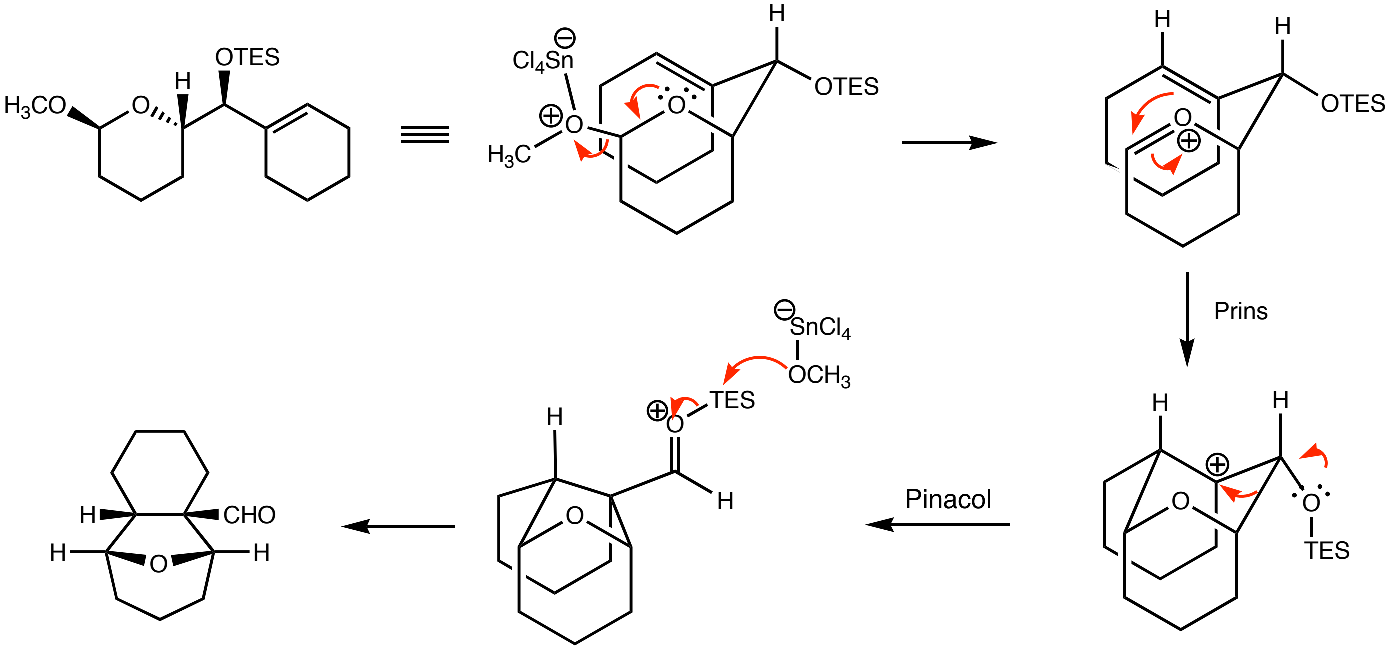
Question 8. Barriault recently published the following Lewis-acid mediated reaction cascade as a strategy to rapidly assemble highly functionalized bicycloalkanones. Using clear 3D representations, please provide a mechanism that includes a rationalization for the relative stereochemistry observed in the product.


OTBS
H
Me
Me
O
O
+
$SnCl_4$ (1.0 equiv)
TMSOTf (0.25 equiv)
CH_2Cl_2, –78 °C
96% yield
LA
Dienophile
O-LA
‡
LAO
R
Endo Diels-Alder (on convex face, regiochemistry as dictated by product)
Pinacol Rearrangement (bond which is correctly aligned migrates)
Prins
acetonide cleavage
LA

Synthesis of Highly Functionalized Bicyclo[m.n.1]alkanones via a Cationic Reaction Cascade. Lavigen, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921-5923

Question 9. Using clear 3D representations, provide a mechanism for the transformation below.





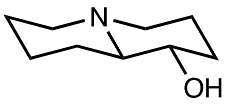
Stereocontrolled Construction of Either Stereoisomer of 12-Oxatricyclo[6.3.1.0^{2,7}]dodecanes Using Prins-Pinacol Reactions. Overman, L. E.; Velthulsen, E. J. *Org. Lett.* **2004**, *6*, 3853-3856.

Chem 206 *Due: Friday, Sept. 29th*

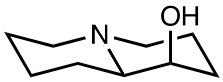
Problem Set 2: Conformational Analysis *Name:*__________________________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

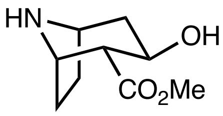
Question 1. The given below pairs of hydroxylated piperidines exhibit substential differences in pKa. These pKa differences could be attributed to stereoelectronic effects. Using FMO theory, provide an explanation that accounts for the different basicity of the diastereomeric piperidines below. Be sure to include 3D drawings to your explaination and clearly identify the interacting orbitals.



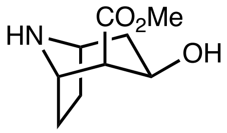
pKa 8.73



pKa 10.2



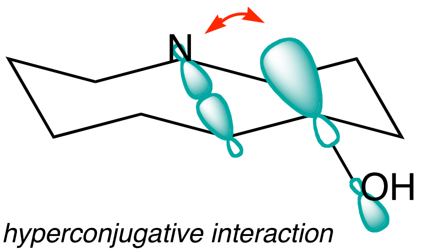
pKa 8.2



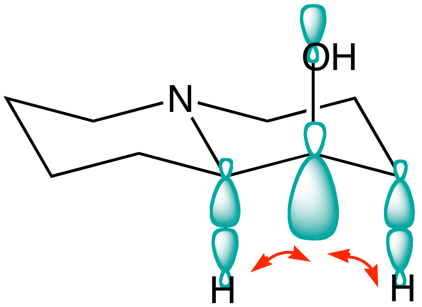
pKa 9.2

- -

σ(C–N) → σ*(O–H)



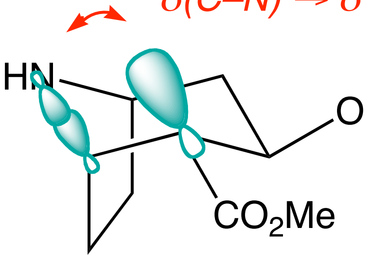
The hyperconjugative interaction σ(C–N) → σ(O–H) is responsible for reducing the electron density around nitrogen.*



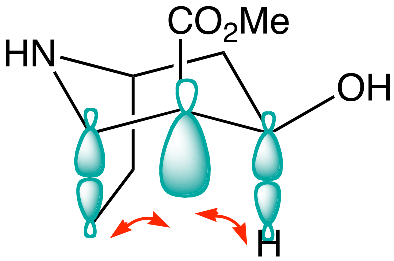
σ(C–H) → σ*(O–H)

The present hyperconjugative interaction σ(C–H) → σ(O–H) does not influence the electron density distribution around nitrogen. Hence, the basicity of the nitrogen is retained.*

σ(C–N) → σ*(C–CO_2Me)



Similarly, the same reasoning could be applied to the bridged piperidine case. However, σ•(C–CO_2Me) is the accepting orbital in this case.

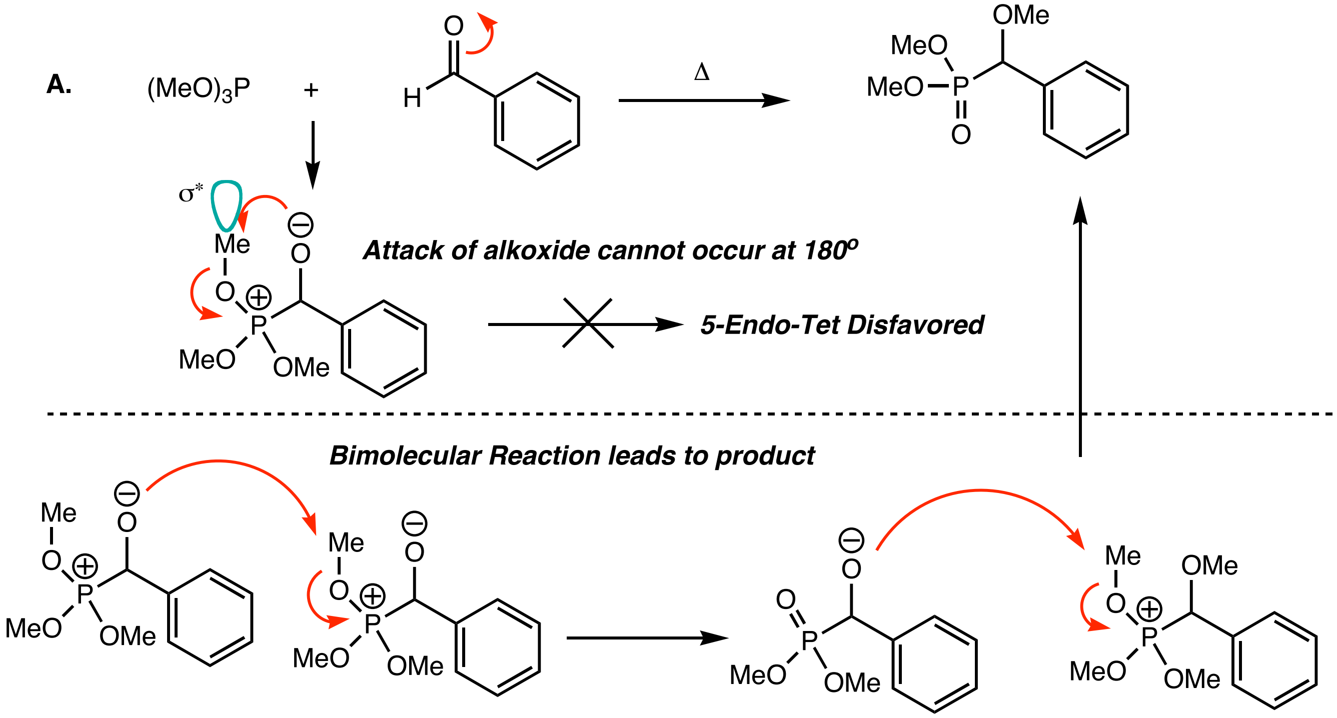


σ(C–C) → σ*(C–CO_2Me)

σ(C–H) → σ*(C–CO_2Me)

Question 2. For each of the following two transformations please provide a plausible reaction mechanism. Be sure to dicuss the relevant issues regarding orbital overlap requirements.

A.

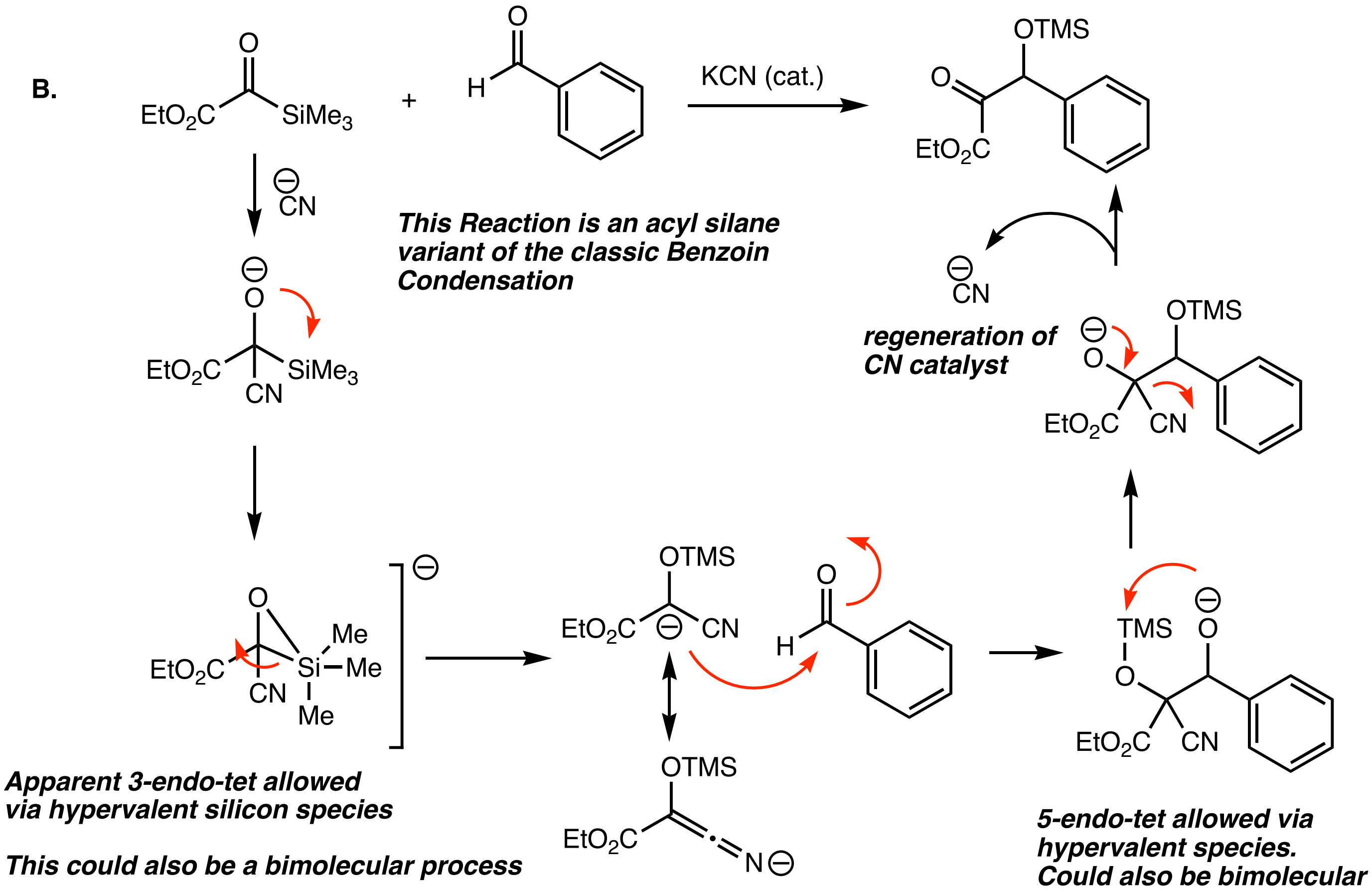


Attack of alkoxide cannot occur at 180°

5-Endo-Tet Disfavored

Bimolecular Reaction leads to product

B.



This Reaction is an acyl silane variant of the classic Benzoin Condensation

regeneration of CN catalyst

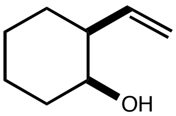
Apparent 3-endo-tet allowed via hypervalent silicon species

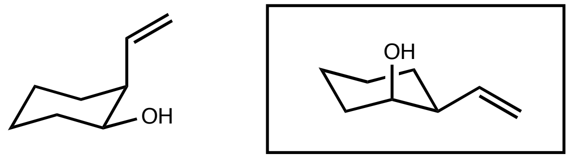
This could also be a bimolecular process

5-endo-tet allowed via hypervalent species. Could also be bimolecular

Question 3.

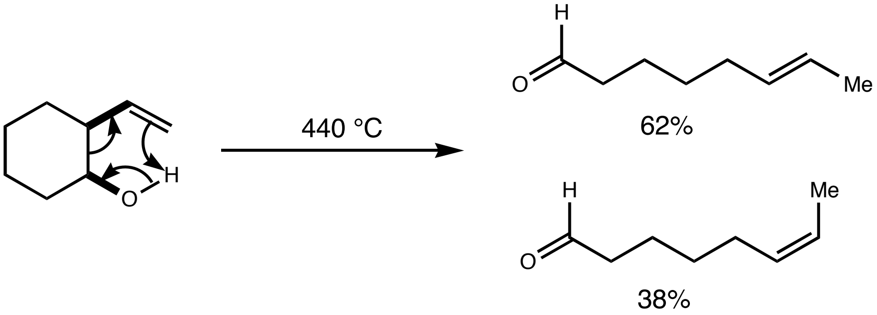
Part A. Draw the two chair conformers of the vinylcyclohexanol shown below. Based on A values, predict which of the two is the most stable.

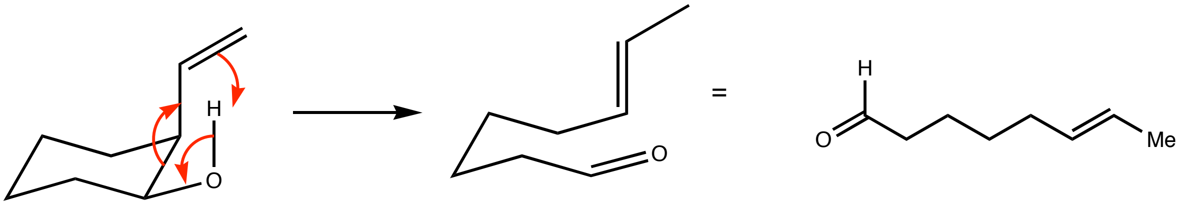


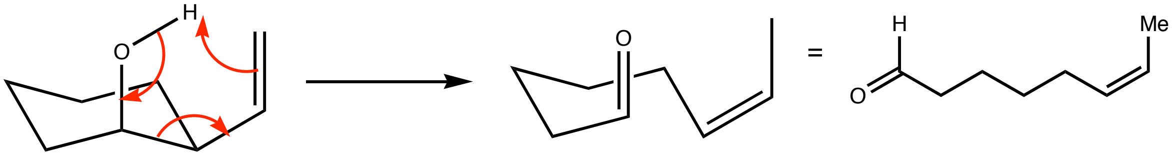


$A_{CH=CH2} > A_{OH}$ thus $CH=CH_2$ will be equatorial in most stable conformer.

Part B. Vinylcyclohexanols undergo retro-ene reactions at high temperatures as shown below. Sketch out 3-D transition states leading to the two products.





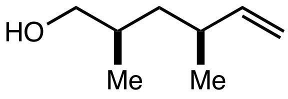


Part C. Assuming A values are valid at 440 °C, can these be used to account for the product distribution? If not, can you think of another explanation?

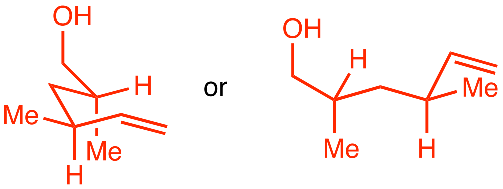
In this case, the least stable (and hence least abundant) conformer leads to the favored product. This is possible so long as the two conformers are interconverting rapidly (as you would expect at 440 °˘C) and that one conformer reacts faster than the other. This must be the case here. This is an example of the Curtin-Hammett principal at work.

Question 4. The structural unit of β-turns is present in many proteins and bioactive peptides and has important implications for both structure and function. As such, the synthesis of β-turn mimics has been an intensive area of research. While most solutions to creating such turns have relied on covalent linkages, Hoffmann and coworkers have developed an approach based on acyclic conformational preferences (*Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1745-1747).

Part A. Please provide a clear 3-dimensional representation of the lowest energy conformer of **1**.



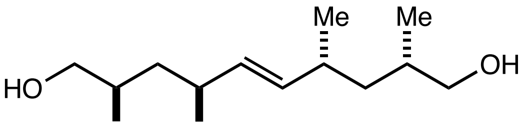
1



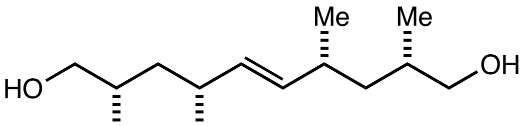
Minimized syn-pentanes

Vinyl group less hindered than Me groop.

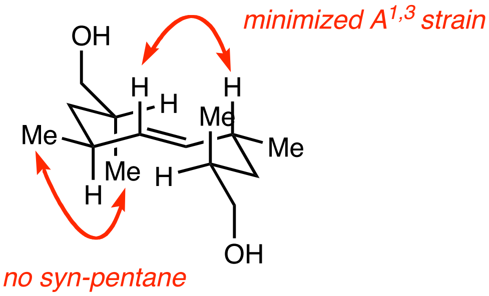
Part B. Based on your analysis of **1** please draw the low energy conformations of **2** and **3**, and comment on which structure you think could be used as a β-turn mimic. ***Note:*** A β-turn is a structural feature that creates a U-turn in a peptide, bringing the termini into proximity.

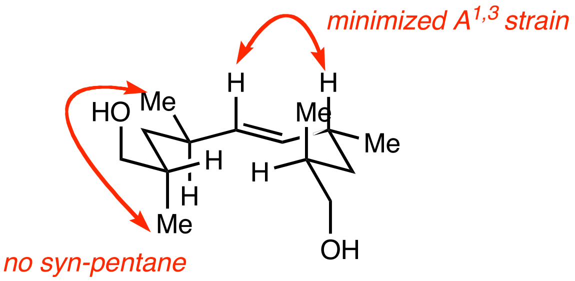


2

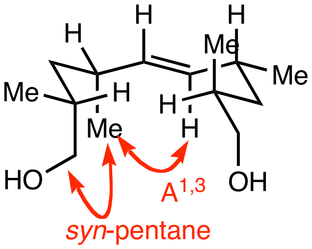


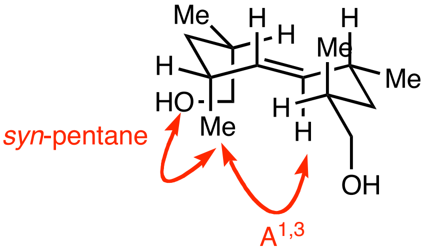
3



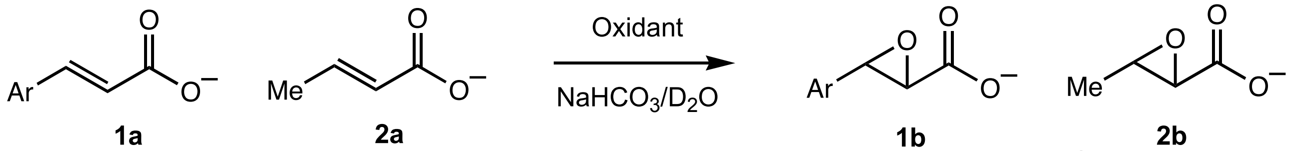


*The alternative conformations suffer from unavoidable syn-pentane interactions and $A^{1,3}$ strain. Structure **2** prefers the termini "trans", while structure **3** prefers termini "cis". On this basis **3** could be incorporated into a β-turn mimic.*

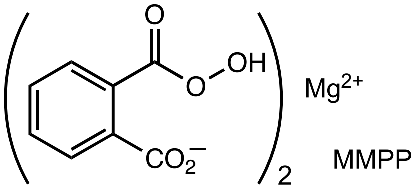


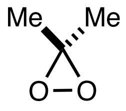


Question 5. The following epoxidation studies performed in aqeous medium have been reported by Breslow and Biscoe. It was noted that cinnamates **1a** have similar epoxidation rate as crotonates **2a** if MMPP is used for epoxidation. However, the oxidation of styrenes **1a** is faster if dimethyldioxyrane (DMDO) and oxaziridinium **3** are used as epoxidizing agents.

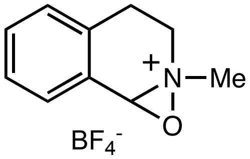


Ar	MMPP (**1b**:**2b**)	DMDO (**1b**:**2b**)	Oxaziridinium **3** (**1b**:**2b**)
p-CF_3Ph	16:84	22:78	92.7:7.3
Ph	44:56	61:39	96.5:3.5
2-Naphthyl	47:53	68:32	99.8:3.2





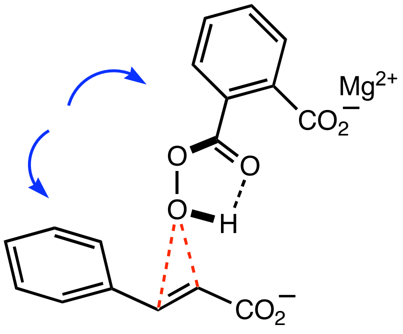
DMDO



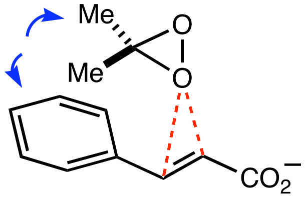
3

Using 3D drawings of the epoxidation transition states, eplain why oxaziridinium **3** shows the highest selectivity for the cinnamic acid epoxidation and MMPP--the lowest.

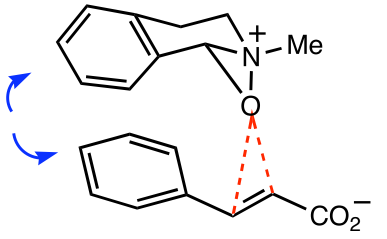
*In polar, protic D_2O, hydrophobic effects play a very strong impact on reactivity of the substrates. Thus, the transition state for epoxidation of nonpolar substrates like **1a** is more stable when nonpolar oxidants like **3** are used. In other words, nonbonding hydrophobic interactions between the oxidant and substrate stabilize the corresponding transition state in aqueous medium.*



Aromatic rings are far away, low hydrophobic stabilization of the TS.

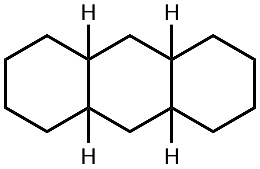


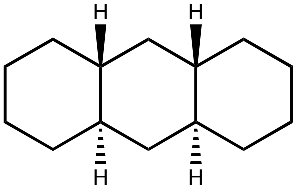
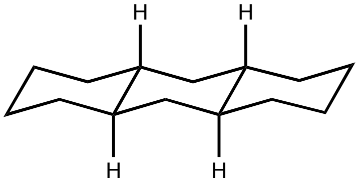
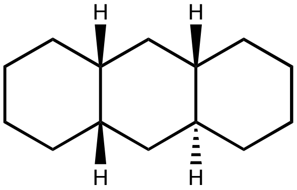
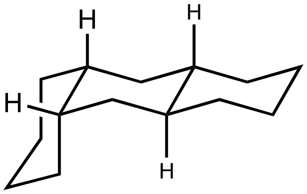
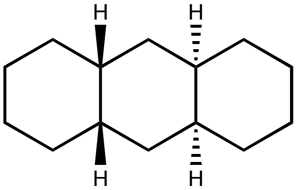
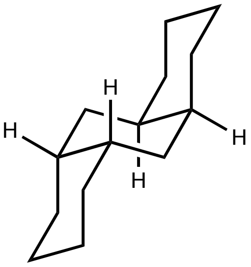
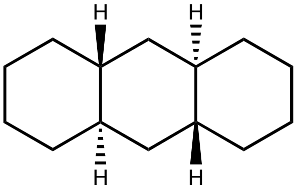
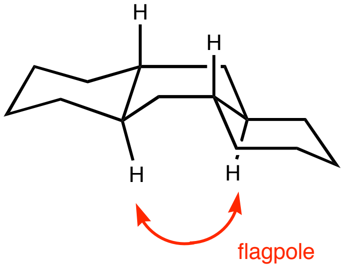
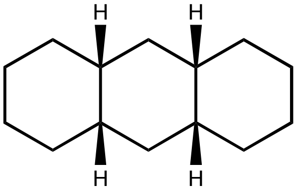
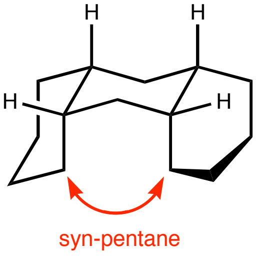
Isopropyledene methyl groups could hydrophobically interact with the aromatic substituents thus stabilizing the TS.



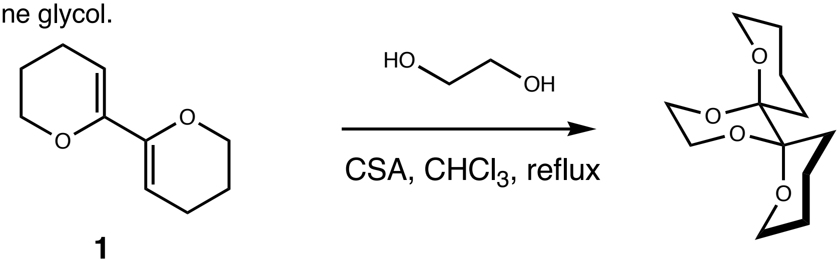
Aromatic groups can engage into π-stacking interactions. This TS has maximum stability in an aqeous environment.

Question 6. Draw all possible diastereomers of this tricyclic ring system in 2D and 3D. Based on your 3D drawings, rank each structure in terms of energy. Clearly identify all gauche-butane and syn-pentane interactions.



2D Structure	Corresponding 3D Structure
	
3 gauche: 2.4 Kcal/mol 	
6 gauche: 4.8 Kcal/mol 	
1 flagpole (boat): 6.4 Kcal/mol 	
1 syn-pentane + 4 gauche: 6.9 Kcal/mol 	

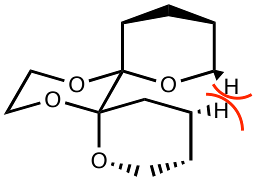
Question 7. The dispiroketal (Dispoke) protecting group is of great utility for the selective protection of 1,2-diols. Provide a 3-D representation of the expected product for the acid-catalyzed reaction of *bis*-dihydropyran **1** with ethylene glycol.



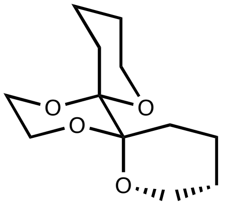
1

aa/aa

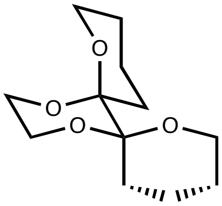
The *cis* isomer has 4 possible conformations:



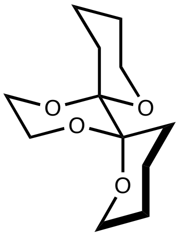
ea/ee



ea/ea

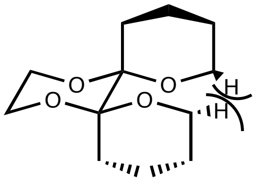


ee/aa

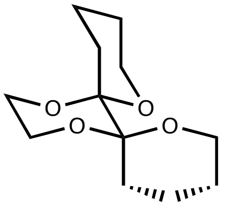


aa/ea

The *trans* isomer has 5 possible conformations:



ee/ee



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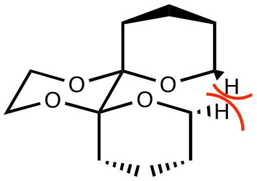
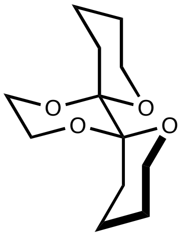
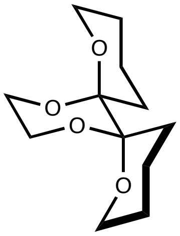


ea/ae



ae/ea

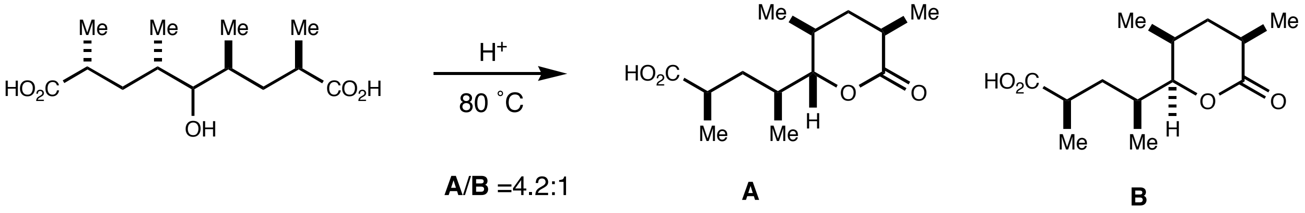


aa/aa

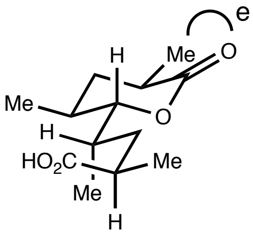
The all axial conformation of the *trans* isomer is preferred sterically and stereoelectronically.

Question 8.

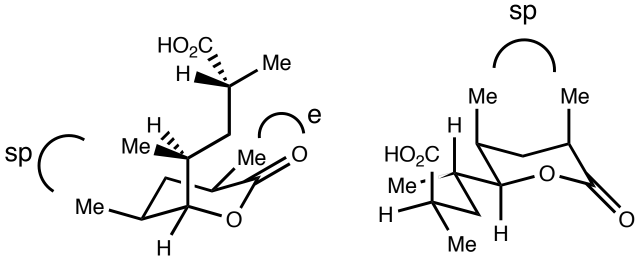
Part A. Rationalize the selectivity observed in the following thermodynamic cyclization:



A/**B** =4.2:1



A

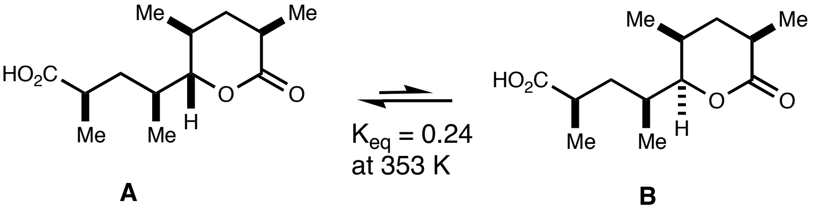


B

*Under equilibrating conditions, diastereomer **A** can adopt a conformation that is clearly favored over both possiblilites for **B**. Note the eclipsing methyl/carbonyl interactions (e) and syn-pentane (sp) interactions in the conformations of diastereomer **B**.*

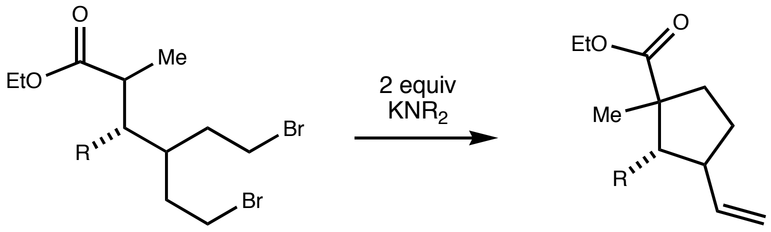
Acc. Chem. Res. **1994**, *27*, 9

Part B. Assuming that equilibration between **A** and **B** is complete, calculate the energy difference between **A** and **B**.

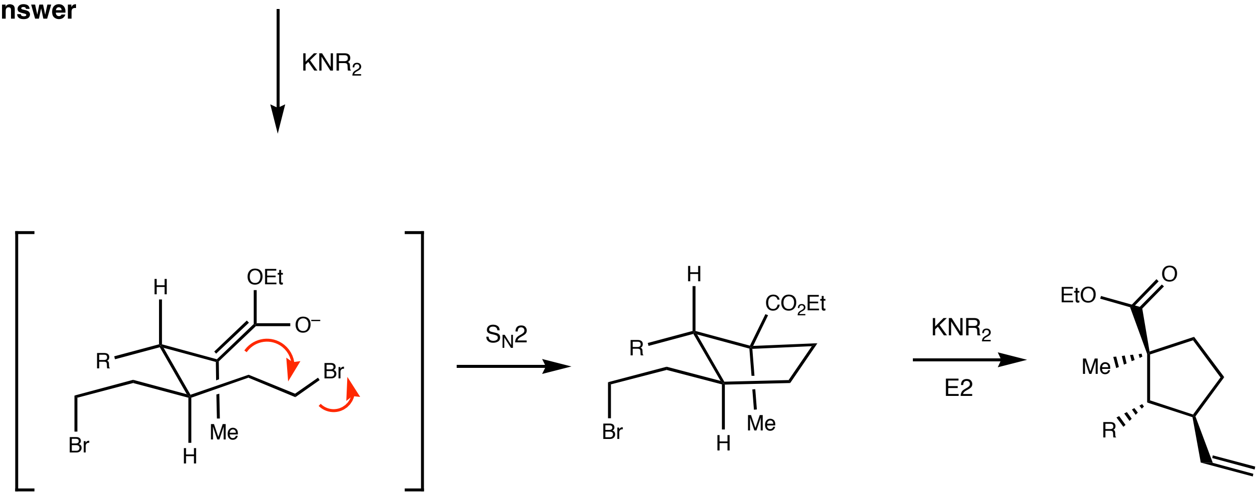


$\Delta G = -2.3RTLog_{10}K$
$\Delta G = -2.3 \cdot 1.99\ cal/(molK) \cdot 353\ K \cdot Log_{10}(.24)$
$\Delta G = +1.0\ kcal/mol$

Question 9. Two new stereocenters have been generated in the illustrated transformation shown below. Based on your knowledge of conformational analysis, provide a mechanism for this transformation that predicts the stereochemistry of the product.



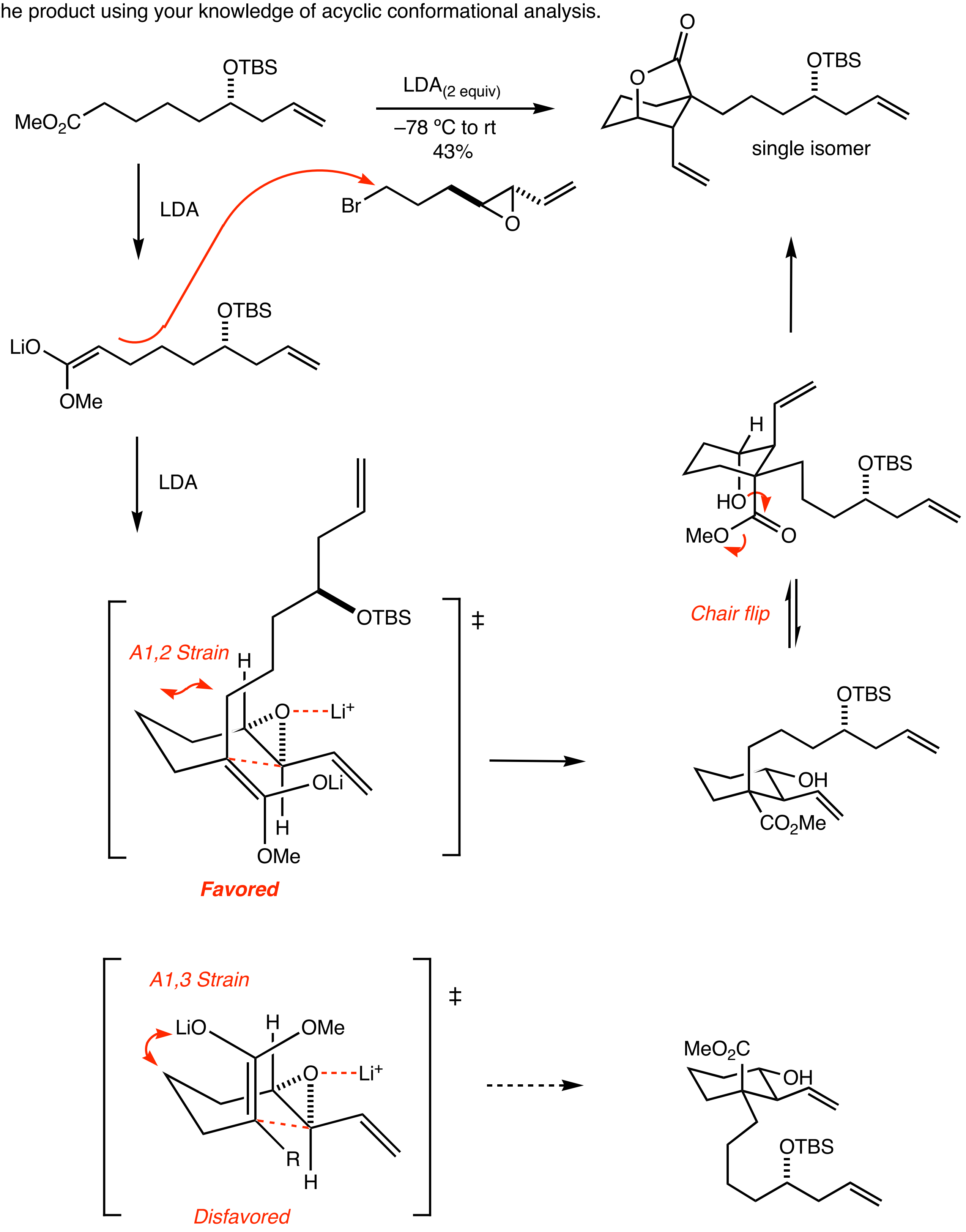
Answer



minimal A(1,3) strain;
psuedo-equatorial side chains.

(*Tetrahedron Lett.* 1**997,** 415)

Question 10. The following cascade alkylation was employed by Stork and coworkers during their synthesis of histrionicotoxin alkoloids. Please propose a mechanism with clear 3D drawings that accounts for the formation of the product using your knowledge of acyclic conformational analysis.



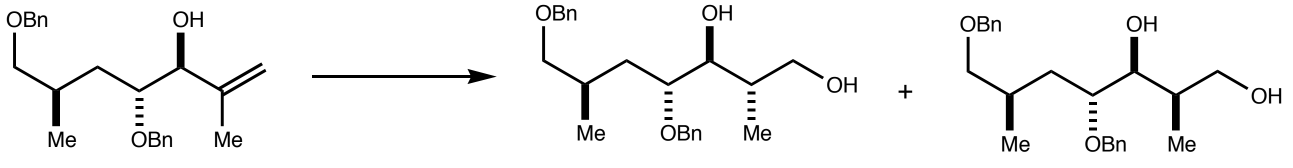
Chem 206 *Due: Friday, Oct. 6*

Problem Set 3 *Name:________________TF:___________*

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1.

Rationalize the following outcome of the two hydroboration reactions shown below.

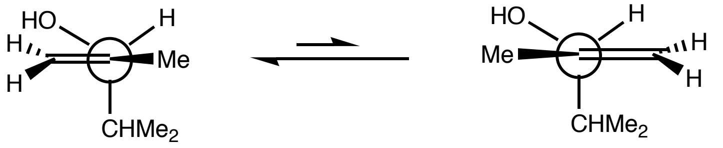


anti *syn*

	anti : syn	yield
9-BBN	85 : 15	70%
BH3*THF	05 : 95	84%

- *In the favored transition states, torsional interactions will be minimized, placing the large group (R_L) anti to the incoming reagent.*

- *Recall that for 1,2-disubstituted olefins, 1,2 allylic strain (R_m = Me, OH) is dominant over 1,3 allylic strain:*

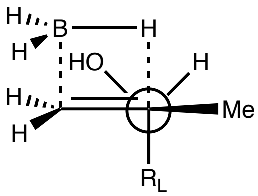


ΔE = 1.6 kcal/mol
(molecular mechanics)

- *These features predict the product for the case of the small reagent BH_3•THF.*

- *For the more bulky $(Cy)_2BH$, the selectivity turns over because the dominant interaction now is that between the ligands on boron and the larger hydroxyl group. A 180° rotation releaves this interaction by replacing it with a smaller ligand - hydrogen interaction. This lower energy transition state leads to the observed product.*

- *For more discussion, see Houk, JACS, **1995**, 9434 and references therein.*



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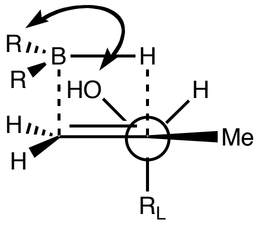
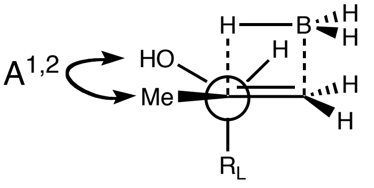


disfavored



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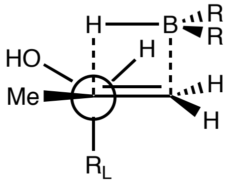

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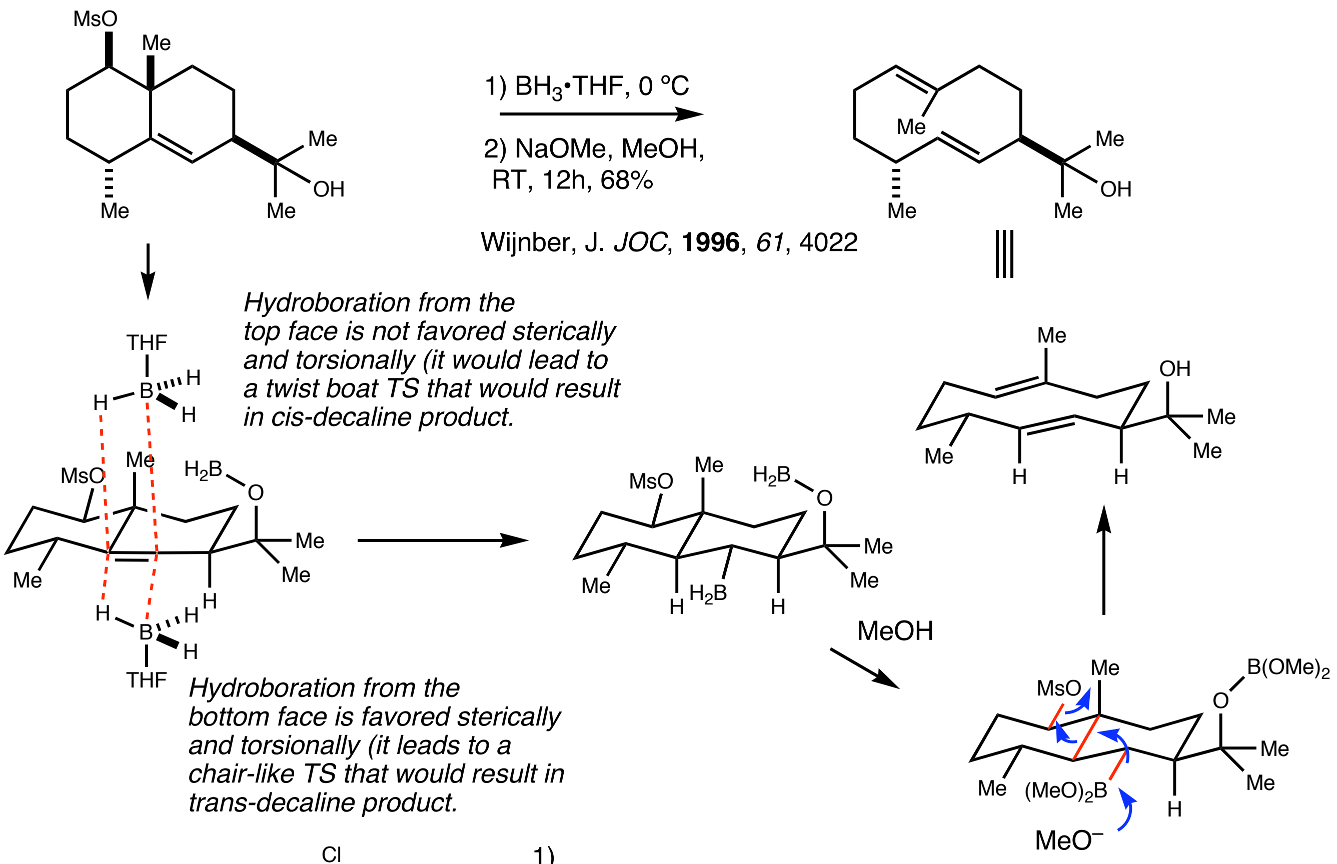
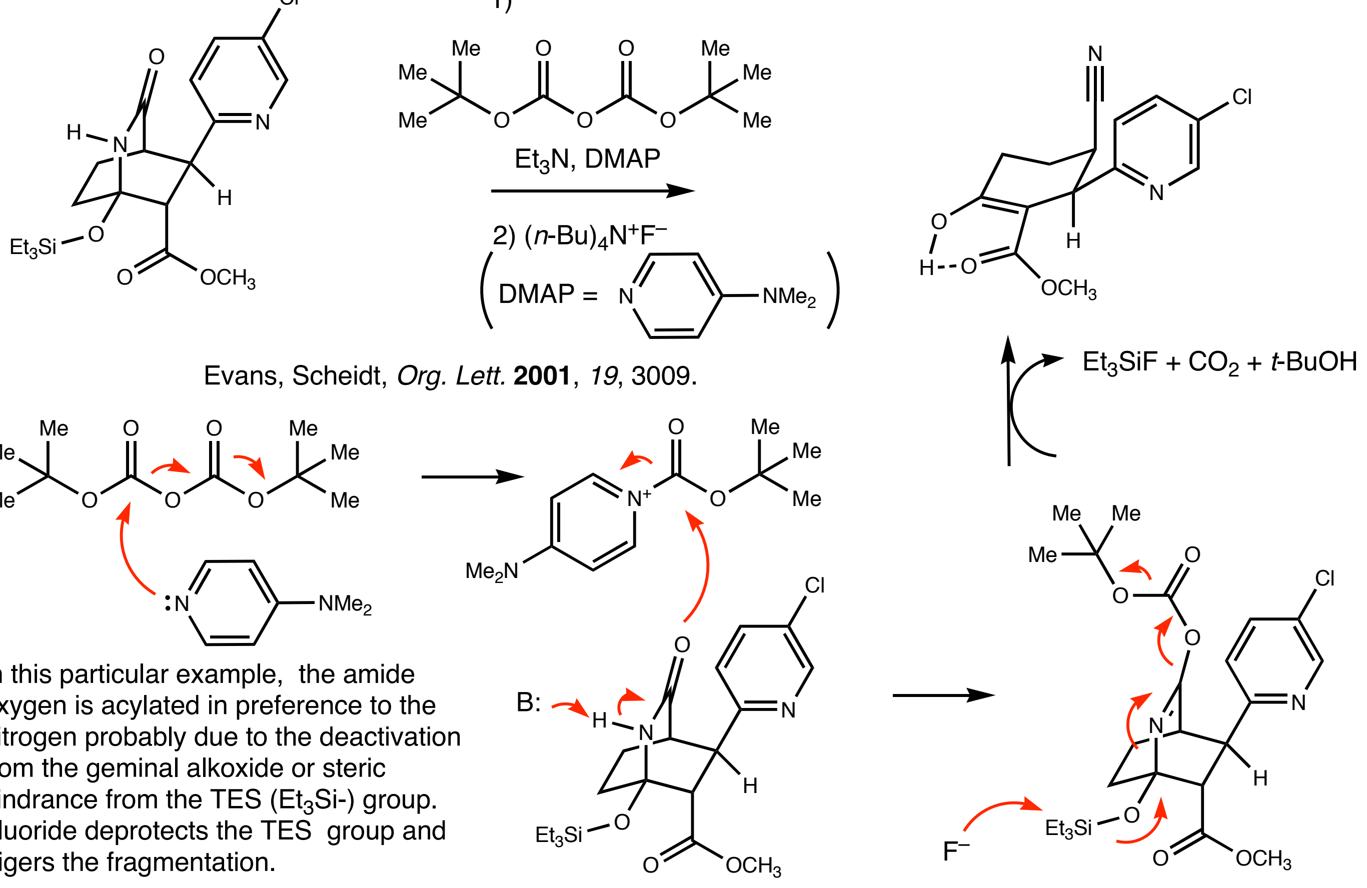
Question 2. Please provide mechanisms with clear 3D drawing that expain the outcomes of the following reactions:



Wijnber, J. *JOC*, **1996**, *61*, 4022

Hydroboration from the top face is not favored sterically and torsionally (it would lead to a twist boat TS that would result in cis-decaline product.

Hydroboration from the bottom face is favored sterically and torsionally (it leads to a chair-like TS that would result in trans-decaline product.

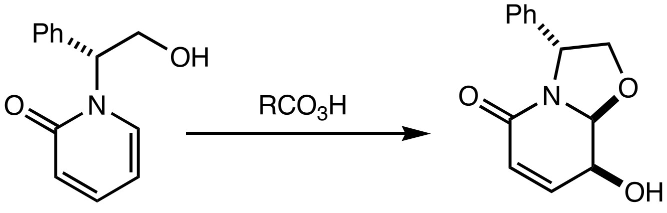


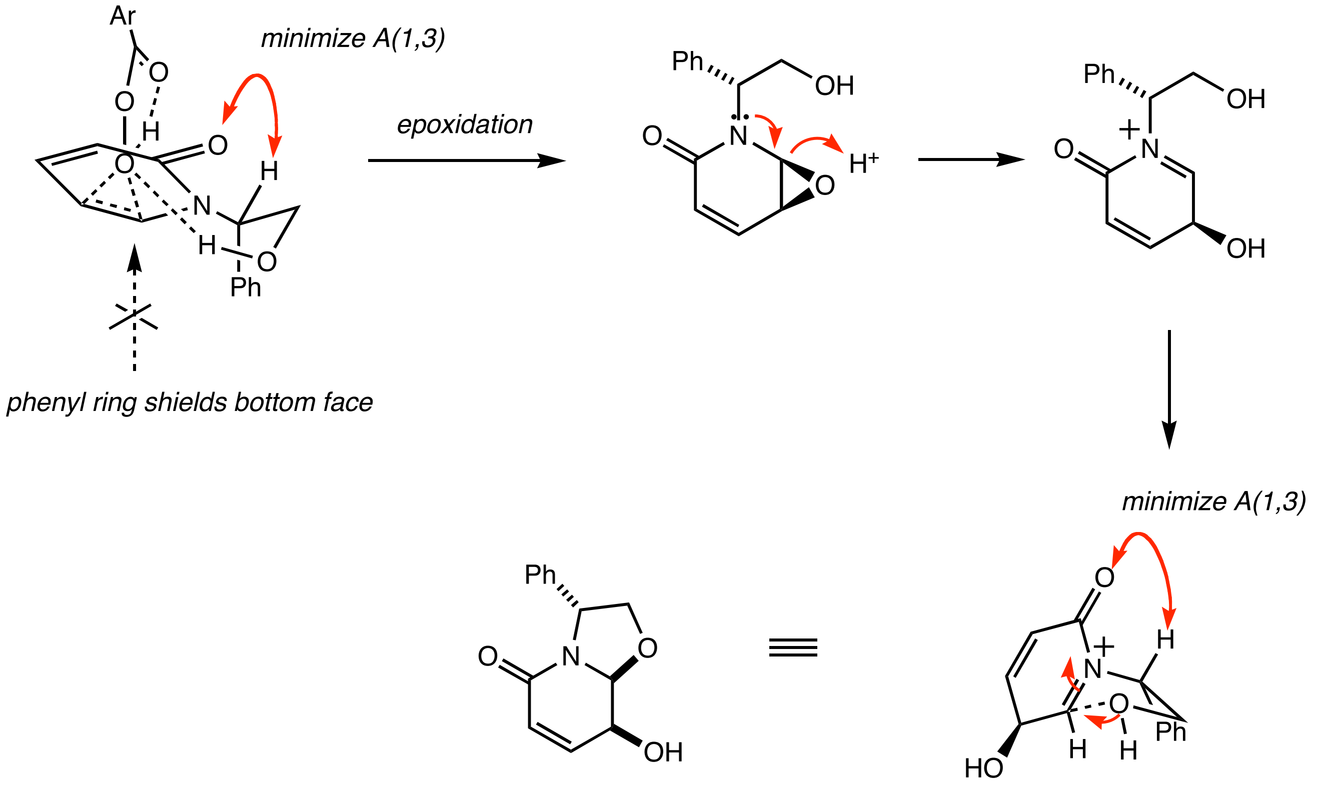
Evans, Scheidt, *Org. Lett.* **2001**, *19*, 3009.

In this particular example, the amide oxygen is acylated in preference to the nitrogen probably due to the deactivation from the geminal alkoxide or steric hindrance from the TES (Et_3Si-) group. Fluoride deprotects the TES group and trigers the fragmentation.

Question 3.

Provide a mechanism for the following reaction which is consistent with the product stereochemistry. Since stereochemical issues are at stake, carefully rendered 3-D conformational drawings should be incorporated into your answer.

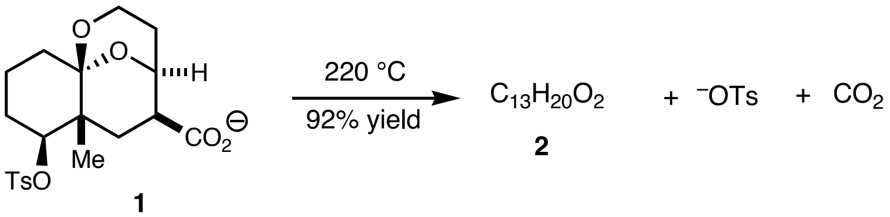




Question 4.

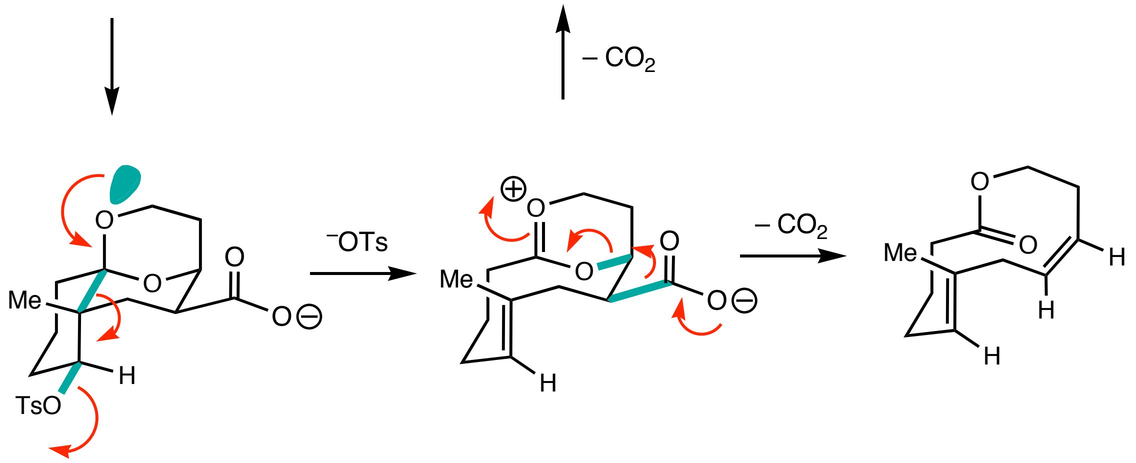
Carboxylate **1** undergoes a complex fragmentation-decarboxylation cascade upon heating to 220 °C. The product **2**, $C_{13}H_{20}O_2$, contains two double bonds and an ester/lactone moiety based on IR and NMR data.

Predict the structure of **2** including the stereochemistry of both double bonds. Identify the stereoelectronic requirements that must be met in this transformation.

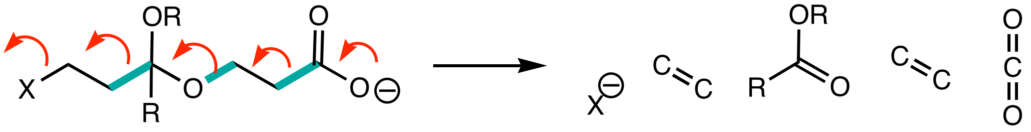


Your Answer:

Option A
2 Steps



Option A
1 Step

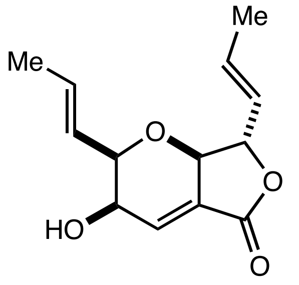


Stereoelectronic requirement: All participating bonds and orbitals must be arranged in an anti-periplanar orientation

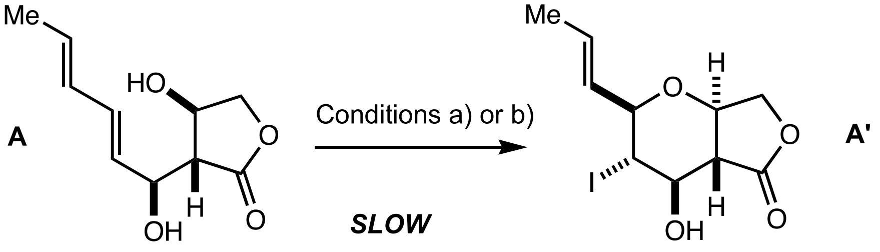
(Eschenmoser et al., Angew. Chem. Int. Ed. **1979, *18, 6***34, 636).

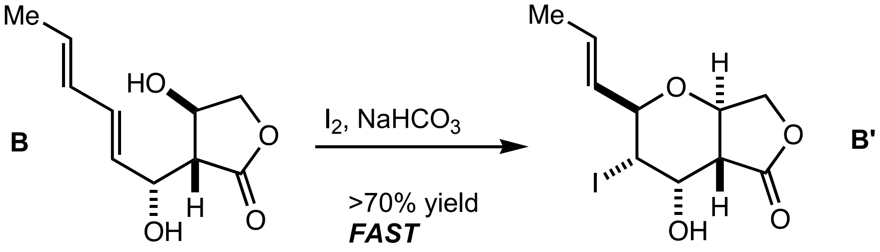
Question 5.

During the synthesis of the anti-tumor agent Waol A, Snider (*Org. Lett.* **2003**; 5(4); 451-454) and coworkers prepared the diastereomeric aldol adducts **A** and **B**. These substrates underwent iodoetherification at vastly different rates. In fact, to achieve sufficient conversion a more reactive iodonium reagent (bis(sym-collididne) $AgPF_6$) was necessary. *Please provide a mechanism for the reactions (**A** to **A'** and **B** to **B'**) that accounts for the observed selectivity and difference in rate. 3-dimensional representations are required.*



Waol A (FD-211)

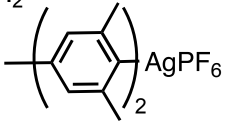




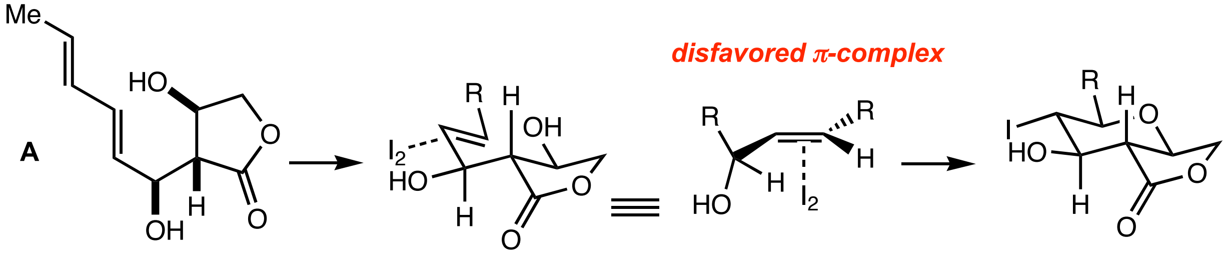
Conditions:

a) I_2, $NaHCO_3$ = 5% conv

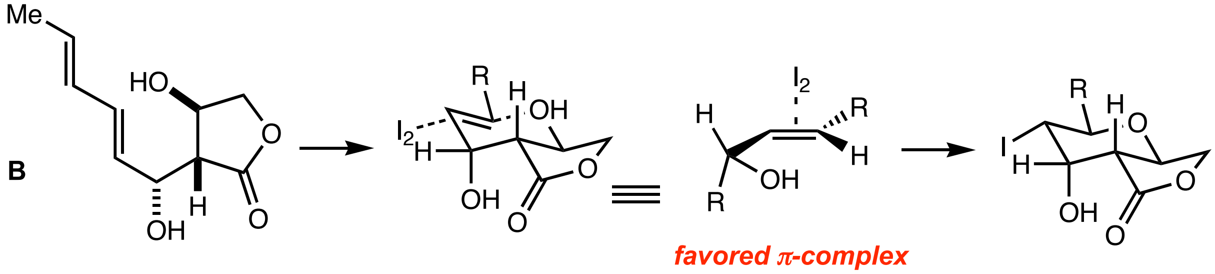
b) I_2 = 88% yield



Your Answer --

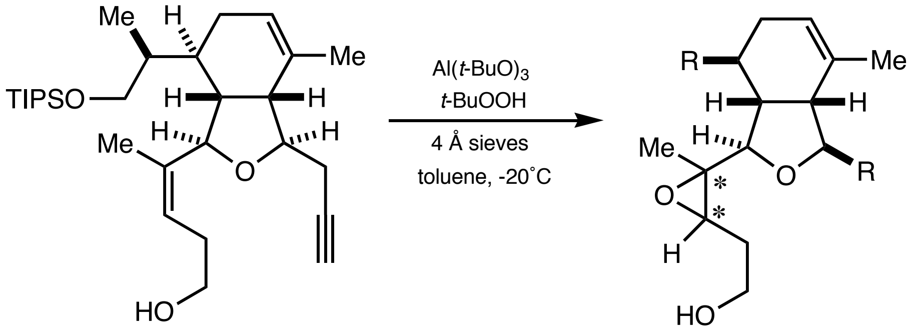


The inside alkoxy effect is operational in the given examples. In **A**, the allylic alcohol can interact with the π system, and withdraw electron density; the olefin in **A** in less reactive (less nucleophilic) in the illustrated conformation. Conversely, **B** orients the hydroxy group in the sigma framework. In this orientation, σ* C-O does not act to withdraw electron density.

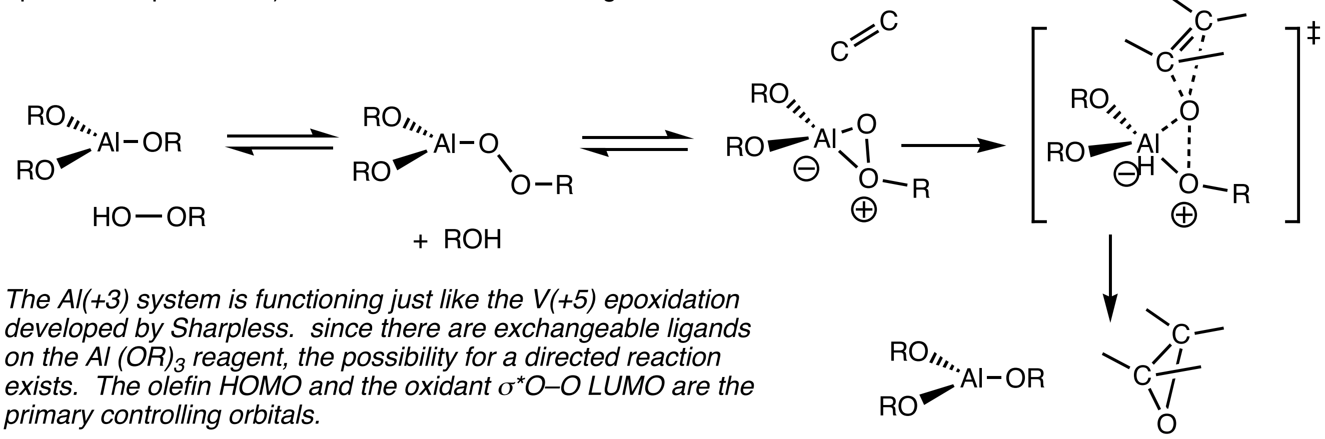


Question 6.

Overman and co-workers recently reported the indicated selective epoxidation in conjunction with a synthesis of briarellins A and E, a new family of diterpenes. It should be noted that the Al(t-BuO)$_3$/(t)-BuOOH reagent system is both highly diastereoselective and site selective. It is also relevant to the mechanism of the reaction that the ring-trisubstituted olefin lacking an allylic oxygen substituent would normally be more prone to epoxidation with a peracid than the acyclic trisubstituted olefin.

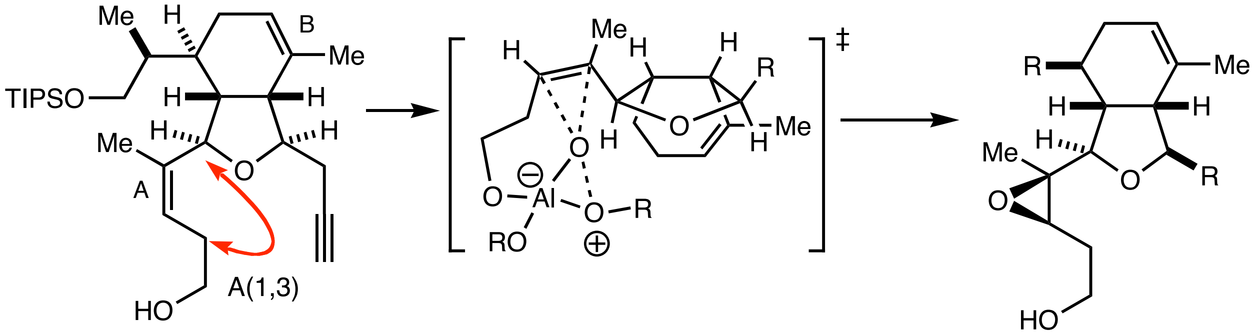


Part A. Provide a general mechanism illustrating how the Al(t-BuO)$_3$/(t)-BuOOH reagent epoxidizes olefins (see Sharpless V^{5+} epoxidation). Three-dimensional drawings are recommended.



*The Al(+3) system is functioning just like the V(+5) epoxidation developed by Sharpless. since there are exchangeable ligands on the Al (OR)$_3$ reagent, the possibility for a directed reaction exists. The olefin HOMO and the oxidant σ*O–O LUMO are the primary controlling orbitals.*

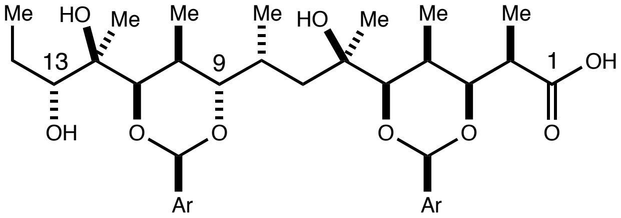
Part B. Provide a general mechanism illustrating how the above epoxidation proceeds and provide the stereochemistry (*) of the product epoxide along with a stereochemical analysis of the noted face selectivity.



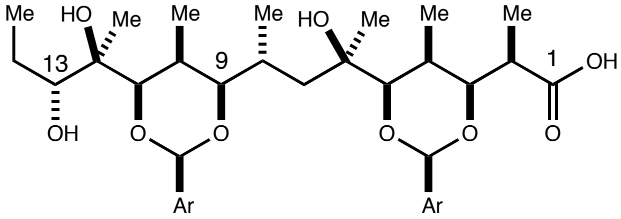
The fact that C=C B is not oxidized suggtests that the reaction is directed by the OH group. A(1,3) interactions provide a strong conformational bias for the (Z)-olefin A the two olefin diastereofaces are strongly differentiated by the fused cycloxexene steric interactions promoting epoxidation from the illustrated diastereoface.

Question 7.

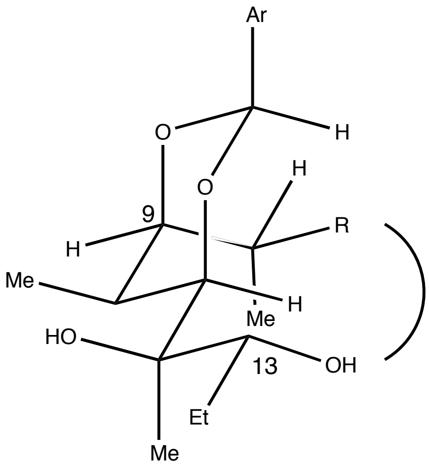
Woodward's synthesis of erythromycin uncovered an interesting relationship between the configuration at C9 and the facility of macrolactonization with the C13 hydroxyl (In the natural product C9 is a ketone). Draw the lowest energy conformation of the C8-C13 region of both diastereomers, and determine why compounds of the 9(S) configuration readily cyclize while those of the 9(R) configuration do not.



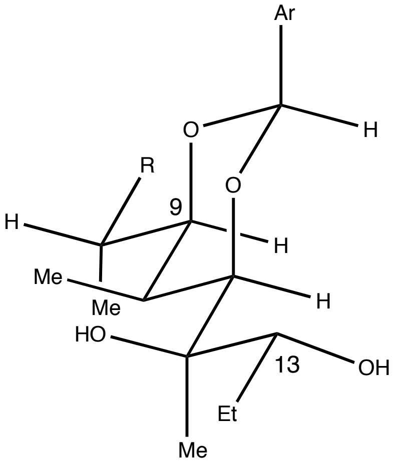
9(S) - macrolactonization possible



9(R) - macrolactonization impossible



close proximity of acid and free hydroxyl

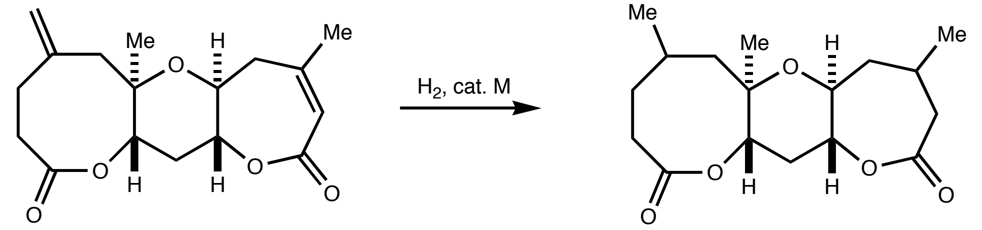


larger distance between hydroxyl and acid precludes cyclization

Woodward, *JACS*, **1981**, *103*, 3210

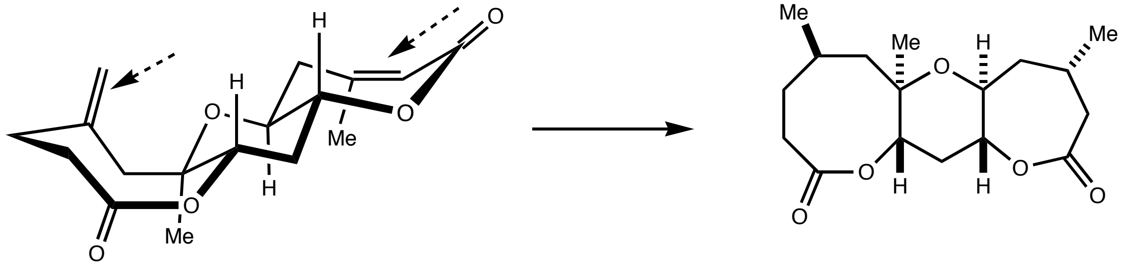
Question 8.

a) Predict the major diastereomer obtained from the following reduction:



The ground-state conformation:

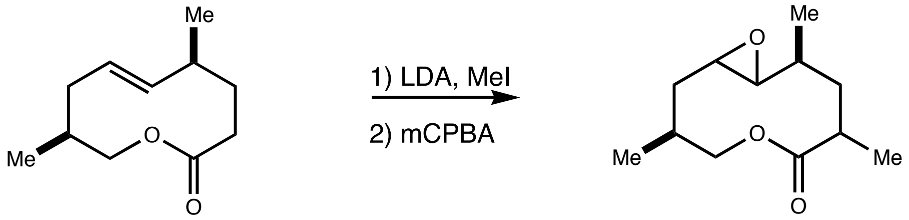
The major diastereomer:

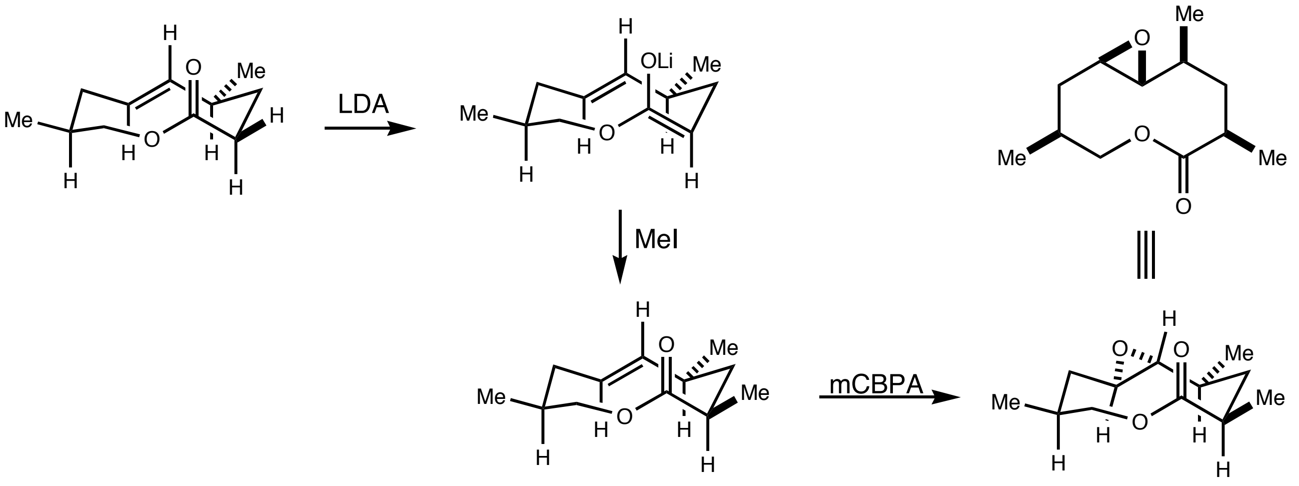


The front face of each olefin is shielded sterically by its corresponding ring. Addition of hydrogen from the back face as shown is consistent with the observed product.

Nicolaou *Nature* **1998**, *392*, 264.

b) Identify the correct diastereomer obtained from the following sequence:

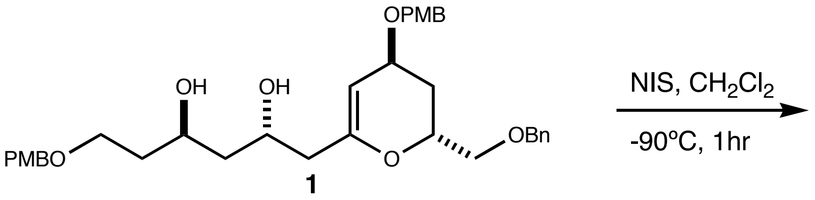




Schreiber *JACS* **1986**, *108*, 2106

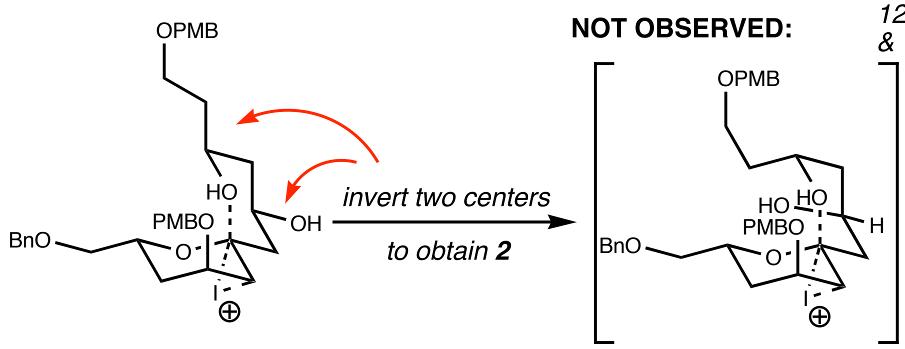
Question 9.

Provide three-dimensional representations of the major diastereomeric addcuts arising from the following **kinetic** iodo-spiroketalizations of diols **1** and **2**. Be sure to provide an explanation for the observed diastereoselectivities in each case.

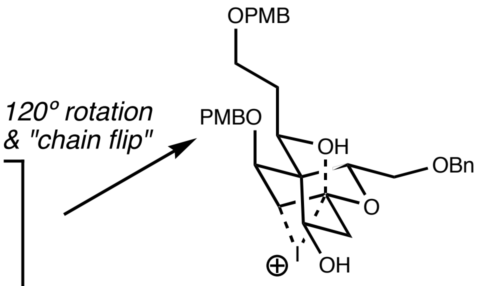


8:1 diastereoselectivity

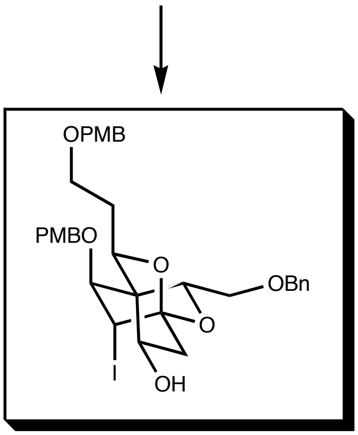
*it's easiest to work from the product derived from **2**:*

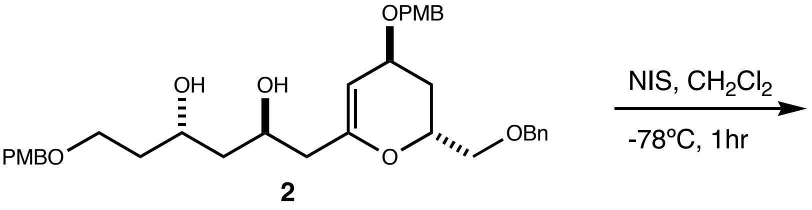


Furst-Platner obeyed in iodonium ring-opening; 3 of 4 substituents axial!



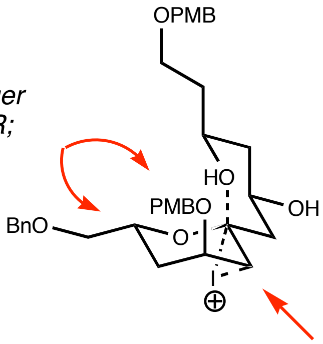
now, 3 of 4 substituents equatorial; kinetic conditions give product with only one anomeric effect.



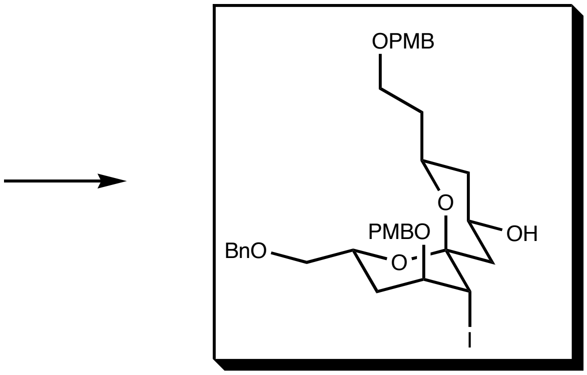


single diastereomer

CH_2OR has larger A-value than OR; CH2OR placed equatorial

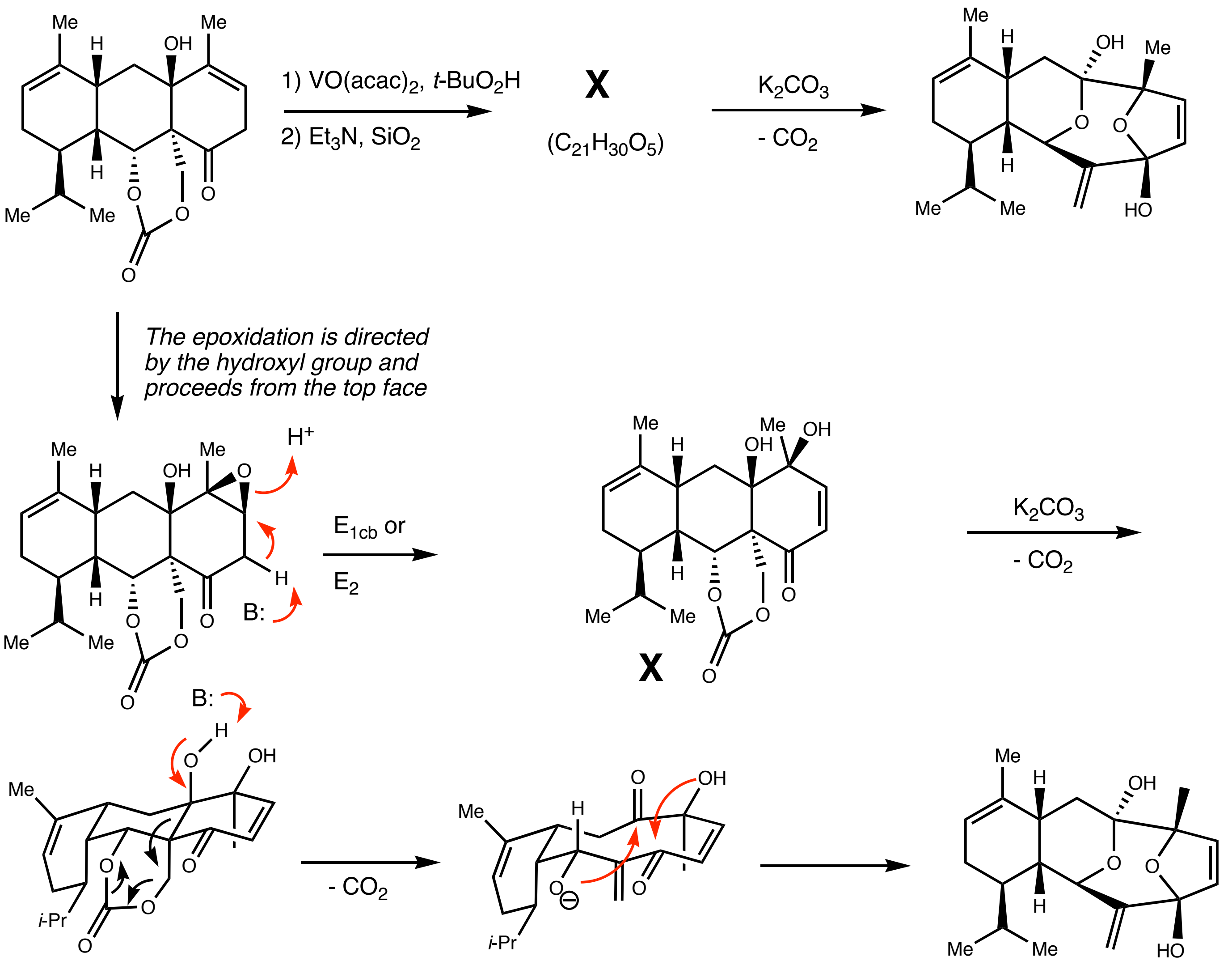


Furst - Platner rule obeyed in iodonium ring opening



3 of 4 substituents equatorial allows for two anomeric effects

Question 10. Please provide a mechanism for the following transformation, including a three-dimensional representation of intermediate **X**.



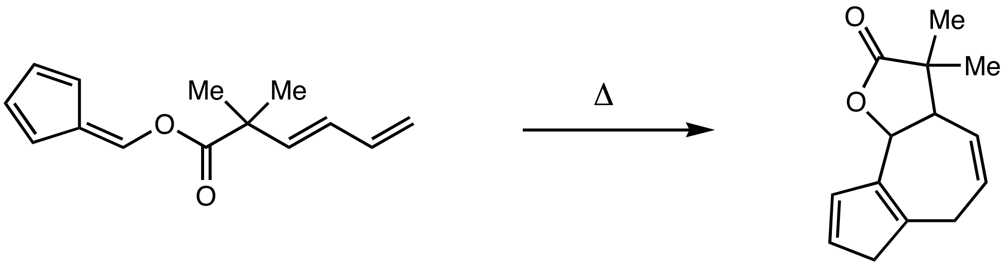
The epoxidation is directed by the hydroxyl group and proceeds from the top face

Winkler *et al. Org. Lett.* **2003,** *5* (10), 1805

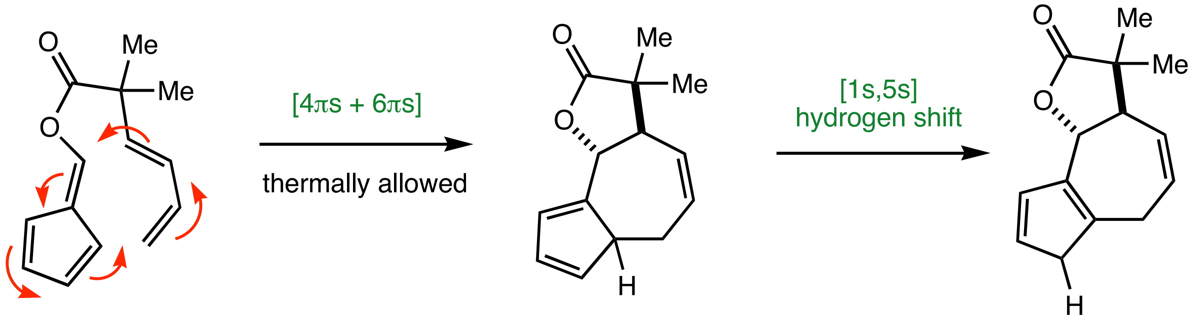
Problem Set 4 *Name:___KEY________TF:___________*

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1. Provide a mechanism for the following transformation with clear representation of FMO and Dewar-Zimmerman analysis. Be sure to label any pericyclic processes. Also, assign the expected relative stereochemistry in the product.

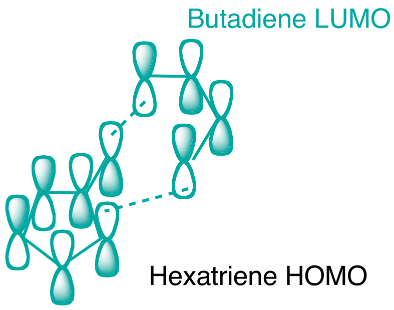


Answer



FMO Analysis:

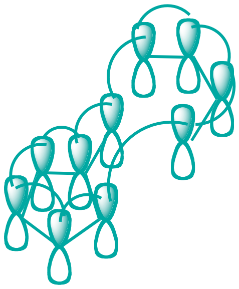
suprafacial in each component



fully bonding ⇒ allowed

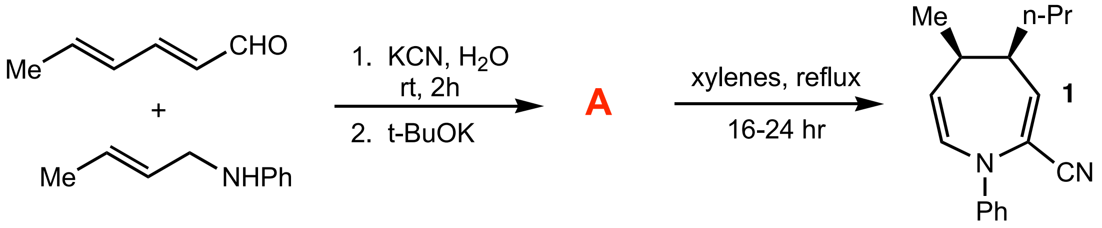
Dewar Zimmerman Analysis:

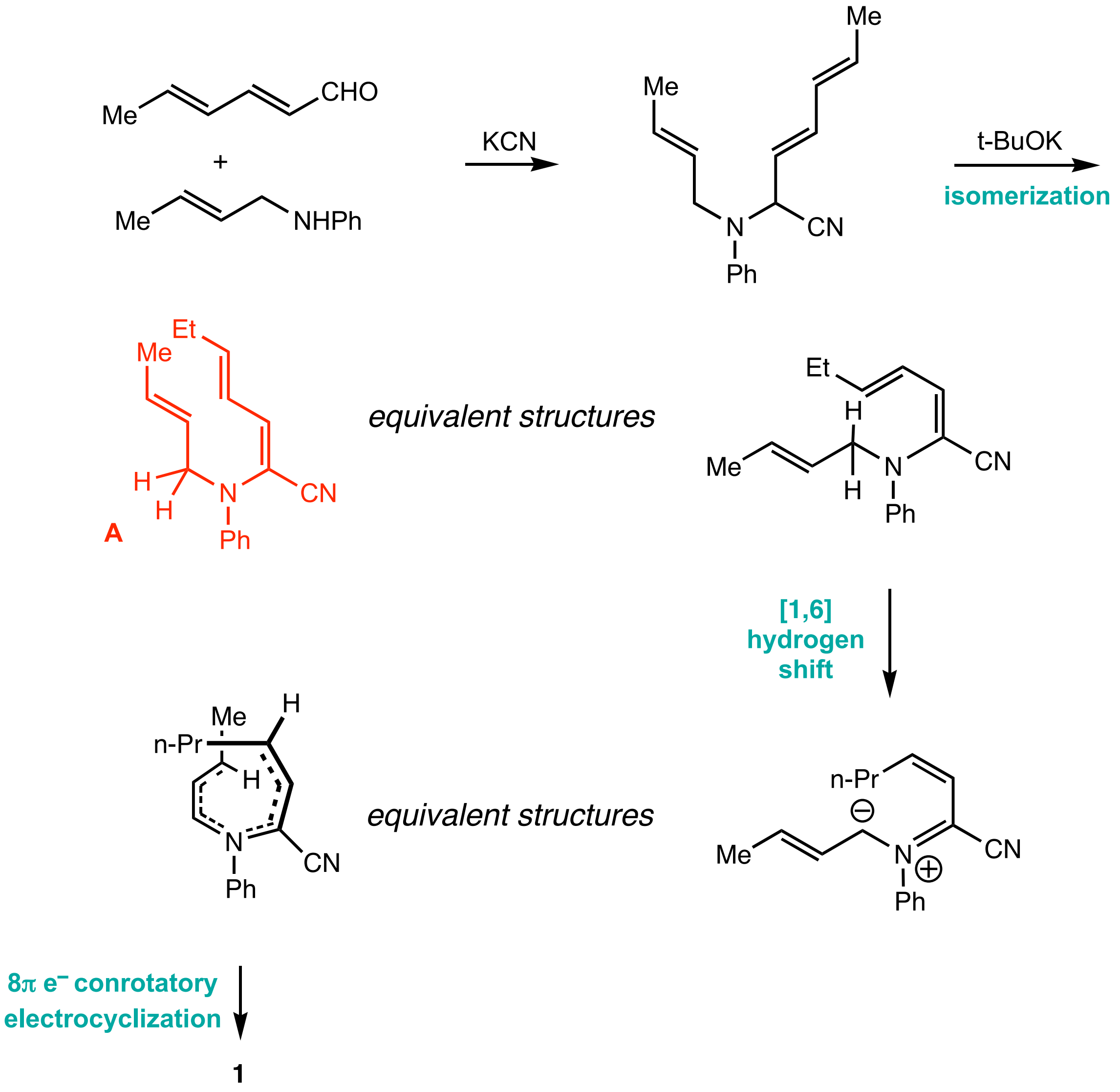
suprafacial in each component



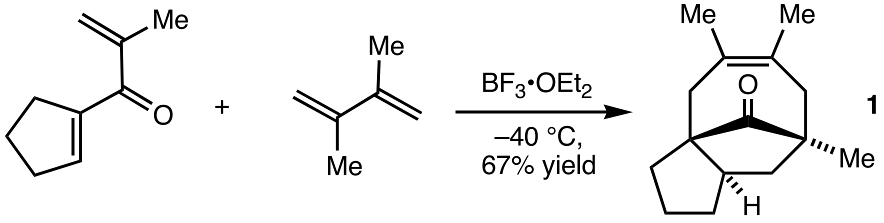
10 π electrons, 0 phase inversions
⇒ Hückel (aromatic) TS
⇒ thermally allowed.

Question 2. The indicated three-step process leads to the production of enamine **1**. Propose a mechanism for the overall transformation that includes the structure of intermediate **A**. Be sure to label any pericyclic processes.





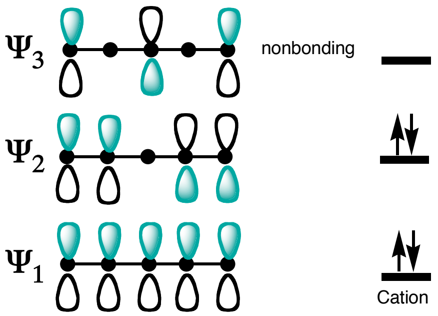
Question 3. The illustrated transformation rapidly facilitates the construction of the complex tricyclic ketone **1** in 67% yield.

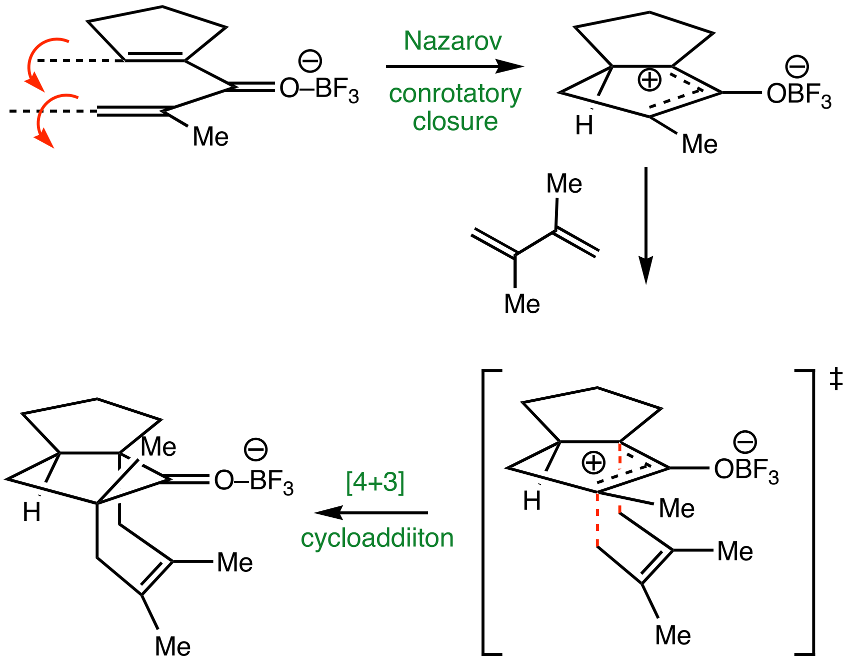


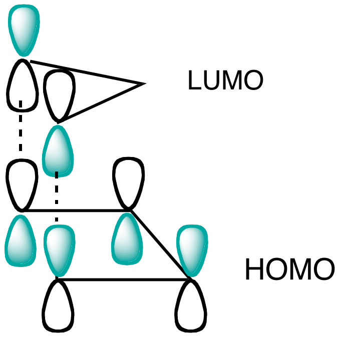
1

Please provide a concise mechanism with FMO analysis for this transformation. Use 3-dimensional representations where appropriate to illustrate your answer. Be sure to label any pericyclic processes.

Answer

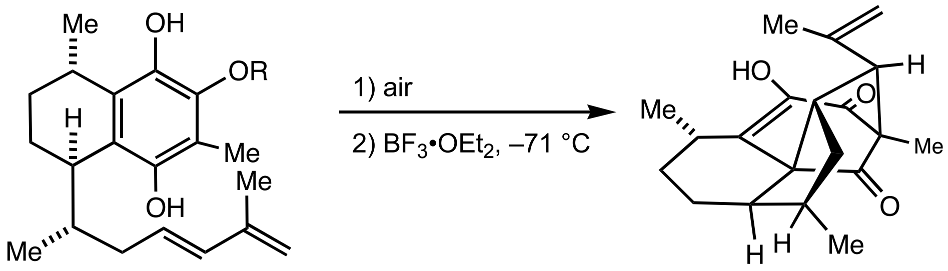




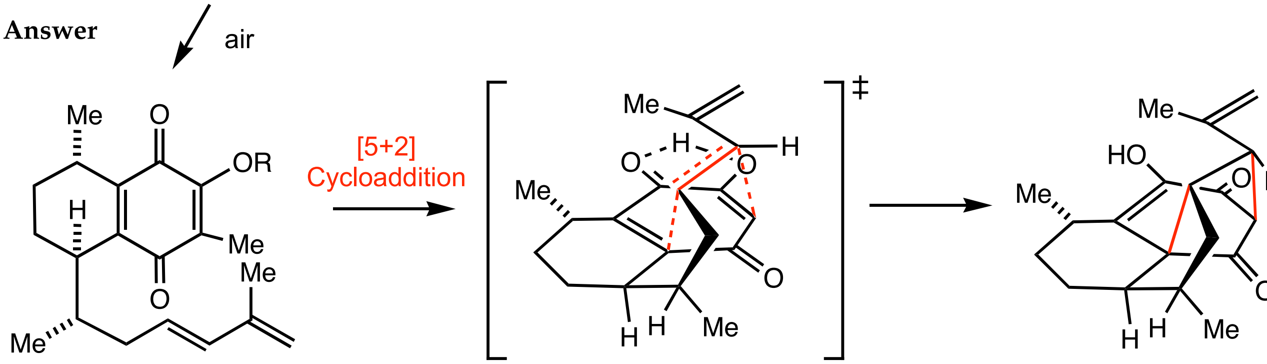


The cycloaddition

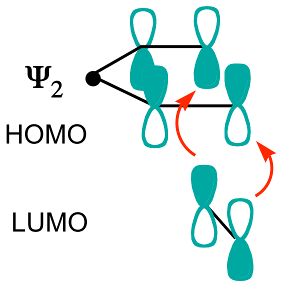
Question 4. Provide a mechanism for this transformation. Determine whether the reaction might be concerted. Also, carry out the relevant FMO analysis. Be sure to label any pericyclic processes.



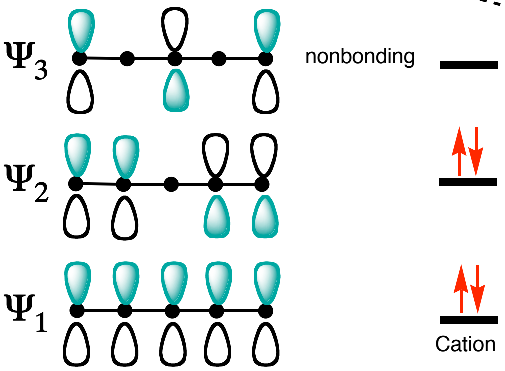
Answer



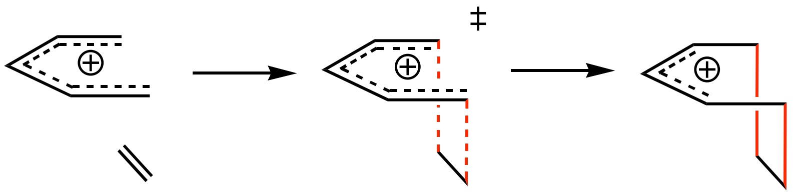
[5+2] Cycloaddition



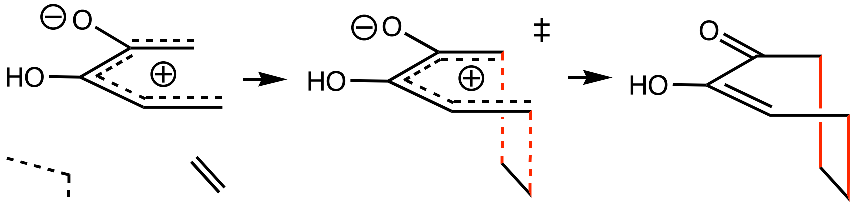
Rxn suprafacial on
both fragments:
Concerted



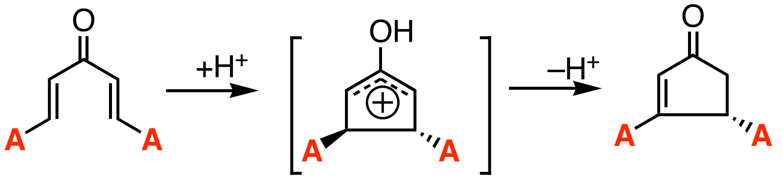
Parent system



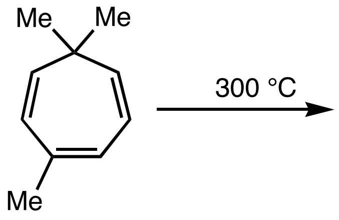
System at hand



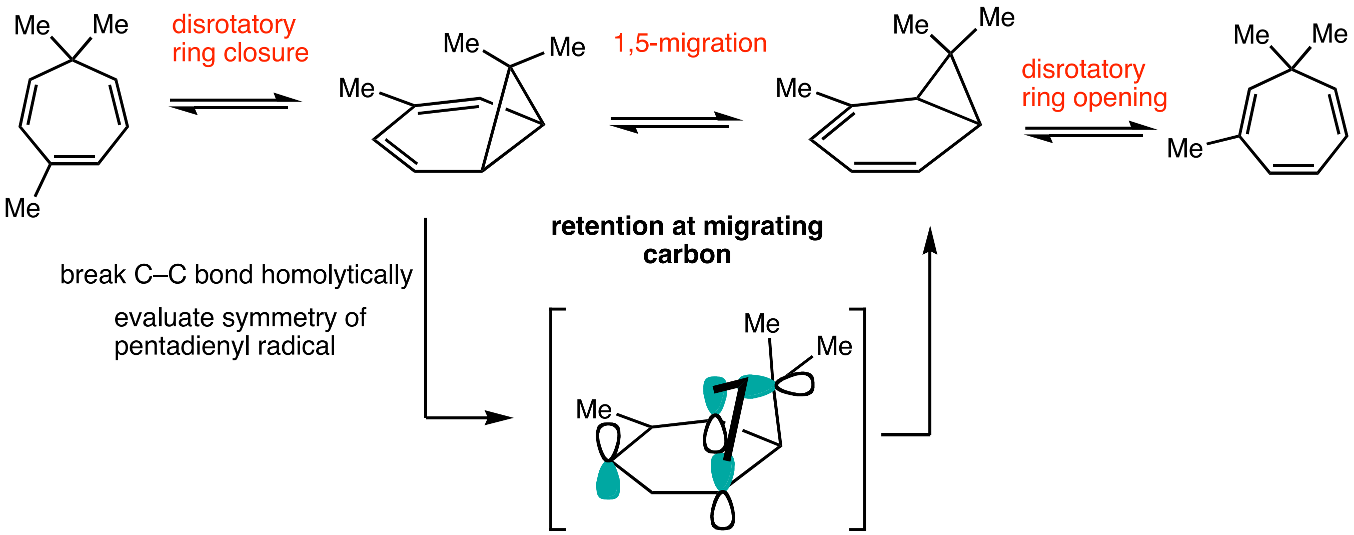
The Nazarov Reaction (Conrotatory Ring Closure)



Question 5. Provide a rationalization of these results with brief FMO analysis. Be sure to label any pericyclic processes. Three-dimensional drawings are recommended.



Answer

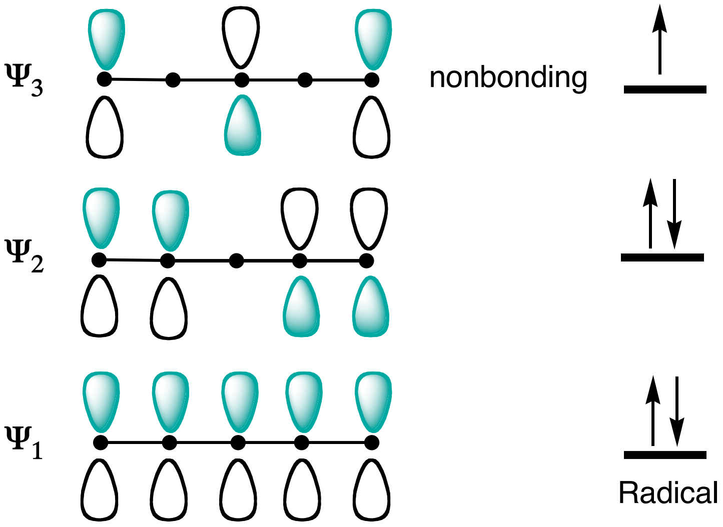


retention at migrating carbon

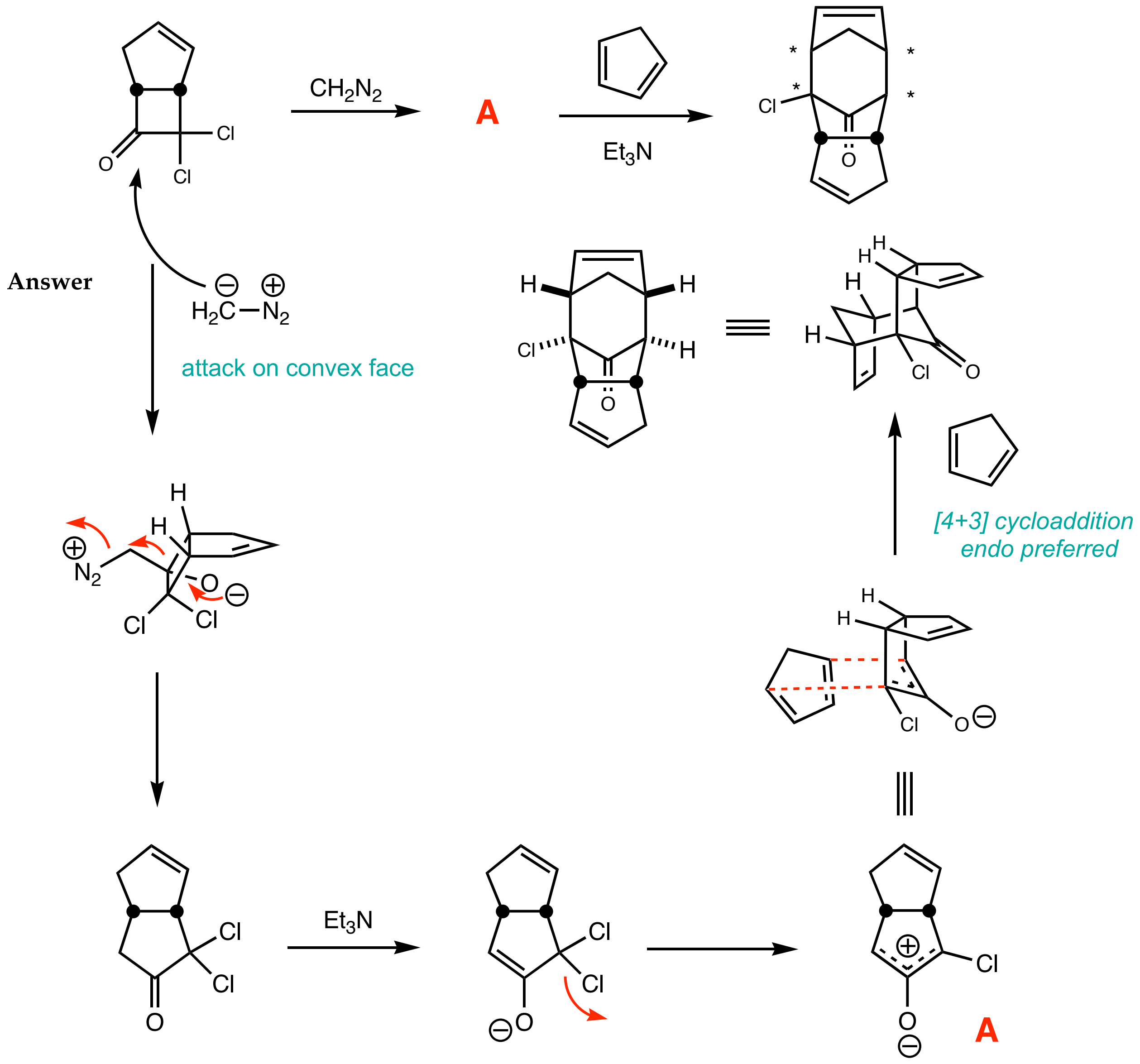
break C–C bond homolytically

evaluate symmetry of pentadienyl radical

HOMO = Ψ_3

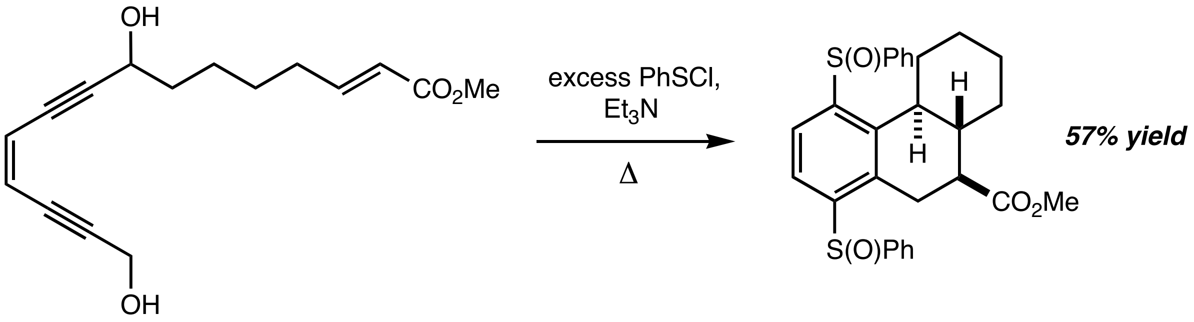


Question 6. Please provide a mechanism using 3-D representations where appropriate. Please identify intermediate **A** and assign the relative stereochemistry of the product. Be sure to label any pericyclic processes.

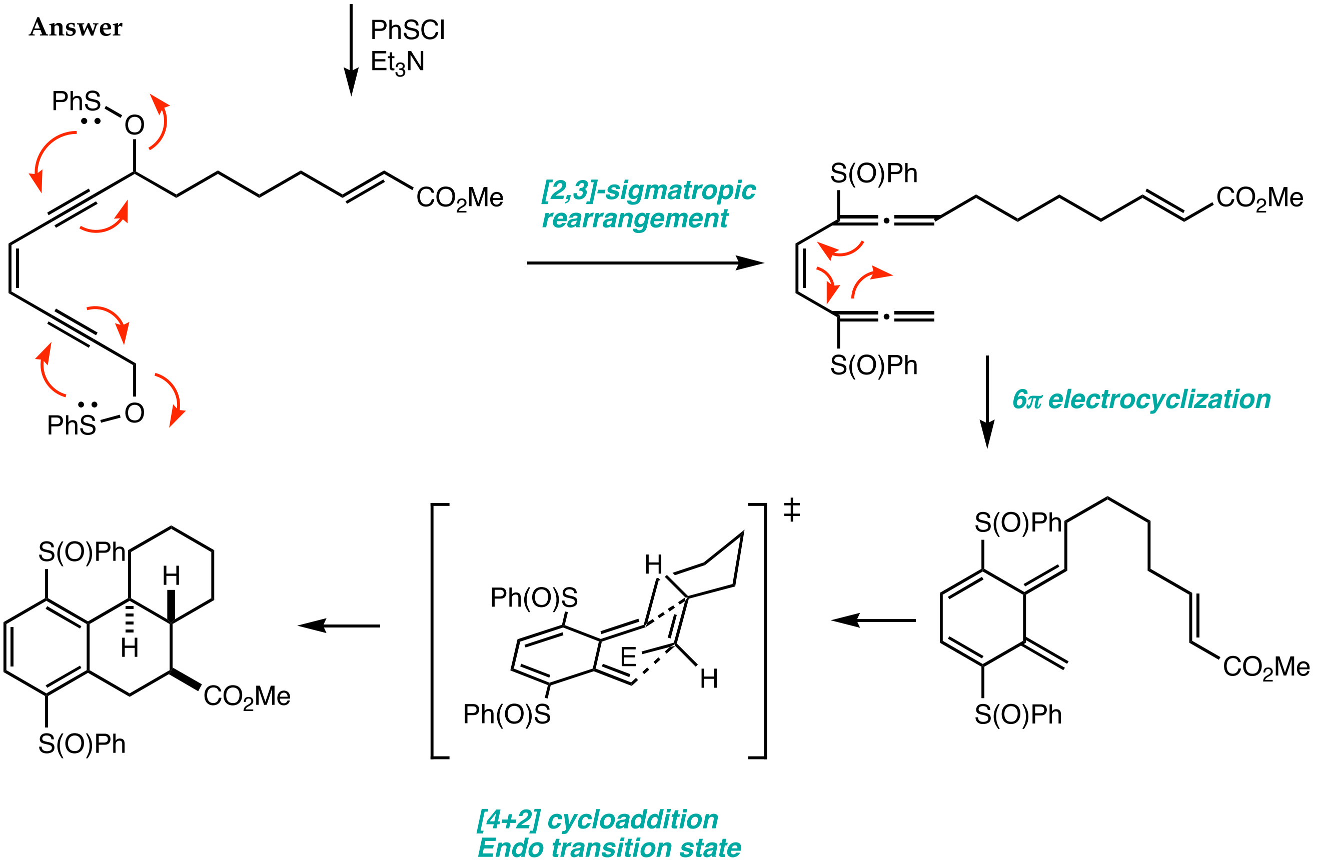


reference : *Org. Lett.* **2001**, *3*, 2533

Question 7. In the space below please provide a detailed mechanism for this reaction. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.

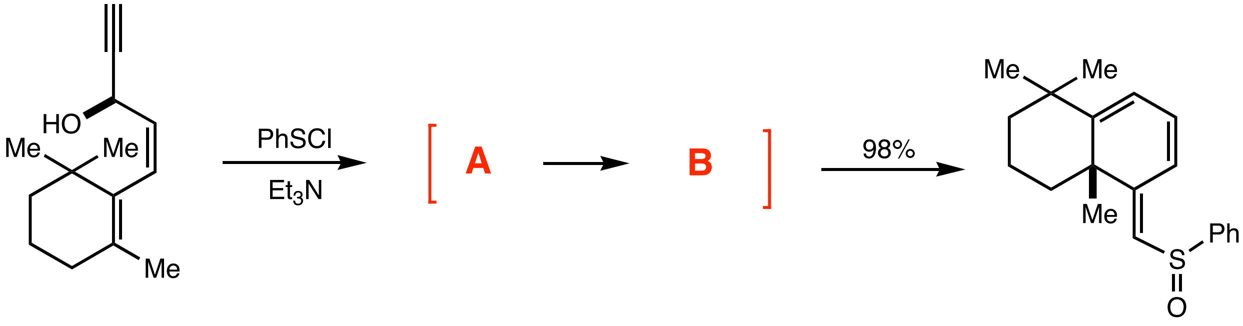


Answer

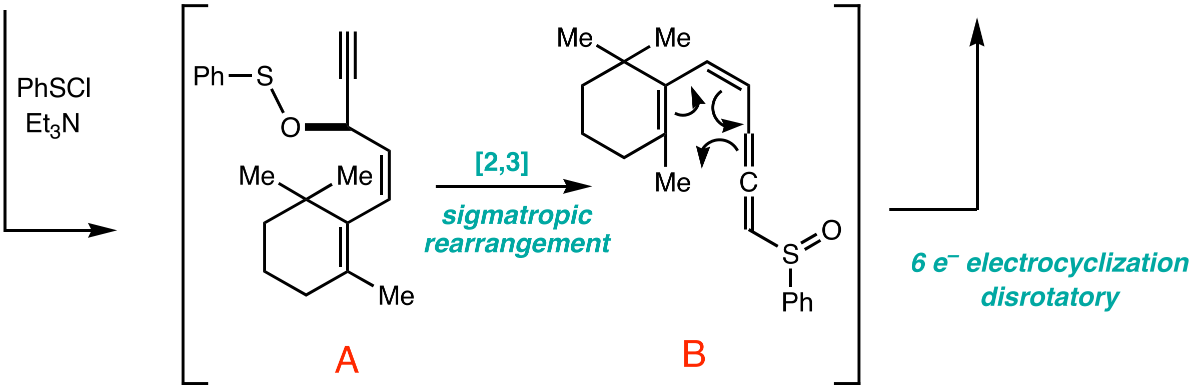


reference : *Org. Lett.* **2006**, *8*, 95

Question 8. Provide a mechanism for the following transformation. Identify **A** and **B** in your reaction sequence. Be sure to account for the observed sterochemical outcome and to clearly label any pericyclic processes.

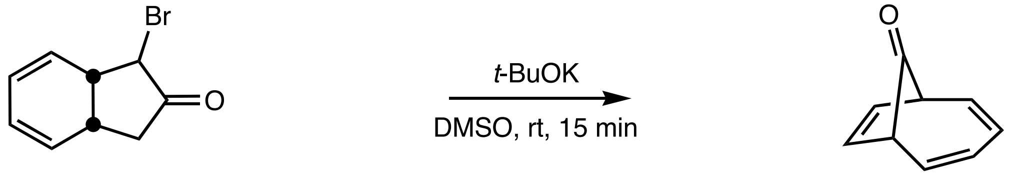


Answer

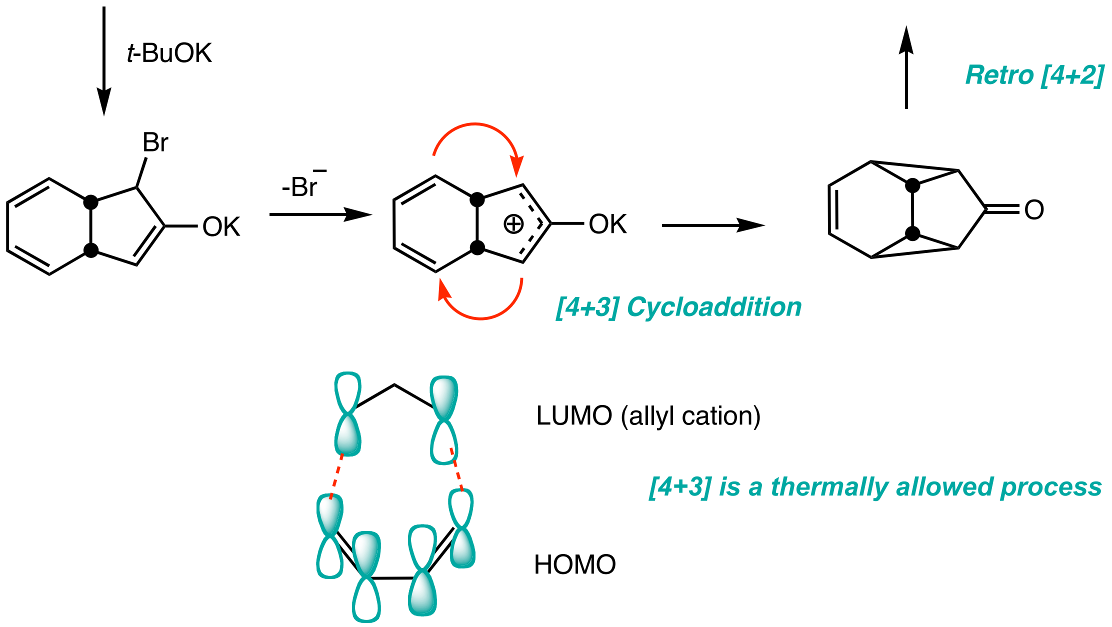

PhSCl
Et_3N
Ph
S
O
Me
Me
Me
A
[2,3]
sigmatropic rearrangement
Me
Me
Me
C
S
O
Ph
B
6 e⁻ electrocyclization disrotatory

reference : JACS **1985**, *107*, 1034

Question 9. In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.

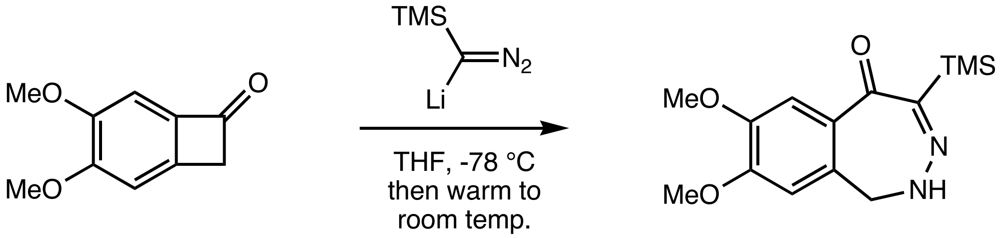


Answer

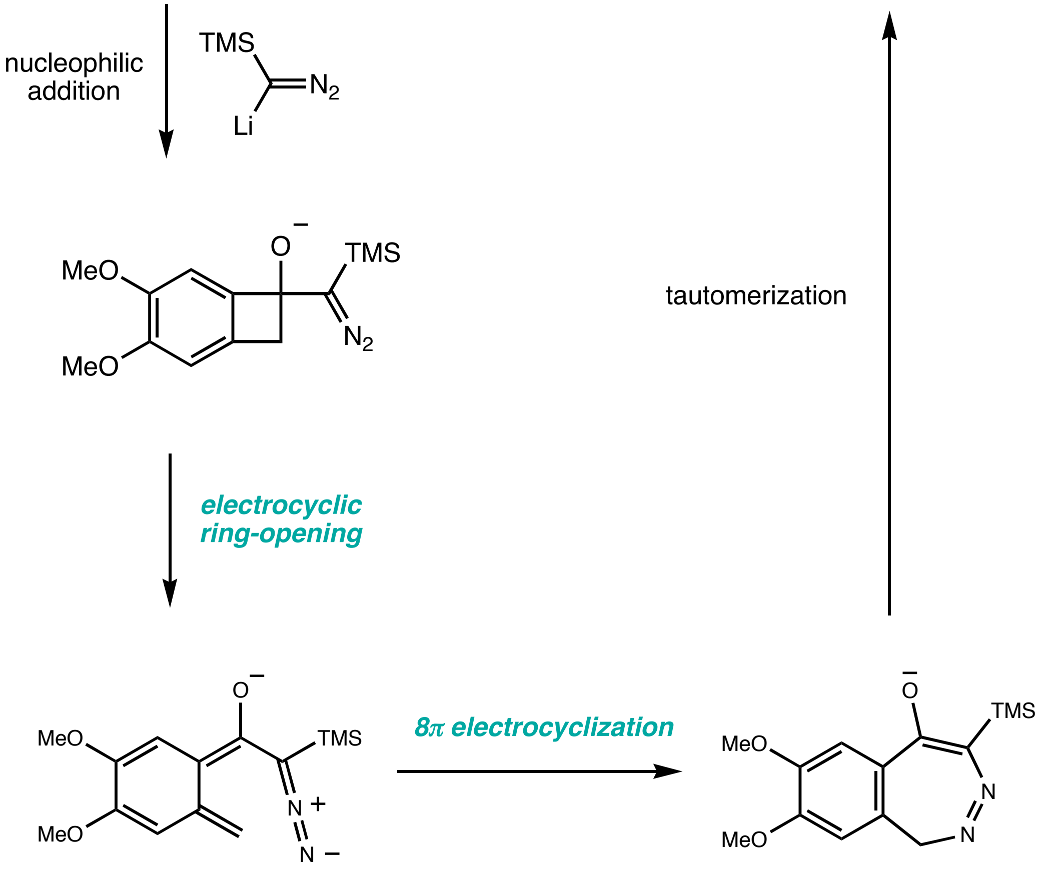


reference : *JACS*, **1973**, *95*, 2230

Question 10. In the space below, please provide a detailed mechanism for this interesting transformation. Be sure to clearly indicate all intervening pericyclic processes.



Answer



reference : *JACS* **2006**, *128*, 13072.

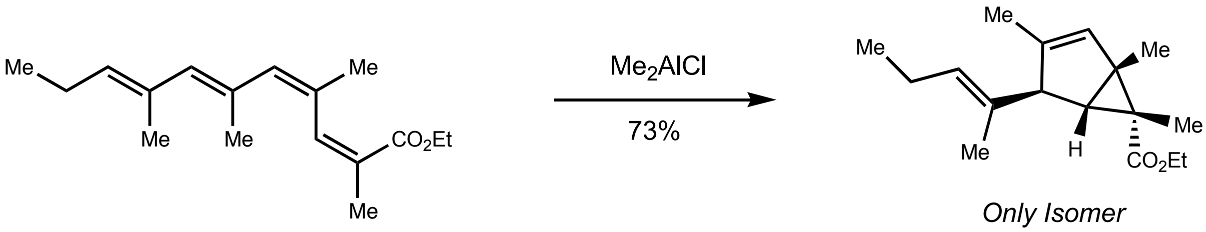
Chem 206 *Due: Friday, Oct. 27*

Problem Set 5

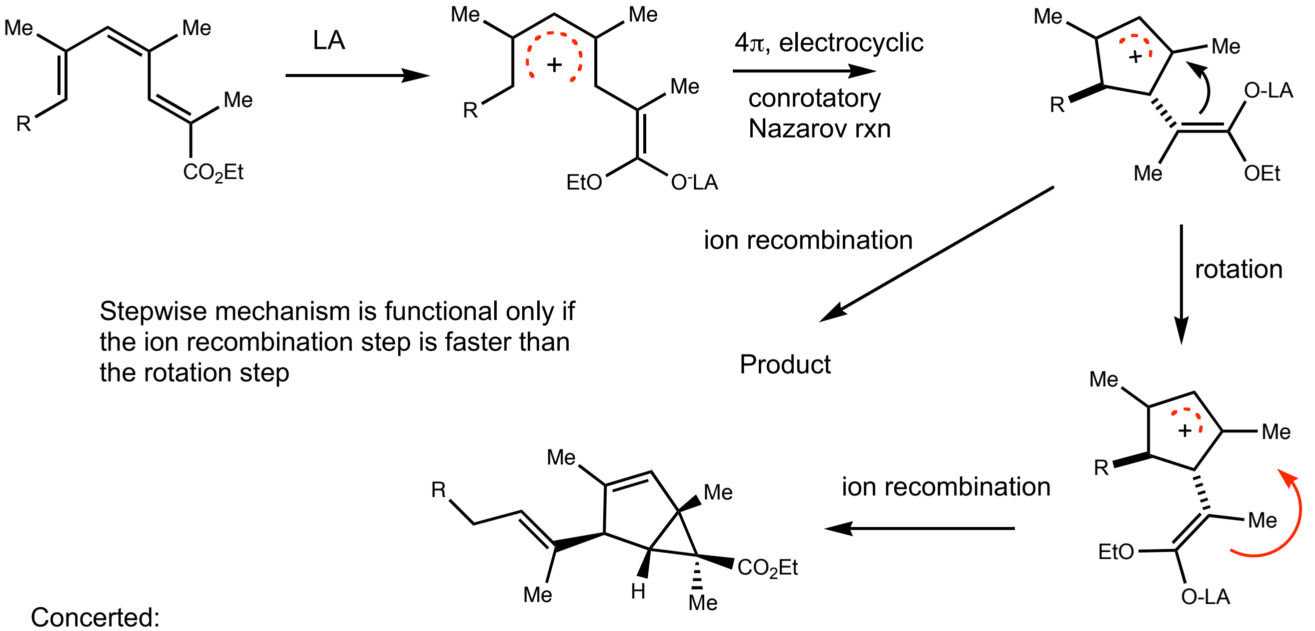
Name:________________ TF:____________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Question 1. As it has been disclosed byTrauner *et al.*, the following transformation is possible under Lewis Acid catalysis conditions. To explain the formation of the product, the authors propose that this transformation could be either concerted or stepwise.

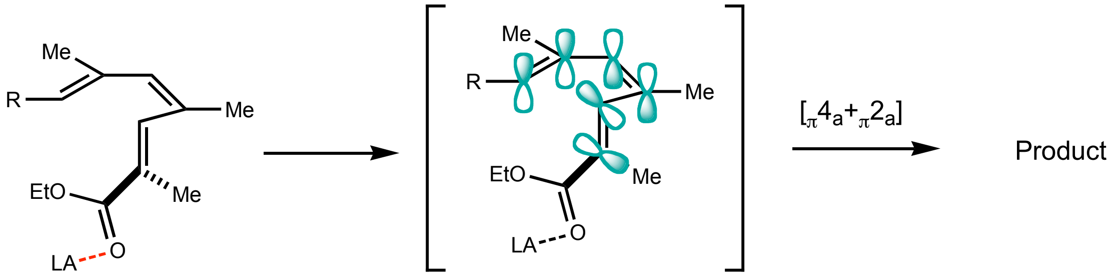


Please provide one stepwise and one concerted mechanism that would account for the stereochemistry of the product. Please, label and classify all of the pericyclic processes involved. Using the FMO analysis predict whether the proposed concerted mechanism is allowed.



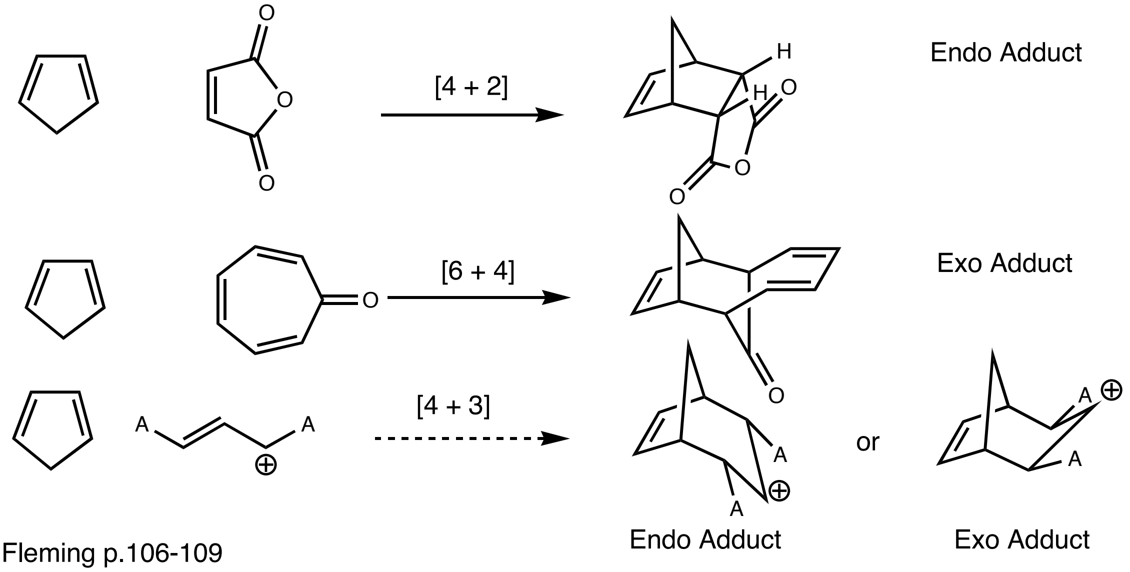
Stepwise mechanism is functional only if the ion recombination step is faster than the rotation step

Concerted:

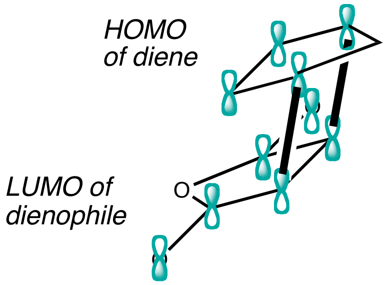


Angew. Chem. Int. Ed. **2003**, *42*, 549-552.

Question 2. While the Dewar-Zimmerman, Woodward-Hoffman and Frontier Molecular Orbital theory are quite good at predicting which cycloadditions are allowed and which are forbidden, only FMO theory is able to explain some observed phenomena. For example, when cyclopentadiene reacts with maleic anhydride, the predominant mode of additions is endo, as shown below. When cyclopentadiene reacts with tropanone, the predominant mode of addition is exo, also shown below. Please rationalize this selectivity using FMO theory. What mode of addition would you expect for the allyl cation plus cyclopentadiene?

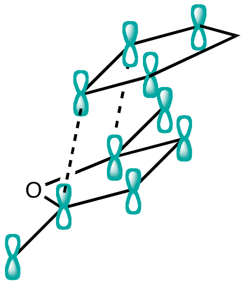


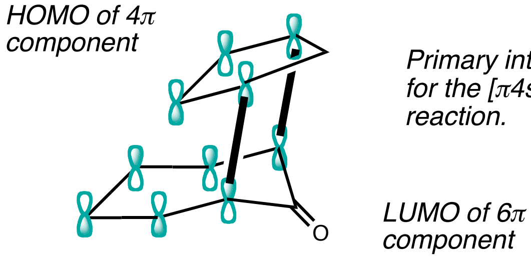
Please see Fleming p.106-109



Primary interactions for the [π4s+π2]s reaction.

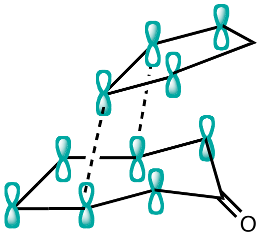
Secondary interactions stabilize the endo transition state for the [π4s+π2s] reaction. Since the exo transition state has no such stabilization, the reaction prefers the endo even at the cost of increased steric congestion.

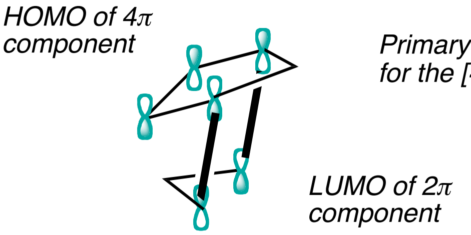




Primary interactions for the [π4s+π2]s reaction.

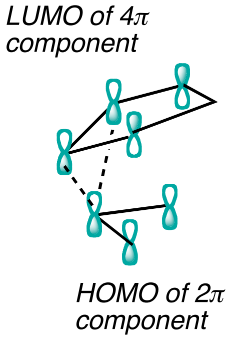
*Secondary interactions **destabilize** the endo transition state because the interference is destructive. Since the exo transition state has no such interaction the reaction prefers the exo transition state.*





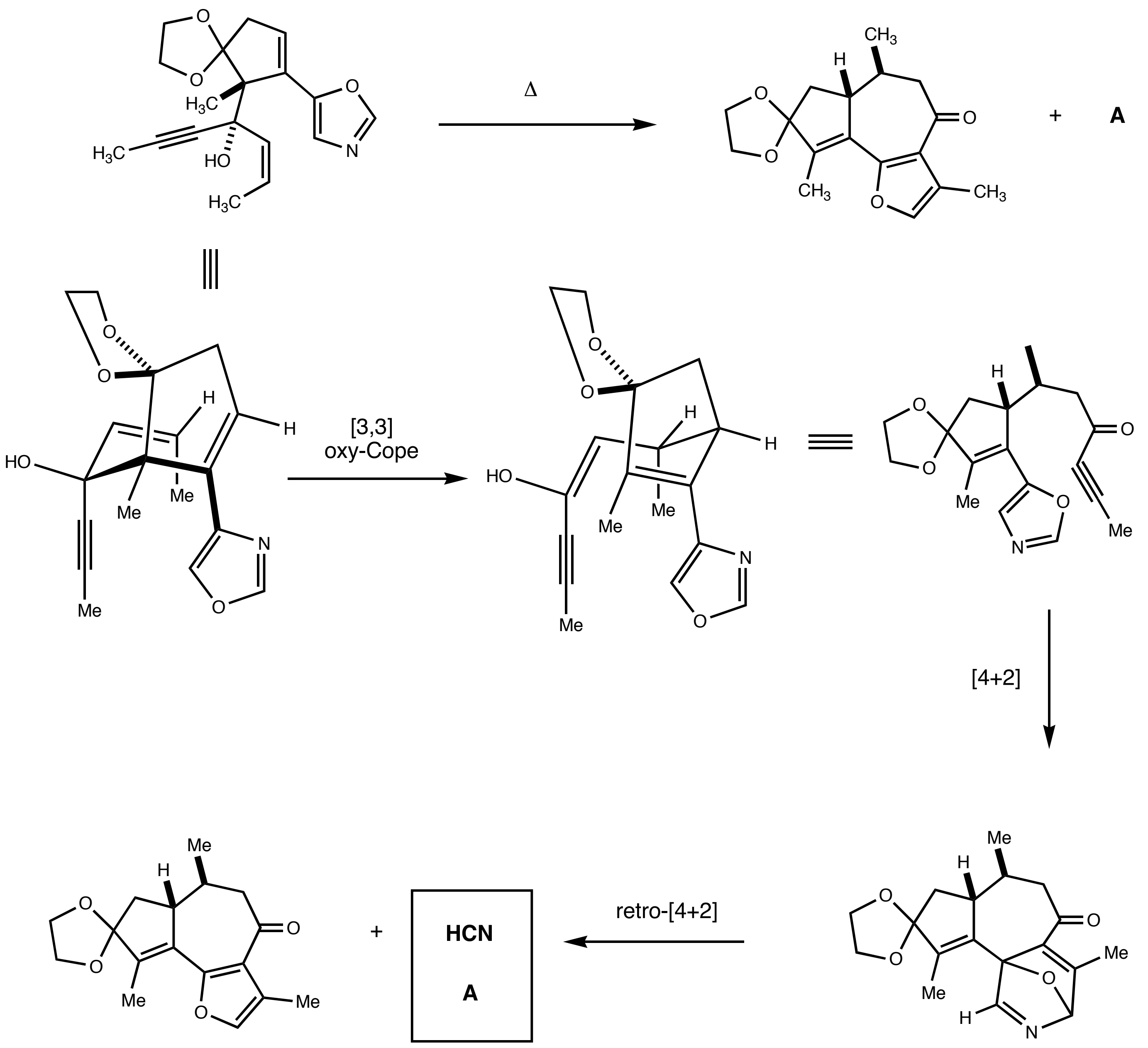
Primary interactions for the [4+3].

*The normal HOMO/LUMO pair that we would examine tells us nothing about secondary interactions because of the node on C2 in the allyl cation. If we take the other HOMO/LUMO pair we see again that secondary interactions **destabilize** the endo transition state. We expect exo attack to be operative for the allyl cation due to this electronic effect and also because the exo attack is less sterically congested.*



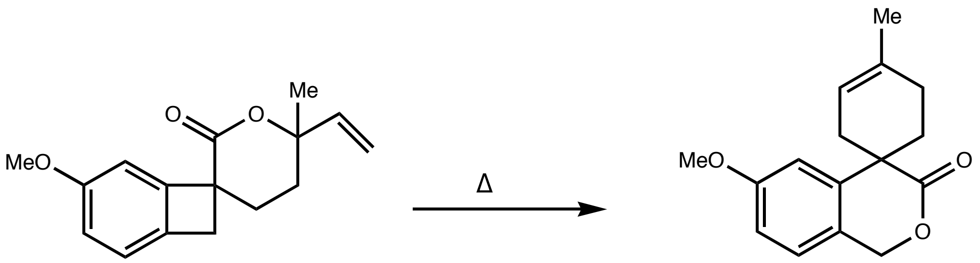
However, other factors like dipole minimization in the transition state and counterion effect are known to overcome the inherent bias for the exo product and endo selectivity is often observed.

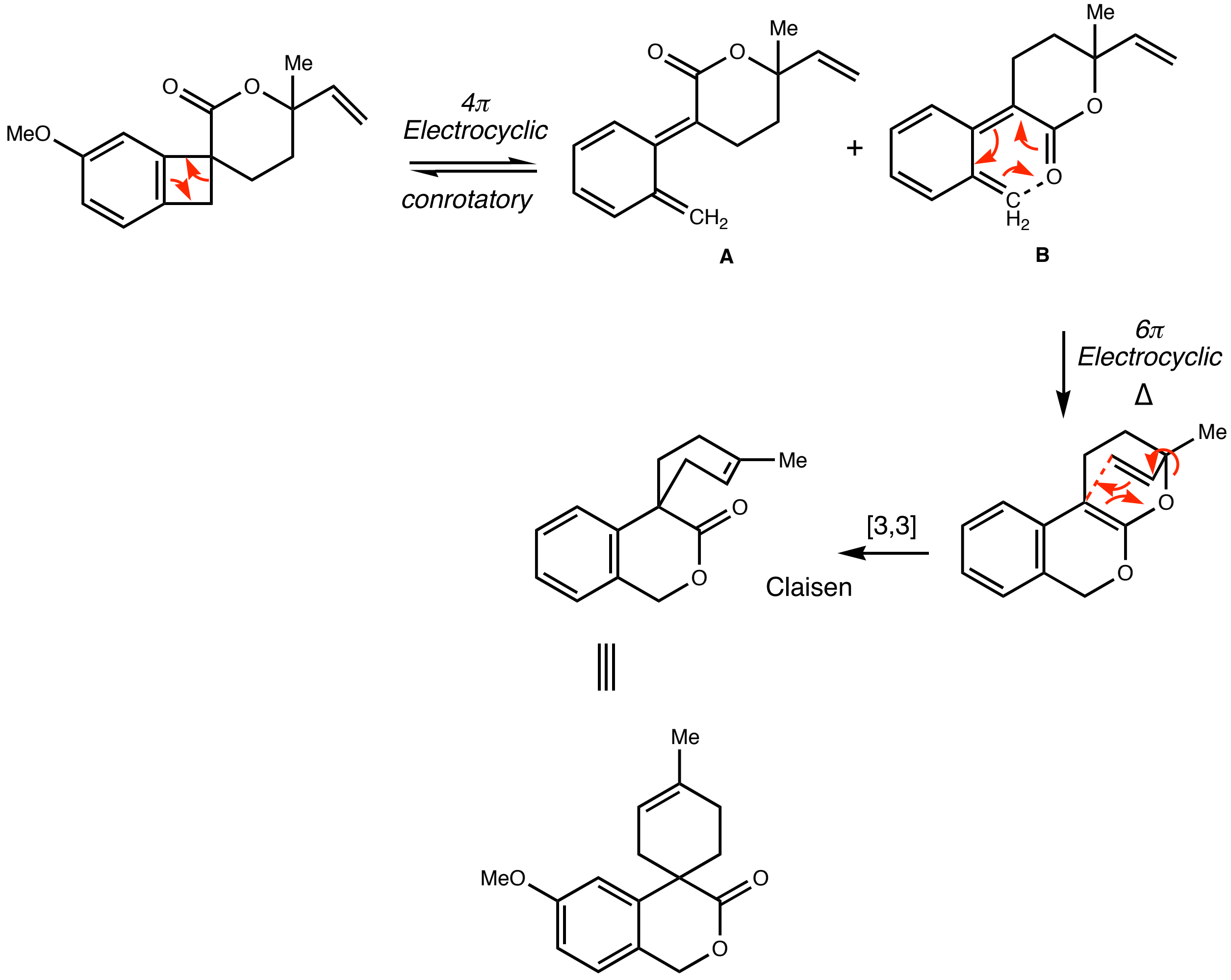
Question 3. Propose a mechanism for the following transformation. Note that in addition to the product shown, a stoichiometric amount of **A** is formed. What is **A**?



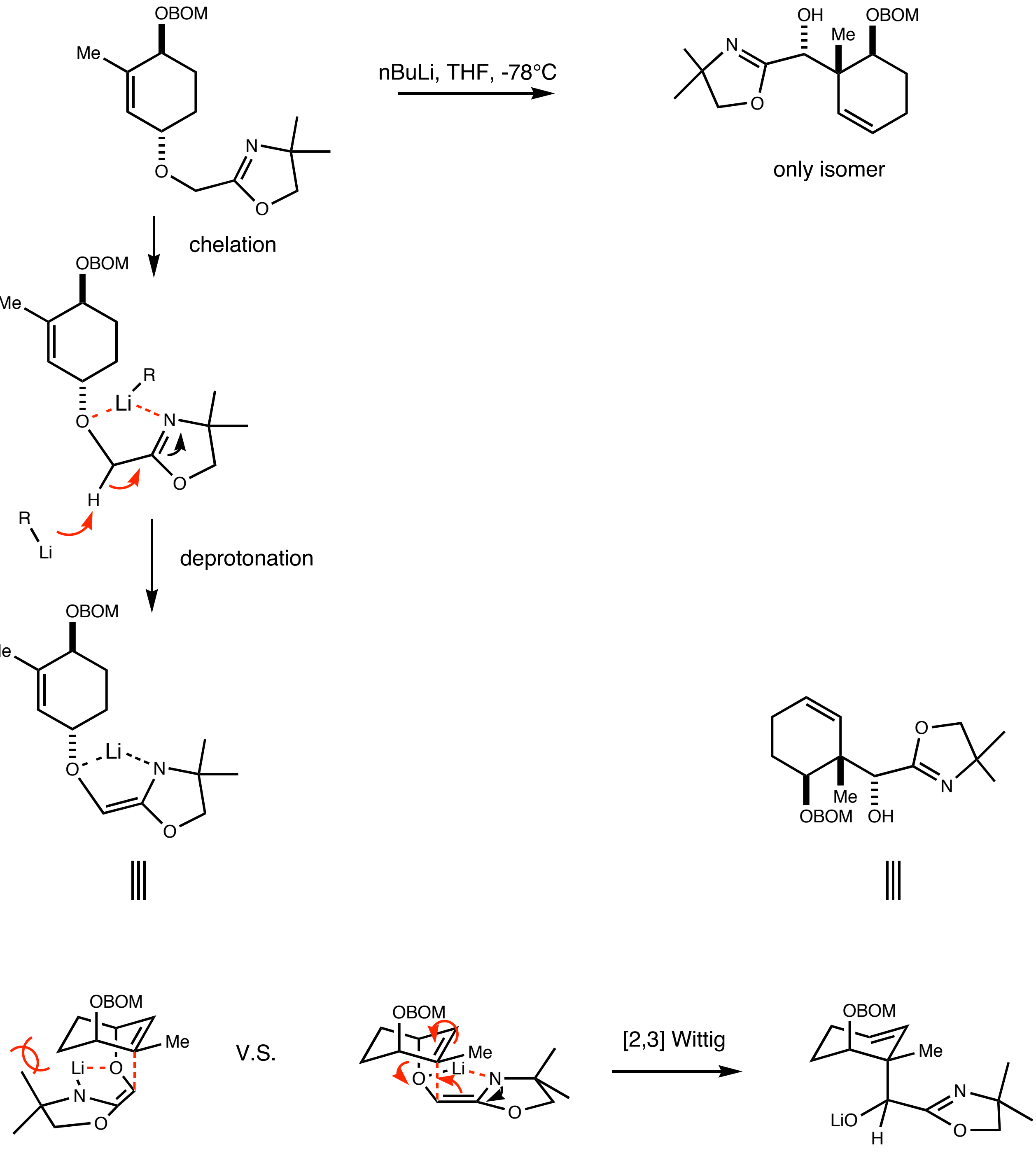
JACS, **1984**, 3041

Question 4. Give a mechanism for this transformation labeling all pericyclic reactions.



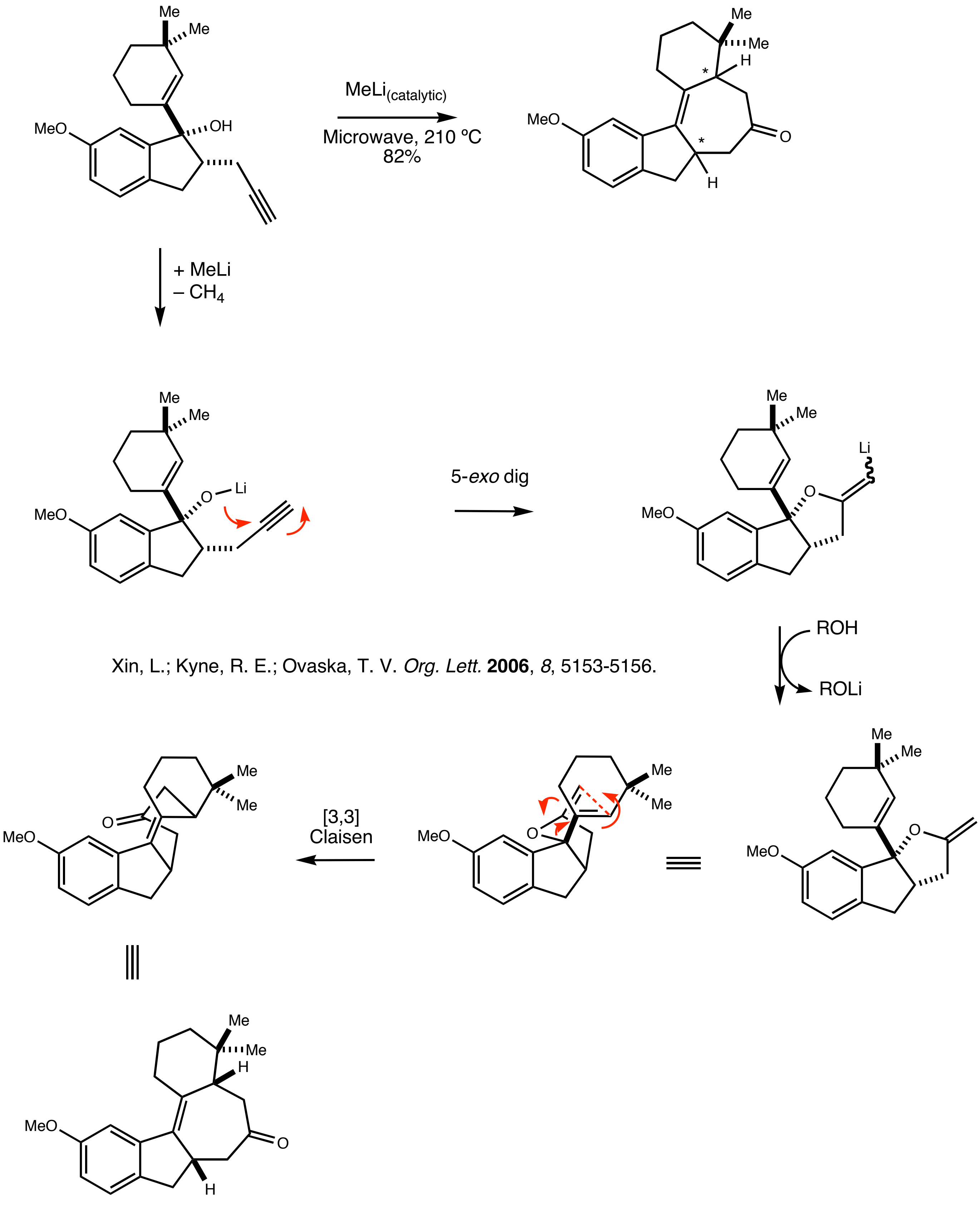


Question 5. Provide a mechanism for this transformation and explain the observed diastereoselectivity using clear, 3D transition state drawings.



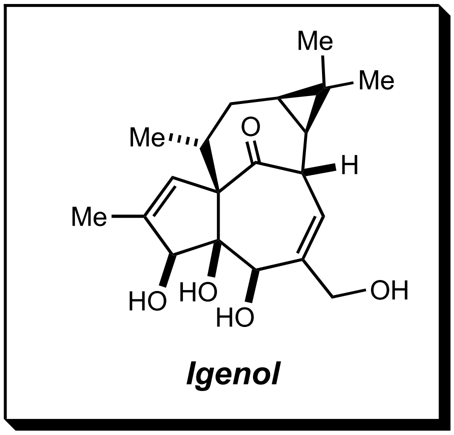
Jongwon Lim, Ph. D. Thesis, Harvard University.

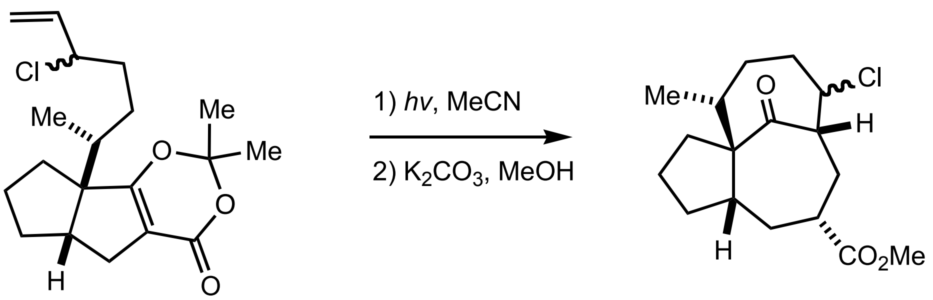
Question 6. The illustrated transformation was recently developed by Ovaska Coworkers. Using *clear 3D drawings* provide a mechanism for this transformation and predict the stereochemistry of the product.

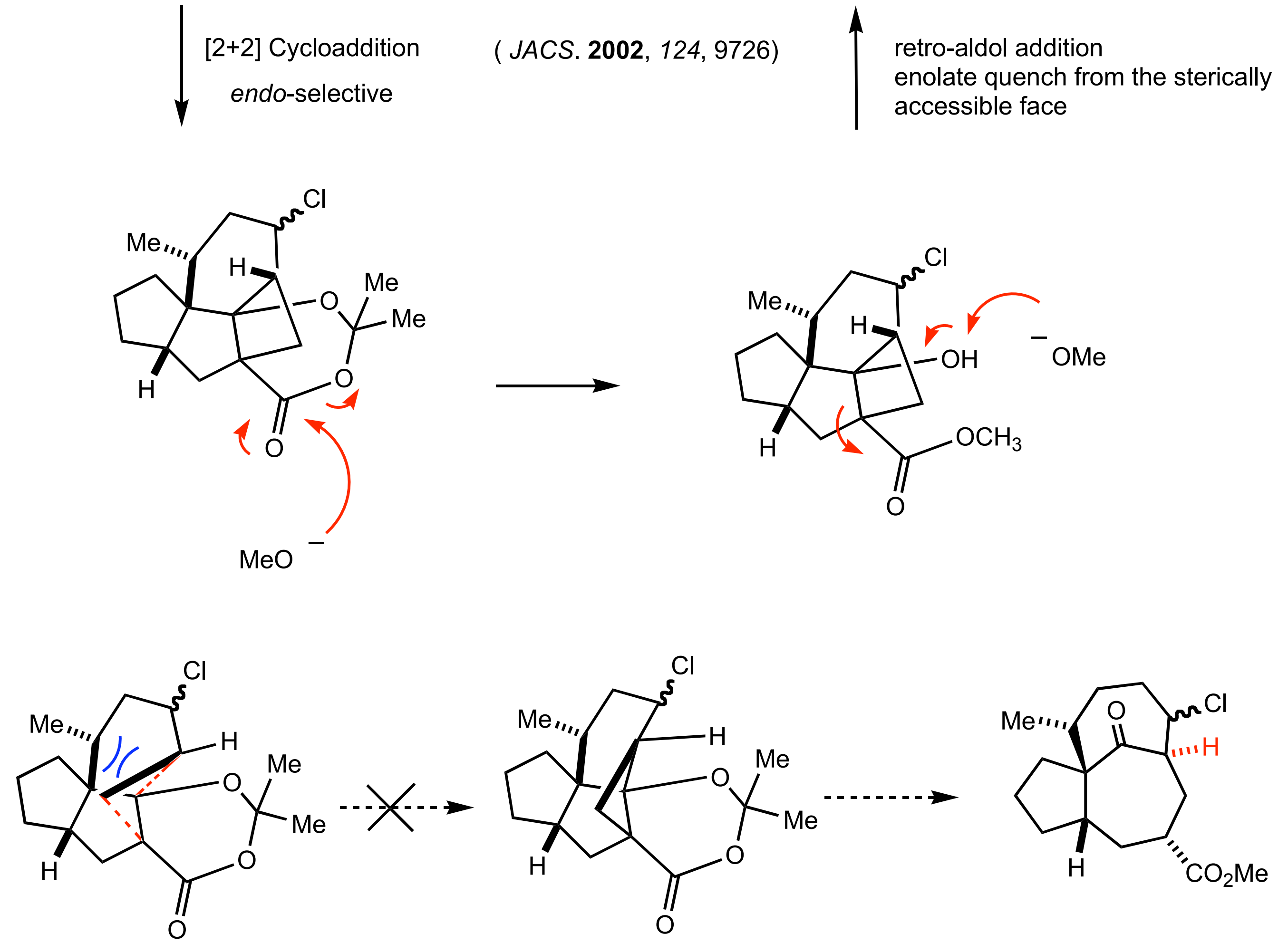


Xin, L.; Kyne, R. E.; Ovaska, T. V. *Org. Lett.* **2006**, *8*, 5153-5156.

Question 7. The following reaction sequence was excecuted to construct the core of Ingenol by Winkler and Coworkers. Provide the mechanism of the indicated transformation using clear 3D drawings. Explain the diastereoselectivity of this reaction



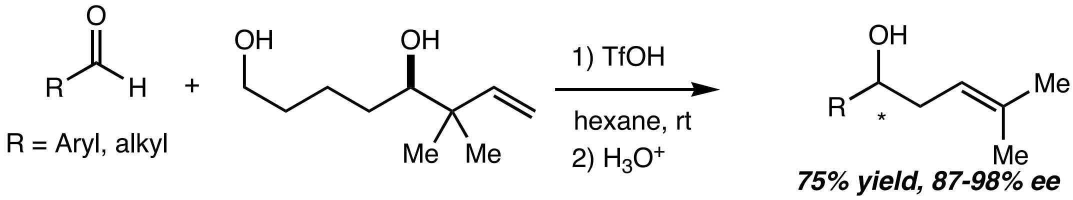




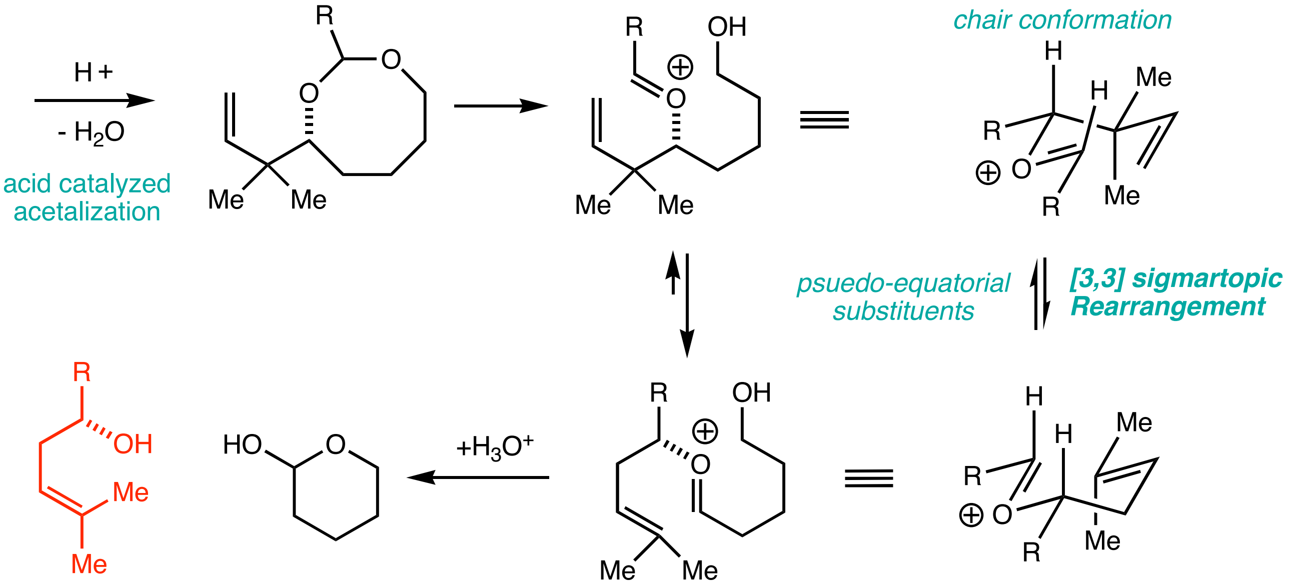
(*JACS*. **2002**, *124*, 9726)

1) *Exo* product has unfavorable syn pentane interactions in the transition state and is not observed.
2) Hard to achieve the required orbital overlap.

Question 8. The prenyl group is an essential unit in the biosynthesis of terpene natural products. Due to the large number of natural products that contain this moiety, methods for its selective introduction into molecules are highly useful. Loh and Cheng have descibed a general regioselective and highly enantioselective prenylation of aldehydes, as shown below.

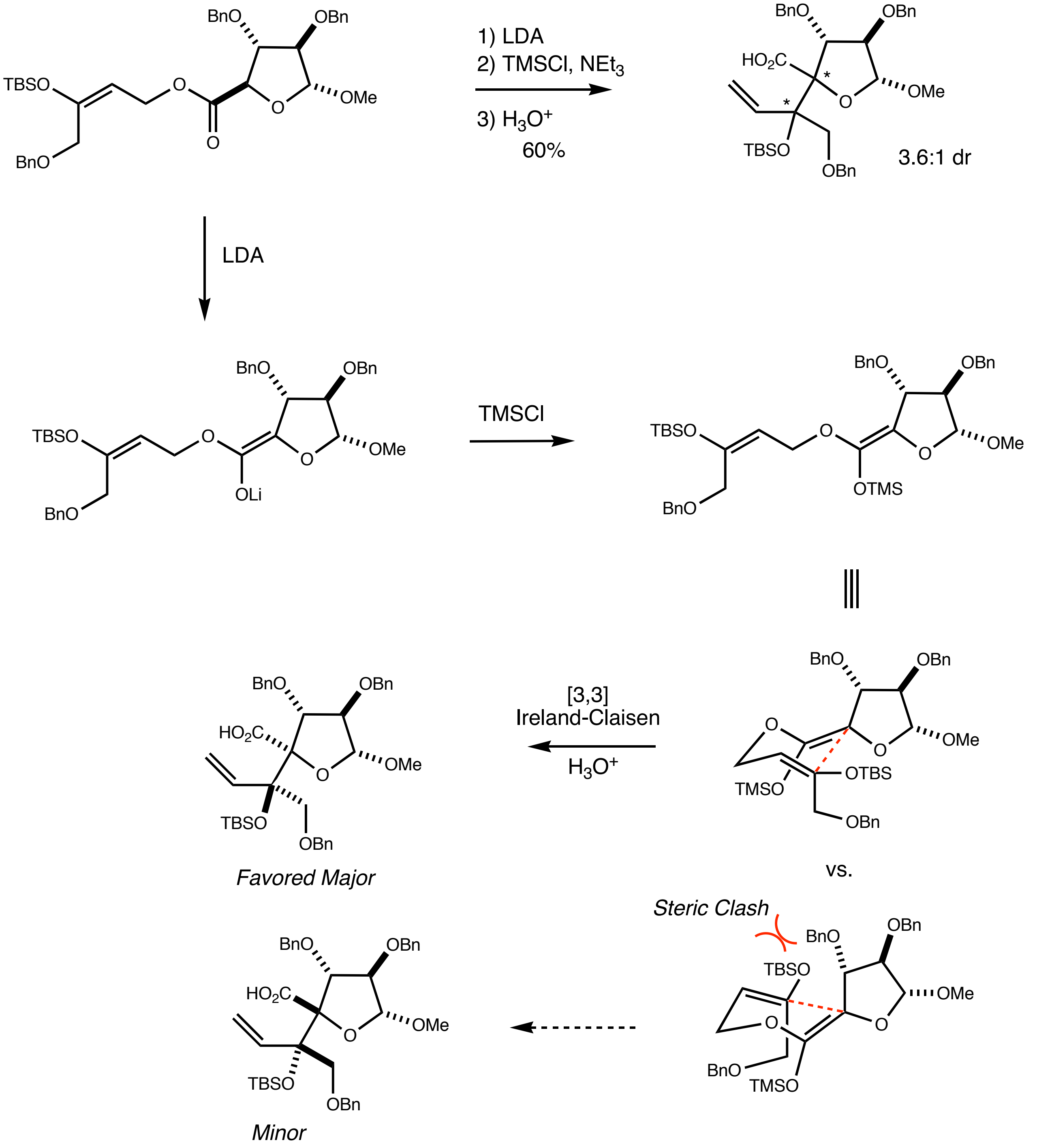


Please provide a general mechanism for this interesting reaction and using clear three-dimensional drawings predict the absolute stereochemical outcome.



(*JACS.* **2003,** *125,* 4990)

Question 9. The following transformation has been recently employed during the total synthesis of Zaragozic Acid C. Using clear 3D drawings provide the mechanism for this reaction sequence and predict the stereochemistry of the major diastereomer of the product.



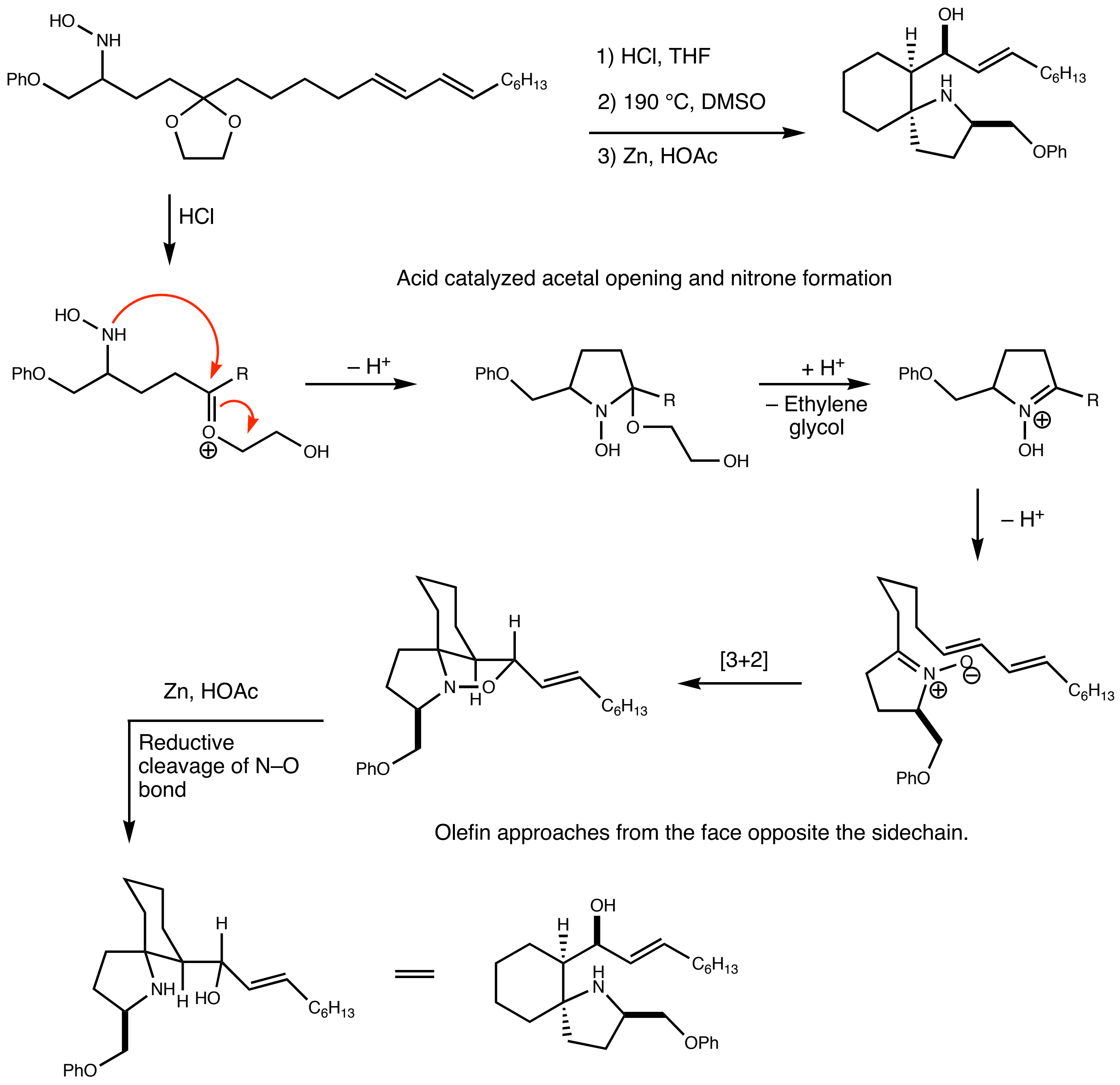
Rizzacasa *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 6376-6380.

Problem Set 6 *Name:* ***ANSWER KEY*** *TF:* ____________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate. CLASSIFY ALL PERICYCLIC REACTIONS.

Question 1.

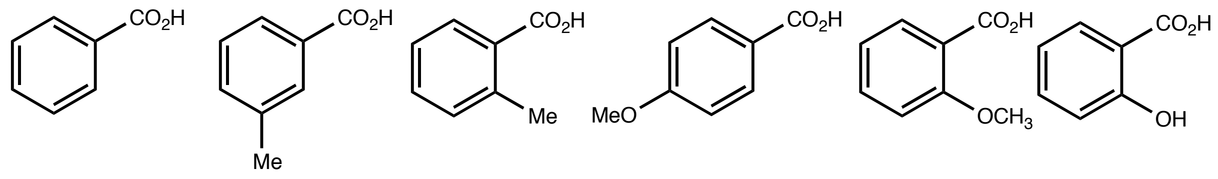
In the Weinreb synthesis of the proposed structure of lepadiformine the following synthetic sequence was executed. Please provide a mechanism and clear 3-D depictions of all relevant intermediates that explains the stereochemical outcome of the reaction.



Acid catalyzed acetal opening and nitrone formation

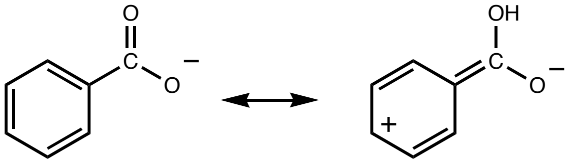
Olefin approaches from the face opposite the sidechain.

Question 2. For the set of carboxylic acids shown below, briefly rationalize the given pKa's.

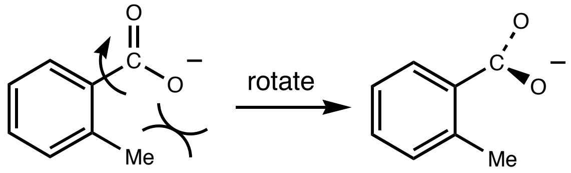


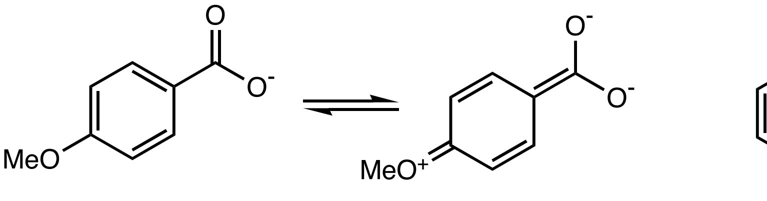
pK_a 4.20 4.24 3.91 4.47 3.85 2.97

Donation of electron density by resonance can be thought of as a destabilizing influence in the deprotonated carboxylate. This donation is increased by meta-methyl substitution, which increases the electron density in the phenyl ring. However, due to sterics the ortho substituent induces the carboxylate to rotate out of the plane of the phenyl ring, preventing overlap of the two π systems. This steric inhibition of resonance dampens the destabilizing interactionand only the minor stabilizing effect of inductive withdrawal of electron density is felt.

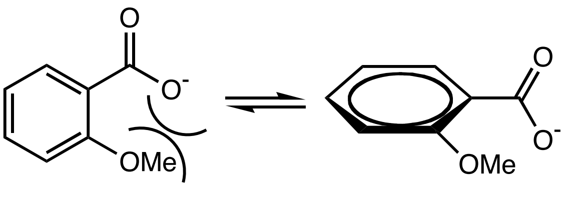


destabilizing resonance interaction

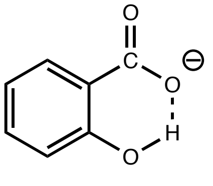




Mesomerically electron donating methoxy group at para position desatbilizing the conjugate base through resonance delocalization



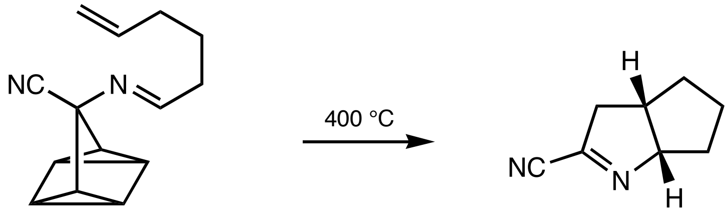
Unable to achive planarity for π overlap



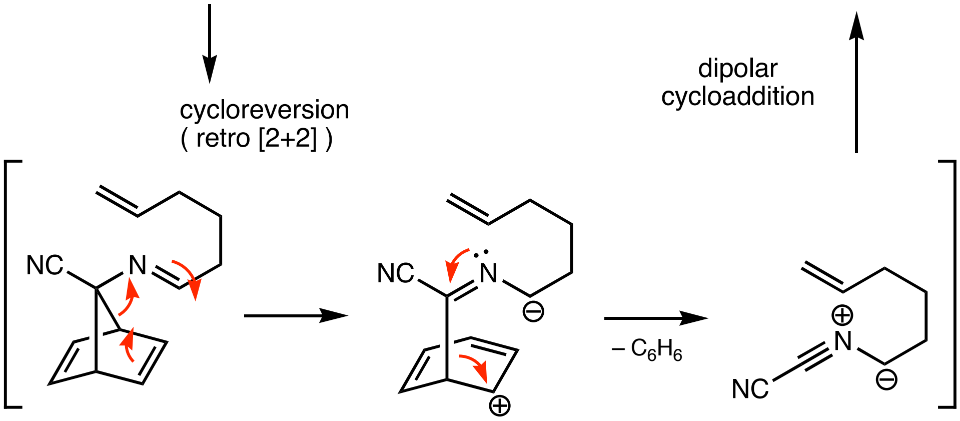
Internal hydrogen bonding stabilizes the conjugate base

Question 3.

Hoffmann has reported the mechanistically interesting thermally induced transformation illustrated below

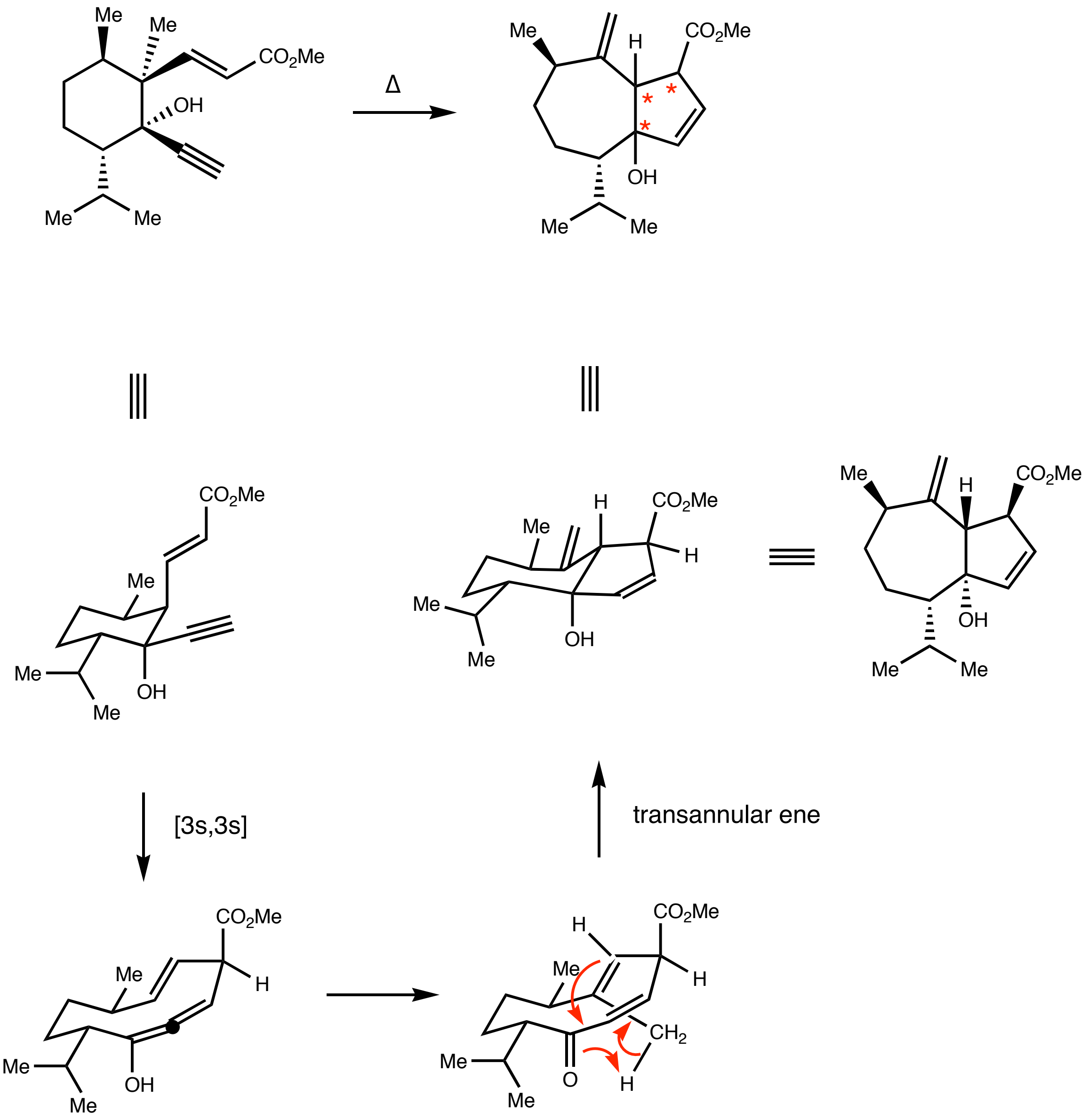


Provide a plausible mechanism for this reaction.



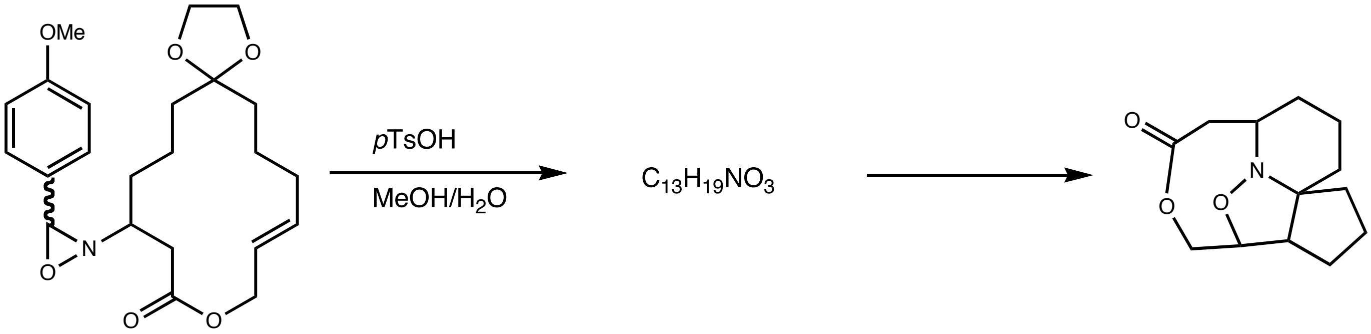
Chem. Ber. **1985**, 634.

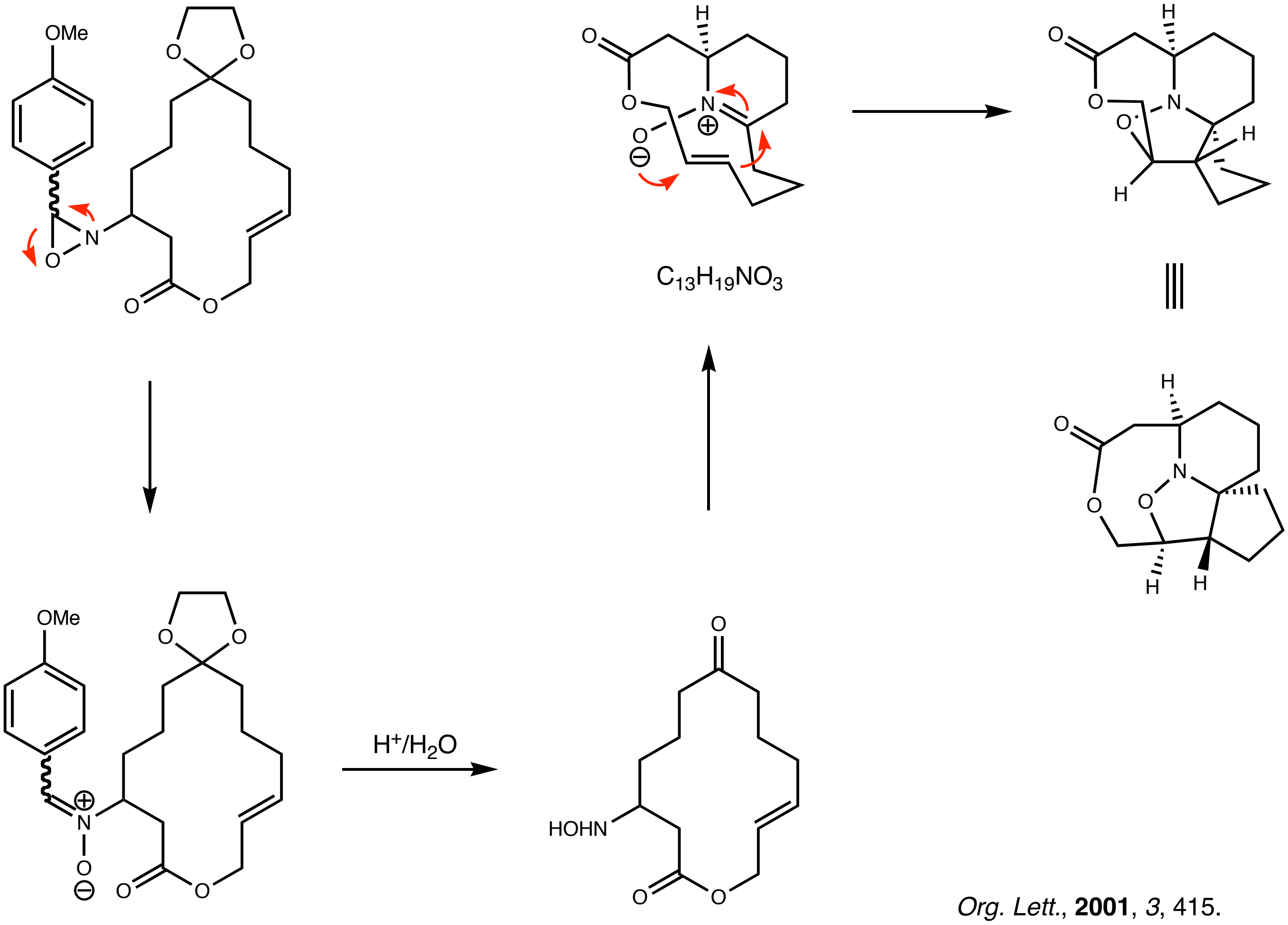
Question 4. Provide a mechanism that predicts the observed stereochemistry at the starred (*) carbon atoms. Draw the starting material, each intermediate, and the product clearly in 3D.



Question 5.

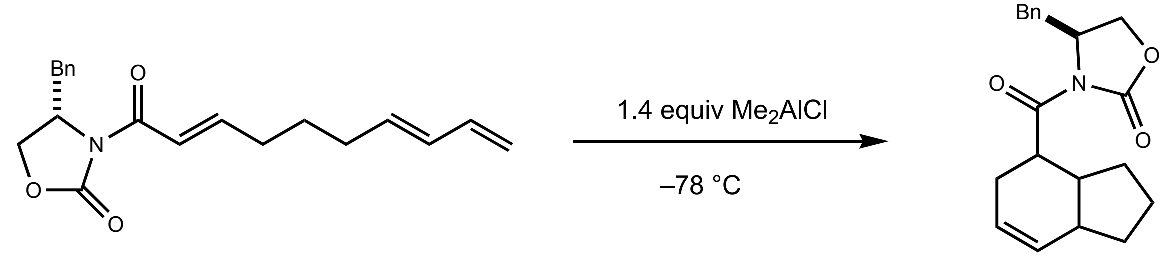
Please provide a mechanism for the following transformation and predict the stereochemistry of the product.

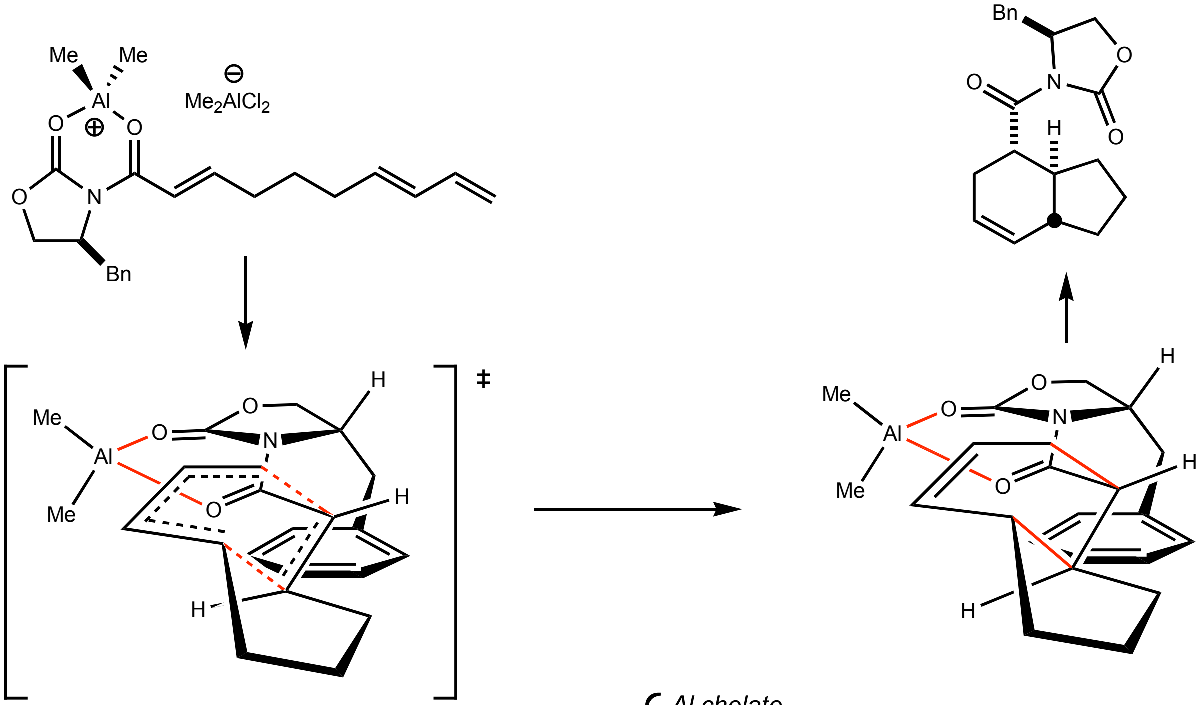




Org. Lett., **2001**, *3*, 415.

Question 6. Provide a mechanism, including a clear 3-dimensional depiction of the transition state, which predicts the major product diastereomer for the following intramolecular Diels-Alder reaction.



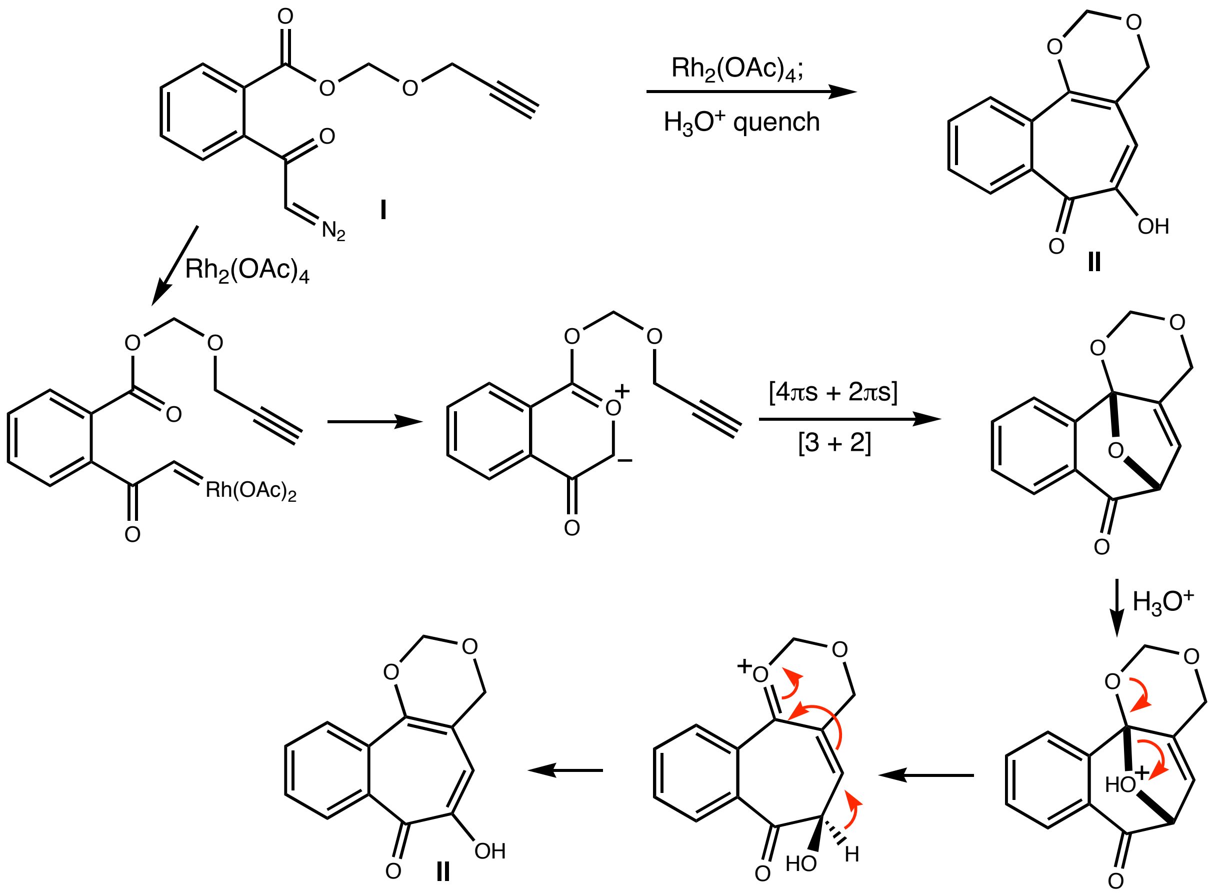


A complete answer addresses each of the following points:

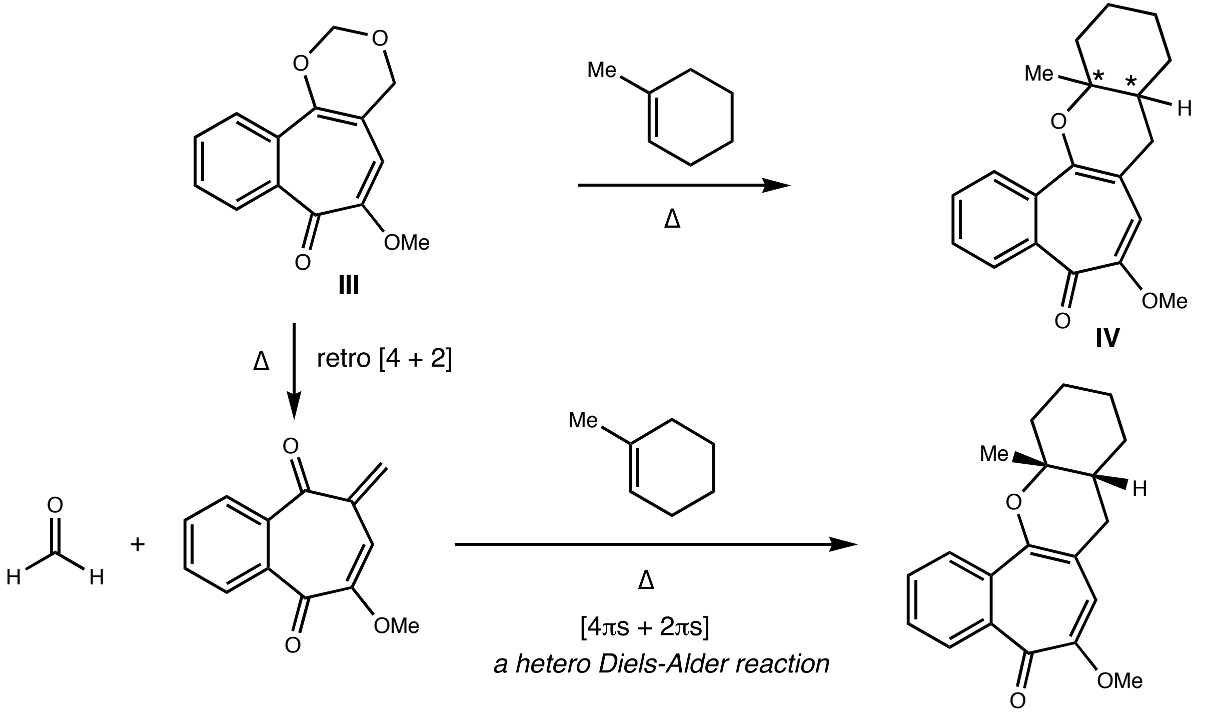
- *Al chelate*
- *s-cis dienophile*
- *boat TS*
- *endo*
- *relative stereochemistry*
- *abolute stereochemistry*
- *π-stacking*

Question 7. This question is taken from recent work reported by Jack Baldwin.

Part A. Provide a mechanism for the conversion of **I** to **II**.



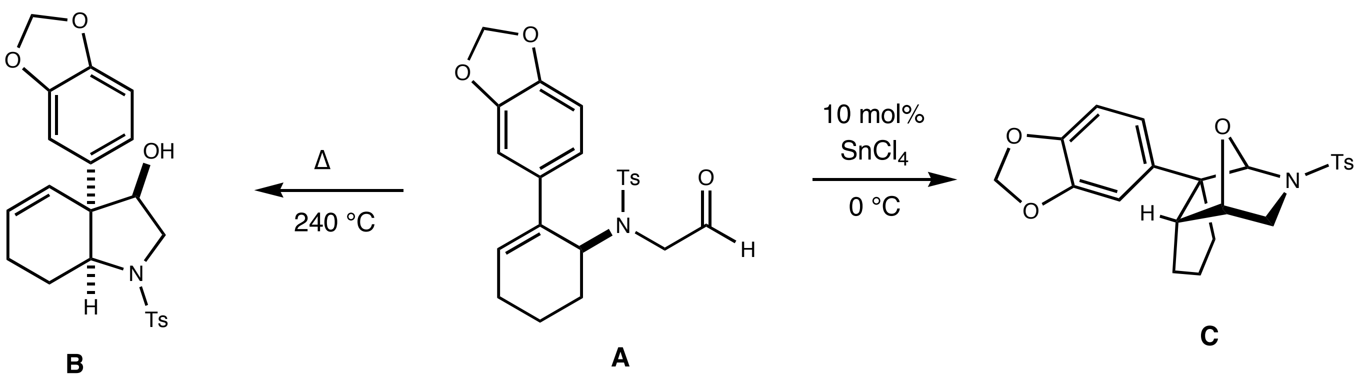
Part B. Compound **II** is protected as its methyl ether **III** and then transformed to **IV**. Provide a mechanism for the conversion of **III** to **IV**. Predict the relative stereochemistry at the starred (*) carbon atoms.

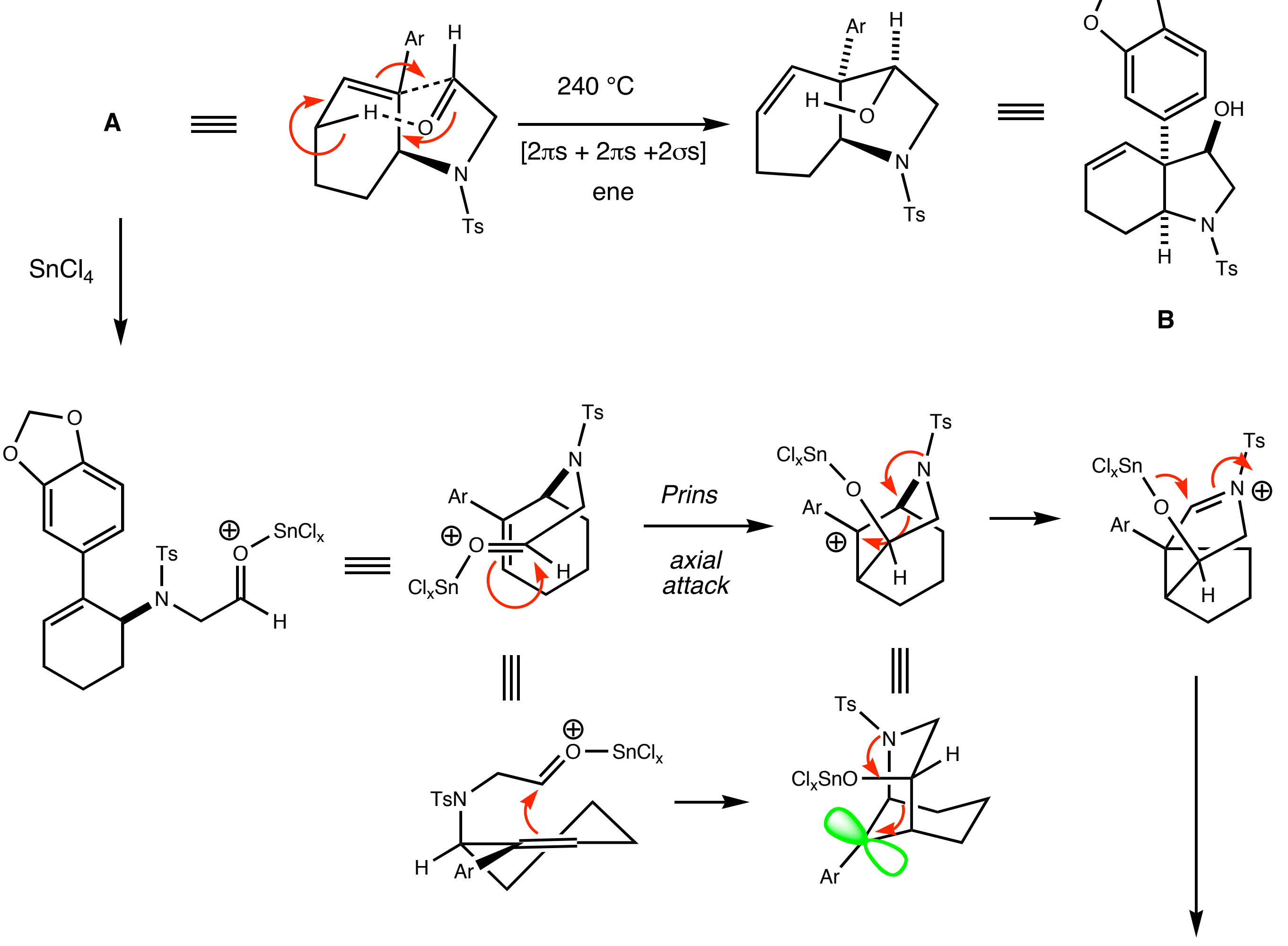


The pericylic reaction is stereospecific, hence the nature of the starting olefin defines the geometry observed in the product.

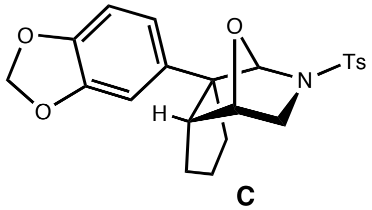
Jack Baldwin (*Org. Lett.*, **1999**, 1933 and1937).

Question 8. Provide mechanisms that account for the stereoselective formation of the products obtained by subjection of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions.

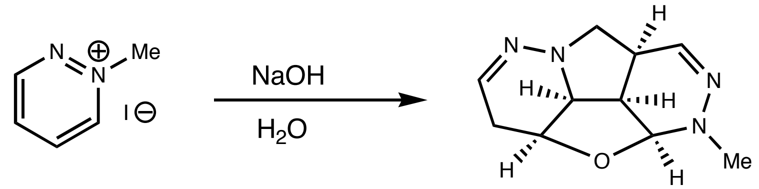


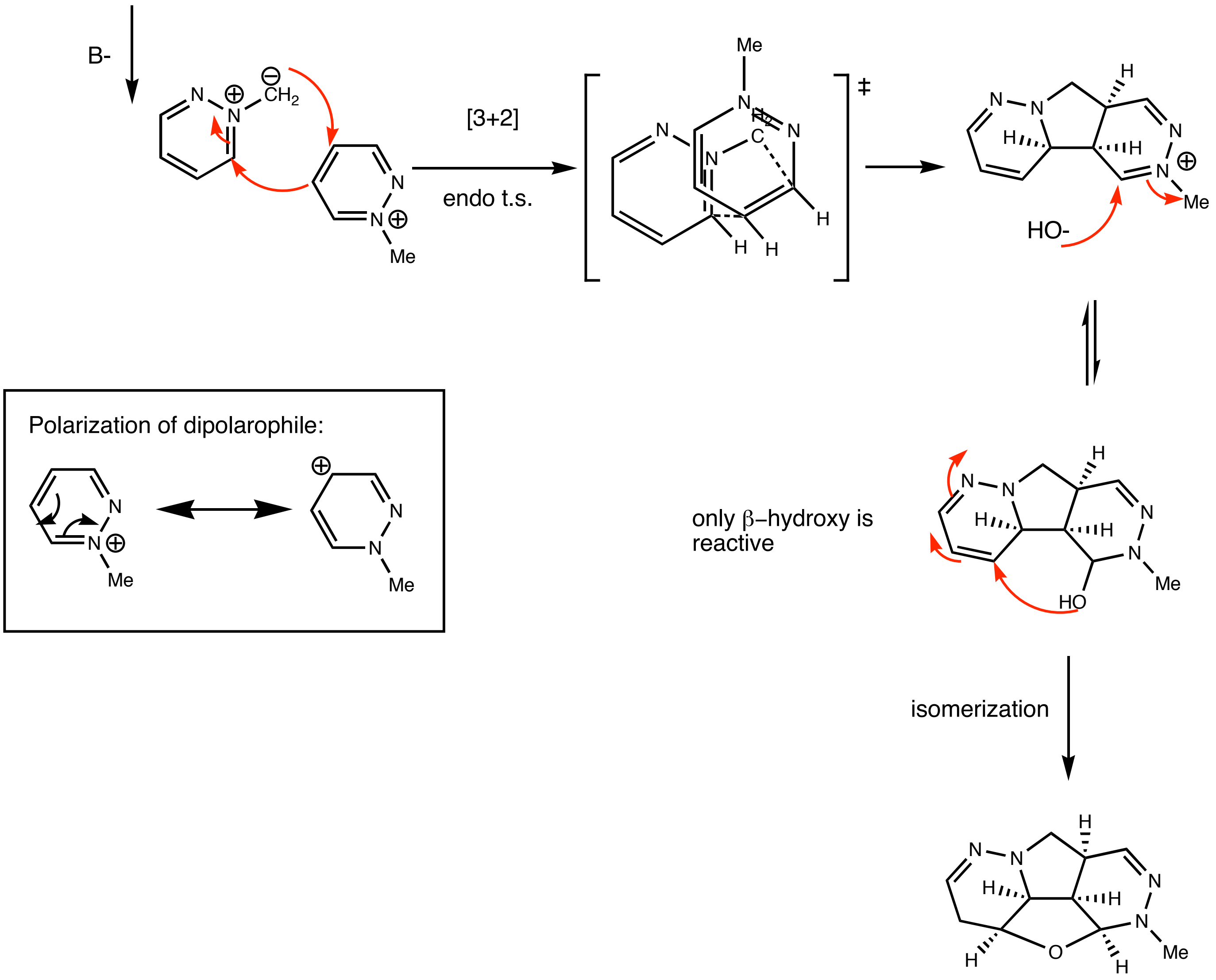


Thermal conditions promote a concerted ene reaction. Under Lewis acidic conditions, a stepwise mechanism predominates where a Prins reaction leads to the stablized benzylic cation. Nitrogen assisted ring contraction leads to the iminium ion which is quenched by the alkoxide.

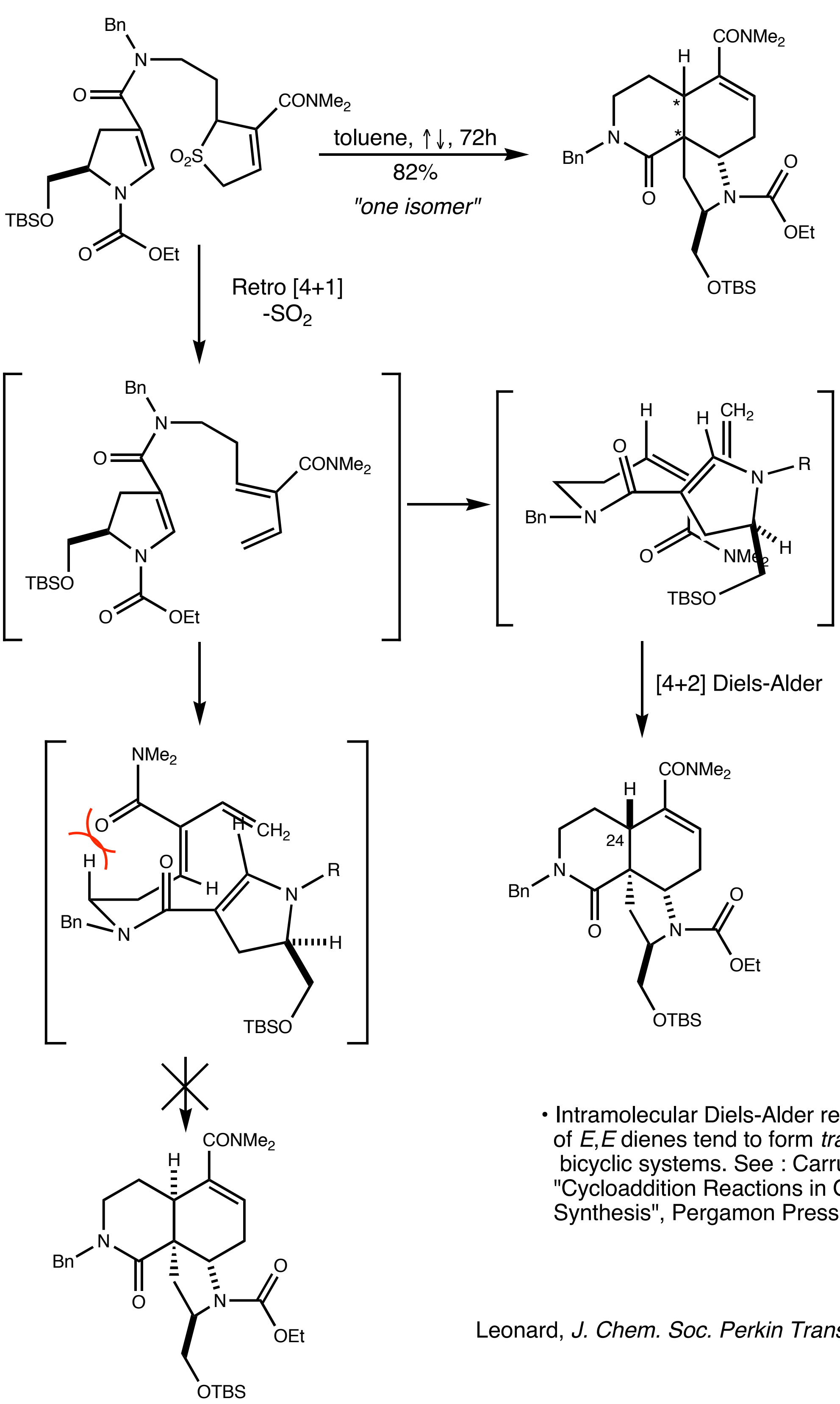

C

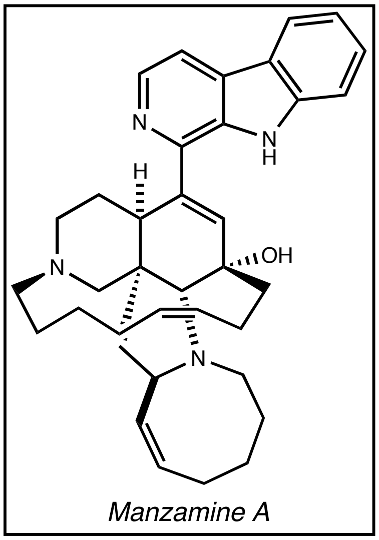
Question 9. Provide a mechanism for the following transformation.





Question 10. The following reaction was utilized in an approach to synthesize the core structure of the manzamines. Provide a mechanism for the transformation, and assign stereochemistry where appropriate.





Manzamine A

- Intramolecular Diels-Alder reactions of *E*,*E* dienes tend to form *trans*-fused bicyclic systems. See : Carruthers, "Cycloaddition Reactions in Organic Synthesis", Pergamon Press, 1990

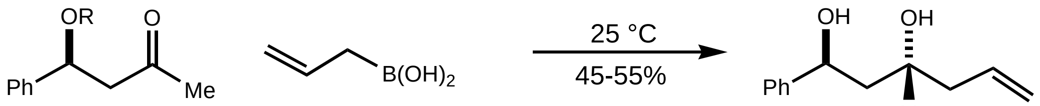
Leonard, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2359

Problem Set 7 *Name:* **Answer Key** *TF:*_______________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

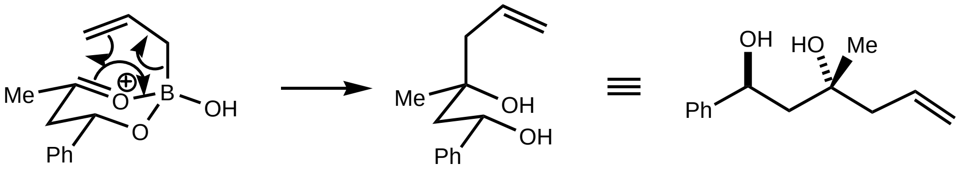
Question 1.

The following transformation was recently reported by Kabalka. Treatment of **1** with allylboronic acid afforded the indicated adduct in high yield with 10:1 diastereoselection. On the other hand, the analogous reaction of **2** was nonstereoselective. Propose a mechanism for this transformation that accounts for the stereochemical outcome of the addition process.



1, R = H
2, R = Me

diastereoselection 10:1



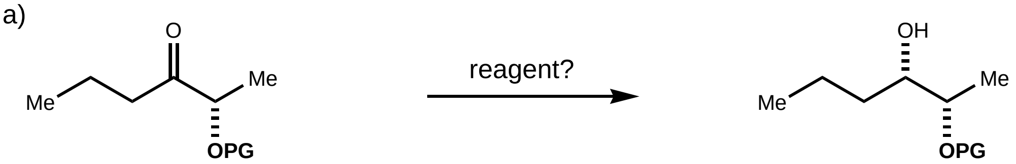
cyclic transition state with all substituents equatorialtransesterification not possible with OMe ether

(*Tetrahedron Lett*. **1996**, *37*, 2181)

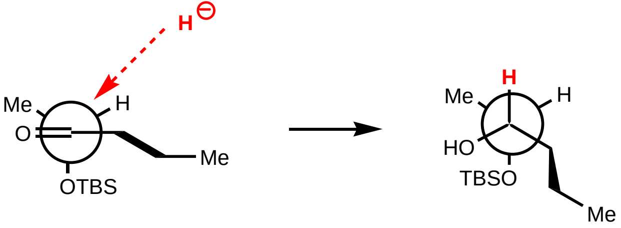
Question 2.

Give your choice of a protecting group and reagent, and justify your answer with 3D drawings:

a)

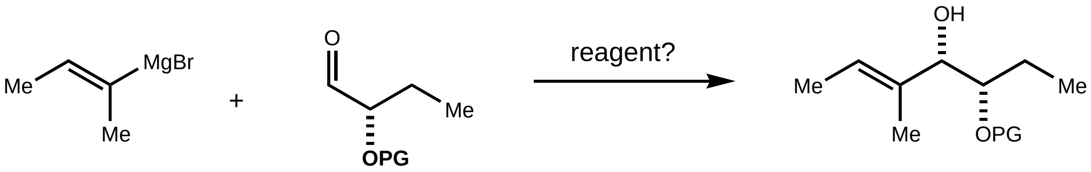


Syn-relationship of the two hydroxyl groups of the product imply that the Felkin-Anh model is operational during the transformation. To prevent chelation, a non-chelating group (such as TMS, TES, TBS, etc. should be chosen). Any hydride source such as LAH, $NaBH_4$, L-Selectride, or Red-Al would give the Felkin selectivity with a non-chelating group. However, if L-Selectride is used, a chelating protecting group (such as MOM-, or BnO-) could still give good Felkin selectivity if an appropriate solvent is used.

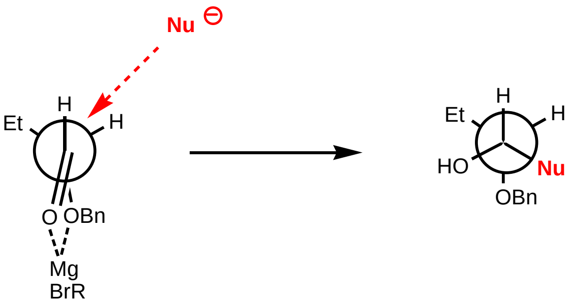


Nakata, *TL* **1983**, *24*, 2653.

b)

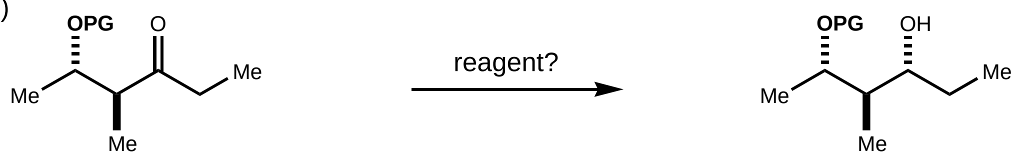


This case is the opposite to the one above. Chelate controled addition is desired. Note that the chelate control addition and Felkin reduction (or Felkin addition and chelate reduction) are complementory methods to construct the same stereoarray. In order to promote chelation, any non-silicon protecting group can be used: PMB-, Bn-, MOM-, BOM-, THP-, etc.

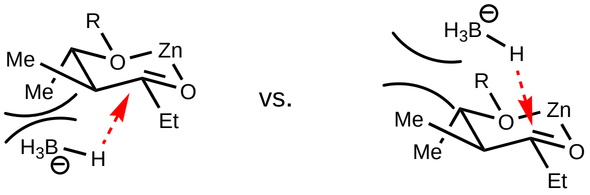


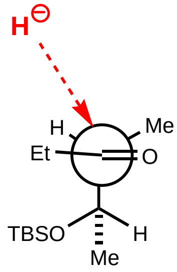
Question 2, continued

c)



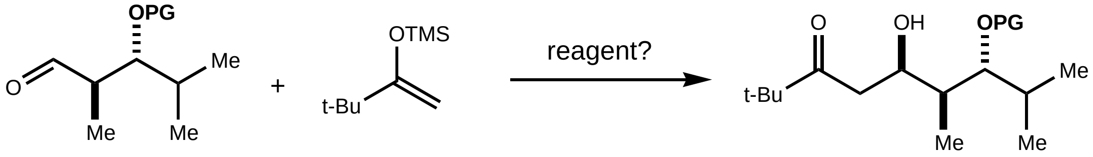
In this case, either chelate-controlled syn-reduction or Felkin-product selective reduction are the options to consider. However, one has to note that if 1,3-syn reduction is used, the α-Me-group precludes the nucleophile from approaching the correct face; low selectivity is usually observed.



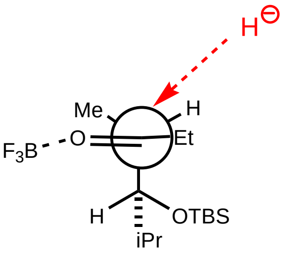


Felkin reduction ia apparently the solution since 1,3-induction reinforces this case. Thus, one needs a non-chelating protecting group and a bulky nucleophile (such as L-Selectride)

d)



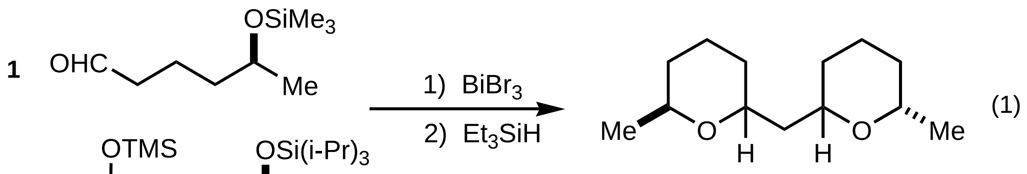
This case is similar to the one above. Felkin is stereoreinforced by 1,3-induction. In this case, if a monodentate Lewis-Acid (such as BF_3-Et_2O) is used, there is no specific requirements to the protecting group. It could be a chelating group (PMB), or a non-chelating group (TBS).



Evans et al., *JACS* **1996**, *118*, 4322

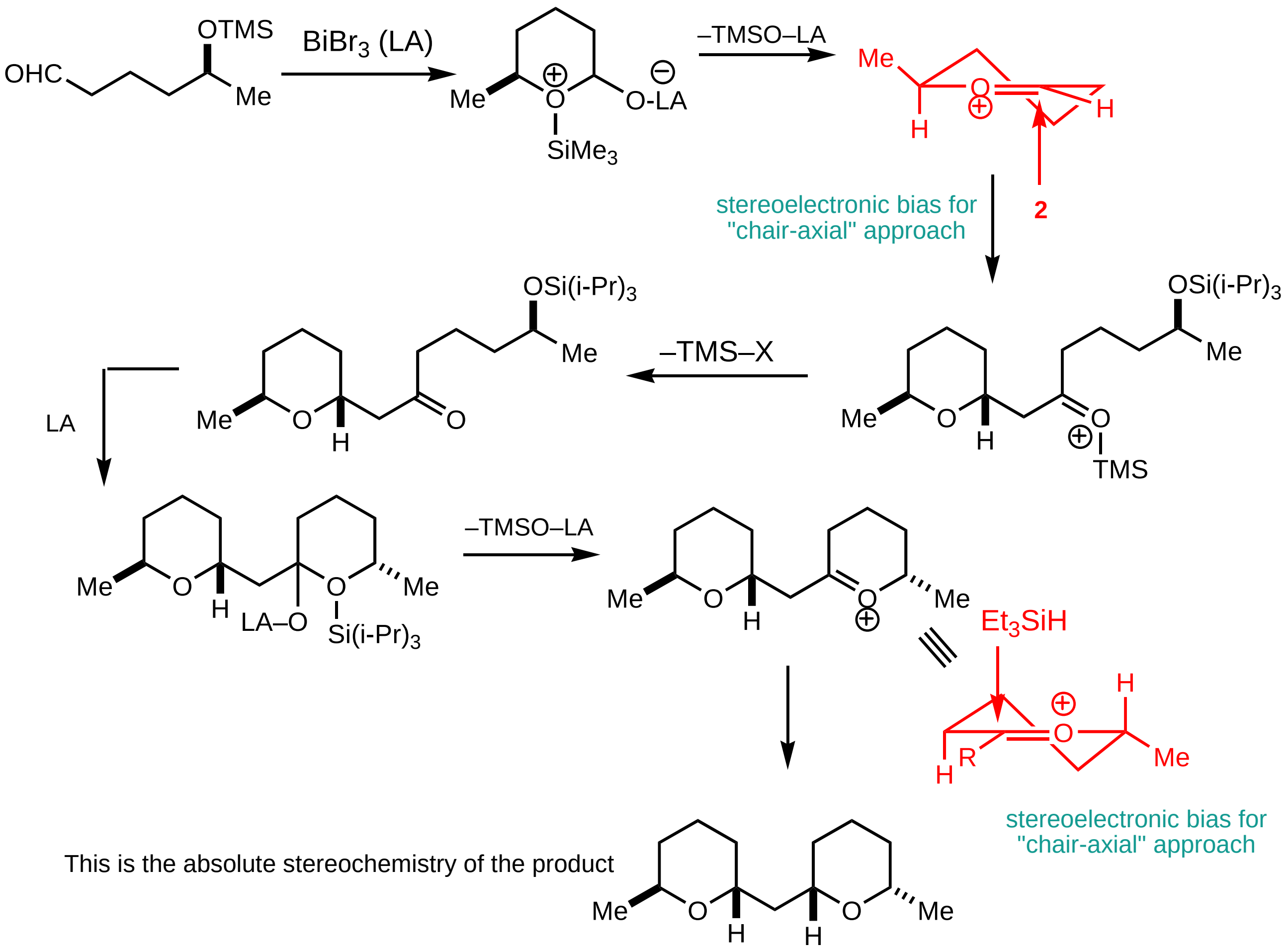
Question 3.

P. A. Evans and co-workers have recently reported a highly diastereoselective approach to the construction of linked tetrahydropyrans. One of their cases is illustrated in Eq 1. In this transformation $BiBr_3$ is employed as a mild Lewis acid.



A single diastereoisomer
diastereoselection: 95:5 (73% yield)

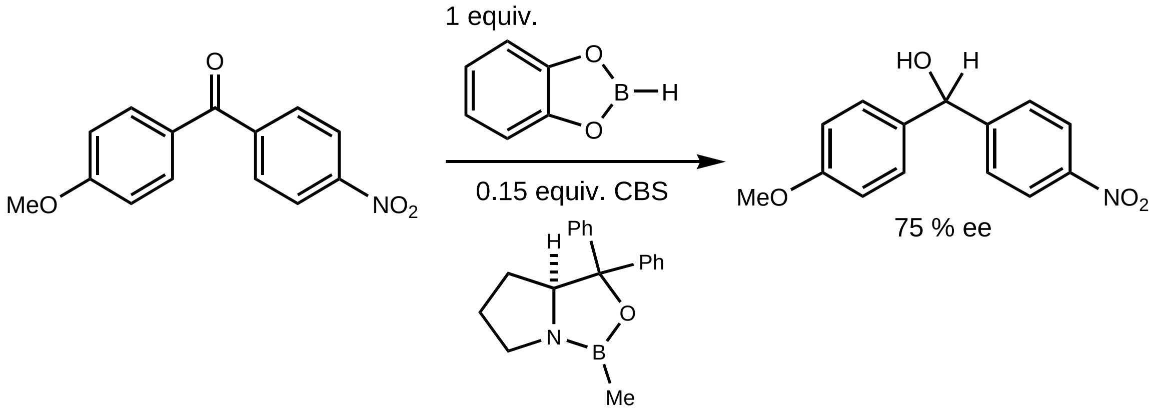
Please provide a mechanism for the reaction cascade that results in the production of the illustrated product. Your answer should include clear 3-D drawings where relevant and should provide the stereochemistry of the major product diastereoisomer.


OHC
OTMS
Me
BiBr3 (LA)
Me
O
SiMe3
O-LA
–TMSO–LA
Me
O
H
H
2
stereoelectronic bias for "chair-axial" approach
OSi(i-Pr)3
Me
–TMS–X
Me
O
H
O
TMS
LA
LA–O
Si(i-Pr)3
–TMSO–LA
Et3SiH
R
stereoelectronic bias for "chair-axial" approach
This is the absolute stereochemistry of the product

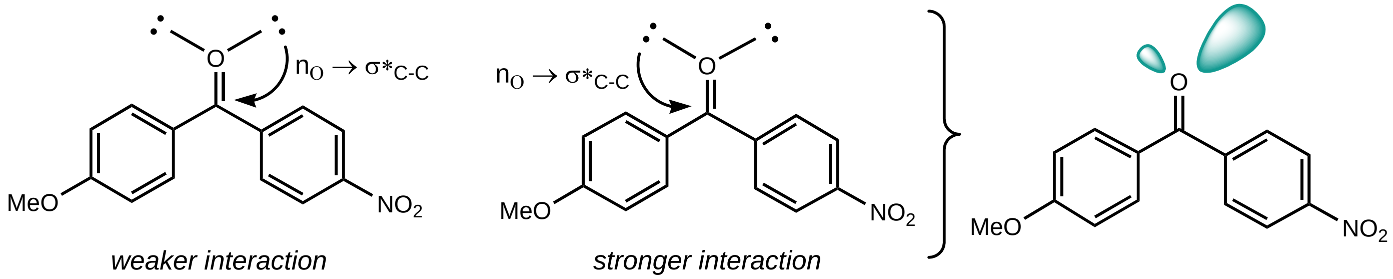
(JACS 2**003,** 1*25,* 11456-11457)

Question 4.

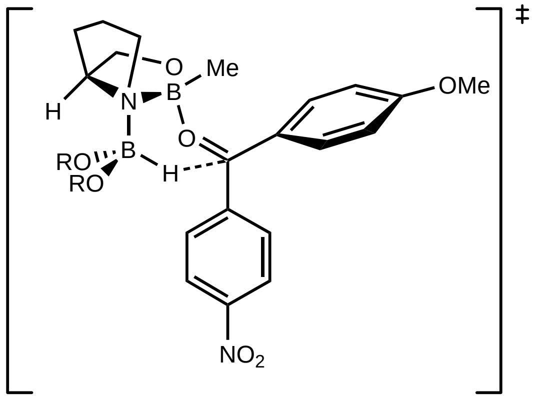
Corey's CBS catalyst for ketone reduction often delivers high yields of enantioenriched secondary alcohols. Provide a clear illustration of the transition state which predicts the absolute stereochemistry of the product obtained in the illustrated reaction. Include an explanation of why the reduction of this practically symmetric ketone is selective.



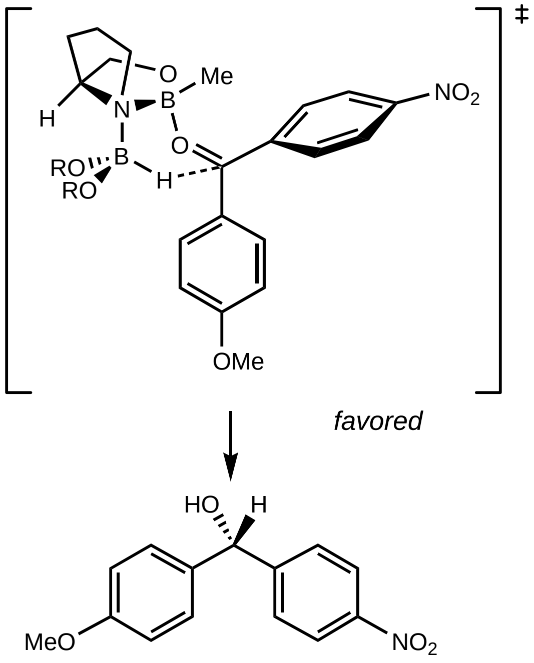
The availability of ketone lone pairs must be considered. Because the antiperiplanar C-C sigma bonds have differing electron density, the ketone lone pairs will be anisotropic. The $n_O \rightarrow \sigma^*_{C-C}$ interaction with the electron rich C-C bond will be weak relative to the $n_O \rightarrow \sigma^*_{C-C}$ interaction with the electron deficient C-C bond. Complexation of the lone pair anti to the p-methoxy phenyl substituent will be favored.


O
$n_O \rightarrow \sigma^*_{C-C}$
MeO
NO2
$n_O \rightarrow \sigma^*_{C-C}$
O
MeO
NO2
O
MeO
NO2

weaker interaction *stronger interaction*



disfavored

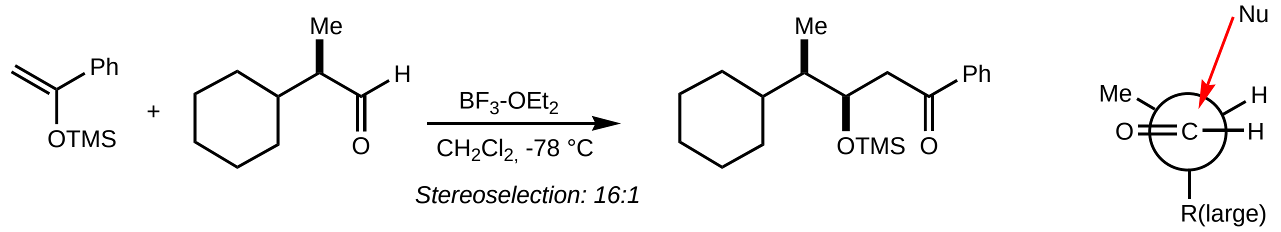


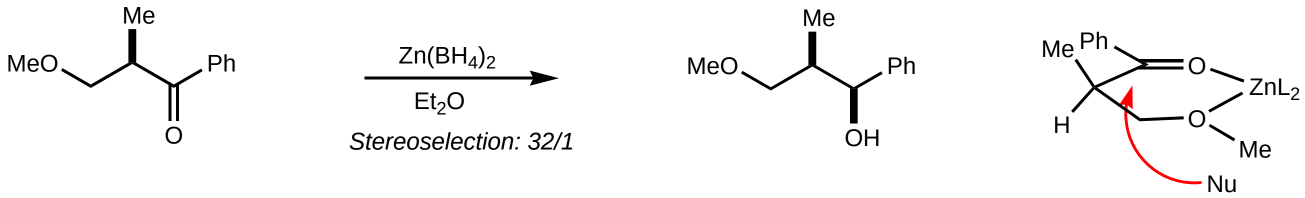
favored

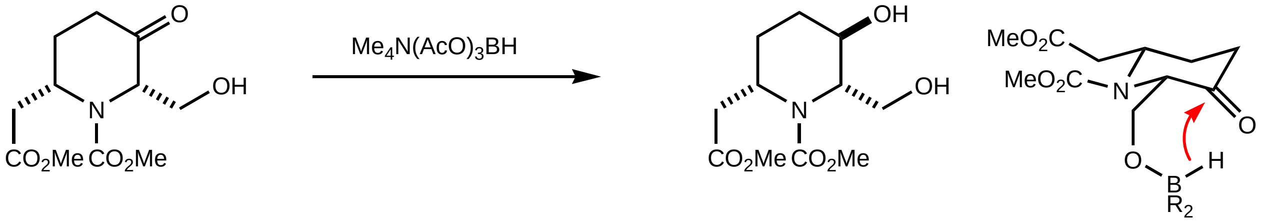
(A*CIE* **1998**, 1987).

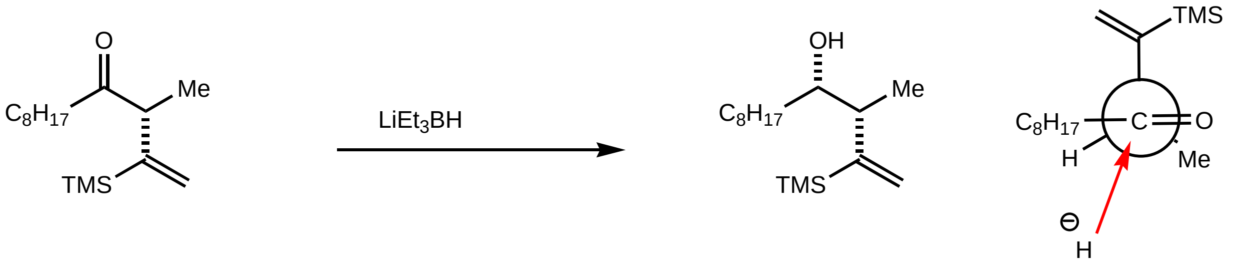
Question 5.

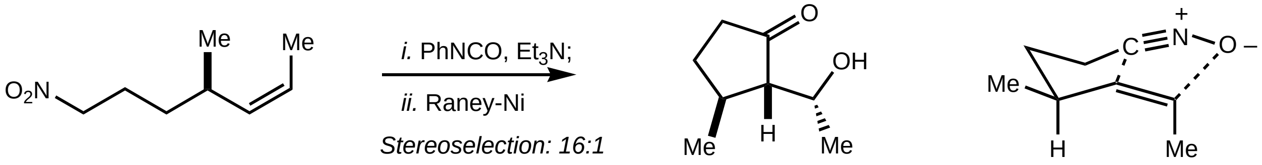
In each of the following reactions, provide the stereostructure of the major product and rationalize the stereochemical outcome using clear 3D-drawings or Newman projections







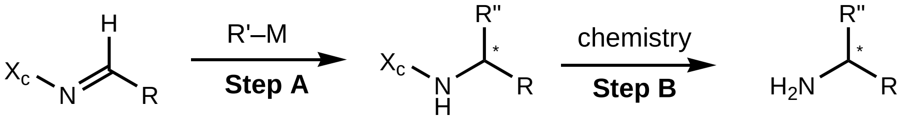




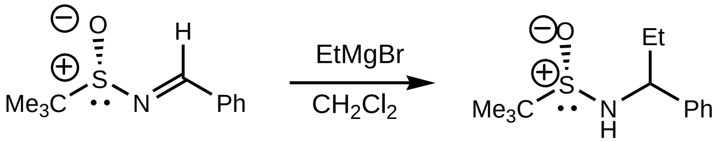
This is another example of a reaction controlled by allylic strain conformational effects.

Question 6.

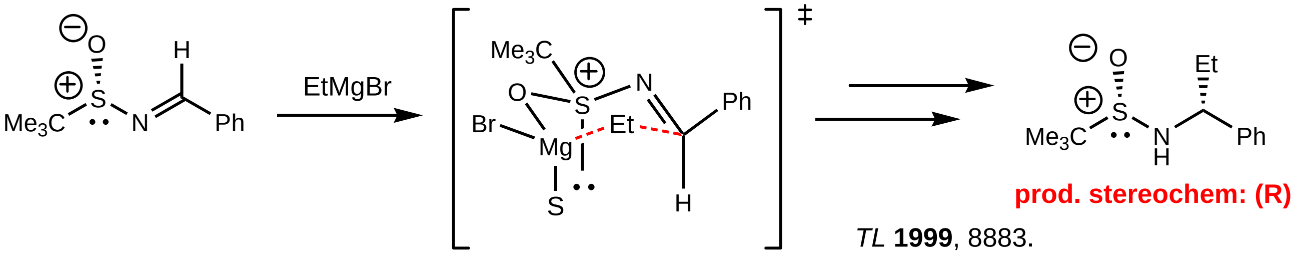
Chiral auxiliaries (Xc) are routinely employed to control the absolute stereochemistry of the addition or organometallic reagents to imines (Step A). A design requirement of these controllers is that they may be readily cleaved after the addition step (Step B). In the two parts of this question posed below are presented two well-established chiral controllers that employ chelate organization as an integral part of the chirality transfer process.



Part A. Provide a mechanism for the following transformation reported by Ellman and co-workers. Include a clear transition state representation that predicts the major product diastereomer. Clearly illustrate the absolute stereochemistry of the product.



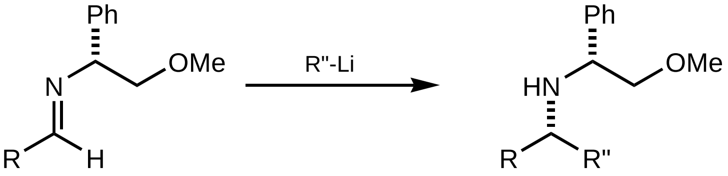
diastereomer ratio 92:8



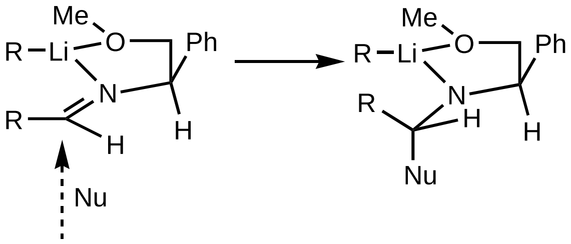
prod. stereochem: (R)

TL **1999**, 8883.

Part B. The following stereoselective transformation has been reported by Fujisawa. Given the stereostructure of the product, rationalize the stereochemical outcome.



diastereomer ratio >97:3



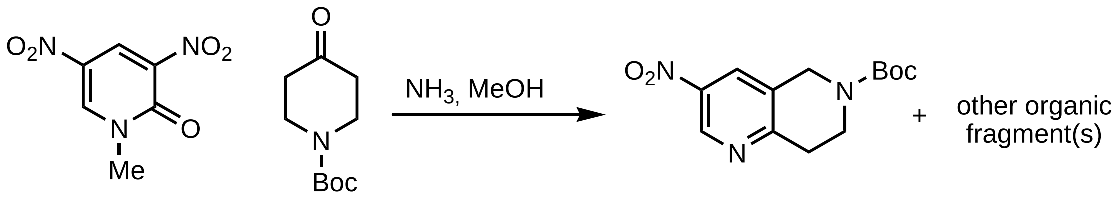
Sterically preferred C=N diastereoface

The stereochemical outcome of this reaction has been rationalized by Fujisawa through the chelate-organized imine complex shown on the left. In this study diastereoface selectivity was noted to be strongly dependant on the nature of the organometallic reagent.

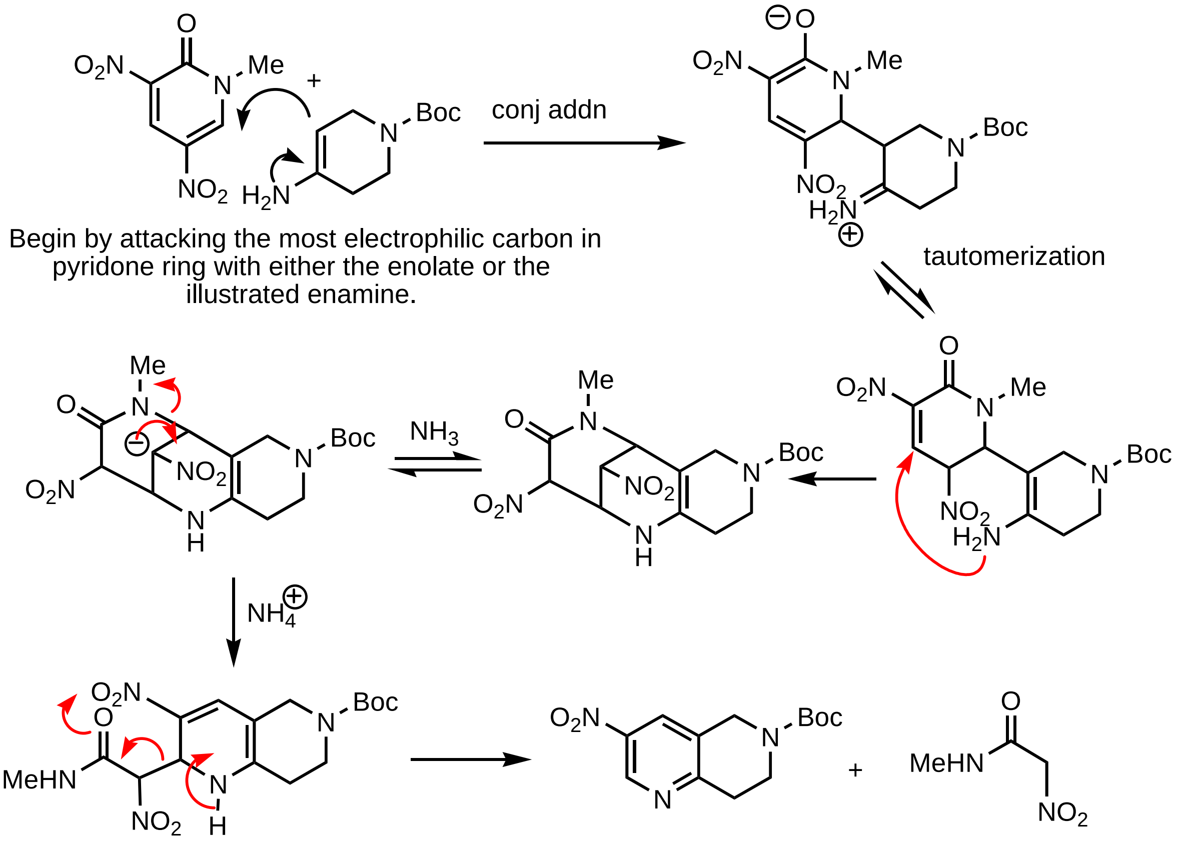
(*Chem.Lett.* **1991**, 1555).

Question 7.

This is a classic problem in multistep electron pushing. The following pyridine synthesis has been reported by Tohda. Provide a plausible mechanism for this complex transformation.



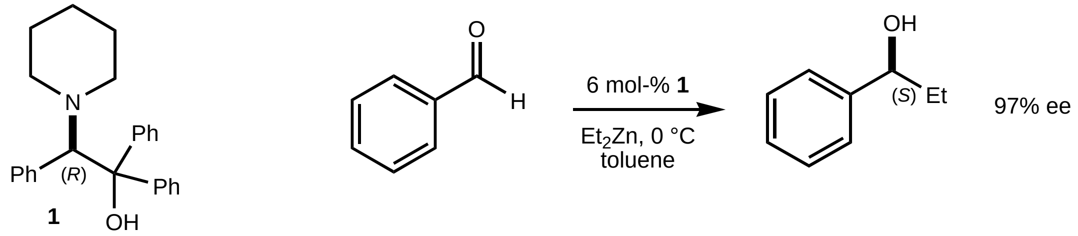
In this multistep transformation, the sequence of chemical events may not be unique.
Let's now begin:



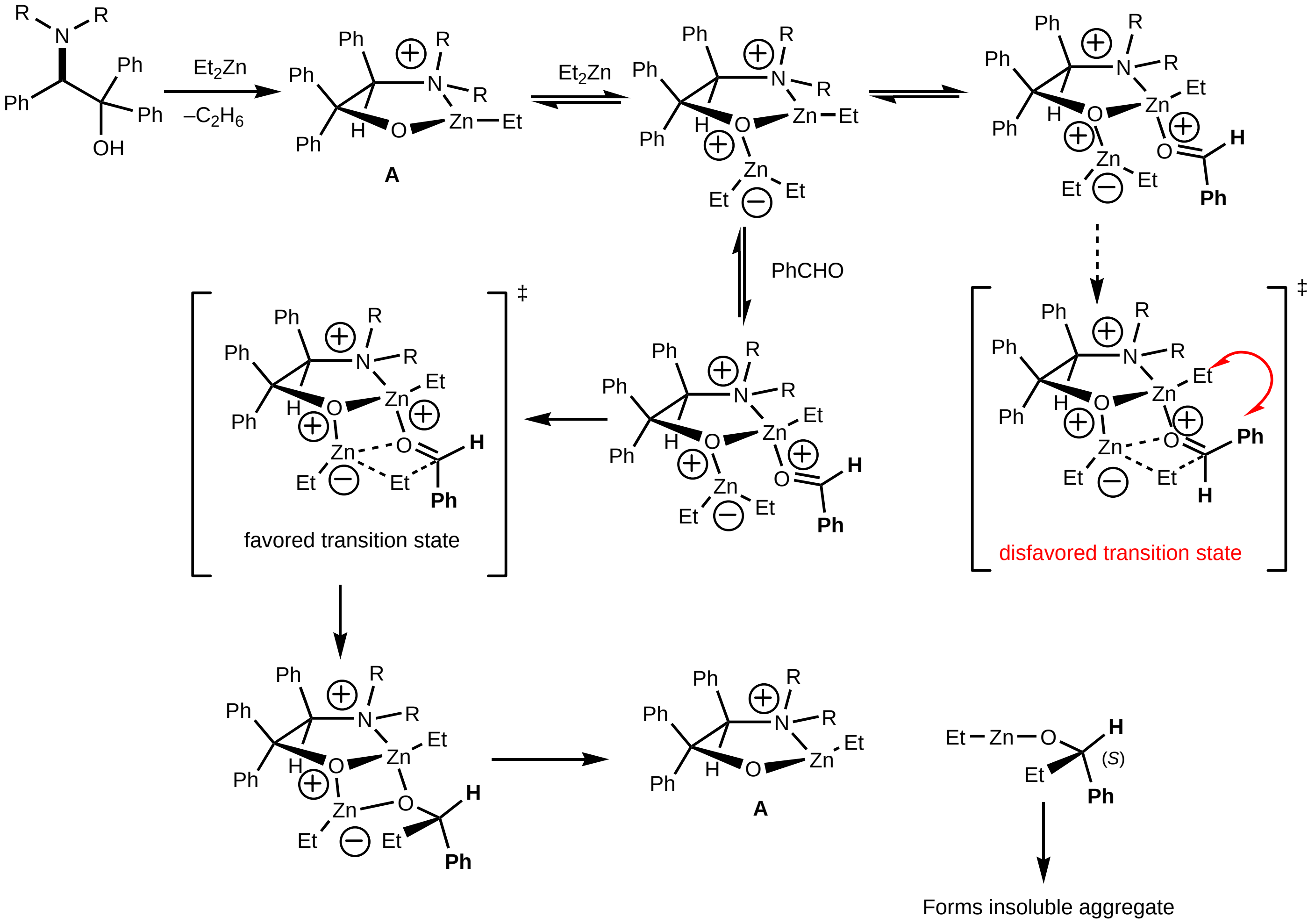
Begin by attacking the most electrophilic carbon in pyridone ring with either the enolate or the illustrated enamine.

Question 8.

Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational investigation that addresses the preferred transition state geometry for this addition process. It should be noted that, while **1** is not the actual catalyst, it is modified under the reaction conditions to the competent catalytic agent.

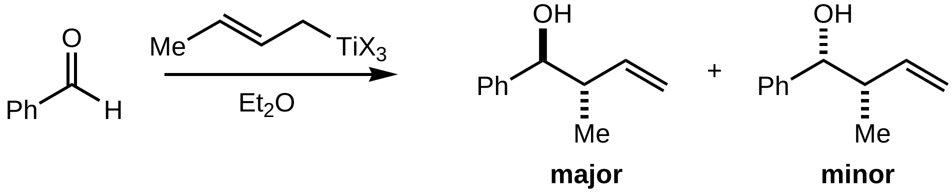


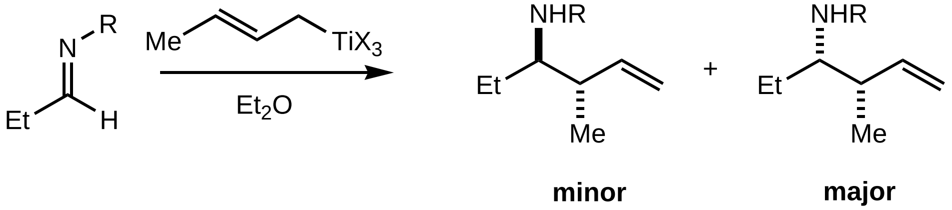
Provide a detailed mechanism for the overall transformation in the space below. Use three-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



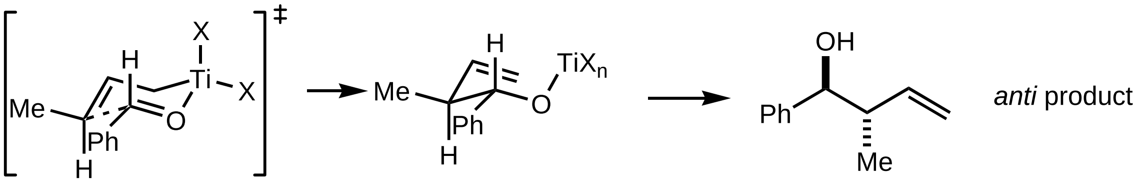
(Pericas, et al. *J. Org. Chem.* **2000**, *65*, 7303 and references cited therein)

Question 9. Crotyltitanium reagents have been developed for addition to C=O and C=N bonds.

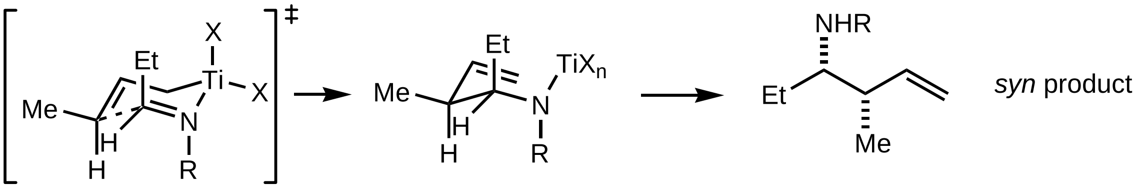




Part A. Provide an explanation, including clear 3D drawings of the transition states, which account for the divergent stereoselectivity observed in the addition reactions illustrated above.

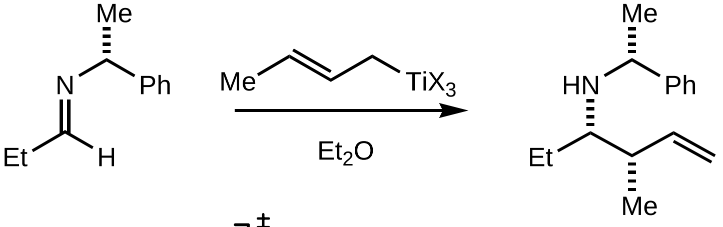


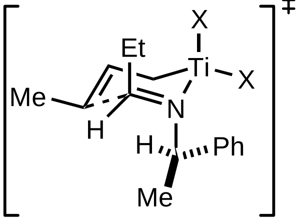
In the Zimmerman-Traxler transition state, the aldehyde is oriented with the large substituent pseudo-equatorial.

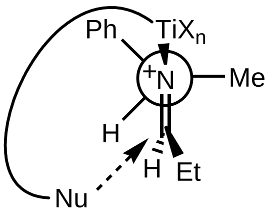


The (E)-imine, by the nature of its geometry occupies a TS conformation in which the large substituent is psuedo-axial, leading to the syn product.

Part B. The use of a chiral imine induces useful levels of asymmetric induction in this reaction. Provide an explanation, including a clear 3D drawing of the transition state, which accounts for the preferred production of the indicated diastereomer.







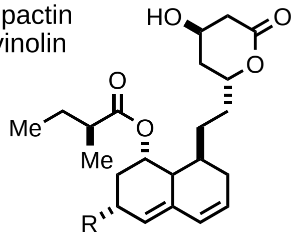
Newman projection:

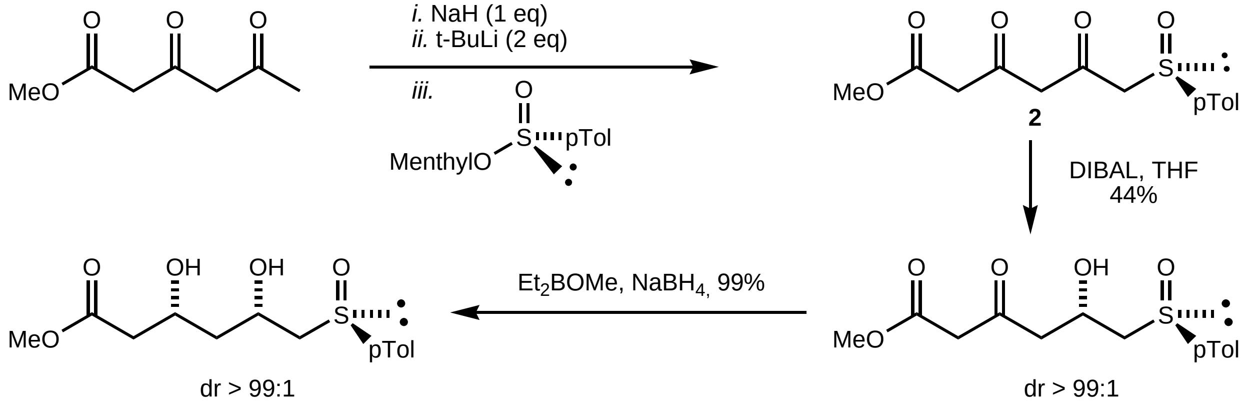
Minimization of eclipsing interactions in the staggered TS (Houk), with the best donor (Me) orthogonal to the iminium N=C.

(*J. Am. Chem. Soc*. **1995**, 3881 and *J. Org. Chem.* **1995**, 8136)

Question 10. Solladie has used a chiral sulfoxide as an auxiliary for the enantioselective synthesis of the lactonic moiety **1** of (+)-Compactin and (+)-Mevinolin**.**

R=H: (+)-compactin
R=Me: (+)-mevinolin

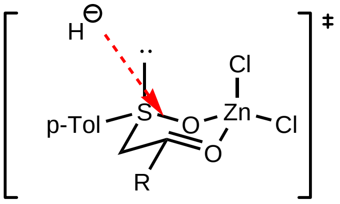




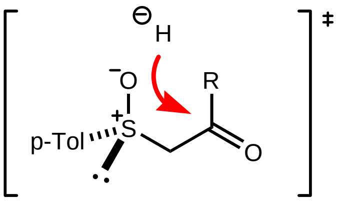
Explain which stereoselectivities are observed in the two reduction steps illustrated above. Use clear 3D drawings for the transition states.
Your answer should also include an explanation for the observation, that the reduction of **2** in the presence of $ZnCl_2$ shows a reversal in diastereoselectivity (dr = 5:95 on a model of **2** with a truncated side-chain).

DIBAL-Reduction:

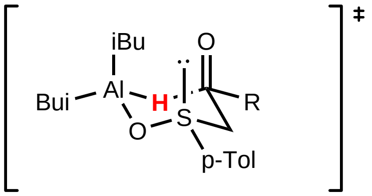
$ZnCl_2$ forms a chelate with the most basic oxygen (S-O):



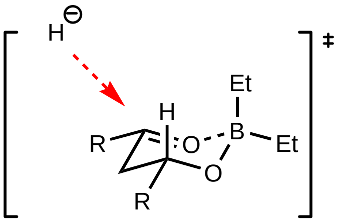
Solladie sugests:
dipole minimized;
attack from the less shielded face (lone pair)



However:
sulfoxide is a strong donor which coordinates the Al;
internal delivery of the H^-



$NaBH_4$-Reduction: Et_2BOMe is a powerful chelating agent
It reacts with ROH and activates the adjacent carbonyl.
$NaBH_4$ delivers an external hydride



(*JOC* 1**995,** 6*0,* 7774 and TetLett **1985**, *26,* 435).

Chem 206 *Due: Monday, Nov. 27*

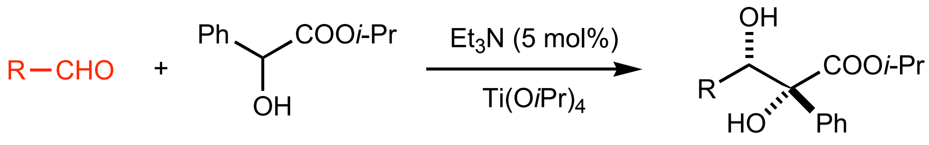
Problem Set 8

Name:_______________TF:____________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

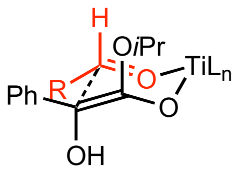
Question 1.

Part A. Rationalize the syn-selectivity of the following reaction with a clear 3-D representation of Zimmerman-Traxler transition state.

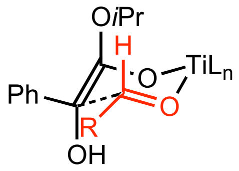


R	yield (%)	ration (syn/anti)
Me	70	55:45
Et	75	79:21
i-Pr	78	94:06

Answer:



or

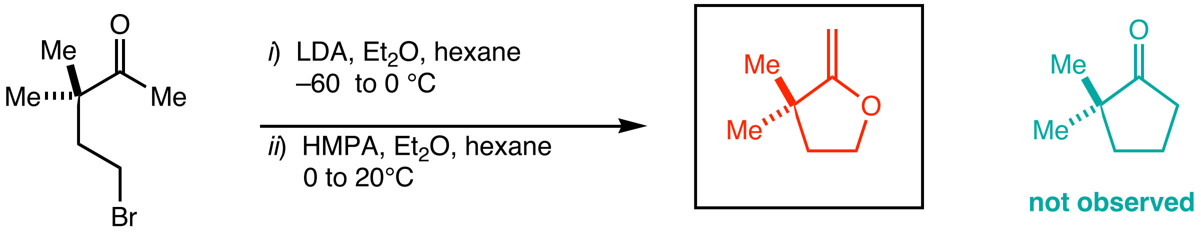


The more sterically demanding R group is, the higher propensity to orient R group pseudo-equatorial position which results higher syn-selectivity.

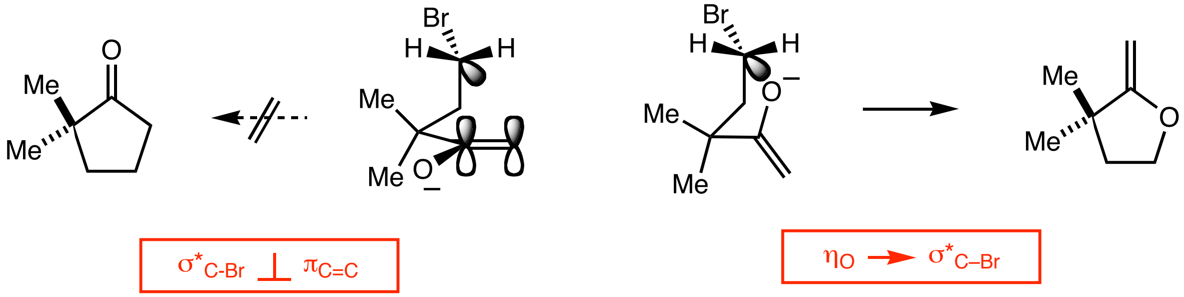
Mahrwald and coworkers recently reported syn-configured aldol products of mandelic acid esters and aldehydes were synthesized by the catalytic use of amines in the presence of titanium(IV) *tert*-butoxide. When chiral *N*-methylephedrine was used as a chiral ligand, anti-configured α,β–dihydroxyesters were isolated with a high degree of enantioselectivity. (*Org. Lett.* **2006**, *8*, 5353-5355)

Question 2.

Predict the product of the reaction below. Include a rationalization based on a detailed analysis of competing transition state geometries.

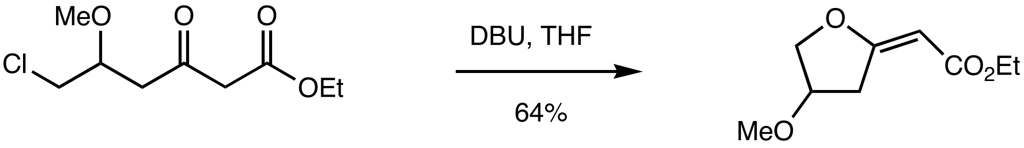


Answer



House, H. O.; Phillips, W. V.; Sayer, T. S. B.; Yau, C. *J. Org. Chem.* **1978**, 700-710.

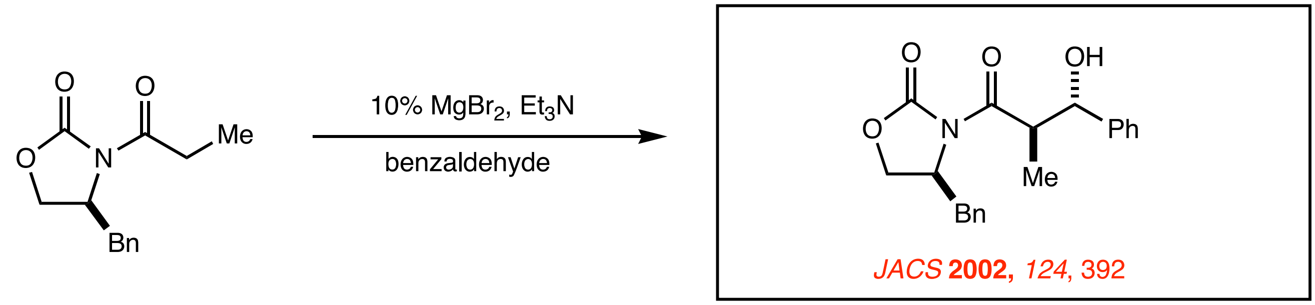
Similarly, see: Langer, P.; Krummel, T. *Chem. Eur. J.* **2001**, *7*, 1720-1727:



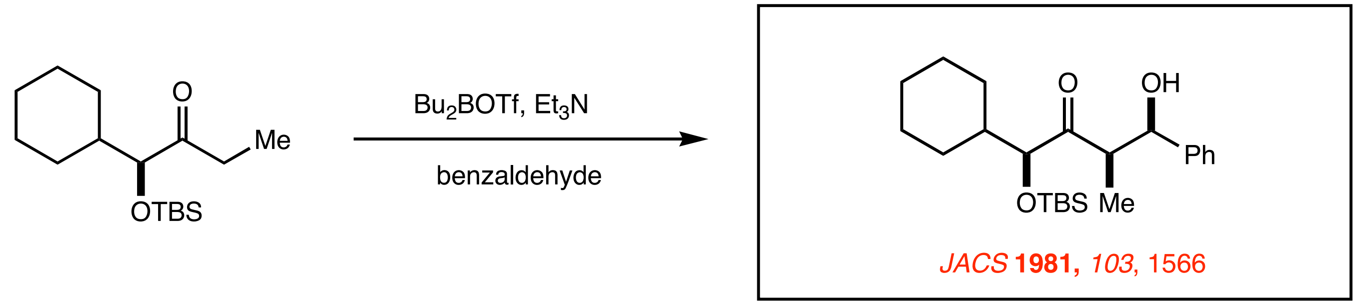
(*E*) : (*Z*) > 98 : 2

Question 3.

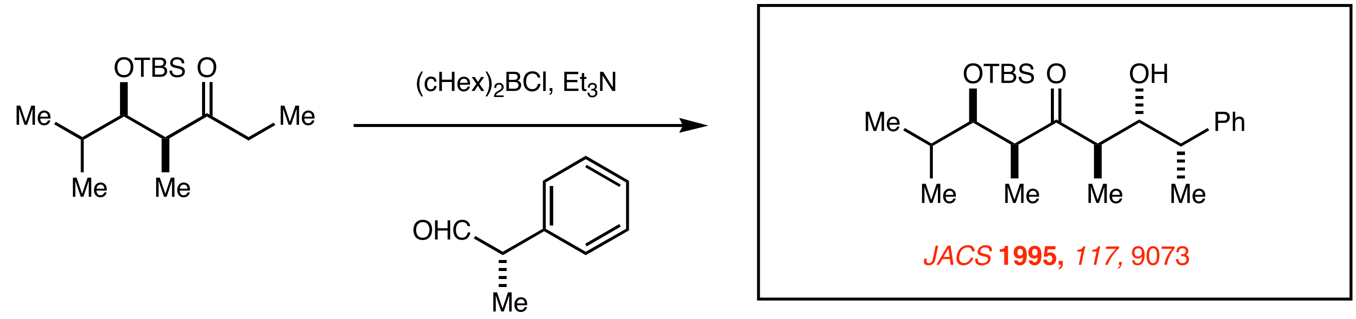
For each of the following aldol reactions provide the major product that you would expect to form under the given conditions. Provide the expected stereochemical outcome



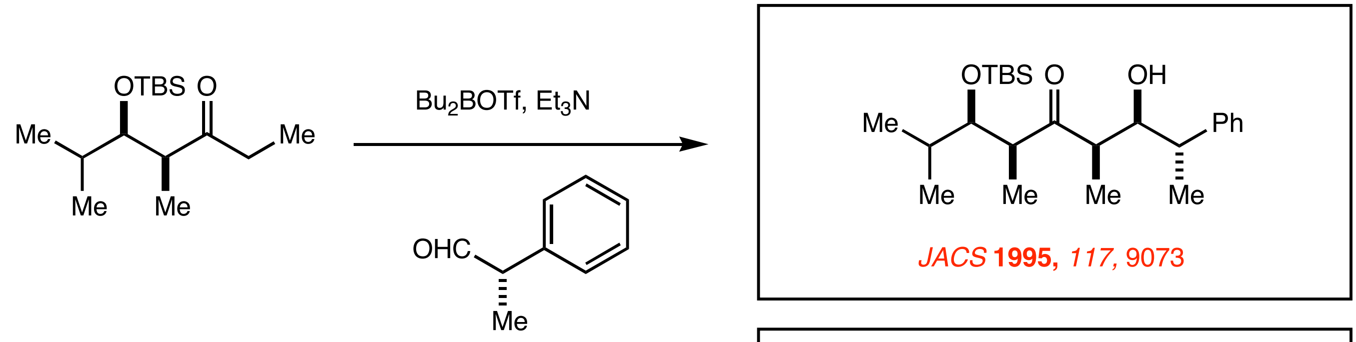
JACS **2002,** *124*, 392



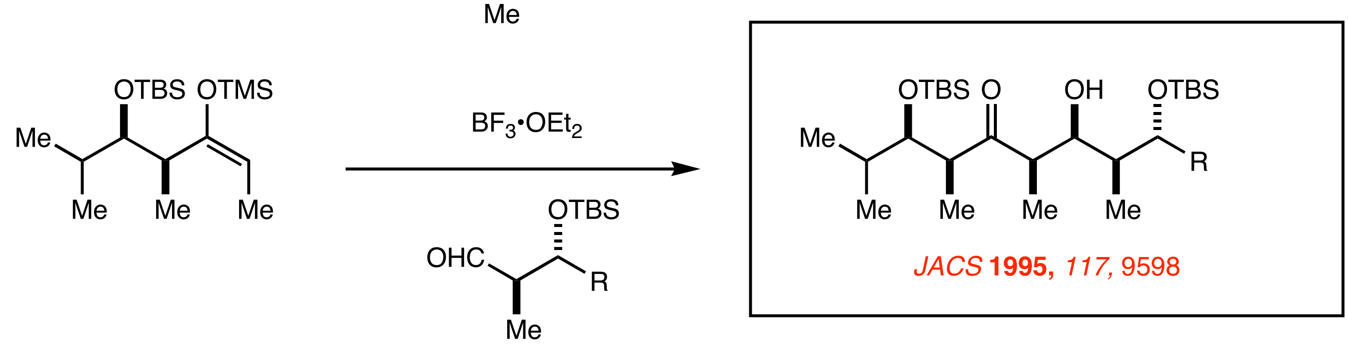
JACS **1981,** *103*, 1566



JACS **1995,** *117*, 9073



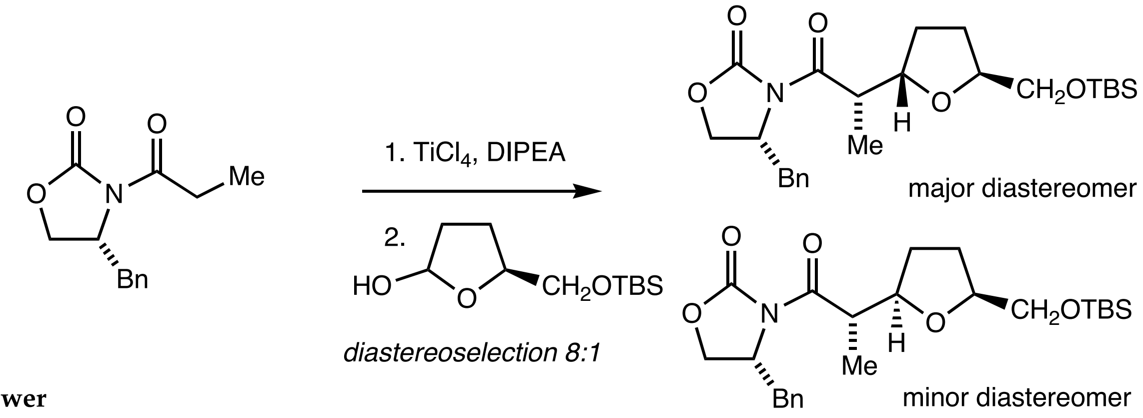
JACS **1995,** *117*, 9073



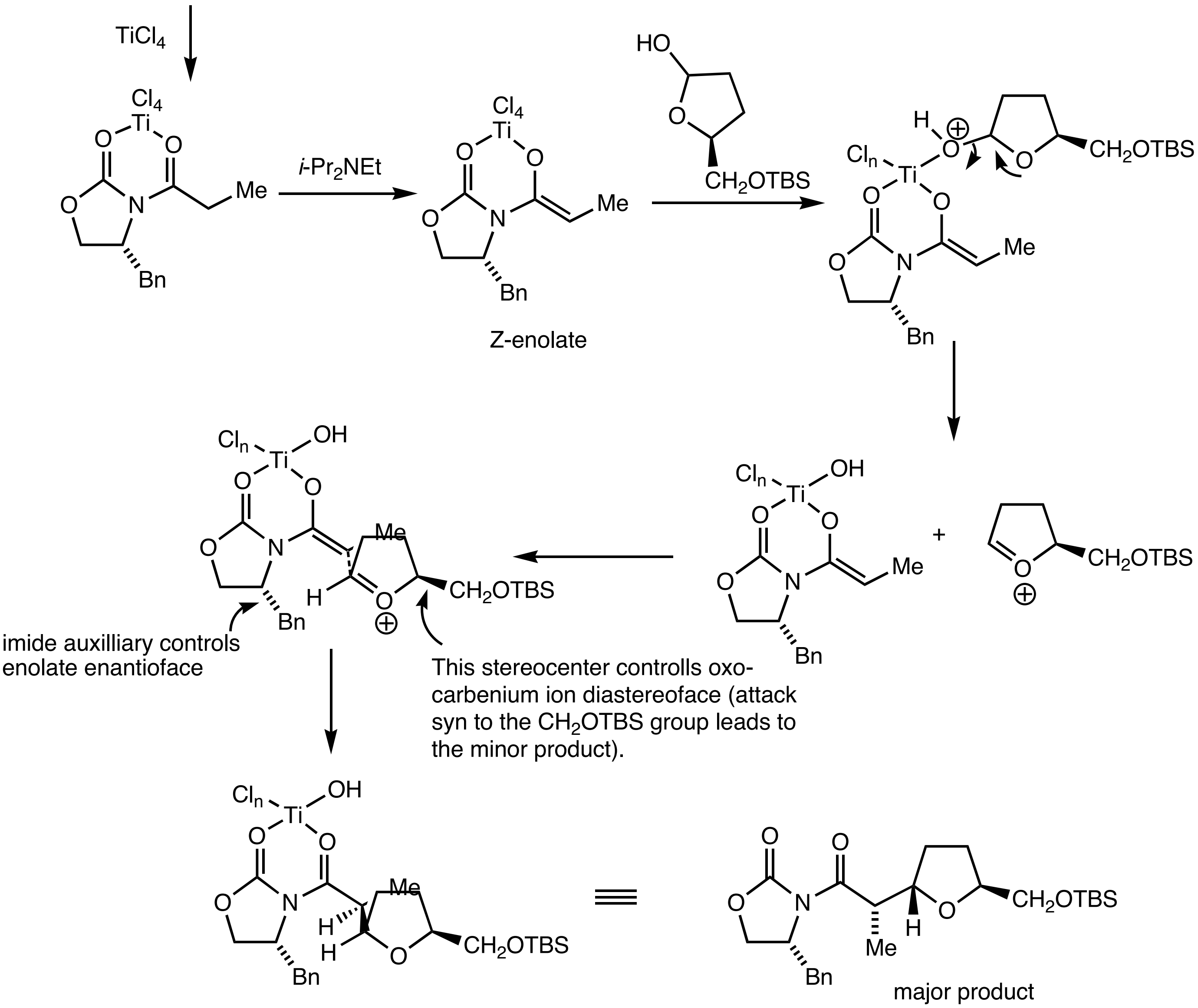
JACS **1995,** *117*, 9598

Question 4.

From your knowledge of the chemistry of the indicated *N*-acyloxazolidinone, provide a mechanism for the indicated transformation which is consistant with the observed stereochemistry at the two newly formed stereocenters.



Answer

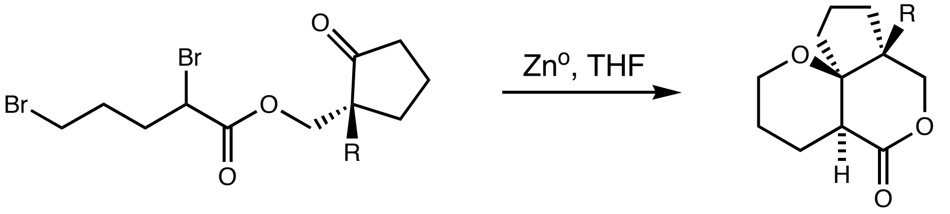


imide auxilliary controls enolate enantioface

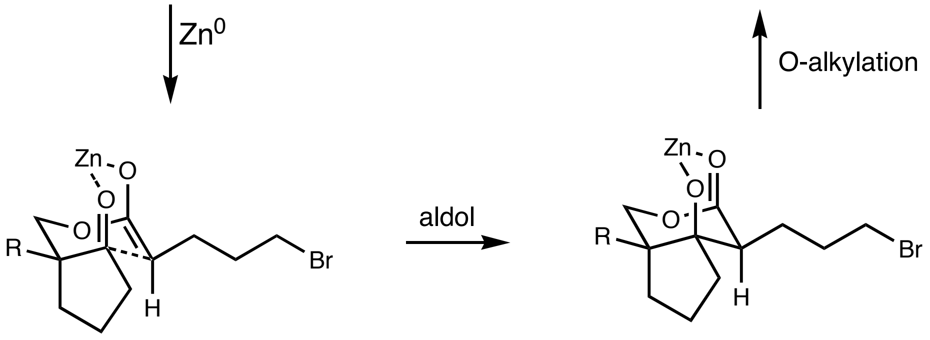
This stereocenter controlls oxo-carbenium ion diastereoface (attack syn to the CH_2OTBS group leads to the minor product).

Question 5.

Provide a mechanism that accounts for observed stereochemistry of the illustrated transformation



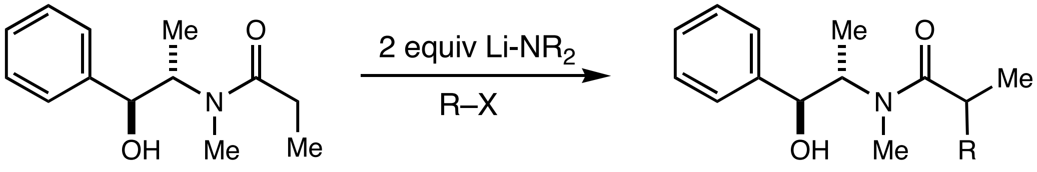
Answer



(Heathcock, *JACS*, **1989**, 1530).

Question 6.

The Myers pseudoephedrine-derived propionamide **1,** upon successive enolization with $LiN(I\text{-}Pr)_2$ (LDA) and alkylation with alkyl halide R–X, affords **2** with high diastereoselection .

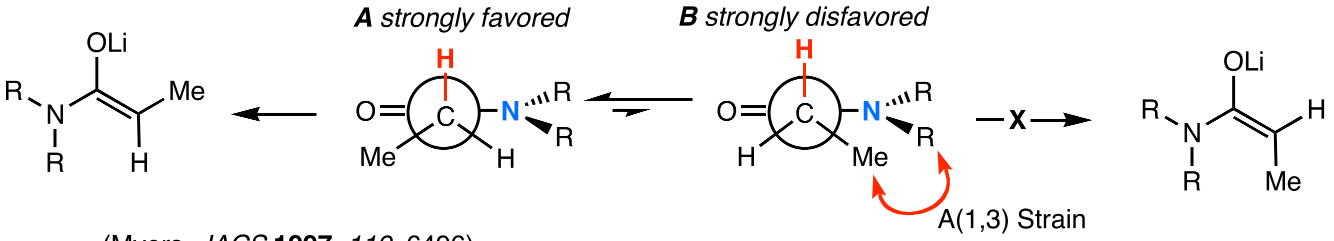


1

2

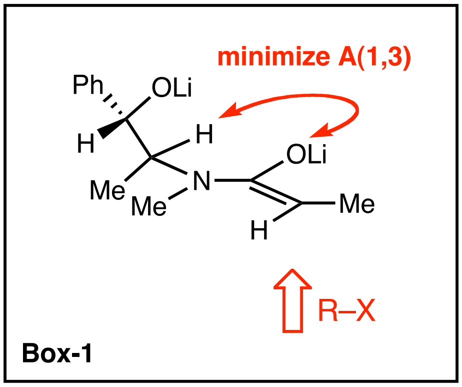
Part A. Enolization of **1** with LDA affords a single enolate geomerty.
Provide an analysis of this enolization event and draw the enolate thus produced.

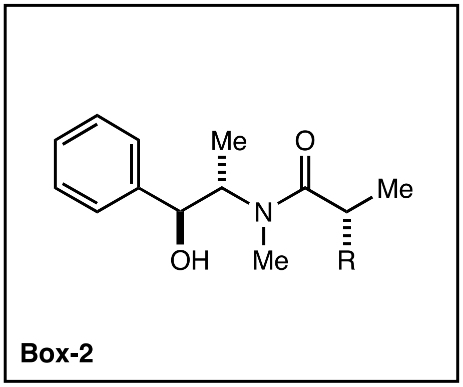
Allylic Strain controls Enolate Geometry. In the deprotonation of conformer **B,** developing A(1,3) strain strongly disfavors the formation of the (E) enolate.



(Myers, *JACS* **1997**, *119*, 6496)

Part B. Provide a 3-dimensional drawing of the transition state for this reaction in **Box-1.** *Hint: In answering this question, you do not need to assume that chelation is involved. Rather, a suitable transition state model may be derived purely from the consideration of non-bonding interactions.*

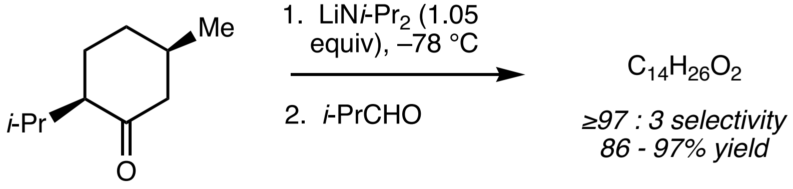




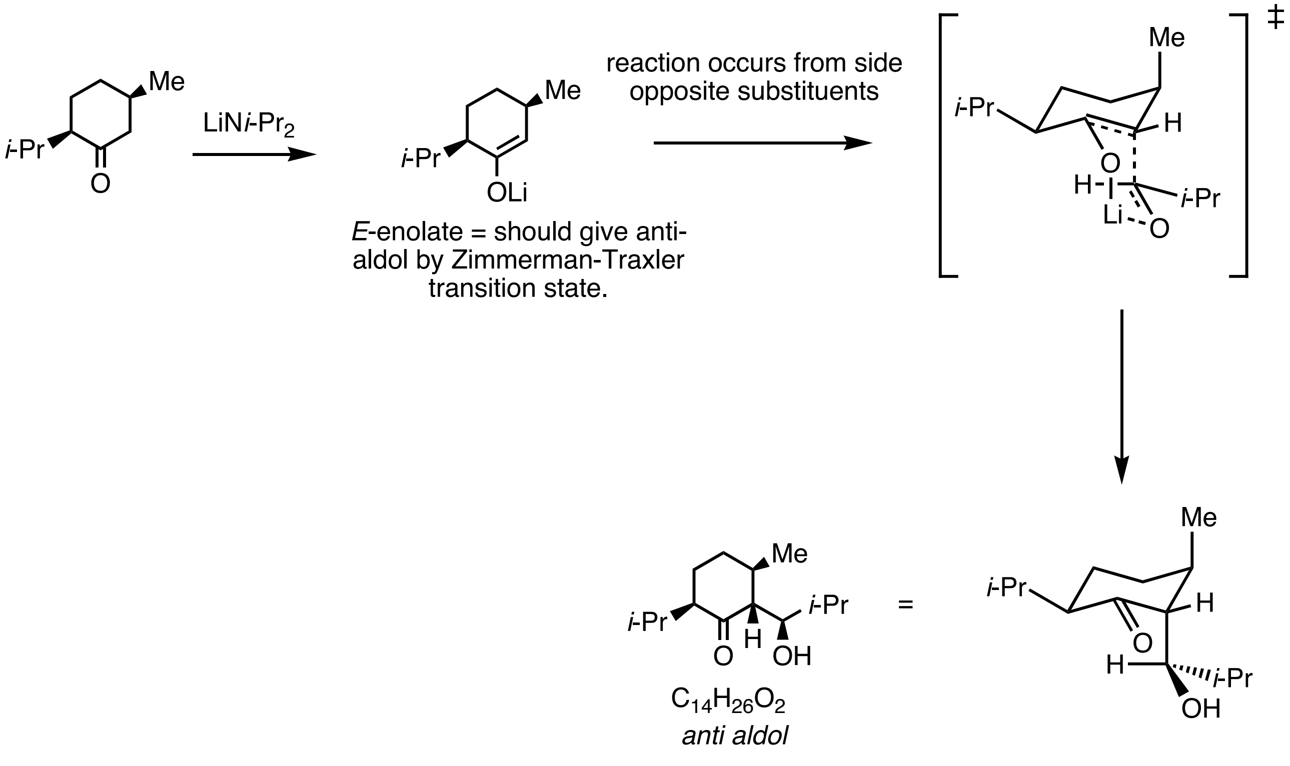
Part C. Provide the absolute stereochemistry of the alkylation product **2** of this reaction in **Box-2**.

Question 7.

Provide the product of the following reaction, including the stereochemistry at all relevant stereogenic centers. Draw a transition structure that clearly indicates how this stereoisomer is formed.



Answer



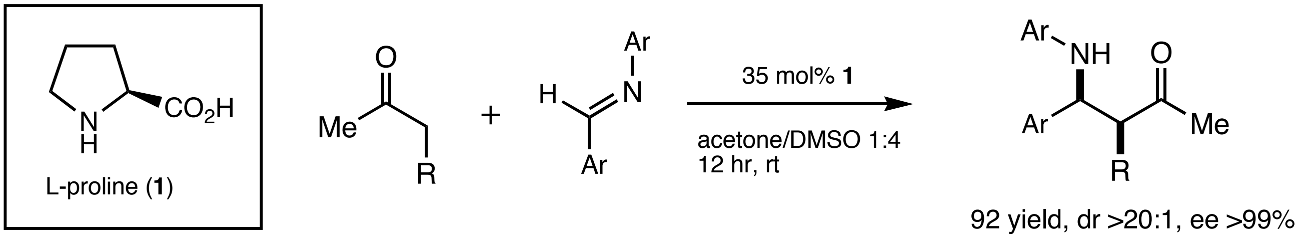
E-enolate = should give anti-aldol by Zimmerman-Traxler transition state.

$C_{14}H_{26}O_2$
anti aldol

J. M. Gardiner, *Tetrahedron Lett.* **1997**, *38*, 9043

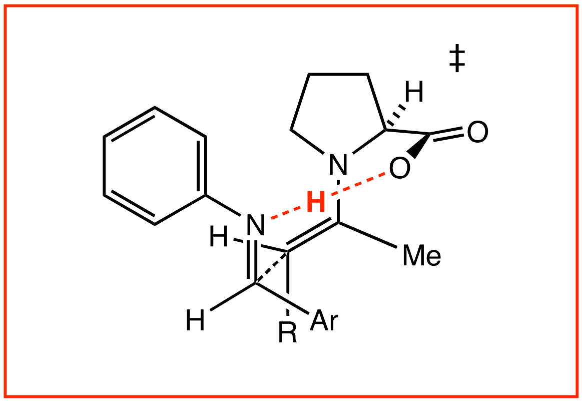
Question 8.

Provide a three-dimenional representation of the transition state for this reaction that rationalizes the diastereo and enantioselection for this process. Briefly identify the transition state stereochemical control elements.



92 yield, dr >20:1, ee >99%

Answer

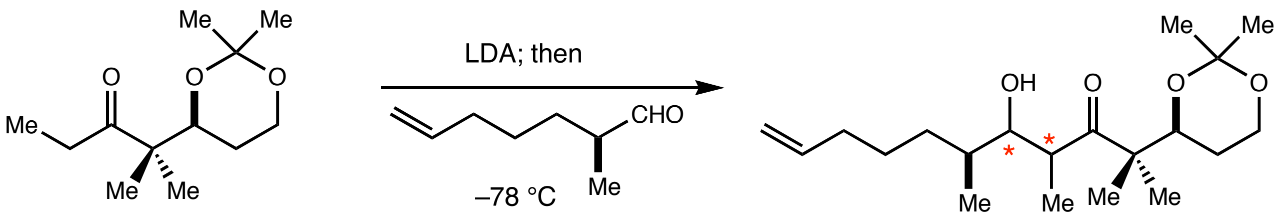


Transition state control elements include intramolecular H–bonding activation of the C=N bond. This interaction defines the reactive pi-face of the enamine C=C. The anti-imine geometry plus the H-bonding activation of the C=N lone pair establishes the reaction diastereoselectivity.

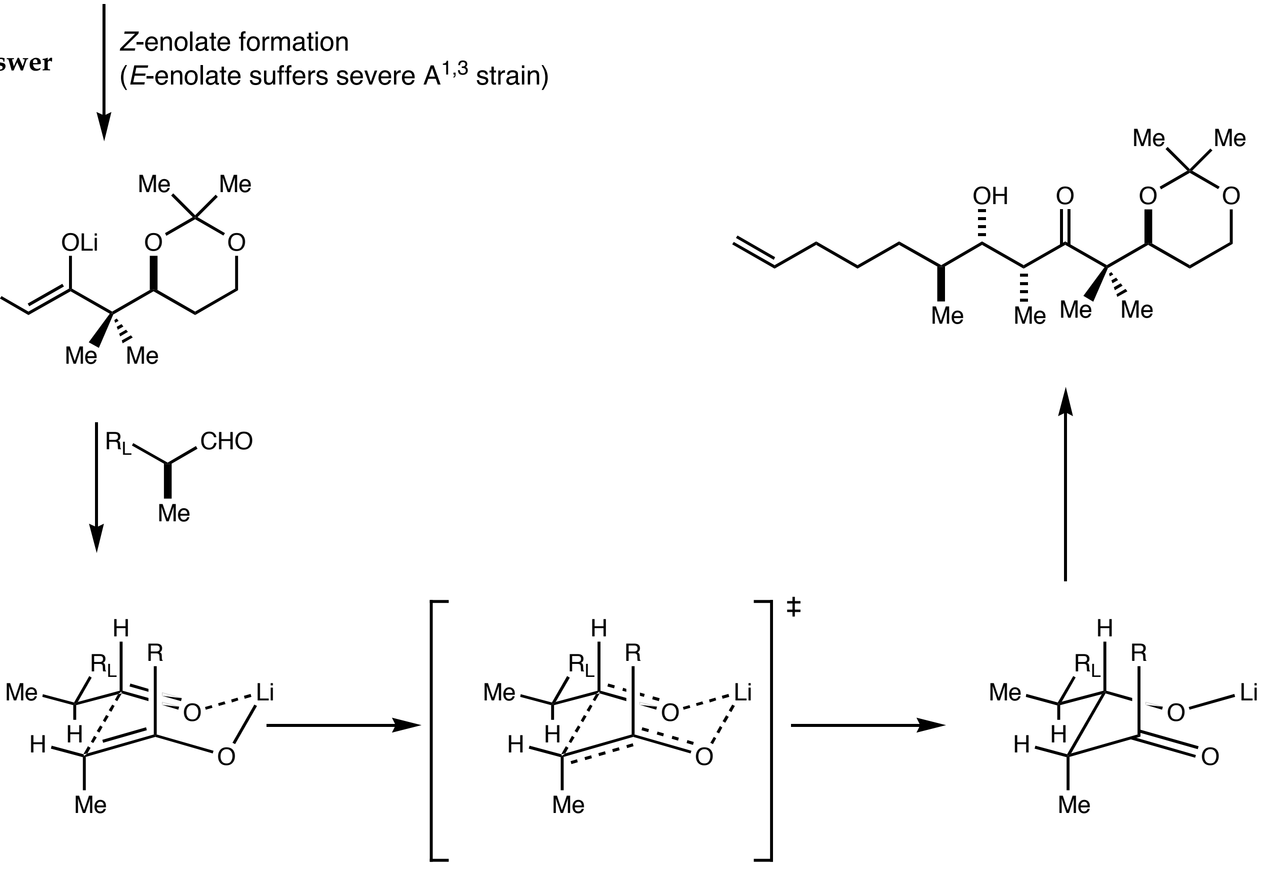
JACS, **2002**, *124*, 827.

Question 9.

Provide a mechanism which clearly predicts the product stereochemistry at the starred (*) carbon atoms .
Provide a clear depiction of the transition state to support your answer.



Answer



Z-enolates give Anti-Felkin addition (syn-pentane interactions in Felkin TS are destabilizing)

(Schinzer, *ACIEE*, **1997**, *36*, 523)

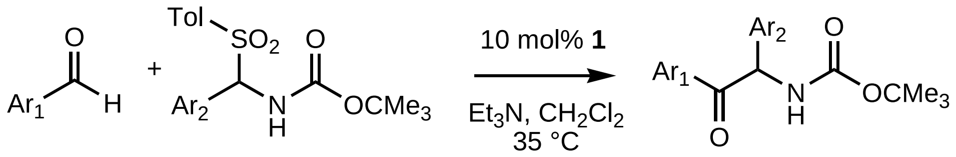
Chem 206 *Due: Friday, Dec. 1*

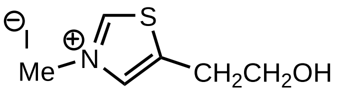
Problem Set 9 *Name:* **Answer Key** *TF:*________________

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

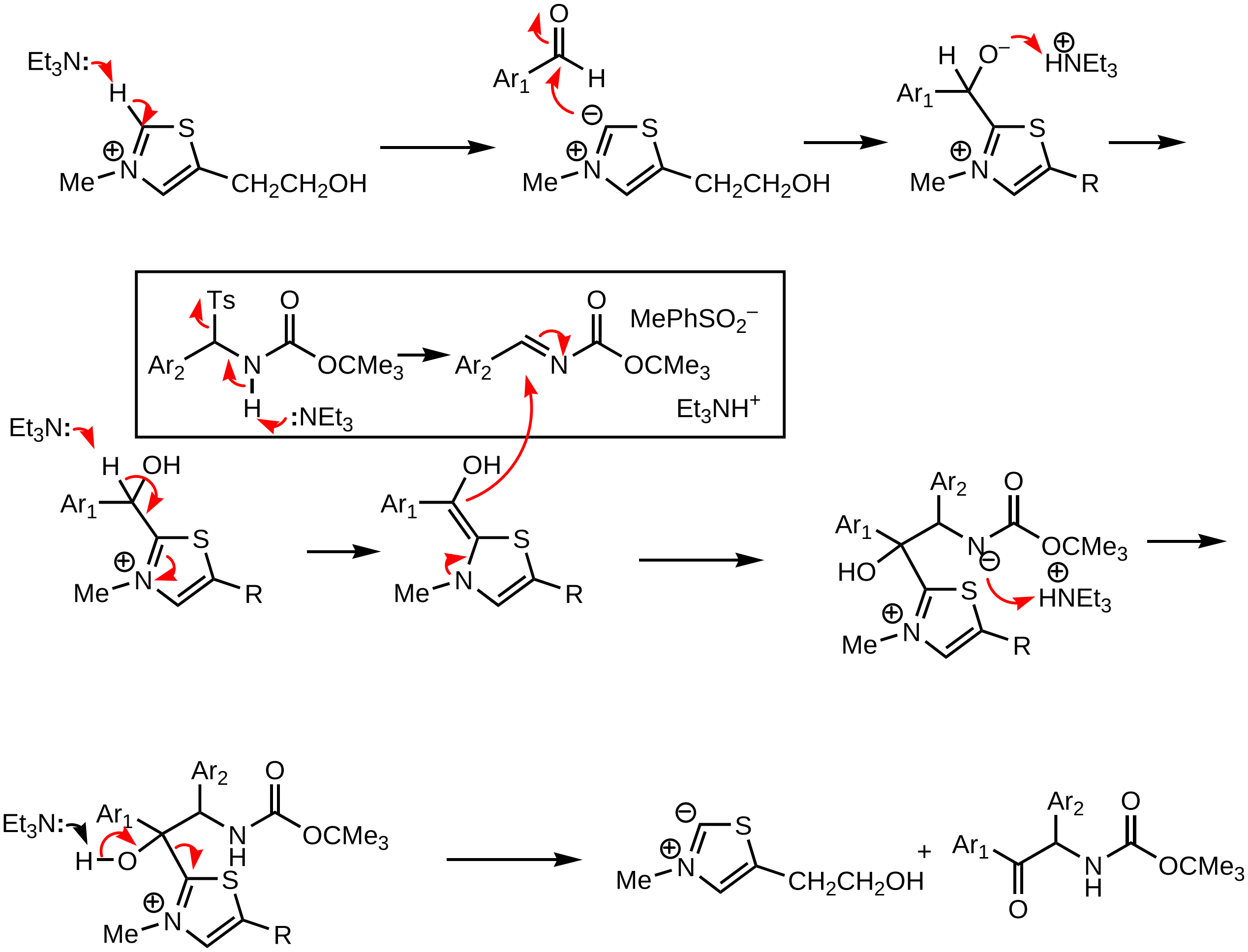
Question 1.

The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group. Provide a mechanism for this transformation in the space below.





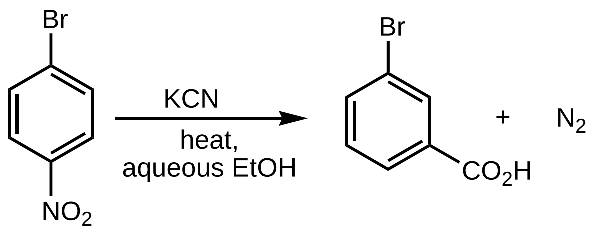
1



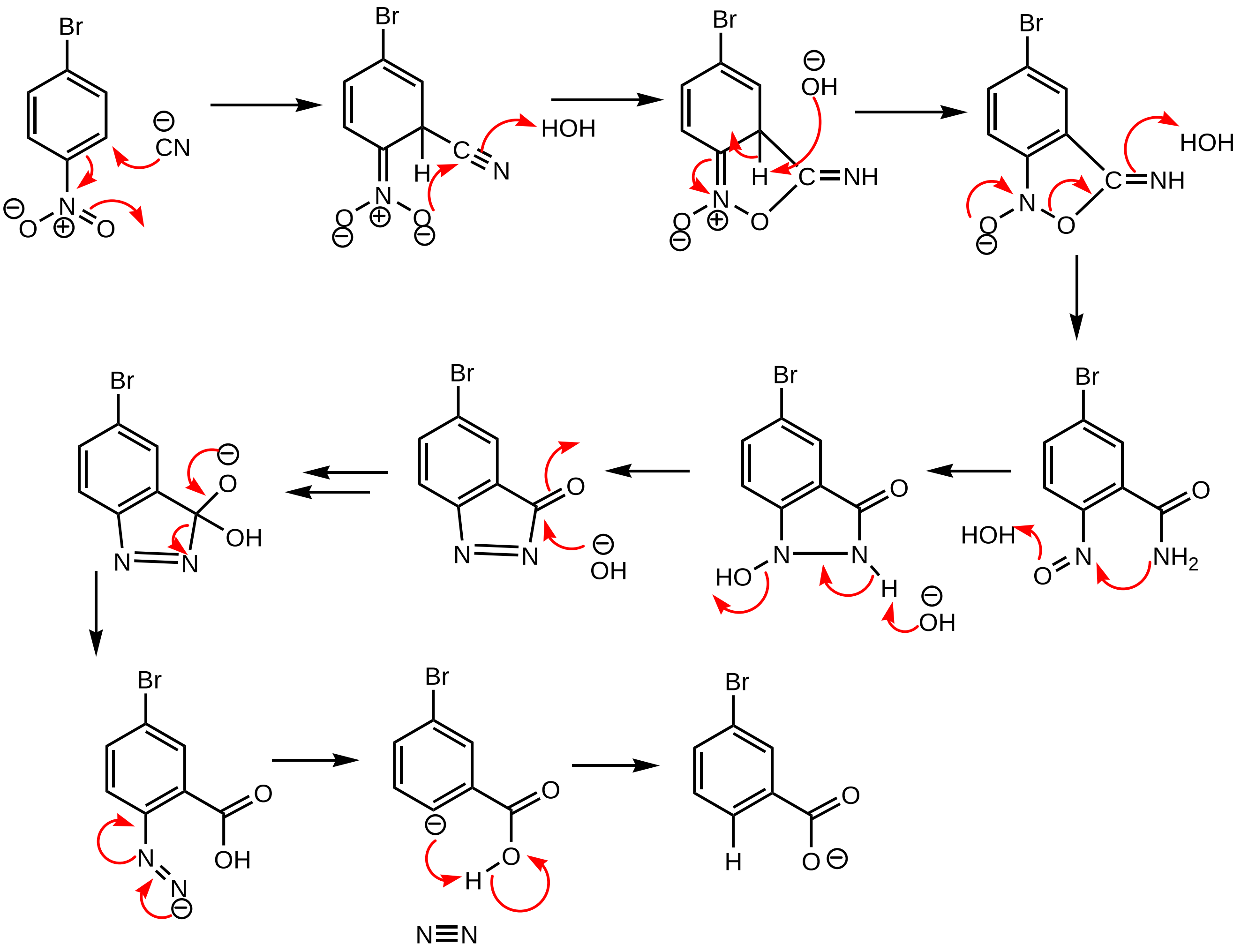
J. Am. Chem. Soc. **2001**, *123*, 9696-9697.

Question 2.

The **Von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If ^{15}N-labeled KCN is used, the N_2 formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.

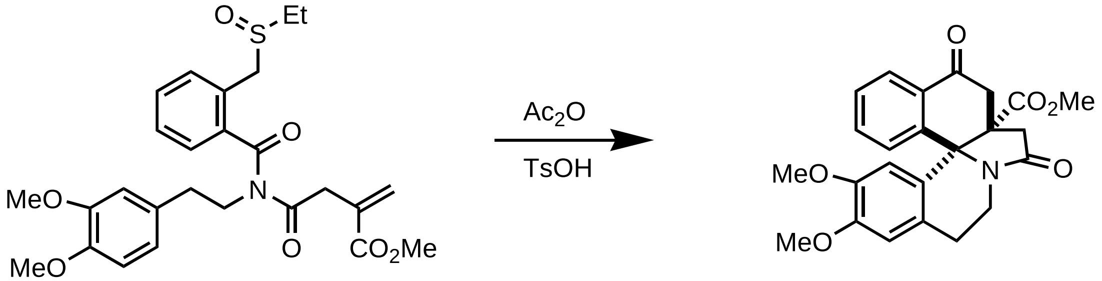


Provide your answer in the space below:

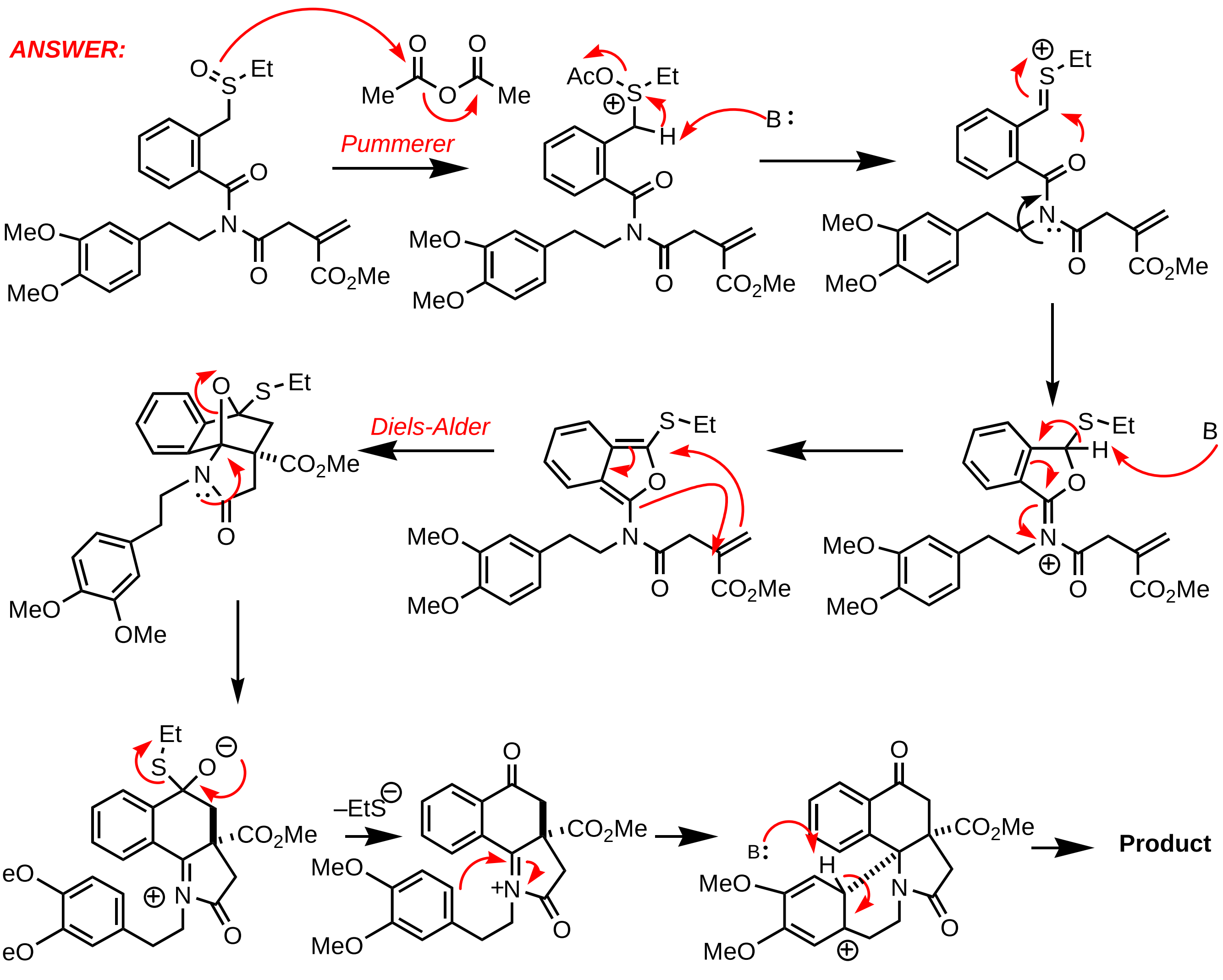


Question 3.

Padwa reported the interesting transformation shown below. Provide a detailed mechanism and identify any organic named reactions in this sequence.



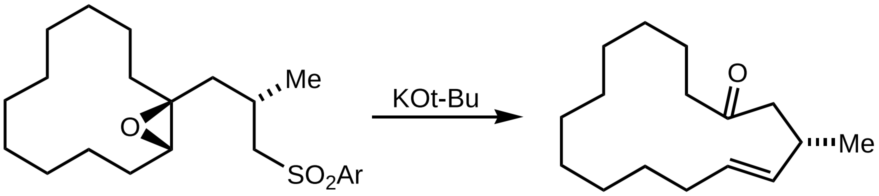
ANSWER:



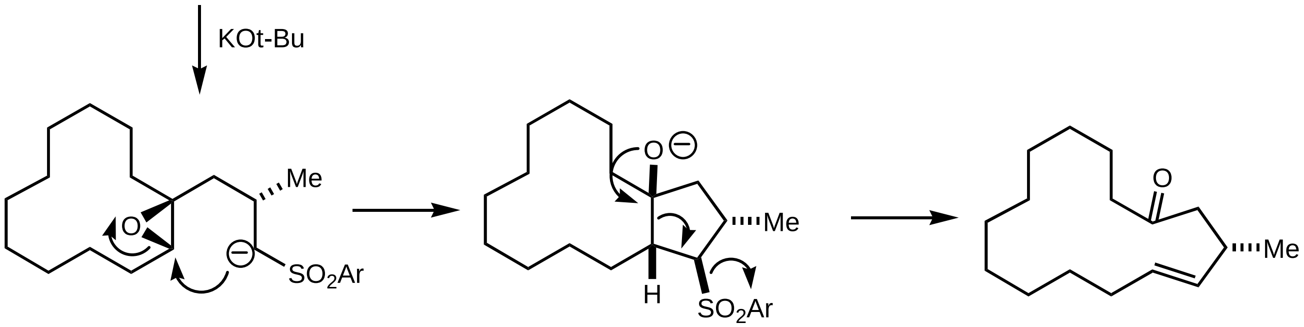
Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 3495-3498.

Question 4.

Fishli and Branca have reported the annulation reaction sequence shown below.



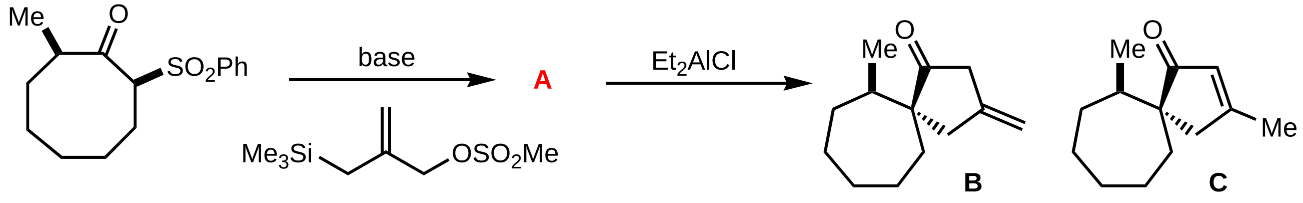
Provide a detailed mechanism for this transformation in the space below.



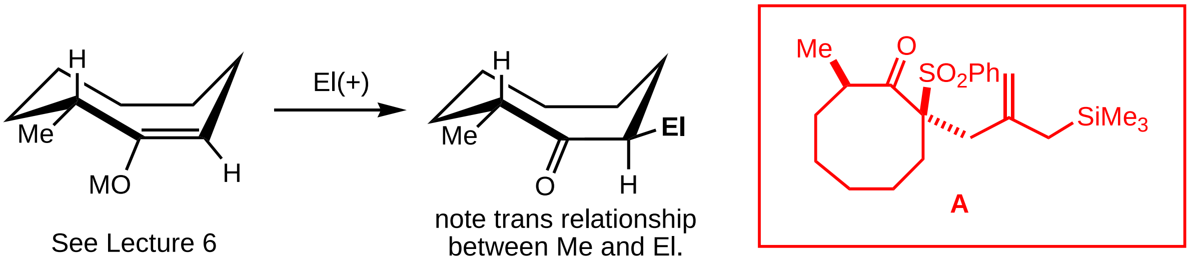
Helv. Chim. Acta **1976**, *59*, 2443

Question 5.

Trost and Adams have reported the interesting spiroannulation reaction sequence shown below. In the first step the enolate alkylation produces a single diastereomeric adduct **A**. Rearrangement of **A** under Lewis acidic conditions affords a mixture of **B** and **C**. As the reaction times are increased more **C** is produced by equilibration.



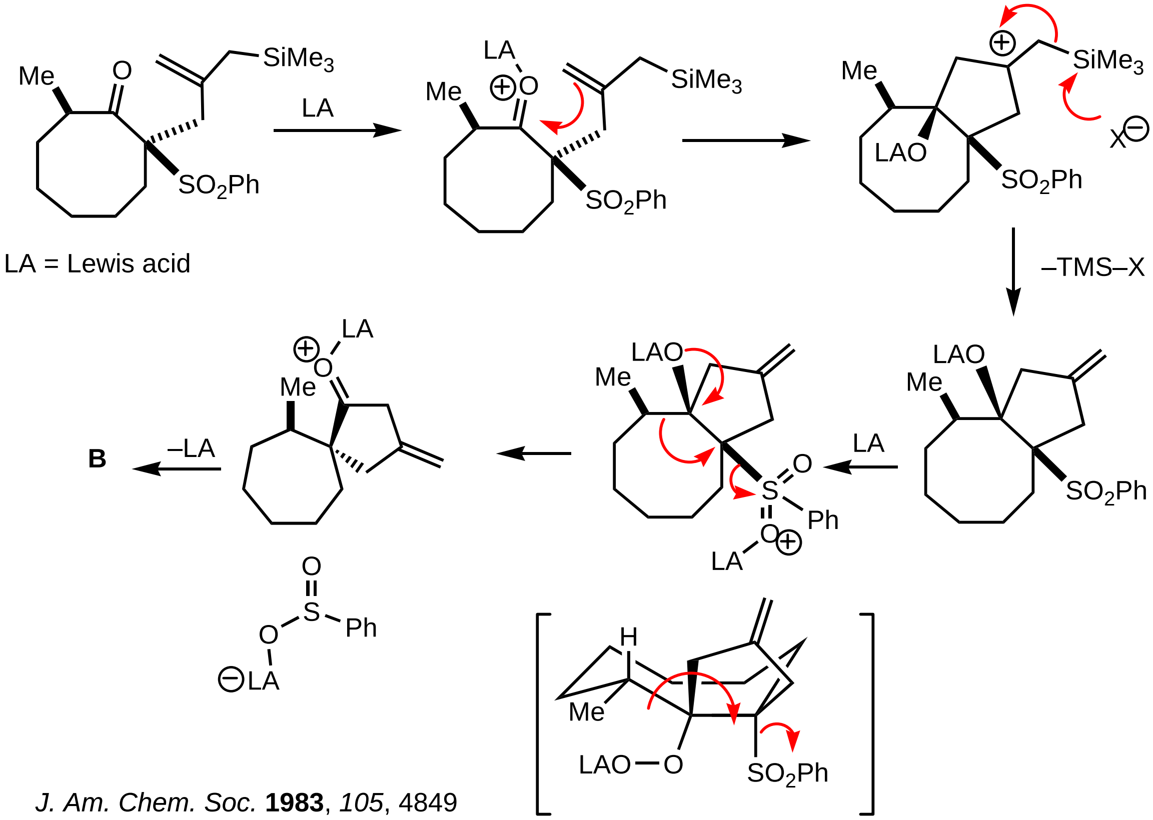
Part A. Using your knowledge of the conformations of eight-membered rings, predict the stereochemical outcome of the the alkylation and identify the full stereostructure of **A**.



See Lecture 6

note trans relationship between Me and El.

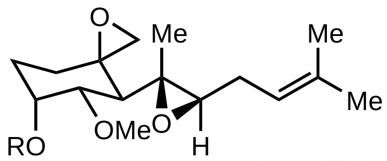
Part B. Provide a detailed mechanism for the transformation of **A** into **B** in the space below.



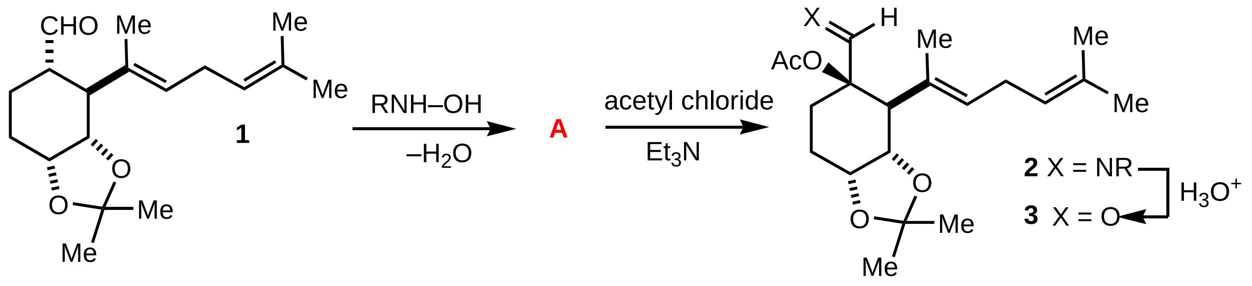
J. Am. Chem. Soc. **1983**, *105*, 4849

Question 6.

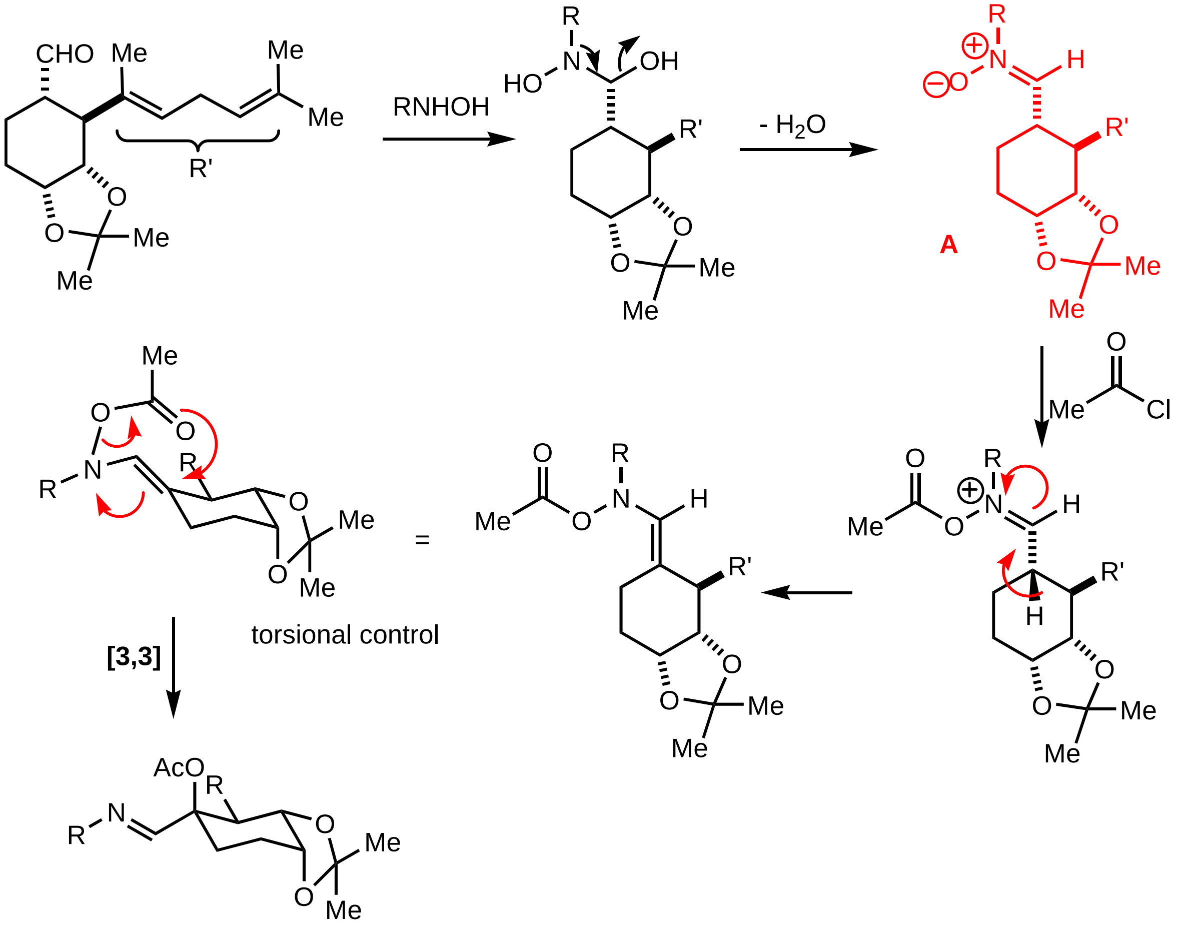
The fumagillin natural products possess several interesting biological properties including antibiotic activity against *Staphylococcus auereus*. In Sorensen's recent synthesis of fumagillol, intermediate **1** was transformed into its α-oxygenated counterpart **3** through the indicated reaction sequence.



fumagillol



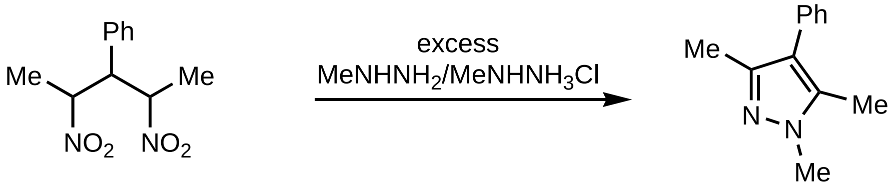
In the space below, identify the structure of intermediate **A** and provide a mechanism for the transformation of **1** into **2**.



Angew. Chem. Int. Ed. **1999**, *38*, 971

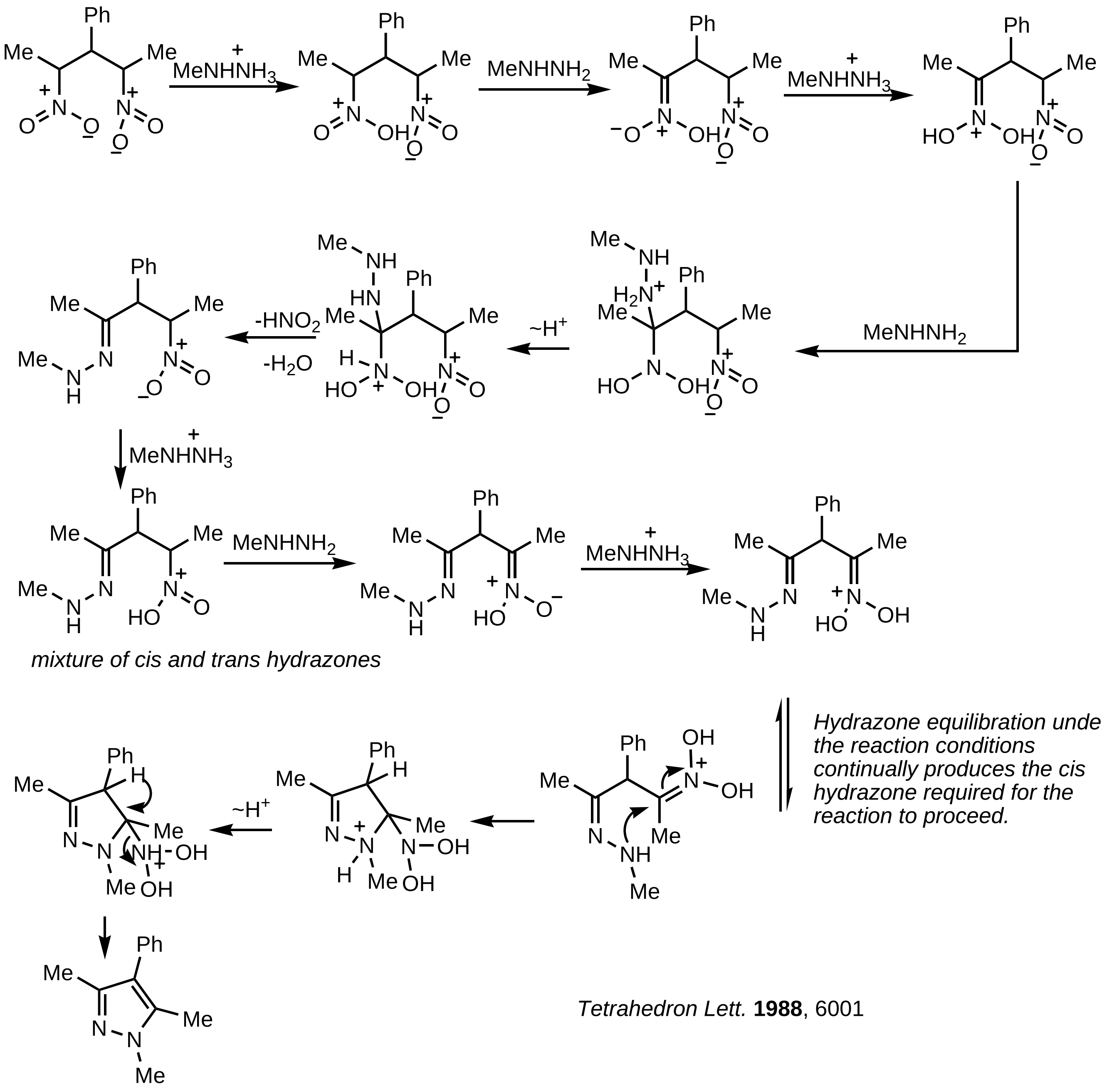
Question 7.

Here is a good exercise that deals with the versatility of the nitro group. Provide a detailed mechanism for the following reaction.



Answer

A double Nef hydrolysis: $MeNHNH_2$ acts as proton shuttle and bis-nucleophile



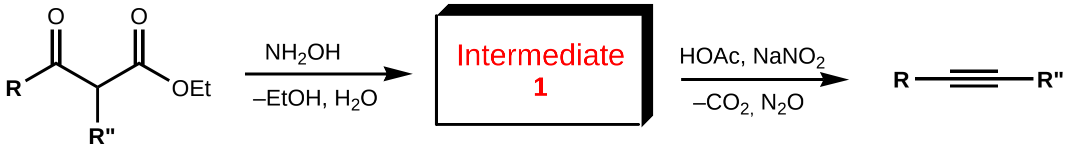
mixture of cis and trans hydrazones

Hydrazone equilibration under the reaction conditions continually produces the cis hydrazone required for the reaction to proceed.

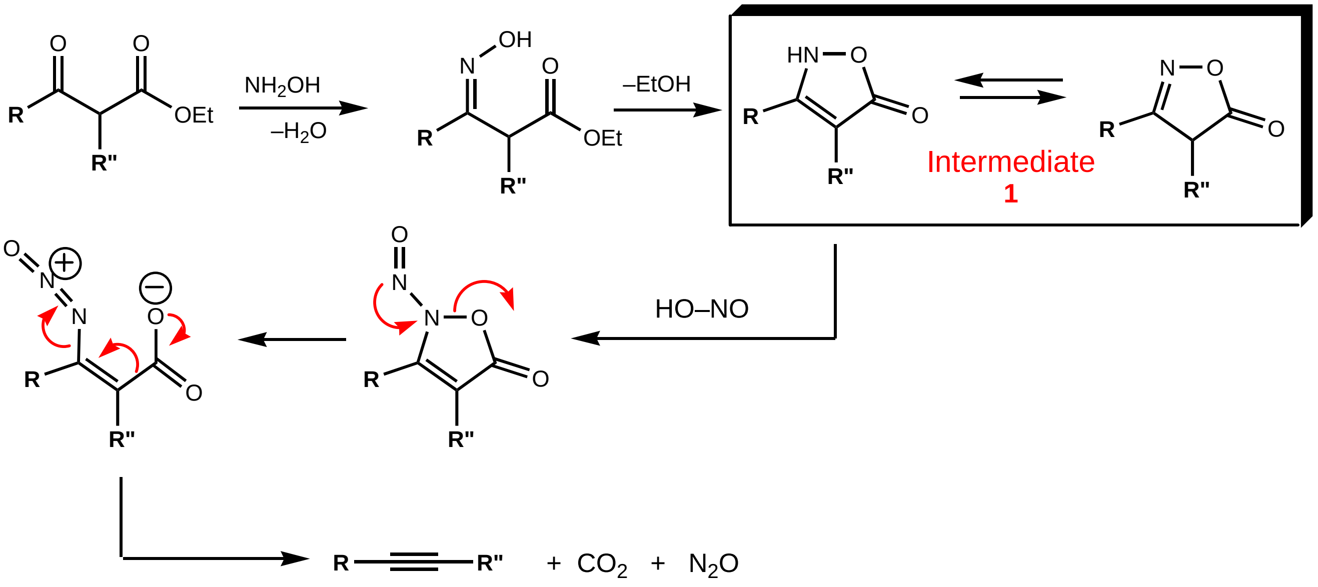
Tetrahedron Lett. **1988**, 6001

Question 8.

S. Zard has recently reported the very clever synthesis of acetylenes from β-keto esters illustrated below. In this article, the authors demonstrate that the transformation exhibits broad scope.



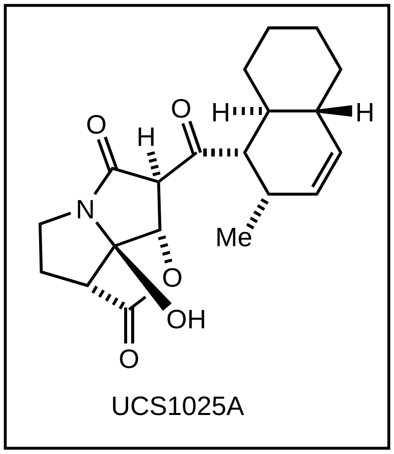
Provide a plausible mechanism for this transformation and identify intermediate **1** in the space below.



Chem. Commun. **2002,**1555-1563

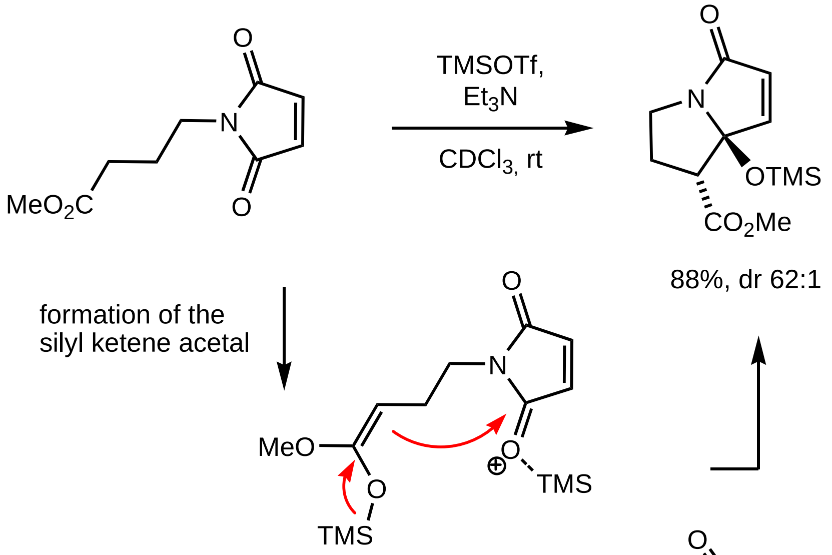
Question 9.

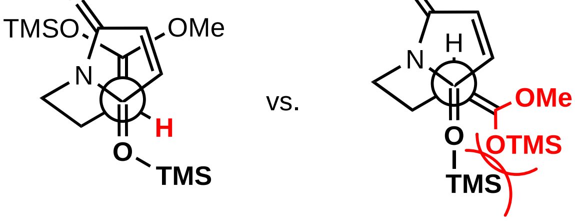
Hoye *et al.* studied the following silylative cyclization in the context of a construction of the telomerase inhibitor UCS1025A.



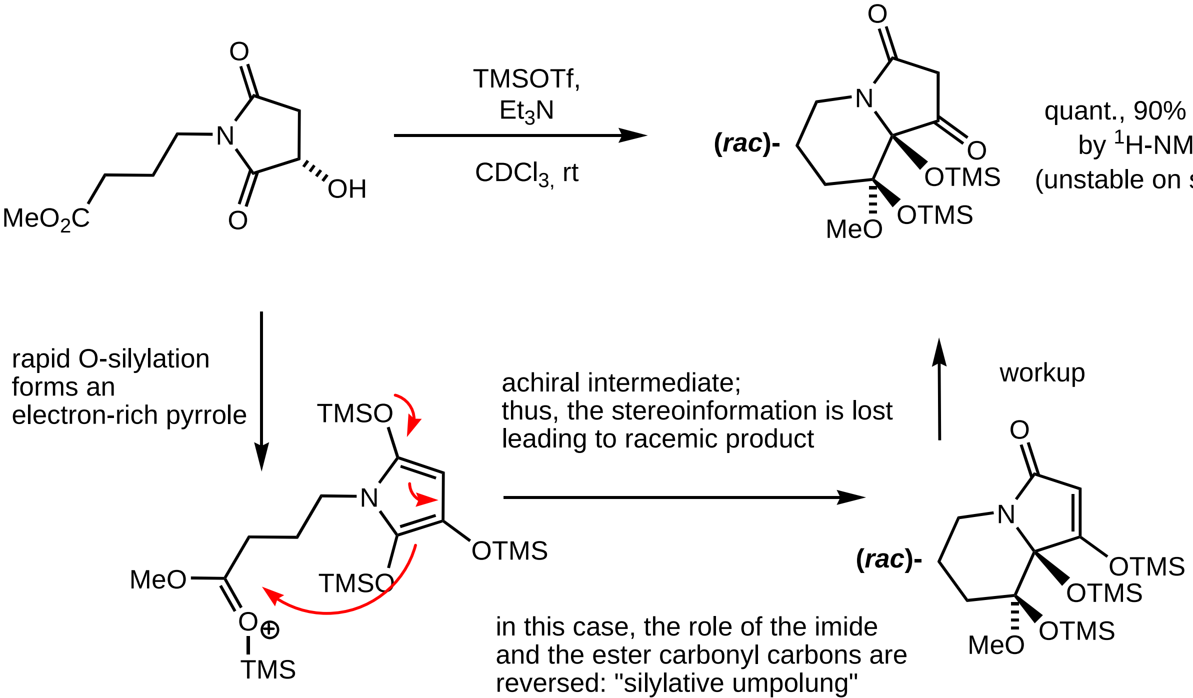
UCS1025A

Part A: Rationalize the mechanism and explain the diastereoselectivity





Part B: The seemingly similar starting material derived from L-malic acid showed a different reaction course. Knowing the outcome, you should be able to provide a good *a posteriori* explanation!



quant., 90% pure by ^{1}H-NMR (unstable on silica)

in this case, the role of the imide and the ester carbonyl carbons are reversed: "silylative umpolung"

silylative activation of the ester

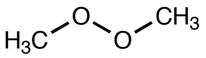
T. R. Hoye, V. Dvornikovs, E. Sizova *Org. Lett.* **2006**, *8*, 5191

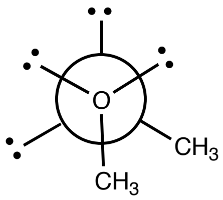
Problem Set 1

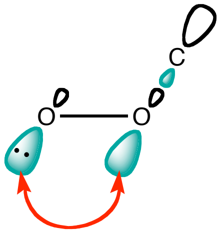
Answer Key

General Instructions: Neatly, in the space allocated, provide concise answers to the following questions using clear three-dimensional representations for all relevant structures. Address stereochemical and stereoelectronic issues where appropriate.

Problem 1. For each of the molecules shown below, hyperconjugative, rather than steric factors, dictate the geometry of the structure. Draw the most stable conformation or geometric isomer and clearly label all dominant hyperconjugative interactions (e.g. $\sigma_{C-C} \rightarrow \sigma^*_{C-O}$).

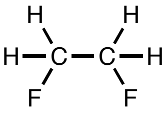


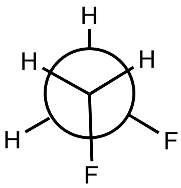


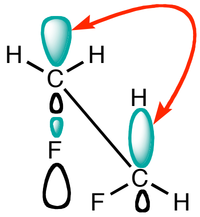


$n_O \rightarrow \sigma^*_{O\text{-}C}$

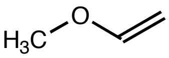
sp^3 lone pair on oxygen into $\sigma^*_{O\text{-}C}$. There are two such interactions.



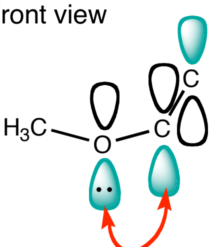




$\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}F}$
There are two such interactions.

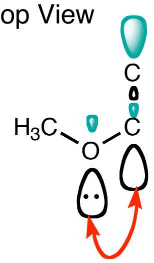


Front view



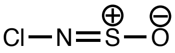
$n_{pO} \rightarrow \pi^*_{C\text{-}C}$

Top View



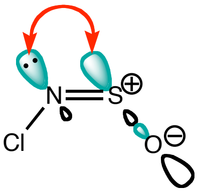
$n_{\sigma O} \rightarrow \sigma^*_{C\text{-}C}$

p-orbital lone pair on oxygen into $\pi^*_{C\text{-}C}$ makes molecule planar, sp^2 lone pair on oxygen into $\sigma^*_{C\text{-}C}$ enforces *s-cis* geometry about the central O-C bond.

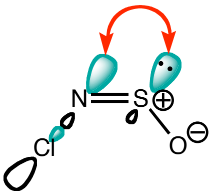


$Cl{-}N{=}\overset{\oplus}{S}{-}\overset{\ominus}{O}$

$n_{\sigma N} \rightarrow \sigma^*_{S\text{–}O}$

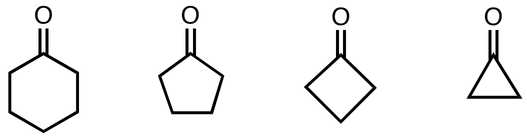


$n_{\sigma S} \rightarrow \sigma^*_{N\text{–}Cl}$



also $n_{Cl} \rightarrow \sigma^*_{N\text{-}S}$, $n_O \rightarrow \sigma^*_{N\text{–}S}$

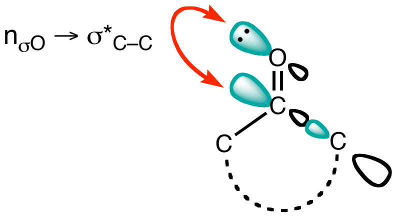
Problem 2. Ring strain dramatically affects the carbonyl infrared stretching frequency.



$\bar{\nu}_{C=O}$ (cm $^{-1}$) 1715 1745 1788 1813

Part A. Explain the above trend using molecular orbital theory.

The hyperconjugative interaction illustrated below will increase the triple bond character of the carbonyl group.

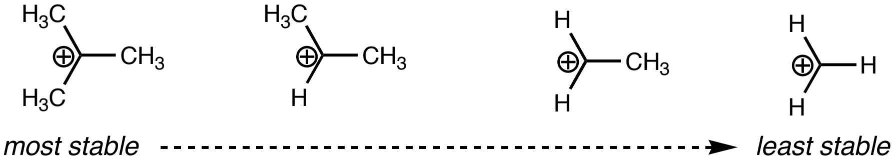


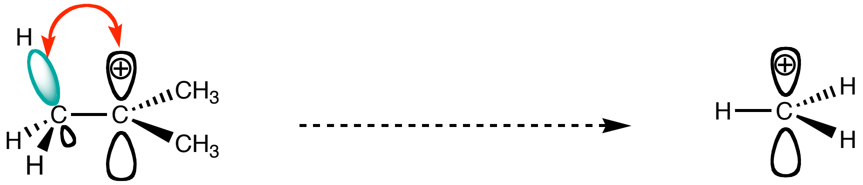
The orbital overlap responsible for C–C bond formation within the ring becomes less efficient as the size of the ring decreases. As a result, the energy of σ^*_{C-C} decreases with decreasing ring size and the hyperconjugative interaction depicted above becomes increasingly important thus increasing the order and strength of the C=O bond.

Part B. Can you find an alternative explanation for the above trend that relies on basic organic chemistry principles?

The p character of the orbitals forming the C–C bonds within the ring will increase as bond angles decrease. This would increase the s character of the carbon orbital in the C–O bond resulting in a shorter, stronger bond.

Problem 3. Carbocations are stabilized by alkyl substitution.Using frontier molecular orbitals, explain how increased alkyl substitution leads to the observed stability order. Identify the molecular orbitals (including the stereoelectronic requirement) involved in the stabilizing interaction.

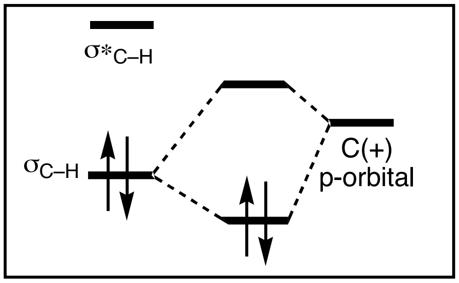




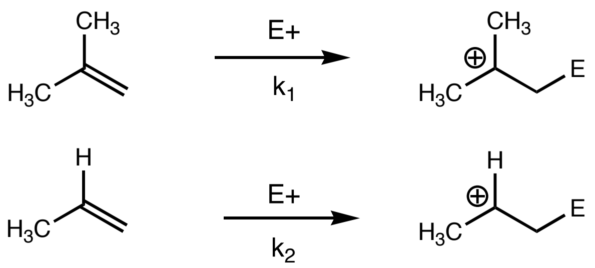
3 stabilizing $\sigma_{C\text{–}H} \rightarrow p$ interactions

0 stabilizing $\sigma_{C\text{–}H} \rightarrow p$ interactions

There is a stabilizing interaction between $\sigma_{C\text{-}H}$ and the unoccupied p orbital on the sp^2 hybridized carbocation. This occurs 3 fold in the *tert*-butyl cation but not at all in the methyl cation. The $\sigma_{C\text{–}H}$ and p orbitals must be in the same plane in order for this interaction to occur.

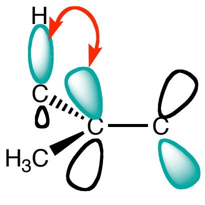


Problem 4. Alkyl groups enhance the nucleophilicity of double bonds in reactions with electrophiles.



$k_1/k_2 = 2.5 \times 10^4$

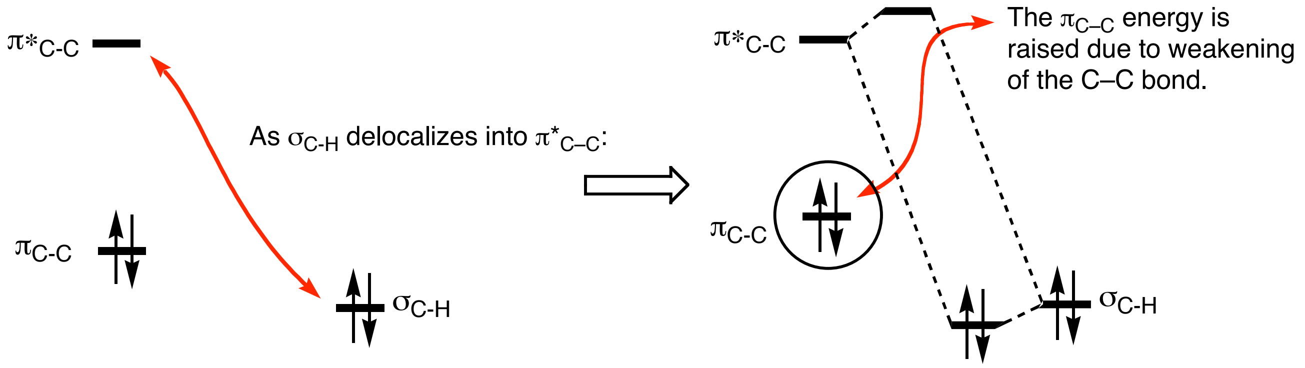
Part A. Identify and draw the principal orbital interaction that contributes to this observation.



$\sigma_{C\text{-}H} \rightarrow \pi^*_{C\text{-}C}$

Each additional alkyl group results in an additional interaction.

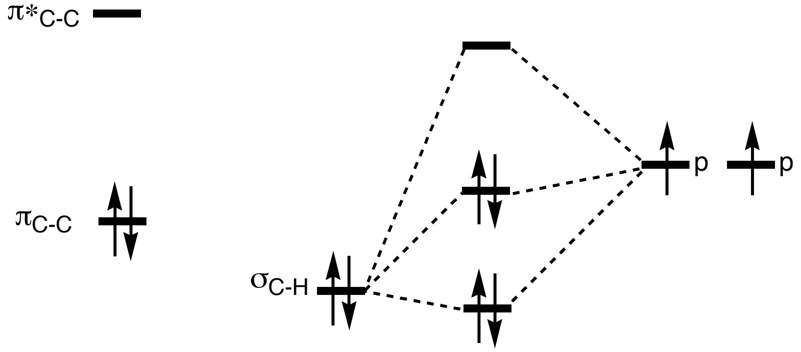
Part B. Use orbital energy diagrams to explain why the interaction which you have identified causes an increase in the nucleophilicity of the carbon–carbon double bond.



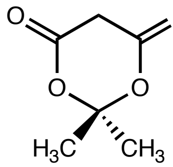
As $\sigma_{C\text{-}H}$ delocalizes into $\pi^*_{C\text{–}C}$:

The $\pi_{C\text{–}C}$ energy is raised due to weakening of the C–C bond.

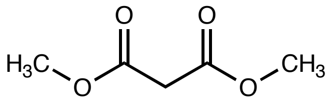
The system can also be broken down into its constituent orbitals (one $\sigma_{C\text{–}H}$, and two p orbitals) and rebuilt. The same answer is obtained (i.e. the energy of the HOMO generated is higher than that of $\pi_{C\text{-}C}$)



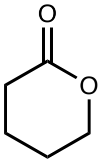
Problem 6. Gao and coworkers recently performed a variety of high level calculations on Meldrum's acid (**1**) in order to rationalize its enhanced acidity relative to dimethyl malonate (**2**). Upon calculating strain energies on the basis of the isodesmic reaction: Ester + Cyclohexane → Lactone + *n*-Heptane, the authors found that Meldrum's acid possessed a lower strain energy than 2-oxacyclohexanone (**3**). The result seemed rather counterintuitive given the presence of two ester functional groups in **1** versus a single ester functional group in **3**.



1
pKa = 7.3 (DMSO)



2
pKa = 15.9 (DMSO)



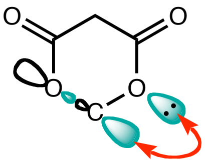
3

Computed Strain Energies at the B3LYP/aug-cc-pDVZ Level

Ester	Lactone	Strain Energy (Kcal/mol)
methyl pentanoate	2-oxacyclohexanone	9.8
methyl pentanoate anion	2-oxacyclohexanone anion	5.5
dimethyl malonate	Meldrum's acid	5.7
dimethyl malonate anion	Meldrum's acid anion	–7.9

Part A. Identify a stabilizing effect that could account for the surprisingly low strain energy of **1** (it should be noted that the strain energy includes the cost of changing the ester conformation from *Z* to *E*).

The authors propose that cyclization of **2** to **1** introduces a hyperconjugative effect which would partially compensate for the cost associated with changing two ester conformations from *Z* (such as in **2**) to *E* (such as in **1** and **3**) and the strain associated with the presence of four sp^2-hybridized atoms in a six-membered ring. Meldrum's acid also has fewer 1,3-diaxial interactions than 2-oxacyclohexanone.



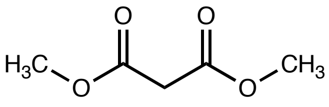
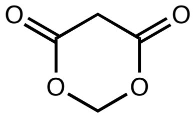
$n_{\sigma O} \rightarrow \sigma^*_{C–O}$

The methyl groups were removed for clarity

There are two such hyperconjugative interactions in Meldrum's acid. Only one is depicted here.

Part B. The strain energy difference between neutal Meldrum's acid and its anion (7.9 Kcal/mol) does not entirely account for the 11.4 Kcal/mol difference in acidity calculated between **2** and **4**. Could the effect identified in part A account for the remaining 3.5 Kcal/mol of added acidity of **4** relative to **2**? If so, what must be assumed? Explain.

Gas Phase Acidities obtained from B3LYP/Aug-cc-pVDZ calculations

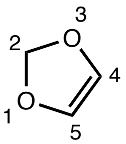
Compound	ΔG_{gas} (Kcal/mol)
 **2**	336.5
 **4**	325.1

The anomeric effect can be used to account for the additional 3.5 Kcal/mol in acidity if one assumes that it stabilizes the anion to a greater extent than neutral Meldrum's acid. The authors verified this hypothesis using Weinhold's natural orbital analysis and natural orbital deletion scheme. The localized bonding and antibonding orbitals corresponding to the anomeric interactions were identified via Weinhold's natural bond orbital analysis and removed to evaluate the energy of a reference system lacking anomeric charge delocalization. The anomeric effect was found to stabilize Meldrum's acid anion by an additional 3.3 Kcal/mol relative to the neutral species. The authors suggest that the energy of the nonbonding orbitals corresponding to the oxygen lone pairs is increased in the anion thus allowing for an enhanced $n_{\sigma O} \rightarrow \sigma^*_{C\text{–}O}$ interaction. The authors conclude that the enhanced acidity of Meldrum's acid is due to a combination fo the two *E*-ester conformations and an anomeric effect. Adding these two effects (7.9 + 3.3 = 11.2 Kcal/mol) gives a number that is in excellent agreement with the calculated difference in acidity between **2** and **4** (11.4 Kcal/mol). The experimental value for the acidity difference between **1** and **2** in DMSO is 11.6 Kcal/mol.

Primary Reference: Byun, K.; Mo, Y.; Gao, J. *J. Am. Chem. Soc.* **2001**, *123*, 3974-3979

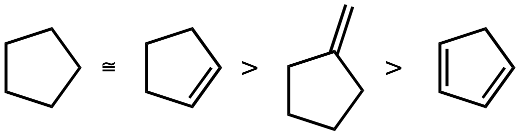
Relevant literature:
For articles concerning the acidity of Meldrum's acid see: (a) Evanseck, J. D.; Houk, K. N.; Briggs, J. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 10630-10638. (b) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870-1872. (c) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872-1874.
For an article concerning Weinhold's natural orbital analysis see: Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 593-609.

Problem 7. Experiments involving IR and Raman spectroscopy indicate that 1,3-dioxole is puckered with a dihedral angle of 24° and an energy barrier to planarity of 275 cm^{-1}. The molecule was expected to be planar given the absence of torsional strain (see strain trend for 5-membered rings below).



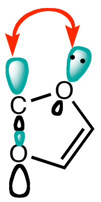
1,3-dioxole
4-3-2-1 dihedral angle = 24°
energy barrier to planarity = 275 cm^{-1}

Strain trends:

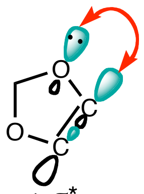


■ Decrease in eclipsing strain more than compensates for the increase in angle strain.

Part A. Identify the dominant hyperconjugative interactions in a hypothetically planar 1,3-dioxole molecule.



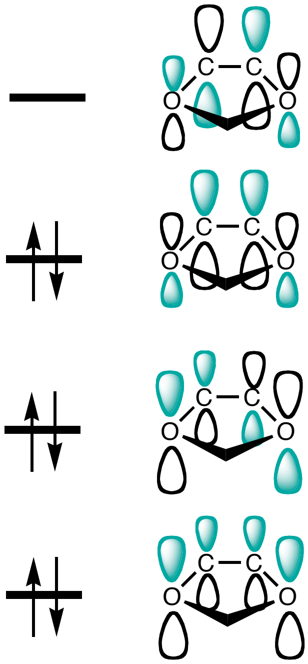
$n_{\sigma O} \rightarrow \sigma^*_{C\text{–}O}$

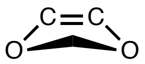


$n_{\sigma O} \rightarrow \sigma^*_{C\text{–}C}$

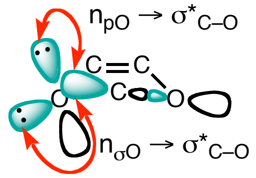
Part B. Draw a molecular orbital diagram of the π-system of hypothetically planar 1,3-dioxole. Can you explain why the molecule is puckered? (Note that in the absence of a particular hyperconjugative interaction identified above, planar 1,3-dioxole has been calculated to be more stable than its puckered counterpart.)

The π-system contains six electrons, two of which must be placed in antibonding orbitals. Although bonding does prevail, the system would benefit from delocalization of electron density. Puckering (and/or a potential change in oxygen hybridization to a state between sp^2 and sp^3) would decrease the electron density in the π-system and allow for some overlap between the p-orbitals on oxygen and $\sigma^*_{C\text{–}O}$ (denoted as $n_{pO} \rightarrow \sigma^*_{C\text{–}O}$). The overall effect is stabilizing even if the loss of hyperconjugation in $n_{\sigma O} \rightarrow \sigma^*_{C\text{–}O}$ is equal to the gain in $n_{pO} \rightarrow \sigma^*_{C\text{–}O}$ since electron density is removed from the π-system. In the absence of the anomeric effect, the energy of the system would not be lowered upon puckering given that the planar structure is theoretically more stable.





puckered 1,3-dioxole


$n_{pO} \rightarrow \sigma^*_{C\text{–}O}$
$n_{\sigma O} \rightarrow \sigma^*_{C\text{–}O}$

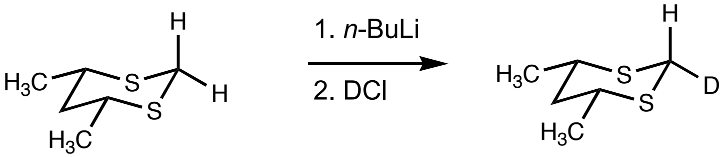
Two of each of these hyperconjugative interactions occur in puckered 1,3-dioxole.

Primary Reference: Suárez, D.; Sordo, T. L.; Sordo, J. A. Anomeric Effect in 1,3-Dioxole: A Theoretical Study. *J. Am. Chem. Soc.* **1996**, *118*, 9850-9854.

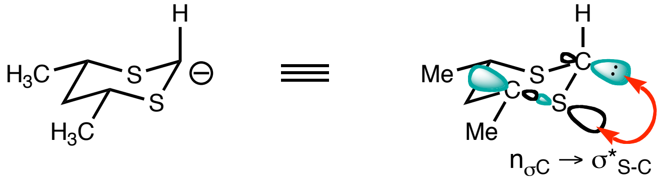
Relevant Literature: For similar calculations performed on 1,3-benzodioxole see: Moon, S.; Kwon, Y.; Lee, J.; Choo, J. Conformational Stabilization of 1,3-Benzodioxole: Anomeric Effect by Natural Bond Orbital Analysis. *J. Phys. Chem. A* **2001**, *105*, 3221-3225. For a dipole based approach that arrives at the same answer see: Box, V. G. S. The Role of Lone Pair and Dipolar Interactions in the Non-Planarity of 1,3-Dioxolane and 1,3-Dioxole. *J. Mol. Model.* **2001**, *7*, 193-200.

Problem 8. Many factors influence the reactivity and conformational bias of cyclic systems including steric, electronic, and stereoelectronic effects. For each of the following cases involving a six-membered heterocycle, provide a rationalization for the observed selectivity, including clear 3-dimensional representations where relevant.

Part A. Eliel and coworkers disclosed that the successive deprotonation of conformationally locked **1** followed by trapping with an electrophile occurs with high selectivity at the equatorial position (*J. Am. Chem. Soc.* **1974**, *96*, 1807.)

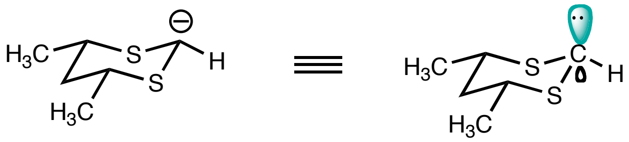


1



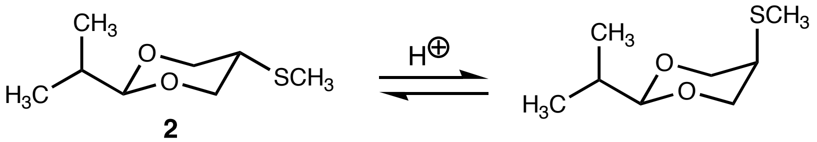
The equatorial anion is stabilized by two hyperconjugative interactions with the adjacent S-C antibonding orbitals.

Eliel *et al. JACS* **1974**, *96*, 1807.



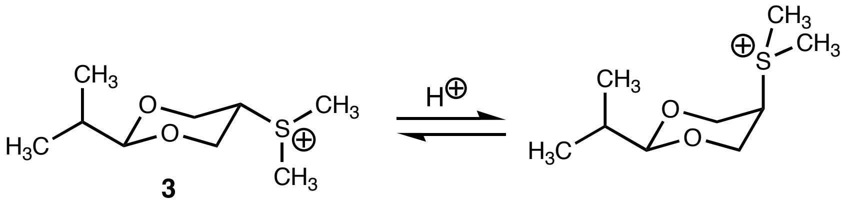
No such stabilizing interactions are available for the axial anion, making it much less stable and therefore less likely to form.

Part B. Eliel has also reported that the acid-catalyzed equilibrium of dioxane **2** favors the equatorial isomer, while the related equilibration of dioxane **3** prefers the axial isomer (*J. Am. Chem. Soc.* **1974**,*96*, 1939). Please provide a rationalization of these observations that is based on stereoelectronic arguments.



2

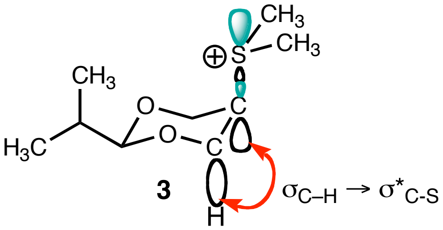
ΔG = +1.1 kcal/mol



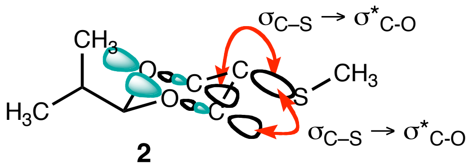
3

ΔG = –2.0 kcal/mol

For steric and stereoelectronic reasons, the equatorial isomer is preferred for compound **2**. However, the result with compound **3** is not immediately rationalized using a purely steric argument. Upon methylation of the sulfur atom, the C–S bond in **3** becomes a better acceptor and a poorer donor. Hence, the equatorial position is no longer favored by stereoelectronic effects and the compound adopts a conformation which allows for the $\sigma_{C–H} \rightarrow \sigma^*_{C\text{-}S}$ hyperconjugative interaction to take place.



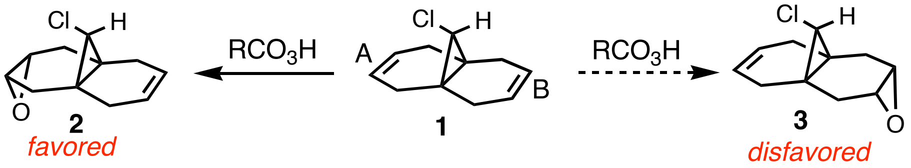
3


$\sigma_{C–S} \rightarrow \sigma^*_{C\text{-}O}$
$\sigma_{C–S} \rightarrow \sigma^*_{C\text{-}O}$

2

Eliel *et al. JACS* **1974**, *96*, 1939.

Problem 9. The following publication (*J. Org. Chem.* **1991**, *56,* 5553) reported the surprisingly selective olefin epoxidation illustrated below. In this reaction, olefin B in **1** was found to be much less reactive than olefin A.

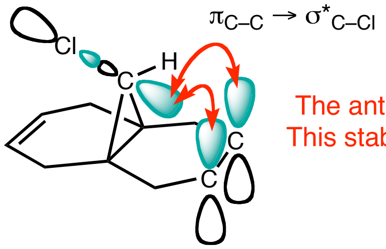


2 *favored*

1

3 *disfavored*

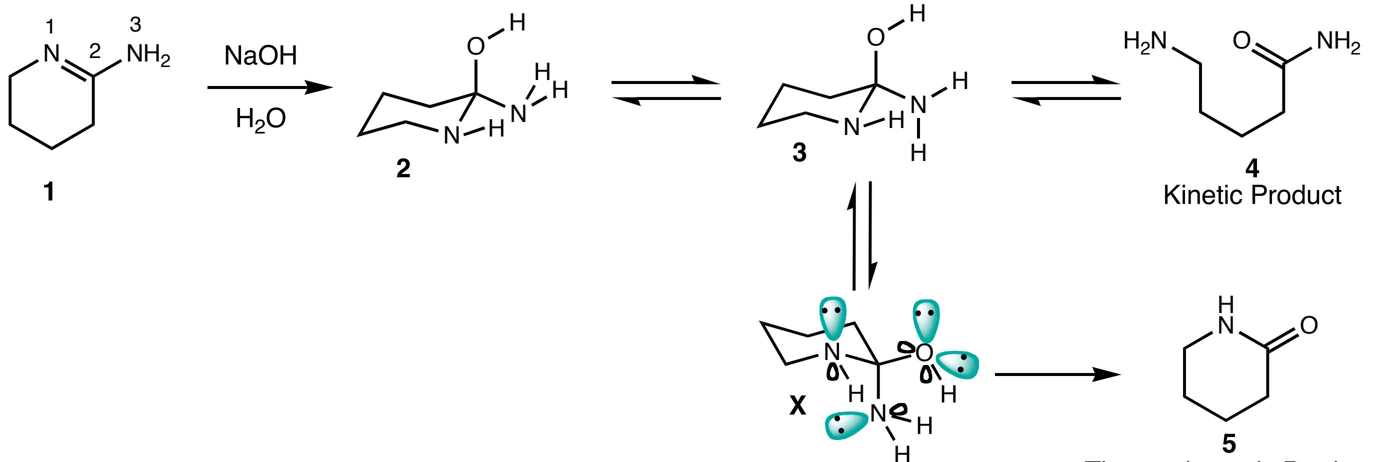
Using your knowledge of stereoelectronic effects, provide an explanation for the reduced reactivity of olefin B in diene **1**.



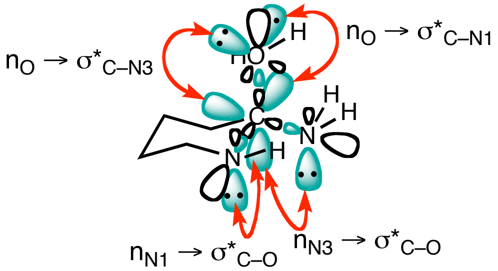
$\pi_{C-C} \rightarrow \sigma^*_{C-Cl}$

The antibonding C–Cl orbital is well positioned to interact with π_{C-C}. This stabilizing interaction will reduce the nucleophilicity of the bond.

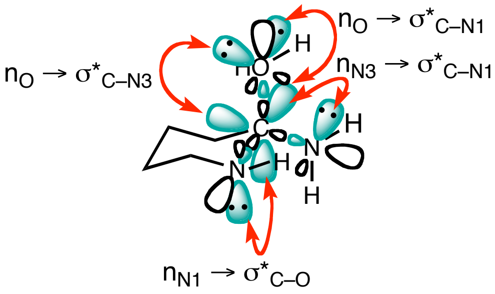
Question 10. Hydrolysis of amidine **1** with sodium hydroxide initially produces kinetic product **4** exclusively. As the reaction progresses, **4** is converted to the thermodynamic product **5**.



Part A. Identify the dominant hyperconjugative interactions in intermediate **2** (If you are looking for an extra challenge, try to explain why **2** was invoked as the first intermediate).

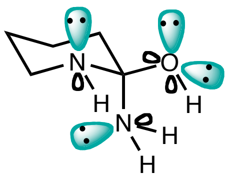

$n_O \rightarrow \sigma^*_{C–N3}$
$n_O \rightarrow \sigma^*_{C–N1}$
$n_{N1} \rightarrow \sigma^*_{C–O}$
$n_{N3} \rightarrow \sigma^*_{C–O}$

Part B. Explain why **4** is the kinetic product of the hydrolysis.


$n_O \rightarrow \sigma^*_{C–N1}$
$n_{N3} \rightarrow \sigma^*_{C–N1}$
$n_O \rightarrow \sigma^*_{C–N3}$
$n_{N1} \rightarrow \sigma^*_{C–O}$

The energy of activation for C–N1 bond cleavage must be lower than that for C–N3 bond cleavage. There are two hyperconjugative interactions ($n_{N3} \rightarrow \sigma^*_{C–N1}$ and $n_O \rightarrow \sigma^*_{C–N1}$) in intermediate **3** that weaken the C–N1 bond and one $n_{N1} \rightarrow \sigma^*_{C–O}$ that strengthens it. On the other hand, there is only one interaction ($n_O \rightarrow \sigma^*_{C–N3}$) that weakens the C–N3 bond and one ($n_{N3} \rightarrow \sigma^*_{C–N1}$) that strengthens it. Hence, cleavage of the C–N1 bond is likely to be faster which would lead to kinetic product **4**. This assumes that elimination from **3** occurs faster than from **2** since elimination from **2** would be unselective. This is a reasonable assumption given that no particular bond cleavage is favored in **2**.

Part C. Draw the conformation of intermediate **X** (including lone pairs of electrons) which is most likely to lead to thermodynamic product **5**.



The hyperconjugative interactions available in this conformation weaken the C–N3 bond relative to the C–O and C–N1 bonds.

Perrin, C. L.; Arrhenius, G. M. L. A Critical Test of the Theory of Stereoelectronic Control. *J. Am. Chem. Soc.* **1982**, *104*, 2839-2842.

Shair

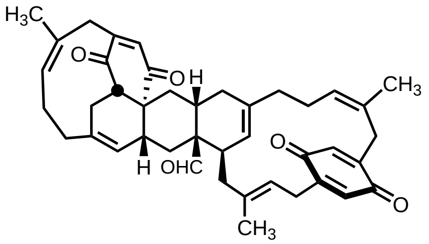
Problem Set 1

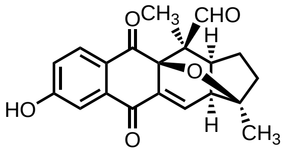
Chem 215

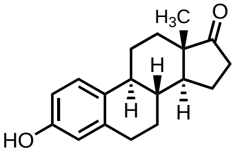
Posted: Wednesday, September 19, 2007
Due: Monday, October 1, 2007

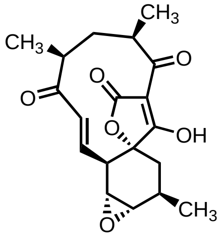
(Additional reading: pg 104-105 of Kürti & Czacó)

1. Use the Diels-Alder transform to greatly simplify the following targets. Be sure to consider, and indicate, any transforms that are necessary to establish a viable Diels-Alder transform. Provide clear 3-dimensional drawings indicating endo/exo orientation in the transition states for the reactions you propose.

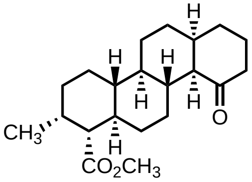




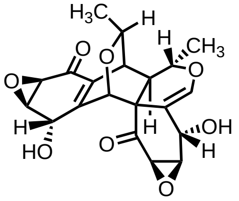




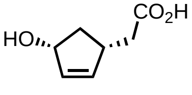
2. Conduct a thorough and systematic retrosynthetic analysis of the following target using the Diels-Alder transform with the goal of generating an acyclic precursor. Critically evaluate your pathways and present your best strategy in the synthetic direction.

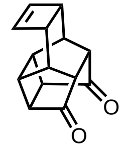


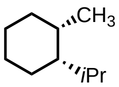
3. The following structure was assembled by the dimerization of an enantiomerically pure precursor. Identify the precursor. Caution: this problem is not as trivial as it may seem at first; consider stereochemistry carefully.

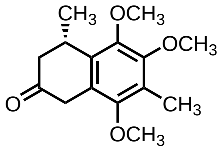


4. Develop practical synthetic routes to the following molecules (targets are achiral or racemic).

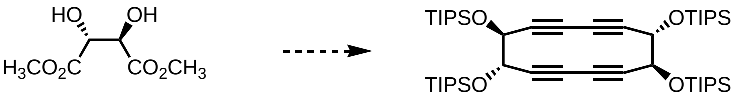


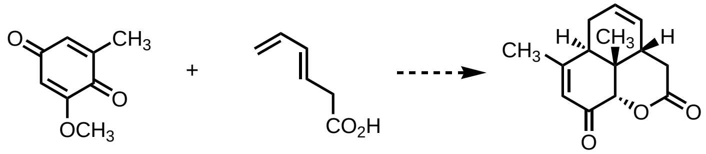




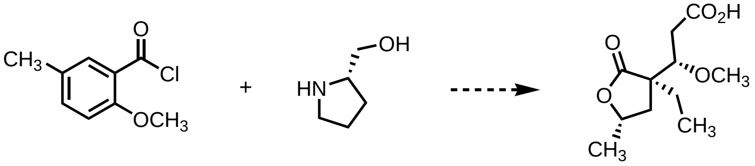


5. Develop a practical synthetic route to the targets shown from the starting materials given and any other necessary reagents.





(racemic)



Shair

Problem Set 2

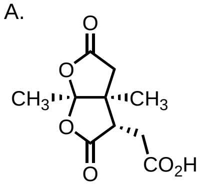
Chem 215

Posted: October 1, 2007
Due: October 10, 2007

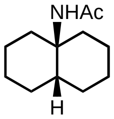
In addition to the Diels-Alder reaction, the Beckmann rearrangement (SANROS 50-51), free radical dehalogenation, asymmetric Birch reduction (SANROS 60-61), Rubottom Oxidation (SANROS 388-389), and the Grob fragmentation (SANROS 190-191) reactions will be helpful to you in solving this problem set.

1. Develop practical synthetic routes to the following molecules using the Diels-Alder transform as a key simplifying operation. All targets are racemic (or achiral).

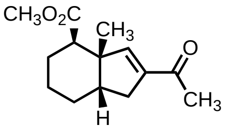
A.



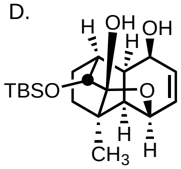
B.



C.

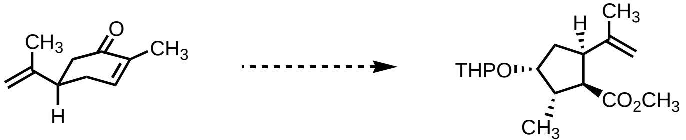


D.



2. Provide synthetic routes to the following molecules from the substructure shown. Targets that must be prepared in optically active form are so noted.

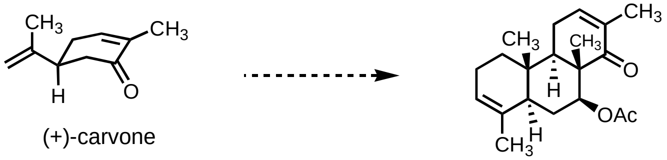
A.



(–)-carvone

(optically active)

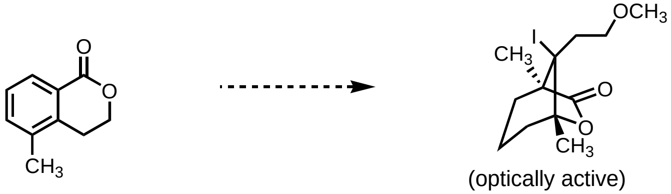
B.



(+)-carvone

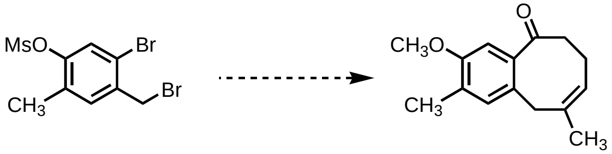
(optically active)

C.

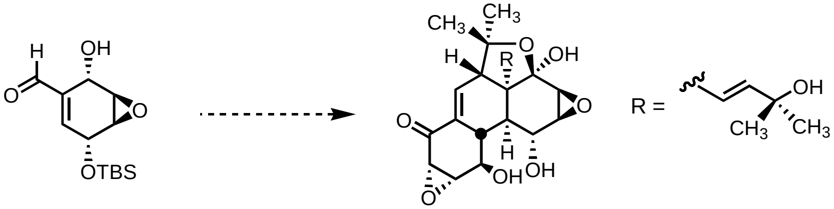


(optically active)

D.



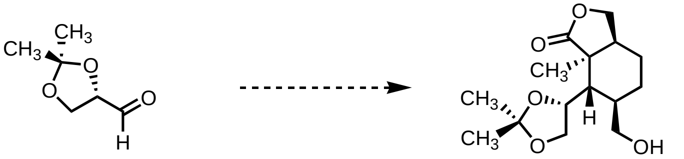
E.



(optically active)

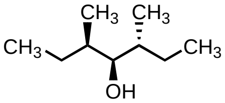
(optically active)

F.

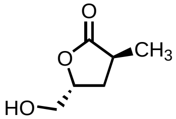


3. Develop practical asymmetric synthetic routes to the following molecules. Present only your best route, in the forward direction.

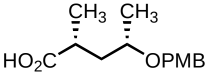
A.



B.



C.

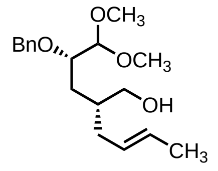


Posted: Wednesday, October 10, 2007
Due: Wednesday, October 24, 2007

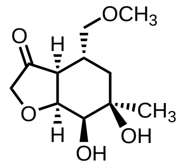
The following reactions may be helpful to you in solving this problem set: Claisen rearrangement (SANROS 88-91, 226-227), Cope and oxy-Cope rearrangements (SANROS 98-99, 324-325), Corey–Fuchs alkyne synthesis (SANROS 104-105), Heck reaction (SANROS 196-197), Seyferth–Gilbert homologation (SANROS 402-403), Sonogashira cross-coupling (SANROS 424-425), Stille cross-coupling (SANROS 428-429), Suzuki cross-coupling (SANROS 448-449), Takai reaction (SANROS 452-453).

1. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules. Present only your best route, in the forward direction.

A.

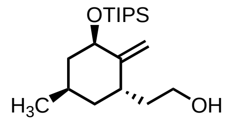


B.

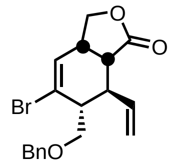


(racemic)

C.

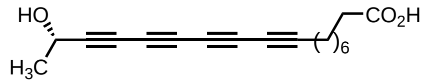


D.

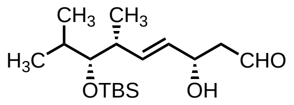


(racemic)

E.

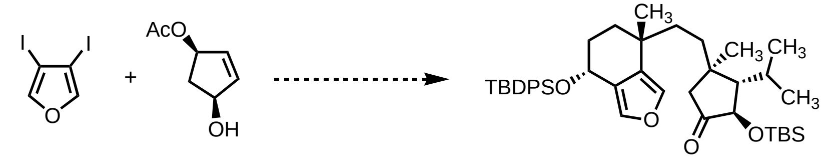


F.

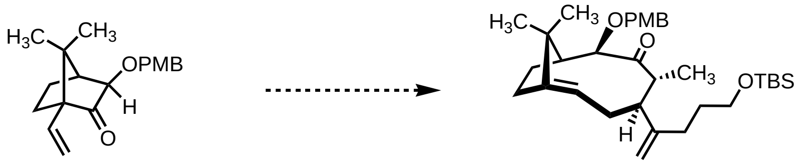


2. Develop synthetic routes to the targets shown using the starting materials given and any other necessary reagents.

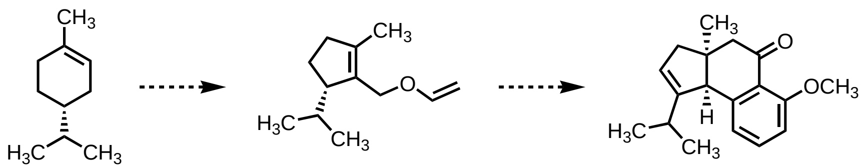
A.



B.



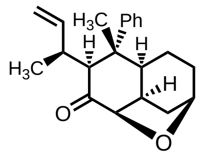
3. Provide a synthesis of intermediate **3A** from the substructure shown. From **3A**, provide a synthesis of the final compound.



intermediate **3A**

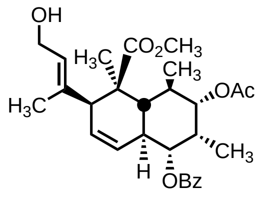
4. Develop practical synthetic routes to the following molecules.

A.



(racemic)

B.



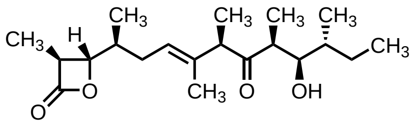
Shair Problem Set 4 *Chem 215*

Posted: Wednesday, October 24, 2007
Due: Wednesday, November 7, 2007

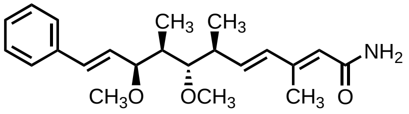
The following reactions may be helpful to you in solving this problem set: pp 162-163; 220-223; 316-317; 406-411; 456-457 (Evans modification of the Tishchenko reaction).

1. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules. Present only your best route, in the forward direction.

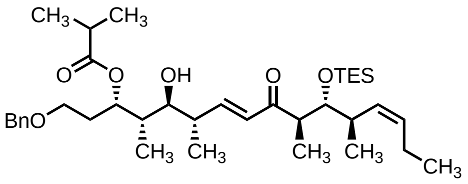
A.



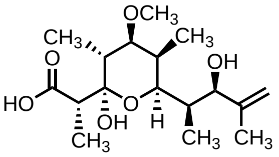
B.



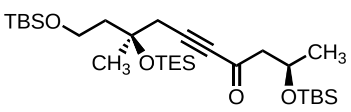
C.



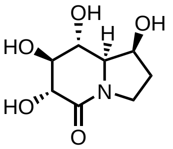
D.



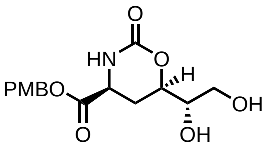
E.



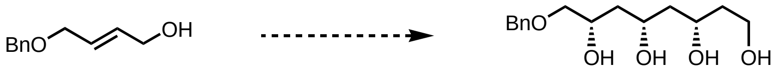
F.



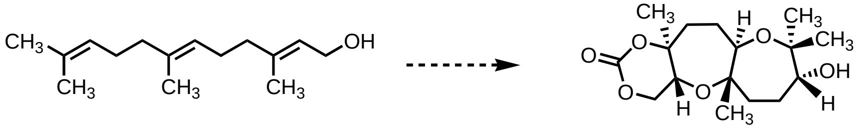
G.



2. Provide a synthetic route to the following polyol from the starting material given using an iterative asymmetric epoxidation strategy to set your stereocenters.



3. Provide an enantioselective synthetic route to the following molecule from the substructure shown.



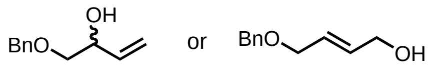
E,E-farnesol

Shair Problem Set 5 *Chem 215*

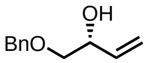
Posted: Wednesday, November 7, 2007
Due: Monday, November 26, 2007

1. Provide enantioselective routes to the targets shown, starting from one of the precursors provided.

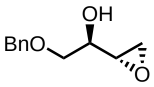
Precursors



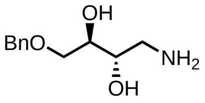
A.



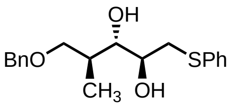
B.



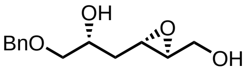
C.



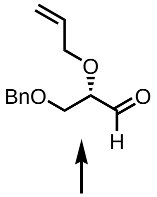
D.



E.

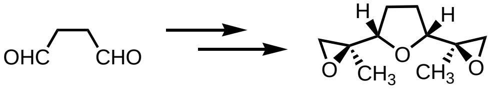


F.



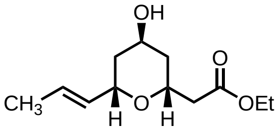
(provide a route from each starting material)

2. Provide an enantioselective route to the target shown from the precursor provided.

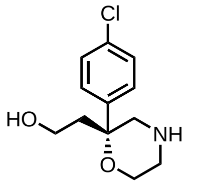


3. Provide enantioselective routes to the targets shown from commerically available starting materials.

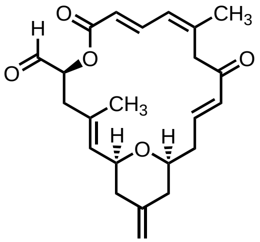
A.



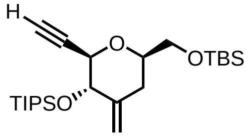
B.



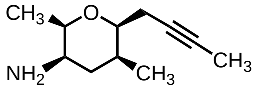
C.



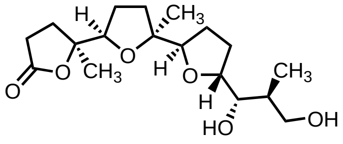
D.



E.



F.

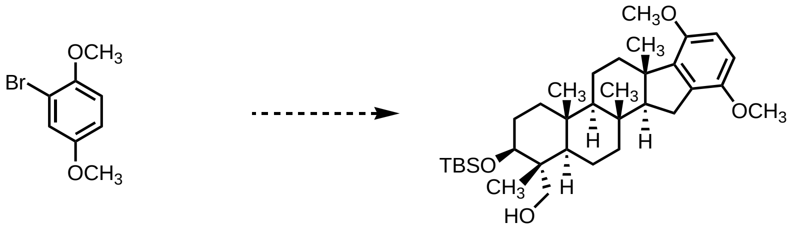


Shair Problem Set 6 *Chem 215*

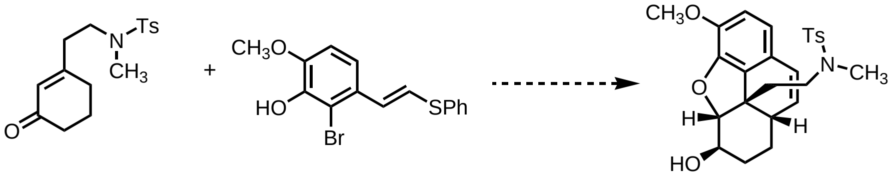
Posted: Monday, November 26, 2007
Due: Wednesday, December 5, 2007

1. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules from the indicated starting materials. Present only your best route, in the forward direction.

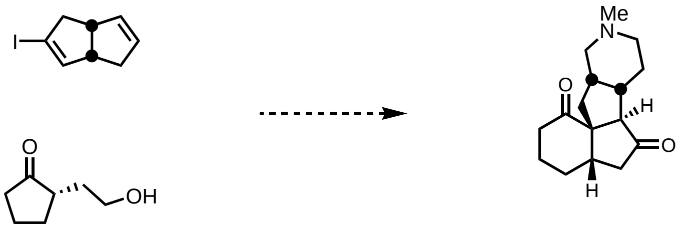
A.



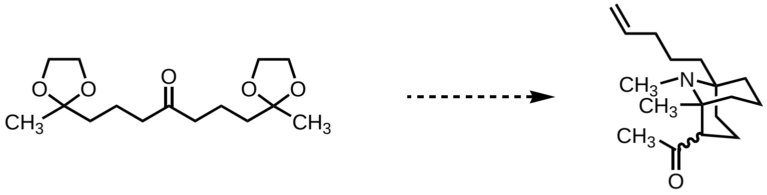
B.



C.

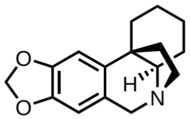


D.



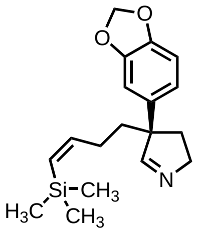
racemic

2. Develop a practical synthetic route to the following molecule from each of the indicated starting materials.



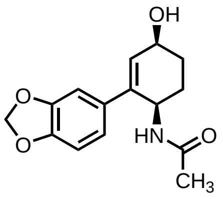
racemic

A. From:



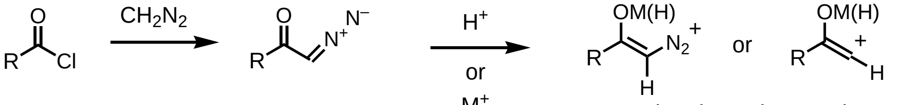
racemic

B. From:



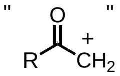
racemic

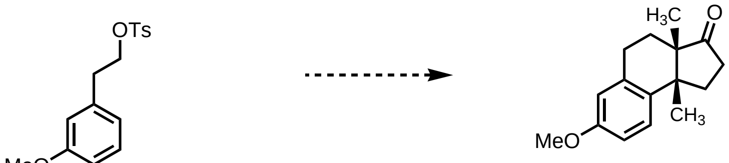
3. α-Diazoketones react with strong Brønsted or Lewis acids to generate cationic species which are capable of alkylating weak nucleophiles such as olefins. The nature of the reactive intermediate and the mechanism of the alkylation are not firmly established but the reactions proceed as if there were a cation generated $\alpha-$ to the ketone. Employ this methodology to the preparation of the tricyclic compound below.



Postulated reactive species

Postulated reactive species behave as:



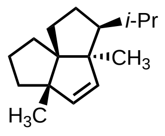


(racemic)

Posted: Wednesday, December 5, 2007
Due: Wednesday, December 12, 2007

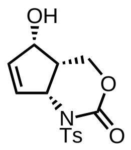
1. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following materials. Present only your best route, in the forward direction.

A.

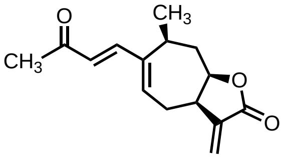


racemic

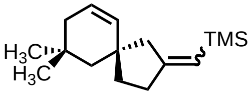
B.



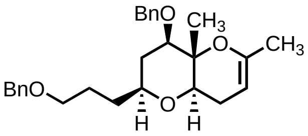
C.



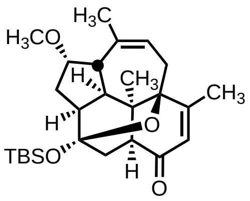
D.



E.

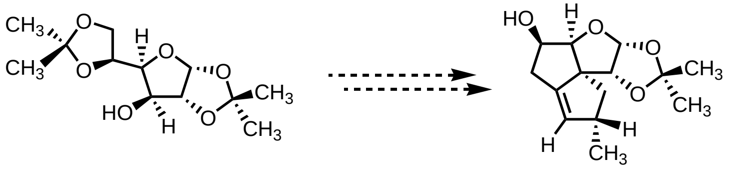


F.

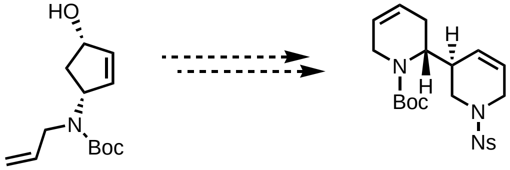


2. Develop practical asymmetric synthetic routes to the following materials from the indicated starting materials. Present only your best route, in the forward direction.

A.



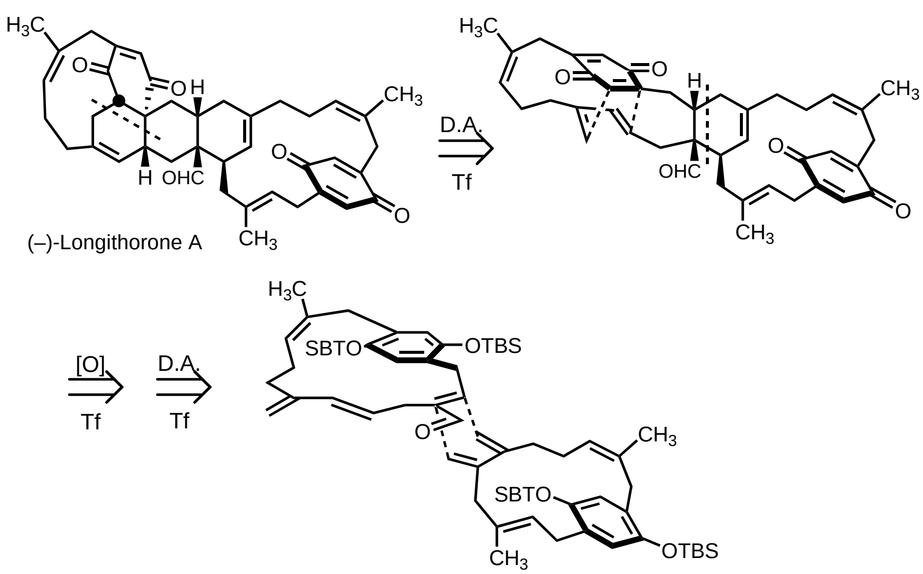
B.



Ns = nosyl (2-nitrobenzenesulfonyl)

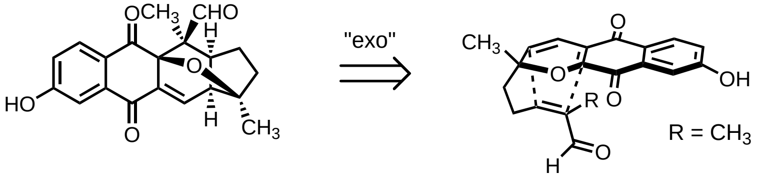
Due: Monday, October 1, 2007

1. Use the Diels-Alder transform to greatly simplify the following targets.



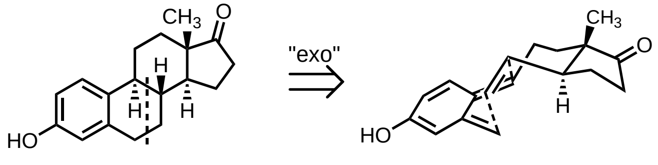
(–)-Longithorone A

Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773-775.



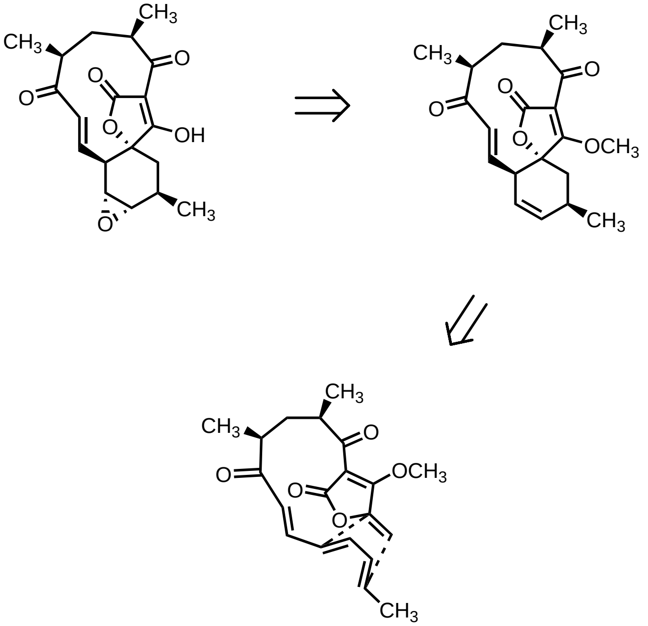
Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554-9555.

In practice, the phenol was introduced after the Diels-Alder.



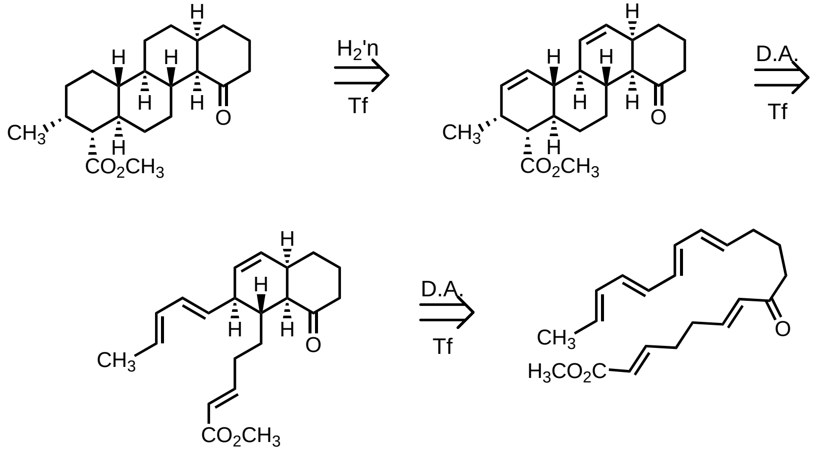
Estrone

Funk, R. L.; Vollhardt, P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253-5261.

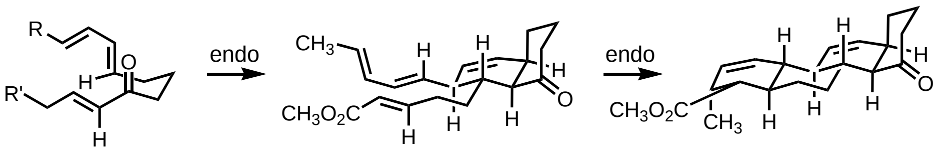


Zapf, C. W.; Harrison, B. A., Drahl, C. Sorensen, E. *Angew. Chem. Int. Ed.* **2005,** *44, 6533-6537*.

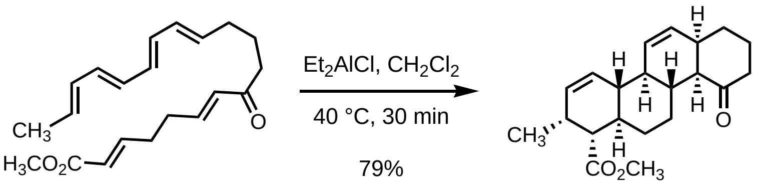
2. Conduct a thorough and systematic retrosynthetic analysis of the following target using the Diels-Alder transform with the goal of generating a linear precursor.



Stereochemistry



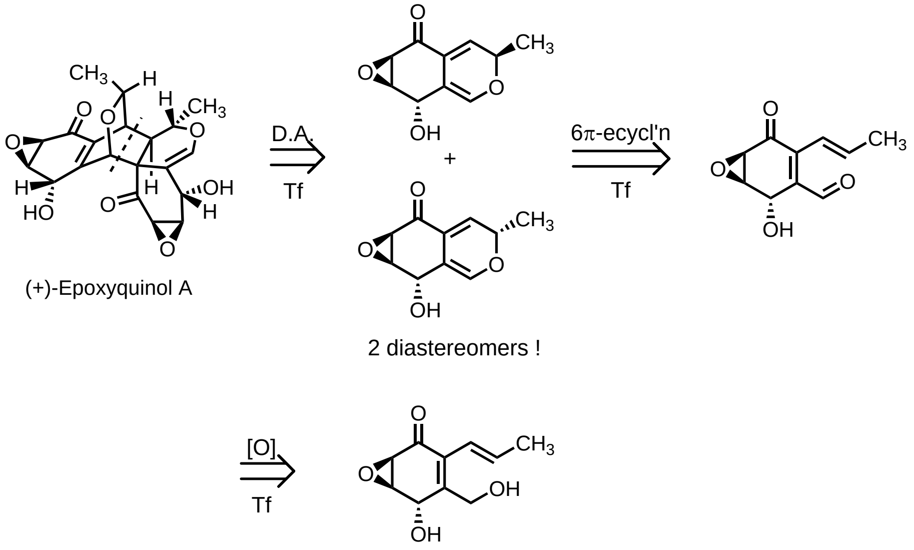
Conditions



Nörret, M.; Sherburn, M. S. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4074-4076.

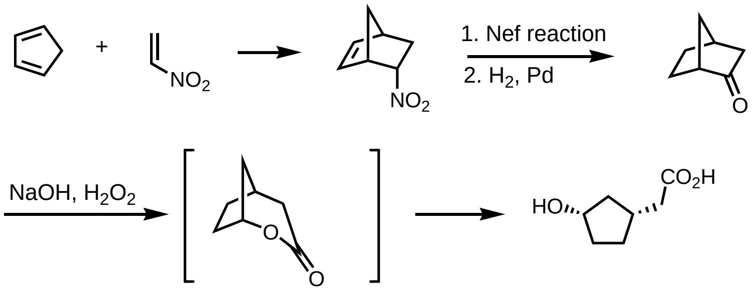
3. Propose a strategy to construct the following molecule from a linear precursor.

In practice, epoxiquinol A was formed in 40% yield in one pot from the alcohol shown upon oxidation with MnO_2.

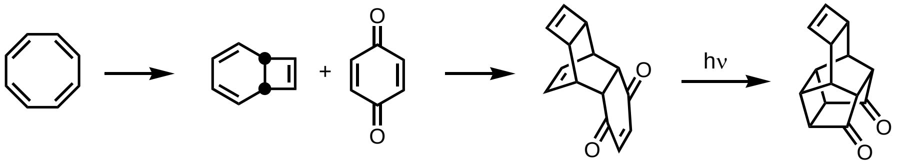


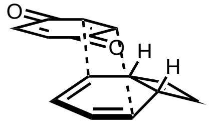
Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3192-3194.

4. Develop practical synthetic routes to the following molecules (targets are achiral or racemic).

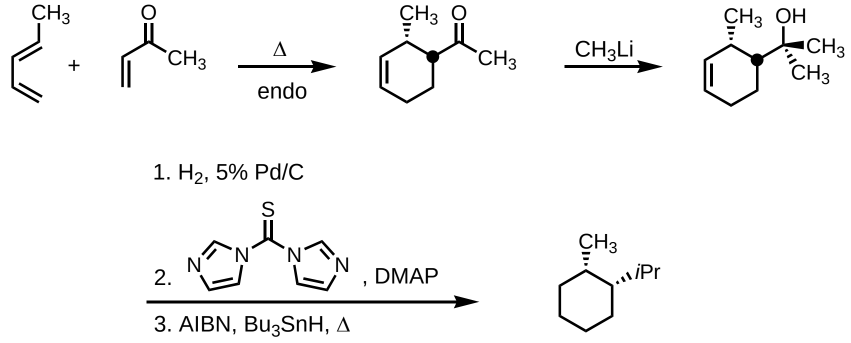


Greene, A. E.; Le Drian, C.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7584-7485.

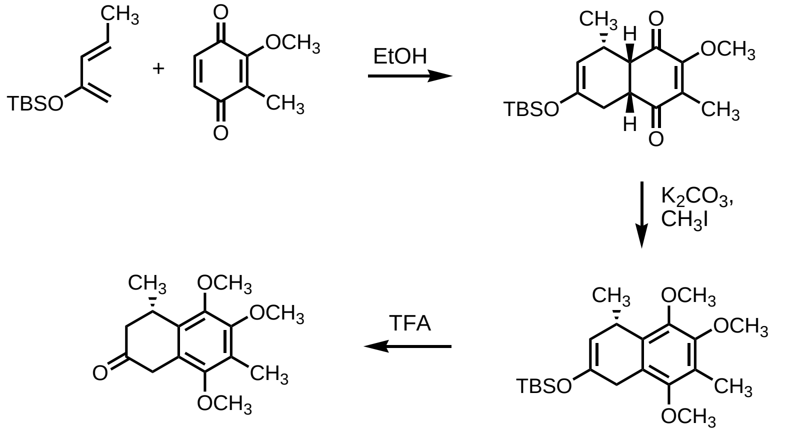




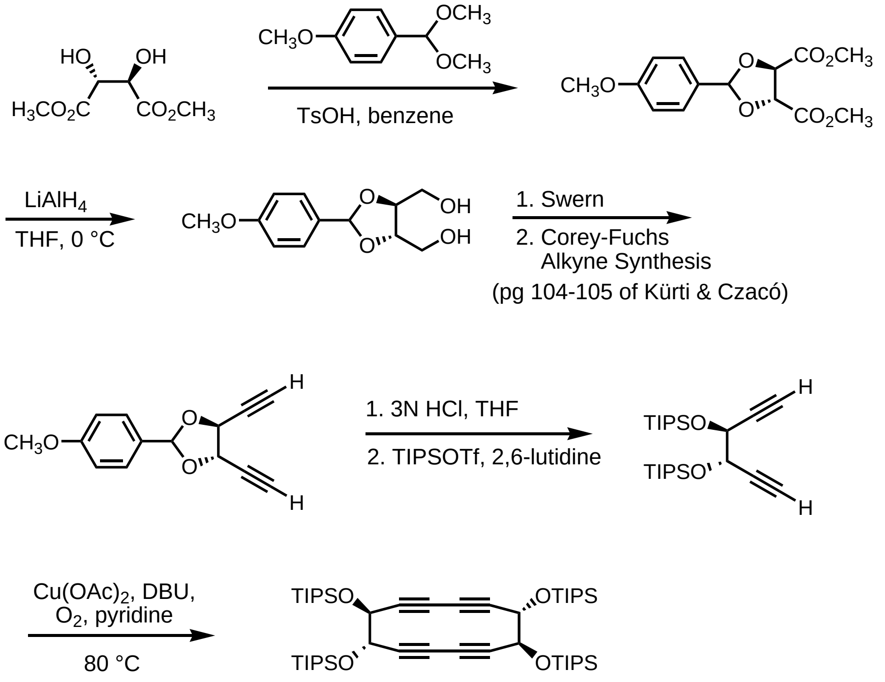
Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062-3075.



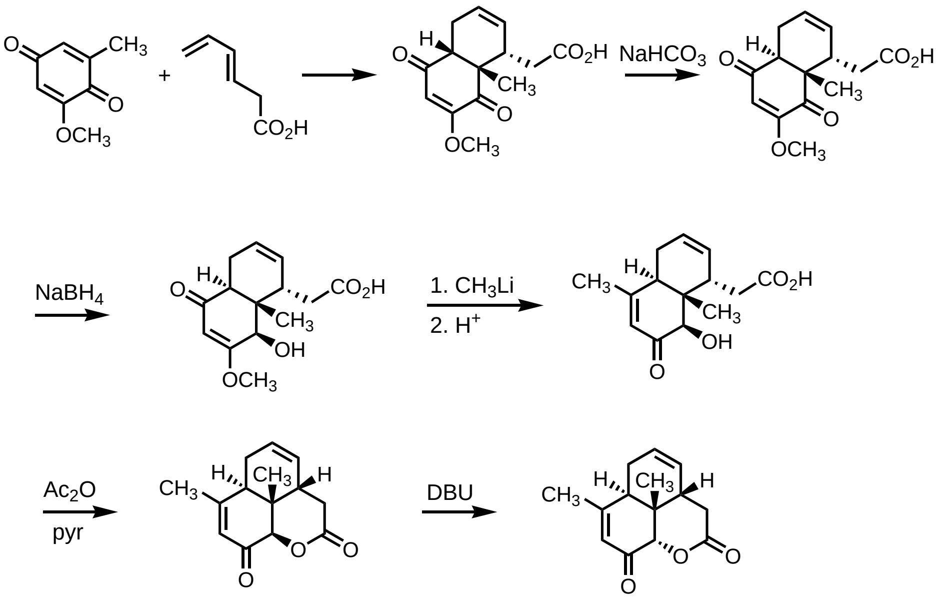
Güner, O. F.; Ottenbrite, R. M.; Shillady, D. D. *J. Org. Chem.* **1988**, *53*, 5348-5351.



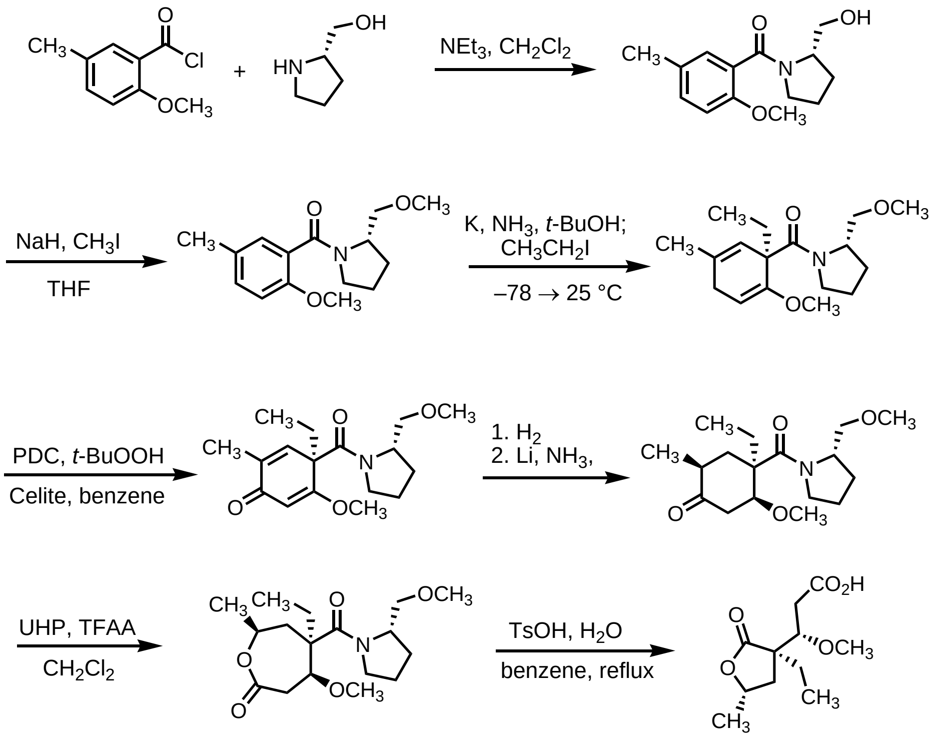
Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2482-2486.



Myers, A. G.; Goldberg, S. D. *Tetrahedron Lett.* **1998**, *39*, 9633-9636.



Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Trueblood, K. N.; Liu, Y.-X. *J. Org. Chem.* **1986**, *51*, 4347-4353.

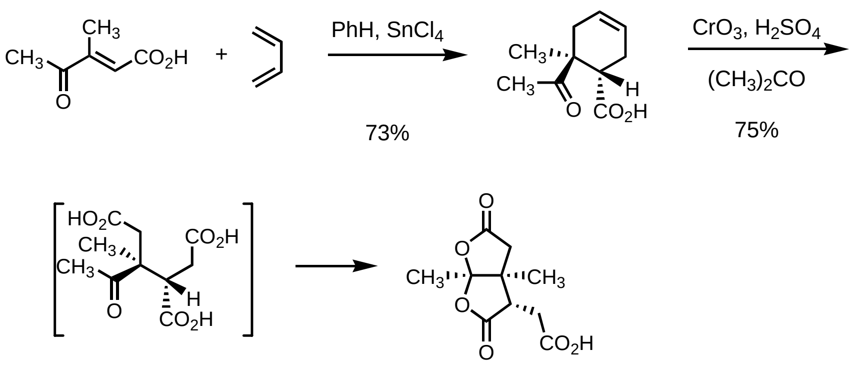


Schultz, A. G.; Malachowski, W. P.; Pan, Y. *J. Org. Chem.* **1997**, *62*, 1223-1229.

Due: October 10, 2007

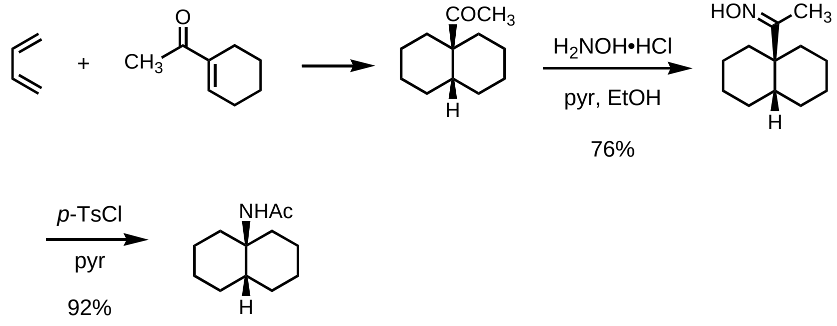
1. Develop practical synthetic routes to the following molecules using the Diels-Alder transform as a key simplifying operation. All targets are racemic (or achiral).

A.



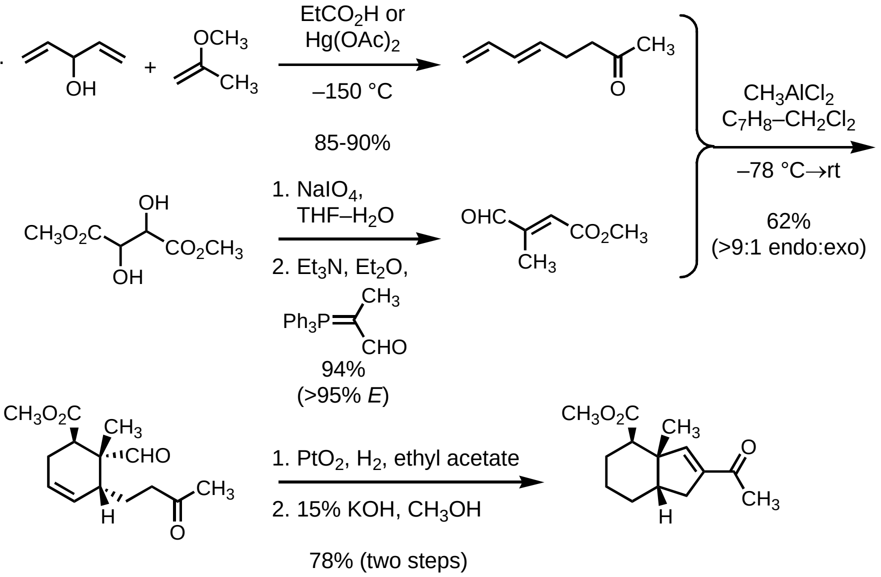
Eschenmoser, A.; Wintner, C. E. *Science* **1977**, *196*, 1410-1420.

B.



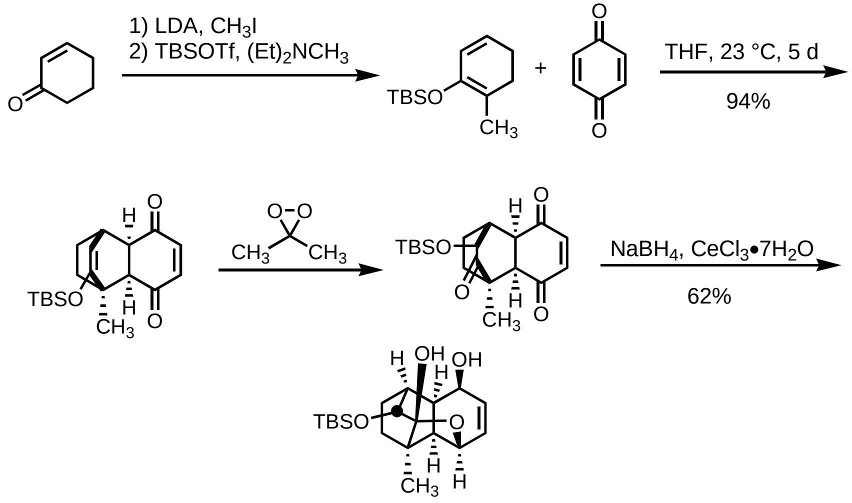
Hill, R. K.; Conley, R. T.; Chortyk, O. T. *J. Am. Chem. Soc.* **1965**, *87*, 5646-5651.

C.



Reddy, D. S.; Palani, K.; Balasubrahmanyam, D.; Kamath, V. B.; Iqbal, J. *Tetrahedron Lett.* **2005**, *46*, 5211-5213.

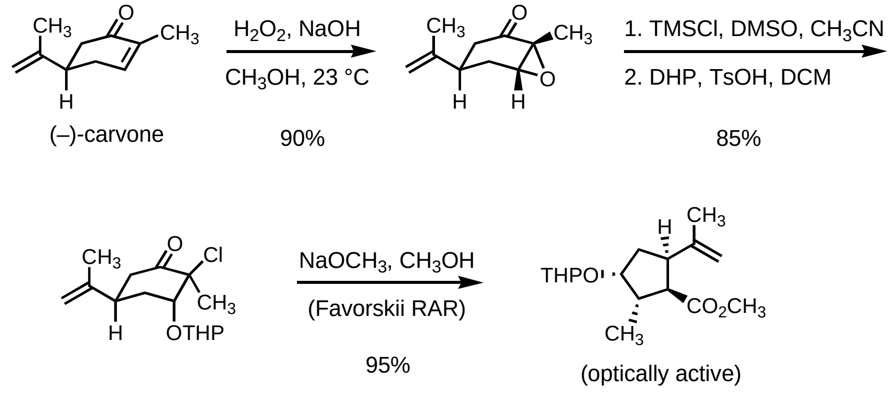
D.



Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1994,** *116*, 11213-11228

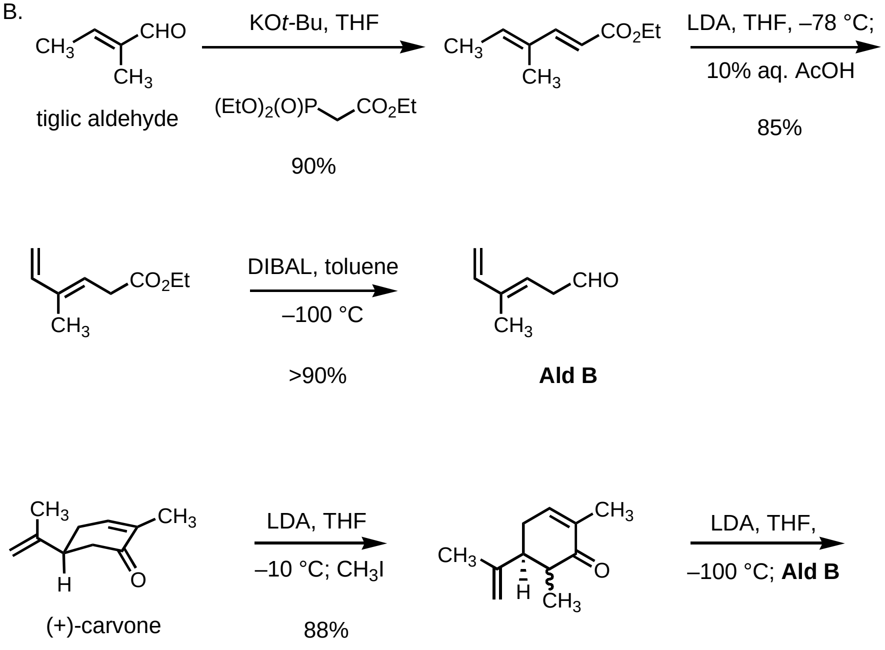
2. Provide synthetic routes to the following molecules from the substructure shown. Targets that must be prepared in optically active form are so noted.

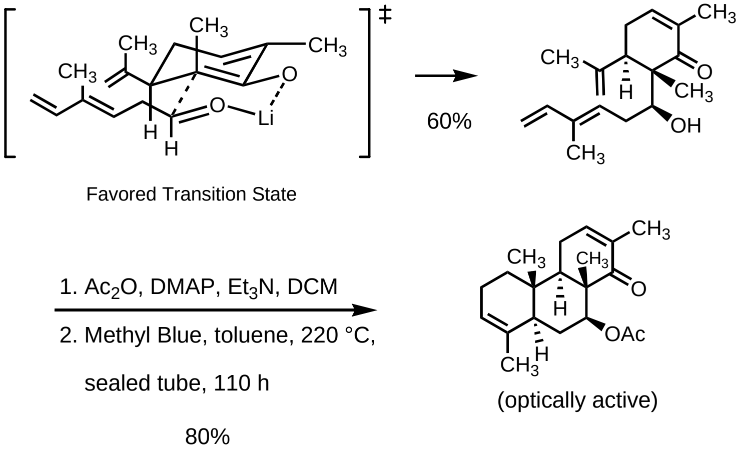
A.



Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479-481.

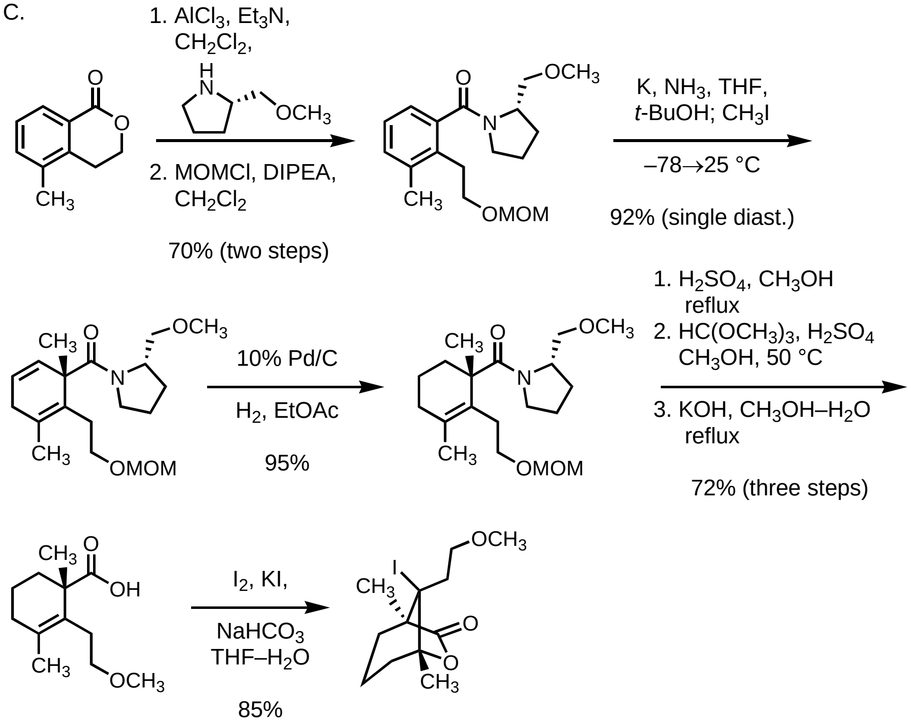
B.





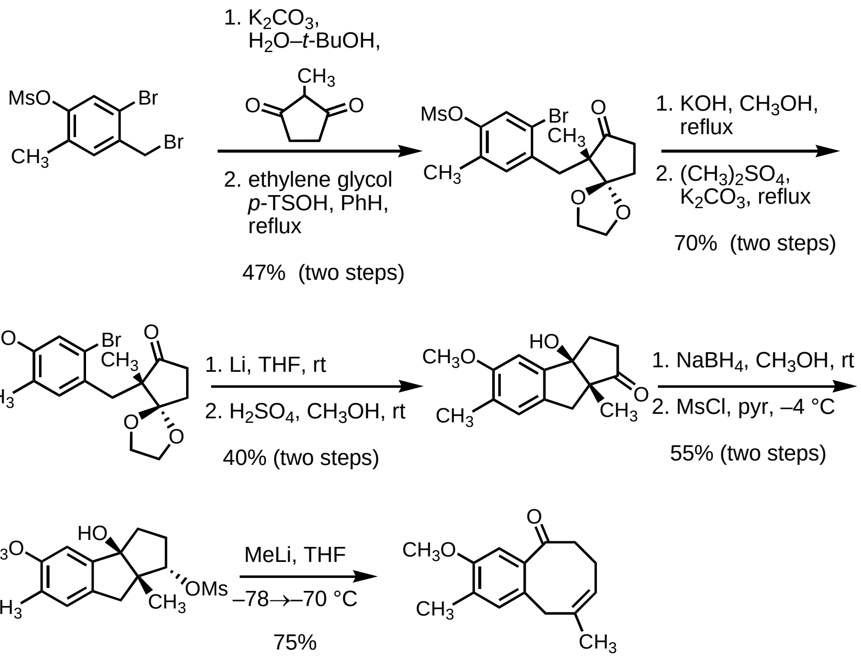
Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 2187-2194.

C.



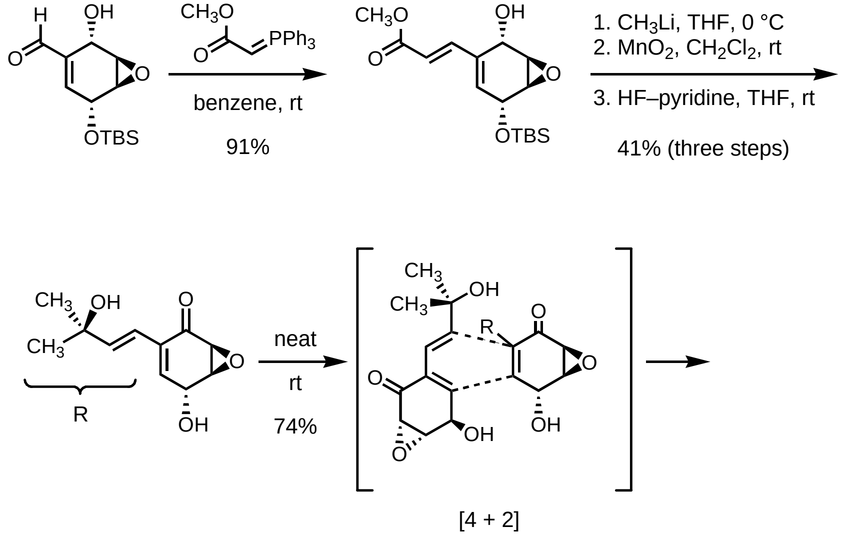
Schultz, A. G.; Kirincich, S. J. *J. Org. Chem.* **1996**, *61*, 5626-5630.

D.

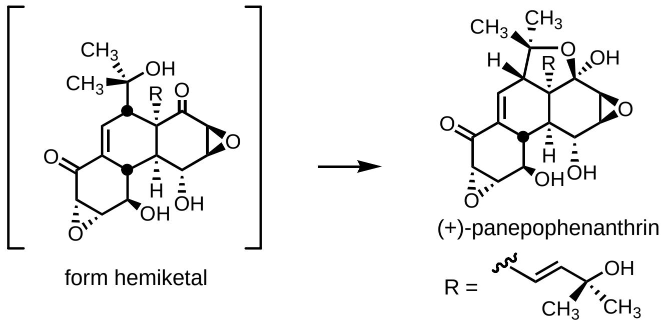


Villagómez-Ibarra, R.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Tetrahedron* **1995**, *51*, 9285-9300.

E.



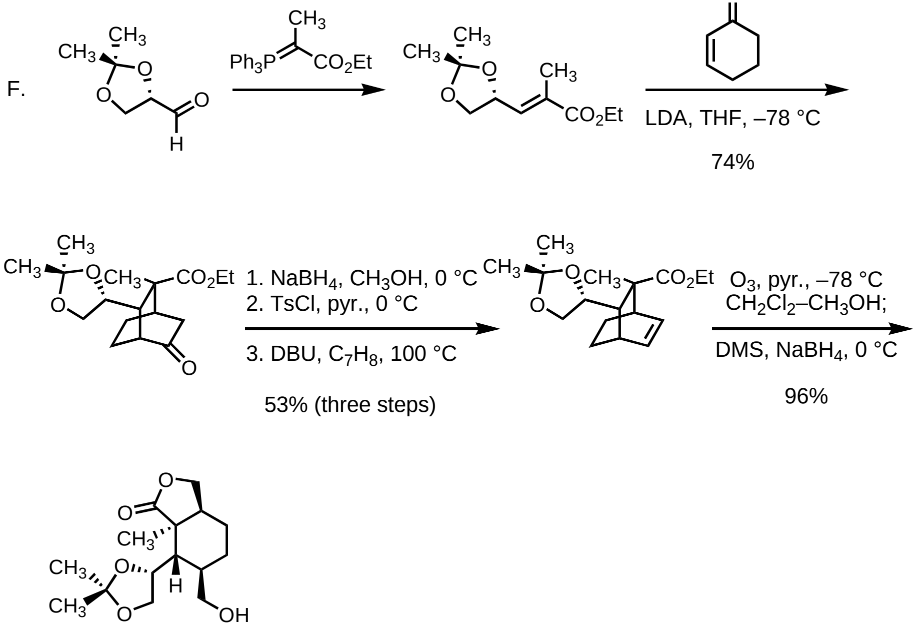
E. (continued).



Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2004**, *45*, 1985-1987.

For a discussion of the dimerzation event, see: Lei, X.; Johnson, R. P.; Porco, J. A. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3913-3917.

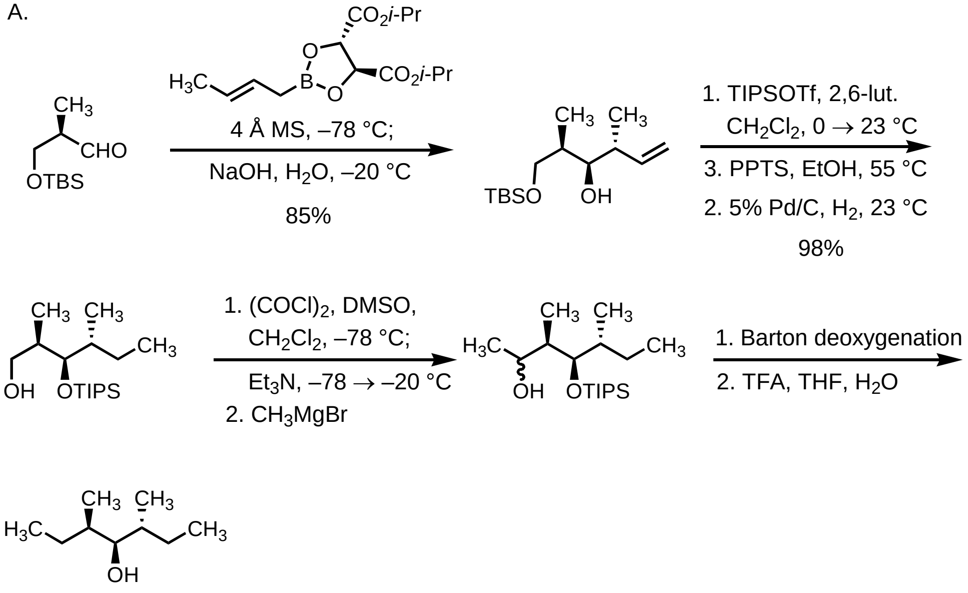
F.



Mikyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107-7110.

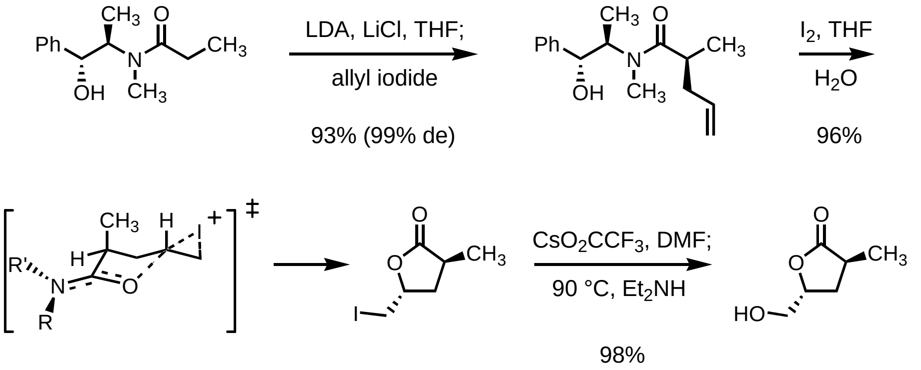
3. Develop practical asymmetric synthetic routes to the following molecules. Present only your best route, in the forward direction.

A.



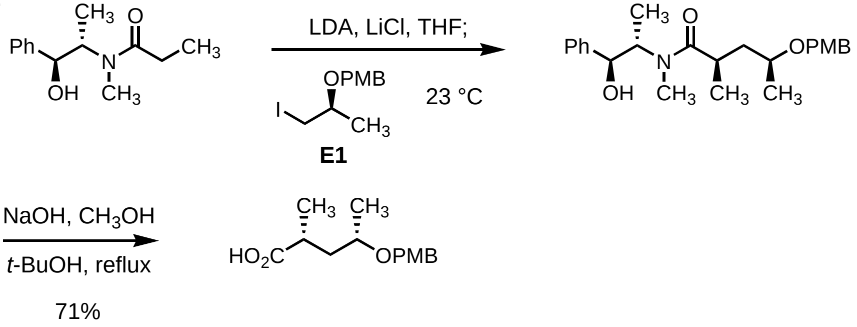
Mandal, A. K. *Org. Lett.* **2002**, *4*, 2043-2045.

B.



Myers, A. G.; Siu, M.; Ren, F. *J. Am. Chem. Soc.* **2002**, *124*, 4230-4232.

C.



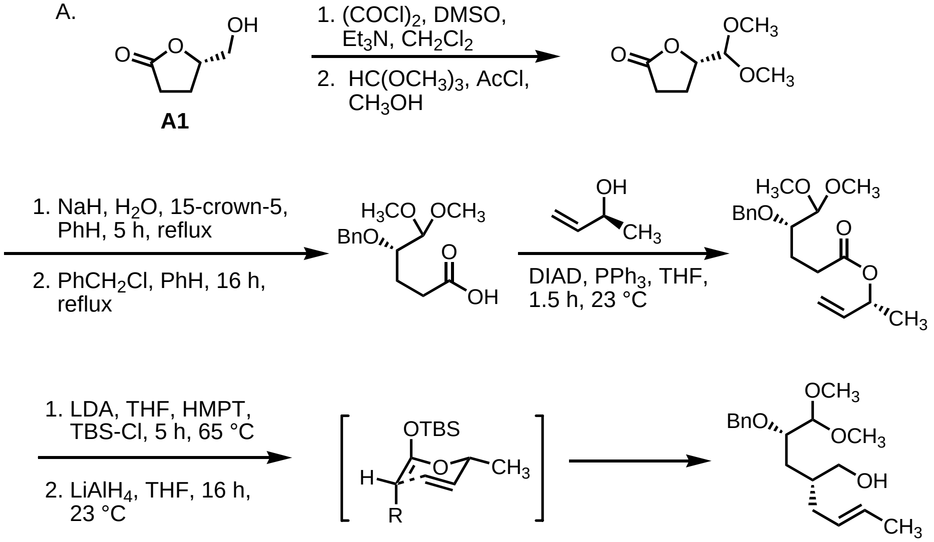
Lee, D.-H.; Rho, M.-D. *Tetrahedron Lett.* **2000**, *41*, 2573-2576.

In practice, iodide **E1** was derived from (*S*)-Lactate. Possible alternative preparations may rely on electrophilic hydroxylation of an oxazolidinone enolate.

Due: Wednesday, October 24, 2007

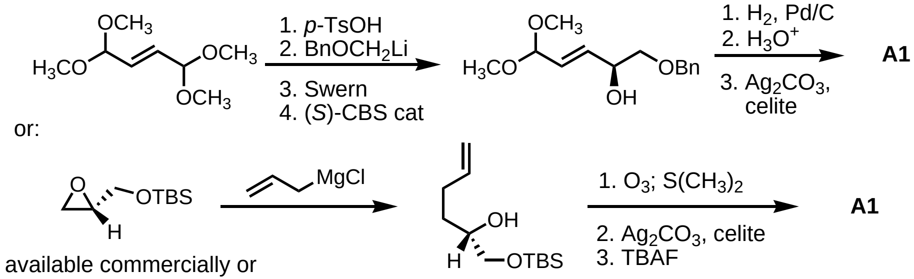
1. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules. Present only your best route, in the forward direction.

A.


OH
O
A1
1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2
2. $HC(OCH_3)_3$, AcCl, CH_3OH
OCH_3
OCH_3
1. NaH, H_2O, 15-crown-5, PhH, 5 h, reflux
2. $PhCH_2Cl$, PhH, 16 h, reflux
H_3CO OCH_3
BnO
OH
CH_3
DIAD, PPh_3, THF, 1.5 h, 23 °C
1. LDA, THF, HMPT, TBS-Cl, 5 h, 65 °C
2. $LiAlH_4$, THF, 16 h, 23 °C
OTBS
H
R
CH_3

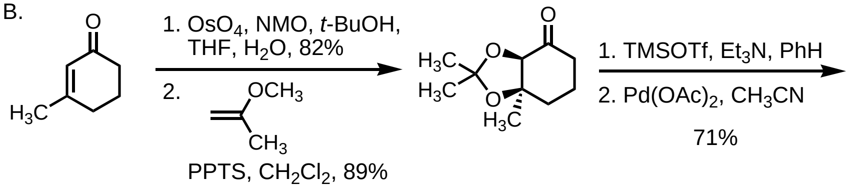
Höch, S.; Koch, F.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **2004**, *15*, 1801–1808.

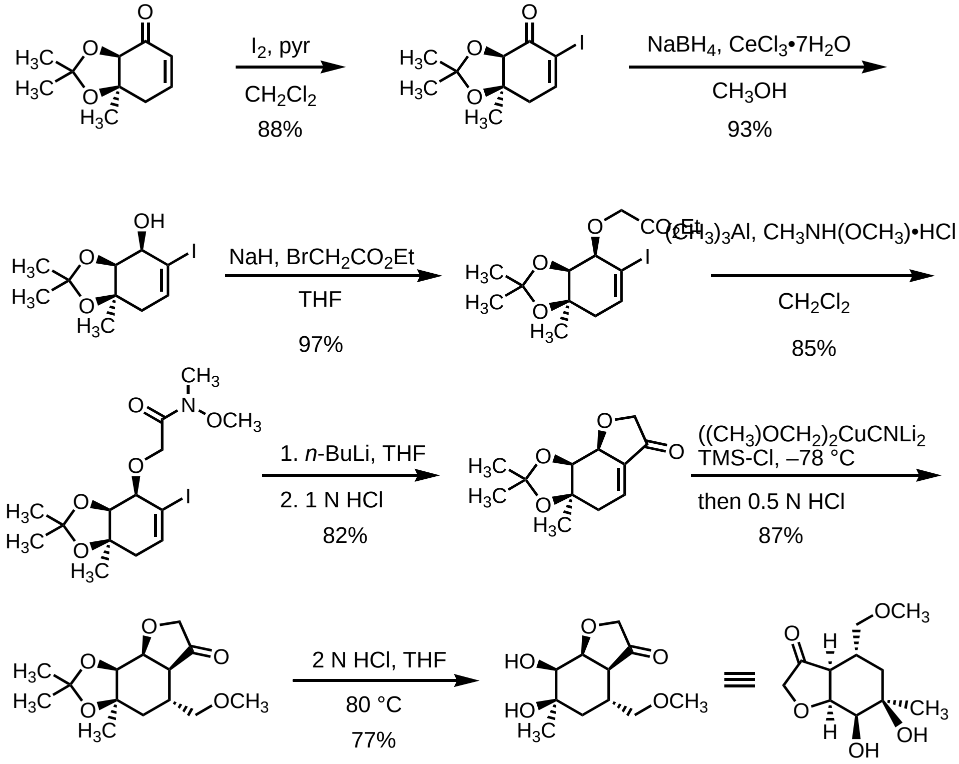
A1 is commercially available in enantiopure form. Alternative preparations are proposed below:



available commercially or
by Sharpless Asym. Epox.

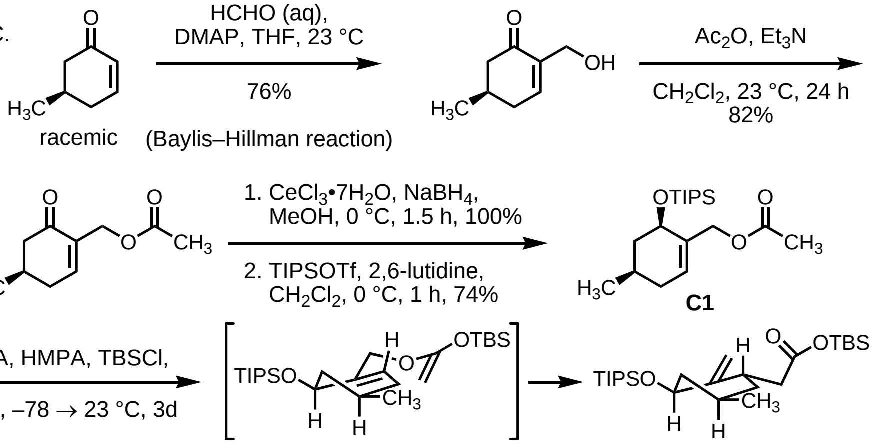
B.

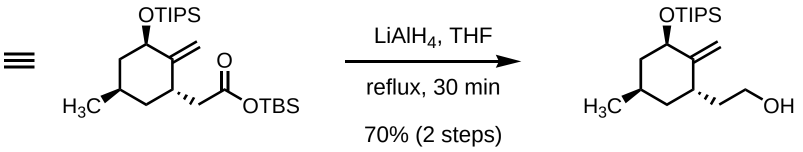

O
H_3C
1. OsO_4, NMO, t-BuOH, THF, H_2O, 82%
2. OCH_3 CH_3 PPTS, CH_2Cl_2, 89%
1. TMSOTf, Et_3N, PhH
2. $Pd(OAc)_2$, CH_3CN
71%



Sha, C.-K.; Huang, S.-J.; Zhan, Z.-P. *J. Org. Chem.* **2002**, *67*, 831–836.

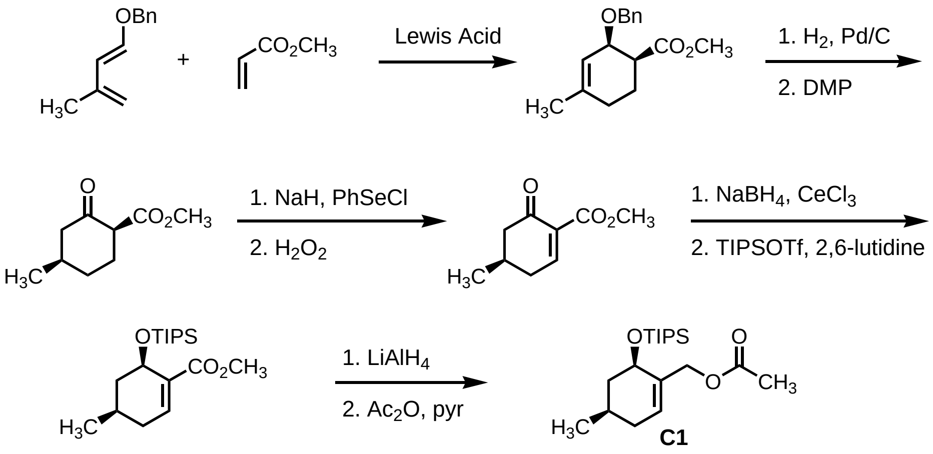
C.


O
H_3C
racemic
HCHO (aq), DMAP, THF, 23 °C
76%
(Baylis–Hillman reaction)
OH
Ac_2O, Et_3N
CH_2Cl_2, 23 °C, 24 h
82%
CH_3
1. $CeCl_3$•$7H_2O$, $NaBH_4$, MeOH, 0 °C, 1.5 h, 100%
2. TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 74%
OTIPS
C1
LDA, HMPA, TBSCl,
THF, –78 → 23 °C, 3d
TIPSO
OTBS
H

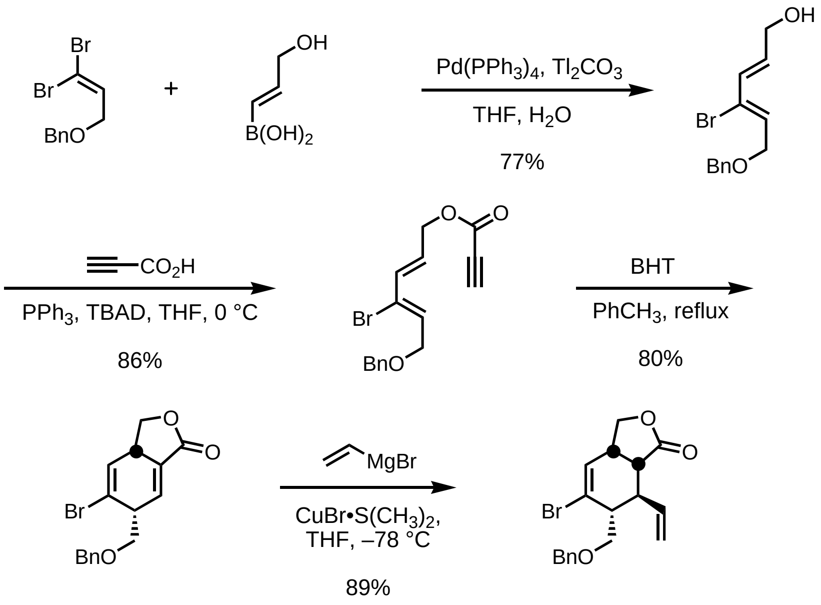


Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053–4065.

An alternative preparation of **C1** is proposed below:

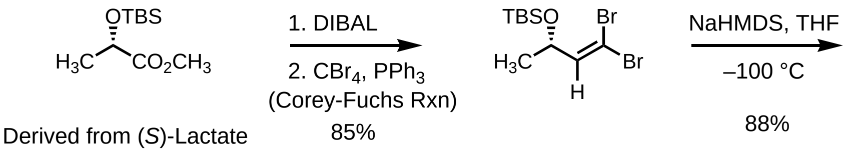


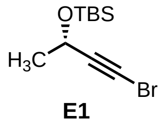
D.



Clarke, P. A.; Cridland, A. P. *Org. Lett*. **2005**, *7*, 4221–4224.

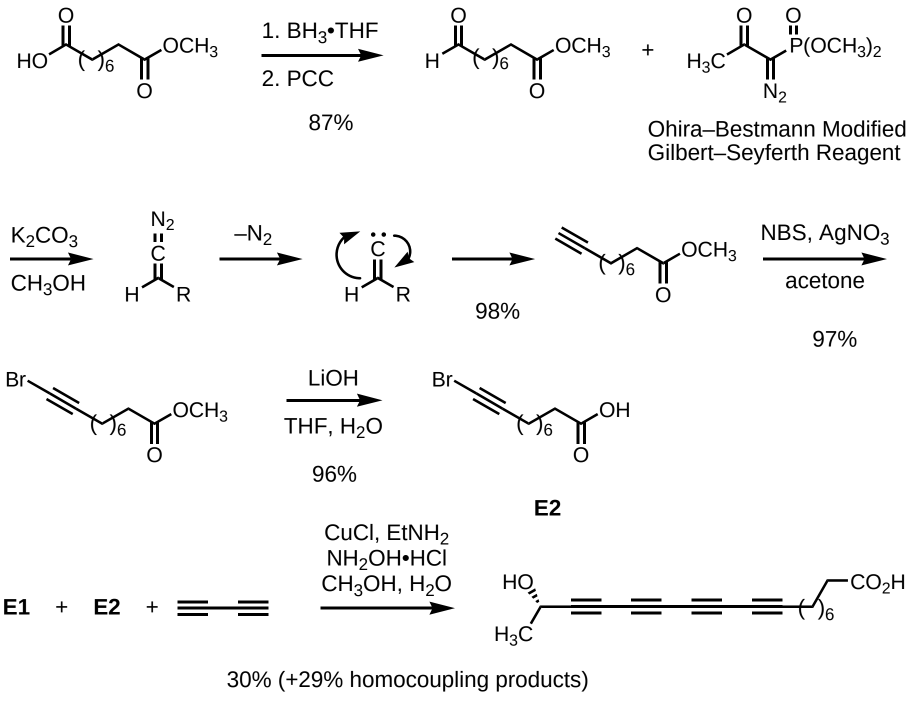
E.





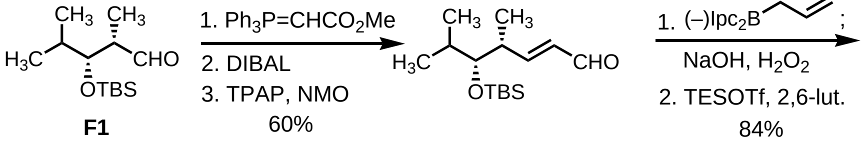
E1

An alternative synthesis of **E1** could include acetylene addition to acetaldehyde, oxidation, and CBS Reduction.

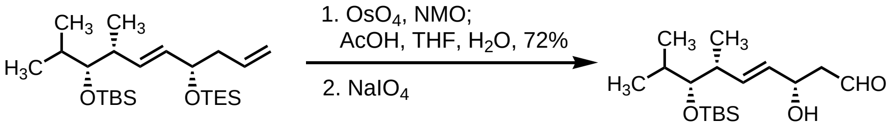


Gung, B. W.; Dickson, H. *Org. Lett*. **2002**, *4*, 2517-2519.

F.



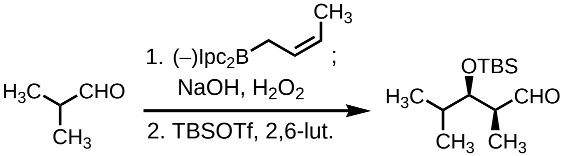
F1 was prepared by an asymmetric aldol reaction.



Protecting the alcohol as the TES ether resulted in much better yield in the dihydroxylation step.

Rychnovsky, S. D.; Rodriguez, C. *J. Org. Chem.* **1992**, *57*, 4793-4795.

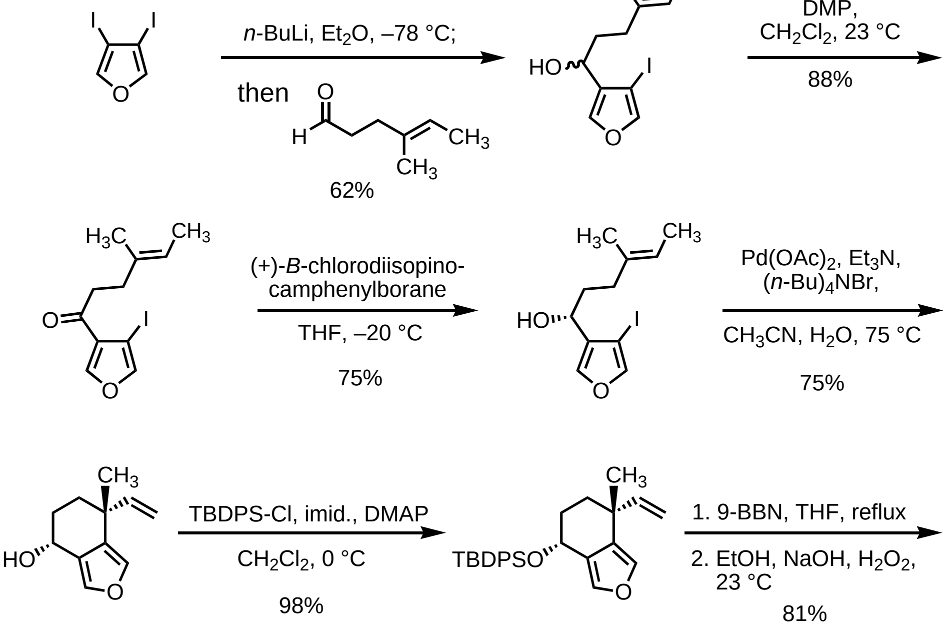
A feasible alternative for the preparation of **F1** is shown below:

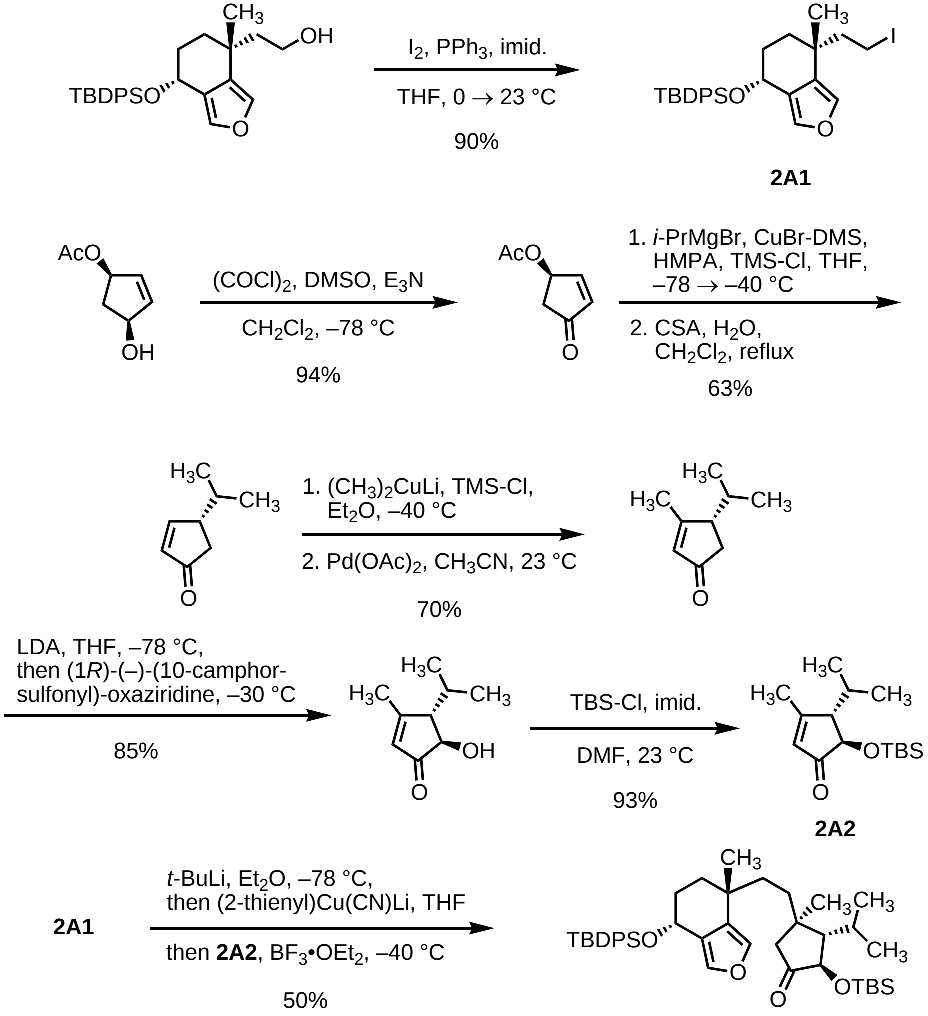


F1

2. Develop synthetic routes to the targets shown using the starting materials given and any other necessary reagents.

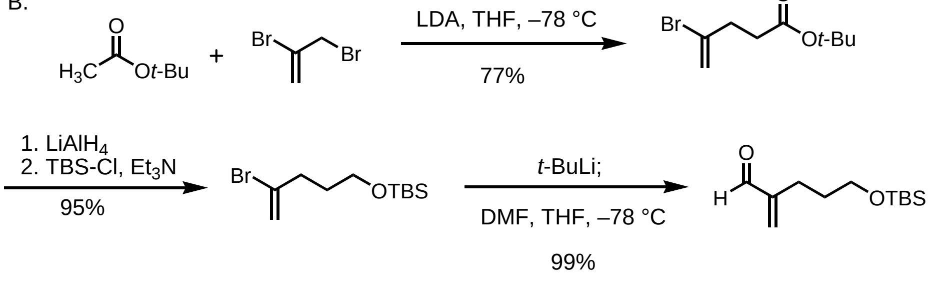
A.

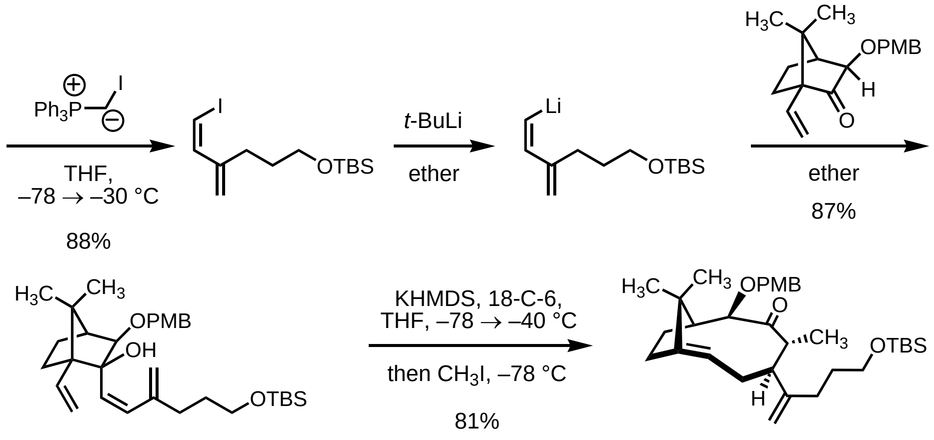




Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett*. **2005**, *7*, 3425–3428.

B.

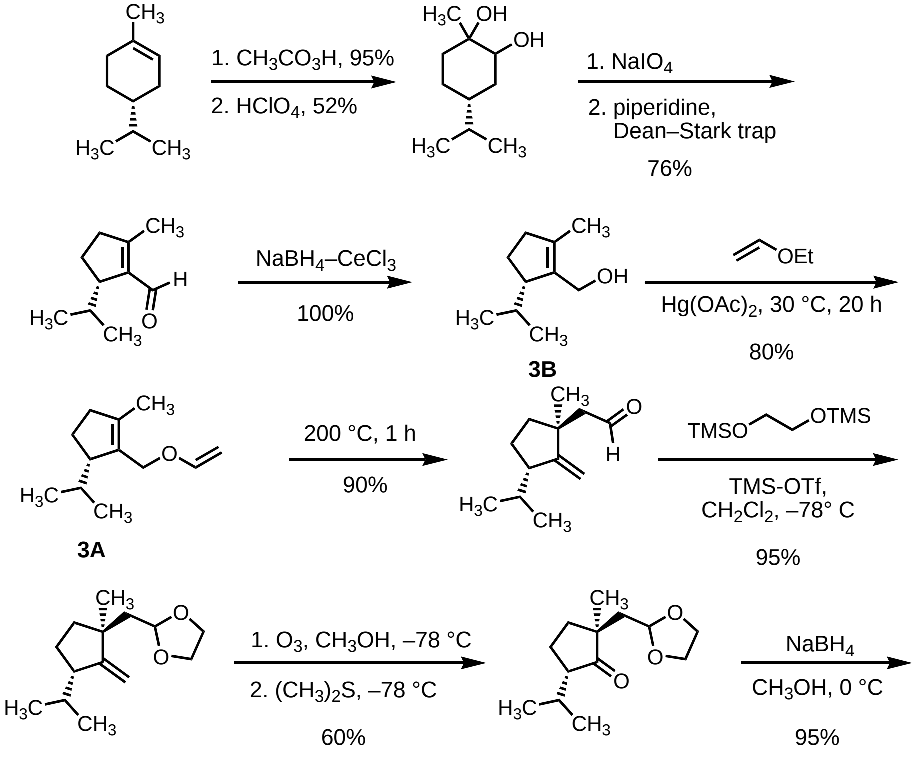


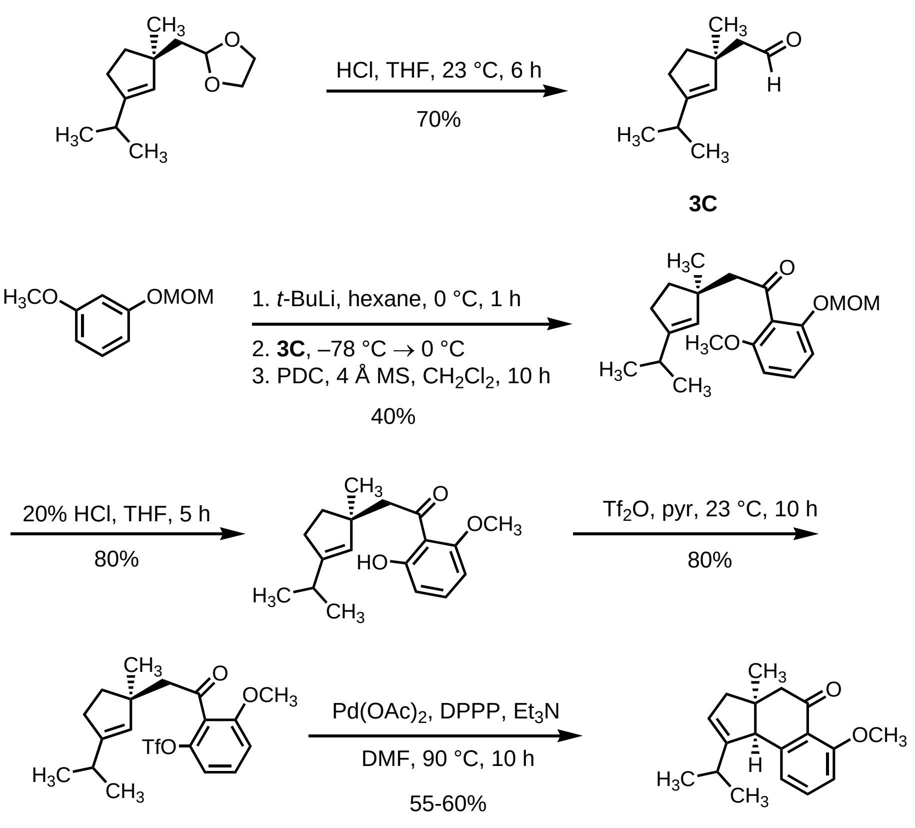


Paquette, L. A.; Hofferberth, J. E. *J. Org. Chem.* **2003**, *68*, 2266–2275.

Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452–5464.

3. Provide a synthesis of intermediate **3A** from the substructure shown. From **3A**, provide a synthesis of the final compound.



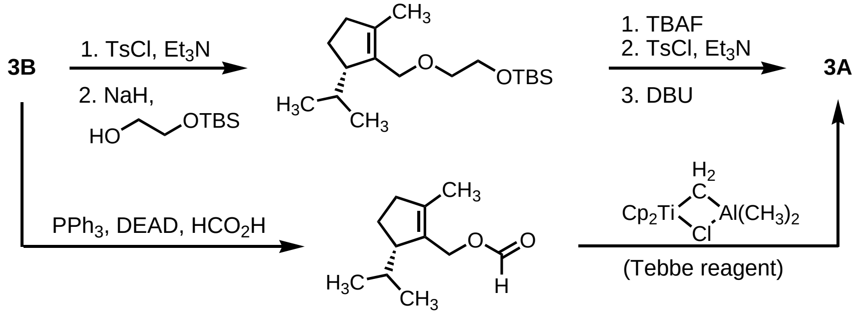


Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049–7053.

Mehta, G. Krishnamurthy, N.; Karra, S. R.; *J. Am. Chem. Soc.* **1991**, *113*, 5765–5775.

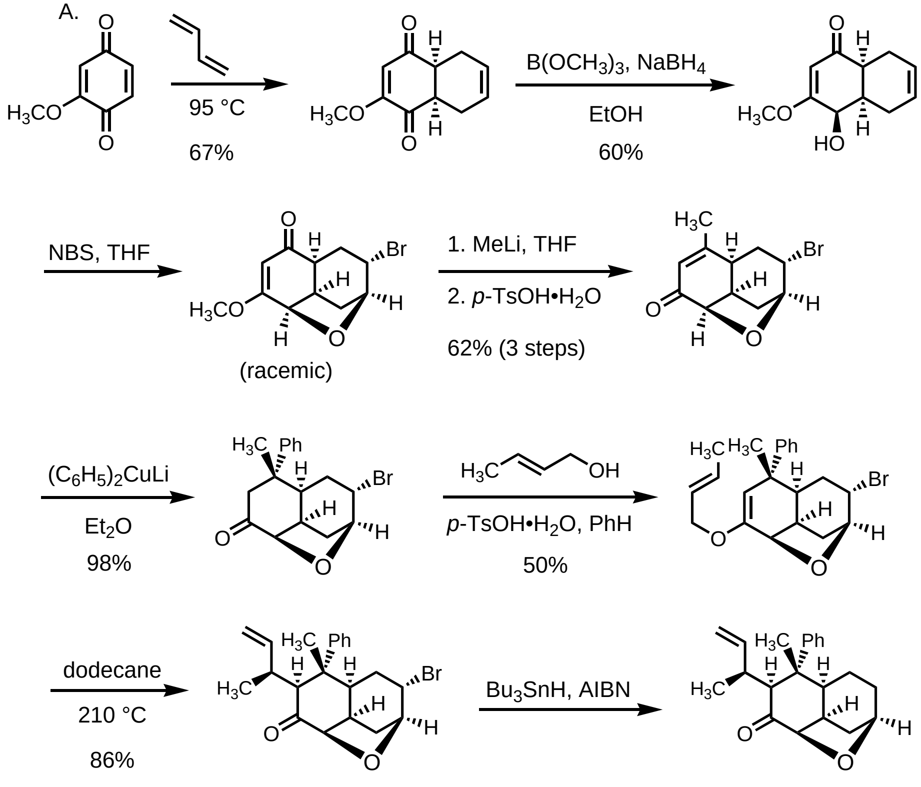
van Tamelen, E. E.; Milne, G. M.; Suffness, M. I.; Chauvin, M. C. R.; Anderson, R. J.; Achini, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 7202–7204.

Alternatives for the synthesis of **3A** from **3B**:



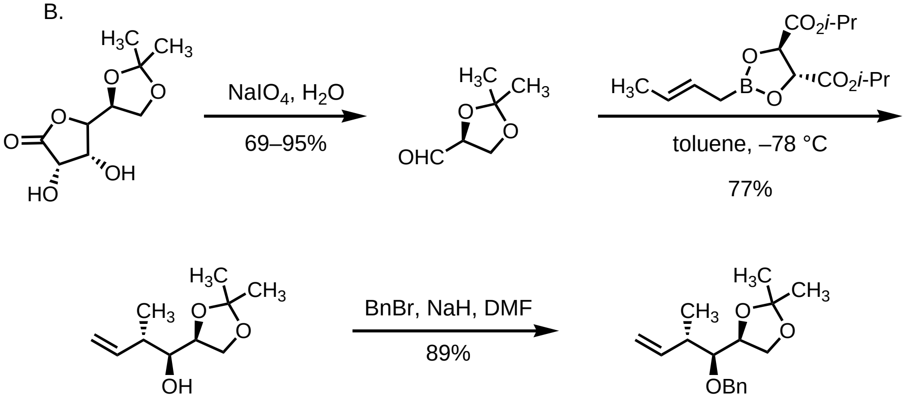
4. Develop practical synthetic routes to the following molecules.

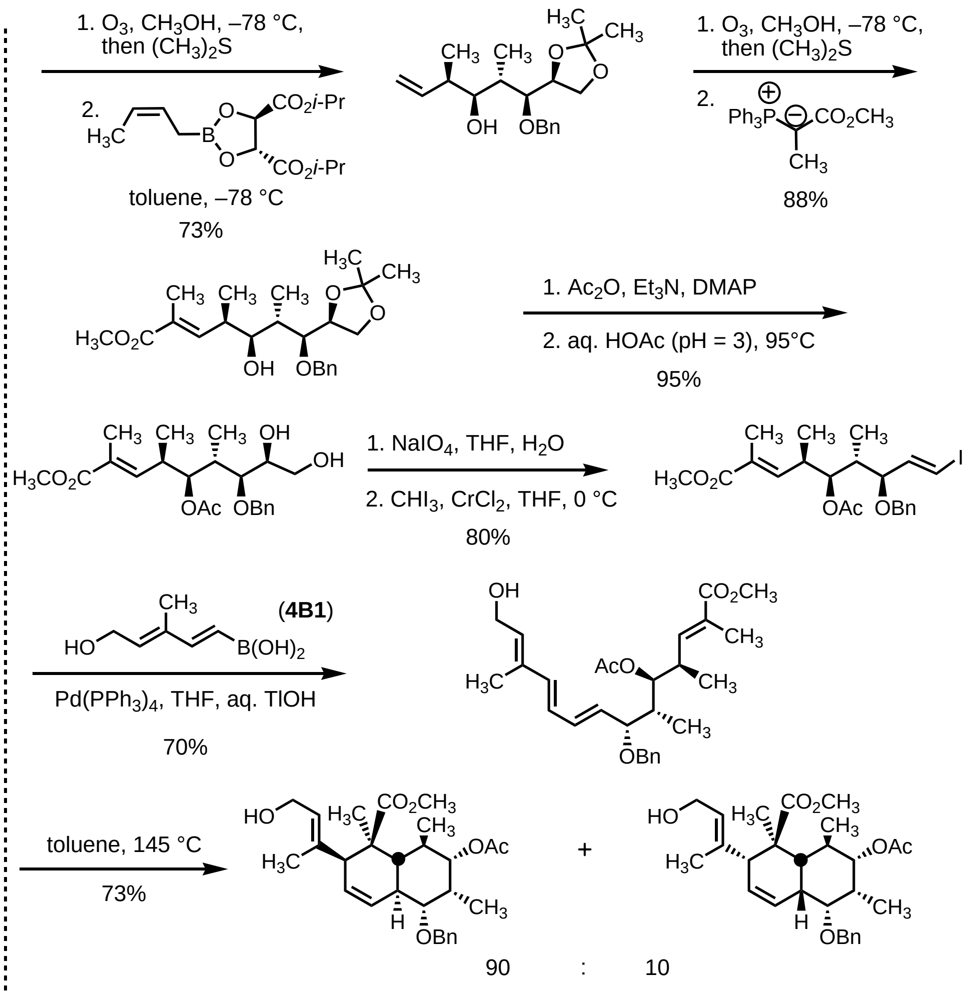
A.



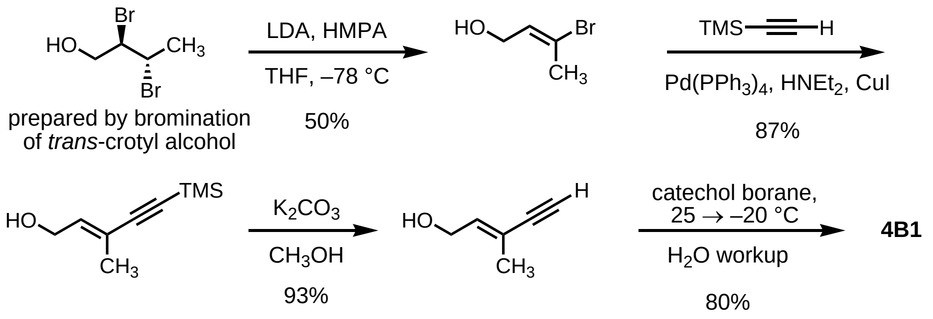
Pratt, D. V.; Hopkins, P. B. *J. Org. Chem.* **1988**, *53*, 5885-5894.

B.





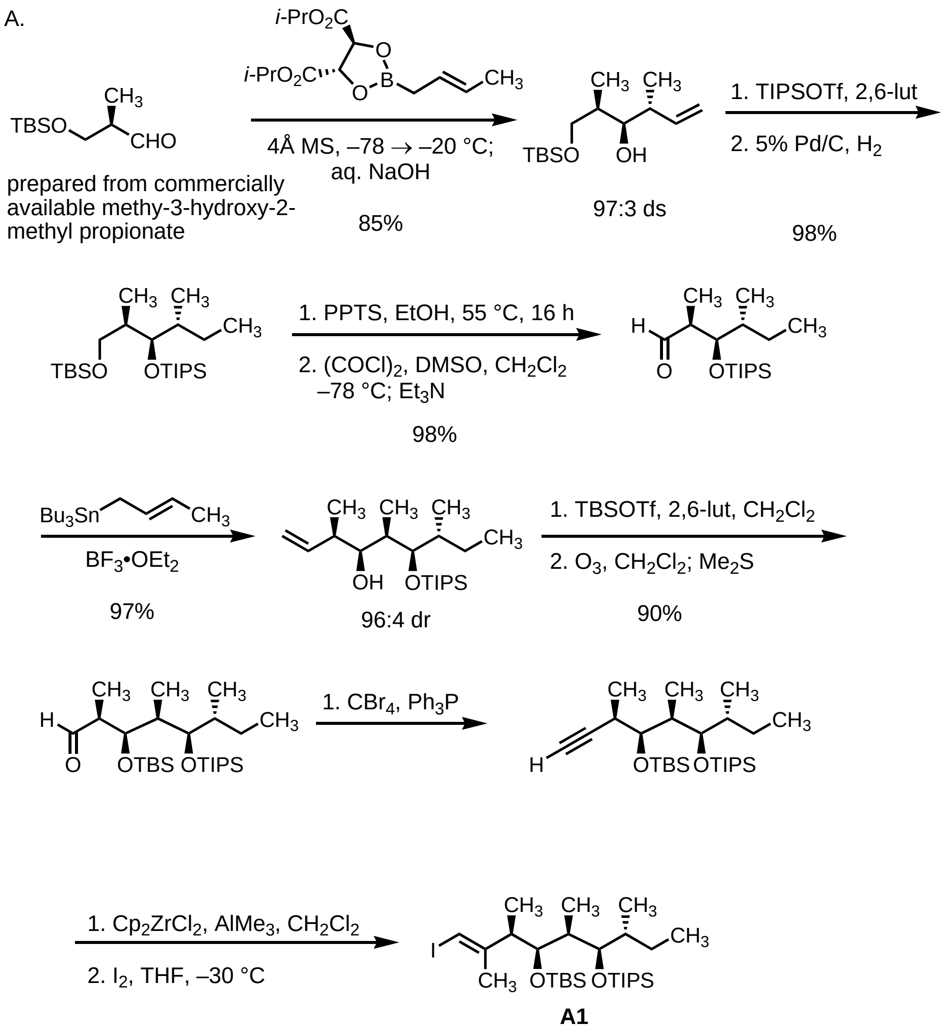
Preparation of **4B1**:



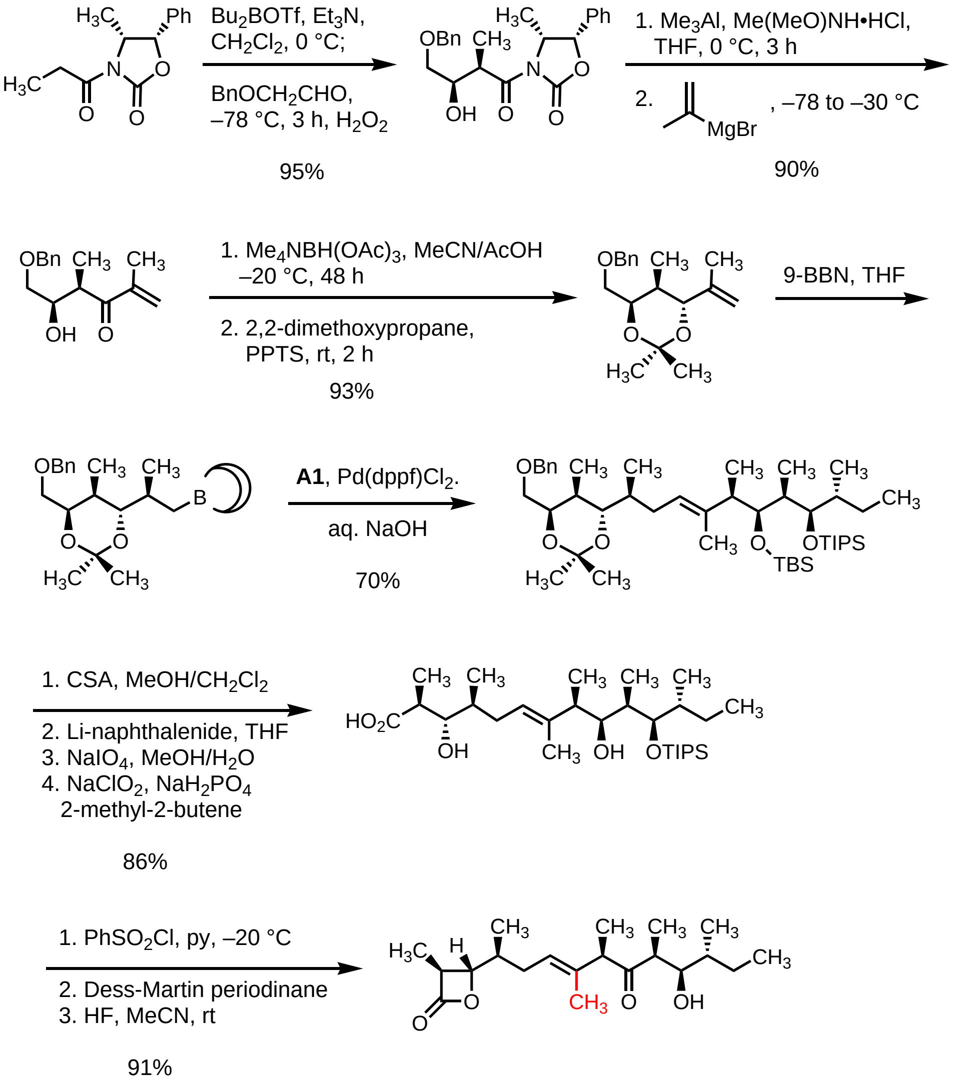
Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2268–2278.

Due: Wednesday, November 7th, 2007.
Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules. Present only your best route, in the forward direction.

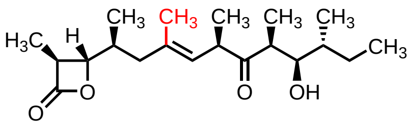
A.



prepared from commercially available methy-3-hydroxy-2-methyl propionate

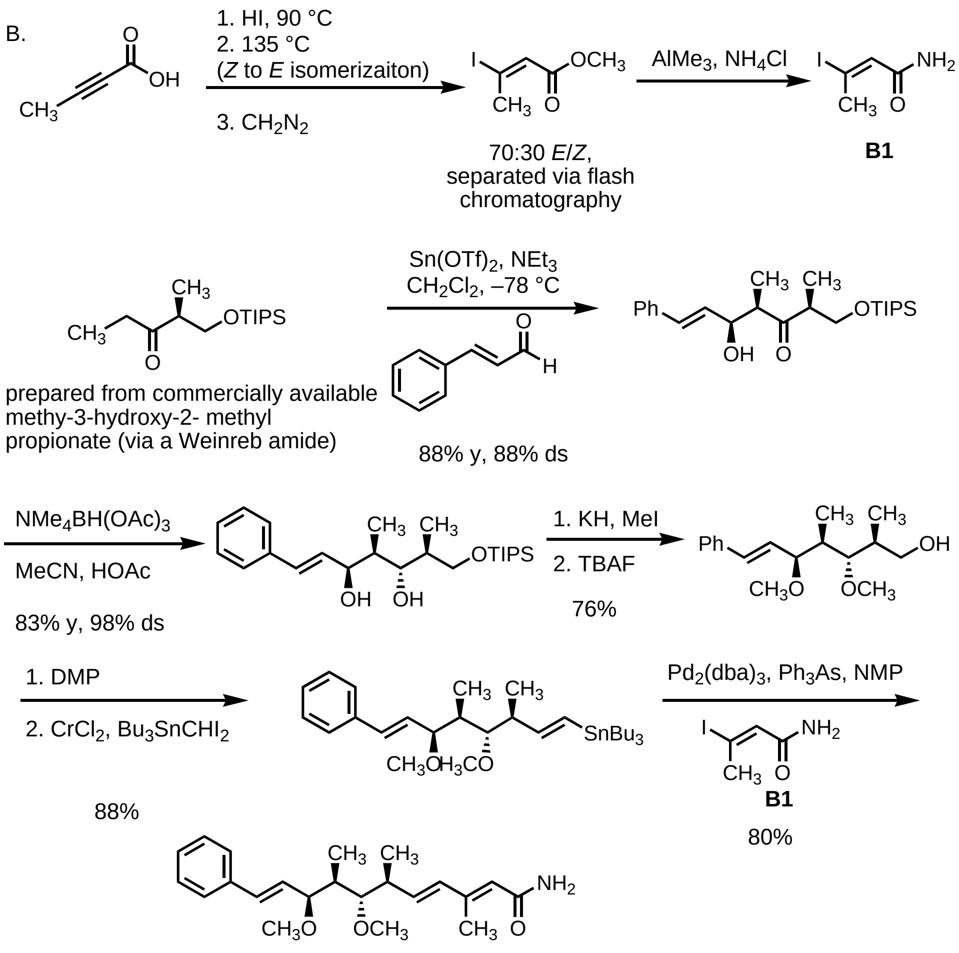


Adapted from the synthesis of (–)-Ebelactone A: Mandal, A. K. *Org. Lett*, **2002**, *4*, 2043-2045.



(–)-Ebelactone A

B.

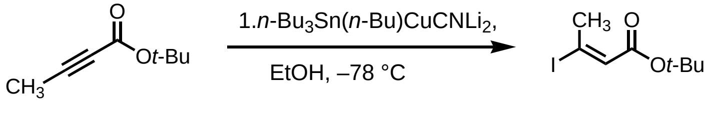


(+)-Crocacin C

Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *4*, 3365-3367.

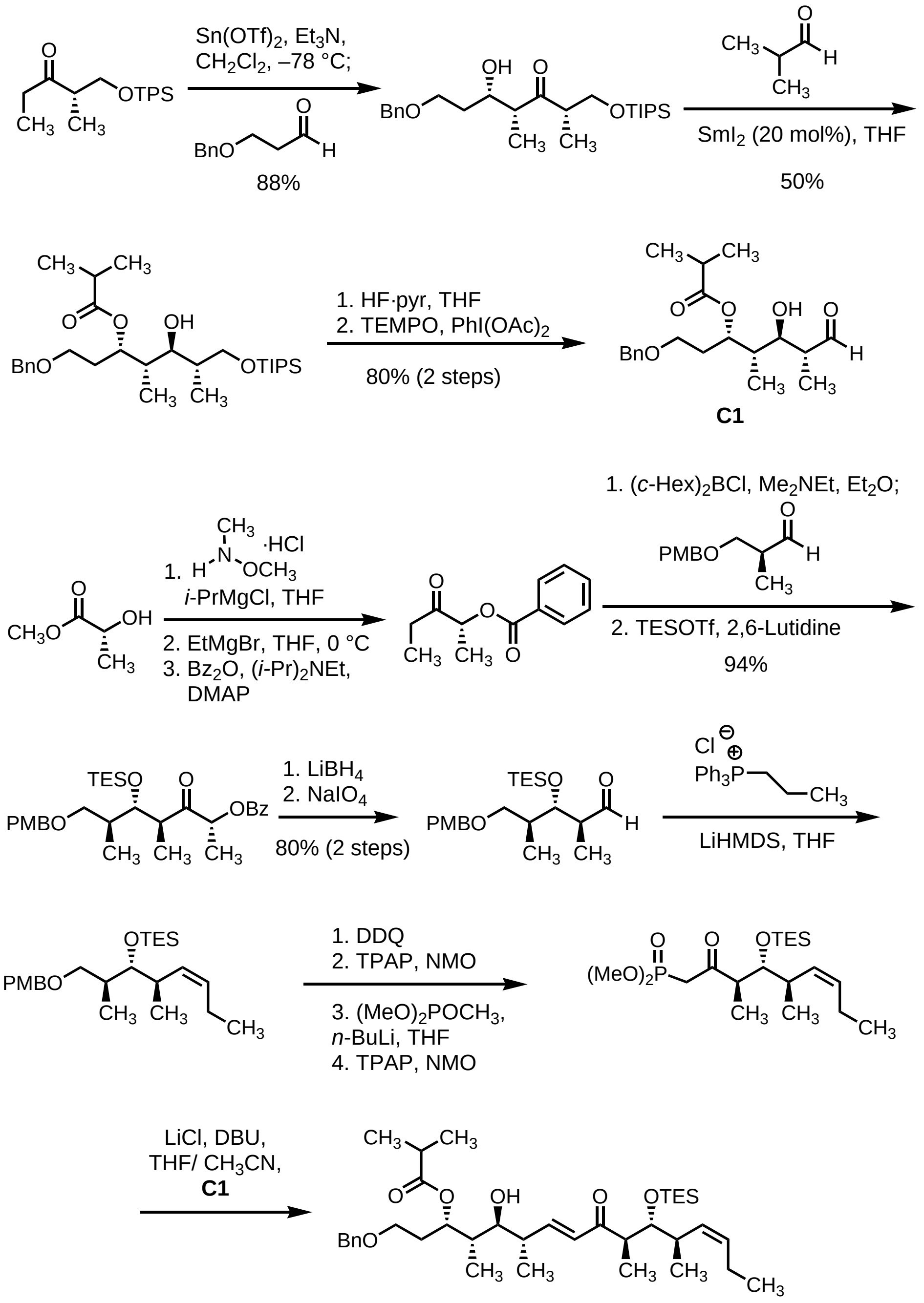
(also see Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2001**, *4*, 3951-3954.)

Consider the following preparation of a compound similar to **B1**:



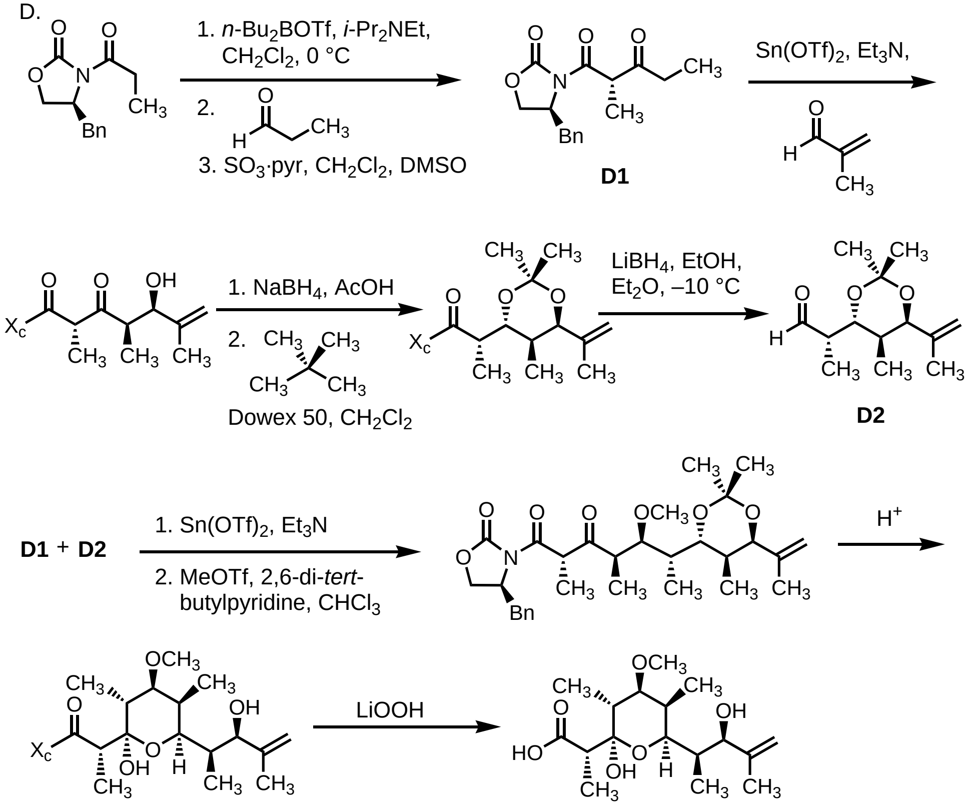
Otaka, A.; Mitsuyama, E.; Kinoshita, T.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2000**, *65*, 4888-4899.

C.



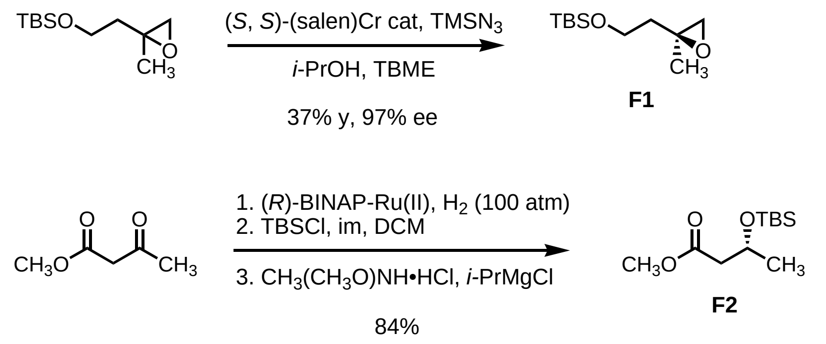
Adapted from:
Paterson, I.; Blakey, S. B.; Cowden, C. J. *Tetrahedron Lett*. **2002**, *43*. 6005-6008.

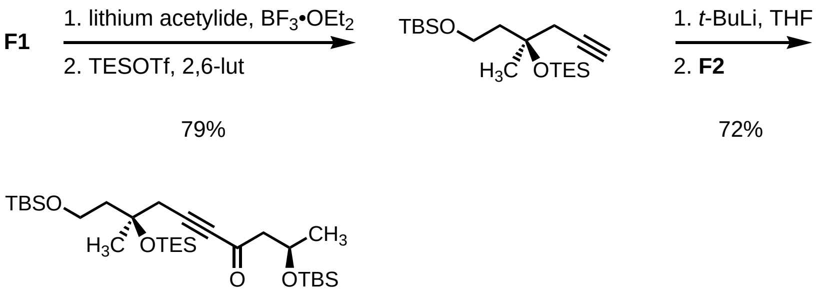
D.


1. n-Bu_2BOTf, i-Pr_2NEt, CH_2Cl_2, 0 °C
2. H, CH_3
3. SO_3·pyr, CH_2Cl_2, DMSO
Bn
D1
$Sn(OTf)_2$, Et_3N,
X_c
1. $NaBH_4$, AcOH
2. Dowex 50, CH_2Cl_2
$LiBH_4$, EtOH, Et_2O, –10 °C
D2
D1 + **D2**
1. $Sn(OTf)_2$, Et_3N
2. MeOTf, 2,6-di-*tert*-butylpyridine, $CHCl_3$
H^+
OCH_3
LiOOH
HO

Adapted from:
Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448–3467.

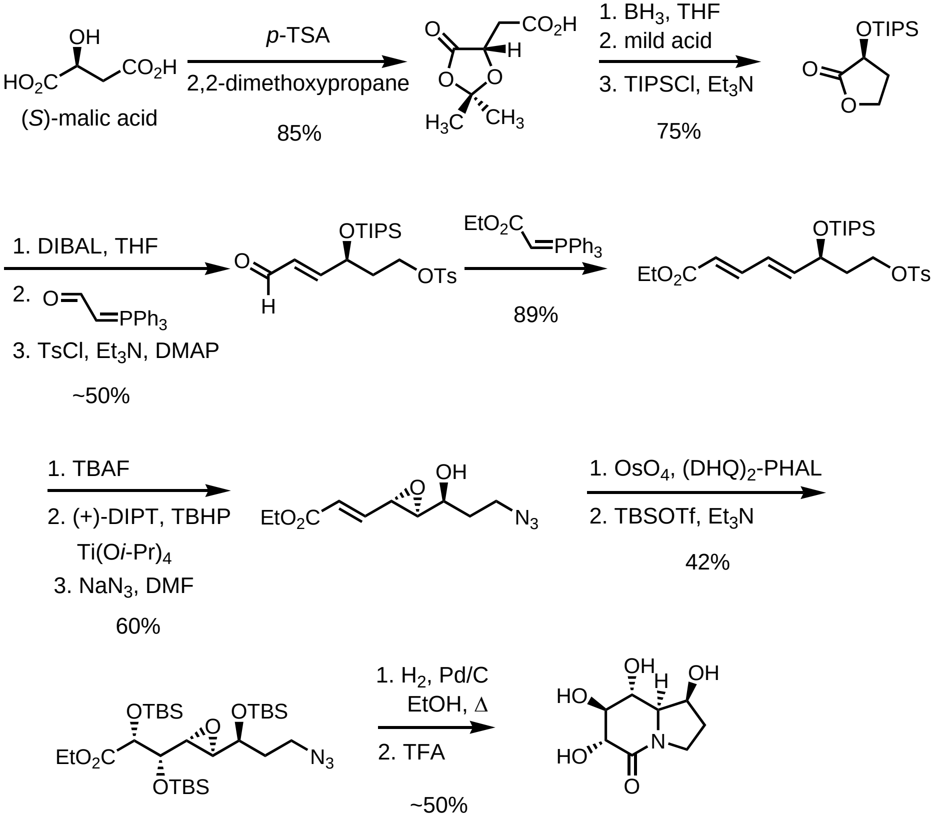
E.


TBSO
(S, S)-(salen)Cr cat, $TMSN_3$
i-PrOH, TBME
37% y, 97% ee
F1
1. (R)-BINAP-Ru(II), H_2 (100 atm)
2. TBSCl, im, DCM
3. $CH_3(CH_3O)NH$•HCl, i-PrMgCl
84%
OTBS
F2



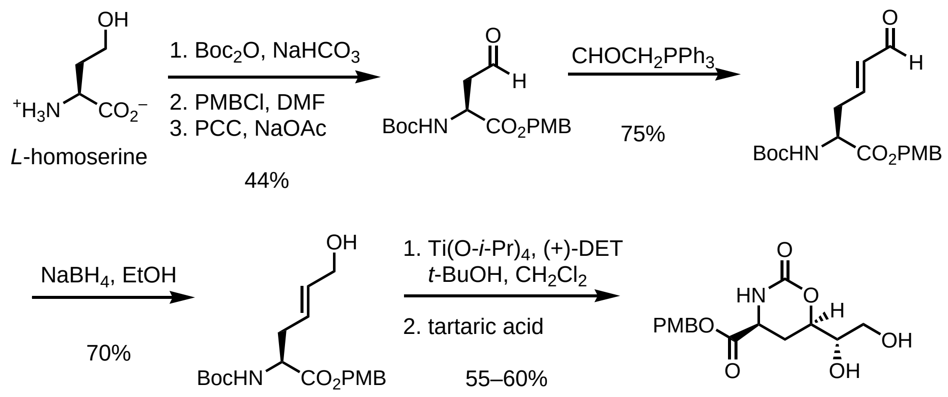
Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624-9635.

F.



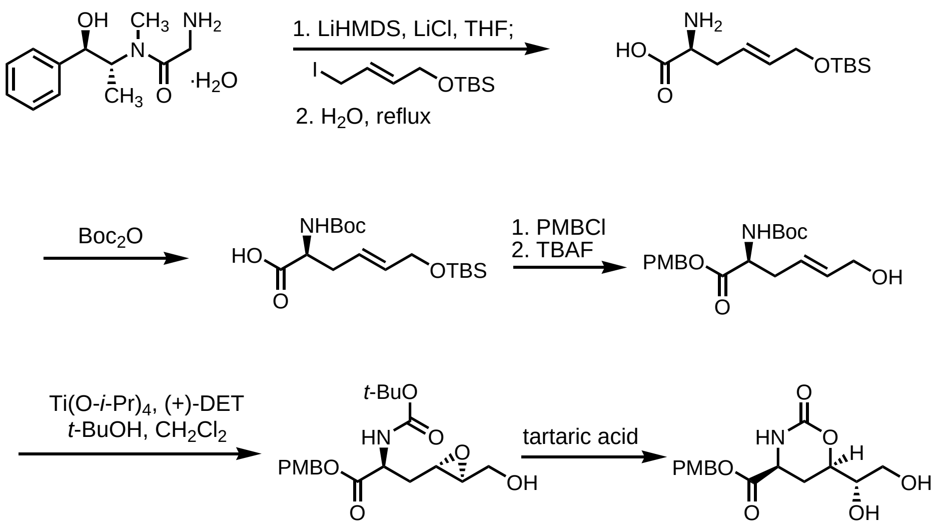
Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096-7099.

G.

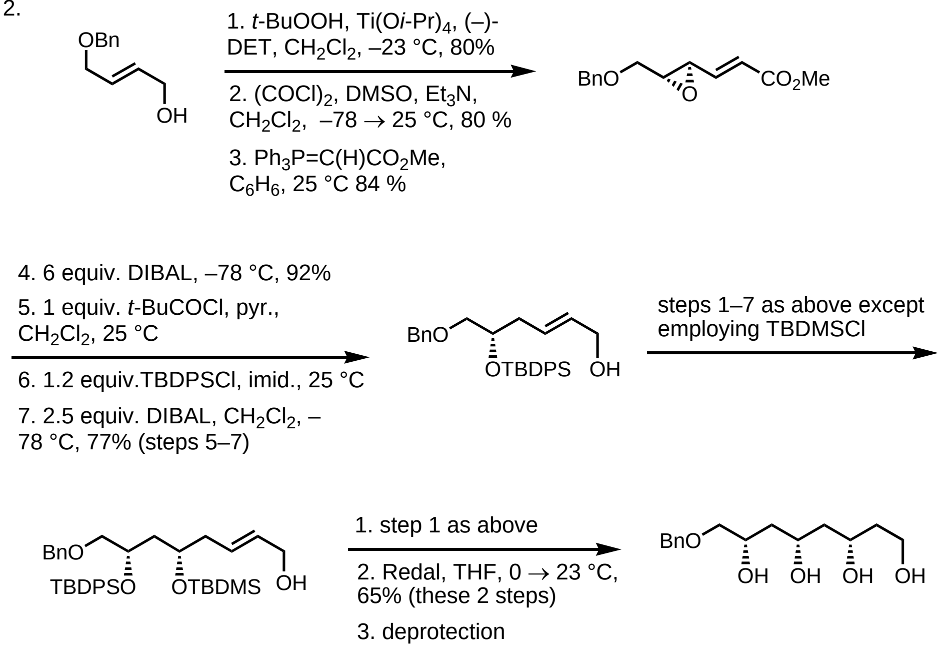


Baldwin, J. E.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3605-3608.

An alternate route using pseudoephedrine glycinamide hydrate:



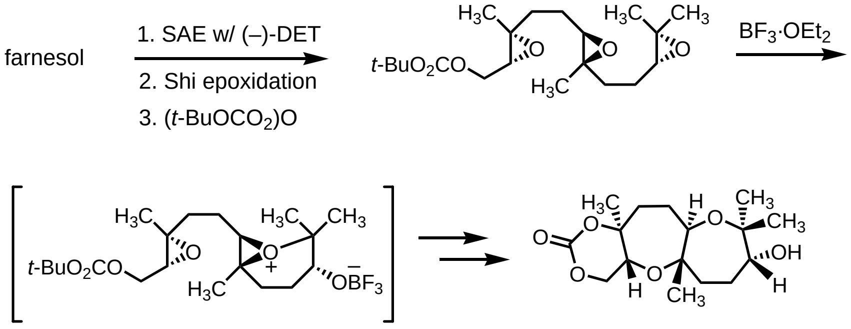
2.



1. t-BuOOH, Ti(Oi-Pr)$_4$, (–)-DET, CH$_2$Cl$_2$, –23 °C, 80%
2. (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, –78 → 25 °C, 80 %
3. Ph$_3$P=C(H)CO$_2$Me, C$_6$H$_6$, 25 °C 84 %
4. 6 equiv. DIBAL, –78 °C, 92%
5. 1 equiv. t-BuCOCl, pyr., CH$_2$Cl$_2$, 25 °C
6. 1.2 equiv.TBDPSCl, imid., 25 °C
7. 2.5 equiv. DIBAL, CH$_2$Cl$_2$, –78 °C, 77% (steps 5–7)
steps 1–7 as above except employing TBDMSCl
1. step 1 as above
2. Redal, THF, 0 → 23 °C, 65% (these 2 steps)
3. deprotection

Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292-1293.

3.



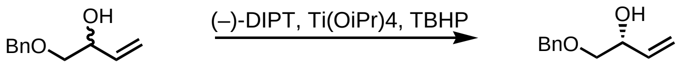
Regiochemistry of epoxide opening is dictated by the buildup of positive charge at the more substituted carbon. Please note that the cascade can proceed starting as shown or starting with BF$_3$ complexation at the other epoxide.

McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917-2919.

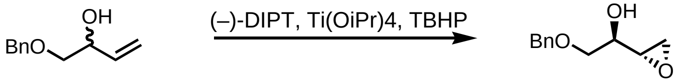
Due: Monday, November 26, 2007

1. Provide enantioselective routes to the targets shown, starting from one of the precursors provided.

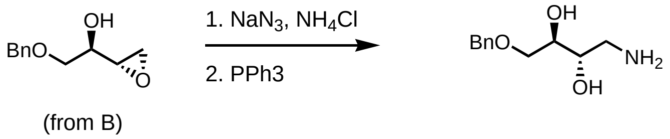
A.



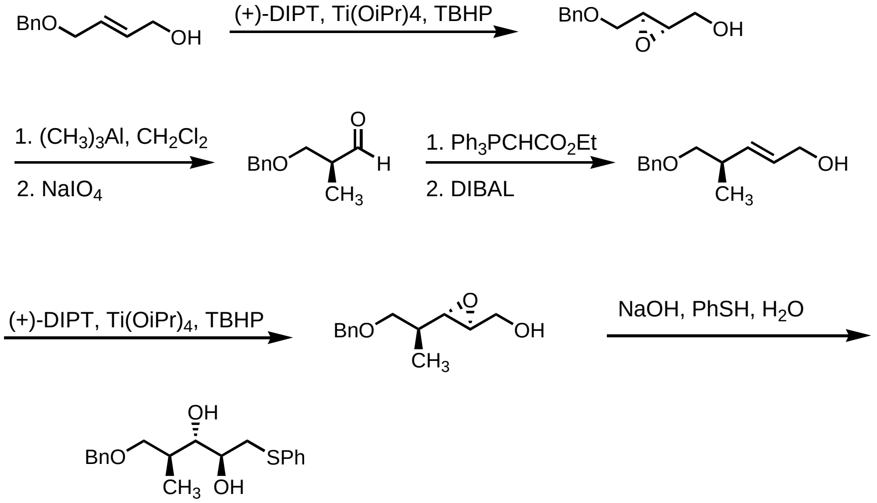
B.



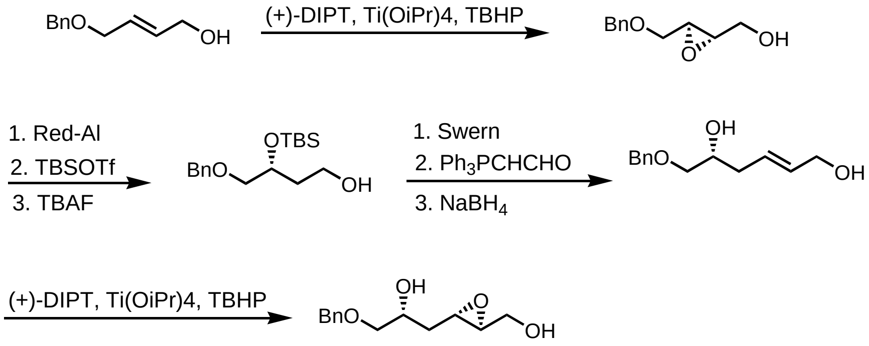
C.



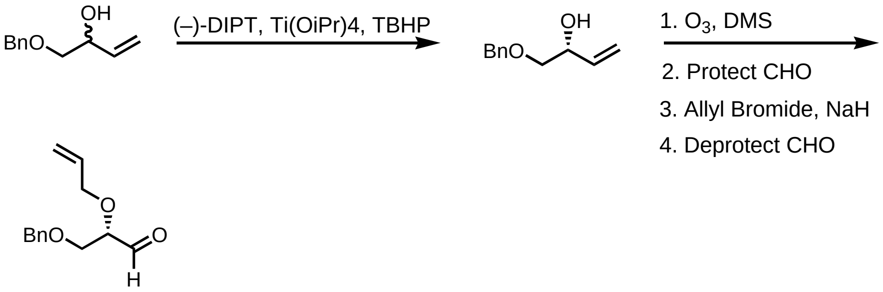
D.

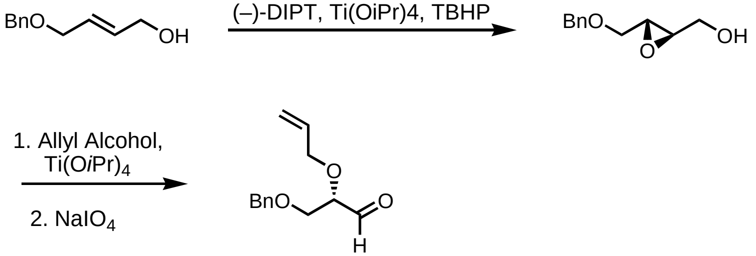


E.

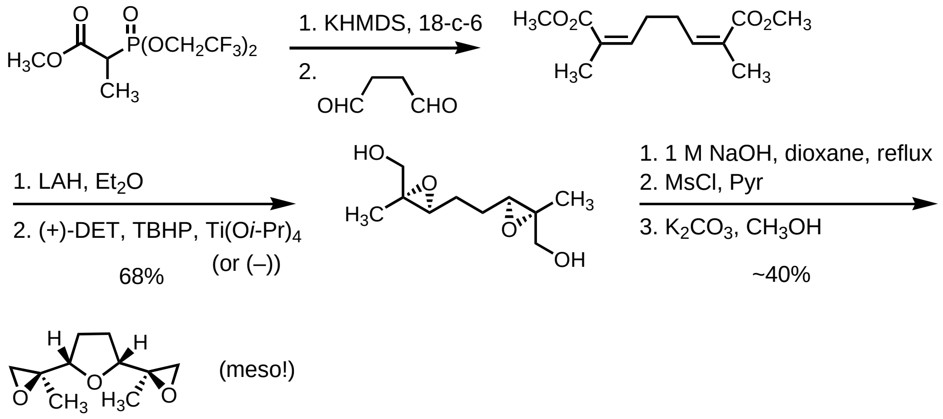


F.





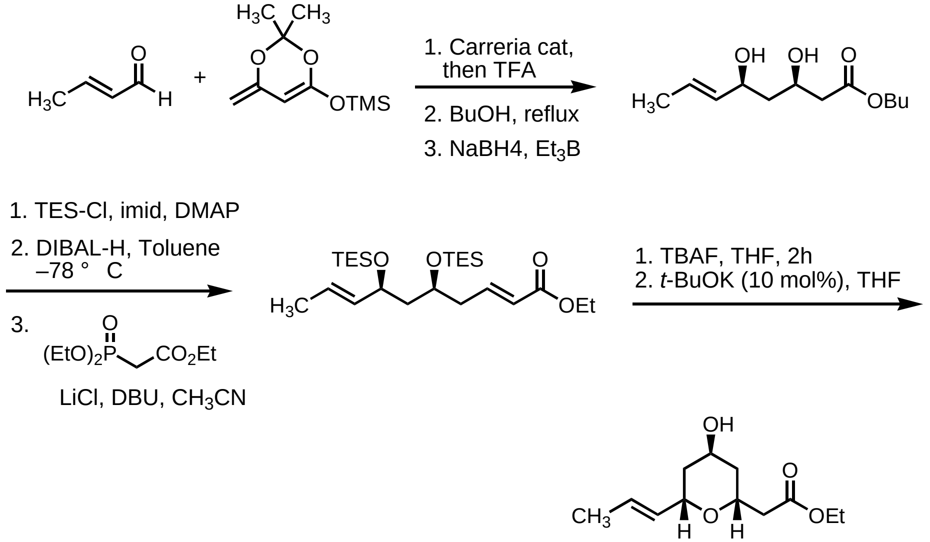
2. Provide an enantioselective route to the target shown from the precursor provided.



Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **2000**, *122*, 7124-7125.

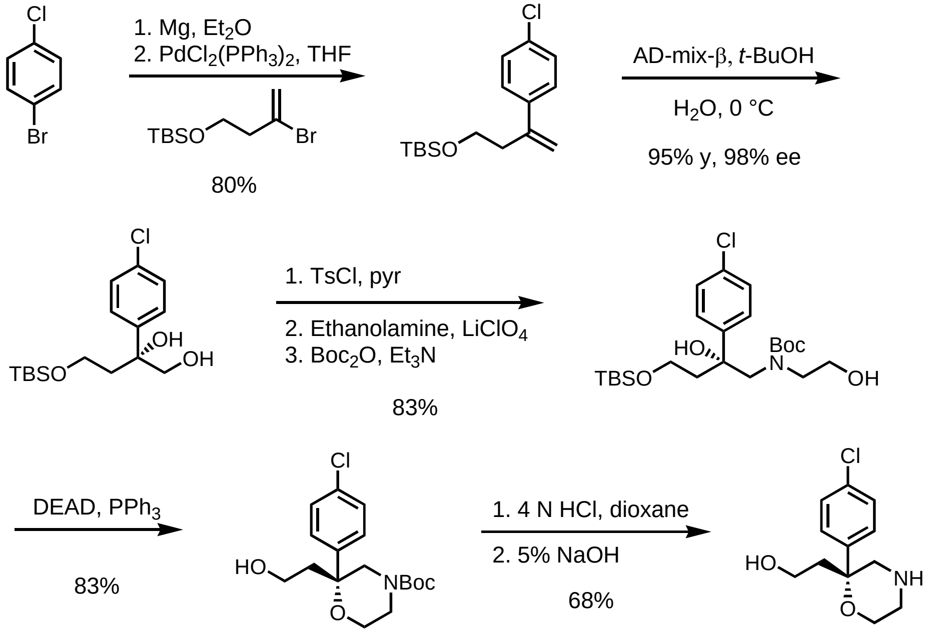
3. Provide enantioselective routes to the targets shown from commercially available starting materials.

A.



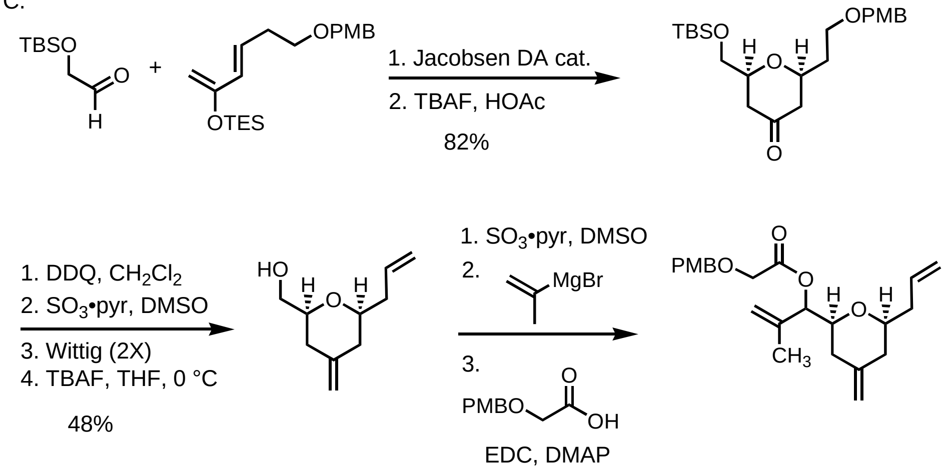
Fettes, A. Carreira, E. M.; *Angew. Chem. Int. Ed. Eng.*, **2002**, *41*, 4098-4101.

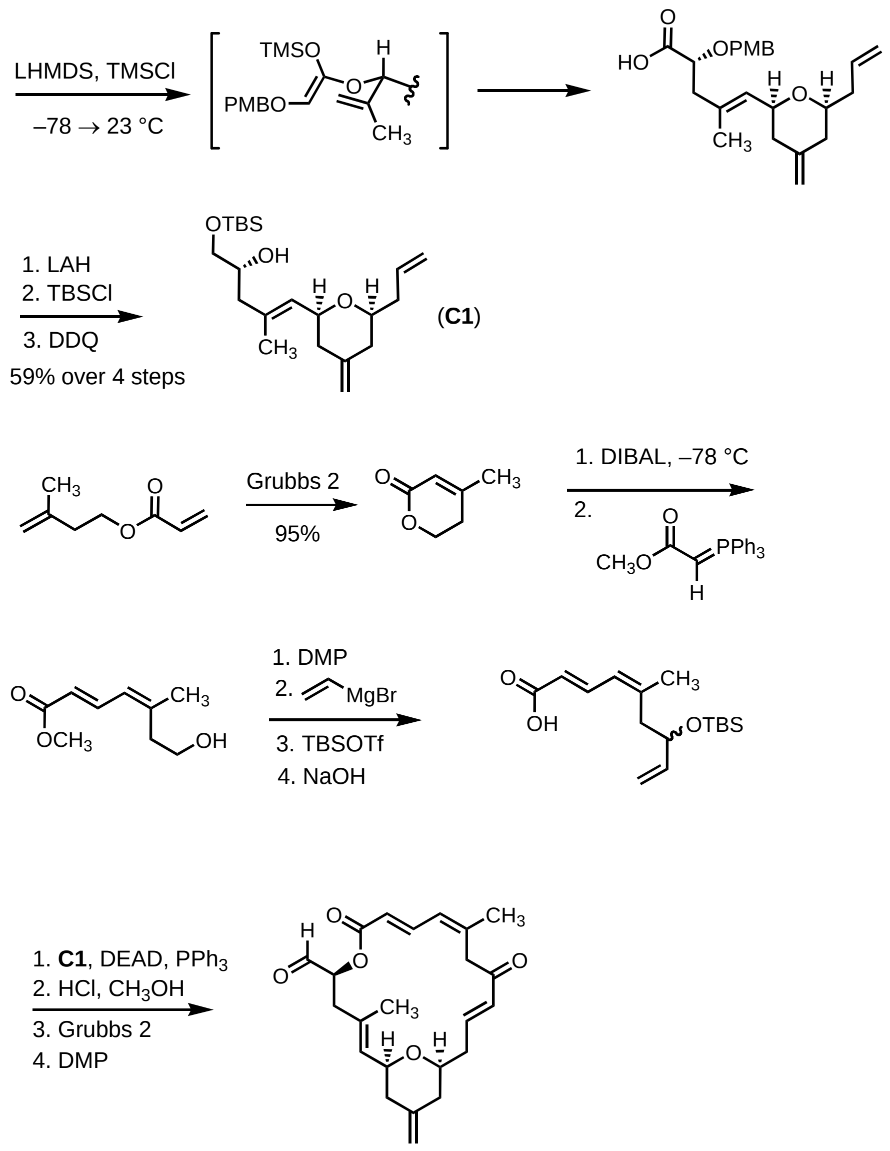
B.



Nishi, T.; Ishibashi, K.; Nakajima, K.; Iio, Y.; Fukazawa, T. *Tetrahedron Asymm.* **1998**, *9*, 3251-3262

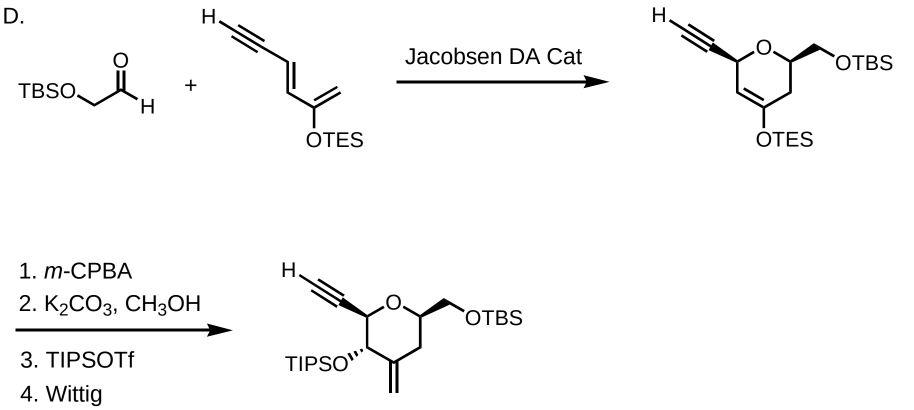
C.





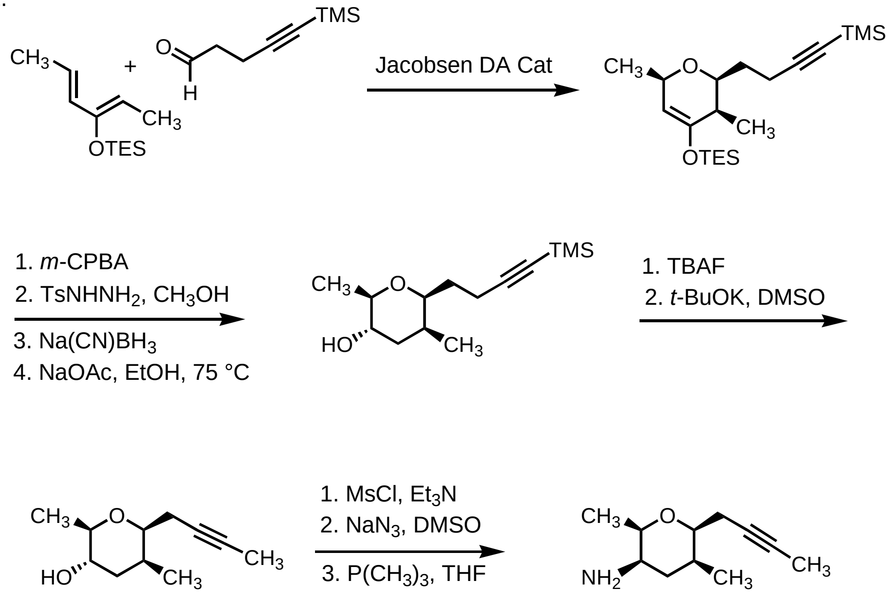
Louis, I.; Hungerford, N. L.; Humphries, E. J.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 1117.

D.



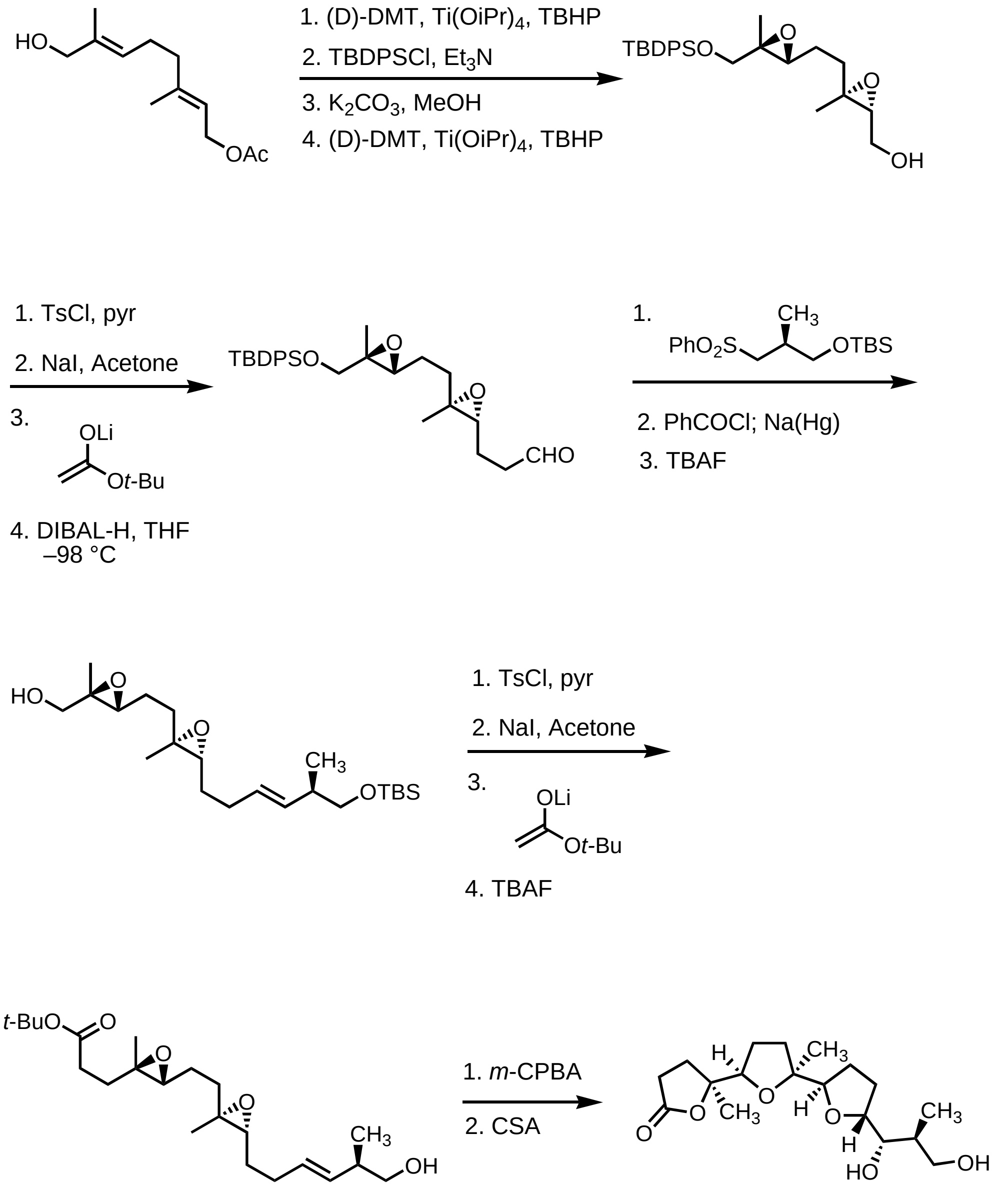
Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974-9983.

E.



Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974-9983.

F.

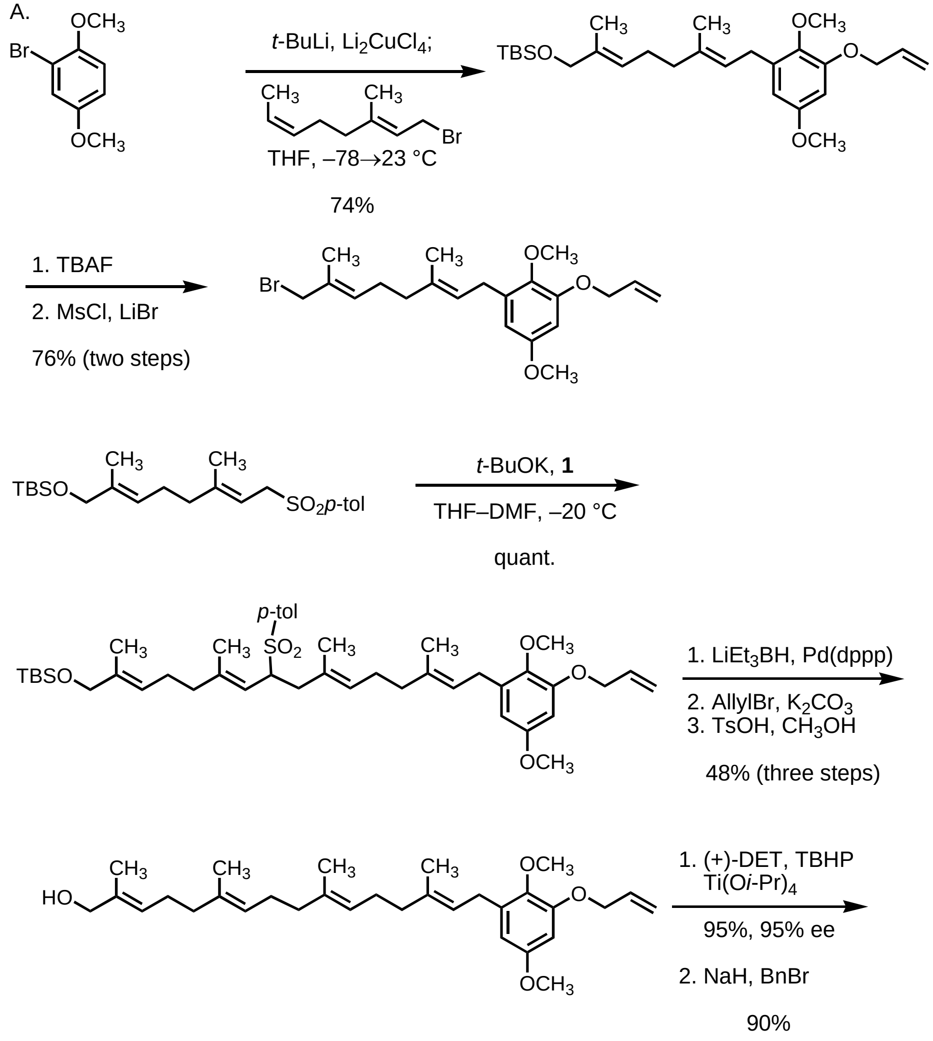


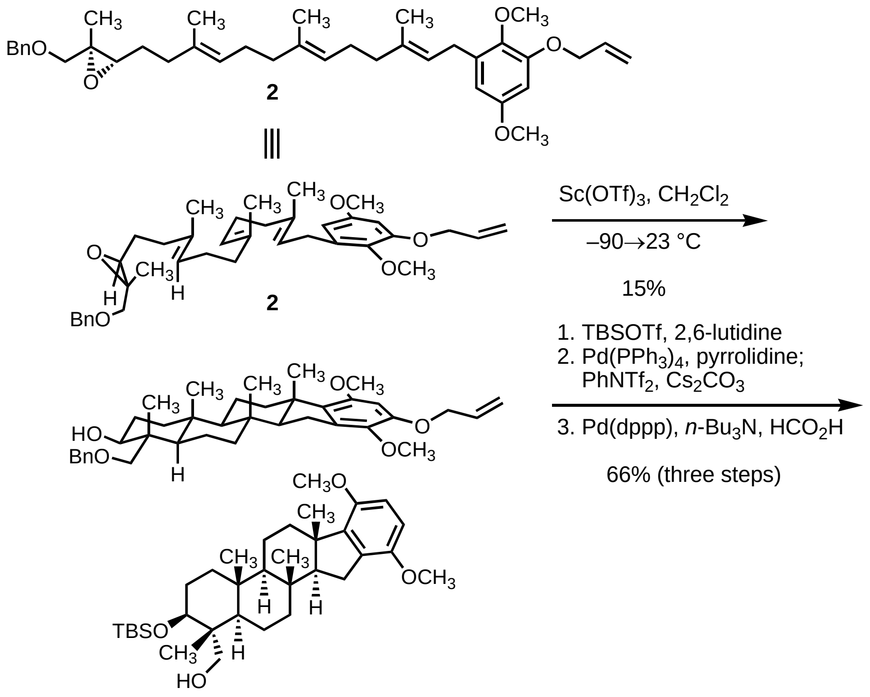
Paterson, I.; Boddy, I.; Mason, I. *Tetrahedron Lett.* **1987**, *28*, 5205.

Due: Wednesday, December 5, 2007

1. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules from the indicated starting materials. Present only your best route, in the forward direction.

A.

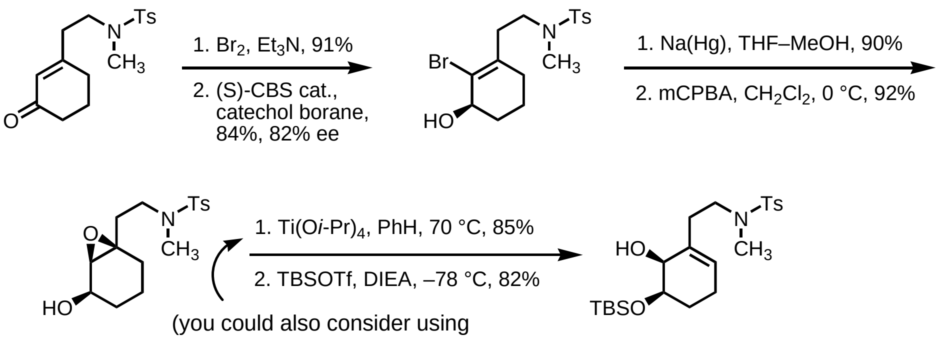



BnO
CH_3 CH_3 CH_3 CH_3 OCH_3
O
O
OCH_3
2
|||
CH_3 CH_3 CH_3 OCH_3
O
CH_3
H
H
BnO
O
OCH_3
2
$Sc(OTf)_3$, CH_2Cl_2
–90→23 °C
15%
CH_3 CH_3 CH_3 CH_3 OCH_3
HO
BnO
H
O
OCH_3
1. TBSOTf, 2,6-lutidine
2. $Pd(PPh_3)_4$, pyrrolidine; $PhNTf_2$, Cs_2CO_3
3. Pd(dppp), n-Bu_3N, HCO_2H
66% (three steps)
CH_3O
CH_3
CH_3 CH_3
H
H
OCH_3
TBSO
CH_3
H
HO

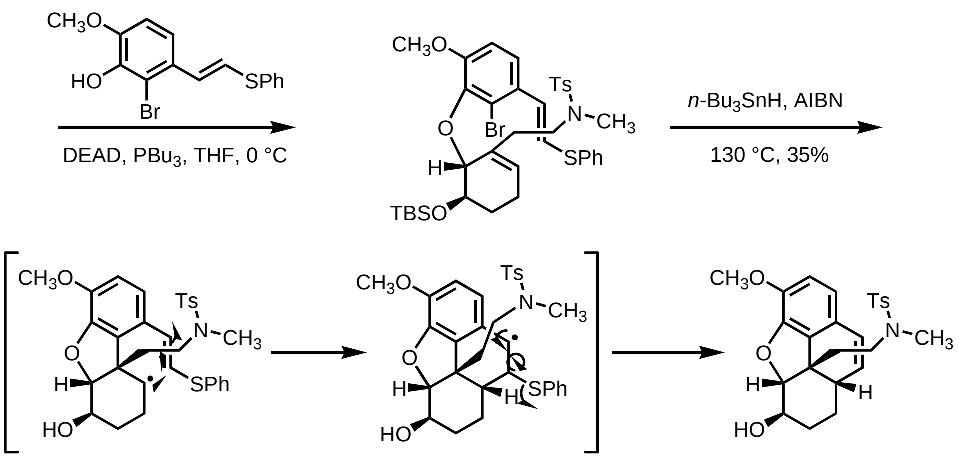
Note: The polyene cyclization was unsuccessful without additional activation of the aryl ring (e.g., by installation of the *O*-allyl function found in **2**). As this could only be determined experimentally, solutions that do not incorporate this modification are acceptable.

Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206–12207.

B.

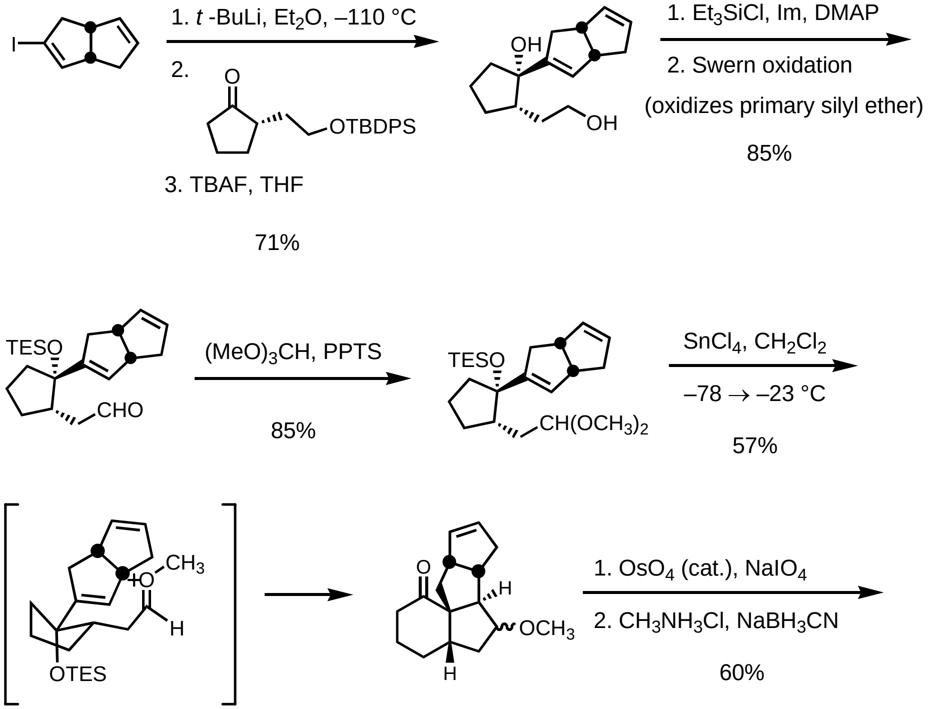

N
Ts
CH_3
O
1. Br_2, Et_3N, 91%
2. (S)-CBS cat., catechol borane, 84%, 82% ee
Br
HO
N
Ts
CH_3
1. Na(Hg), THF–MeOH, 90%
2. mCPBA, CH_2Cl_2, 0 °C, 92%
O
HO
N
Ts
CH_3
1. $Ti(Oi\text{-}Pr)_4$, PhH, 70 °C, 85%
2. TBSOTf, DIEA, –78 °C, 82%
HO
TBSO
N
Ts
CH_3

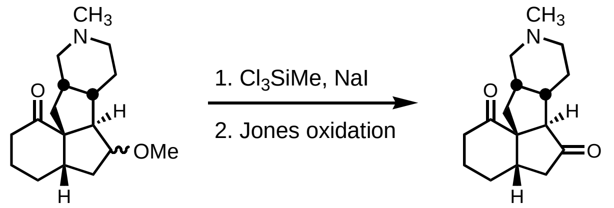
(you could also consider using $LiNEt_2$ for this transformation)



Parker, K, A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449-455.
Parker, K, A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.

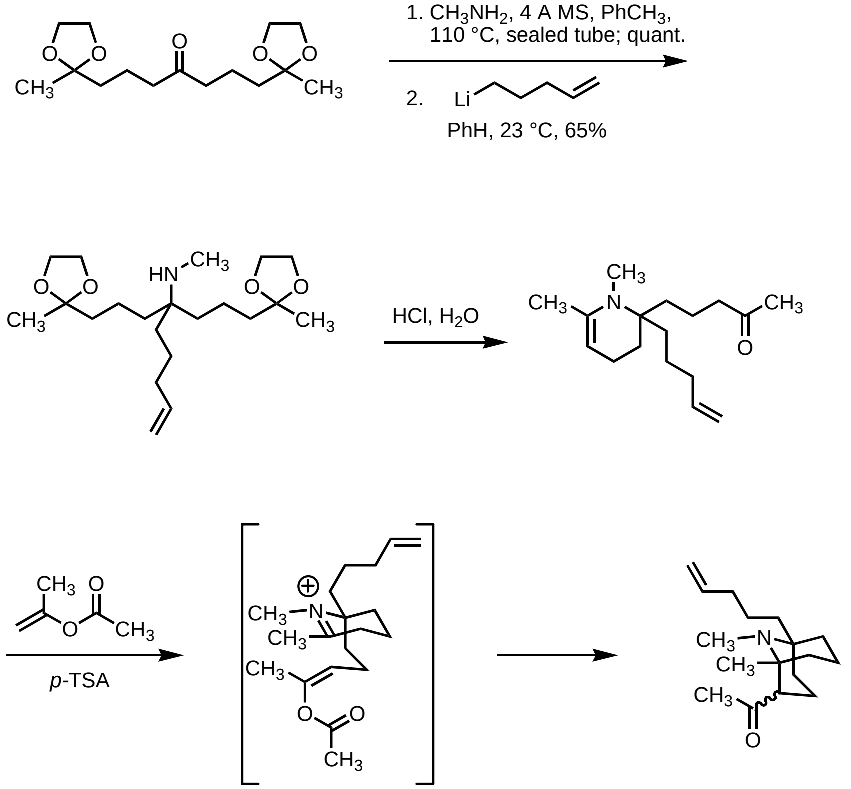
C.





Hirst, G. C.; Johnson, T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992–2993.

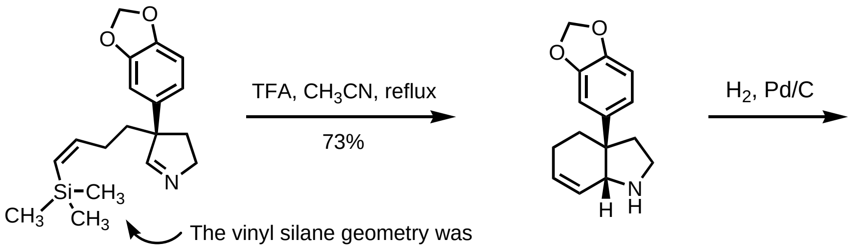
D.


1. CH$_3$NH$_2$, 4 A MS, PhCH$_3$,
110 °C, sealed tube; quant.
2.
PhH, 23 °C, 65%
HCl, H$_2$O
p-TSA

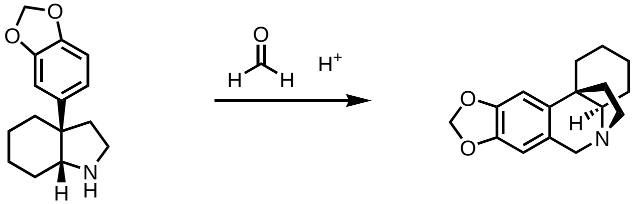
Corey, E. J. Balanson, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 6516–6517.

2. Develop a practical synthetic route to the following molecule from each of the indicated starting materials. Present only your best route, in the forward direction.

A.

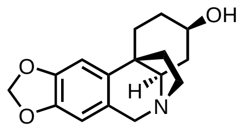


The vinyl silane geometry was critical; little product was observed using the *E*-vinyl silane.

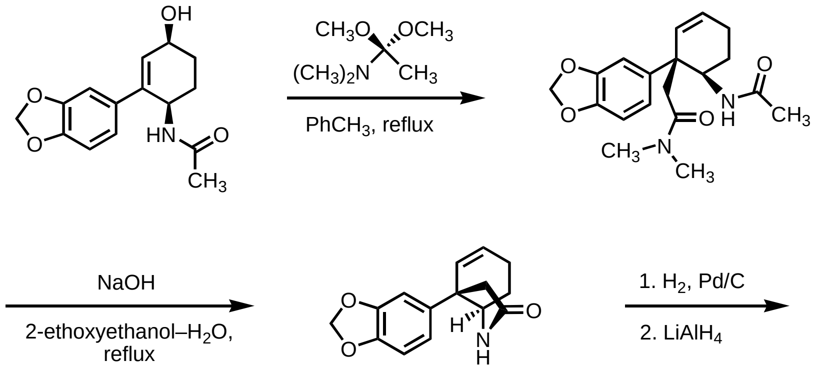


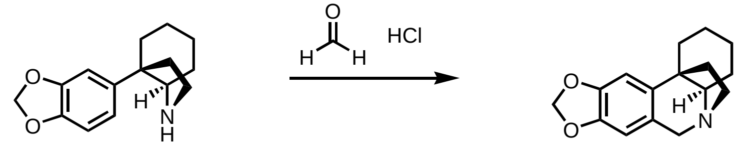
Adapted from: Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739–5742.

Their target:



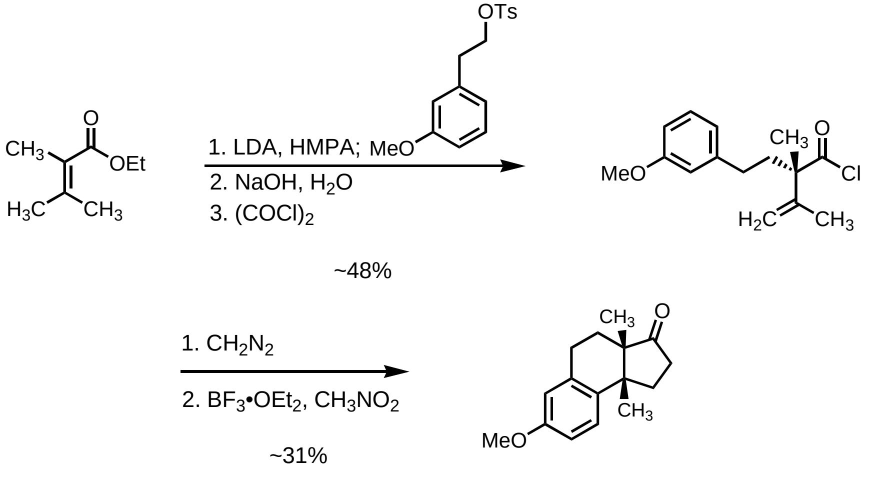
B.





Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670–3671.

3.

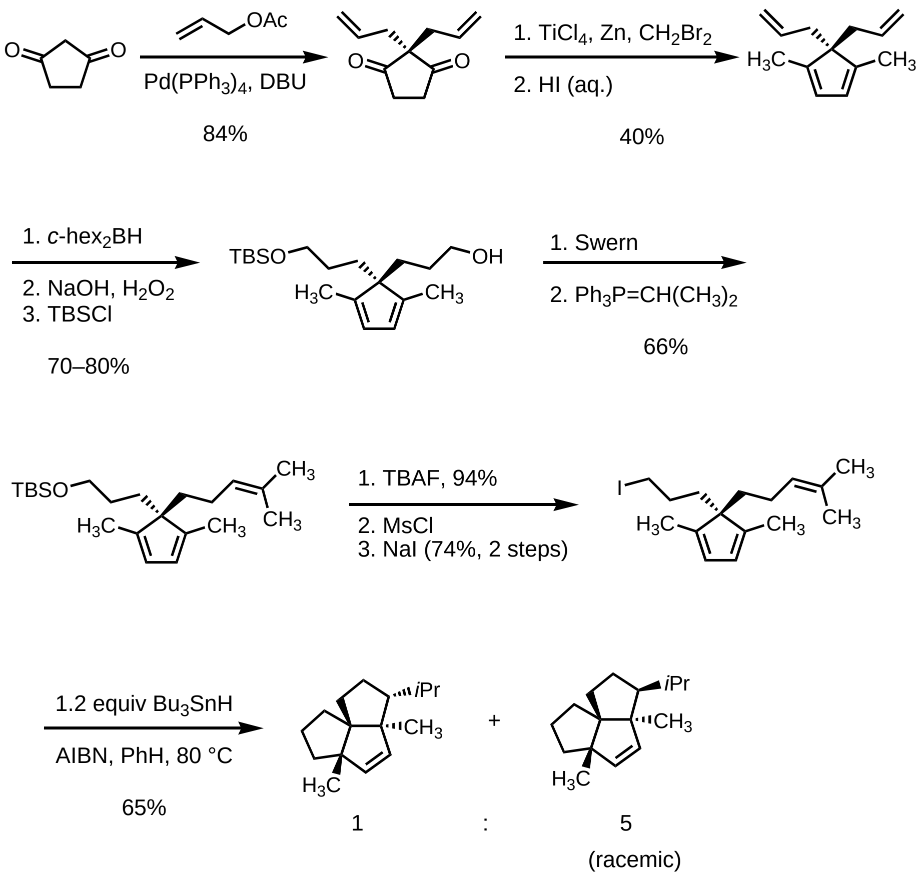


Smith, A.B., III; Dieter, R. K. *J. Org. Chem.* **1977**, *42*, 396–397.

Due: Wednesday, December 12, 2007.

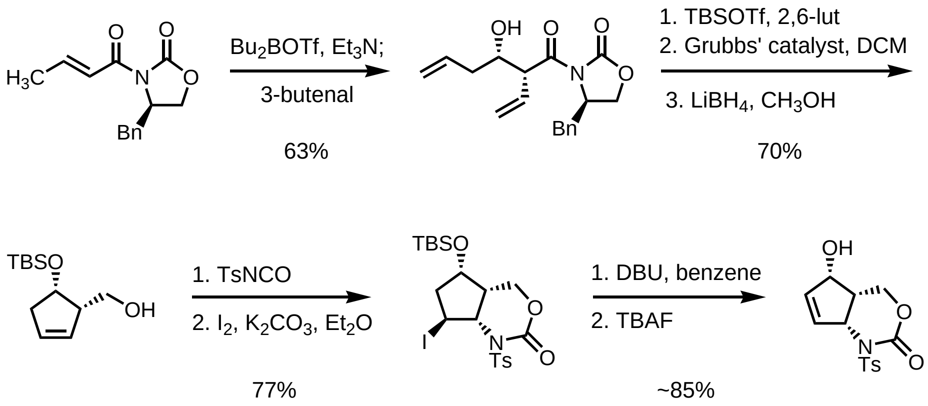
Develop practical asymmetric (unless otherwise noted) synthetic routes to the following molecules. Present only your best route, in the forward direction.

A.



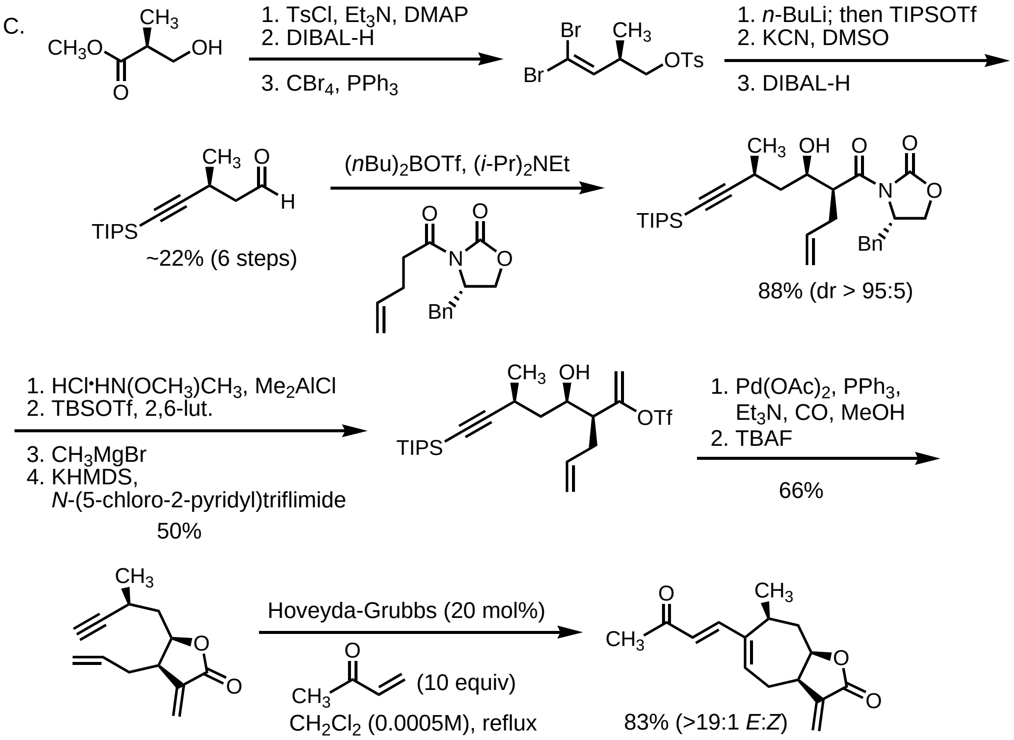
Schwartz, E. C.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272-9284.

B.



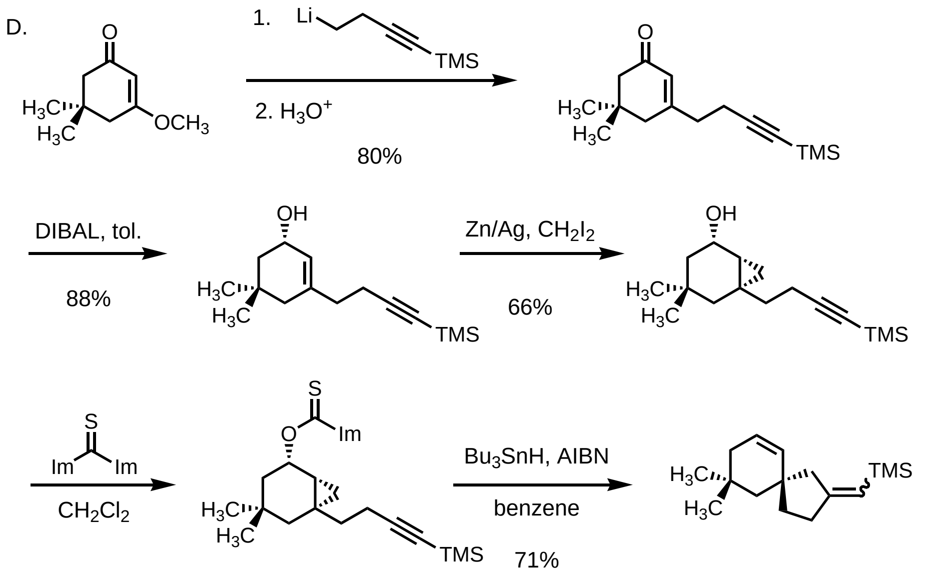
Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.* **2001**, *66*, 4012-4018.

C.



Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4621-4623.

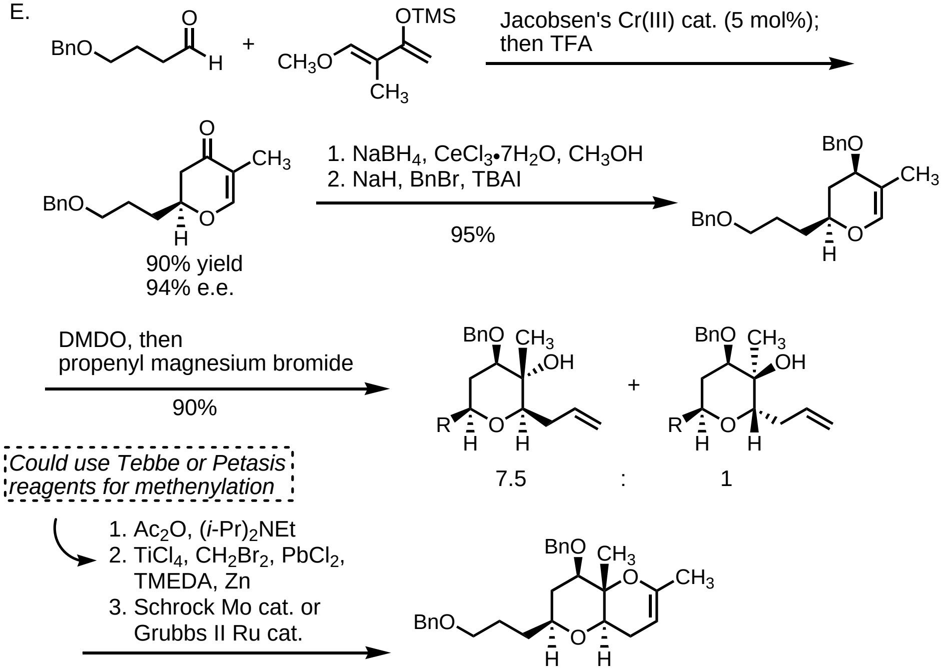
D.



For an asymmetric synthesis, consider employing a kinetic resolution of the allylic alcohol by one of the following methods: Shi epoxidation; SAE; or Charette asy. cyclopropanation.

Batey, R. A.; Harling, J. D.; Motherwell, W. B. *Tetrahedron*, **1992**, *48*, 8031-8052.

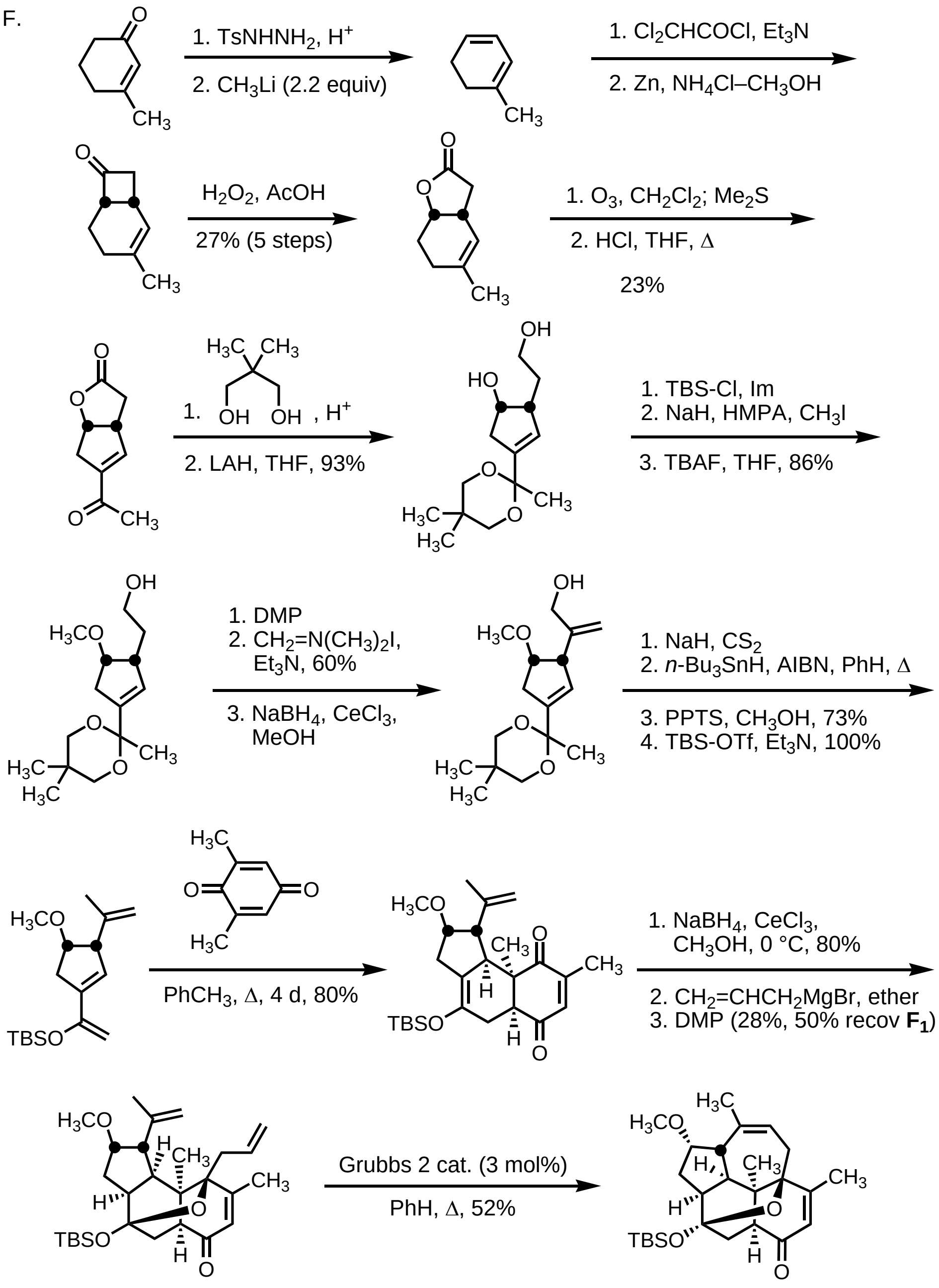
E.


Jacobsen's Cr(III) cat. (5 mol%); then TFA
90% yield
94% e.e.
1. $NaBH_4$, $CeCl_3$•$7H_2O$, CH_3OH
2. NaH, BnBr, TBAI
95%
DMDO, then
propenyl magnesium bromide
90%
7.5 : 1
1. Ac_2O, $(i\text{-}Pr)_2NEt$
2. $TiCl_4$, CH_2Br_2, $PbCl_2$, TMEDA, Zn
3. Schrock Mo cat. or Grubbs II Ru cat.
70-80%

Could use Tebbe or Petasis reagents for methenylation

Rainer, J. D. et al. *Chem. Eur. J.* **2006**, *12*, 1736-1746.

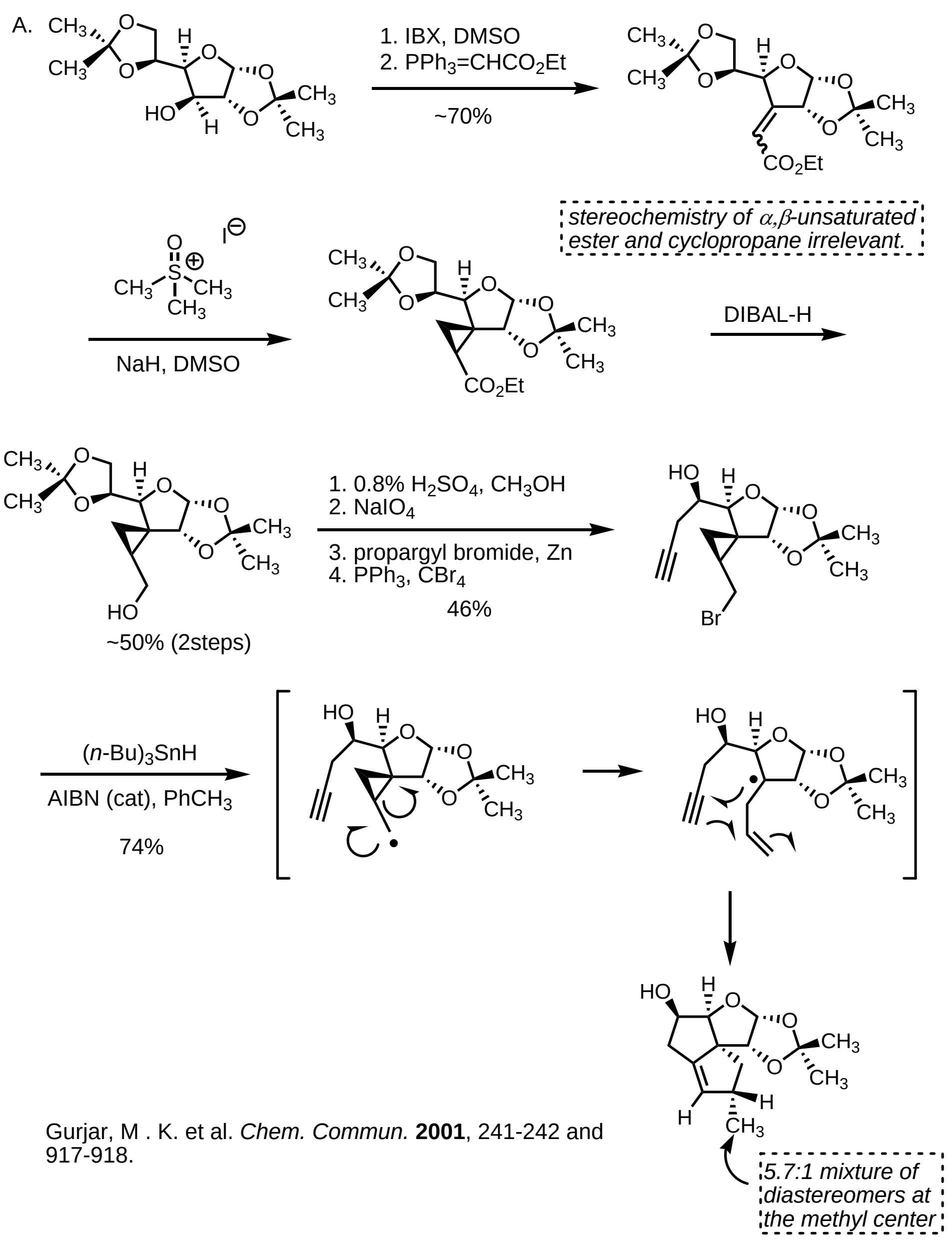
F.



Zhao, L.; Burnell, D. J. *Org. Lett*. **2006**, *8*, 155-157.

2. Develop practical asymmetric (unless otherwise noted) synthetic routes to the following materials from the indicated starting materials. Present only your best route, in the forward direction.

A.

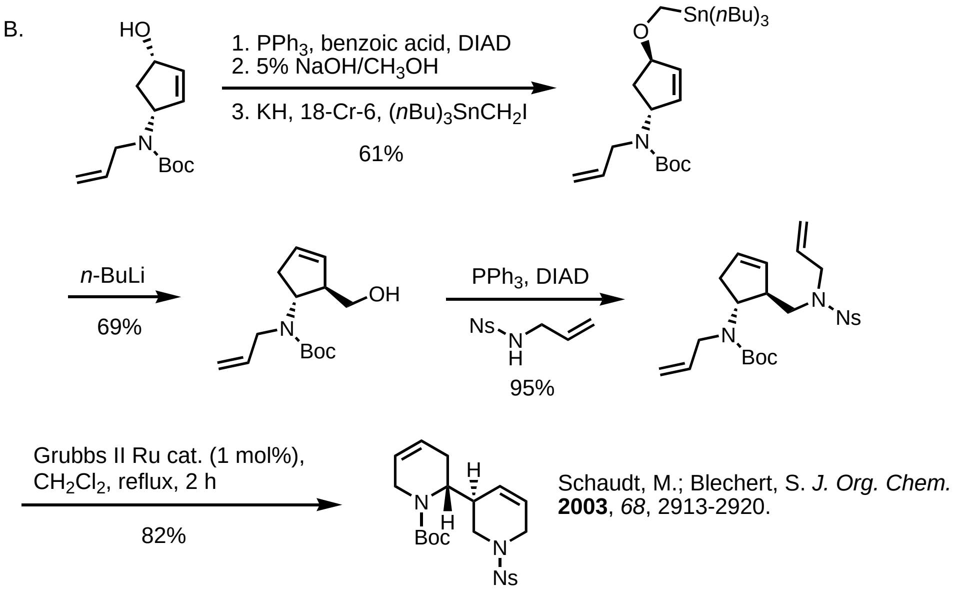


stereochemistry of α,β-unsaturated ester and cyclopropane irrelevant.

5.7:1 mixture of diastereomers at the methyl center

Gurjar, M . K. et al. *Chem. Commun.* **2001**, 241-242 and 917-918.

B.

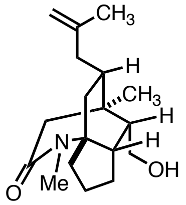


HO
N
Boc
1. PPh$_3$, benzoic acid, DIAD
2. 5% NaOH/CH$_3$OH
3. KH, 18-Cr-6, (nBu)$_3$SnCH$_2$I
61%
O
Sn(nBu)$_3$
n-BuLi
69%
OH
PPh$_3$, DIAD
Ns–NH
95%
Ns
Grubbs II Ru cat. (1 mol%),
CH$_2$Cl$_2$, reflux, 2 h
82%
H

Schaudt, M.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 2913-2920.

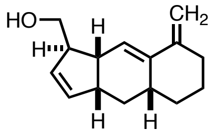
Provide concise synthetic routes to **two** of the three targets shown below. Each molecule is worth 50 points. Use of the chiral pool intermediates, their enantiomers, and the chiral auxiliaries presented in lecture is permitted. If you work on all three molecules, be sure to indicate which two are to be graded and present only one solution per problem. Present the routes in the forward direction in the blue books. Make sure to write your name on every blue book you submit for grading. Provide clear structural drawings and denote all reagents that you propose to use. The exam is closed book, and closed notes. Partial credit is given, and can be substantial, but only if a solution or partial solution appears. In other words, something is better than nothing. *Note:* Illegible answers will receive no credit.

A



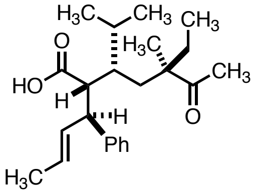
racemic

B

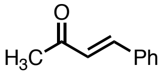


single enantiomer

C



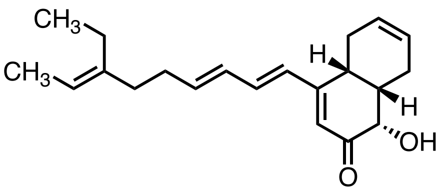
single enantiomer

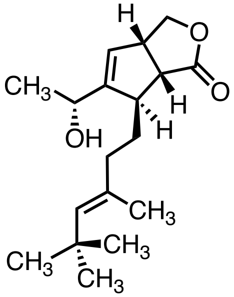
using 

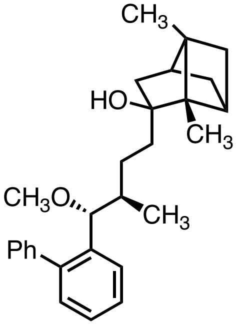
as one of the starting materials

Myers | Hour Exam 1 October 25, 2005 | *Chem 215*

Provide enantioselective synthetic routes to only **two** of the three targets shown below (each problem is worth 50 points). Present your routes in the *forward* direction. Provide clear structural drawings and denote all reagents that you propose to use. Solutions should be presented in the blue books provided; make sure to write your name on every blue book you submit for grading. The exam is closed book, closed notes. Molecular models are permitted in the exam, but should not be required. The exam is designed to require 60 minutes, but you will be permitted the full 90 minutes of the class period to take the exam. *A comment on examsmanship* - partial credit is given, and can be substantial, but can only be given if a solution, or partial solution appears. In other words, you must write something to obtain partial credit.

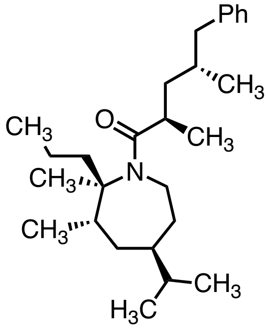


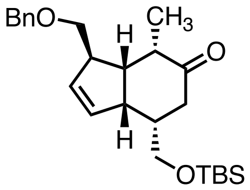


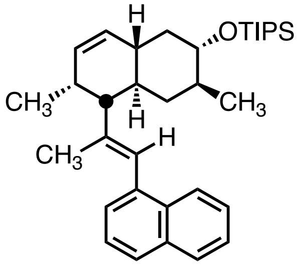


Myers Hour Exam 1 October 24, 2006 *Chem 215*

Provide enantioselective synthetic routes to only **two** of the three targets shown below (each problem is worth 50 points). Present your routes in the *forward* direction. Provide clear structural drawings and denote all reagents that you propose to use. Solutions should be presented in the blue books provided; make sure to write your name on every blue book you submit for grading. The exam is closed book, closed notes. Molecular models are permitted in the exam, but should not be required. The exam is designed to require 60 minutes, but you will be permitted the full 90 minutes of the class period to take the exam. *A comment on examsmanship* - partial credit is given, and can be substantial, but can only be given if a solution, or partial solution appears. In other words, you must write something to obtain partial credit.

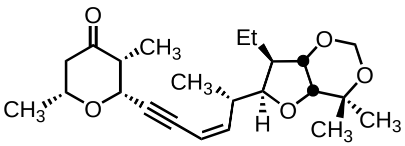




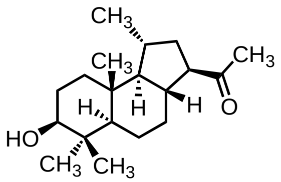


Myers Hour Exam 2 November 28, 2006 *Chem 215*

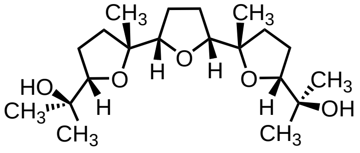
Provide enantioselective synthetic routes to only **two** of the three targets shown below (each problem is worth 50 points). Present your routes in the *forward* direction. Provide clear structural drawings and denote all reagents that you propose to use. Solutions should be presented in the blue books provided; make sure to write your name on every blue book you submit for grading. The exam is closed book, closed notes. Molecular models are permitted in the exam, but should not be required. The exam is designed to require 60 minutes, but you will be permitted the full 90 minutes of the class period to take the exam. *A comment on examsmanship* - partial credit is given, and can be substantial, but can only be given if a solution, or partial solution appears. In other words, you must write something to obtain partial credit.



A



B

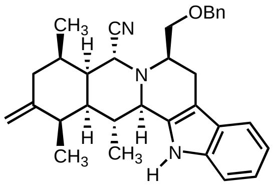


(meso)

C

Myers Hour Exam 2 *Chem 215*

Provide **enantioselective** synthetic routes to only **two** of the three targets shown below (each problem is worth 50 points). Use of chiral pool intermediates as starting materials is permitted. If you work on all three problems be sure to indicate which **two** are to be graded and present only **one** solution per problem. Present your routes in the **forward** direction. Provide clear structural drawings and denote all reagents that you propose to use. Solutions should be presented in the blue books provided; make sure to write your name on every blue book you submit for grading. The exam is closed book, closed notes. Molecular models are permitted in the exam. The exam is designed to require 60 minutes, but you will be permitted the full 90 minutes of the class period to take the exam. *A comment on examsmanship* - partial credit is given, and can be substantial, but can only be given if a solution, or partial solution appears. In other words, you must write something to obtain partial credit.



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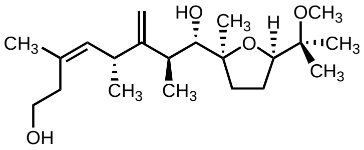
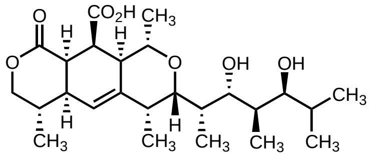


B

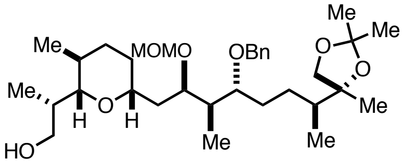


C

Shair Exam 2 - November 23, 2004 *Chem 215*

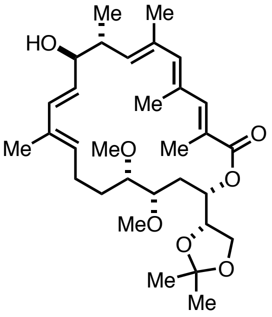
Provide concise synthetic routes to **two** of the three targets shown below. Each molecule is worth 50 points. Use of the chiral pool intermediates, their enantiomers, and the chiral auxiliaries presented in lecture is permitted. If you work on all three molecules, be sure to indicate which two are to be graded and present only one solution per problem. Present the routes in the forward direction in the blue books. Make sure to write your name on every blue book you submit for grading. Provide clear structural drawings and denote all reagents that you propose to use. The exam is closed book, and closed notes. Partial credit is given, and can be substantial, but only if a solution or partial solution appears. In other words, something is better than nothing. *Note:* Illegible answers will receive no credit.

A



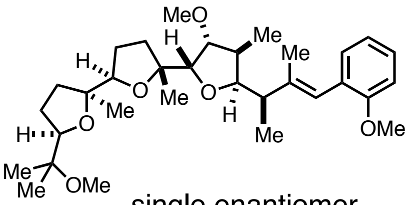
single enantiomer

B



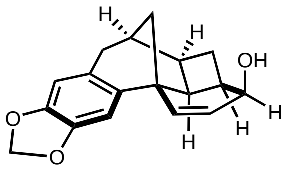
single enantiomer

C

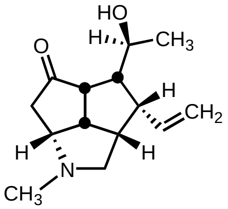


single enantiomer

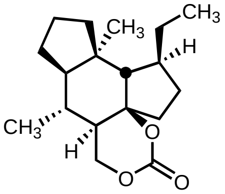
Provide **enantioselective** synthetic routes to only **two** of the three targets shown below (each problem is worth 50 points). Use of chiral pool intermediates as starting materials is permitted. If you work on all three problems be sure to indicate which **two** are to be graded and present only **one** solution per problem. Present your routes in the **forward** direction. Provide clear structural drawings and denote all reagents that you propose to use. Solutions should be presented in the blue books provided; make sure to write your name on every blue book you submit for grading. The exam is closed book, closed notes. Molecular models are permitted in the exam. The exam is designed to require 60 minutes, but you will be permitted the full 90 minutes of the class period to take the exam. *A comment on examsmanship* - partial credit is given, and can be substantial, but can only be given if a solution, or partial solution appears. In other words, you must write something to obtain partial credit.



A



B

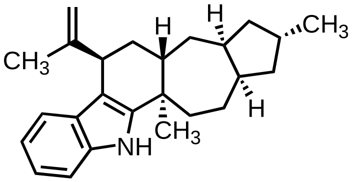


C

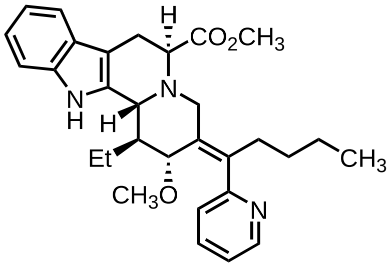
Philip Hogan

Myers Hour Exam 2 December 19, 2006 *Chem 215*

Provide enantioselective synthetic routes to only **two** of the three targets shown below (each problem is worth 50 points). Present your routes in the *forward* direction. Provide clear structural drawings and denote all reagents that you propose to use. Solutions should be presented in the blue books provided; make sure to write your name on every blue book you submit for grading. The exam is closed book, closed notes. Molecular models are permitted in the exam, but should not be required. The exam is designed to require 60 minutes, but you will be permitted the full 90 minutes of the class period to take the exam. *A comment on examsmanship* - partial credit is given, and can be substantial, but can only be given if a solution, or partial solution appears. In other words, you must write something to obtain partial credit.



A



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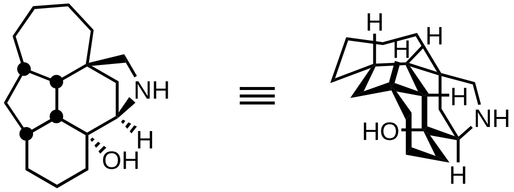
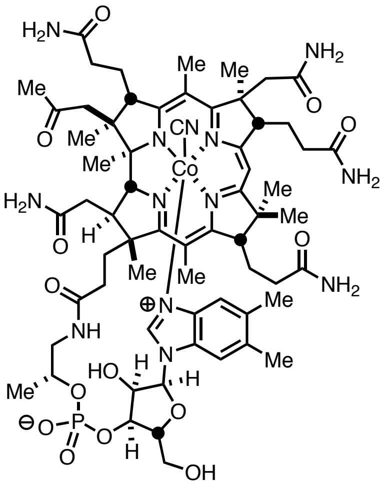


C

Philip Hogan


H$_2$N
O
Me
O
Me
Me
N
CN
Co
N
Me
Me
NH$_2$
O
NH$_2$
O
H$_2$N
O
H
N
N
Me
Me
Me
Me
O
NH$_2$
O
NH
Me
O
⊖O
P
O
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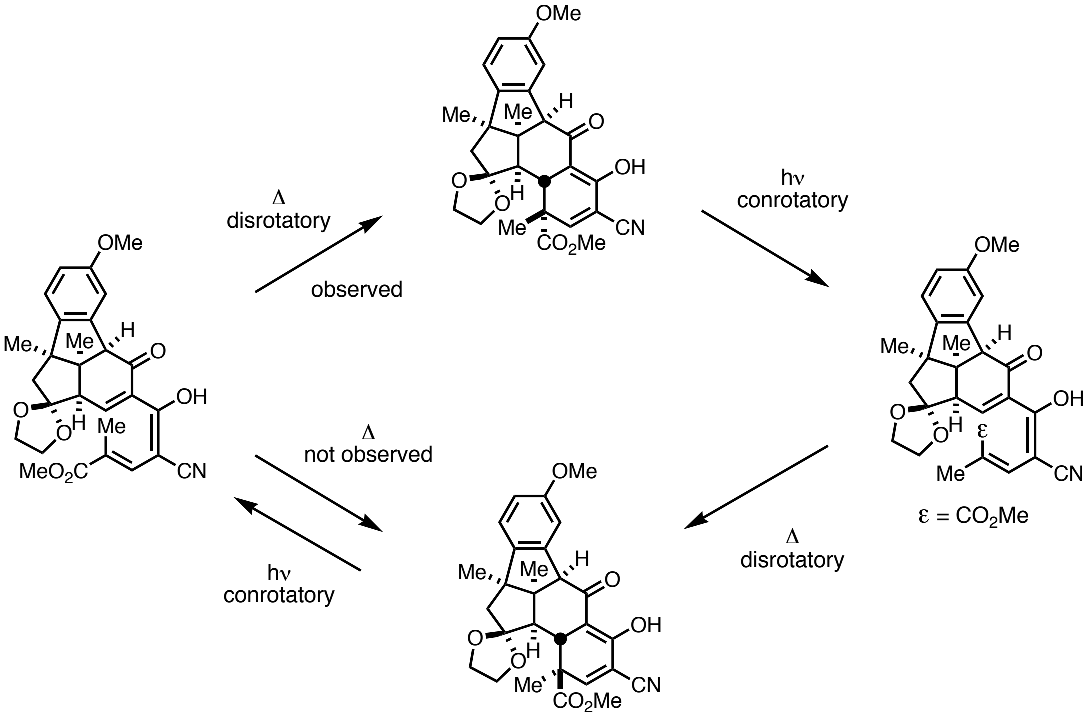
HO
H
H
O
H
OH
⊕N
N
Me
Me

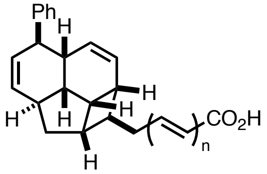
(-)-vitamin B_{12}


Δ
disrotatory
observed
hν
conrotatory
Δ
not observed
hν
conrotatory
Δ
disrotatory
ε = CO$_2$Me
OMe
Me
Me
H
O
OH
CN
O
O
H
MeO$_2$C
CO$_2$Me
ε

Monday, September 17, 2007

Reading Assignment: Corey & Cheng Ch 1-3; Handout: Reduction;
SANROS pp 44-47, 140-141, 186-187, 308-309, 486-489, 496-497

Syntheses Discussed:



Endiandric Acid A, n = 0
Endiandric Acid B, n = 1

Partial List of Topics Discussed:

- Transform
- Retron
- Part Retron
- Full Retron
- Functional Group Interconversions

Partial List of Transforms Covered:

Diels-Alder Reaction

[2+2] Photocycloaddition

C=O Reduction

Wittig Reduction

Syn Opening of Epoxides with $LiNEt_2$

Ketal Hydrolysis

C=C Oxidative Cleavage

Nef Reaction

C=C Reduction

Barton Deoxygenation

Barton Decarboxylation

Wolff-Kishner Reduction

Nitroalkane Reduction

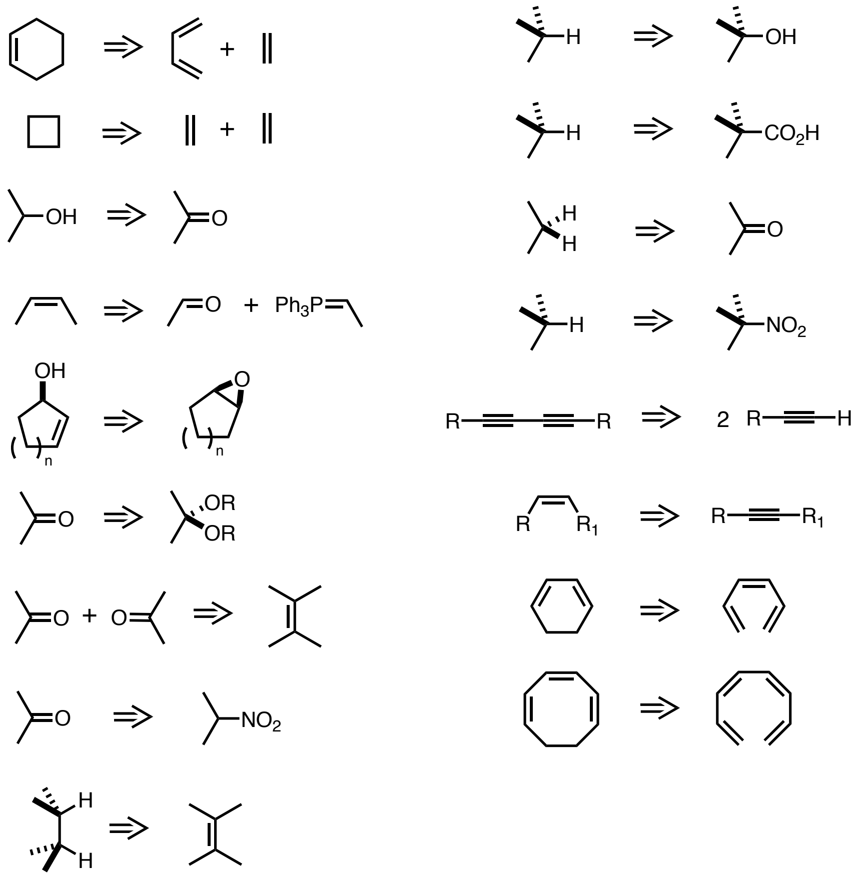
Glaser Coupling Reaction

Lindlar Reduction

1,3,5-Hexatriene Electrocyclization

1,3,5,7-Octatetraene Electrocyclization

Graphical Transform Guide:



References:

Endiandric Acids A and B:
Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc*. **1982**, *104*, 5555-5557.
Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. J. *Am. Chem. Soc*. **1982**, *104*, 5558-5560.
Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. J. Am. Chem. Soc. **1982**, *104*, 5560-5562.

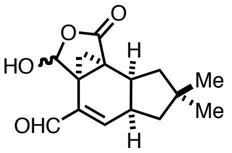
Diels-Alder Reaction in Synthesis:
Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed. Engl*. **2002**, *41*, 1668-1698.

Lecture 2: Transform-Based Retrosynthetic Analysis

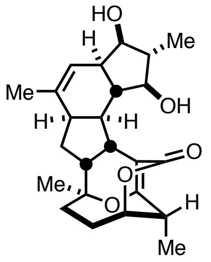
Wednesday, September 19, 2007

Reading Assignment: Corey & Cheng, Chapters 1-3.
SANROS pp 8-9, 50-51, 102-103, 172-173, 266-267, 362-363.

Syntheses Discussed:



Marasmic Acid



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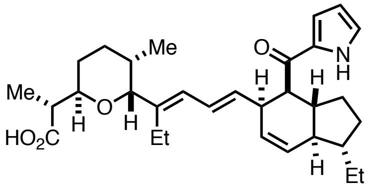


Indanomycin

Partial List of Transforms Covered:

Wittig Reaction with Stabilized Ylides

Desaturation by Selenoxide Elimination

Alkylative Cyclopropanation

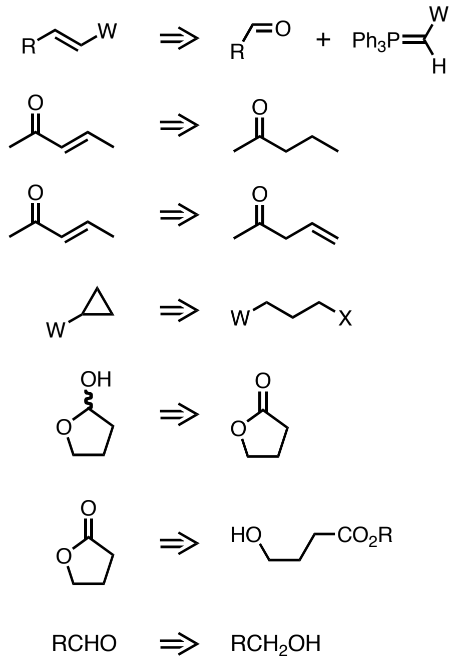
Reduction of Lactones to Lactols

Lactonization

Oxidation of Alcohols to Aldehydes

Enone Isomerization

Graphical Transform Guide:



References:

Marasmic Acid:
Greenlee, W. J.; Woodward, R. B. *J. Am. Chem. Soc*. **1976**, *98*, 6075-6076.
Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3367-3375.
Boeckman, R. K., Jr.; Ko S. S. *J. Am. Chem. Soc*. **1980**, *102*, 7146-7149.

FR182877:
Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed. Engl*. **2002**, *41*, 1787-1790.
Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc*. **2002,** *124*, 4552-4553.

Indanomycin:
Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem*. **1984**, *49*, 3429-3432.
Roush, W. R.; Myers, A. G. *J. Org. Chem*. **1981**, *46*, 1509-1511.
Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem*. **1985**, *50*, 1440-1456.
Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem*. **1994**, *59*, 332-347.

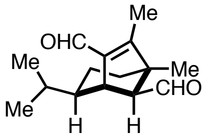
Lecture 3: Bidirectional Searching in Synthetic Simplification

Monday, September 24, 2007

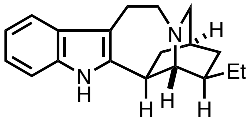
Reading Assignment: Corey & Cheng Ch 5-6;
Handouts: Oxidation, Protective Groups, and Birch Reduction;
SANROS pp 154-155, 164-165, 354-355, 470-471

Partial List of Topics Discussed: Bidirectional Searching in Synthetic Simplification, Substructure Matching, Identifying and Clearing Obstacles to Implementing Powerfully Simplifying Transforms in Synthetic Problem Solving.

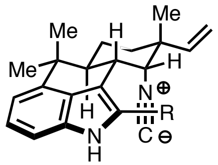
Syntheses Discussed:



Helminthosporal



Ibogamine



R=H: Hapalindole U
R=*tert*-prenyl: Ambiguine H

Partial List of Transforms Covered:

Aldol, Aldol-Dehydration

Alkylation of α-Formylated Ketones

Sulfur Ylide Epoxidation

Carbonyl Homologation Reactions

Quinone Diels-Alder Reaction

Fischer Indole Synthesis

Beckmann Rearrangement

Reduction of Enediones to Diones

Olefin Epoxidation

Reductive Epoxide Opening

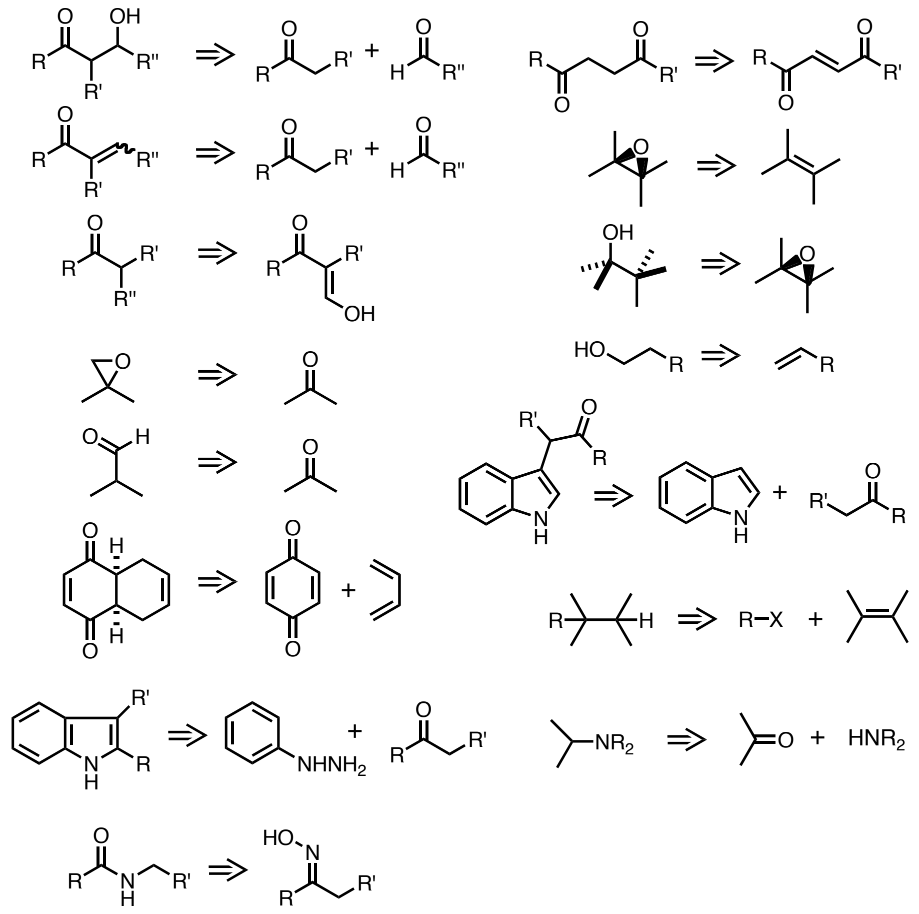
Hydroboration/Oxidation

Oxidative Coupling

Reductive Heck Reaction

Reductive Amination

Graphical Transform Guide:



References:

Helminthosporal:
Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1963**, *85*, 3527-3528.
Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 3528-5733.

Ibogamine:
Sallay, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 6762-6763.

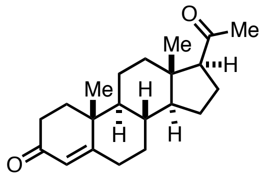
Hapalindole U, Ambiguine H:
Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.

Wednesday, September 26, 2007

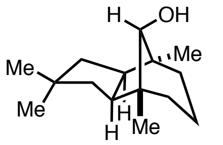
Reading Assignment: Corey & Cheng Ch. 5-6
SANROS pp 28-29, 38-39, 116-117, 130-133, 190-191, 384-385, 444-445.

Partial List of Topics Discussed:
- Mechanistic Development of Transforms
- Introduction to the Cation-Olefin Cyclization
- Topological Strategies-Rearrangement and Connective Transforms

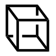
Syntheses Discussed:

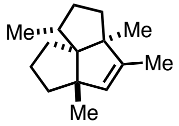


Progesterone

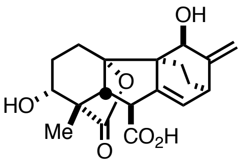


α-Caryophyllene Alcohol


Cubane



Isocomene



Antheridic Acid

Partial List of Transforms Covered:

Cation-Olefin Cyclization

Alcohol Dehydration

1,2-C-C Shift

Vinyl Cyclopropane Rearrangement

Carbenoid-Mediated Cyclopropanation

Electrophilic Bromonation

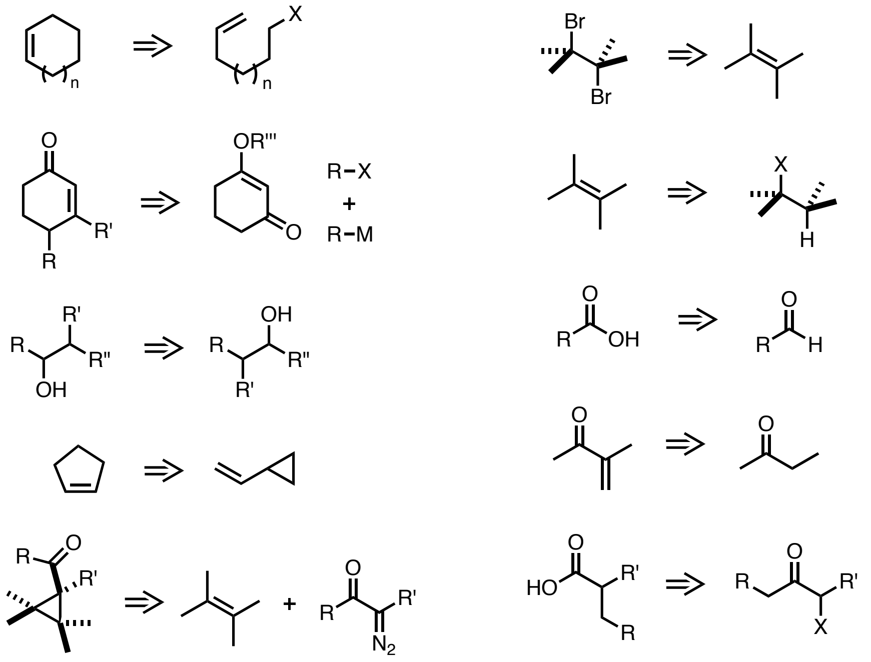
E2 Elimination

Sodium Chlorite Oxidation of Aldehydes to Carboxylic Acids

Eschenmoser's Salt

Favorskii Rearrangement

Graphical Transform Guide:



References:

Progesterone:
Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332-4334.
Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274-4282.

Antheridic Acid:
Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574-5576.

α-Caryophyllene Alcohol:
Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1964**, *86*, 1652-1653.
Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5733-5735.

Isocomene:
Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130-7131.

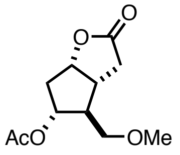
Cubane:
Eaton, P. E.; Cole, T. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 962-964.
Eaton, P. E.; Cole, T. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 3157-3158.

Monday, October 1, 2007

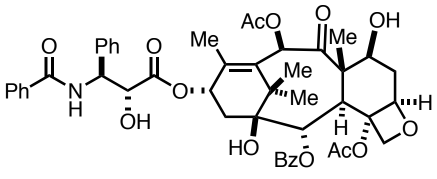
Reading Assignment: "Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts" Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986-2012.
Handouts: Asymmetric Alkylation of Enolates and Asymmetric Allylation Reactions
SANROS pp 88-91, 98-99, 138-139, 324-325, 388-389.

Partial List of Topics Discussed: Topological Strategies- The Power of Connective Transforms in Synthetic Simplification, An Introduction to Stereochemical Strategies, The Use of Chiral Auxiliaries for Stereochemical Control.

Syntheses Discussed:



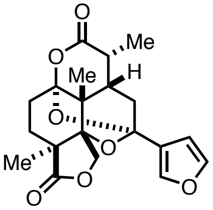
Corey Lactone



Taxol

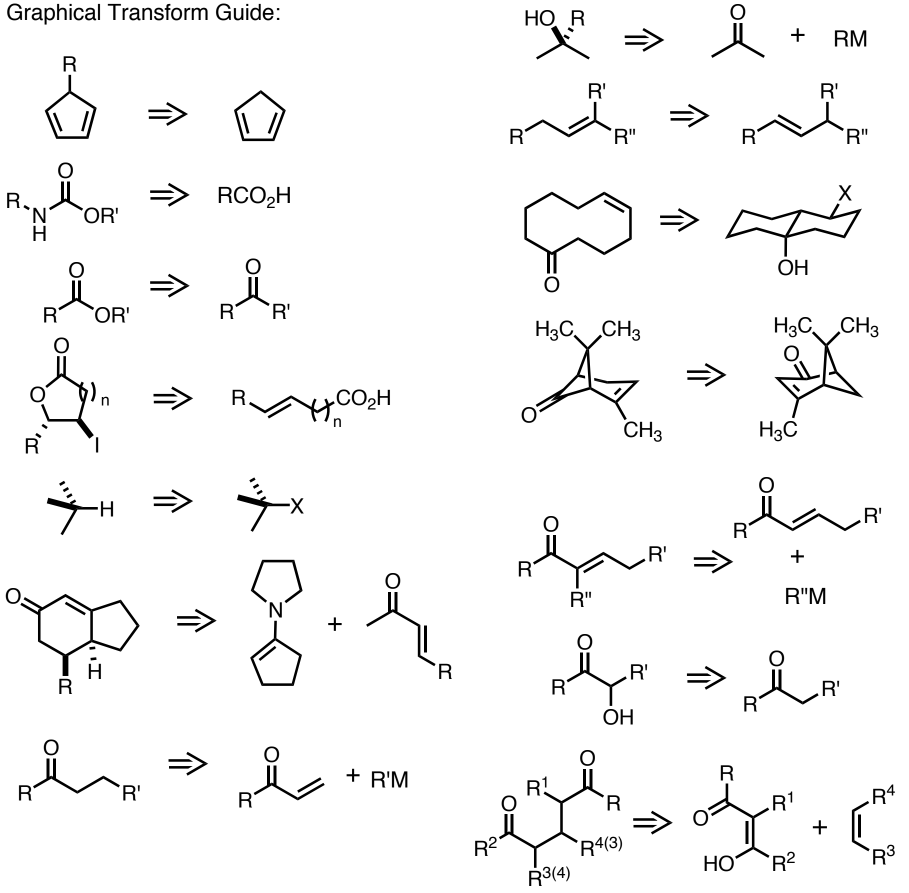
Partial List of Transforms Covered:

- Alkylation of Cyclopentadienyl Anion
- Curtius Rearrangement
- Baeyer-Villager Oxidation
- Iodolactonization
- Radical Dehalogenation
- Enamine Alkylation/Robinson Annulation
- Conjugate Addition (Conjugate Addition of Cuprates)
- Addition of Organometallic Reagents to Carbonyl Compounds
- Rhodium(III) Catalyzed Olefin Isomerization
- Grob Fragmentation
- Photochemical Isomerization of Verbenone
- α-Alkylation of Extended Enolates
- Hydroxylation of Enolates
- Tandem Michael/Aldol Reaction
- de Mayo Reaction



Saudin

Graphical Transform Guide:



References:

Saudin:
Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425-7426.

Taxol:
Wender, P. A.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 2755-2756.
Wender, P. A.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758.

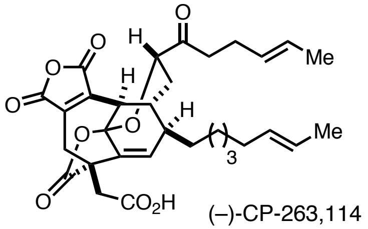
Prostaglandin $F_{2\alpha}$:
Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. H. *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677.

Wednesday, October 3, 2007

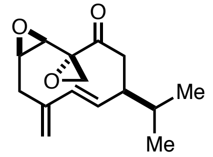
Reading Assignment: "The Thermal, Aliphatic Claisen Rearrangement" Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423-1452. "The Ireland-Claisen Rearrangement" Pereia, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17-29.
SANROS pp 56-57, 108-109, 294-295, 500-501.

Partial List of Topics Discussed: Topological Strategies-Transforms Involving Sigmatropic Rearrangements, Stereochemical Strategies Continued: Asymmetric Catalysis and Kinetic Resolution, Use of Chiral Controller Groups for Absolute Stereochemical Control

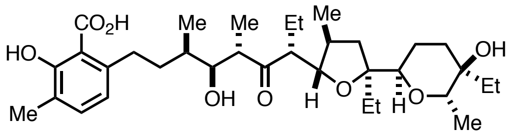
Syntheses Discussed:



(–)-CP-263,114



(±)-Periplanone B



Lasalocid A

Partial List of Transforms Covered:

Cope Rearrangement

Oxy-Cope Rearrangement (Oxy Anion Accelerated Cope Rearrangement)

Dieckman Condensation

Rubottom Oxidation

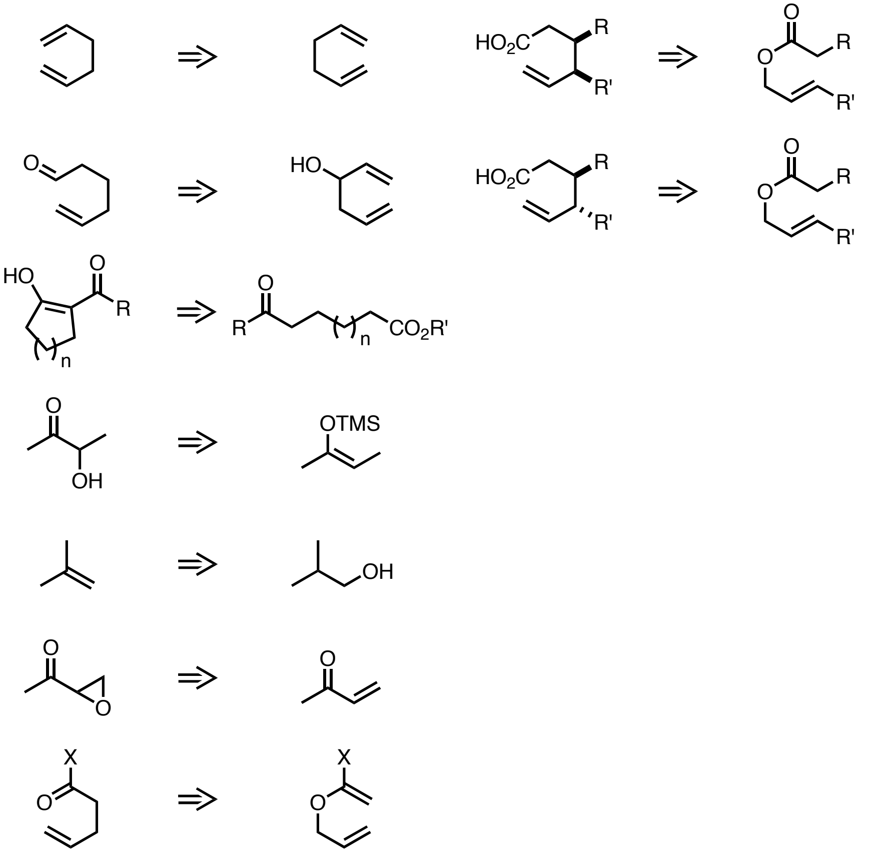
Selenenylation/Elimination of Unhindered Alcohols

Nucleophilic Epoxidation

Claisen Rearrangement

Ireland Ester Enolate Claisen Rearrangement

Graphical Transform Guide:



References:

(+)-CP-263,114:
Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424-7425.

Periplanone B:
Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493-2495.
Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038-4039.

Lasalocid A:
Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGrarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988-2006.
Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155-1157.

Shair

Lecture 7: Targeting Strategic Bonds Using Anionic Intermediates

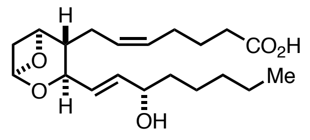
Chem 215

Wednesday, October 10, 2007

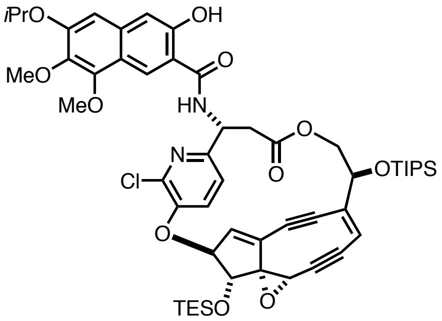
Reading Assignment: Handouts: Magnesium-Halogen Exchange, Organolithium Reagents, Lithium-Halogen Exchange, Directed Ortho Metalation, The Stille Reaction, The Suzuki Reaction, and The Heck Reaction

Partial List of Topics Discussed: Functional-Group Based Strategies, Strategic Bond Analysis, Targeting σ-Bonds with Absolute Stereochemical Control by Asymmetric Alkylation and Allylation Reactions, Use of Organometallic Intermediates for Strategic Bond Construction

Syntheses Discussed:



TXA$_2$



Kedarcidin Chromophore Core

Partial List of Transforms Covered:

Corey-Nicolaou Macrolactonization

Dehydration with Mukaiyama's Salt

Dehydration with Martin Sulfurane

Mitsunobu Reaction

Directed Lithiations

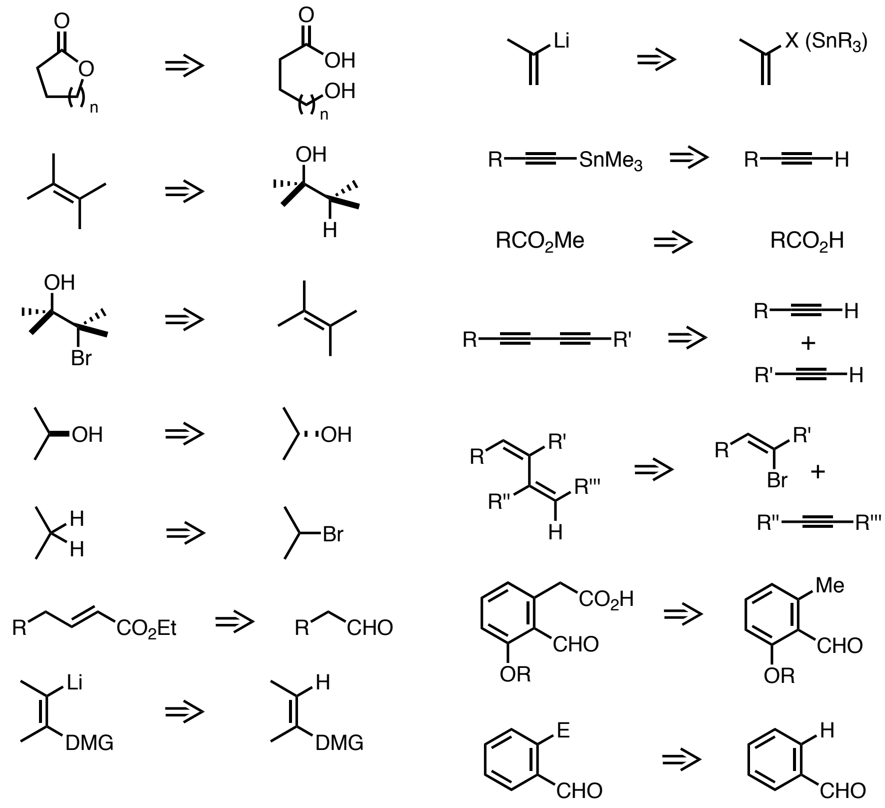
Lithium-Halogen Exchange

Bergman Cyclization

Aldehydes in Directed Metalation Reactions

Yamaguchi Macrolactonization

Graphical Transform Guide:



References:

TXA$_2$:
Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. *Nature* **1985**, *315*, 511-513.

Kedarcidin Chromophore Core:
Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1062-1067.

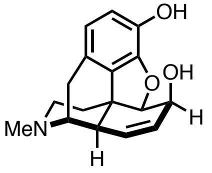
Kedarcidin Chromophore Core Mechanism Studies:
Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *J. Am. Chem. Soc.* **2002**, *124, 4583-4585*

Monday, October 15, 2007

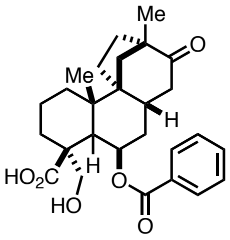
Reading Assignment: Prepare for Exam I.
SANROS pp 212-215, 310-311, 402-403, 424-425, 438-439, 448-449.

Partial List of Topics Discussed: Organopalladium Chemistry for Strategic Bond Construction

Syntheses Discussed:



(–)-Morphine



Scopadulcic acid A

Partial List of Transforms Covered:

The Heck Reaction

Iodine Trapping of Organolithium Intermediates

Addition of Allyl Silanes to Iminium Ions

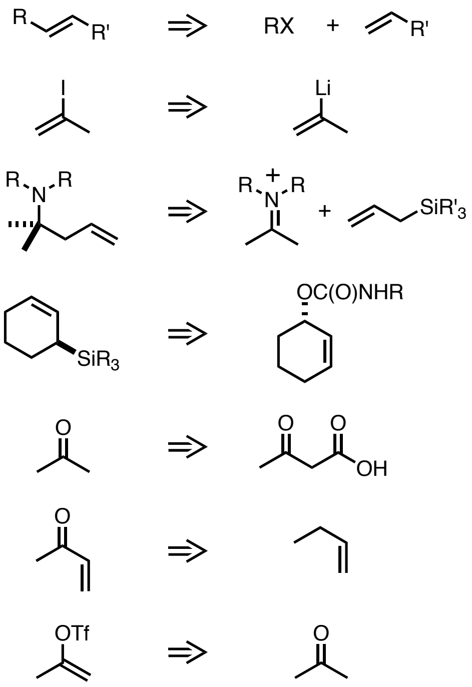
1,3 Addition of Silyl Cuprates to Allyl Carbamates

Decarboxylation of β-Keto Carboxylates

Allylic Oxidation with Chromium (VI) Reagents

McMurry's Reagent (Comins' Modified McMurry Reagent)

Graphical Transform Guide:



References:

(–)-Morphine:
Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028-00129.
Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453-3456.

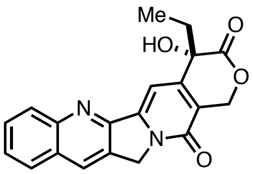
Scopadulcic acid A:
Kucera, D. J.; O'Connor, S. J.; Overman, L.E. *J. Org. Chem.* **1993**, *58*, 5403-5406.
Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467-5480.

Monday, October 15, 2007

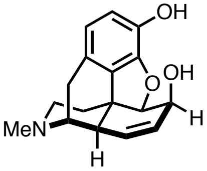
Reading Assignment: Prepare for Exam I.
SANROS pp 212-215, 310-311, 402-403, 424-425, 438-439, 448-449.

Partial List of Topics Discussed: Organopalladium Chemistry for Strategic Bond Construction

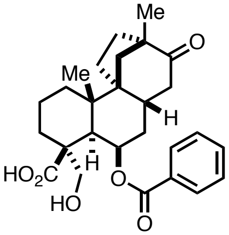
Syntheses Discussed:



(+)-Camptothecin



(–)-Morphine



Scopadulcic acid A

Partial List of Transforms Covered:

The Heck Reaction

Iodine Trapping of Organolithium Intermediates

Addition of Allyl Silanes to Iminium Ions

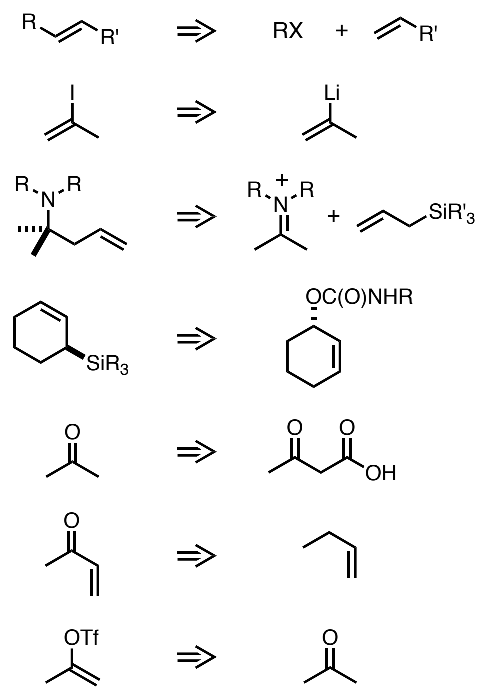
1,3 Addition of Silyl Cuprates to Allyl Carbamates

Decarboxylation of β-Keto Carboxylates

Allylic Oxidation with Chromium (VI) Reagents

McMurry's Reagent (Comins' Modified McMurry Reagent)

Graphical Transform Guide:



References:

(+)-Camptothecin:
Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255-4257.

(–)-Morphine:
Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028-00129.
Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453-3456.

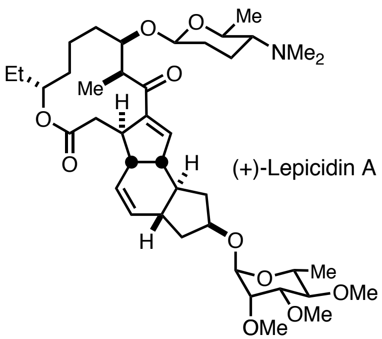
Scopadulcic acid A:
Kucera, D. J.; O'Connor, S. J.; Overman, L.E. *J. Org. Chem.* **1993**, *58*, 5403-5406.
Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467-5480.

Monday, October 22, 2007

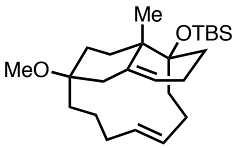
Reading Assignment: "Applications of Ni(II)/Cr(II)-Mediated Coupling Reactions to Natural Products Synthesis" Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343-350.
Handouts: Stereoselective, Directed Aldol Reaction and Horner-Wadsworth-Emmons Olefination

Partial List of Topics Discussed: Organopalladium-Based Transforms Continued, Focus on Transforms Targeting Stereogenic sp^2-Hybridized Carbon Centers

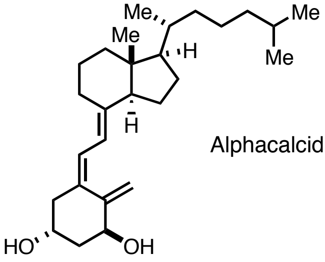
Syntheses Discussed:



(+)-Lepicidin A



Transannular Macrocyclization Substrate



Alphacalcidiol

Partial List of Transforms Covered:

The Suzuki Reaction with Alkyl Boranes

E-Vinyl Stannanes from Alkynes

Alkylation of *E*-Vinyl Stannyl Cuprates to form *E*-Vinyl Stannanes

Takai's Synthesis of *E*-Vinyl Iodides from Aldehydes

Stork and Zhao's Wittig-Based Synthesis of *Z*-Vinyl Iodides from Aldehydes

Stabilized Wittig Olefination

Horner-Wadsworth-Emmons Olefination

Still Modification of Horner-Wadsworth-Emmons Olefination

Matteson's Synthesis of *E*-Vinyl Boronic Acids from Aldehydes

Iodination of Terminal Alkynes

The Gilbert Reaction

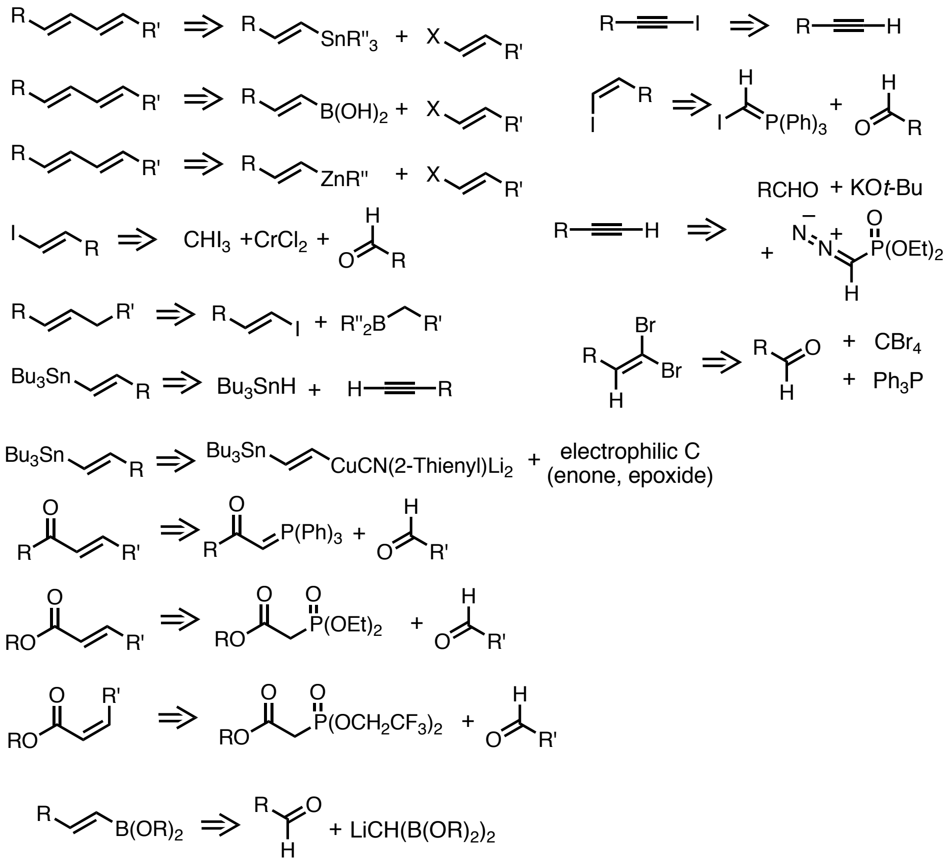
The Corey-Fuchs Reaction

The Stille Reaction

The Suzuki Reaction

The Negishi Reaction

Graphical Transform Guide:



References:

(+)-Lepicidin A:
Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260-2262.
Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513.

(–)-Lepicidin A (Core Nucleus):
Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157-3160.

Transannular Macrocyclization Substrate:
Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695-2698.

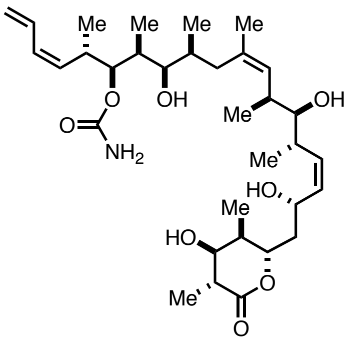
Alphacalcidiol:
Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845.

Wednesday, October 24, 2007

Reading Assignment: Corey & Cheng Ch 4; SANROS pp 230-231, 400-401.

Partial List of Topics Discussed: Stereochemical Strategies in Synthetic Simplification: Powerful Transforms Targeting σ-Bonds Between Stereogenic sp^3-Hybridized Carbon Centers I

Synthesis Discussed:



(+)-Discodermolide

Partial List of Transforms Covered:

Syn Diastereoselective Aldol Reaction

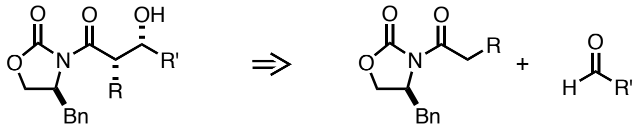
Anti Diastereoselective Aldol Reaction

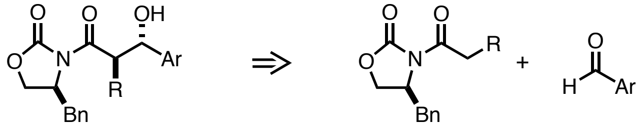
Synthesis of Carbamates from Alcohols

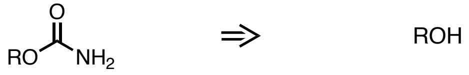
p-Methoxyphenyl Acetals from Oxidation of *p*-Methoxybenzyl Ethers

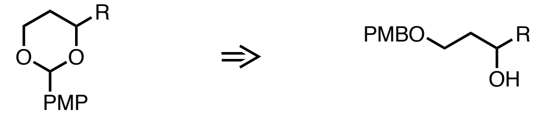
Reductive Opening of *p*-Methoxyphenyl Acetals

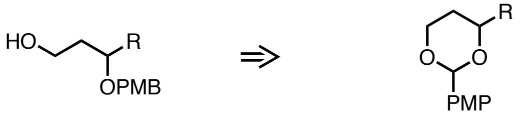
Graphical Transform Guide:











References:

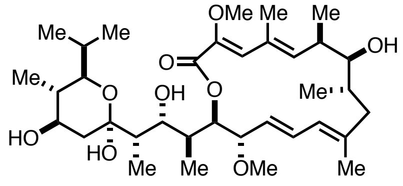
(+)-Discodermolide
Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654-8664.
Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823-1826.

Lecture 11: Targeting σ-Bonds Between Stereogenic sp^3-Hybridized Carbon Centers II

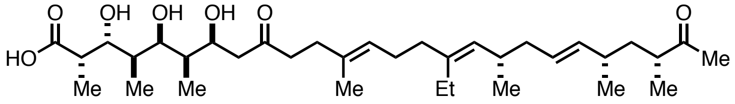
Monday, October 29, 2007

Reading Assignment: "Substrate-Directable Chemical Reactions" Hoveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370. Handouts: Sharpless Asymmetric Epoxidation Reaction and Sharpless Asymmetric Dihydroxylation Reaction.
SANROS pp 412-413.

Synthesis Discussed:



(–)-Bafilomycin A_1



Premonensin

Partial List of Transforms Covered:

Anti Diastereoselective Crotylation Reactions

Syn Diastereoselective Crotylation Reactions

Elimination of Geminal Vinyl Dibromides to form Alkynes

Synthesis of Vinyl Iodides Using Schwartz' Reagent

Diastereoselective Aldol Reactions of β-Ketoimides (anti-syn shown)

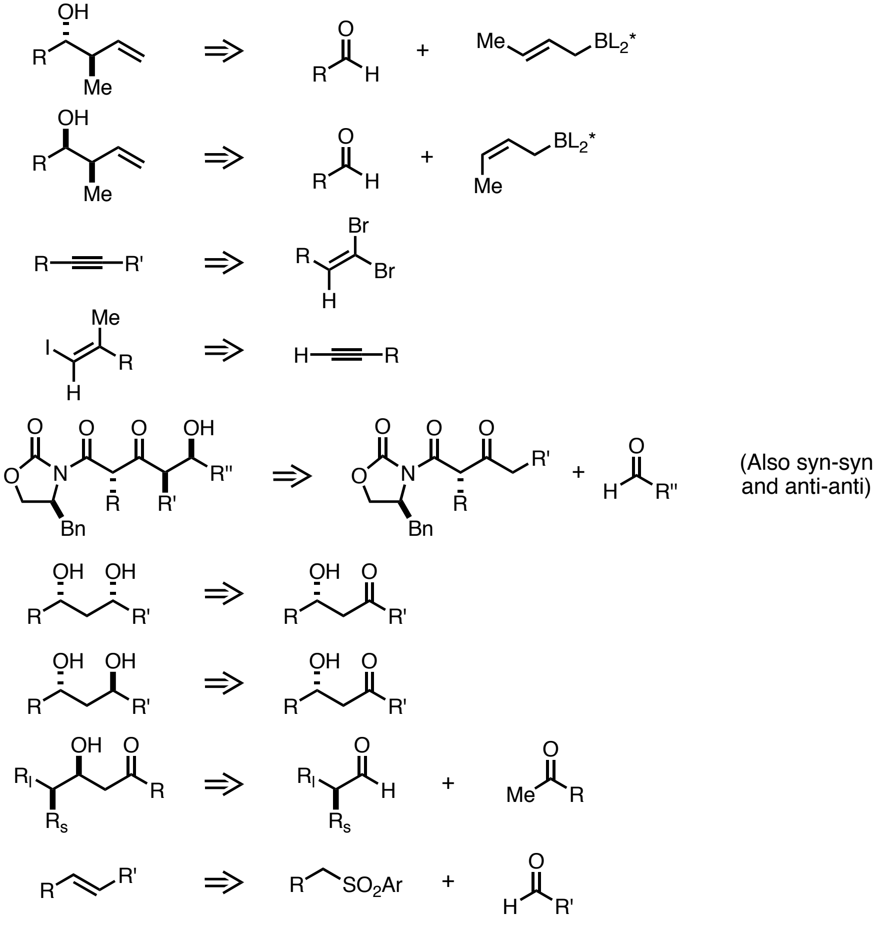
Syn Directed Reduction of β-Hydroxy Ketones

Anti Directed Reduction of β-Hydroxy Ketones

Felkin-Anh Selective Aldol Reactions

Julia-Lythgoe Olefination, Modified Julia Olefination

Graphical Transform Guide:



References:

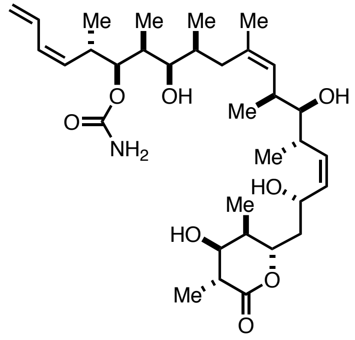
(–)-Bafilomycin A_1:
Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1652-1655.
Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587-3590.

Premonensin:
Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1985**, *108*, 2476-2478.

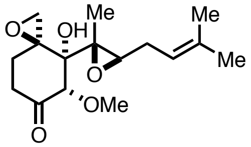
Wednesday, October 31, 2007

Reading Assignment: "Substrate-Directable Chemical Reactions" Hoveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.
SANROS pp 220-223, 336-337, 368-369, 406-411.

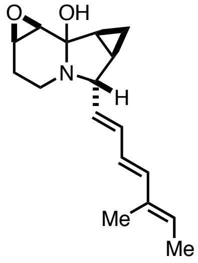
Syntheses Discussed:



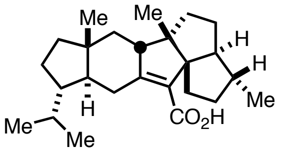
(+)-Discodermolide



(±)-Ovalicin



(±)-Indolizomycin



(±)-Retigeranic Acid

Partial List of Transforms Covered:

Weinreb Amides from Esters

Anti Diastereoselective Aldol Reactions of Lactate-Derived Ketones

Heteroatom-Directed Epoxidation of Olefins with *m*-CPBA

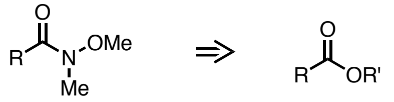
Heteroatom-Directed Epoxidation of Olefins with VO(acac)$_2$

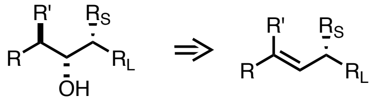
Heteroatom-Directed Cyclopropanation of Olefins with Simmons-Smith Reagent

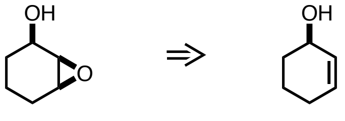
Heteroatom-Directed Hydrogenation of Olefins with Cationic Transition Metal Complexes

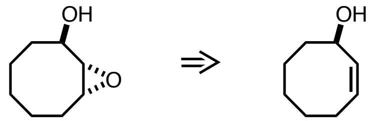
Conformation-Controlled Hydroboration of Olefins with Borane

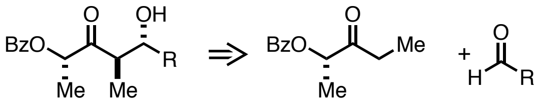
Graphical Transform Guide:

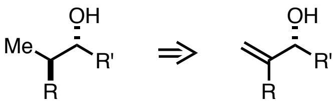


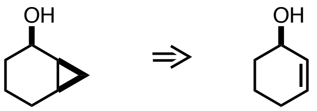












References:

(+)-Discodermolide:
Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535-9544.

(±)-Indolizomycin:
Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30-39.

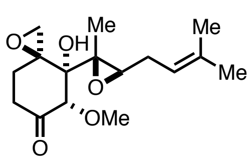
(±)-Ovalicin:
Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256-257.

(±)-Retigeranic Acid:
Corey, E. J.; Desai, M. J.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339-4341.

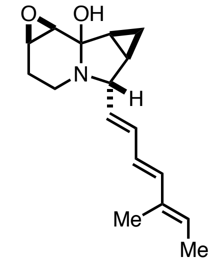
Wednesday, October 31, 2007

Reading Assignment: "Substrate-Directable Chemical Reactions" Hoveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.
SANROS pp 220-223, 336-337, 368-369, 406-411.

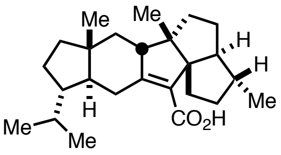
Syntheses Discussed:



(±)-Ovalicin



(±)-Indolizomycin



(±)-Retigeranic Acid

Partial List of Transforms Covered:

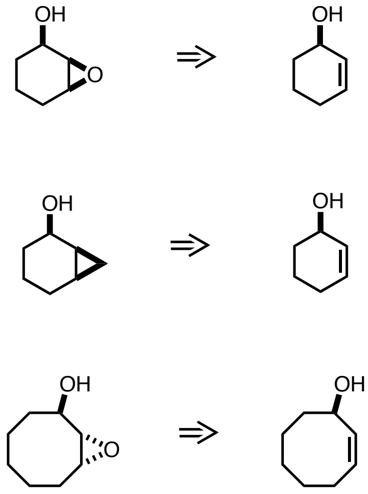
Heteroatom-Directed Epoxidation of Olefins with *m*-CPBA

Heteroatom-Directed Epoxidation of Olefins with VO(acac)$_2$

Heteroatom-Directed Cyclopropanation of Olefins with Simmons-Smith Reagent

Heteroatom-Directed Hydrogenation of Olefins with Cationic Transition Metal Complexes

Graphical Transform Guide:



References:

(±)-Indolizomycin:
Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30-39.

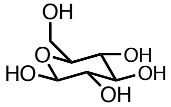
(±)-Ovalicin:
Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256-257.

(±)-Retigeranic Acid:
Corey, E. J.; Desai, M. J.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339-4341.

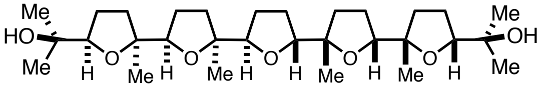
Monday, November 5, 2007

Reading Assignment: Handouts: Jacobsen Asymmetric Epoxidation Reaction, Shi Epoxidation, Jacobsen Catalytic Asymmetric Epoxide-Opening Reaction, Transformations of 2,3-Epoxy Alcohols, Asymmetric Diels-Alder Reactions, and The Noyori Asymmetric Hydrogenation Reaction

Syntheses Discussed:



L-Hexoses



Glabrescol

Partial List of Transforms Covered:

Sharpless Asymmetric Epoxidation

Payne Rearrangement/Nucleophilic Opening of Terminal Epoxides

Pummerer Rearrangement

Epoxides from 1,2-Diols

1,2-Diols from Epoxides

Sharpless Kinetic Resolution

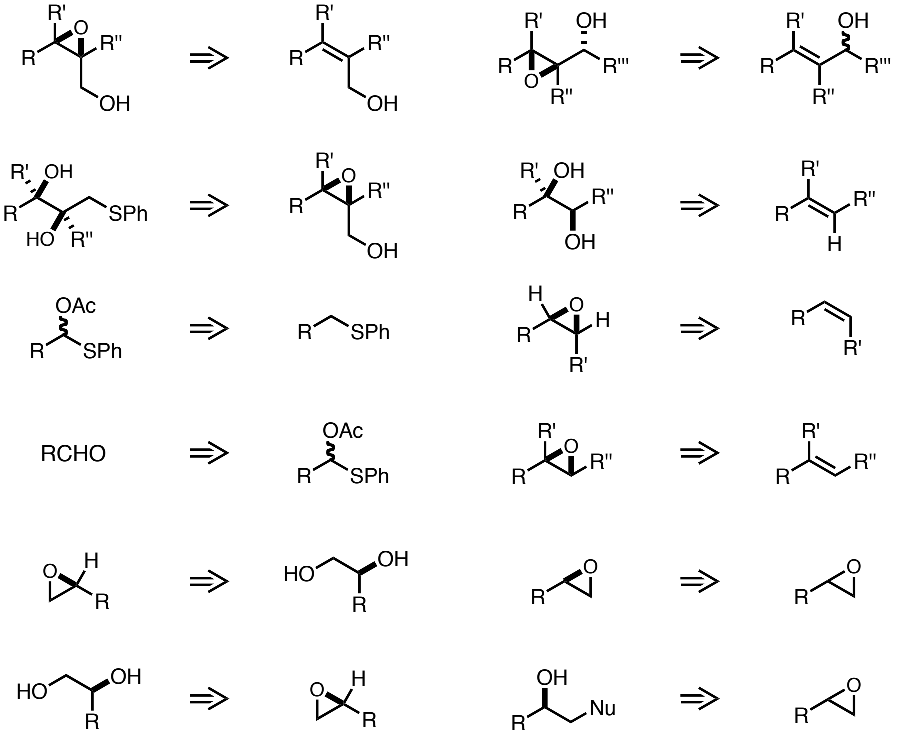
Sharpless Asymmetric Dihydroxylation

Jacobsen Asymmetric Epoxidation

Shi Asymmetric Epoxidation

Jacobsen Hydrolytic Kinetic Resolution

Graphical Transform Guide:



References:

L-Hexoses:
Koo, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J.; *Tetrahedron* **1990**, *46*, 245-264.

Glabrescol:
Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831-4832.
Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328-9329.
Hioki, H.; Kanehara, C.; Ohnishi, Y.; Umemori, Y.; Sakai, H.; Yoshio, S.; Matsushita, M.; Kodama, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2552-2554.

Shair

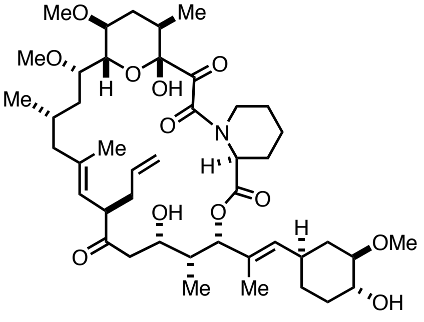
Lecture 14:Organic Synthesis with the Goal of Exploring the Cellular Mechanism of FK506.

Chem 215

Wednesday, November 7, 2007

Reading Assignment: SANROS pp 10-11, 204-205, 382-383, 490-491.

Syntheses Discussed:



FK506

Partial List of Transforms Covered:

Noyori Asymmetric Hydrogenation Reaction

Frater-Seebach Alkylation

Iodoetherification

Reductive Cleavage of Iodoethers

Opening of Epoxides with the Lithium Ethoxyacetylide

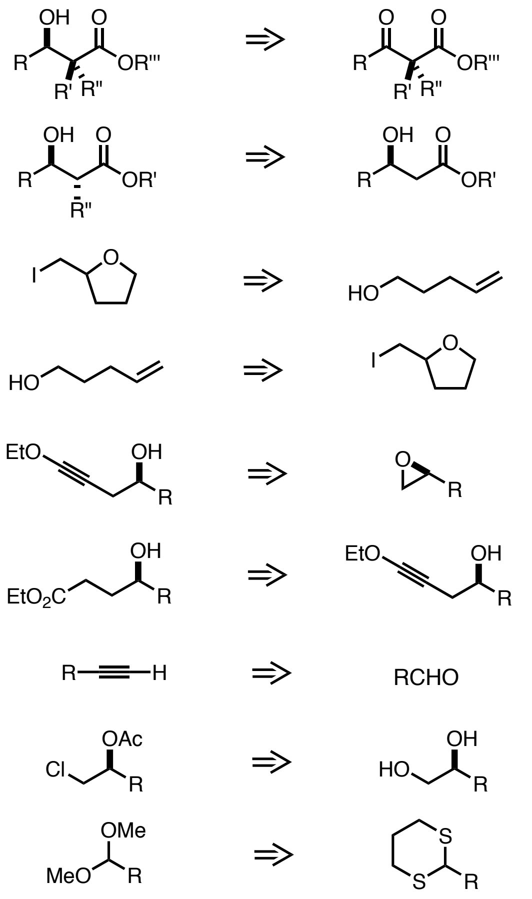
Oxymercuration of Ynones to form Esters

Gilbert-Seyferth Reagent

Moffatt Reagent

Dimethylacetals from Dithianes using the Stork Reagent

Graphical Transform Guide:



References:

FK506 Synthesis:
Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583-5601.

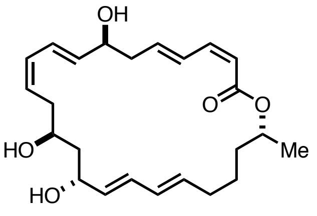
FK506 Biological Mechanism:
Rosen, M. K.; Standaert, R. F.; Galat, A.; Nakatsuka, M.; Schreiber, S. L. *Science*. **1990**, *248* (4957), 863-866.

FK506-FKBP Complex Structure:
Van Duyne, G. D.; Standaert, R. F.; Karplus, P. A.; Schreiber, S. L.; Clardy, J. *Science*. **1991**, *252* (5007), 839-842.

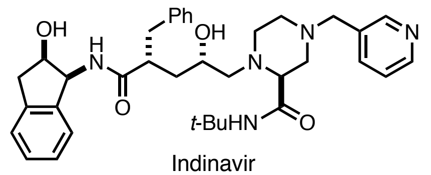
Wednesday, November 14, 2007

Reading Assignment: SANROS pp 168-169, 268-269, 318-319, 350-351, 364-365.

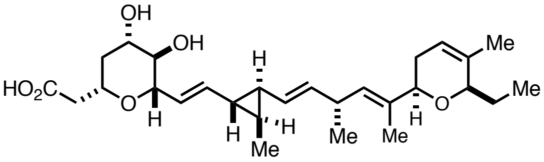
Syntheses Discussed:



Macrolactin A



Indinavir



Ambruticin

Partial List of Transforms Covered:

Carreira Acetate Aldol Additions with Silyl Ketene Acetals

Jacobsen Asymmetric Hetero Diels-Alder Reaction

Ritter Reaction of Epoxides with Acetonitrile to form Oxazolines

Hydroboration-Elimination of Silyl Enol Ethers to form Olefins

Silyldiazo Lithium Addition to Aldehydes to form Alkynes

Syn Alkyl Stannylation of Alkynes

Cross Coupling of Vinyl Halides with Grignards

Asymmetric Hydroformylation of Olefins

Asymmetric Simmons-Smith Cyclopropanation of Allylic Alcohols

Conjugate Addition of Alcohols to α,β-Unsaturated Esters to form Tetrahydropyrans

Acylation of Alcohols to from α-Diazoesters

Intramolecular Asymmetric Cyclopropanation of Allylic Diazoacetates

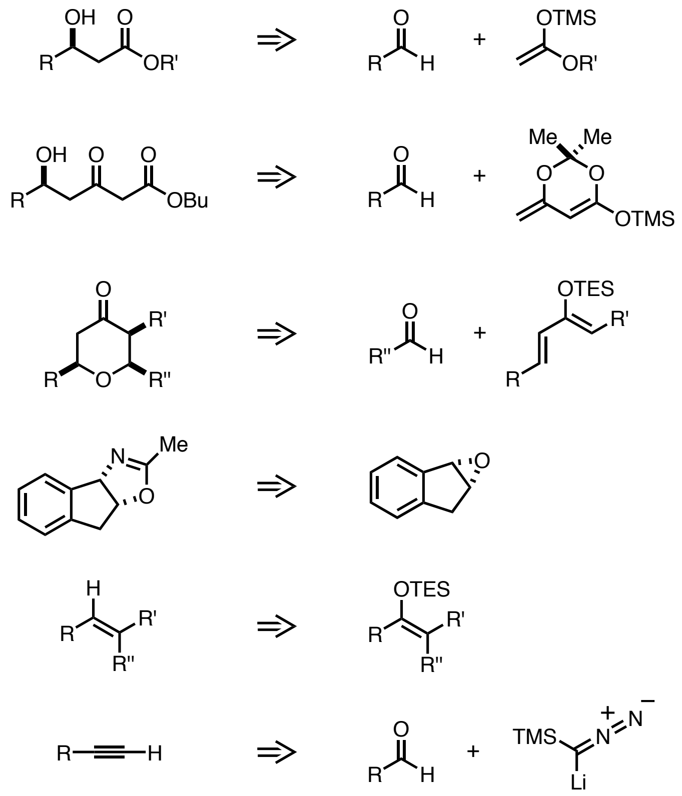
Lewis Acid-Catalyzed Opening of β-Tosyloxy Epoxides

Olefin Metathesis

Alkylation of Alcohols with Trimethyltinmethyliodide

[2,3]-Wittig Rearrangement

Graphical Transform Guide:



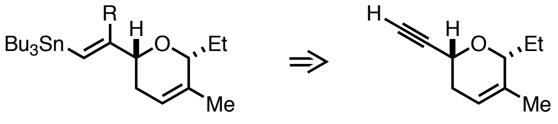
References:

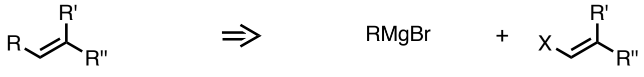
Macrolactin A:
Kim, Y.; Singer, R. A.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1261-1262.

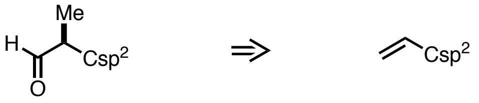
Ambruticin:
Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772-10773.
Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432-12433.

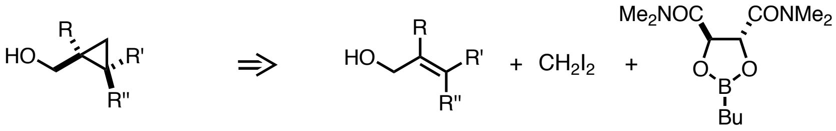
Indinavir:
Maligres, P. E.; Upadhyay, V.; Rossen, K.; Cianciosi, S. J.; Purick, R. M.; Eng, K. K. Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 2195-2198.
Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburg, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993-3996.

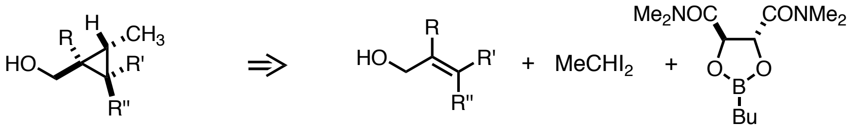
Graphical Transform Guide Continued:

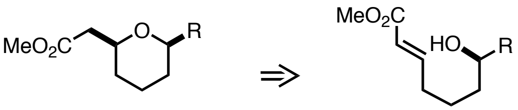


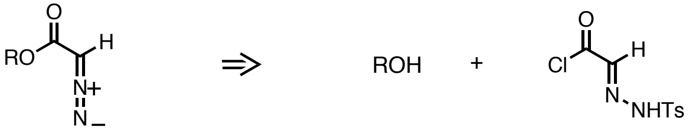


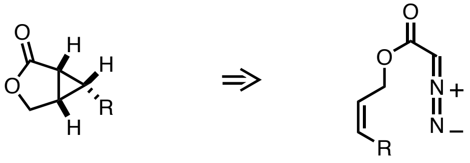


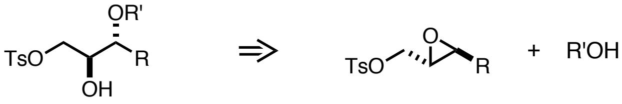


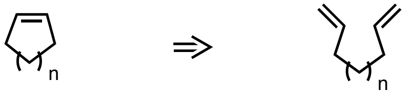




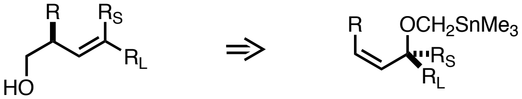


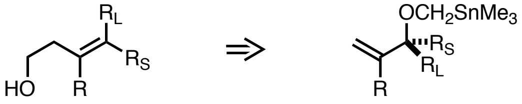






ROCH$_2$SnMe$_3$ ⇒ ROH + ICH$_2$SnMe$_3$



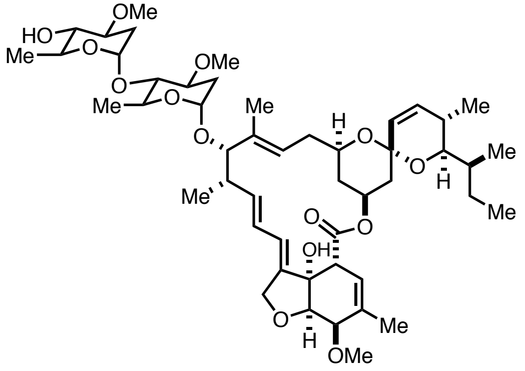


Lecture 16: Oxonium Ions in Synthesis

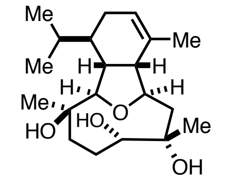
Monday, November 19, 2007

Reading Assignment: Prepare for Exam II.
SANROS pp 64-65, 314-315, 334-335.

Syntheses Discussed:



spiroketal region of Avermectin A_{1a}



Cladiell-11-ene-3,6,7-triol

Partial List of Topics Covered:

Allylsilane Nucleophiles

S_N2' Reactions with Cuprates

DIBAL Reduction of Nitriles

Hetero Diels-Alder Reaction with Danishefsky's Diene

Hydroxybromination

Hemiacetal Reduction

Oxidative Cyclization to Give Spiroketals

Prins-Pinacol Reaction

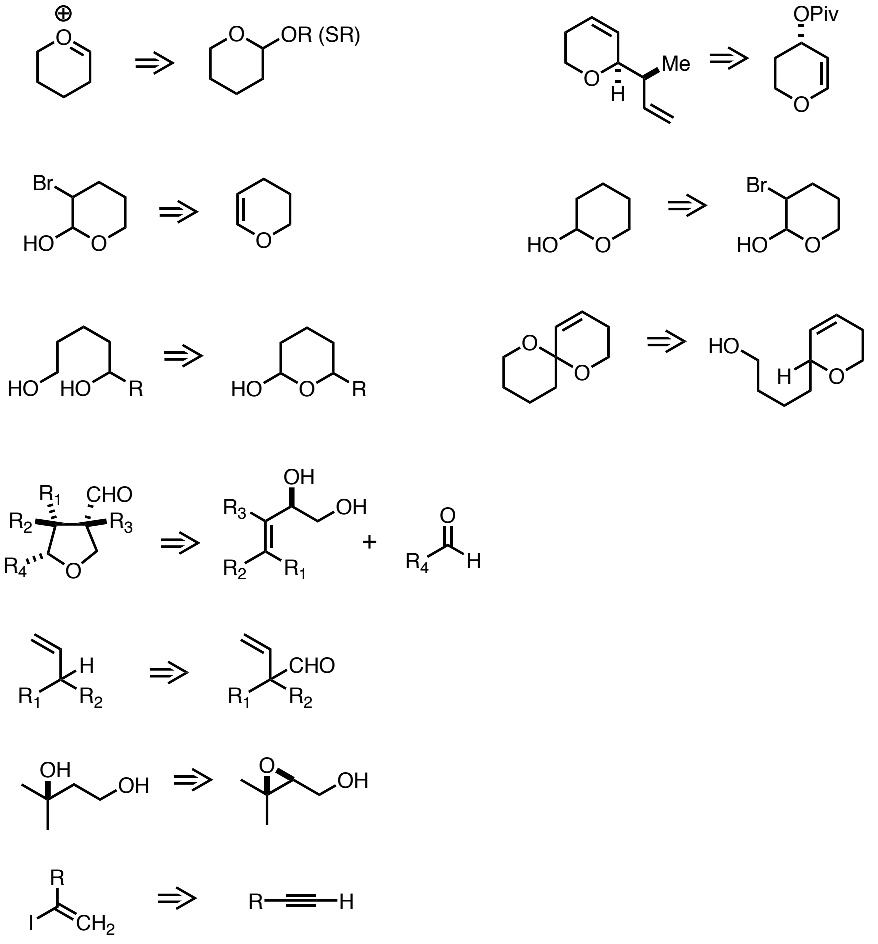
Photochemical Deformylation

Hydroxyl Directed Reductive Opening of Epoxides

Alkyne Iodoboration

Kishi-Nozaki Vinyl-Chromium/Aldehyde Coupling.

Graphical Transform Guide:



References:

Avermectin A_{1a}:
Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967-2980.

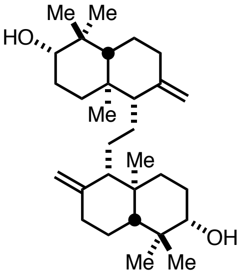
Cladiell-11-ene-3,6,7-triol:
MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033-9044.

Lecture 17: Targeting Strategic Bonds Using Cationic Intermediates

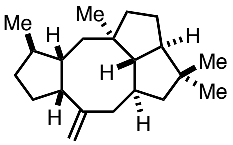
Monday, November 26, 2007

Reading Assignment: SANROS pp 248-249, 274-275, 348-349.

Syntheses Discussed:



(+)-Onocerin



(+)-Epoxydictymene

Partial List of Topics Covered:

Cation-Olefin Cyclization with Allyl Silanes

Alkylation of Silylated Imines

Brook Rearrangement

Cation-Olefin Cyclization with Silyl Enol Ethers

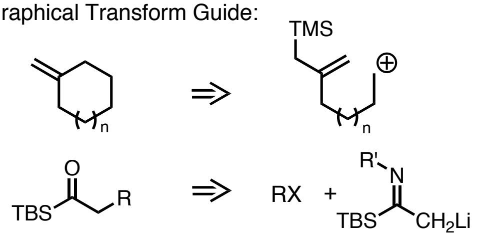
Cross Coupling with Trimethylsilylmethylzinc Bromide

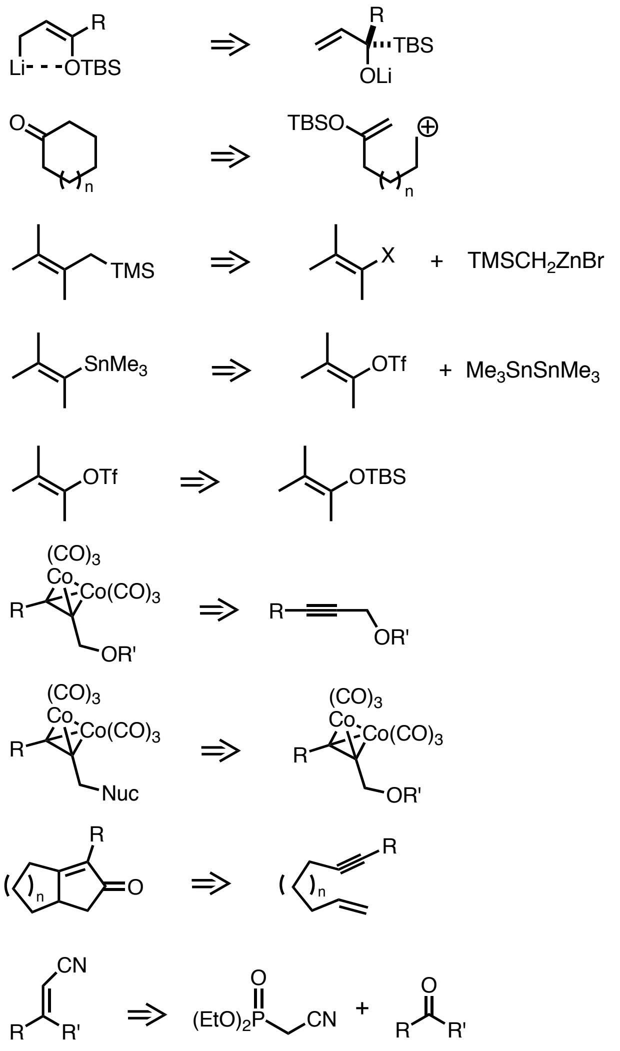
Vinyl Triflates from Silyl Enol Ethers

Lewis Acid Promoted Nicholas Reaction

Pauson-Khand Reaction

Graphical Transform Guide:





References:

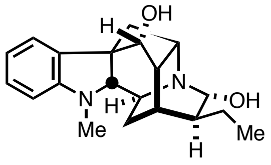
(+)-Onocerin:
Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290-11291.

(+)-Epoxydictymene:
Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.*, **1997**, *119*, 4353-4363.

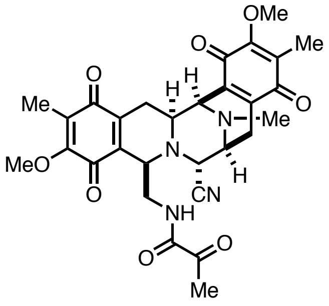
Lecture 18: Targeting Strategic Bonds Using Cationic Intermediates: Focus on Alkaloid Synthesis

Wednesday, November 28, 2007

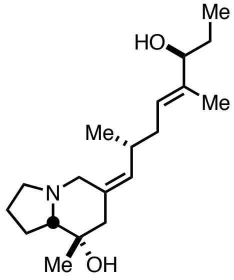
Syntheses Discussed:



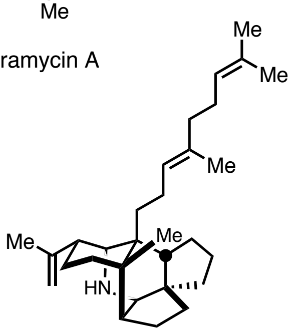
Ajmaline



(–)-Saframycin A



(+)-Pumiliotoxin A



Proto-Daphniphylline

Partial List of Transforms Covered:

Mannich Reaction

Pictet-Spengler Reaction

Alkylation of Pseudoephedrine Glycinamide

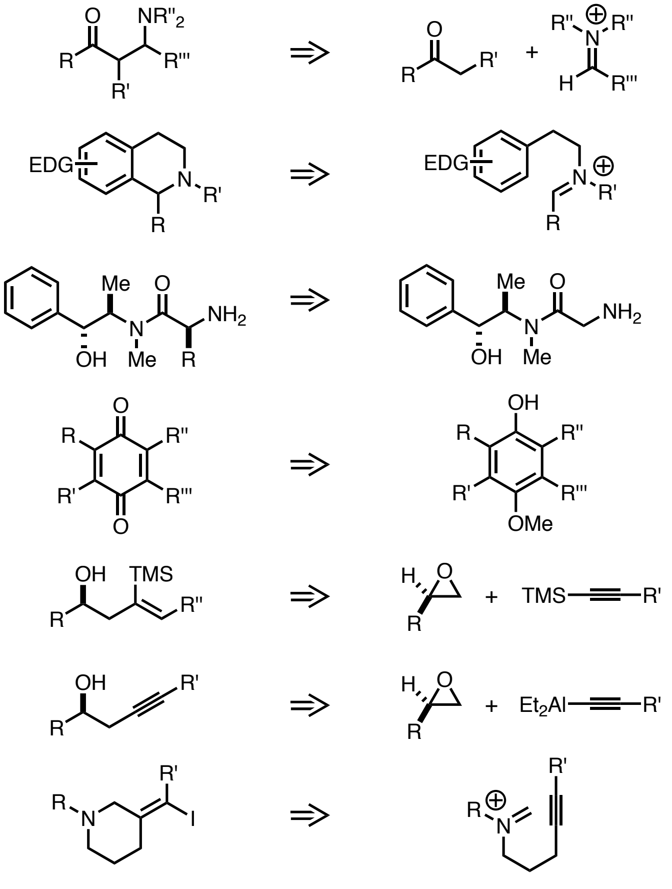
Oxidative Demethylation of Hydroquinones to form Quinones

Addition of Silylvinyl Alanates (prepared from Silylated Alkynes) to Epoxides

Opening of Epoxides with Alkynylalanes

Antarafacial Addition of Iminium Cations and Iodide Ion across Alkynes

Graphical Transform Guide:



References:

Ajmaline:
van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136-2137.

(–)-Saframycin A:
Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828-10829.

Proto-Daphniphylline:
Ruggeri, R. B.; Heathcock, C. H. *Pure & Appl. Chem.* **1989**, *61*, 289-292.
Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532-1534.

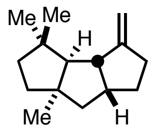
(+)-Pumiliotoxin A:
Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901-904.
Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192-4201.

Lecture 19: Targeting Strategic Bonds Using Free-Radical Intermediates

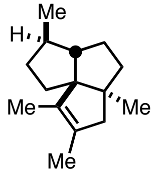
Monday, December 3, 2007

Partial List of Topics Discussed: Radical Chain Processes, AIBN as a Practical Radical Initiator, and Relative Rates of Trapping Radicals with Different Hydrogen Atom Donors

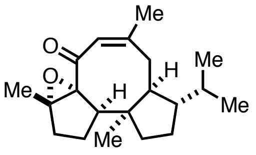
Syntheses Discussed:



(±)-Capnellene



(±)-Silphiperfolene



(±)-7,8-Epoxy-4-basmen-6-one

Partial List of Transforms Covered:

5-*Exo*-Trig Radical Cyclizations

6-*Exo*-Trig Radical Cyclizations

Fragmentation of Cyclopropylcarbinyl Radicals to Allyl Radicals

5-*Exo*-Dig Radical Cyclizations

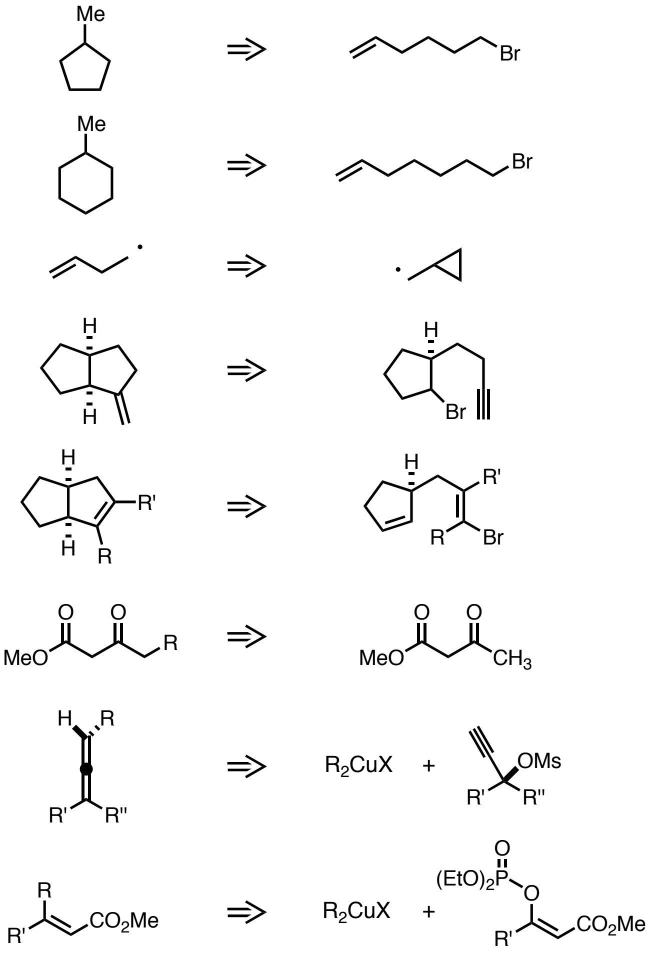
5-*Exo*-Trig Radical Cyclizations with Vinyl Radicals

Kinetic δ-Alkylation of the Dianion Derived from Methyl Acetoacetate

Allenes From Propargylic Mesylates

Trisubstituted Olefins from Cuprate Additions to Enol Phosphates

Graphical Transform Guide:



References:

(±)-Capnellene:
Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991-4994.

(±)-Silphiperfolene:
Curran, D. P.; Kuo, S.-C. *Tetrahedron* **1987**, *43*, 5653-5661.

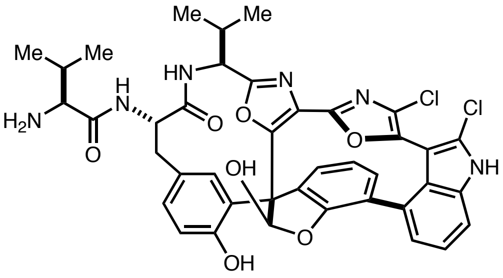
(±)-7,8-Epoxy-4-basmen-6-one:
Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057-3083.
Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926-7927.

Lecture 20: The Synthesis of Diazonamide A

Wednesday, December 5, 2007

Reading Assignment: Handout: The Olefin Metathesis Reaction

Syntheses Discussed:



(–)-Diazonamide A

Partial List of Transforms Covered:

Benzylic Oxidation/Cyclodehydration Sequence for the Synthesis of Oxazoles

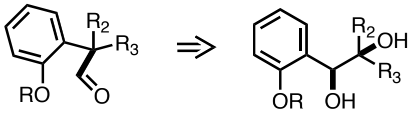
Phenolic Coupling

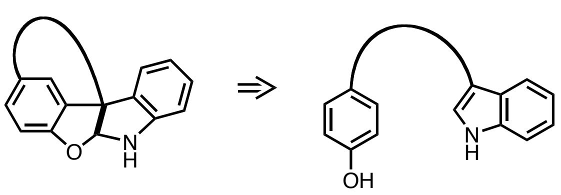
Ring Contracting Pinacol Rearrangement

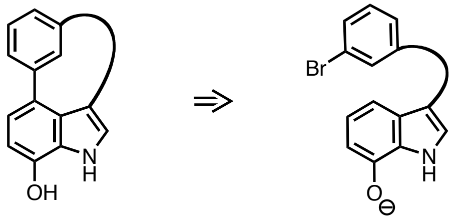
Biaryl Bond Synthesis Through Photoinduced Electron Transfer

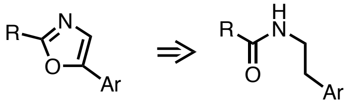
Chlorination of 3-Substituted Indoles

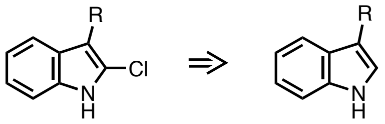
Graphical Transform Guide:











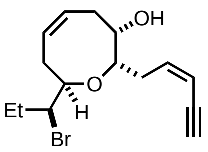
References:

(–)-Diazonamide A:
Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4765-4769.
Li, J.; Burgett, A. W.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4770-4773.
Nicolaou, K. C.; Bella, M.; Chen, D. Y.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3495-3499.
Burgett, A. W. G.; Li, Q., Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4961-4966.

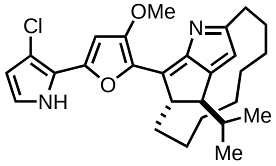
Lecture 21: The Olefin Metathesis Reaction

Monday, December 10, 2007

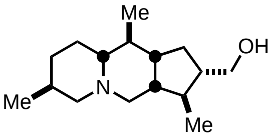
Syntheses Discussed:



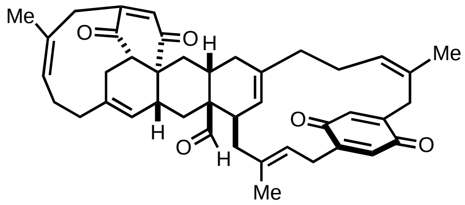
(+)-Prelaureatin



(±)-Roseophilin



(–)-Dendrobatid Alkaloid 251F



(–)-Longithorone A

Partial List of Transforms Covered:

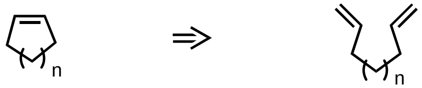
Olefin Metathesis

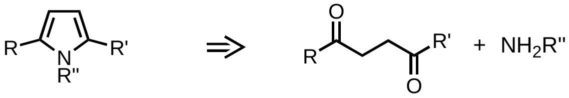
Knorr Pyrrole Synthesis

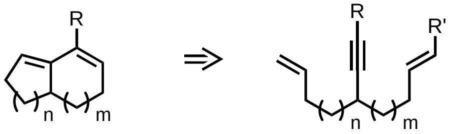
Enyne Metathesis

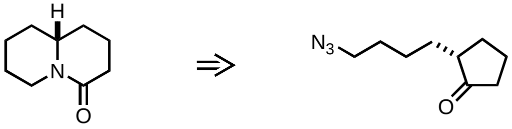
Intramolecular Schmidt Reaction

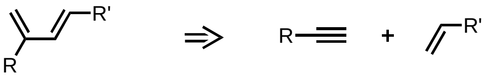
Graphical Transform Guide:

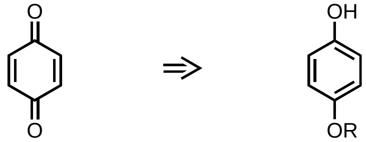












References:

(+)-Prelaureatin:
Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473-5476.

(±)-Roseophilin:
Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649-652.

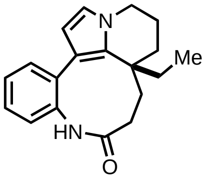
(–)-Dendrobatid Alkaloid 251F:
Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974-9975.

(–)-Longithorone A:
Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124, 773-775.*

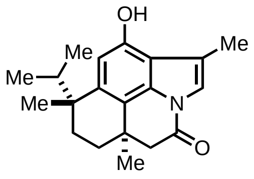
Wednessday, December 12, 2007

Reading Assignment: Handouts: C-H Activation; "C-H Bond Functionalization in Complex Organic Synthesis" Godula, K.; Sames, D. *Science* **2006**, *312*, 67-72. "Direct sp^3 Bond Activation Adjacent to Nitrogen in Heterocycles" Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069-1084. "Catalytic Enantioselective C-H Activation by means of Metal-Carvenoid-Induced C-H Activation" Davies, H. M. L.; Deckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861-2903. "σ-Chelation-Directed C-H Functionalizations Using Pd(II) and Cu(II) Catalysts: Regioselectivity, Stereoselectivity and Catalytic Turnover" Yu, J. -Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041-4047.

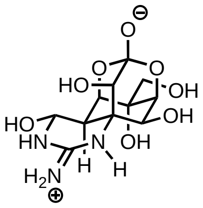
Syntheses Discussed:



Rhazinilam



Teleocidin B-4
core structure



(–)-Tetrodotoxin

Partial List of Transforms Covered:

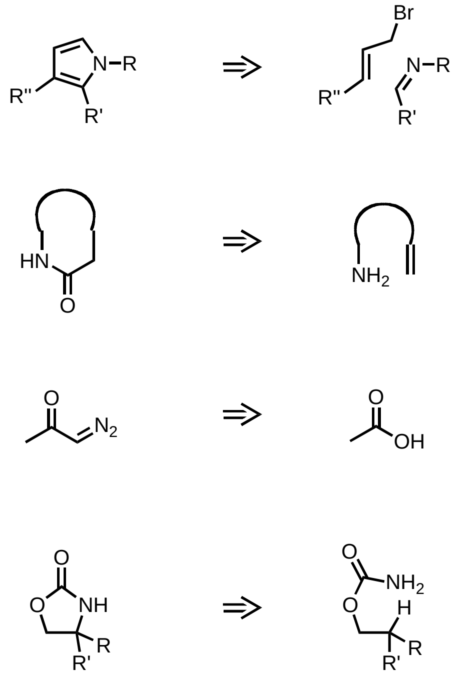
Pyrrole Synthesis from Iminium Salt

Macrolactam Formation

Diazoketone from Carboxylic Acid

C-H Amination

Graphical Transform Guide:



References:

Rhazinilam:
Johnson, J. A.; Sames, D. *J. Am. Chem Soc.* **2000**, *122*, 6321-6322.
Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem Soc.* **2002**, *124*, 6900-6903.

Teleocidin B-4 core:
Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem Soc.* **2002**, *124*, 11856-11857.

(–)-Tetrodotoxin:
Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510-11511.

Bond Dissociation Energies ($DH°_{298}$, kcal mol^{-1}) for A-B Bonds

A•\B• ($\Delta H°_f$)	H (52.1)	F (18.8)	Cl (29.0)	Br (28.6)	I (26.0)	OH (8.9)	NH_2 (44.5)	Me (35.1)	Et (29.0)	^{i}Pr (21.5)	^{t}Bu (12.3)	Ph (80.5)	CN (105.0)
Me (35.1)	104.9	115	83.7	72.1	57.6	92.1	85.2	90.1	89.0	88.6	87.5	103.5	122.4
Et (29.0)	101.1	111	84.8	72.4	56.9	94.0	84.8	89.0	87.9	87.1	85.6	102.2	121.6
^{i}Pr (21.5)	98.6	110.6	85.2	73.9	57	95.5	86.0	88.6	87.1	85.6	82.7	101.0	120.9
^{t}Bu (12.3)	96.5	113	84.9	72.6	55.6	95.8	85.7	87.5	85.6	82.7	78.6	98.3	117.8
Ph (80.5)	112.9	127.2	97.1	84	67	112.4	104.2	103.5	102.2	101.0	98.3	118	134
$PhCH_2$ (49.7)	89.7	98.7	74	63	51	82.6	71.7	77.6	76.7	76.4	72.3	97	107.4
Allyl (41.4)	88.8	-	71	59	45.6	80.1	-	76.5	75.4	75.2	73.2	87.6	108.7
Vinyl (71.1)	110.7	123.3	91.2	80.8	-	-	-	101.4	100.0	99.2	97.8	116	133
HC≡C (135.6)	133.3	125	104	98	79	-	126	126.5	125.1	124.5	122.3	141	156
CF_3 (−112.6)	105.8	129.6	85.3	69.7	54.1	-	101	103	-	-	-	111	112
CHO (10.1)	88.1	-	-	-	-	109.5	101	84.8	83.3	83.1	-	99.3	109
Ac (−2.4)	89.4	122.2	84.7	71.7	53.8	109.9	99.1	84.5	83.5	81.9	79.4	98.8	-
CN (105.0)	126.3	115	101	87.2	76.5	-	119	122.4	121.6	120.9	117.8	134	136.7
OH (8.9)	118.8	51.4	55.8	50	51	50.4	63	92.1	94.0	95.5	95.8	112.4	-
OMe (4.3)	104.6	-	48.0	-	-	45	54.6	83.2	84.8	85.8	84	101	-
OEt (−3.6)	104.7	-	-	-	-	43	-	82.7	85.1	-	-	100	-
OPh (11.6)	86.7	-	-	-	-	-	-	62.9	64.1	-	-	78.1	-
OAc (−43.0)	112	-	-	-	-	40.6	-	91	92	-	92	103	-
SH (34.2)	91.2	54.8	-	-	49	-	-	74.7	73.6	73.4	72.0	86.2	-
MeS (29.8)	87.4	-	70	-	49	-	-	73.6	72.4	72.4	70.4	85.4	-
PhS (58.0)	83.5	-	31	-	-	-	-	67	65	-	-	76	-
NO (21.8)	49.5	56.2	38.0	28.7	18	48.0	-	41.1	41.0	-	39.9	54.2	48.8
NO_2 (8.2)	70	52.9	33.9	20	19	49.1	55	61.0	61.6	62.9	62.8	72.5	-
$SiMe_3$ (3.6)	94.7	160	117.1	101.4	82.1	133	-	94.4	-	-	-	-	-
H (52.1)	104.2	136.3	103.2	87.5	71.3	118.8	107.6	104.9	101.1	98.6	96.5	112.9	126.3

Double and triple bonds: $H_2C{=}CH_2$ (174.1), $H_2C{=}O$ (178.8), HC≡CH (230.7), HC≡N (223.4)

Sources: A. Streitwieser, revised and updated by R. G. Bergman (9/8/2003), S. J. Blanksby and G. B. Ellison *Acc. Chem. Res.* **2003**, *36*, 255-263, Y.-R. Luo *Comprehensive Handbook of Chemical Bond Energies* (CRC Press, 2007), revised and updated (9/19/2018, Y.M.W.).

Comparison of thermodynamic and kinetic parameters

Thermodynamic:

$$A \overset{K}{\rightleftharpoons} B$$

forward rate const.: k_1
reverse rate const.: k_{-1}

$$Q = [B] / [A]$$

$$K = Q_{eq} = [B]_{eq} / [A]_{eq}$$

$$\Delta G = RT \ln(Q / K),\ \Delta G^\circ = -RT \ln K$$

When $Q = 1$, $\Delta G = \Delta G^\circ$
At equilibrium, $Q = K$, so $\Delta G = 0$

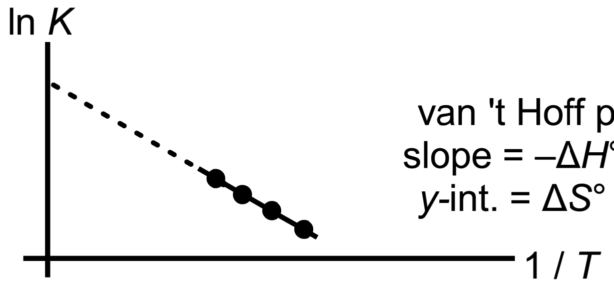
When $\Delta G^\circ = 0$, $K = 1$

$$\boxed{K = \exp(-\Delta G^\circ / RT)}$$

Since $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$,
$\ln K = -\Delta G^\circ / RT = -\Delta H^\circ / RT + \Delta S^\circ / R$

298 K: $\Delta G^\circ = -1.36$ kcal/mol (lg K)

K ranges from 0 to ∞ in principle



van 't Hoff plot:
slope = $-\Delta H^\circ / R$
y-int. = $\Delta S^\circ / R$

Kinetic:

$$A \xrightarrow{k} B$$

Arrhenius (overall kinetics)

$$\boxed{k = A \exp(-E_a / RT)}$$

Eyring (single step)

$$\boxed{k = (k_B T / h) \exp(-\Delta G^\ddagger / RT)}$$

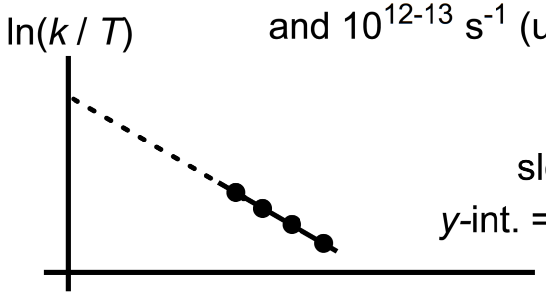
For a single-step rxn:

$$E_a = \Delta H^\ddagger + RT,\ A = (e k_B T / h) \exp(\Delta S^\ddagger / R)$$
(e = 2.718...)

Since $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$,
$\ln(k / T) = \ln(k_B / h) + \Delta S^\ddagger / R - \Delta H^\ddagger / RT$

298 K: $\Delta G^\ddagger = 23$ kcal/mol $\Rightarrow k = 10^{-4}\ s^{-1}$

k has upper limit of $10^{9\text{-}10}\ M^{-1}s^{-1}$ (bimol.)
and $10^{12\text{-}13}\ s^{-1}$ (unimol.)



Eyring plot:
slope = $-\Delta H^\ddagger / R$
y-int. = $\ln(k_B / h) + \Delta S^\ddagger / R$

$$K = k_1 / k_{-1} \text{ and } \Delta G^\circ = \Delta G^\ddagger_1 - \Delta G^\ddagger_{-1}$$

R. G. Bergman